Review

Candidemia and invasive candidiasis: A review of the literature for the burns surgeon

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Advances in critical care, operative techniques, early fluid resuscitation, antimicrobials to control bacterial infections, nutritional support to manage the hypermetabolic response and early wound excision and coverage has improved survival rates in major burns patients. These advances in management have been associated with increased recognition of invasive infections caused by \textit{Candida} species in critically ill burns patients. \textit{Candida albicans} is the most common species to cause invasive \textit{Candida} infections, however, non-\textit{albicans} \textit{Candida} species appear to becoming more frequent. These later species may be less fluconazole susceptible than \textit{Candida albicans}. High crude and attributable mortality rates from invasive \textit{Candida} sepsis are multi-factorial. Diagnosis of invasive candidiasis and candidemia remains difficult. Prophylactic and pre-emptive therapies appear promising strategies, but there is no specific approach which is well-studied and clearly efficacious in high-risk burns patients. Treatment options for invasive candidiasis include several amphotericin B formulations and newer less toxic antifungal agents, such as azoles and echinocandins. We review the currently available data on diagnostic and management strategies for invasive candidiasis and candidemia; whenever possible providing reference to the high-risk burn patients. We also present an algorithm for the management of candidemia and invasive candidiasis in burn patients.

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spp. with or without disseminated candidiasis

Candida are generally considered to be colonizing organisms frequently isolated from mucosal sites where they are now major causes of morbidity and mortality in hospitalized patients, including severe burns patients, associated with an increased incidence of life-threatening opportunistic fungal infections [4,6,11]. As patients with impaired host defenses, including severe burns, now survive longer.

The ultimate goal of burn wound management is closure and healing of the wound. Early surgical excision of burned tissue, with extensive debridement of necrotic tissue and grafting of skin or skin substitutes, greatly decreases mortality rates associated with severe burns. Moreover, advances in patient care including increasing use of broad-spectrum antibiotics, immunosuppressive and anti-neoplastic agents, prosthetic devices and total parenteral nutrition (TPN) [1–10], have been associated with an increased incidence of life-threatening opportunistic fungal infections [4,6,11] as patients with impaired host defenses, including severe burns, now survive longer.

Candida species (spp.) are commensal and opportunistic pathogens present on virtually all humans. Candida spp. are known human pathogens associated with more than 20 Candida species are known human pathogens.

Patients at highest risk of Candida bloodstream infections (BSIs) are in neonatal, surgical, hematological and burn units [2]. The precise incidence rates of candidemia remain difficult to establish, partly due to the use of different denominators between published studies. However, since the 1980s, Candida spp. have ranked fourth as the most common cause of BSI in data from the US Centers for Disease Control (CDC) National Nosocomial Infections Surveillance (NNIS) system; also accounting for >85% of all fungemias [1–3,5,7,8,11,13,15–34]. Over the period 1980–1990, hospitals reporting data to the NNIS system reported a steady increase in the rate of nosocomial fungal infections from 2.0 to 3.8 per 1000 discharges [35] and an increase from 5.4% to 9.9% in the proportion of fungi causing nosocomial BSIs [35]. This reported trend is likely multi-factorial; including changes in clinical practice such as increased use of long-term venous catheters, use of broad-spectrum antibacterial agents and improved laboratory techniques for identification of unusual Candida species [1,8,11,13,16,19,20,36–40].

Amongst the 200 species described in the genus Candida, more than 20 Candida species are known human pathogens.
Medically important Candida spp. include C. albicans, C. glabrata, C. parapsilosis complex, C. tropicalis, C. krusei, C. lusitaniae, C. guilliermondii and C. dublinensis [12]. The specific epidemiology regarding the incidence of candidemia and distribution of Candida spp. (C. albicans versus non-albicans Candida spp.) varies markedly between institutions and patient cohorts. Currently, C. albicans and non-albicans Candida spp. each account for approximately half of all episodes of candidemia and invasive candidiasis. C. albicans was previously associated with 70–90% of isolates [4,6,7,14,17,22,36,41–43]. The recent Australian population-based surveillance found C. albicans was the predominant species (47.3%), with the next most frequent isolates being C. parapsilosis (19.9%) and C. glabrata (15.4%) [1]. C. albicans was also the commonest pathogen in surgical patients (54.4%) [1]. A recent study in a French burns unit identified C. albicans (65%), C. parapsilosis (25%) and C. tropicalis (10%) as the most common isolates in episodes of candidemia [44].

3. Significance of candida sepsis

The attributable mortality rate of candidemia from various studies is estimated to be >30% (range 24–60%, median 38%), with a crude mortality rate of >50% (range 13–90%, median 55%) reported, amongst widely divergent patient cohorts [1,4,5,10,11,14,15,17–20,23–27,34,36–37,41–43]. Patient outcomes appear worst for C. glabrata and C. tropicalis infections, and to a lesser extent C. krusei [2,35]. The attributable mortality rate for candidemia in burns is reported as ranging from 14% to 70%. However, in a recent study where patients were matched for extent of burn and age there was no demonstrated increase in attributable mortality due to candidemia [44]. In burns patients the highest rates of candida sepsis infection and mortality are seen in the group of patients with large burns (i.e., total body surface area (TBSA) 30–60%) and in those with open wounds 28 days or more after thermal injury [15].

Candidemia not only increases patient mortality, but also extends the patient length of stay (LOS) and increases the total cost of medical care. It has been estimated that each episode of invasive candidiasis costs approximately $40,000 US (~A$43,000) [14] with the estimated cost likely to increase further with the widespread use of newer, more expensive antifungal agents [53]. Although candidemia and invasive candidiasis are likely to be expensive in burn patients, to the best of our knowledge, no recent studies determining the costs specifically in burn patients have been published.

4. Risk factors

There are many risk factors for candidal colonization and infection including; host barrier disruption (e.g., major burn), acute or chronic graft versus host disease particularly with gut involvement, antibiotics, neutropenia, cancer, invasive procedures, ICU admission, steroids and hyperglycemia, severe catabolism secondary to injury, total parenteral nutrition (TPN), mechanical ventilation, prolonged hospitalization, malnutrition, multiple medical co-morbidities and stress ulcer prophylaxis [1–9,11,13–17,35–37,40]. Some risk factors facilitate Candida colonization (e.g., steroids), others contribute to tissue or bloodstream invasion (e.g., intravascular catheters), while others impair host defenses [15]. The risk factors for candidiasis with corresponding odds ratio is presented in Table 1.

In patients with candidemia, 84–90% of colonizing and infecting strains are identical, with the time from colonization to infection typically brief [4,44]. In burn patients, prior Candida species colonization typically precedes systemic candidiasis [13,48].

Non-albicans Candida spp. occur more commonly in patients who have received systemic therapy or prophylaxis with azoles. They are also isolated more frequently in hematologic patients with prolonged neutropenia than in non-neutropenic patients in the surgical intensive care unit (ICU) [12].

Risk factors for selected non-albicans Candida spp. infections are shown in Table 2 [5,13,14,16,37,38]. Most reports show the presence of two or more independent risk factors increases the risk of candidemia in a multiplicative fashion [6].

A number of risk stratification schemata that take into account risk factors have been developed to help predict those patients likely to benefit most from prophylactic, pre-emptive or empiric antifungal treatment strategies. The “colonization index” (CI) has been reported to be helpful in the setting of ICU and general surgical patients. The CI quantifies the degree of colonization established as the ratio of the number of distinct body sites colonized with genotypically identical strains of Candida spp., over the total number of sites sampled [2,23,33].

### Table 1 – Risk factors for candidiasis with corresponding odds ratio (or 95% confidence interval (CI) of odds ratio).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>2.1–6.5</td>
</tr>
<tr>
<td>Steroids</td>
<td>2.2–4.3</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>2.2–30.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.4</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>2.5–15.5</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>2.7–36.7</td>
</tr>
<tr>
<td>Candida species colonization</td>
<td>3.0–17.9</td>
</tr>
<tr>
<td>Vascular access</td>
<td>3.3–17.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3.7–17.4</td>
</tr>
<tr>
<td>Stress ulcer prophylaxis</td>
<td>4.6</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>7.7–28.8</td>
</tr>
<tr>
<td>Bladder catheter</td>
<td>6.2–6.5</td>
</tr>
</tbody>
</table>

Data derived from Refs.: [1–9,11,13–17,35–37,40].

### Table 2 – Risk factors for infections with non-albicans Candida species.

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Riskfactor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. krusei</td>
<td>Leukemia, fluconazole prophylaxis, neutropenia</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>Leukemia, cancer, neutropenia</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>Central venous catheters, other intravascular lines, total parenteral nutrition</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>Fluconazole prophylaxis, increasing age</td>
</tr>
</tbody>
</table>

Data derived from Refs.: [5,13,14,17,37,40].
It has been retrospectively validated to be useful for risk stratification in determining those most likely to benefit from receipt of pre-emptive antifungal therapy. Another scoring system, the “candida score”, has been studied in critically-ill non-neutropenic patients with *Candida* colonization, in predicting those most likely to benefit from antifungal prophylaxis [56]. This method utilizes a simple bed-side scoring system based on risk factors with variable weightings. A “candida score” of ≥2.5 may distinguish between patients with invasive candidiasis versus colonization alone [56]. However, strategies for identification of patients at highest risk of invasive candidiasis remain controversial in non-neutropenic hosts and as such further studies are required to assess their generalizability and clinical utility for burn patients most likely to benefit from antifungals [23].

5. **Pathogenesis**

*Candida* spp. infections typically originate from the patient’s endogenous microflora [3,5,10,13,29]. The major steps in the pathogenesis of invasive candidiasis include: (1) increasing fungal colonization, characteristically secondary to broad-spectrum antimicrobials; (2) failure of skin and mucosal barriers, often a result of the use of intravascular devices, severe burns or recent surgery; and (3) immune dysfunction (e.g., neutropenia) that enables fungal access and ultimately allows dissemination [2,12,13]. Moreover, nosocomial transmission from exogenous sources such as contaminated medical devices and the hands of hospital personnel may occur. *C. albicans* survives for up to 4 months in the hospital environment, and hydrotherapy water immersion equipment, a particular concern in burns patients undergoing rehabilitation [3,5,13,14,29,57]. Nonetheless, for 54% of patients with candidemia the portal of entry remains undefined [13].

5.1. **Immunopathogenesis of invasive candidiasis**

All arms of the host immune system are implicated in the control of candidal infections. Alterations to host cellular defences and normal host flora typically precede *Candida* spp. colonization [3,58,59]. Polymorphonuclear cells act as the first line defence against intravascular spread of *Candida* spp. by damaging and killing fungal pseudohyphae and blastospores [60]. Patients who have prolonged neutropenia or neutrophil dysfunction are at high-risk of developing invasive candidiasis and candidemia [60]. Additionally, lymphocytes are important for the development of cell-mediated immunity (CMI) to *Candida* spp. and in the prevention of mucosal candidiasis. Patients who have global T-cell deficiencies (e.g., advanced HIV disease) have a strong predisposition to mucocutaneous candidiasis, but seldom develop invasive disease [60].

Protective immunity against fungal pathogens is achieved by the integration of two distinct arms of the immune system, the innate and adaptive responses. Two distinct types of T-helper cell (Th) lymphocytes produce different patterns of cytokines: Th1 cells secrete cytokines like interleukin-2 (IL-2) and interferon-γ (IFN-γ), whereas Th2 cells produce cytokines including IL-4, IL-5, IL-6, IL-10, and IL-13. Until recently, the immunopathogenesis of fungal infections and fungal diseases was explained mostly in terms of Th1/Th2 balance. While Th1 responses driven by the IL-12/IFN-γ axis are significant in protection against *C. albicans* infection [64], other cytokines and T cell-dependent pathways are now recognized. IL-17-producing T cells (Th17) have pivotal roles in both innate and acquired immune response to fungal infections. The Th17 pathway may play an inflammatory role previously ascribed to unrestrained Th1 responses and serves to foster the seemingly paradoxical relationship of chronic inflammatory responses to fungi such as *C. albicans* and fungal persistence in the face of an ongoing inflammation [61,62]. Regulatory T cells have become recognized as providing the host with immune defense mechanisms adequate for protection, without necessarily eliminating fungal pathogens or causing an unacceptable level of tissue damage [62]. In sepsis and burns an early shift towards Th2 cytokine profiles is seen, resulting in depressed CMI responses [61]. Serious burn induces diminished production of IL-12, shifting to the Th2 phenotype with increased production of IL-4 and IL-10, cytokines inhibitory to Th1-cell function [60].

Host immune responses are dependent upon specific ligand–receptor systems, which activate intracellular signaling pathways with distinct differences in the immune consequences [62]. Complement and immunoglobulins are necessary for efficient opsonization and intracellular killing of *Candida* spp., and deficiency of either, can be associated with complicated candidiasis [60]. Cells of the innate immune system express a variety of pattern-recognition receptors (PRRs); which play a crucial role in host recognition of fungi such as *C. albicans* via pathogen-associated molecular patterns (PAMPs) located in the cell wall [61,62]. Recognition of PAMPs by PRRs leads to a variety of signalling pathways generally mediated by differential cytokine production. A schematic representation of the process is outlined in Fig. 1.

Monocyte and T-cell interactions play a critical role in the systemic response to infection in burns. Macrophages and the activation of an inflammatory cascade that includes interleukin (IL)-1, IL-6, tumor necrosis factor–α (TNF-α) and PGE2 are likely causative factors [61]. Generation of burn-associated type 2 T-cells have been shown to significantly increase the susceptibility of burn animals to infection with *C. albicans* and likely increased susceptibility of burns patients to *C. albicans* infection [61]. Burn wound excision and grafting normalizes TNF-α production, independent of when post-burn the procedure was performed [61]. In contrast, elevated production of other inflammatory mediators (IL-1β, IL-6, nitric oxide, and PGE2) post-burn is unaffected by early burn wound excision and grafting [61].

5.2. **Fungus-specific mechanisms of pathogenesis**

*Candida* adheres to vaginal, gastrointestinal, and oral epithelial cells, endothelium, polymorphs and lymphocytes. Additionally, *Candida* spp. that persist within the biofilm matrix (e.g., on intravascular catheters) have reduced apoptosis. Current concepts in microbial pathogenesis and virulence suggest that when fungal population densities decrease, quorum sensing systems turn off fungal virulence genes (virulome), as in biofilms, thereby avoiding host detection [61]. Biofilm “persister cells” develop several other unique phenotypic and genotypic characteristics, including resistance to most
antifungal agents [60]. Biofilms role in the development and propagation of invasive candidiasis is an area of active research.

Tissue invasion involves enzymatic activation of phospholipases, lipases, proteinases and adhesins [2,6,16]. Invasion of epithelial and sub-epithelial tissues involves yeast filamentation, likely enhancing the ability of yeast invasion into tissues via burrowing-like processes. Following yeast angio-invasion, budding via unicellular buds facilitates hematogenous dissemination. Hematogenous dissemination typically evolves by a miliary pattern with fungal abscesses and granulomata [2,6,16,29]. Finally, it has been shown that most infection-related changes in C. albicans gene expression reflect environmental adaptation; initial yeast contact with the host, and disease progression are associated with fungal metabolic and stress (e.g., heat shock proteins) adaptation responses.

6. Candidiasis in burns

Invasive candidiasis occurs in 2–21% of burn patients, with a crude mortality of 30–90% [7,44]. Up to 30–63% of burn patients have at least one positive culture for Candida spp. and there is a 3–5% incidence of candidemia [23]. Burn wounds are a major risk factor for fungal infections; rising further with increases in burn wound size and depth, and patient age [32,33,59,63]. Burn patients with central venous catheters (CVCs) have amongst the highest risk for candidemia of any hospitalized cohort [15].

The burn wound is initially sterile, but within the first 48-h it becomes colonized, initially with bacteria [58]. Complex interactions between bacteria and fungi in burn wounds may initially limit fungal growth [58]. In addition to the ubiquity of fungi in the environment, the loss of protective barriers renders burn patients particularly vulnerable [8,49,52,59,64]. Burn injury suppresses cell-mediated immunity and in combination with broad-spectrum antimicrobials, Candida overgrows on mucosal surfaces [65]. Mucosal disruption, as in burns, also enables fungal translocation. Gastrointestinal mucosal atrophy is correlated with percent body burns and ileus frequently complicates those with >25% TBSA burns [64]. Lamina propria lymphocytes play an important role in intestinal mucosal immunity to C. albicans, through increased levels of specific IgA antibodies in intestinal mucus. Positive cultures of C. albicans have been found in lymph nodes 12-h after burn and persistence of these organisms in regional nodes for some time thereafter [65].

The widespread introduction of effective topical antibacterial antibiotics in burns has also been linked with increased fungal burn wound infection rates [31].

7. Diagnosis

Candida species can cause disease anywhere, thus presenting a very wide spectrum of clinical manifestations (see Table 3) [5,8,11,15–16,27,29,35,46,65]. Clinical presentation with candidiasis also depends on the patients’ immune status, chiefly the ability to produce adequate inflammatory responses. These factors can make candida infection difficult to diagnose. Diagnosis is additionally often delayed by low-levels and intermittent presence of Candida species in blood, and the slow growth of fungi on standard laboratory media [7,13,14,20,66]. Early diagnosis is essential for optimal management, especially in critically ill patients [67].

Currently no single diagnostic tool provides satisfactory yields rapidly. Candida is commonly grown from non-sterile
mucosal sites (urinary tract and lungs), therefore frequently contaminating or colonizing burn wounds [6,15]. Revised diagnostic criteria for IFIs, including candidiasis, have been recently published [68], however, these definitions have not specifically addressed invasive burn wound fungal infections. The proposed definitions of burn wound infections that have been developed have been directed at surveillance of burn wound infections in a single institution or as standardized criteria for multi-center clinical trials or national registries [69,70]. Suggested criteria for diagnosis of invasive candidiasis include; culture of Candida species from normally sterile sites, clinical signs of infection at sites of Candida isolation and absence of other potential pathogens [19].

### 7.1. Colonization and invasive disease

Colonization is the presence of Candida species in non-sterile samples from the oropharynx, stomach, urine, skin or tracheal aspirates [56]. Candida colonization is strongly linked with receipt of antibiotics, particularly broad-spectrum antibiotics. Some studies demonstrated that colonization with Candida is highly predictive of Candida disease, particularly in those with severe end-organ dysfunction or high APACHE II scores (e.g., >15) [6,16,23]. Differentiation between colonization and invasive infection remains crucial for determining when to initiate treatment [59].

### 7.2. Microscopy and histopathology

Historically, the gold-standard for the diagnosis of fungal burn wound infection required the demonstration of fungal hyphae invading viable tissue [15]. Histopathology alone is unable to determine the best antifungal agent, as correlation with culture results can be poor [39] and microscopy and culture of tissue is necessary [37]. Microscopy with gram- or fluorescent-stains can give reliable preliminary results within an hour [37].

### 7.3. Culture and molecular identification

The historical approach of confirming candidal burn wound infection with semi-qualitative cultures from punch or full thickness skin biopsies is no longer widely used. Currently the gold-standard for diagnosis of invasive candidiasis is culture of Candida species from a normally sterile body site [4,5,7,10,14,23,66]. Isolation of Candida species from a single blood culture is considered diagnostic of true candidemia [23,24,57]. Blood cultures have relatively low yields, approximating 50% of all episodes of candidemia [6,7,9,14,20,23,28,29,46,66], increasing to 70% with newer blood culture systems [27,57]. Disseminated candidiasis generally refers to confirmed hematogenous dissemination, where the organism is demonstrated from culture or histology at two or more, normally sterile non-adjacent sites [2,6,25]. In the ICU or burns unit, candiduria might be an indicator of disseminated candidiasis, but it has very low diagnostic specificity [1,5,7,46].

C. albicans can be reliably identified in 2–4 h using a germ-tube test. Use of chromogenic agar (CHROMagar Candida ID media) also allows for prompt speciation of common Candida spp.: C. albicans, C. glabrata, C. parapsilosis and C. krusei, based on isolate colony colors.

Rapid identification using peptide nucleic acid fluorescence in situ hybridization (PNA FISH) techniques from blood culture bottles is rapid (within 2.5 h), provided the bottles test positive and yeasts are visible on gram stain, and is highly specific and sensitive for Candida spp. [71]. Sequencing of fungal DNA from positive blood culture bottles, by rapid PCR techniques has also been reported from a number of laboratories, including our own [72].

PCR using primers specific for fungal DNA directly from blood, has been reported to be more sensitive than blood cultures, thereby potentially facilitating early diagnosis of fungemia [36,56]. However, contamination difficulties, sample volume and sample imprecision, optimum sampling frequency, and difficulty distinguishing colonization and infection for validation purposes, mostly limits utility of PCR to the research setting [37,67]. Moreover, little agreement exists regarding the best method for susceptibility testing.

### 7.4. Serology and antigen detection

Many serological or antigen detection assays have been developed to detect candidal proteins, metabolites, DNA and polysaccharides for diagnosis of systemic candidal infection [34,67]. Currently, few of these assays have adequate sensitivity and/or specificity [34] and anti-Candida antibody detection is unable to differentiate between colonization and invasive infection [34]. Presently, detection of circulating β-(1 → 3)-α-glucan and candidal galactomannan appear the most promising assays, with two β-(1 → 3)-α-glucan assays commercially available [76,77]. Depending on the cutoff value used, the sensitivity and specificity have been reported to be

### Table 3 – Spectrum of clinical manifestations from hematogenous candidiasis and candidemia.

| General: fever, sweats, chills, malaise, anorexia, weight loss |
| Musculoskeletal: limitations of movement |
| Respiratory: (productive) cough, hemoptysis, pleurisy |
| Cardiovascular: dyspnea, murmurs |
| Central nervous system: headaches, nausea, vomiting, neck stiffness, confusion |
| Ophthalmic: pain, blurred vision |
| Urinary tract: frequency, urgency, dysuria, hematuria |
| Abdominal: pain, hepatomegaly, jaundice |

Data derived from Refs.: [5,8,11,15–17,28,30,46,71].
64.4% and 92.4%, respectively; with positive predictive values of 89% and negative predictive values of 73% [4,7,6,77].

8. Prevention

The most important measures against candidiasis are to minimize modifiable predisposing factors. Skin and gastrointestinal tract are the major reservoirs of Candida species [41]. Invasive procedures result in disruption of the integrity of the cutaneous barrier [41]. While administration of broad spectrum antibiotics select for Candida spp. at mucosal surfaces, ineffective antibacterial therapy in the critically ill with septicemia likely increases patient mortality [2]. Reduction in Candida “colonization pressure” and colonization rates is likely an effective prevention strategy [2]. As hyperalimentation is a risk factor for candidiasis in non-neutropenic patients, TPN should be judiciously applied in critically ill patients [2]. Consequently, there has been a trend towards the application of early enteral nutrition to manage the hypercatabolic post-burns state.

Although endogenous colonization is a major source of Candida infection; carriage on hands of hospital personnel is common, with carriage rates of up to 75% in nurses [2,15]. Alcohol and chlorohexidine hand-rubs are effective in killing Candida species and may reduce the risk of transmission of Candida from health-care worker to patients [78]. Adequate infection control practices, starting with careful hand hygiene, not only for staff but also visitors, are important prevention strategies [28].

9. Therapy of candidemia and invasive candidiasis

The best treatment strategy for serious Candida spp. infections remains contentious. Conventional amphotericin B deoxycholate (cAmB-D) has served as the gold-standard treatment, but its toxicity underscores the need for alternative antifungals. Newer options for patients with candidemia or invasive candidiasis include lipid formulations of amphotericin (L-AmB), fluconazole and broad-spectrum triazoles such as voriconazole, and the echinocandins (caspofungin, micafungin and anidulafungin). The choice of antifungal therapy for an individual should be tailored to the clinical status of the patient, current or prior use of antifungals, and local epidemiology and susceptibility patterns of Candida spp. [7].

Though fungal identification and susceptibility results are often not immediately available effective empiric antifungal therapy is essential for prompt clinical resolution [7].

Antifungal recommendations for immunocompromised patients cannot be systematically applied to all critically ill non-neutropenic patients [11]; in burn patients, there is limited data to guide clinical practice. Furthermore, some antifungals such as fluconazole have a reduced serum half-life with increased clearance in burn patients [8] leading to the recommendation for more aggressive dosing strategies.

Regular surveillance cultures are suggested by some authors as a means of facilitating early diagnosis and optimal management of invasive candidal sepsis [18,21,45] though the clinical utility of this approach remains largely unstudied.

9.1. Prophylaxis

Prophylaxis entails administering a drug to prevent disease in a high-risk population (e.g., burn patients) prior to any clinical signs of infection [27,57]. A meta-analysis suggests that fluconazole prophylaxis reduces overall mortality rates in unselected non-neutropenic critically ill patients, with fluconazole prophylaxis in this setting reducing invasive fungal infections by half and total mortality by quarter [79]. However, even with a local incidence of disease of 10%, to prevent one death, the estimated number of patients needed to treat was 94 [79]. Some experts advocate prophylaxis or pre-emptive treatment in high-risk patients, especially if colonized at one or more sites, due to the high burden and costs associated with treatment of invasive candidiasis [14,15,45,80] while others suggest that fluconazole prophylaxis might only modify the mode of death, and not overall mortality rates [9]. As such the widespread use of prophylaxis in surgical intensive care and burns units is not a common practice for three reasons: (1) the incidence of candidemia and disseminated candidiasis is relatively low, (2) increased resistance with widespread prophylaxis is a genuine concern, and (3) the cost-benefit ratio is generally suboptimal.

9.2. Pre-emptive treatment

Pre-emptive treatment is aimed at prevention of invasive candidiasis on the basis of individual risk profile, which includes Candida colonization, but in the absence of clinical signs of infection [27,34,57]. It is considered in a patient with combination of multi-site Candida colonization (more than two sites) with at least two major risk factors (prolonged antibiotics, extensive burns, Candida colonization, TPN, major abdominal surgery, ileus, renal replacement therapy) or at least three minor risk factors (older age, length of stay in ICU >10 days, invasive catheterization, candiduria, renal insufficiency or diabetes mellitus). Pre-emptive treatment has been found to reduce the frequency of candidemia, but with no impact on mortality [81].

9.3. Empiric treatment

Antifungal therapy is often started empirically in neutropenic patients who remain febrile despite broad-spectrum antibiotics; however, in critically ill burns patients there is limited data to support this strategy. Moreover, the threshold for empiric therapy remains controversial, as premature therapy leads to overtreatment, unnecessary toxicity and drug resistant Candida species [43]; yet delayed therapy in critically ill and septic patients has been associated with increased mortality [4,5,10,14,23,48]. Unit specific Candida spp. distribution, demonstrated efficacy of the antifungal therapies and knowledge of patient specific risk factors are important in choosing empiric antifungals [5,16,26]. A cost-effectiveness decision model demonstrated that in ICUs with a low prevalence of invasive candidiasis, culture-based therapy was the preferred strategy while in ICUs where the likelihood
of invasive candidiasis was >2.5%, empiric fluconazole therapy was the most effective strategy in reducing mortality at an acceptable cost [82]. Further, if the prevalence of fluconazole resistance was >24%, empirical use of caspofungin was preferred, although at a much higher cost per life saved. However, this study's results are difficult to generalize as a prevalence of invasive candidiasis of approximately 12% was used for the cost-effectiveness decision model in this study [82].

### 9.4. Treatment of invasive disease

Consultation with an infectious disease specialist and/or clinical microbiologist can optimize and reduce antifungal usage, and likely reduces the emergence of multi-resistant fungi. At some institutions implementation of published guidelines [83], and infectious disease consultation services [84], have been found to improve outcomes in patients with candidemia.

A delay in initiating appropriate antifungals is associated with a poorer outcome and prolonged hospitalization [21,27,45]. One study demonstrated that a delay of ≥12 h in administration of appropriate empiric antifungals after collection of a positive fungal blood culture was predictive of increased mortality [42]. Antifungal therapy is recommended for any episode of candidemia.

Standard amphotericin B [±5-flucytosine] was the accepted treatment for invasive candidal infection until the late 1980s, when fluconazole and itraconazole became alternatives. Table 4 summarizes the current antifungal treatment dosing recommendations for candidal infections [27,30,31,34,37,49,50,52,60,69,85–90]. The treatment guidelines are largely based on data from randomized controlled clinical trials in patients with proven candidemia; although these trials recruited relatively few patients with proven invasive candidiasis without candidemia [88,89]. Current treatment recommendations for candidemia and invasive candidemia are summarized in the flow chart (Fig. 2) [34,38,52,57]. For details of dosing recommendations in pediatrics of antifungal treatment for candidal infections, the review by Blyth et al., should be consulted [91].

Candidemia presents a broad clinical spectrum of illness and all patients who have candidemia should have a dilated eye examination by an ophthalmologist to exclude endophthalmitis. Guidelines recommend daily blood cultures after initiating therapy to confirm the date of sterilization. If blood cultures remain positive, then a search for metastatic foci, such as deep abscesses or endocarditis should be undertaken. Antifungal therapy should be continued for at least 2 weeks after the last positive blood culture and after resolution of all clinical signs and symptoms of infection [22,43].

### Table 4 – Agents for the treatment of candidemia and disseminated candidiasis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin B formulations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>IV</td>
<td>Dose 0.7–1.0 mg/kg/day</td>
</tr>
<tr>
<td>Amphotericin B lipid formulations</td>
<td>IV</td>
<td>Not FDA approved as primary therapy. Used commonly due to less toxic than amphotericin B deoxycholate. Dose 3–5 mg/kg/day</td>
</tr>
<tr>
<td>Liposomal (AmBisome, Abelcet)</td>
<td>IV</td>
<td>Dose 5 mg/kg/day</td>
</tr>
<tr>
<td>Lipid complex (ABLC)</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Colloidal dispersion (ABCD)</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td><strong>Azoles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>IV and oral</td>
<td>Commonly used for susceptible Candida spp. Dose 400 mg/day IV or oral but may need up to 8 mg/day in unstable burns patients. Increased dose recommended on basis of decreased half-life and increased clearance in burns patients.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>IV and oral</td>
<td>Multiple cytochrome p450 interactions. Dose IV—6 mg/kg q12 h for 24 h, then 3 mg/kg q12 h. Do not use IV if creatinine clearance &lt;50 mL/min. Dose oral—&gt;40 kg patient: 400 mg q12 h for 24 hours then 200 mg q12 h. Levels may be of guidance in prolonged therapy. Not approved for use in systemic candidiasis</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Echinocandins</td>
<td>IV</td>
<td>Broad spectrum against Candida species FDA approved for disseminated candidiasis. Dose 70 mg daily (first day), then 50 mg daily (Reduce to 35mg/day in moderate to severe hepatic dysfunction). FDA approved for disseminated candidiasis. Dose 200 mg/day (first day), then 100 mg/day.</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>IV</td>
<td>Under evaluation for disseminated candidiasis. Dose 100 mg daily.</td>
</tr>
<tr>
<td>Micafungin</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

Note: Although ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in the table.

FDA: U.S. Food and Drug Administration.
Data derived from Refs.: [28,31,32,35,37,38,40,49,50,52,60,69,85–96].
9.4.1. **Amphotericin B—deoxycholate formulation (cAmB-D)**

AmB binds ergosterol creating pores in the cell membrane of fungi, thereby altering cell permeability, causing leakage of cellular components and ultimately cell death [6,65]. This polyene antifungal remains the antifungal with the broadest fungicidal activity against *Candida* species. Except for many strains of *C. lusitaniae*, all *Candida* species remain sensitive to amphotericin B (AmB) [2,10] though strains of *C. glabrata* and *C. krusei* may have reduced susceptibility. The clinical utility of cAmB-D in standard doses of 0.6–1.0 mg/kg/day (higher doses used for *C. glabrata* and *C. krusei*) is expected to diminish, because of its very narrow therapeutic window and significant toxicity [4–7,10,12–15,25,28,29,65,80]. The major disadvantages of cAmB-D relative to other AmB preparations include: nephrotoxicity, electrolyte disturbances and acute infusion-related side-effects. Continuous infusions of cAmB-D have been associated with significantly less toxicity, but because efficacy data are currently limited, it is not widely used. The low acquisition cost of cAmB-D maintains its standard as drug of first choice in resource poor settings [83,92].

9.4.2. **Amphotericin B—lipid formulations**

Lipid formulations of AmB have a more favorable toxicity profile than cAmB-D in patients with severe systemic fungal infections [4,6,13,14,15,16,29,65]. Unfortunately all lipid formulations are considerably more expensive than cAmB-D. There are three lipid formulations of AmB available: liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC) and amphotericin B colloidal-dispersion (ABCD) [10,28,93]. ABCD will not be discussed further, as this product is not approved for treatment of proven candidiasis.

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**Fig. 2 – Flow chart for treatment of candidemia or invasive candidiasis.** The suggested antifungals for invasive candidemia treatment. Data derived from following references: [35,38,40,52,60]. AmB: Amphotericin B. Levels of evidence is indicated in brackets where (A) is excellent evidence with several level I or II studies with low risk of bias, (B) is good evidence with one or two level II studies with low risk of bias or multiple level III studies with low risk of bias, (C) is satisfactory evidence with level III studies with low risk of bias, or level I or II studies with moderate risk of bias, and (C) is poor evidence with level IV studies, or level I to III studies with high-risk of bias [113].
Nephrotoxicity with lipid formulations of AmB is minimized due to the preferential accumulation within organs of reticuloendothelial system, rather than the kidneys [16,35,68]. There is evidence suggesting that L-AmB is superior to the ABLC formulation in terms of toxicity profile [28,38]. Due to the lack of comparative data, it is uncertain what, if any, differences between the lipid formulations AmB are in terms of clinical efficacy for proven candidiasis [38,52,81]. ABLC is given in a dose of 5 mg/kg/day for the treatment of candidiasis. L-AmB is usually prescribed in a dose of 3–5 mg/kg/day, when given to treat candidiasis. Higher doses of lipid formulations of AmB (L-AmB 5 mg/kg/day or ABLC 5 mg/kg/day) are generally recommended to treat C. krusei and C. glabrata infections [7,10,92]. Most, but not all strains of C. lusitaniae demonstrate both in vitro and clinical resistance to all AmB products.

9.4.2. Azoles. Azole antifungals impair fungal cell synthesis of ergosterol by inhibiting the cytochrome P450 dependent enzyme sterol 14-α-demethylase, resulting in increased membrane permeability and inhibition of cell growth and reproduction [6,37,65].

9.4.3. Fluconazole

Fluconazole may be the drug of first choice in clinically stable patients who are not on azole prophylaxis and with proven fluconazole-susceptible Candida spp., as recommended in most current guidelines [88,92]. However, the utility of fluconazole as empiric therapy for unspeciated Candida isolates is limited by its reduced activity against some species, including C. glabrata, which is an emerging fungal pathogen. Fluconazole prophylaxis may contribute towards shift towards the non-albicans Candida species, especially the more resistant C. krusei and C. glabrata. Initial isolates of Candida species that are susceptible to fluconazole can develop secondary resistance [83,94].

Thus, initial AmB therapy has been the standard approach with step-down oral therapy to fluconazole once the isolate identity (and or susceptibility) has been determined [92]. Fluconazole’s efficacy has been reported to be equivalent to AmB in the treatment of candidemia, [10,33,93].

Side effects reported include headache, nausea and abdominal pain, mild elevation of transaminases, hair loss, anorexia and rarely fulminant hepatitis. Adverse events usually occur in doses >400 mg/day, with neurotoxicity reported mostly in doses >1200 mg/d [5,30,94].

9.4.4. Itraconazole

Itraconazole has improved activity against C. glabrata, although like fluconazole, itraconazole lacks reliable activity against C. krusei [39]. Its poor oral bioavailability and the lack of clinical trials of the newly available parenteral formulation, has limited the use of itraconazole for candidiasis [7,15]. Of note, intravenous itraconazole is no longer available in the USA. Itraconazole is nowadays mostly used to treat mucosal candidiasis [13,29].

9.4.4.1. Newer triazoles. Newer triazoles include voriconazole and posaconazole [37]. They are generally well tolerated, have a broad spectrum of antifungal activities and an enhanced in vitro potency against Candida species, including the fluconazole-resistant strains [7,10,13,29,42].

9.4.5. Voriconazole

Voriconazole has been shown to be as effective as and safer than AmB in the treatment of candidemia in non-neutropenic patients [95]. The activity of voriconazole against Candida species is superior to that of fluconazole, with minimal inhibitory concentrations that are a log or more, less than fluconazole [37]. Voriconazole has significantly greater in vitro activity against C. krusei isolates, compared to fluconazole, because of more effective binding of its cytochrome P-450 isoenzyme. Conversely, one area of controversy is the efficacy of voriconazole against fluconazole-resistant C. glabrata, because cross-resistance amongst azoles can occur [94]. Voriconazole is a highly lipophilic compound metabolized by cytochrome P-450 with significant drug interactions and demonstrates a non-linear pharmacokinetic profile [5]. Observed side effects include hepatotoxicity, visual disturbances, rash or hallucinations, which are generally transient and reversible [10,42].

9.4.6. Posaconazole

Posaconazole is the newest azole, but it is available only as an oral suspension. Posaconazole is not currently approved for the treatment of systemic candidiasis, however, it has been shown to be effective for oropharyngeal candidiasis and in salvage therapy for systemic candidiasis [97].

9.4.6.1. Echinocandins. Available echinocandins (caspofungin, micafungin, and anidulafungin) belong to a new class of antifungals that act as fungal cell-wall β-(1,3)-D-glucan synthase inhibitors [29,30]. These rapidly fungicidal lipopeptides inhibit the homopolysaccharide β-1,3-D-glucan synthesis, a critical set of enzymes involved in the Candida cell wall synthesis, leading to osmotic instability and fungal cell death [29,30]. In current guidelines, all three echinocandins are labelled as equally effective for the treatment of candidemia and invasive candidiasis. They are effective in candidemia as an alternative as an alternative to AmB due to their potential to treat those species with intrinsic resistance or reduced susceptibility to the other antifungals, for instance C. krusei and C. glabrata [29,30]. Echinocandins do not interact with multiple different cytochrome P-450 enzymes, as azoles do; and may be preferred alternative antifungal agents, in patients taking other medications that utilize P-450 pathways [37]. The echinocandins are active in vitro against almost all Candida species. The highest minimum inhibitory concentrations (MICs) are found for Candida species, including the fluconazole-resistant C. glabrata [7,10,13,29,42].

9.4.7. Caspofungin

Caspofungin is a water soluble, semi-synthetic, amine-derived polypeptide [29,31]. Caspofungin has been demonstrated to be as effective as AmB in invasive candidiasis [97], but it is less toxic than AmB. A study comparing caspofungin and AmB in the treatment of candidal oesophagitis found that caspofungin was at least as effective as AmB with fewer adverse events.
(4% compared to 24% of patients who withdrew due to an adverse event) [98].

9.4.8. Anidulafungin
Anidulafungin was found to be superior to fluconazole in the treatment of invasive Candida infections in a group of predominantly non-neutropaenic patients [99]. It was also found to be at least equivalent to liposomal AmB the treatment of candidiasis [29,30]. Anidulafungin has superior in vitro activity versus the azoles against C. albicans, C. tropicalis, and C. krusei [29,30].

9.4.9. Micafungin
In a large prospective trial, micafungin was compared with L-AmB as first-line therapy for invasive candidiasis and candidemia and was shown to be as effective but less toxic than L-Amb [100]. Non-inferiority and similar safety profiles compared to caspofungin for treatment of candidemia and invasive candidiasis has also been shown [86]. No loading dose is needed. Micafungin appears to be effective for candidiasis, but has not yet been granted FDA approval for this indication.

9.4.9.1. 5-Flucytosine (flucytosine).
This fluorinated pyrimidine is a fungal deaminase, exhibiting inhibitory activity against fungi by interfering with: pyrimidine metabolism, RNA, DNA and protein synthesis in fungi [11,37]. Resistance is a problematic with monotherapy; therefore it is usually used in combination with other antifungals [7,12,22,64]. 5-FC should only be used in combination with another antifungal agent or in cases of severe candidiasis (e.g., central nervous system, endophthalmitis or heart valve infections) [11]. Severe adverse events include myelosuppression with neutropenia and thrombocytopenia, and acute liver failure [36].

9.5. Combination therapy
Due to the limited range of the available antifungal and increasing reports of resistance, the option of combination therapy has been explored to improve cure rates, allow for dose reduction, and thus, toxicities. For example, AmB and 5-flucytosine are known to be synergistic in vitro [81]; the combination used to treat cryptococcosis. Polyene and azole combinations are controversial as they are antagonistic in vitro. However, a clinical study by Rex and colleagues demonstrated synergy with either polyenes or triazoles [29]. Early data on echinocandin and triazole combination therapy are also encouraging [38]. However, combination therapy should not generally be used outside the context of a clinical trial, until better data on efficacy and safety from prospective, randomized clinical trials demonstrate superiority over monotherapy [47].

9.6. Novel therapies
Efungumab (Mycobrag™) is a recombinant human monoclonal antibody against heat-shock protein 90, which acts synergistically against Candida spp. when combined with AmB. A recent double-blind, randomized study, comparing lipid-associated AmB combined with efungumab versus placebo [40], showed a complete overall response by day 10, of 84% for the efungumab combination therapy group, compared with 48% in the placebo group (p < 0.001) [40]. Fungal attributable mortality rates at 4 weeks after treatment was higher in the placebo group 18% versus the combination group 4%; p = 0.025 [40]. Efungumab is not yet licensed and the drug is not currently available.

10. Other strategies
10.1. Topical therapy
Given increased rates of fungal infections have occurred in burn patients, in recent years, use of topical antifungals is an appealing way to prevent invasive candida wound infection. Traditional topical antimicrobial agents that contain silver, such as silver sulfadiazine, confer wide antimicrobial coverage and are most useful for deeper burns (e.g., third-degree burns).

Four widely used topical antimicrobial agents in burns—silver sulfadiazine cream, mafenide acetate cream, silver nitrate cream, and nanocrystalline silver dressings—dramatically decrease the burden of organisms, including fungi, in burn wounds. They reduce the incidence of burn wound infections when routinely applied to partial- and full-thickness burns. Silver has microbicidal properties related to its effect on respiratory enzymes in cell walls of micro-organisms. Silver sulfadiazine has historically been used initially, but its value can be limited by bacterial resistance, poor wound penetration, or toxicity (leukopenia). Moreover, if used indiscriminately, these antifungal agents are associated with cellular toxicity and delayed healing. Synthetic dressings (e.g., nanocrystalline silver dressings) provide broader antimicrobial coverage than other available topical preparations, moderate ability to penetrate eschars, and reduced cytotoxic effects of silver by providing controlled release of silver into the wound. In addition the number of dressing changes is limited thereby reducing the risk of nosocomial infections as well as treatment costs. When invasive candida wound infection is diagnosed, topical therapy should be changed to mafenide acetate. Mafenide acetate in the cream formulation penetrates eschars and thus can treat deeper infections and its use without dressings allows regular examination of the wound. Other occlusive dressings that have been evaluated for the local management of burns include hydrocolloid dressings that have been shown to as effective as silver sulfadiazine and less expensive than collagen-based dressings. Silicone mesh dressings adhere gently to the wound bed and allows wound exudate to escape resulting in faster healing than silver sulfadiazine. For deep burns biologic dressings based on collagen or skin cells are an option, though should only be applied by a burn specialist.

When superficial fungal infection occurs, nystatin may be mixed with silver sulfadiazine or mafenide acetate as topical therapy. Nystatin powder (6 million units/g) has previously been effective in small numbers of patients for treatment of burn wound infections caused by Candida spp. or other fungi, e.g., Aspergillus or Fusarium spp. [101,102] The American Burn
Association has published guidelines that address the management of burn wound infections; however, further research is needed so that more comprehensive guidelines can be established for the local treatment of burns.

Antifungal prophylaxis using non-absorbable agents has been proposed to reduce the gut fungal load or colonization and to decrease superficial mucosal infections [12,28]. A meta-analysis of randomized clinical trials of non-absorbable antifungal prophylaxis with AmB or nystatin showed significantly reduced rates of fungal infections (relative risk [RR], 0.30; \( p < 0.00001 \)); with reduced incidence of candiduria (RR, 0.27; \( p = 0.01 \)), although fungemia and catheter-related fungal sepsis were not significantly reduced [103].

10.2. Removal of IV catheters

Current expert consensus recommends the removal of IV catheters in candidemic patients, whenever feasible, due to the high affinity of Candida species to prosthetic material [1,6,15,18,45,49,51,57,104]. Catheter preservation has been associated with prolonged candidemia and worst outcomes especially so in critically ill unstable patients [11,51]. Catheters should not be changed over a guidewire, as this can result in line contamination, and re-infection [57]. Candida species are commonly associated with biofilms and become resistant to many appropriately dosed antifungals [29]. Inadequacy of antifungal therapy and lack of removal of central lines have been associated with poorer outcomes in non-neutropenic patients with candidemia [41]. Mandatory catheter removal is not without controversy, with some reports suggesting insufficient evidence to support routine catheter removal [7,11]. However, if the line is no longer required it should be removed.

10.3. Improving host defenses

To enhance immune response against pathogenic fungi use of hematopoietic growth factors or immune modulators like granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF, \( \gamma \)-interferon, and immune effector cells (e.g., GM-CSF primed white cell transplants) in patients with refractory or recurring candidiasis are under investigation [33,64]. G-CSF use is mostly restricted to neutropenic patients, and is likely to reduce the risk of invasive fungal infections [28]. G-CSF may not significantly alter the extent of organ involvement in established disseminated candidiasis, but it has significant efficacy in prevention of invasive candidiasis [105].

11. Conclusions

Candidiasis is an emerging infectious disease. Due to difficulty in diagnosis and its high associated high mortality rates, approaches to prophylactic or empirical therapy in high-risk patients have been proposed; however, prophylactic and pre-emptive antifungal therapy in burn patients remains controversial. When used, the choice of antifungal agent depends upon local patterns of resistance and incidence of non-albicans Candida isolates, previous exposure to antifungals, patient co-morbidities, and the patient’s overall clinical status.

In the last few decades, the range of antifungal agents to treat candidemia and invasive Candida infections has been significantly extended. Improvements include better drug safety, superior pharmacokinetic properties and fewer drug-drug interactions. Nevertheless, direct comparisons between antifungals are difficult, because the design and interpretation of published trials on treatment of candidemia and invasive candidiasis have varied significantly. L-AmB is known to be as effective as cAmB-D; notwithstanding, the former has a higher risk of nephrotoxicity than either azoles or echinocandins. Currently available echinocandins have been established as highly effective and safe alternatives to previous antifungals. Adequate antifungal dosing, choice of agent, and administration for an adequate duration are important in burns patients.

Finally, significant gaps remain in our knowledge of the optimal diagnostic and management approach for candidiasis in burn patients. Data is mainly extrapolated from trials in neutropenic cancer or non-neutropenic ICU patient populations, who likely have significant differences to burn patients. These gaps in our knowledge provide opportunities to plan high-quality studies in burn patients.

Conflict of interests

There are no conflicts of interests or funding directly related to this article. However, Dr. Chris Heath is/has been on Antifungal Advisory Boards for Gilead Sciences, Pfizer Australia, Merck Sharp and Dohme, Australia, and Schering-Plough, Australia, and has received honoraria for lectures and/or travel assistance to scientific meetings from Gilead Sciences, Australia, Merck Sharp and Dohme, Australia, Basilea Pharmaceutica Ltd, Switzerland, and Schering-Plough, Australia.

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