Invasive Candidiasis

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KEYWORDS

• *Candida* • Invasive candidiasis • Antifungals • Bloodstream infection
• Fungal infection

KEY POINTS

- *Candida* is a leading cause of hospital-acquired bloodstream infections, particularly in patients admitted to intensive care units.
- Nonculture-based molecular diagnostic assays improve time to treatment, thereby potentially influencing morbidity and mortality.
- Echinocandins are the treatment of choice for most cases of invasive candidiasis (IC) that do not involve the central nervous system and/or the eyes.
- Targeted antifungal prophylaxis decreases rates of IC and may influence mortality.
- *Candida auris* represents an emerging public health concern worldwide due to its inherent antifungal resistance and lethality, and its ability to persist on inanimate material.

INTRODUCTION

Invasive infection due to *Candida* species is a condition associated with medical progress. It is a common health care-associated infection (HAI) and is widely recognized as a major cause of infection-related morbidity and mortality. There are at least 15 distinct *Candida* species that cause human disease, but over 95% of invasive disease is caused by the 6 most common pathogens: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and, in some regions, *Candida auris*. Serious infections due to these organisms are collectively referred to as invasive candidiasis (IC). Mucosal *Candida* infections, including those involving the oropharynx, esophagus, and vagina, are not part of this review. The focus of this review will be on the epidemiology, pathogenesis, diagnosis, clinical manifestations, treatment, and prevention of IC.

EPIDEMIOLOGY

Candidemia ranks as the fourth most common cause of HAIs and second most common cause of health care-associated bloodstream infections (BSI) in the United

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Abbreviations	
AMB	amphotericin B
BDG	β-D-glucan
BSI	bloodstream infection
CLSI	Clinical and Laboratory Standards Institute
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CVC	central venous catheter
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
HAI	health care-associated infection
IAC	intra-abdominal candidiasis
IC	invasive candidiasis
ICU	intensive care unit
IE	infective endocarditis
LFAmB	lipid formulations of AmB
MALDI-TOF	matrix-assisted laser desorption/ionization time-of-flight
MIC	minimum inhibitory concentration
PCR	polymerase chain reaction
PNA-FISH	peptide nucleic acid fluorescent in situ hybridization
Th17	T helper 17

States.[1] However, when looking at national trends for all BSIs, *Candida* was not among the top 10 organisms diagnosed in the years 1996 to 2016, according to the SENTRY antimicrobial surveillance program.[2] This finding most likely represents the uncommon occurrence of community-onset candidemia without any health care-associated exposures. Recent estimates have put the incidence at 6 to 10 per 100,000 inhabitants in the United States and between 2 to 14 per 100,000 inhabitants at other locations around the world.[3,4]

Candidemia and IC remain as the diseases that generally require multiple risks along the path to disease development that are usually associated with significant medical care. Hospitalizations for IC are in a decline, with the most notable decreases seen in children less than 1 year old and adults more than 65 years old.[5] However, it is important to recognize the importance of local epidemiology, as active surveillance across 4 states has shown significant variability in temporal trends during the 2012 to 2016 surveillance period.[6] Although *C albicans* continues to be the most common pathogen overall, there has been a shift over the past decade to non-albicans species comprising greater than 50% of cases. The SENTRY program has seen a shift in causative species from 1997 to 2016, with *C albicans* now accounting for less than half of cases alongside a slight increase in *C glabrata* (as also known as *Nakaseomyces glabrata*).[7] *C parapsilosis* (~12% to 17%), *C tropicalis* (~8% to 10%), and *C krusei* (~2% to 3%, also known as *Pichia kudriavzevii*) make up the bulk of all other cases diagnosed worldwide. During the 2006 to 2016 portion of this ongoing surveillance program, North American rates can be broken down as follows: *C albicans* 42.7%, *C glabrata* 24.3%, *C parapsilosis* 14.8%, *C tropicalis* 8%, and *C krusei* 2.9%.[7]

Intensive care unit (ICU) admission is generally regarded as a risk factor for candidemia/IC and is recognized in at least 50% of patients with this diagnosis.[6] Many well-recognized risk factors for IC are frequently seen in hospitalized patients, but these are particularly common in critically ill patients requiring intensive care (**Table 1**).[8,9] A recent meta-analysis addressed risk factors for IC, independently re-identifying several known risk factors and adding blood transfusions (odds ratio of 4.9).[10] Among these risk

Table 1
Risk factors for invasive candidiasis

Immunocompromised	Nonimmunocompromised	Neonates
In addition to →	Broad-spectrum antibiotics	← In addition to
Granulocytopenia	Any type of renal dialysis	Gestational age
Stem cell transplantattion	Central venous catheter	Low APGAR
Mucositis	Intravenous drug use	Length of intensive care unit stay
Graft vs host disease	Severity of illness	H_2 blocker
Type of chemotherapy	Total parenteral nutrition	Shock
Organ transplants	Gastrointestinal perforation or surgery	Intubation
—	Candida colonization	Gastrointestinal disease
—	Diabetes	Congenital malformations
—	Length of stay in ICU	—
—	Pancreatitis	—
—	Sepsis	—

factors, many were associated with intravenous access, likely underlied by the tendency of *Candida* to adhere to materials such as catheters, allowing it to gain access to the bloodstream.[10] Additionally, certain risk factors can predispose to particular *Candida* species. For example, malignancy and transplantation, both stem cell and solid organ, have been show to increase the likelihood of *C glabrata*, whereas this organism is a rare pathogen in the neonatal ICU.[11,12] *C krusei* is most often seen among patients with underlying hematological malignancies who are receiving fluconazole prophylaxis.[13] Because antifungal resistance varies with species, it is important to know the local prevalence of selected *Candida* species and rates of fluconazole and echinocandin resistance. Fluconazole resistance has been increasing within *C tropicalis* and *C parapsilosis*. Recently, fluconazole-resistant *C parapsilosis* have been identified, and in parts of Asia and Africa, the prevalence of fluconazole and multidrug-resistant strains of *C tropicalis* have reached 20% to 50%.[14–19]

C auris is a highly resistant species with 5 recognized clades which was first recognized as causing isolated outbreaks internationally with sparse appearances in a few US states. However, it has significantly expanded in recent years and has now become a dominant fungal pathogen in some countries and has an increasing role in US infections.[20–22] The United States experienced a 44% increase in clinical cases in 2019 to a 95% increase in 2021, and noninvasive isolates increased by 200% in 2021.[23] *C auris* has a tendency for multidrug resistance, with most isolates resistant to fluconazole and some resistant to all antifungal drug classes including triazoles, echinocandins, and polyenes. Another hallmark of *C auris* is its ability to colonize the skin and adhere to surfaces in the hospital environment in spite of typical means of decontamination of patient rooms.[24,25] Early identification and infection prevention are crucial to prevent spread in the hospital environment.

PATHOGENESIS

Candida species are a commensal in the human gastrointestinal tract and additionally are common colonizers of the skin and genitourinary tract. The development of invasive disease generally requires both an increase in fungal burden as well as alteration

of the surface, whether that is the skin or mucous membranes.[26] This is frequently aided by the presence of prosthetic material ranging from intravascular catheters to indwelling urinary catheters, given the innate ability of *Candida* to develop biofilms promoting adherence.[27] The ability of *Candida* to form biofilms is also an important aspect in the development of antifungal resistance through 2 different mechanisms. First is the decreased ability of antifungal agents to penetrate the biofilm along with the upregulation of antifungal resistance mechanisms.[28–30] Second is the development of persister cells. These cells use a variety of mechanisms to cope with the increased reactive oxidase stress brought on by fungicidal drugs.[31,32]

The development of IC induces a response from all arms of the immune system. T cells contribute to cell-mediated immunity by trafficking to the site of inflammation and acting directly to mitigate mucosal disease. T helper 17 (Th17) cells, common mediators of the antifungal response, are particularly important, and patients with deficiencies in Th17 cells have been found to have increased *Candida* colonization and invasive disease.[26] Meanwhile, plasma cells contribute to humoral immunity by producing *Candida*-targeting antibodies, which opsonize *Candida* cells and promote their clearance. Cells of the innate immune system also contribute to the anti-candida response. Monocytes promote the inflammatory response through phagocytosis, cytokine production, and antigen processing and presentation to adaptive immune cells.[33] Polymorphonuclear cells use opsonization to mediate killing; neutrophils attack by both oxidative and nonoxidative mechanisms, with dysregulation of this inflammatory response leading to sepsis that differs from bacterial-induced sepsis.[34]

DIAGNOSIS

The gold standard of diagnosis in IC is culture, in particular culture from sterile sites such as blood, peritoneal fluid, and pleural fluid. However, blood cultures are insensitive and identify only approximately 50% of all patients with IC based on data from several autopsy studies. Most (95%) blood cultures that are ultimately positive for *Candida* species become positive within 96 hours, but time to positivity is species dependent; for example, *C glabrata* grows much more slowly than *C albicans*. Other factors that influence the sensitivity of blood culture include the volume of blood, antifungal drug exposure, and the specific blood culture technique. The reliance on blood culture remains a significant obstacle to making clinical decisions regarding early intervention with antifungal therapy. The development of reliable nonculture assays is critical to providing the opportunity for early intervention with more targeted antifungal therapy among large numbers of vulnerable patients.[35]

Data from several retrospective studies suggest that early and effective treatment confers a survival benefit from *Candida* sepsis.[36,37] Moreover, early identification to the species level facilitates therapeutic decision making based on the likelihood of fluconazole susceptibility or resistance and allows informed alterations in therapy while awaiting formal antifungal sensitivity data. Thus, the development of rapid, nonculture-based technologies is a high priority in the effort to influence management and improve outcomes for patients with IC.

At present, there are 5 Food and Drug Administration (FDA)-approved technologies that may help to bridge this gap: matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF), peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), the β-D-glucan (BDG) (Fungitell among others) assay, the T2Candida assay, and the BioFire FilmArray blood culture identification (BCID) panel.

MALDI-TOF is a postculture technique that utilizes mass spectroscopy and requires pure growth of an organism on artificial media; therefore, it has no influence on time to

diagnosis of candidemia. MALDI-TOF can provide species identification within 10 to 15 minutes once an organism is isolated on artificial media. This is generally 1 to 1.5 days sooner than conventional methods, with the most dramatic difference noted for non-albicans *Candida* species.[38–40]

PNA-FISH can be performed directly on a positive blood culture result rather than waiting for the growth of pure colonies.[41] The test exists as commercially available multispecies kits, with a positive result narrowing the identification to a paired result (*C albicans*/*C parapsilosis* vs *C glabrata*/*C krusei* vs *C tropicalis*), not to the level of single-species specificity.[42] Although this assay provides prompt species identification, diagnosis is reliant on a positive culture.

BDG is a cell wall constituent of *Candida* spp., *Aspergillus* spp., *Pneumocystis jirovecii*, selected dematiaceous fungi, the endemic fungi, and several other less common invasive pathogens. In this respect, it is a pan-fungal diagnostic test. The assay has performance characteristics that are reasonably well defined among patients with IC. Using a cutoff value of 80 pg/mL in patients with proven IC, in meta-analyses of BDG studies the pooled sensitivity and specificity for diagnosing IC were 75% to 80% and 80%, respectively.[43–45] Its performance is optimized by requiring 2 successive positive assays to define a true-positive result. True-positive results are not specific for IC, and, for this reason, among patient populations that are also at risk for invasive mold infections, such as hematopoietic cell transplant recipients, BDG offers a theoretic advantage over other assays. The test is limited by its nonspecificity, expense, limited in-house testing availability, and the time required to perform the test.

The T2Candida assay is a polymerase chain reaction (PCR)-based assay that uses magnetic resonance detection to identify the presence of *Candida* organisms in whole blood. The assay groups results as *C albicans*/*C tropicalis*, *C krusei*/*C glabrata*, or *C parapsilosis*.[46] The unique feature of this assay is that it is performed on whole blood, ideally collected simultaneously with routine or fungal blood cultures. Once the specimen has been processed, results are available in as soon as 3 to 4 hours. The largest prospective study of this assay to date showed excellent positive and negative predictive values of 91.7% and 99.6%, respectively.[47] A multicenter trial by Clancy and colleagues found high sensitivity of T2Candida in candidemic patients (88.9%). Prior antifungal treatment was associated with persistently positive T2Candida once blood cultures had cleared.[48]

The Biofire FilmArray BCID assay utilizes multiplex PCR analysis to identify 24 organisms (8 gram-positive bacteria, 11 gram-negative bacteria, and 5 *Candida* species) as well as 3 resistance genes (*mecA*, *vanA*/*B*, and bla_{KPC}) from positive blood culture bottles. Results are available in about 1 hour. In a large multicenter trial of both clinical and seeded blood culture specimens, sensitivity and specificity for the detection of *Candida* were 99.2% and 99.9%, respectively.[49] The recently FDA-cleared BCID2 panel detected additional pathogens and resistance genes, including *C auris*.

Other non-FDA-approved tests include several commercially available PCR assays. A major limitation of PCR studies is the lack of standardized methodologies and multicenter validation of assay performance. Compared with cultures, PCR assays of various blood fractions have been shown to shorten the time to diagnosis of IC and initiation of antifungal therapy.[50,51] The pooled sensitivity and specificity of PCR for suspected IC in a recent meta-analysis were 95% and 92%, respectively. In probable IC, sensitivity of PCR and blood cultures was 85% and 38%, respectively.[50]

In Europe, a whole-blood, multiplex real-time PCR (SeptiFast, Roche) that detects 19 bacteria and 6 fungi (*C albicans*, *C glabrata*, *C parapsilosis*, *C tropicalis*, *C krusei*, and *Aspergillus fumigatus*) has been investigated in several studies of sepsis and neutropenic fever. In one study among newborns and children with suspected sepsis, this test showed sensitivity and specificity of 85% and 94%, respectively.[52]

Also used in Europe, though not FDA approved for use in the United States, are the mannan antigen and anti-mannan antibody tests. In a 2010 meta-analysis, the sensitivity and specificity were 58% and 93% for the mannan antigen test and 59% and 83% for the anti-mannan test; when combined, the sensitivity and specificity reached 83% and 86%.[53] It has been posited that mannan antigen and anti-mannan antibody may be useful specifically for detecting central nervous system (CNS) infections. Though they appear to have limited sensitivity in this setting (20% serum sensitivity and 50% CNS sensitivity in a 2022 study), at least one case report has indicated their usefulness in detecting a chronic candida CNS infection in which cultures were repeatedly negative (2022 study and case report).[54,55]

ANTIFUNGAL SUSCEPTIBILITY TESTING

Once an organism has been isolated, an important step in characterizing the organism is antifungal susceptibility testing. Efforts to develop standardized, reproducible, and relevant susceptibility testing methods for fungi have resulted in the development of the Clinical and Laboratory Standards Institute (CLSI) M27-A3 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodologies for susceptibility testing of yeasts.[56] Interpretive breakpoints for susceptibility take into account the minimum inhibitory concentration (MIC), as well as pharmacokinetics/pharmacodynamics data and animal model data. Breakpoints have been established for most antifungals for the 5 most common *Candida* species (**Table 2**).[57–61] In many instances, clinical breakpoints have decreased from those used previously. For *C glabrata*, there are no breakpoints established for itraconazole, posaconazole, or voriconazole.

The susceptibility of *Candida* to the currently available antifungal agents is generally predictable based on species. Antifungal resistance in *C albicans* remains uncommon.[62] Recent surveillance studies suggest triazole resistance among *C glabrata* isolates has become common enough that is it difficult to rely upon these agents for therapy without susceptibility testing.[63,64] A similar trend has begun to emerge for a smaller proportion of *C glabrata* isolates and the echinocandins.[64,65]

There are currently no established susceptibility breakpoints for *C auris*, although tentative breakpoints have been proposed by the Centers for Disease Control and Prevention. Most isolates are highly resistant to fluconazole, with a much smaller proportion showing increased MICs to all major antifungal classes. Resistance varies by geographic clade. In a study of 54 isolates from 4 countries, 22 (41%) were resistant to 2 or more classes of antifungals, including 2 isolates in India that were resistant to fluconazole, voriconazole, echinocandins, and amphotericin B (AmB).[66] Among 35 isolates in the United States, 30 (86%) were resistant to fluconazole, 15 (43%) to AmB, and 1 (3%) resistant to echinocandins.[67]

The value of susceptibility testing for other *Candida* species is less clear, although resistance among *C tropicalis* and *C parapsilosis* is increasingly reported from institutions that use antifungal agents extensively.[68,69] Because of these trends, susceptibility testing is generally recommended to guide the management of candidemia and IC.[70]

CLINICAL MANIFESTATIONS

IC is generally categorized as IC with candidemia, IC without candidemia, and candidemia alone. Candidemia is the most easily recognized manifestation of IC, but it can involve virtually any anatomic site. A few syndromes comprise almost all cases. A review of these most common syndromes in addition to less common but classic clinical manifestations follows.

Table 2
Clinical breakpoints for antifungal agents against common *Candida* species

		Clinical Breakpoint (μg/mL)[a]			
Organism	Antifungal Agent	Susceptible	Susceptible Dose-Dependent	Intermediate	Resistant
C albicans	Fluconazole	≤2	4	—	≥8
	Itraconazole	≤0.12	0.25–0.5	—	≥1
	Voriconazole	≤0.12		0.25–0.5	≥1
	Posaconazole	—		—	—
	Anidulafungin	<0.25		0.25	≥1
	Capsofungin	≤0.25		0.25	≥1
	Micafungin	≤0.25		0.12	≥1
	Rezafungin	≤0.25		—	—
C glabrata	Fluconazole	—	≤32	—	≥64
	Itraconazole	—		—	—
	Voriconazole	—		—	—
	Posaconazole	—		—	—
	Anidulafungin	≤0.12		0.25	≥0.5
	Capsofungin	≤0.12		0.25	≥0.5
	Micafungin	≤0.06		0.12	≥0.25
	Rezafungin	≤0.5		—	—
C parapsilosis	Fluconazole	≤0.2	4	—	≥8
	Itraconazole	—		—	—
	Voriconazole	≤0.12		0.25–0.5	≥1
	Posaconazole	—		—	—
	Anidulafungin	≤2		4	≥8
	Capsofungin	≤2		4	≥8
	Micafungin	≤2		4	≥8
	Rezafungin	≤2		—	—
C tropicalis	Fluconazole	≤2	4	—	≥8
	Itraconazole	—		—	—
	Voriconazole	≤0.12		0.25–0.5	≥1
	Posaconazole	—		—	—
	Anidulafungin	<0.25		0.5	≥1
	Capsofungin	≤0.25		0.5	≥1
	Micafungin	≤0.25		0.5	≥1
	Rezafungin	≤0.25		—	—
C krusei	Fluconazole	—		—	—
	Itraconazole	—		—	—
	Voriconazole	≤0.5		1	≥2
	Posaconazole	—		—	—
	Anidulafungin	≤0.25		0.5	≥1
	Capsofungin	≤0.25		0.5	≥1
	Micafungin	≤0.25		0.5	≥1
	Rezafungin	≤0.25		—	—

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Candidemia

BSI with *Candida* is the most recognized form of IC, accounting for more than half of all cases enrolled into epidemiologic and antifungal clinical trials. A positive blood culture result for *Candida* should be thoroughly investigated due to the high risk of morbidity

and mortality. All-cause mortality rates vary across the age spectrum, and are especially high with *Candida* sepsis, ranging from 5% to 71%.[71–76] However, most experts agree that the attributable mortality associated with candidemia is 15% to 20% in adults. Among the many clinical manifestations of IC, candidemia is given the most attention in epidemiologic surveys and clinical trials because of its frequency, the ease of defining the disorder, and the ease of identifying patients for inclusion into clinical trials.[2,5–9,11,77–79]

Central venous catheters (CVCs) and other intravascular devices are commonly implicated in patients with candidemia, but other sources must be considered, especially among neutropenic patients, in whom the gastrointestinal tract is a common source. Most experts agree that thoughtful, patient-specific management of CVCs is critical in the overall management of candidemia.[80] Several investigators have shown that mortality is directly linked to the timing of therapy and/or source control.[36,37,81–83] That is, earlier intervention with appropriate antifungal therapy and removal of a contaminated CVC or drainage of infected material is generally associated with better overall outcomes.[36,37,81–83]

Neonatal Candidiasis

Candida spp. are the third most common pathogen associated with BSI in neonatal ICUs in the United States, although the incidence has decreased dramatically recently.[5,84–87] Neonatal candidiasis is associated with significant risk of death, neurodevelopmental impairment in extremely low birth weight infants who weigh less than or equal to 1000 g, and increased health care costs.[88–91] These infants are at high risk of CNS involvement as a complication of candidemia.[92,93] *C albicans* and *C parapsilosis* have previously accounted for 80% to 90% of neonatal IC, but a recent study indicates that *C auris* may be on the rise, especially in low and middle income countries, where it accounted for 14% of infections.[5,12,84,94]

Neonatal candidiasis differs from invasive disease in older patients in that neonates are more likely to present with nonspecific or subtle signs and symptoms of infection.[78] Meningitis is frequently associated with candidemia in neonates, but approximately half of those with *Candida* meningitis do not have a positive blood culture.[92] CNS involvement should be assumed in the neonate who has candidemia together with signs and symptoms suggesting meningoencephalitis, because cerebrospinal fluid (CSF) findings of *Candida* infection may be unreliable.[78]

Acute Disseminated Candidiasis

Acute disseminated candidiasis is a life-threatening infection occurring almost exclusively among patients with neutropenia who have received cytotoxic chemotherapy for a hematologic malignancy. *C albicans*, *C tropicalis*, *C glabrata*, and *C krusei* are the most common causative organisms. Most of these patients are acutely ill, have positive blood cultures and a characteristic diffuse, discrete hemorrhagic and papular rash consistent with small vessel vasculitis. Multiple organ involvement is common; autopsy studies demonstrate that the lungs are the most common target for metastatic infection, followed by the GI tract, kidneys, liver, and spleen.[95]

Endovascular Infection

The chief categories of endovascular *Candida* infection are infective endocarditis (IE) and infection involving implantable intracardiac devices.[96] The incidence of *Candida* endocarditis has increased concurrent with the general increase in IC as a health care-associated complication, but is seen more frequently as a community-acquired infection, often in association with illicit injection drug use.[97] Endocarditis should be

suspected clinically when blood cultures are persistently positive, when a patient with candidemia has persistent fever despite appropriate treatment, or when a new heart murmur, heart failure, or embolic phenomena occur in the setting of candidemia.[98] Most cases of IE occur in the setting of recent or remote cardiac valvular surgery, but other risk factors include injection drug use, cancer chemotherapy, prolonged presence of CVCs, and valvular damage from a prior episode of bacterial endocarditis.[96,97,99] The signs, symptoms, and complications are generally similar to those of bacterial endocarditis, except for the frequent occurrence of large emboli to major vessels. A prospective cohort of endocarditis via the International Collaboration on Endocarditis examined the epidemiology and treatment impact of *Candida* IE and noted 59% mortality at 1 year.[99] Almost 3-quarters of cases were attributed to *C parapsilosis* and *C albicans*, and approximately 50% were associated with a prosthetic valve.

There are a few case reports and a single retrospective review of *Candida* infections of pacemakers and cardiac defibrillators.[100–105] Based on data from a recent systematic review, removal of the entire device combined with prolonged (weeks) antifungal therapy led to improved outcomes when compared with antifungal therapy alone.[106] Despite occasional success, experience suggests that medical therapy alone is usually inadequate. There are also isolated case reports of *Candida* infections involving ventricular assist devices, but there is no consensus on acute and long-term management of these difficult cases.[107–110]

Vertebral Osteomyelitis and Forms of Osteoarticular Candidiasis

Vertebral osteomyelitis, with or without discitis, is a disorder that is usually associated with unrecognized or inadequately treated candidemia. This is described with many of the pathogenic *Candida* species, and symptoms usually manifest several weeks to months after an episode of candidemia. The intervertebral disc and vertebral bodies are the preferred sites of involvement, with patients presenting with chronic progressively severe local back pain, usually without concomitant fever, weight loss, or other constitutional symptoms. As with other forms of vertebral osteomyelitis and discitis, nerve root compression syndromes including complete loss of function are associated with advanced disease.

Candida bone infections can occur at other sites, usually as a consequence of BSI, and less commonly through direct inoculation.[111] The sternum and ribs constitute a large proportion of cases.[111,112] Systemic manifestations of infection are uncommon in nonneutropenic patients, with dominant complaints of local pain, erythema, and swelling in nearly all patients.[111]

Candida prosthetic joint infections are uncommon as an intraoperative event or resulting from candidemia in a patient with a preexisting prosthetic joint.[113,114] Prosthetic hips and knees are the most common sites of involvement. Clinical signs and symptoms are usually indolent and include localized pain and swelling, usually without systemic symptoms.

Endophthalmitis

Most cases of *Candida* endophthalmitis are endogenous, that is, a consequence of candidemia. Endogenous infections usually manifest as isolated chorioretinitis without involvement of the vitreous. Chorioretinitis with extension into the vitreous leads to vitritis and is the most serious and sight-threatening complication of ocular candidiasis.[115–118] Estimates of ocular involvement associated with candidemia have ranged as high as 37%, but more recent data suggest that this is a much less common complication, with estimates ranging from 5% to 15%.[119,120] *C albicans* accounts for

the vast majority of cases of ocular candidiasis, but all common *Candida* species have been reported.

Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)

Chronic disseminated candidiasis occurs almost exclusively among patients who have undergone myeloablative chemotherapy associated with neutropenia. Upon recovery from neutropenia, patients with this disorder develop low-grade fever; right upper quadrant pain, often associated with a palpable and tender liver; splenomegaly; and an elevated serum alkaline phosphatase. Imaging studies (MRI, computed tomography [CT], or abdominal ultrasound) reveal multiple focal abnormalities in the liver, spleen, kidneys, and rarely the lungs.[121] Parenchymal lesions develop following neutrophil recovery, suggesting that an adequate host inflammatory response is a prerequisite to the development of radiographically visible lesions. Among patients with a history of documented candidemia, the diagnosis can be inferred from clinical, laboratory, and radiographic findings. In the absence of documented candidemia, a CT-directed liver biopsy for histopathology and culture is necessary to firmly establish a diagnosis.[121,122]

Other

Candida has been reported as an etiologic agent of infection in virtually every visceral organ and body cavity; however, these remain relatively rare manifestations of disease. *Candida* species may cause meningitis, septic arthritis in native joints, tenosynovitis, isolated involvement of the kidney or the intra-abdominal cavity, and rarely pneumonia. Among these, intra-abdominal candidiasis (IAC) is by far the most common. Estimates of the incidence of IAC vary due the difficulty in making a firm diagnosis, and it is clear that IAC is greatly underdiagnosed.[123] The diagnosis of IAC is typically based on the isolation of *Candida* species from sterilely obtained specimens and/or positive nonculture-based diagnostics (eg, BDG) and a compatible clinical scenario. Intraperitoneal *Candida* infections are clearly associated with poor outcomes.[124,125] *Candida* pneumonia is a rare disorder that is seen almost exclusively among severely immunocompromised patients; the isolation of *Candida* from respiratory secretions should be viewed with skepticism unless accompanied by histopathologic evidence confirming invasive disease. Meningitis is a rare complication of candidemia, but it should be considered as a potential complication among patients with prosthetic devices in the CNS, such as intraventricular shunts.[126,127]

TREATMENT

General Principles of Therapy

Recommendations for treatment of IC are based on data derived from controlled clinical trials among patients with candidemia and other forms of IC, anecdotal reports, and expert opinion (**Table 3**).[70] Among published clinical trials, approximately 85% of subjects are enrolled with candidemia, and 15% with noncandidemic IC.[128–133] There have been no prospective studies evaluating treatment for the less common forms of IC. Insights into the appropriate management of these patients are entirely derived from anecdotal experience and retrospective case series.

The management of IC has evolved significantly over the last 3 decades, but the general principles of therapy remain the same. There are several important considerations in choosing initial antifungal therapy among patients with proven or suspected IC. What is the presumed source of *Candida* infection, and is it an easily removable or drainable source? What is the severity of illness? What are the comorbidities and

Table 3
Treatment of candidemia and other forms of invasive candidiasis therapy

Condition	Primary	Alternative	Duration	Comments
Candidemia				
Non-neutropenic adults	Capso 70 mg loading, then 50 mg/d; Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d	Flu 800 mg/d loading, then 400 mg/d	14 d after last positive blood culture and resolution of signs and symptoms	Remove all intravascular catheters, if possible
Neonates	AmB 1.0 mg/kg/d IV; or Flu 12 mg/kg/d IV	LFAmB 3–5 mg/kg/d	14–21 d after resolution of signs and symptoms and negative repeat blood cultures	Must rule out occult CNS and other organ involvement. Use LFAmB with caution if urinary involvement suspected
Neurtopenia	Capso 70 mg loading, then 50 mg/d; Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d	LFAmB 3–5 mg/kg/d or Flu 800 mg loading, then 400 mg/d	14 d after last positive blood culture and resolution of signs and symptoms and resolved neutropenia	Remove of all intravascular catheters is controversial in neutropenic patients, GI source is common
Chronic disseminated candidiasis	LFAmB, 3–5 mg/kg/d; or Capso 70 mg loading, then 50 mg/d; or Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d	Flu 6 mg/kg/d	3–6 mo and resolution or calcification of radiologic lesions	Flu may be given after 1–2 wk of LFAmB or an echinocandin if clinically stable or improved; steroids may be beneficial in patients with persistent fever
Endocarditis	LFAmB 3–5 mg/kg/d ± 5-FC 25 mg/kg PO qid; or Capso 150 mg/d; Mica 150 mg/d; Anid 200 mg/d	Flu 6–12 mg/kg/d IV/PO	At least 6 wk after valve replacement	Valve replacement is almost always necessary; long-term suppression with Flu has been successful among selected patients who cannot undergo valve replacement. Consider step-down to Vori or Posa for susceptible, Flu-resistant isolates

(*continued on next page*)

Table 3
(*continued*)

Condition	Primary	Alternative	Duration	Comments
Osteoarticular	Flu 400 mg/d or Capso 50 mg/d, Mica 100 mg/d or Anid 100 mg/d	LFAmB 3–5 mg/kg/d	6–12 mo±surgery	Step-down therapy to Flu after at least 2-wk induction with an echinocandin or LFAmB
Endophthalmitis	Flu 800 mg loading, then 400 mg/d, or Vori 400 mg × 2 loading, then 300 mg bid, or LFAmB 3–5 mg/kg/d	Intravitreal AmB 5–10 μg or Vori 100 μL	4–6 wk at least after surgery	Vitrectomy usually is performed when vitritis is present
Cystitis	Flu 200 mg/d, or 6FC 25 mg/kg qid for Flu-resistant isolates	AmB 0.3–0.6 mg/kg/d	1–2 wk	Echinocandins have minimal role in cystitis. For upper tract disease, treat as for candidemia

underlying disorders? What are the dominant *Candida* species in this unit/location? What are the susceptibility patterns of *Candida* species in this particular health care setting? Is there a recent history of antifungal exposure? Is there clinical evidence to suggest involvement of the CNS, cardiac valves, liver, spleen, eyes, and/or kidneys? Has the patient traveled to or lived in an area that is endemic to multidrug-resistant *Candida* species such as *C auris*? Is there a patient history of intolerance to a specific antifungal agent?

Regardless of the choice of initial therapy for IC, a specific length of therapy is recommended depending on the site of involvement, and, in the case of candidemia, the rapidity of clearance of *Candida* from the bloodstream. For patients with documented candidemia, 14 days of effective antifungal therapy following the first negative blood culture is recommended. The American Academy of Ophthalmology no longer recommends a dilated funduscopic examination to exclude occult ocular involvement in all non-neutropenic patients with documented candidemia, though an ophthalmologic consult is recommended for patients with signs and symptoms of ocular disease and those who are unable to respond verbally such as unconscious and intubated patients.[134] The European Confederation on Medical Mycology has taken a similar position in their most recent treatment guidelines for candidiasis (in press). Other groups disagree with this position, suggesting that fundoscopy for all candidemic patients be performed.[135] This controversy will likely not be resolved without a prospective observational study. For neutropenic patients, ophthalmologic examination should be delayed until neutrophil recovery, as the characteristic findings of ocular candidiasis are often delayed.

Echinocandins

The echinocandins (caspofungin, anidulafungin, micafungin, and rezafungin) demonstrate significant fungicidal activity against most *Candida* species, and each of these agents has demonstrated success in approximately 70% to 75% of patients in randomized, comparative clinical trials.[128,130,131,136–138] These agents are only available as parenteral preparations.[139–141] Despite this limitation, documented superb efficacy, few drug interactions, excellent patient tolerance, and concerns about fluconazole resistance have led clinicians to favor the echinocandins as initial therapy for most adult patients with candidemia. These agents (with the exception of rezafungin) are sufficiently similar to be considered interchangeable.[131,142] However, despite very similar pharmacokinetics, standard dosing for caspofungin (70 mg loading dose, then 50 mg daily), micafungin (100 mg daily), and anidulafungin (200 mg loading dose, then 100 mg daily) differs slightly. The MICs of the echinocandins are low for most *Candida* species, including *C glabrata* and *C krusei.*[58,143,144] *C parapsilosis* demonstrates innately higher MICs to the echinocandins compared with other *Candida* species, but recent data suggest this may be clinically insignificant.[145]

A combined analysis of 7 of the largest randomized clinical trials comparing treatment for candidemia and IC involving almost 2000 patients found that initial therapy with an echinocandin was a significant predictor of survival.[80] The emergence of echinocandin-resistant *Candida* isolates, especially *C glabrata*, has been clearly documented, and this finding appears to be associated with worse clinical outcomes.[64,146–151] Fluconazole resistance is a frequent finding among echinocandin-resistant isolates, further limiting therapeutic choices.

Rezafungin is structurally similar to anidulafungin and was approved by the FDA in early 2023 for the treatment of candidemia and IC in adults 18 years old or older with no alternative treatment options.[152] It is unique in that it has increased molecular stability compared with other echinocandins, leading to an extended half-life allowing

dosing once every 7 days.[152] Less frequent dosing is not only more convenient but also may reduce harm by negating the need for a peripherally inserted catheter, therefore, reducing the potential for catheter-related adverse outcomes. In addition, it achieves high drug plasma concentration early in therapy, which may lead to more rapid clearance of candida species from blood and tissue and prevent the opportunity for the development of resistance.[152] This is especially encouraging as the emergence of antifungal resistance is becoming an increasing concern.

The safety of rezafungin and the possibly accelerated clearance of candidemia were demonstrated in the phase 2 STRIVE study.[152] The recently completed phase 3 ReSTORE trial demonstrated that rezafungin (400 mg loading dose, then 200 mg weekly thereafter) was noninferior to capsofungin in 14-day global cure and 30-day all-cause mortality in patients with candidemia and IC.[153] A follow-up analysis confirmed these findings were true for all major *Candida* species present in the trial (*C albicans*, *C glabrata*, and *C tropicalis*).[152] Rezafungin is a promising new agent, especially for outpatients who require extended echinocandin therapy for the treatment of IC.

Rezafungin also has a potential role for the prevention of candidiasis, aspergillosis, and pneumocystosis following stem cell transplantation. An ongoing randomized clinical trial comparing the efficacy of weekly rezafungin to standard of care daily fluconazole and trimethoprim/sulfamethoxazole for prevention of invasive fungal infection in these high-risk patients (ReSPECT trial, MundiPharma) should provide important insights into the role of rezafungin in this population.

Triazoles

Fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole demonstrate similar in vitro activity against most *Candida* species.[56–59] Each of the azoles has less activity against *C glabrata* and *C krusei* than against most other *Candida* species. All of the azole antifungals inhibit cytochrome P450 enzymes.[154] In earlier clinical trials, fluconazole showed efficacy comparable with that of AmB deoxycholate for the treatment of candidemia.[155,156] Fluconazole is readily absorbed, with oral bioavailability resulting in concentrations equal to ~90% of those achieved by intravenous administration.[157] Among the triazoles, fluconazole has the greatest penetration into the CSF and vitreous, achieving concentrations of more than 70% of those in serum.[158–160] For this reason, it is often used in the treatment of CNS and intraocular *Candida* infections. Fluconazole achieves urine concentrations that are 10 to 20 times the concentrations in serum, thus it is the preferred treatment option for symptomatic *Candida* cystitis. For patients with IC, fluconazole should be administered with an average loading dose of 800 mg (12 mg/kg), followed by an average daily dose of 400 mg (6 mg/kg). A higher dose level (800 mg daily, 12 mg/kg) has been suggested for therapy of susceptible *C glabrata* infections, but this has not been validated in clinical trials.

Voriconazole is effective for IC, but its role in the routine management of this disorder is limited.[161,162] Its clinical use is generally limited to step-down oral therapy in patients with infection due to *C krusei* and fluconazole-resistant, voriconazole-susceptible *C glabrata*. It is available in oral and intravenous formulations. Following 2 loading doses of 6 mg/kg every 12 hours, a maintenance dosage of 3 mg/kg every 12 hours is recommended. Voriconazole does not accumulate in its active form in the urine and thus should not be used for urinary candidiasis.

Other currently available azoles offer little benefit in the management of IC. Itraconazole is only available in oral formulations. It has not been well studied for IC and is generally reserved for patients with mucosal/esophageal candidiasis who have failed fluconazole.[163] Posaconazole does not have an indication for primary therapy

for IC. It demonstrates in vitro activity against *Candida* species that is similar to that of voriconazole, but clinical data are inadequate to make recommendations for treatment of IC. Isavuconazole is a recently approved expanded-spectrum triazole antifungal with excellent in vitro activity versus *Candida* spp. However, a recent trial comparing treatment with isavuconazole versus an echinocandin for IC did not meet predetermined criteria for noninferiority, and it is unlikely to play an important role in management of IC.[132]

The major role for fluconazole in the current management of IC is for step-down therapy for a presumed susceptible *Candida* isolate once the patient is clinically stable following induction with an echinocandin. This transition usually occurs within 3 to 7 days of echinocandin therapy but is variable depending on patient response and clinician preference. Several recent open-label, noncomparative studies have examined outcomes when this strategy was used in candidemic patients. There has been no observed difference in outcomes among patients who received only an echinocandin compared with those who were switched to an oral azole.[164–166] From these data, step-down therapy to fluconazole or voriconazole is reasonable for patients who are infected with a susceptible organism and are improved clinically.

Amphotericin B Formulations

Most published experience with AmB for the treatment of IC is with the deoxycholate preparation (AmB-d). Two lipid formulations of AmB (LFAmB) have been developed and are generally available: AmB lipid complex and liposomal AmB. These agents possess the same spectrum of activity versus *Candida* spp. as AmB-d, but daily dosing regimens and toxicity profiles differ for each agent. For most forms of IC, the typical intravenous dosage for AmB-d is 0.5 to 0.7 mg/kg daily, but dosages as high as 1 mg/kg daily may be considered for IC caused by less susceptible species, such as *C glabrata* and *C krusei*. The usual dosage for LFAmB is 3 to 5 mg/kg daily. LFAmB all have considerably less nephrotoxicity and generally fewer infusion-related reactions than AmB-d.[167,168] There are no data suggesting superior clinical efficacy of LFAmB versus AmB-d in the treatment of IC. Data demonstrating that AmB-d-induced nephrotoxicity is associated with a 6.6-fold increase in mortality have led many clinicians to use LFAmB in proven or suspected IC, especially in the ICU.[169]

Promising Investigational Antifungals

There are several new investigational antifungal agents that have shown promise in phase 2 and phase 3 clinical trials for IC. These compounds are listed later along with a brief description of their activity and potential roles.

Ibrexafungerp, now FDA approved for the treatment of vulvovaginal candidiasis since 2021, is an oral glucan synthase inhibitor that is administered once daily and has broad activity against most pathogenic *Candida* species. The compound is well tolerated, and a small phase 2 trial comparing ibrexafungerp with standard of care demonstrated comparable efficacy and safety for treatment of IC.[170] A recently completed salvage study with ibrexafungerp for patients with refractory IC or intolerance to conventional antifungals (FURI study, Scynexis, data not yet available) suggests a potential role for this compound among patients with infections caused by drug-resistant *Candida* species as an alternative to parenteral echinocandin therapy.

Fosmanogepix is a guanosine monophosphate inhibitor which can be administered orally or parenterally twice daily. This unique antifungal has broad activity against all pathogenic *Candida* species with the exception of *C krusei*.[171] A recently completed small open-label phase 2 trial of fosmanogepix for IC primarily caused by fluconazole-resistant organisms demonstrated excellent tolerance and efficacy. A

similar open-label study of fosmanogepix for candidemia due to *C auris* demonstrated excellent results in a small cohort of South African patients (Vazquez and colleagues, 2023).[172]

EMPIRIC THERAPY

Empiric therapy for IC in the ICU is a complex issue, and it constitutes one of the most common uses of antifungal compounds in the hospital setting. Current strategies for initiating empirical antifungal therapy include an evaluation of risk factors and use of surrogate markers. Empirical antifungal therapy is often considered in critically ill patients with the risk factors for IC and no other known cause of clinical deterioration. An echinocandin is appropriate in hemodynamically unstable patients, those previously exposed to an azole, and in those colonized with azole-resistant *Candida* species.[70] There are no data guiding the appropriate duration of empiric antifungal therapy among patients who have a clinical response, but it should probably not differ from the treatment of documented candidemia/IC. Conversely, therapy can be stopped after several days in the absence of clinical response if cultures and surrogate markers are negative.

Very few clinical studies have evaluated the efficacy of empiric antifungal therapy in the ICU. In a randomized clinical trial of ICU patients at risk for IC and with unexplained fever, empiric fluconazole (800 mg daily for 14 days) was not associated with better outcomes when compared with placebo.[173]

PREVENTION

For ICUs that show very high rates of IC (>5%), antifungal prophylaxis may be warranted in selected patients who are at highest risk.[174] A recent multicenter, placebo-controlled, blinded clinical trial of caspofungin prophylaxis targeting only those ICU patients who met specific criteria for high risk showed a trend toward reduction of IC.[175]

Several meta-analyses have shown that fluconazole prophylaxis is associated with a reduction in IC, but generally do not show a reduction in mortality.[176,177] A Cochrane analysis confirms the importance of targeted prophylaxis in high-risk patients.[178]

CLINICS CARE POINTS

- Candidemia and invasive candidiasis are constantly emerging healthcare-associated infections linked to well-defined clinical risk factors and associated with significant morbidity and mortality.
- Both culture and non-culture based diagnostics are imperfect, as such, clinical suspicion of invasive candidiasis and early intervention with effective antifungal therapy is key to optimal outcomes.
- Initial therapy with an echinocandin, independent of azole susceptibility, is key to the management of most patients with candidemia and invasive candidiasis.
- Following initial therapy with an echinocandin, step down to an azole (eg fluconazole, voriconazole) is reasonable among patients with susceotible Candida isolates once clinical improvement has occurred.
- Effective source control (eg, removal of central venous catheters) is essential in successful management of these patients.

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