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REVIEW

Epidemiology of Invasive Candidiasis

Derek J Bays[1], Emily N Jenkins[2,3], Meghan Lyman[3], Tom Chiller[3], Nora Strong[4], Luis Ostrosky-Zeichner[4], Martin Hoenigl[5–7], Peter G Pappas[8], George R Thompson III[1,9]

[1]Department of Internal Medicine, Division of Infectious Diseases, School of Medicine, University of California Davis, Sacramento, CA, USA; [2]ASRT, Inc, Atlanta, GA, USA; [3]Mycotic Disease Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA; [4]Division of Infectious Diseases, Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA; [5]Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [6]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, La Jolla, CA, USA; [7]Clinical and Translational Fungal Working Group, University of California San Diego, La Jolla, CA, USA; [8]Division of Infectious Diseases, Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [9]Department of Medical Microbiology and Immunology, University of California-Davis, Davis, CA, USA

Correspondence: Derek J Bays; George R Thompson III, Email djbays@ucdavis.edu; grthompson@ucdavis.edu

Abstract: Invasive candidiasis (IC) is an increasingly prevalent, costly, and potentially fatal infection brought on by the opportunistic yeast, *Candida*. Previously, IC has predominantly been caused by *C. albicans* which is often drug susceptible. There has been a global trend towards decreasing rates of infection secondary to *C. albicans* and a rise in non-*albicans* species with a corresponding increase in drug resistance creating treatment challenges. With advances in management of malignancies, there has also been an increase in the population at risk from IC along with a corresponding increase in incidence of breakthrough IC infections. Additionally, the emergence of *C. auris* creates many challenges in management and prevention due to drug resistance and the organism's ability to transmit rapidly in the healthcare setting. While the development of novel antifungals is encouraging for future management, understanding the changing epidemiology of IC is a vital step in future management and prevention.

Keywords: Candida, epidemiology, resistance, emerging, non-*albicans Candida* species

Introduction

Invasive candidiasis (IC), defined for the purposes of this review as *Candida* spp. in the blood (candidemia) or *Candida* spp. isolated from sterile tissue (hepatosplenic candidiasis and intraabdominal candidiasis, as examples) remains a costly, morbid, and often fatal infection. Candidemia has been found to increase 90-day mortality rates by >28%.[1] For the purpose of this review, *Nakaseomyces glabrata* will be referred to as *Candida glabrata* along with *Pichia kudriavzevii* as *Candida krusei* due to these names predominantly still being used clinically. Since the 1990s, there have been multiple strategies aimed at reducing the incidence of invasive infection, including antifungal prophylaxis in the highest risk groups and infection prevention strategies to reduce the rate of nosocomial infections. However, while there has been an overall reduction in incidence, new challenges have emerged including a shift to non-*albicans Candida* spp., and novel species such as *C. auris*, breakthrough infections, and drug resistance.[2] Here, the changing epidemiology of invasive candidiasis and impact upon treatment are reviewed.

Clinical Manifestations of Candidemia and Invasive Candidiasis

The clinical manifestations of *Candida* infection are broad and range from local infection of the mucus membranes to severe disseminated infection with accompanying sepsis. *Candida* spp. are considered a normal constituent of the human skin, gastrointestinal, and genitourinary microbiomes. Infection occurs when host defenses are impaired or via an imbalance of microbiome with ensuing *Candida* overgrowth (Figure 1).

Host Immune Response

The mucosa is continuously exposed to *Candida* spp, and as such a highly coordinated immune response has evolved for host tolerance and the prevention of invasion. Epithelial cells are an essential barrier to infection and following *Candida* attachment via fungal adhesins, such as the agglutinin-like sequence (Als) protein family,[3] epithelial cells detect pathogen-

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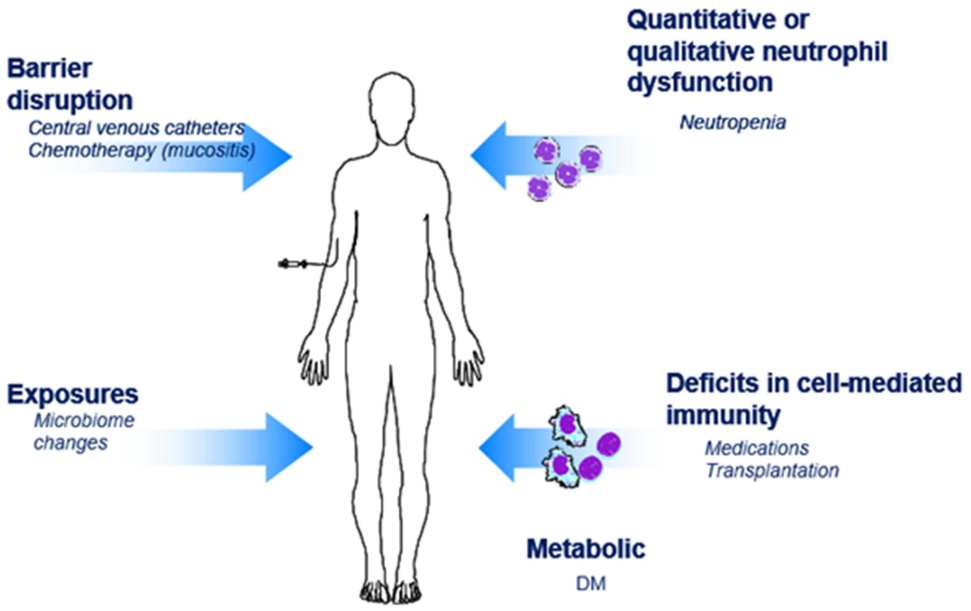

Figure 1 Common risk factors for invasive candidiasis. Risk factors: intravenous catheters, total parental nutrition, post-procedure, broad-spectrum antibiotics, colonization at non-sterile sites, chemotherapy, transplant recipients.

associated molecular patterns (PAMPs), such as mannan and 1,3-β-D-glucan. Immune recognition likely differs between epithelial surfaces and during systemic infection. Toll-like receptors and Dectin-1 are well recognized and critical components of host defense during invasive infection,[4] however epithelial responses may require non-classical receptors such as E-cadherin, EGFR/Her2, and EphA1.[5,6] The response must simultaneously kill fungi while minimizing the surrounding inflammatory reaction and maintaining immune homeostasis. These differences in host immunity may be driven by the form of *Candida* present with the pseudohyphal form present in invasive infections, and yeast on mucosal surfaces.[7]

A number of pattern recognition receptors (PRRs) have been identified including TLR2, TLR4, Dectin-1, FcγR, mannose receptor, galectin 3, MINCLE, and DC-SIGN.[5] Downstream signaling involving CARD9 and SYK have also been observed as essential in the response to *Candida* invasion.[8] A number of host polymorphisms within these genomic regions have been identified and noted to confer increased host susceptibility to infection.[5]

Tissue-resident macrophages play a key role in antifungal defense and produce inflammatory cytokines and chemokine to recruit and activate other immune cells including neutrophils. Neutrophil activation is essential for the clearance of *Candida*, with neutropenia the major risk factor for invasive disease.[5] Neutrophils are additionally the only host cell capable of inhibiting *Candida* germination, and murine models of infection have clearly demonstrated the critical role of neutrophils in candidemia and/or invasive candidiasis.[9]

Following phagocytosis, killing occurs by the generation of NADPH dependent reactive oxidant species (ROS). Patients with defects within this pathway (eg, chronic granulomatous disease) exhibit invasive infection with aspergillosis and other pathogens, but have no observed increase in susceptibility to *Candida* spp.

Natural killer cells appear to have a limited role in host defense against candidiasis. Dendritic cells are an essential factor in the defense against fungal pathogens and are important for processing and presentation of fungal antigens for the activation of T cell responses. T cells are also essential in host defense with both CD4 and CD8 cells providing protective immunity. The production of Th-17 and IFN-γ by Th cells promotes the fungicidal activity of neutrophils and macrophages, and quantitative defects (eg HIV)[10] and qualitative differences (eg, host polymorphisms)[11] in this cellular response pathway have been associated with various forms of candidiasis.

Clinical Manifestations

Local mucocutaneous infections include thrush (oral candidiasis), esophageal and vaginal yeast infections, and chronic mucocutaneous candidiasis. Those with thrush most commonly have underlying diabetes with poor glycemic control,

local glucocorticoid exposure via inhalation (eg, for asthma), or involve neonates with immature host responses. Esophageal infection may co-occur with oral thrush or in isolation and is typically a harbinger of more serious underlying immunologic defects primarily those with T-cell defects (eg, AIDS, solid organ, hematologic stem cell transplant recipients, neonates with immature host response). Vulvovaginal candidiasis may occur with any of the above underlying conditions or following recent antibiotic use with the ensuing loss of protective bacterial species. Chronic mucocutaneous infection occurs in those with polymorphisms in specific genomic regions particularly in those with STAT1 gain of function mutations[12] or in autosomal recessive polyglandular autoimmune syndrome type I.[13]

In contrast, invasive disease primarily occurs in those with a clear breach in host defenses (Figure 1). Risk factors for invasive infection include significant disruptions in the mucosal barrier (mucositis following receipt of chemotherapy) in conjunction with underlying neutropenia. These patients additionally frequently receive broad-spectrum antibiotics significantly altering the gastrointestinal microbiome and have central venous catheters – both additional risk factors for infection. Total parental nutrition, hemodialysis, intravenous drug use, gastrointestinal perforation, and gastrointestinal surgery all pose additional risk factors for invasive disease.[14]

Diagnostics

Our understanding of IC epidemiology is significantly affected by the sensitivity and specificity of currently available diagnostics. The gold standard for diagnosis of IC is a positive culture obtained from blood or a normally sterile site. Positive results may undergo Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) for more rapid identification to the species level.[15] Blood cultures, however, are positive in only 21–71% of patients later proven by autopsy to have IC.[16] The poor performance of blood cultures may be related to collection methods, in particular the collected blood volume as during candidemia there is typically less than one colony forming unit of *Candida* per mL.[17] However, blood cultures cannot be relied upon in all cases of IC given approximately one-third of patients with IC are categorized as having deep-seated infection without candidemia.[16] In these patients, the diagnosis is established by positive cultures or histopathology from affected sites (eg, intraabdominal fluid collection). In concert, this data has led to the conclusion that the sensitivity for blood cultures for invasive candidiasis is only 50%.[16] The relatively poor performance of blood cultures has led to the development of additional diagnostics including antigen-[18] and molecular-based approaches.[19]

Several assays have been developed to detect the presence of *Candida* antigens including mannan and 1,3-β-D-glucan.[18] Diagnostic testing for mannan antigen is typically performed in concert with testing for anti-mannan antibodies and this approach has shown promising results in pediatric patients and in those with central nervous system (CNS) infections,[18] but performed poorly in a large prospective study of non-neutropenic intensive care unit (ICU) patients at risk of IC due to severe abdominal conditions. In this group, the sensitivity of the mannan antigen was only 43.3% with a specificity of 67.3%.[20] Anti-mannan antibody performance exhibited a sensitivity of only 25.8% but a more favorable specificity of 89%.[20] Others have assessed the performance of combined mannan antigen and anti-mannan antibody, but the sensitivity has been sub-optimal at only 51% with a specificity of 71%.[21] Due to poor performance, this test has not been approved by the US FDA.

1,3-β-D-glucan testing has improved performance characteristics in comparison to mannan antigen testing, with a sensitivity across multiple studies averaging approximately 85% and a high negative predictive value often >95%.[18,22] However, the specificity has generally been below 60% due to the potential for false-positive results associated with multiple potential sources including: hemodialysis with membranes manufactured from cellulose, the receipt of intravenous immunoglobulin or albumin, concurrent antibacterials, severe mucositis, and other fungal infections.[18]

Multiple molecular-based diagnostics have been approved for use and recently reviewed elsewhere in the literature.[19] The T2*Candida* Panel (T2 Biosystems, Lexington, MA, United States) does not require positive blood cultures compared to the commonly used BioFire® FilmArray® Blood Culture Identification (BCID) Panel (BioFire Diagnostics, Salt Lake City, Utah, United States). The T2*Candida* panel has a sensitivity of 91% and a specificity of 94% across multiple studies.[19] However, the panel is only limited to five species of *Candida: C. albicans, C. tropicalis, C. krusei, C. glabrata*, and C. *parapsilosis*. Metagenomic next-generation sequencing (mNGS) to detect microbial cell-free DNA (mcfDNA) in plasma is a promising approach, potentially allowing earlier detection and diagnosis of fungal infections when other

blood biomarkers/tests are still negative.[23] There is limited data thus far for the diagnosis of invasive candidiasis by this methodology, although early reports show potential.[24]

There are clearly limitations in current diagnostics for invasive candidiasis that subsequently affect our understanding of the epidemiology. Yet, it is encouraging that advances continue, and improved/novel techniques will hopefully allow for more rapid diagnosis and treatment while simultaneously improving epidemiologic assessment.

Burden of Invasive Candidiasis

Candidemia causes an estimated 22,000 infections annually in the United States.[25] Candidemia is also the second most common cause of healthcare-associated bloodstream infections (BSIs) nationally.[26] A higher incidence of candidemia has been reported among older adults, males, and those of black/African-American ethnicity.[27,28] Although candidemia is the most common form of IC, *Candida* spp. can cause infections in other sterile or deep-seated body sites, with intra-abdominal candidiasis (IAC) being the second most common type of IC in ICUs.[29–31] IAC covers a wide range of disease manifestations, and a lack of standardized disease definitions has made it difficult to understand and accurately capture the burden of these infections.[29]

Generally, incidence rates for IC and candidemia in the US have decreased over time and plateaued in recent years, likely because of improved infection control practices and implementation of bundles for central line care.[32] In the United States, IC incidence rates were higher over a decade ago, ranging from 22 to 29 infections per 100,000 population during 1996–2003.[33] More recent data using US electronic medical records showed there was no significant change in the incidence between 2009–2017, with an overall incidence of inpatient IC of 90 per 100,000 hospitalizations.[34] A more nuanced assessment using data from active population-based surveillance showed the incidence of candidemia decreased from 2008 to 2017 across multiple US sites,[25,27,35] with a coincident increase in the incidence of IC from non-blood sources, including abdominal sterile sites, from 2009–2017.[34]

While an overall decrease in candidemia incidence was observed over the past decade, the incidence unfortunately increased in the setting of the COVID-19 global pandemic.[36–38] In fact, some studies found higher candidemia incidence among patients with COVID-19 infections compared to those without.[36–40] Candidemia in these patients with COVID-19 but no other underlying comorbidities likely resulted from healthcare-related exposures related to severe COVID-19 infection.[41] Changes to healthcare systems during the COVID-19 pandemic (eg, lapses in infection control practices, increased antimicrobial prescribing) and the high acuity of care required for patients with COVID-19 infections (eg, invasive devices, long lengths of stay), likely contributed to the increased risk of IC among patients with COVID-19.[41,42]

IC remains a threat globally although the scope of the problem is difficult to assess. Data availability varies upon laboratory and surveillance capacity and differences in analytical methodology. The overall pooled incidence of candidemia was 3.9 per 100,000 population based on a meta-analysis of 107 European studies using data reported during 1990 and 2016.[43] Similar to trends in the United States, European studies reported a decrease in candidemia incidence after 2010 and an even lower incidence of IAC compared to candidemia, with IAC incidence being approximately a third of candidemia incidence in 23 European ICUs.[31,43] Currently, there are no population-based data sources for Asia, the Middle East, Africa, or Latin America.[44] However, analyses using limited data from the Middle East and North Africa (MENA) region identified that Qatar had the highest candidemia incidence rate (15.4 per 100,000 population) while Iran had the lowest (0.3 per 100,000 population).[45] In Asia, candidemia incidence was 1.2 episodes per 1000 patients using laboratory data from 25 hospitals in five countries.[46,47] In South America, candidemia incidence ranges from 0.6–6.0 per 1000 hospital admission.[48]

IC is associated with prolonged hospitalizations, high healthcare costs, and increased morbidity and mortality. In a study from 2019, IC accounted for 12,770 US hospitalizations, with an average of 28 workdays lost per hospitalization.[49] The estimated total US economic burden of IC is $1.8 billion.[50] All-cause in-hospital mortality of candidemia has been reported as high as 36% in the US.[27,51,52] In Europe, the 30-day mortality rate of IC was slightly higher at 38–42%.[31,43] Mortality of IC in Asia is comparable, with studies estimating mortality rates to be 40%.[46] Mortality estimates are limited in the MENA region but range from 33–60% in adult populations.[53] In South America, studies found that the mortality rate varies from 30–70%.[48] In the US, all-cause mortality was highest among older adults and lowest among children.[25,27,52] No significant differences in mortality by race or sex were reported.[52]

The overall burden of IC is likely an underestimate, especially considering the challenges and gaps in surveillance globally and the performance characteristics of available diagnostic testing. Many countries have limited diagnostic laboratory capacity to test for and detect IC. Lack of standardized methodologies and denominators limit the ability to compare estimates of IC burden.[44] Furthermore, most IC studies are single-center or smaller multi-center analyses. Even in countries with population-based surveillance systems, candidemia is generally not reportable to public health authorities and reporting is thus voluntary. Even with these limitations in performing a comprehensive assessment, available data confirms the high healthcare burden of IC with high associated patient mortality.

Geographic Differences of Invasive Candidiasis

Epidemiology of the *Candida* spp. causing IC or candidemia varies significantly by geographic region.[18] Independent of these geographic variations, there has been a clear worldwide trend of decreasing proportions of *C. albicans* as the causative pathogen. While the proportion of C. *albicans* was 70–80% in the 1980–1990s,[54] it has now declined to 40–60% in most geographic areas.[25,55,56] While that decreasing trend is ubiquitous, with the series of multicenter European Confederation of Medical Mycology (ECMM) *Candida* studies showing the proportion of *C. albicans* causing candidemia decreased from 56.4% in 1997–1999,[57] to 54% in 2006–2008,[58] to 46.2% in 2018[56] with corresponding increases in non-*albicans* species (Table 1), there are important geographic differences. The actual proportion of *C. albicans* is well over 50–70% in Northern and Middle Europe, while mostly well below 50% in Southern Europe, Latin America, Australia, and the US.[59,60]

The changes in distribution of non-*albicans Candida* spp. also have strong regional variations and it is imperative to understand local epidemiologic patterns when empiric treatment is prescribed rather than relying on regional assessments.[18] The proportion of *C. glabrata* has increased particularly in the US, Australia, and Northern Europe.[25,40,41,55,61] Comparatively, the proportion of *C. parapsilosis* has increased in Asia (including Japan and China), Latin America (including Brazil) and Southern Europe,[31,62–65] and the proportion of *C. tropicalis* has increased particularly in Latin America, and large parts of Asia.[62,66] Summarizing all of Europe together, the increase in the proportion of *C. glabrata* between 2006–2008 (13.8%)[58] to 2018 (21.4%)[56] has been striking. Of note, *Candida* spp. distribution may not vary only between geographical regions, but even between medical centers in close proximity, perhaps affected by factors influencing local epidemiology including prior antifungal exposure and patient age within the ICU.[67] Beyond a global distribution of known pathogens, there have also been global differences in emerging species of *Candida*.

Emerging Species of Candida

As global temperatures rise, fungi are adapting to higher environmental temperatures,[68] resulting in the emergence of new fungal species as human pathogens.[69,70] The most prominent example is *C. auris*, which is theorized to have evolved from a plant saprophyte and possibly became a human pathogen after adaptation to higher temperatures.[71] This hypothesis is strengthened by the observation that an environmental isolate grew slower at mammalian temperatures than clinical strains, a finding consistent with the notion that their ancestor recently adapted to higher temperatures.[72] *C. auris* is now a global human threat, particularly in healthcare settings, causing large outbreaks in ICUs in India, Southern Europe, the United Kingdom, Brazil and the United States.[70,71,73] As a result, *C. auris* has

Table 1 Causative Species for Candidemia Within the European Confederation of Medical Mycology Over Three Separate Time Points

***Candida* Species**	**1997–1999[57]**	**2006–2008[58]**	**2018[56]**
C. albicans	56.4%	54%	46.0%
C. glabrata	13.9%	13.8%	21.0%
C. parapsilosis	13.5%	18.5%	13.0%
C. tropicalis	7.2%	6.0%	7.0%
C. krusei	2.0%	2.5%	3.0%
Other	7.0%	5.2%	10%

been highlighted as one of four fungal pathogens of critical importance in the recently published WHO fungal pathogens priority list in part due to the number of large outbreaks, but also due to the multi-drug resistant nature of the pathogen.[74] There are still notable differences in the epidemiology of *C. auris*, where some countries only see isolated cases reported, potentially due to more strict hospital hygiene measures preventing nosocomial transfer and difficult to control outbreaks,[75] while other countries are at a state of emergency due to larger outbreaks with this multi-drug resistant pathogen.[75,76]

In contrast to *C. auris*, which truly is an emerging pathogen, *Candida* spp. that were defined before as "emerging"[77] (ie, *C. kefyr, C. guilliermondii, C. lusitaniae, C. dubliniensis, C. famata, C. inconspicua, C. rugosa, C. norvegiensis*), may have in fact already "emerged" due to better diagnostic differentiation methods, or were selected by the broad use of antifungal treatment and prophylaxis. For example, *C. dubliniensis* infections increased after introduction of MALDI-TOF as this method reliably differentiated between the phenotypically similar *C. albicans* and *C. dubliniensis*. Others, such as *C. inconspicua, C. norvegensis, C. guilliermondii, C. digboiensis*, and *C. lusitaniae* have intrinsic reduced susceptibility to fluconazole and/or echinocandins and may have thus increased only in patient populations exposed to antifungals.

While not an emergent species, a concerning worldwide increase of clonal outbreaks caused by fluconazole-resistant *C. parapsilosis* is ongoing. Fluconazole-resistant *C. parapsilosis* strains that carry the *ERG11* Y132F mutation may not suffer an associated fitness cost (potentially a survival benefit), and may, therefore, thrive even in the absence of triazole exposure.[64] These properties allow this pathogen, which is associated with high mortality rates among those infected,[64] a viable threat to widescale spread. Understanding the global distribution of not only emerging species, but also emerging drug-resistance trends is vital for determining optimal preventative and treatment strategies, particularly as we attempt to prevent breakthrough infections in vulnerable populations receiving prophylactic antifungals.

Breakthrough Infections Due to Candida

Breakthrough infections due to *Candida* constitute a broad range of clinical entities. Breakthrough infections generally consist of organisms that tend to be antifungal resistant, and occur in patients with multiple risk-factors, have an unrecognized or unremoved source, and/or in those with unfavorable antifungal pharmacokinetic circumstances. Until recently, the term "breakthrough infection" as it relates to fungal infections in general was left to the interpretation of individual investigators and poorly defined. A recent consensus statement from the Mycoses Study Group Education and Research Consortium (MSGERC) together with the European Confederation of Medical Mycology (ECMM) has put forth a consensus definition of breakthrough fungal infections, including candidiasis, which represents a significant step forward towards standardizing these observations.[78] Overall, breakthrough *Candida* infections are generally uncommon, occurring in fewer than 10% of at-risk patients,[79] although they can constitute up to 40% of all *Candida* infections in selected series.[80]

Definition

Breakthrough (BT) *Candida* infection occurs in the setting of an individual receiving either prophylactic, empiric, or preemptive/targeted antifungal therapy. Unlike other fungal infections such as *Aspergillus* or the endemic fungi, BT *Candida* infections require a positive culture from a normally sterile site such as blood, or compelling culture and histologic evidence from a mucosal site such as the oropharynx or esophagus for diagnosis.[81] Thus, by consensus there are only *proven* BT *Candida* infections based on European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) updated criteria.[82] Serologic evidence such as *Candida* PCR, *Candida* mannan and anti-mannan, and 1.3-β-D glucan provide supporting evidence, but are not sufficient as the sole source of evidence for candidiasis.[81] To meet the definition of BT, infection must occur at least 72 hours after initiation of systemic antifungal therapy and no greater than one dosing-interval (8 hours to 7 days depending on the antifungal) after the antifungal agent has been discontinued.[78]

Risk Factors for Breakthrough Candidiasis

There are several readily identifiable risk factors associated with BT candidiasis. Many of these events occur in three main host groups: patients with prolonged ICU stays, solid organ transplant recipients, and those with hematologic malignancies or stem cell transplant recipients.[79] These host risk factors are described below.

Host Factors

Among the three major risk groups for BT infection, there are several shared risk factors including the presence of a central venous catheter, prolonged exposure (>14 days) to two or more broad-spectrum antimicrobials, and iatrogenic immunosuppression.[79] Unique to the ICU group is duration of ICU stay greater than 10 days, concomitant pancreatitis, major trauma including burns, impaired renal function, total parenteral nutrition, and mechanical ventilation.[83] While any of these factors can enhance the risk of BT infection in any of these three major patient groups, they are profoundly impactful and potentially synergistic in the ICU population.

Unique to the transplant population is the enhanced risk of BT *Candida* infections among lung, liver, and small bowel transplant recipients.[80,84,85] In the largest study to date, the TRANSNET database determined that 41% of all proven *Candida* infections were BT candidiasis and that lung transplant recipients had the highest rates of BT infection. In this series, antifungal prophylaxis included fluconazole, other azoles, echinocandins, and amphotericin B.[80] Among those with hematologic malignancy and/or stem cell transplant recipients, specific risk factors for BT candidiasis included mucositis, neutropenia, use of glucocorticoids and other immunosuppressive agents.[79]

A major consideration with respect to host factors pertains to source control. While this most often refers to appropriate management and removal of a central venous catheter or other intravascular device, this can also pertain to inadequate drainage of a contaminated fluid collection such as an intra-abdominal abscess, pleural empyema, or soft tissue abscess.[79]

Pharmacokinetic Factors

BT candidiasis can be the consequence of inadequate drug levels, poor penetration into specific tissues or spaces, or unforeseen drug-drug interactions. Sub-therapeutic drug levels are most common with the triazole antifungals despite adherence to recommended dosing regimens.[86] As such, therapeutic drug monitoring, especially for itraconazole, voriconazole and posaconazole, is recommended even in the setting of antifungal prophylaxis.[87] It is also crucial to recognize that some commonly use agents have limited penetration into critical spaces. For example, echinocandins do not achieve significant penetration into the central nervous system or into the urinary system. Finally, drug-drug interactions, especially between the triazoles and other commonly co-administered agents, are increasingly recognized given the complexity of modern patient management. The sheer variety of immunosuppressive agents such as tacrolimus, cyclosporine, and sirolimus as well as a number of newer anti-cancer agents require a detailed knowledge of these predictable drug interactions which can significantly influence antifungal efficacy.[88]

Antifungal Resistance

A review of the most recent data pertaining to BT *Candida* infections suggests that many, but not all, of these infections occur due to organisms that are resistant to one or more antifungals, and accordingly are dominated by non-*albicans Candida* species, especially *C. glabrata, C. krusei, C. parapsilosis*, and *C. tropicalis*.[89–92] Less common species such as *C. lusitaniae* and *C. guilliermondii* have also been reported.[93] The majority of BT *Candida* infections occur in patients receiving antifungal prophylaxis with a triazole antifungal such as fluconazole, voriconazole, posaconazole or isavuconazole,[94–96] but there are also ample reports of individuals who experienced breakthrough infections while receiving an echinocandins.[97,98]

Outcomes

If recognized early and managed appropriately, most BT *Candida* infections can be treated successfully with antifungal therapy including optimization of dosing, source control, and recognizing potential drug-drug interactions. In most large

series, overall mortality at 30 days is similar for BT *Candida* infections compared to *de novo Candida* infections (~30%).[99,100] BT infections are vital to track as they likely contribute to changes in epidemiology related to non-*albicans* species infections and trends in antifungal susceptibility.

Trends and Antifungal Susceptibility of Candida Species

Investigations of IC over the last three decades have led to numerous investigations of the evolving antifungal susceptibility patterns and documentation of changes over time. Regional and global surveys have documented trends in antifungal susceptibility for the major *Candida* species.[27,101–104] For the purposes of this discussion, antifungal susceptibility is determined on the basis of CLSI and/or EUCAST methodologies, and while these methodologies and breakpoints are not entirely interchangeable, there is enough similarity to allow for general comparisons.[105,106] Each of the five major species and *C. auris* will be reviewed.

C. albicans remains the most common cause of bloodstream infections due to *Candida* and other forms of invasive candidiasis in most regions of the world.[18,27,62,102,103,107–109] In multiple population studies over the last two decades, *C. albicans* is almost uniformly susceptible to fluconazole, the echinocandins, and amphotericin B. Resistance to fluconazole is uncommon, with rates generally ranging between 0% and 3%, but averaging less than 1% overall.[27,62,102,103,109]

In many parts of the world, *C. glabrata* is the second most common cause of IC, particularly affecting older individuals and those with significant underlying immunosuppression.[18] Among the more common *Candida* spp, *C. glabrata* probably poses the greatest risk with regard to the development of antifungal resistance and this may be attributed to the prevalent mutator genotype promoting multi-drug resistance phenotypes.[110] Large population-based surveys conducted by the CDC have demonstrated echinocandin resistance ranges between 2% and 8%, while fluconazole resistance ranges between 7% and 11%.[27] Fluconazole resistance has been reported in up to 75% of *C. glabrata* isolates in single center surveys, and resistance to the echinocandins ranges from 0% to 24% in larger studies.[27,111–113] Rates of echinocandin resistance tend to parallel increases in fluconazole resistance as demonstrated by Alexander et al at a 10-year single center survey.[111] A general consensus suggests that echinocandin resistance rates are generally higher in academic institutions compared to community-based medical centers, however this is not true across all centers. For instance, one recent survey from a large academic medical center tested >800 *C. glabrata* isolates over a 10-year period and detected fewer than 3% echinocandin resistant isolates in any given year, and observed no trend towards emerging resistance.[114] Taken as a whole, there has been a slow but steady increase in resistance rates to both fluconazole and the echinocandins over the last two decades and continued assessment of this ongoing problem is essential.

Similar to *C. glabrata, C. tropicalis* prevalence varies considerably among different regions of the world. This organism is particularly common in the Asian Pacific, Caribbean and Latin America, but less so in North America and western Europe.[62] Historically this organism has been pan-susceptible to triazoles, echinocandins, and amphotericin B. In recent years, however, reports of fluconazole and echinocandin resistance have become more frequent, and the current baseline level of resistance to fluconazole is 3–5% in most regions, but rates as high as 7–43% are reported in some Asian Pacific countries.[115–117] Echinocandin resistance remains low at 0–2% in most surveys.[27,62] Amphotericin B resistance continues to be rare, however, pan-resistant *C. tropicalis* may constitute 1% of isolates as reported in India.[118]

Among the five most common *Candida* species causing invasive candidiasis, *C. parapsilosis* is the least virulent with respect to all-cause mortality.[18] Depending on geographic region, it is the first to fourth most common cause of invasive candidiasis.[18,62,66] However, fluconazole resistance has emerged over the last decade and over 50% of *C. parapsilosis* isolates are resistant in some series.[64,119] In the US, fluconazole resistance rates range between 4–10%; rates are much higher in other parts of the world including Japan, Western Europe, and Latin America. Resistance to the echinocandins has remained relatively infrequent (0–3%) despite a higher baseline susceptible MIC cutoff value compared to the other *Candida* spp. due to a naturally occurring polymorphism in *FKS1*.[62,103,112,120]

C. krusei is considered inherently resistant to fluconazole yet demonstrates variable susceptibility to both voriconazole and posaconazole.[62,103,112] In general, voriconazole has been considered the best oral option for *C. krusei* infections, however, recent population surveys have demonstrated emerging resistance rates to voriconazole, approximating 10% in some regions of the world. Echinocandin and amphotericin B resistance also appears to be emerging, with rates of resistance in the 3% to 10% range among larger multicenter studies.[107,112]

Having only emerged globally since 2009, *C. auris* is relatively new in the clinical arena. While a less common cause of IC in the US, the organism is among the most common *Candida* bloodstream isolates in India and South Africa.[118,121] It is noted for its potential multidrug antifungal resistance, but the data demonstrate resistance to fluconazole, seen in 70% to 90% of isolates, and they are non-susceptible to quaternary-ammonium disinfectants, allowing this pathogen to persist on healthcare related surfaces and cause outbreaks.[122,123] Resistance to the echinocandins (up to 7%) and amphotericin B (up to 35%) vary greatly between geographic regions.[122–124] Resistance to all three classes of antifungals is reported most commonly in India in South Asia (3%), whereas this is much less common in other regions of the world.[122–124] Because of the potential for person-to-person transmission with *C. auris*, infection prevention measures are key to preventing nosocomial spread.

Although many *Candida* species have very predictable antifungal susceptibility patterns (eg, *C. albicans*) it remains essential that all clinically significant isolates be identified to species level with subsequent antifungal susceptibility testing performed.[125] If testing is not routinely available, a sufficient number of local isolates should be regularly characterized, in order to be able to adequately predict susceptibility patterns at the species level in a specific hospital or geographic region.

General Management Principles of IC

The most recent Infectious Disease Society of America (IDSA)[125] and European guidelines[126,127] recommend echinocandins as first-line initial treatment for most invasive candidiasis in both neutropenic and non-neutropenic patients prior to identification to the species level due to their broad spectrum of activity, favorable side effect profile, mortality benefit, and the increasing incidence of azole resistance particularly among non-*albicans Candida* species.[125,128–132] Both guidelines recommend "step-down" to fluconazole (in 5–7 days per IDSA or 10 days per European guidelines) if clinically improved and no triazole resistance is suggested by species identification or susceptibility testing. Due to intrinsic resistance to fluconazole, voriconazole is recommended as step-down for *C. krusei*.[125,133]

Non-neutropenic patients with central venous catheters should undergo catheter removal, however in neutropenic patients who may have a gastrointestinal source of candidemia, an individualized approach to CVC removal is recommended except in the cases of *C. parapsilosis* IC.[125] Echocardiography is recommended to assess for endocarditis in cases of persistent candidemia.[134] With uncomplicated candidemia, treatment duration is 2 weeks after clearance of blood cultures and symptom resolution. All infected intracardiac devices require removal or indefinite oral azole suppression following disease control.[125,132]

Due to potential ophthalmologic complications which significantly affect management, the IDSA recommends a dilated eye exam within one week of diagnosis for non-neutropenic patients and within a week of resolution of neutropenia for neutropenic patients, as evidence of chorioretinitis and endophthalmitis are unlikely until recovery of immune function. Per IDSA and European guidelines, intravitreal treatment is recommended in conjunction with ophthalmology, and consists of fluconazole or voriconazole, if susceptible. Otherwise, intravitreal amphotericin B with or without flucytosine is recommended for ocular involvement, with consideration of vitrectomy. Duration is 4–6 weeks or until resolution on repeat ophthalmologic exam.[125,132]

IDSA recommends treatment of chronic disseminated candidiasis with a liposomal amphotericin B or an echinocandin continued for several weeks with stepdown to fluconazole if susceptible, with therapy continuation until resolution of lesions on repeat imaging. Continuation of therapy throughout high-risk chemotherapy or stem cell transplantation is advised to prevent relapse.

For osteomyelitis, surgical debridement is indicated for large abscesses or joint instability. IDSA recommends an oral azole for 6–12 months or an echinocandin (weaker alternative liposomal amphotericin B) for 2 weeks with step-down to an oral azole for 6–12 months. European guidelines favor an oral azole for 6–12 months or liposomal amphotericin B for 2–6 weeks with step down to an oral azole to complete 6–12 months. For septic arthritis, surgical drainage and removal of any prosthetic device is recommended, with chronic oral azole suppression if a device remains. IDSA recommends an oral azole for 6 weeks or echinocandin for 2 weeks and an oral azole for ≥4 weeks or liposomal amphotericin B for 2 weeks with step down to an oral azole for ≥4 weeks. European guidelines recommend an oral azole for ≥6 weeks or

liposomal amphotericin B for 2 weeks with step down to fluconazole for ≥4 weeks, with voriconazole for ≥6 weeks as an alternative.[125,132]

Central nervous system (CNS) candidiasis has less data on optimal treatment. The IDSA recommends treatment with liposomal amphotericin B with or without flucytosine with potential fluconazole step down if susceptible after clinical response. Duration is dependent upon resolution of symptoms, radiologic, and CSF abnormalities. Echinocandins have poor CNS penetration at normal dosing and are not recommended.[125] European guidelines weakly recommend IV liposomal amphotericin B and flucytosine for 6 weeks followed by 3 weeks of fluconazole, or liposomal amphotericin B and fluconazole for 4 weeks depending on susceptibilities.[132]

The Need for Early Therapy

Attributable mortality from IC remains high and increases with delays in treatment. Blood cultures take an average of 2–3 days to grow *Candida*, or longer depending on the species. Prophylaxis and empiric treatment strategies are all thus routinely employed to decrease mortality.[133,135,136] The IDSA recommends consideration of fluconazole or echinocandin prophylaxis for high-risk ICU patients in units with >5% rate of invasive candidiasis.[125,137] A Cochrane review of prophylaxis in non-neutropenic ICU patients did not find an effect on mortality but did note a significant decrease in invasive fungal infection.[138] European guidelines recommend fluconazole prophylaxis in ICU patients with recent abdominal surgery with recurrent perforation or leakage.[132] Fluconazole, posaconazole, voriconazole, or micafungin are recommended as prophylaxis for allogeneic stem cell transplant patients during the initial neutropenic phase, with transition to fluconazole or posaconazole depending on immune recovery and immunosuppression for graft vs host disease.[131]

The IDSA recommends consideration of empiric antifungal therapy in deteriorating patients with risk factors and surrogate markers suggestive of infection. Therapy should be started as quickly as possible in the setting of septic shock. That said, there has been conflicting data on the benefit of empiric antifungal therapy in patients with septic shock and risk factors for IC. The EMPIRICUS trial failed to show a benefit in the use of empiric micafungin in ICU patients with septic shock and risk factors for IC.[139]

The Antifungal Pipeline for IC

Although morbidity and mortality associated with invasive *Candida* infections remains high, only four major classes of antifungal agents are currently approved for systemic therapy. The echinocandins, as first-line therapy for most *Candida* infections, have an overall failure rate of 25–30% in invasive candidiasis in clinical trials, and notably have little activity within the urinary tract.[18,133,140–144] Multi-drug resistant *Candida* infections are on the rise due to a variety of mechanisms (Table 2), particularly *C. auris*, with widespread azole resistance and the potential for development of resistance to all classes of antifungals during therapy, highlighting the need for new agents to keep up with changes in epidemiology.[133,145–153]

Table 2 Most Common Resistance Mechanisms of Major Candida Species

***Candida* Species**	**Resistance Mechanisms**
C. albicans	Fluconazole – efflux transporters (*MDR1, CDR1, CDR2*) with amino acid substitutions less frequently observed
C. glabrata	Azoles – Changes in drug efflux (Cdr1 and Cdr2)
	Echinocandins – FKS1 polymorphisms in glucan synthase gene
	Mutator phenotype – Mismatch repair defect causing multiple antifungal resistance phenotypes
C. krusei	Fluconazole – Intrinsically resistant due to changes within *ERG11* with other azoles often spared
C. parapsilosis	Fluconazole – amino acid substitution (mainly Y132F) within *ERG11* most commonly with resultant variable susceptibility to voriconazole
C. lusitaniae	Amphotericin B – Mutation or altered expression of ergosterol biosynthetic genes (*ERG3*, etc).
C. auris	Azoles – Majority are fluconazole resistant (*ERG11* mutations) with variable susceptible to other azoles
	Amphotericin B – Hypothesized to be due to alterations in ergosterol biosynthesis
	Echinocandins – Due to mutations in *FKS1*

Encouragingly, a new echinocandin, rezafungin, was approved by the Food and Drug Administration in 2023 for adults with invasive fungal infections after ReSTORE, a Phase 3 clinical trial comparing it to caspofungin for treatment of invasive candidiasis, demonstrated non-inferiority and a 60% cure rate.[154,155] It is similar in structure to anidulafungin but with an extended half-life allowing weekly administration which will improve its suitability for outpatient therapy.[149] Further studies, including ReSPECT, a Phase 3 clinical trial of prophylaxis for invasive fungal infections in patients undergoing allogeneic blood and marrow transplantation are ongoing.[150,156]

Ibrexafungerp is another novel agent which inhibits (1→3)-β-D-glucan synthesis at a different site than echinocandins and thus retains activity against many organisms with echinocandin resistance due to FKS mutations, including many strains of *C. auris*.[156] Importantly, it retains solubility and activity in acidic environments, making it suitable for use in abscesses.[149,157] Clinical trials for infections refractory to other agents have been promising.[150] It has oral bioavailability of 35–50% and good systemic distribution except for the CNS. Ibrexafungerp is currently only FDA approved as oral therapy for vulvovaginal candidiasis, although clinical trials for invasive candidiasis step-down therapy, refractory candidiasis, and *C. auris* are ongoing.[149,156–159]

Lastly, fosmanogepix is another encouraging novel antifungal. Fosmanogepix is a first in class Gwt1 fungal protein inhibitor, which is a class of proteins necessary for mannoprotein anchoring to the cell membrane and cell wall.[160] This novel mechanism provides a broad range of activity against *Candida* spp. including drug-resistant *Candida*.[160] Results from a Phase 2 clinical trial for patients with candidemia from *C. auris* demonstrated safety and efficacy of fosmanogepix.[161] Additionally, data from a Phase 2 study of patients with candidemia with *C. albicans, C. glabrata, C. parapsilosis*, and/or *C. dubliniensis* demonstrated successful outcomes in 16/20 patients without significant adverse events.[162] Phase 3 trials are planned, but these preliminary results are encouraging given the increasing rates of antifungal resistance.

Prevention and Infection Control in the Healthcare Setting

Considering the morbidity and mortality associated with IC prevention is a key priority. To this end, the IDSA collaborated on a joint recommendation for multiple interventions to decrease the risk of all central line associated bloodstream infections (CLABSIs), including candidemia.[163] Implementation of these CLABSI bundles has decreased the incidence of infections.[18] Guidelines include education on appropriate indications for line placement and designation of specific personnel and aseptic technique to place and care for central lines. Upper extremity sites have lower infection risks than lower extremity sites.[163] All insertion sites should be evaluated daily and peripheral lines removed if there are signs of phlebitis, infection, or malfunction.[163] Non-tunneled subclavian lines have lower infection risks than internal jugular or femoral sites, and using the fewest lumens necessary is recommended.[163] Prompt removal of unneeded central lines decreases the risk of infection, and all insertions and accessing of central lines should use with aseptic technique and sterile barrier precautions.[163] Chlorhexidine skin cleansing should occur prior to insertion, and aseptic dressing change schedule based on material. Only replace midlines and central lines if malfunctioning or there is a suspicion of infection. Routine replacement does not decrease infection rate.[163] Daily chlorhexidine bathing of ICU patients decreases risk of bloodstream infections in general, including candidemia.[125,164]

C. auris outbreaks in healthcare facilities has recently seen an increase, greatly facilitated by the COVID pandemic with the large numbers of critically ill, mechanically ventilated patients and likely breaches in infection control practices.[145] This pathogen persists in the healthcare environment and patients can remain colonized for over one year. Due to the ability of *C. auris* to persist and spread throughout healthcare facilities, the CDC released guidance to limit outbreaks.[165,166] Colonization screening is a key strategy to prevent the spread of *C. auris* in healthcare facilities by identifying otherwise unrecognized colonized individuals who need appropriate infection prevention and control measures. Determining who to screen depends on many factors but should be considered for individuals who are at high risk for *C. auris* including patients with epidemiologic linkages to other cases, encounters at high-risk facilities, and risk factors. Screening is recommended using a composite swab of the bilateral axilla and groin. Patients with *C. auris* should be placed under appropriate isolation precautions, which would include contact precautions for acute care hospitals, but enhanced barrier precautions can be considered in nursing home settings. Because patients often remain colonized for long periods of time and can periodically have negative results, isolation precautions should be continued indefinitely throughout the inpatient encounter and for future inpatient encounters, and it is not recommended to repeat screening to

"clear" patients for removal of isolation precautions. Due to the resilient nature of *C. auris* in the environment, it is recommended to perform at least daily cleaning using an appropriate disinfectant[167] of a colonized patient's room along with any surfaces or shared equipment they come into contact with (eg, glucometer, hoyer lift, temperature probe, etc).

Conclusion

Invasive candidiasis continues to pose a global threat. The scope of the problem is likely underrepresented due to limited global surveillance combined with the challenges of diagnostics, even with newer methods clinically available. Nonetheless, it remains a costly and morbid condition even with advances in prevention strategies. While overall incidence does appear to be mostly declining, treatment choices and infection control practices significantly impact the epidemiology of the disease globally and locally. The shift to non-*albicans Candida* spp. combined with the emergence of the multi-drug resistant pathogen, *C. auris*, will play a large role in the evolving treatment practices and shape the future epidemiology of the disease. Recent advances in therapeutics are encouraging, however, as evident by break-through infections and rising drug resistance, antifungal therapy alone is unlikely to be an effective solution in the absence of a holistic approach to *Candida* infections and prevention. Advances in preventative strategies combined with novel agents are needed to decrease the global incidence and improve treatment outcomes.

Disclosure

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