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Emerging Drugs and Vaccines for Candidemia

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Summary

Candidemia and other forms of invasive candidiasis are important causes of morbidity and mortality. The evolving challenge of antimicrobial resistance among fungal pathogens continues to highlight the need for potent, new antifungal agents. MEDLINE, EMBASE, Scopus, and Web of Science searches (up to January 2014) of the English-language literature were performed with the keywords “Candida” or “Candidemia” or “Candidiasis” and terms describing investigational drugs with activity against *Candida* spp. Conference abstracts and the bibliographies of pertinent articles were also reviewed for relevant reports. ClinicalTrials.gov was searched for relevant clinical trials. Currently available antifungal agents for the treatment of candidemia are summarized. Investigational antifungal agents with potential activity against *Candida* bloodstream infections and other forms of invasive candidiasis and vaccines for prevention of *Candida* infections are also reviewed as are selected antifungal agents no longer in development. Antifungal agents currently in clinical trials include isavuconazole, albaconazole, SCY-078, VT-1161, and T-2307. Further data are needed to determine the role of these compounds in the treatment of candidemia and other forms of invasive candidiasis. The progressive reduction in antimicrobial drug development may result in a decline in antifungal drug discovery. Still there remains a critical need for new antifungal agents to treat and prevent invasive candidiasis and other life-threatening mycoses.

Keywords

antifungal agents; *Candida*; candidemia; investigational; vaccines

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Introduction

Invasive fungal infections due to *Candida* species have been a growing challenge over the past decade, both because of a rise in the frequency of infections and an increasing resistance to standard antifungal therapy [1]. *Candida* species are the fourth leading cause of healthcare-associated infections, accounting for approximately 11% of all infections; *Candida* spp. are also responsible for nearly 12% of all central line-associated bloodstream infections, preceded only by *Staphylococcus aureus* and *Enterococcus* species [2]. In the National HealthCare Safety Network data from 2009 to 2010, non-*albicans Candida* spp. were the 4th and *Candida albicans* was the 7th cause of central line associated bloodstream infections [3].

Crude mortality associated with *Candida* infections ranges from 19% to approximately 60% with the wide variability likely due to differences in study populations [4,5]. Similarly, mortality rates attributable to candidemia range from 10% to 49% [6–8]. Candidemia has also been associated with an increase in length of hospital stay and subsequent cost [6,7,9].

Independent risk factors for the development of candidemia include use of broad-spectrum antimicrobial agents, neutropenia, presence of central venous catheters, administration of total parenteral nutrition (TPN), gastrointestinal surgery, chemotherapy, hemodialysis, previous colonization with *Candida* spp., and gastric acid suppression [9].

Critically ill patients are therefore particularly susceptible to *Candida* bloodstream infections, as they present with many of these risk factors. The incidence of candidemia in the intensive care unit (ICU) is variable depending on the studies queried. Recently, the EPIC II investigators surveyed 14000 patients in 1265 ICUs in 76 countries in diverse geographic locations and reported a one-day point prevalence of candidemia of 6.9 per 1000 patients in 2007 [10]. *C. albicans* was the most common organism, and fluconazole was the most common antifungal agent used. The presence of candidemia correlated with increased ICU length of stay and mortality [10].

Although more than one hundred species of *Candida* have been described, the vast majority of cases of candidemia are caused by only five species: *C. albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, and Candida krusei* [11]. While other *Candida* species account for only a very small fraction of infections, recognition and understanding of resistance patterns in these scarcer species may have therapeutic implications. Traditionally, treatment of candidemia has relied mainly on antifungal azoles, polyenes, and echinocandins. In general, *C. albicans, C. parapsilosis, C. tropicalis*, and *Candida lusitaniae* are susceptible to antifungal azoles and echinocandins, with *C. parapsilosis* and *Candida guilliermondii* displaying higher MICs for echinocandins [11]. Echinocandin use has recently been shown to correlate with improved outcomes and a decrease in mortality in a quantitative review of randomized trials for the treatment of invasive candidiasis [12]. However, infections due to *C. glabrata* have increased in frequency over the past decades paralleled by an increase in resistance to fluconazole as well as echinocandins [13,14]. Therefore, given the increasing incidence of multidrug resistant *Candida* species and high mortality with existing treatment, there is a need to develop new antifungal agents. The

objective of this review is to summarize the safety and efficacy of investigational antifungal agents that may potentially be effective treatment for candidemia and other forms of invasive candidiasis.

Magnitude and impact of candidemia

Candida spp. are a common cause of bloodstream infections with a high attributable cost. Early onset candidemia is also occurring with more frequency and is associated with increased mortality, longer hospital stays and subsequently higher hospital costs when compared to bacterial bloodstream infections [15]. Using an Agency for Healthcare Research and Quality dataset from the Nationwide Inpatient Survey 2000 (NIS 2000), Zaoutis and colleagues compared crude data to propensity-score matched data and demonstrated in adults with candidemia a 14.5% increase in mortality and a mean increase in length of stay of 10.1 days resulting in almost $40,000 in additional costs [6]. In pediatric patients (> 30 days and < 18 years old), they compared data using the 2000 Kids' Inpatient Database (KID 2000) and found with propensity-matched analysis, that pediatric candidemia was associated with an absolute 10% increase in mortality and an approximate 21-day increase in length of stay with an additional $92,000+ in hospital costs.

In neonates, *Candida* spp. are the third most common cause of bloodstream infection and the primary cause of invasive fungal infection [16]. In data extracted from the 2003 Kids' Inpatient Database from the Healthcare Cost and Utilization Project [16], the highest risk neonates were extremely low birth weight (ELBW)(<1000g). The ELBW infants experienced propensity score-adjusted mortality rates of 11.9% without comparable increases in the non- ELBW infants. ELBW infants with candidiasis had an increased hospital cost of over $39,000. Non-ELBW neonates had longer hospital stays (16 days) and increased hospital costs ($122,302).

In the United States for the year 2000, there were 30 adult and 43 pediatric cases of candidemia per 100,000 hospital admissions [6]. These numbers suggest that more preventive action may be necessary.

Existing treatment

There has been a great expansion of antifungal agents against *Candida* spp. bloodstream infections over the past two decades, which now include three major classes of drugs: 1) Triazoles (fluconazole, voriconazole), 2) echinocandins (caspofungin, micafungin, anidulafungin) and 3) polyenes (amphotericin B deoxycholate [AmB-d], liposomal amphotericin B [L-AmB], amphotericin B lipid complex [ABLC], and amphotericin B colloidal dispersion [ABCD]) (Table 1). The Clinical and Laboratory Standards Institute (CLSI) has developed methodology for susceptibility testing of *Candida* species to fluconazole, itraconazole, voriconazole, flucytosine, and the echinocandins, which are increasingly used to manage the treatment of candidemia [17,18].

Factors to consider when choosing an antifungal agent for the treatment of candidemia include prior antifungal exposure, intolerance to an antifungal agent, current epidemiology

and susceptibility patterns, severity of illness, comorbidities, and involvement of the central nervous system, heart valves, or other organ systems [19].

For the treatment of candidemia in adult nonneutropenic patients, the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines suggest initial therapy with fluconazole 800 mg [12 mg/kg] IV x 1, then 400 mg [6 mg/kg] IV daily or an echinocandin including caspofungin 70 mg IV x 1, then 50 mg IV daily, micafungin 100 mg IV daily, or anidulafungin 200 mg IV x 1 then 100 mg IV daily for two weeks after clearance of *Candida* spp. from the blood [19]. For patients who are not critically ill and have had no recent azole exposure, fluconazole is recommended as initial therapy. In contrast, an echinocandin is recommended in patients with moderately severe to severe illness or with recent azole exposure.

Because of varying susceptibilities of clinical isolates, special attention must be paid to the species of *Candida* being treated. For candidemia due to *C. glabrata* or *C. krusei*, an echinocandin is preferred for initial therapy; for *C. albicans* or *C. parapsilosis*, fluconazole is recommended. AmB-d 0.5–1 mg/kg IV daily or a lipid formulation of amphotericin B 3–5 mg/kg IV daily are alternative antifungal agents if a patient is intolerant to-or there is limited availability of other drugs. Current IDSA guidelines recommend two weeks of therapy for candidemia without persistent fungemia or metastatic complication after clearance of *Candida* from the blood and resolution of symptoms of candidemia.

In neutropenic patients, candidemia may be life-threatening and was historically treated with AmB [20]. Fluconazole is often used for prophylaxis to prevent candidemia in neutropenic patients, which has led to a decreased role for treatment of candidemia in these patients [21]. The availability of echinocandins and antifungal triazoles such as voriconazole have resulted in increased use in neutropenic patients with candidemia and an echinocandin is now recommended for initial therapy [19]. It should be noted, however, that this recommendation comes from information from single-arm studies or from subset data from randomized controlled trials [19].

Scientific rationale: targets of antifungal agents

The cell of *Candida* spp. is composed of a protective outer cell wall surrounding an inner cell membrane. Components of the cell wall include (1→6)-β-D-glucan-branched (1→3)-β-D-glucan cross linked to chitin, branched (1→6)-β-D-glucan, and mannoproteins [22,23]. The cell wall functions as a barrier to protect the cell from the outside environment, is involved in adhesion to surfaces, and biofilm formation [23]. The main component of the cell membrane is ergosterol, which is involved in regulation of membrane fluidity, asymmetry, and integrity [22,24].

Figure 1 illustrates the site of action of selected antifungal agents [25]. The majority of available antifungal agents target the cell wall by inhibiting (1→3)-β-D-glucan synthase (echinocandins) or target the cell membrane by binding to ergosterol (amphotericin) or inhibiting ergosterol biosynthesis (antifungal azoles).

Novel targets of investigational drugs include glycosylphosphatidylinositol (GPI) biosynthesis, histone deacetylases, and heat shock proteins. Cell wall proteins may contain a GPI anchor, which anchors the protein to the plasma membrane [23]. Inhibiting GPI biosynthesis results in inhibition of fungal cell growth, hyphal elongation, and adhesion [26]. Histone deacetylases are enzymes involved in the regulation of chromatin structure and transcription through lysine deacetylation of histones [27,28]. They are involved in gene regulation, cell proliferation, cell death, and motility [28]. Heat shock protein 90 (HSP 90) is located on the cell wall, aiding the pathogen's response to stressful stimuli, such as antifungal agents, by promoting formation of resistance mechanisms [29–31]. It also stimulates the release of endothelial nitric oxide and bradykinin, potentially contributing to symptoms associated with sepsis [32–35].

Investigational antifungal agents

Emerging antifungal agents currently in clinical trials for *Candida* spp. infections (Table 2) as well as selected antifungal agents no longer in development are reviewed below. While many compounds are not currently being evaluated in the treatment of candidemia or are not in active clinical development, they are included in this review as a proof of concept with regard to mechanism of action, and with the hope that investigation of promising compounds will be renewed in the future.

Isavuconazole

Isavuconazonium (BAL-8557) is a water soluble prodrug of the antifungal triazole isavuconazole (BAL-4815) [36], which is being developed by Astellas Pharma in collaboration with Basilea Pharmaceutica for the treatment of invasive fungal infections including candidiasis and aspergillosis. Isavuconazonium has been granted an application under orphan drug designation by the FDA for treatment of invasive aspergillosis and mucormycosis. It inhibits ergosterol biosynthesis by inhibiting lanosterol 14α-demethylase [36]. BAL-8557 is converted by plasma esterases to isavuconazole and BAL-8728 (prodrug cleavage product) [36,37]; the conversion is rapid and complete with >98% converted to isavuconazole [37]. Advantages of BAL-8557 are that a cyclodextrin solubilizer is not required due to its water solubility [38], an oral dosage form is available, unlike the echinocandins, and it may be better tolerated than voriconazole.

Several *in vitro* and *in vivo* studies indicate that isavuconazole is active against *Candida* spp. [39–44]. Seifert and colleagues reported that isavuconazole was active *in vitro* against *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* (Table 3) [44]. Isavuconazole was also active against *C. guilliermondii* and *C. lusitaniae* [42].

Limited available data suggest that isavuconazole increased survival and decreased tissue burden in a *C. albicans* mouse model of disseminated candidiasis [41]. Isavuconazole was active against *C. tropicalis* but less active against *C. krusei* in a disseminated murine model of candidiasis [40]. Four days post infection in temporarily neutropenic mice infected with *C. tropicalis*, isavuconazole 60 mg/kg PO BID and 90 mg/kg PO BID reduced kidney fungal burden by 2.29 $\log_{10}$ CFU/g and 2.23 $\log_{10}$ CFU/g, respectively, compared to controls ($p<0.001$). Furthermore, in persistently neutropenic mice infected with *C. tropicalis*,

isavuconazole 120 mg/kg PO BID reduced kidney fungal burden by 2.15 $\log_{10}$ CFU/g and 3.01 $\log_{10}$ CFU/g compared to controls 4 and 7 days post infection ($p<0.001$). Additionally, in persistently neutropenic mice infected with *C. krusei*, isavuconazole 90 mg/kg PO BID and 150 mg/kg PO BID decreased kidney fungal burden by 1.53 $\log_{10}$ CFU/g and 1.69 $\log_{10}$ CFU/g compared to controls ($p<0.0001$). Brain fungal burden of *C. krusei* in mice treated with isavuconazole 120 mg/kg PO BID (temporarily neutropenic) and 150 mg/kg PO BID (persistently neutropenic) significantly decreased by 1.21 $\log_{10}$ CFU/g and 0.84 $\log_{10}$ CFU/g, respectively, compared to controls.

The pharmacodynamic parameter associated with isavuconazole efficacy in a *C. albicans* murine model of disseminated candidiasis was the AUC/MIC ratio [45]. The postantifungal effect *in vitro* in a *C. albicans* strain exposed to isavuconazole for three hours was 2 hours at concentrations 2 X MIC, 5 hours at concentrations 5 to 100 X MIC, but not seen at concentrations below the MIC [45].

Two phase 1 clinical trials (single and multiple dose studies) of IV and oral BAL-8557 in healthy volunteers and one phase 1 clinical trial in patients with mild to moderate liver disease have been published [37,46,47]. The pharmacokinetic parameters of IV isavuconazole in healthy volunteers included a half-life of 76.2 to 104 hours [37], a dose proportional AUC, a clearance of 3.19 to 4.06 L/hour, and a Vd of 470 to 542 L [46]. The isavuconazole half-life was increased and clearance was decreased in patients with mild to moderate liver disease due to alcoholic cirrhosis [47]. After a single IV dose of BAL-8557 180.5 mg, the isavuconazole half-life and clearance were 302 hours and 1.43 L/hour, respectively, in patients with moderate liver disease compared to 123 hours and 2.73 L/hour, respectively, in healthy volunteers.

Adverse events observed in the multiple dose phase 1 trial were dose dependent [46]. In the isavuconazole 50 mg/day group there were 18 adverse events and in the isavuconazole 100 mg/day group there were 21 adverse events. One serious adverse event, rhinitis, was reported in the high dose group but was not thought to be related to isavuconazole. Mild to moderate adverse events in the high dose group included headache (5), rhinitis (3), nasopharyngitis (3), abnormal liver function test (1), back pain (1), pharyngolaryngeal pain (1), abdominal pain (1), gingivitis (1), and fatigue (1). Mild to moderate adverse events in the low dose group included nasopharyngitis (4), headache (2), rhinitis (2), back pain (1), pain in extremity (1), dizziness (1), cough (1), abdominal pain (1), diarrhea (1), and fatigue (1).

Isavuconazole is currently being studied in a Phase 3 clinical trial for the treatment of candidemia and other invasive *Candida* infections (NCT00413218).

Albaconazole

Albaconazole (UR-9825) is an orally and topically administered antifungal triazole being developed by Actavis. As with other antifungal triazoles, albaconazole inhibits ergosterol biosynthesis by inhibiting lanosterol 14α-demethylase [48]. Phase 2 clinical trials have been conducted with albaconazole for vulvovaginal candidiasis, tinea pedis and toenail onychomycosis [49].

While albaconazole is being targeted for dermatophyte infections, it is active *in vitro* and *in vivo* against *Candida* spp. [50–52]. Ramos and colleagues reported that albaconazole was active *in vitro* against *Candida* spp., including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. guilliermondii* (Table 3) [51]. However, albaconazole MICs were increased in isolates with a fluconazole MIC ≥ 16 mg/L, including *C. albicans* (MIC_{50} ≤ 0.0002 mg/L, MIC_{90} 0.03 mg/L), *C. tropicalis* (MIC_{50} ≥ 8 mg/L, MIC_{90} 64 mg/L), *C. glabrata* (MIC_{50} 0.06 mg/L, MIC_{90} 1 mg/L) and *C. krusei* (MIC_{50} ≤ 0.0002 mg/L, MIC_{90} 0.06 mg/L).

In a rabbit model of disseminated candidiasis, albaconazole (0.5 mg/kg/day PO) significantly decreased *C. albicans* CFU in kidneys and lungs compared to controls [52]. In the albaconazole (0.5 mg/kg/day PO) and control groups, CFU in kidneys and lungs were 0.68 log CFU/g and 0.39 log CFU/g and 4.48 log CFU/g and 3.04 log CFU/g, respectively.

MGCD290

Shared targets for histone deacetylase inhibitors are similar for cancer and *Candida* spp. therapy. The histone deacetylase inhibitor 4-sodium phenylbutyrate was being evaluated by Lunamed for cervical intraepithelial neoplasia and chronic candidiasis in a terminated Phase 2 clinical trial. MGCD290 was a Hos2 fungal histone deacetylase inhibitor being developed by Mirati Therapeutics [28]. While it was targeted for the treatment of vulvovaginal candidiasis, a recent Phase 2 clinical trial failed to show a significant benefit of oral MGCD290 combined with fluconazole compared to fluconazole alone [53].

MGCD290 was only moderately active *in vitro* against *Candida* spp., including *C. albicans*, *C. glabrata*, and *C. krusei* [28]. However, MGCD290 potentiates the effect of antifungal triazoles [28]. With *Candida* spp. that were not susceptible to fluconazole, the combination of MGCD290 and fluconazole resulted in a reduction of fluconazole MIC. Furthermore, the combination of MGCD290 and fluconazole was synergistic in 26 out of 30 *Candida* spp. isolates. Limited available *in vivo* data also indicated that the combination of fluconazole and MGCD290 increased survival and decreased kidney fungal load compared to fluconazole alone in a mouse model of disseminated candidiasis [54,55].

Four Phase 1 single and multiple ascending dose studies of oral MGCD290 with or without fluconazole have been presented as conference abstracts [56–58]. Limited available data suggest a mean half-life of 10 to 11 hours and an AUC that is dose proportional in humans. No significant adverse effects were observed in these studies.

MK-3118/SCY-078

MK-3118 is an oral and parenteral semi-synthetic enfumafungin derivative being developed by Scynexis Inc. [59–60]. It acts as a specific inhibitor of (1→3)-β-D-glucan synthase, preventing appropriate cell wall formation [59,61,62]. In an *in vitro* study of 113 clinical isolates of *Candida* spp. tested by CLSI broth microdilution, MK-3118 and caspofungin showed similar MICs against *C. parapsilosis* (MIC_{90} 0.5 mg/L, for both), *C. tropicalis* (MIC_{90} 1 mg/L, for both), *C. albicans* (MIC_{90} 1 mg/L versus 2 mg/L, respectively), and *C. krusei* (MIC_{90} 2 mg/L versus 1 mg/L, respectively); it showed lower MICs than caspofungin

against *C. glabrata* (MIC_{90} 2 mg/L versus 16 mg/L, respectively) [60]. MK-3118 was shown to be active (with an MIC of ≤ 1 mg/L) against 32 out of 34 fluconazole-resistant isolates and was also active (with an MIC of ≤ 1 mg/L) against 22 out of 31 isolates with mutations associated with echinocandin resistance; in contrast, caspofungin was only active against 4 out of 31 such isolates.

MK-3118 was evaluated in a complement-deficient murine model [63]. Mice infected with a strain of *C. albicans* were treated with MK-3118 12.5 mg/kg PO BID for 7 days, resulting in a 4.7-log reduction in CFU/g of kidney at the end of treatment compared with control mice. In mice infected with *C. tropicalis*, MK-3118 25 mg/kg PO BID resulted in a 2.6 to 3.8 log reduction in CFU/g of kidney compared to control.

Two Phase 1 randomized, double-blinded, placebo-controlled ascending dose escalation studies in healthy volunteers have also been conducted, in which subjects received single or multiple doses of MK-3118 from 10 mg to 1600 mg or 300 mg to 800 mg once daily for 28 days, respectively [64,65]. Limited available data suggest a harmonic mean half-life of approximately 20 hours and an AUC that is dose-proportional in humans [65]. MK-3118 was generally well tolerated [64,65]. The most common adverse effects were diarrhea/loose stools, abdominal pain/cramps, and headache [64,65]. Gastrointestinal complaints were most notable at higher doses (≥600 mg daily) and on the first day of therapy [64].

VT-1161

Viamet Pharmaceuticals is developing several metalloenzyme inhibitors of lanosterol demethylase (CYP51) including VT-1598, VT-1129, and VT-1161 [66]. While oral VT-1129 is in preclinical development targeted for cryptococcal meningitis, it is also active *in vitro* and *in vivo* against *Candida* spp. [67–69]. Oral VT-1161 is currently in Phase 2 clinical trials targeted for onychomycosis and candidiasis.

VT-1161 is active *in vitro* and *in vivo* against *Candida* spp. [67–71]. It was active *in vitro* against *C. albicans*, *C. glabrata*, and *C. parapsilosis* (Table 3) [67]. In *C. albicans* isolates with reduced susceptibility to fluconazole (MIC 32 to > 64 mg/L), the VT-1161 MIC ranged from ≤ 0.03 to 0.5 mg/L [69]. However, in *C. albicans* isolates that were resistant to fluconazole (MIC > 64 mg/L), the VT-1161 MIC ranged from 0.25 to > 16 mg/L [67].

VT-1161 has demonstrated activity in several murine models of candidiasis [68,70,71]. Hoekstra and colleagues reported that VT-1161 significantly increased survival in mice infected with a strain of *C. albicans* that was susceptible to fluconazole (MIC_{50} 2 mg/L) [68]. The percent survival with VT-1161 5, 10, and 20 mg/kg/day PO ranged from 90 to 100% compared to 0% in controls (p=0.0001). Kidney fungal burden with VT-1161 10 and 20 mg/kg/day PO ranged from 1.7 to 2.1 log CFU, compared with 5.7 log CFU with fluconazole 10 mg/kg/day. In mice infected with *C. albicans* with decreased susceptibility to fluconazole (MIC 32 mg/L), the percent survival with VT-1161 at doses ≥ 2.5 mg/kg/day PO was ≥90% compared to 10% ($p \leq 0.01$) survival in control mice who received vehicle [70]. Kidney fungal burden with VT-1161 dosed at ≥ 2.5 mg/kg/day PO was 3.45 to 4.03 $\log_{10}$ CFU/g and with controls was 6.2 $\log_{10}$ CFU/g ($p<0.001$). VT-1161 also increased survival and decreased kidney fungal burden in a *C. glabrata* murine infection model [71].

T-2307

T-2307 is an injectable arylamidine being developed by Toyama currently in Phase 1 clinical trials. The mechanism of action in yeast involves impairment of mitochrondrial function [72]. T-2307 is active *in vitro* against *Candida* spp. including *C. albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, and C. guilliermondii* (Table 3) [73]. It was also active against *C. albicans* strains that were not susceptible to fluconazole (MIC 16 to > 64 mg/L), with T-2307 MIC ranging from 0.0005 to 0.001 mg/L. In addition, in a *C. albicans* mouse model of disseminated candidiasis, T-2307 0.01 mg/kg/day and 0.02 mg/kg/day subcutaneously significantly increased survival compared to controls [73]. In a *C. glabrata* murine model of disseminated candidiasis, kidney fungal burden in the T-2307 0.05 mg/kg/day, 0.1 mg/kg/day, and control groups were 4 log CFU/ kidneys, 3.86 log CFU/ kidneys, and 5.26 log CFU/ kidneys, respectively ($p<0.05$) [74].

Investigational antifungal vaccines

A *Candida* vaccine may be a useful preventive strategy to avoid the morbidity, mortality, and cost associated with *Candida* spp. infections. Possible indications include prevention of vaginal candidiasis, denture stomatitis, oral candidiasis, and candidiasis in immunocompromised patients [75]. The rationale and strategies in *Candida* vaccine development has been recently reviewed [75,76]. Currently, there are no commercial vaccines for the prevention of *Candida* spp. infections. Emerging *Candida* vaccines in development are briefly reviewed below.

NDV-3 (rAls3p-N)

NDV-3 is a prophylactic recombinant vaccine with an Alhydrogel® adjuvant against the N-terminal region of the agglutinin-like sequence 3 protein (Als3p) being developed by NovaDigm Therapeutics [77,78]. Als3p is an adhesin and invasin protein, with a broad array of substrate affinity, allowing *Candida* spp. to bind to each other, as well as host epithelial and endothelial surfaces [77–83]. Because of colonization and/or previous infection, the majority of healthy individuals have detectable anti-Als3p antibodies [77,84]. This priming facilitates strong B-cell and T-cell responses upon vaccination, which promote opsonophagocytic killing and block fungal adherence [77,78,83,85]. Aside from its potential use in *Candida* infections, it has also shown activity against *S. aureus* [77,78].

In a murine model of disseminated candidiasis, mice were immunized with a subcutaneous injection of rAls3p-N with Freund's adjuvant at day 0, and a booster at day 2 [78]. Mice were subsequently infected with *C. albicans* two weeks following the final dose. Serum antibody titers and animal survival were evaluated. Antibody titers in vaccinated mice were significantly higher compared to titers in unvaccinated mice. Survival at day 28 was also improved with vaccination. However, antibody titers in vaccinated mice did not significantly correlate with survival.

rAls3p-N with an Alhydrogel® adjuvant also increased survival and antibody titers compared to control mice in a model of disseminated candidiasis [85]. In IFN-γ deficient mice, vaccination only marginally improved survival. However, IFN-γ deficient mice who received CD4+ lymphocytes from vaccinated wild type mice had improved survival,

suggesting that vaccine efficacy is dependent upon Type 1 immunity [83,85]. Additionally, $gp91^{phox-/-}$ deficient mice (which have defective phagocytes) and IL-17A deficient mice (Th17 cells are known to act by recruiting phagocytes) also were not protected by vaccination, indicating that functional phagocytes are also necessary to mediate vaccine efficacy [83]. Nonetheless, an IgG titer cut-off of ≥1:6400 was found to have sensitivity of 84% and specificity of 86% for protection from infection, suggesting that despite cell-mediated immunity, antibody titer thresholds may serve as a potential surrogate marker [85].

A Phase 1 double-blinded, placebo-controlled ascending dose escalation study in healthy volunteers (n = 40) has also been conducted, in which subjects received a single dose of NDV-3 30 mcg or 300 mcg on day 0; approximately 60% of subjects received a second dose at day 180 [77]. Plasma antibody titers (IgG and IgA1) significantly rose following vaccination, compared with placebo ($p < 0.001$). Based on seroconversion, defined as ≥ 4-fold rise in antibody titer over baseline, a single dose of 30 mcg or 300 mcg resulted in seroconversion rates of 13% and 53%, respectively, by day 7, and 100% seroconversion in both groups by day 14. Revaccination resulted in a further increase in antibody titers. Maximal response rates with IFN-γ and IL-17A producing PBMCs were seen at day 28 in the 30 mcg group, and seen earlier, at day 7, in the 300 mcg group. Revaccination increased these response rates further.

rAls3p-N was generally well-tolerated [77]. The most common adverse events was mild injection site pain, which resolved within 2–3 days following vaccination. Common systemic adverse events (not dose-dependent) included fatigue and headache, were usually mild or moderate, and all resolved within a few days [77].

rHyr1p-N

rHyr1p-N is a prophylactic recombinant vaccine against the N-terminal region of Hyr1p being developed by NovaDigm Therapeutics [86,87]. Hyr1 encodes glycosylphosphatidylinositol, a protein expressed on the cell surface of *C. albicans* and non-albicans *Candida* spp., mediating resistance to opsonophagocytic killing [86–89]. Direct vaccination results in the development of neutralizing antibodies, allowing for protection via development of active immunity; these neutralizing antibodies have also been shown to provide protection via passive immunity [87].

In a disseminated candidiasis murine model, mice were vaccinated with 2 subcutaneous injections of rHyr1p-N at day 0 and day 21 [86]. Mice were subsequently infected with *C. albicans* at day 35. Survival was significantly improved with vaccination with rHyr1p-N (Freunds or Alhydrogel® adjuvant) compared to controls at 35 days post-infection (60–100% versus 0%).

Furthermore, in a *C. albicans* mouse model of disseminated candidiasis vaccination with rHyr1p-N with an Alhydrogel® adjuvant resulted in increased survival and an approximately 1 $\log_{10}$ decrease in CFU/g of kidney 3 days post-infection compared to control mice [87]. Vaccinated mice infected with non-albicans *Candida* spp. also demonstrated a 0.65 to 1.69 $\log_{10}$ reduction in CFU/g of kidney compared to controls. Passive immunization with rabbit anti-Hyr1p antibodies (1 mg or 3 mg) given 2 hours prior

to *C. albicans* infection was protective in mice up to 28 days post-infection (survival was 30 – 40% in vaccinated mice versus 0% in the control group, p = 0.001). rHyr1p-N was also evaluated in a neutropenic murine model. Following vaccination, mice were made neutropenic with cyclophosphamide and subsequently infected with *C. albicans*. Vaccination resulted in a 1.5 $\log_{10}$ reduction in CFU/g of kidney 10 days post-infection compared with control mice (p = 0.002). The survival rate at 28 days post-infection also significantly improved. All mice in the control group died before day 14; however, 20% of vaccinated mice were alive 28 days post-infection (p = 0.007).

Investigational antifungal agents and vaccines no longer in development

Aminocandin

Aminocandin was an echinocandin antifungal agent being developed by Novexel/AstraZeneca. It was a noncompetitive inhibitor of (1→3)-β-D glucan synthase [90]. Aminocandin was a promising antifungal agent, with its long half-life of 48 to 58 hours [91] it had a potentially useful role as long term antifungal therapy in the ambulatory setting. As with other echinocandins, aminocandin was active *in vitro* against *C. albicans*, *C. glabrata*, *C. tropicalis*, and C. *krusei* (Table 3) [92,93]. However, aminocandin MICs were increased with *C. parapsilosis* and *C. guilliermondii* [92,93]. Aminocandin was also active *in vivo* against *C. albicans*, *C. tropicalis*, and *C. glabrata* in murine infection models [90,94–96]. The pharmacodynamic parameter that correlated with aminocandin efficacy in a *C. albicans* murine model of disseminated candidiasis was the peak/MIC ratio [97]. Fungistatic activity *in vivo* occurred at a peak/MIC ratio of 3.72 with maximum killing at a peak/MIC ratio of 10.

E-1210

E-1210 was a novel, broad spectrum antifungal agent being developed by Eisai. It had a unique mechanism of action as an inhibitor of GPI biosynthesis [98]. Only preclinical information has been presented and published. Chemical, *in vivo* pharmacokinetic, and microbiological studies of E-1211, a water soluble prodrug of E-1210, have also been presented as conference abstracts [99,100]. E-1210 was active *in vitro* against several *Candida* spp., including *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* (Table 3) [26]. However, it had poor activity *in vitro* against *C. krusei* with MIC values of 2 to > 32 mg/L [26,101]. E-1210 was also active *in vitro* against *Candida* spp. that were resistant to fluconazole and caspofungin [26]. In mouse models of disseminated candidiasis, E-1210 significantly increased survival of mice infected with *C. albicans* and *C. tropicalis* [102]. Pharmacodynamic parameters that correlated with the efficacy of E-1210 in a murine model of disseminated candidiasis were AUC/MIC and T>MIC [103]. In a time kill assay E-1210 was fungistatic with maximum activity at 8 X MIC against a strain of *C. albicans* [101].

Efungumab

Efungumab was a recombinant monoclonal antibody being developed by Novartis Pharmaceuticals [29,32,104,105]. It was derived from anti-HSP 90 antibody cDNA of patients who recovered from deep-seated, invasive candidiasis. Efungumab binds to the middle region of HSP 90, preventing communication between the terminal regions, hence

preventing necessary conformational changes [29]. In addition to promising data from preclinical investigations and patient case reports with efungumab, a randomized, double-blinded trial in patients with culture-confirmed invasive candidiasis, compared liposomal amphotericin B or amphotericin B lipid complex alone with liposomal amphotericin B or amphotericin B lipid complex in combination with efungumab [32–34,105–108]. The primary outcome, the composite of complete clinical response and mycological clearance on day 10, favored combination therapy (84% vs. 48%, $p < 0.001$). The rate of mycological clearance was more than twice as fast with efungumab and mycological resolution was achieved in 89% of the combination therapy group compared with 54% in the amphotericin group at day 10 ($p < 0.001$).

Efungumab was generally well tolerated. Safety concerns centered on a cytokine release syndrome characterized by hypertension, nausea, and vomiting [29,33,34,104]. Unfortunately, additional concerns regarding structural inconsistencies between manufactured batches, possibly due to an unpaired cysteine at position 28, also remained [104]. Despite these promising clinical results, development of this product was abandoned in 2010. Nonetheless, the concept of HSP-90 inhibition holds promise as a novel strategy to combat invasive candidiasis.

Sordarins

Sordarin is a natural product isolated from *Sordaria araneosa* [109,110]. Since its discovery, several structurally related compounds have been isolated and/or developed [110–113]. Sordarin, and its derivatives, bind to elongation factor 2 (eEF2), stabilizing the eEF2/ribosome complex via a likely additional interaction with ribosomal subunit protein (rpP0), and preventing the final step of translocation in protein synthesis [109–114]. Despite eEF2 being highly conserved among eukaryotes, sordarin and its derivatives only interact with a very specific region of eEF2, which is unique to fungal species, particularly *Candida* spp. [109–111,113–115]. Sordarin derivatives have been evaluated in murine models of disseminated candidiasis [112,113,116]. While these agents have not been tested in humans to date, low cytotoxicity has been reported for some compounds [111].

MAb B6.1

MAb B6.1 was a prophylactic and therapeutic IgM-monoclonal antibody that specifically targeted (1→2)-β-mannotriose; it was formerly under development by LigoCyte Pharmaceuticals [117–122]. (1→2)-β-mannotriose is an acid-labile component of the phospholipomannan complex, expressed uniformly on the surface of *C. albicans* and other pathogenic non-albicans *Candida* species, which displays adhesion [117,118,120,121,123,124]. The vaccine facilitates opsonophagocytic killing via the classical pathway of the complement system [117–123,125]. By using B6.1 in combination with conventional antifungal agents, which damage cell wall structure, B6.1 may be able to more efficiently bind its target [117,123]. Simultaneously, B6.1 interferes with the binding ability of adhesin, and may allow conventional antifungal agents to exert their full effects [123].

In a disseminated candidiasis murine model, mice were infected with *C. albicans* and subsequently treated with a single dose of B6.1 intraperitoneally one hour later, resulting in a 28% reduction in CFU/g of kidney at 48 hours after infection compared with control mice [123]. Mean survival time was significantly increased from 9.2 +/− 3.4 days in control mice to 30.2±16.9 days with amphotericin B 0.5 mg/kg/B6.1 combination therapy ($p < 0.001$). In addition, in a mouse model of disseminated candidiasis, B6.1 was given in combination with fluconazole 0.8 mg/kg, which resulted in a 70% reduction in CFU/g at 48 hours after infection compared with control mice ($p < 0.05$) [117]. Mean survival time was 9.2 ± 3.3 days in control mice and 33.0±16.6 days with fluconazole 0.8 mg/kg/B6.1 combination therapy ($p < 0.05$). B6.1 was also evaluated in a *C. albicans* neutropenic murine model, in which vaccination resulted in a significant reduction in CFU/g of kidney at 48 hours post-infection compared with control mice ($p < 0.01$) [121]. Furthermore, mean survival time in mice with prolonged neutropenia was also significantly increased from 5.2 days to 12.3 days if mice continued to receive B6.1 every other day following infection.

Potential development challenges

There has been an alarming decline in research, development, and FDA approval of new antimicrobial agents. A study by Spellberg and colleagues indicated that from 1983 to 1987 compared to 1998 to 2002, there was a 56% decrease in new antibacterial agents approved by the FDA [126]. A recent update on the progress of the IDSA 10 x ′20 initiative suggests a continued decline of antibacterial drugs approved by the FDA, with five drugs approved from 2003 to 2007 and two drugs approved from 2008 to 2012 [127]. The etiology of the decline in antimicrobial drug development includes high cost with a low rate of return compared to drugs used to treat chronic conditions, limitations on the use of newly approved antibacterial agents, and trial design and regulatory issues [128].

As large pharmaceutical companies continued to withdraw from antimicrobial drug development, antifungal drug discovery suffers as an innocent bystander. In the last 13 years, only five antifungal agents have been approved by the FDA including caspofungin (2001), voriconazole (2002), micafungin (2005), posaconazole (2006), and anidulafungin (2006) [129]. This is especially alarming with the emergence of resistant *Candida* spp. and the paucity of oral antifungal agents currently available to treat infections caused by these organisms. However, despite the current outlook with regard to the development of new antifungal agents, we retain hope that ongoing regulatory reform will rejuvenate the development of these important antimicrobial compounds in the future [130].

Future Directions/Conclusion

Candida spp. are a common cause of bloodstream infections with high attributable mortality and cost. Rapid diagnostics and new antifungal agents are needed for the treatment of candidemia, as the mortality rate with existing antifungal agents is high and resistance is emerging. Antifungal agents in clinical trials include isavuconazole, albaconazole, SCY-078, VT-1161, and T-2307. Currently, only isavuconazole is being studied in a Phase 3 clinical trial for the treatment of candidemia and other invasive *Candida* infections. Further data is needed to determine the role of these antifungal agents in the treatment of candidemia

and other forms of invasive candidiasis. Unfortunately, the progressive decline in antimicrobial drug development by large pharmaceutical companies may result in a dearth of antifungal drug discovery and development. Nonetheless, there still remains interest and recognition of the critical need for developing new antifungal agents for treatment and prevention of invasive candidiasis, as well as other life-threatening mycoses. Indeed, compounds that are beyond the scope of this manuscript are undergoing early development that may lead to important new advances in patient care.

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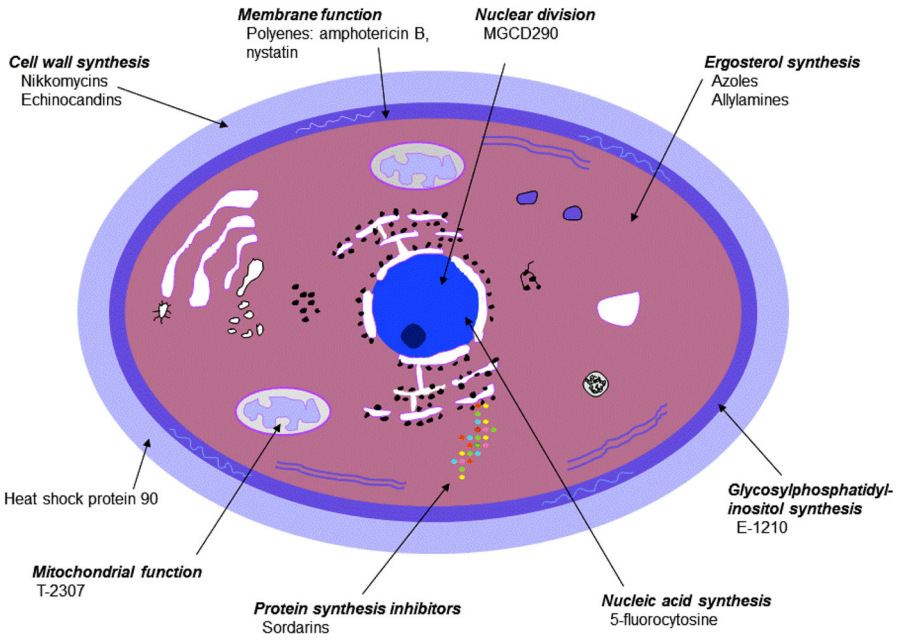

Figure 1.

Site of action in *Candida* spp. of selected antifungal agents.[1]

[1]Modified from figure by Georgopapadakou NH and Walsh TJ [25]

Table 1

Currently available antifungal agents for the treatment of candidemia.

Name	Class	Mechanism of action	Company	FDA approved indications
Fluconazole	Antifungal triazole	Inhibitor of lanosterol 14α-demethylase, leading to inhibition of ergosterol biosynthesis	Pfizer / various	• Treatment of candidemia, disseminated candidiasis, and pneumonia, as well as *Candida* urinary tract infections, peritonitis, oropharyngeal and esophageal candidiasis. • Prophylaxis of candidiasis in patients undergoing bone marrow transplantation.
Voriconazole	Antifungal triazole		Pfizer / various	• Candidemia (nonneutropenic patients) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, wounds, esophageal candidiasis.
Anidulafungin	Echinocandin	Inhibitor of (1→3)-β-D-glucan synthase	Pfizer	• Candidemia, *Candida* intra-abdominal abscess and peritonitis, esophageal candidiasis.
Caspofungin	Echinocandin		Merck	• Treatment of candidemia, *Candida* intra-abdominal abscess and peritonitis, pleural space infection, esophageal candidiasis. • Empirical therapy for presumed fungal infections in febrile neutropenia.
Micafungin	Echinocandin		Astellas Pharma US Inc.	• Treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscess, esophageal candidiasis. • Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.
Amphotericin B deoxycholate	Polyene	Binds ergosterol in the cell membrane leading to changes in membrane permeability	X-GEN Pharmaceuticals Inc.	• Treatment of invasive infections due to *Candida* species.
Amphotericin B lipid complex	Polyene		Sigma-Tau Pharmaceuticals Inc.	• Treatment of invasive fungal infections in patients who are refractory to or intolerant to amphotericin B deoxycholate.
Liposomal amphotericin B	Polyene		Astellas Pharma US Inc.	• Treatment of patients with *Candida* species infections refractory to amphotericin B deoxycholate or in patients with renal impairment. • Empirical therapy for presumed fungal infection in febrile neutropenia.

Table 2

Investigational antifungal agents currently in clinical trials for *Candida* spp. infections.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Isavuconazole	Originator: Basilea Pharmaceutica Licensee: Astellas	Antifungal triazole	Candidemia, other invasive *Candida* spp. infections, Aspergillus infection, Mucormycosis infection	Phase 3	Inhibitor of lanosterol 14α-demethylase
Albaconazole	Originator: Palau Pharma Licensee: Actavis	Antifungal triazole	Vulvovaginal candidiasis, tinea pedis, onychomycosis	Phase 2	Inhibitor of lanosterol 14α-demethylase
MK-3118/ SCY-078	Originator :Scynexis	Derivative of enfumafungin (hemiacetal triterpene glycoside)		Phase 1	Inhibitor of (1→3)-β-D- glucan synthase
VT-1161	Viamet	Not in public domain	Onychomycosis, candidiasis	Phase 2	Inhibitor of lanosterol demethylase (CYP51)
T-2307	Toyama	Arylamidine		Phase 1	Impairment of mitochondrial function

Table 3

Summary of *in vitro* activity of investigational agents against *Candida* spp.

***Candida* spp.**	**N[1]**	**Antifungal agent**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**Reference**
C. albicans	166	isavuconazole	0.002	0.004	0.0005 to 0.016	[44]
	70		≤0.015	0.03	≤0.015 to 2	[43]
	33		0.0007	0.0013	<0.0004 to 0.0026	[42]
	42		0.015	0.015	≤0.008 to 0.03	[39]
	131	albaconazole	≤0.0002	≤0.0002	≤0.0002 to 0.03	[51]
	26		0.125	1	0.015 to 2	[50]
	11	MGCD290	4	16	0.5 to 16	[28]
	29	MK-3118/ SCY-078	0.12	1	0.06 to 2	[60]
	25	VT-1161	≤ 0.03	≤ 0.03	≤ 0.03 to >16	[67]
	40	T-2307	0.0005	0.002	0.00025 to 0.0039	[73]
	291	aminocandin	0.25	0.25	0.06 to 0.5	[92]
	21	E-1210	0.015	0.06	0.008 to 0.12	[26]
	52		≤0.008	≤0.008	≤0.008 to 0.016	[101]
C. glabrata	46	isavuconazole	0.25	0.5	0.063 to 4	[44]
	37		0.25	1	≤0.015 to 2	[43]
	25		0.0039	0.02	0.0011 to 0.64	[42]
	25		0.5	1	0.12 to 8	[39]
	34	albaconazole	0.06	0.12	≤0.0002 to 1	[51]
	17		0.25	1	0.25 to 8	[50]
	14	MGCD290	2	4	0.5 to 4	[28]
	29	MK-3118/ SCY-078	0.5	2	0.5 to 2	[60]
	25	VT-1161	0.06	0.25	≤0.03 to 2	[67]
	25	T-2307	0.0039	0.0078	0.0039 to 0.0078	[73]
	67	aminocandin	0.25	0.25	0.12 to 0.5	[92]
	20	E-1210	0.03	0.06	≤0.008 to 0.25	[26]
	44		0.06	0.06	≤0.008 to 0.06	[101]

Candida spp.	N[1]	Antifungal agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	Reference
C. krusei	11	isavuconazole	0.5	0.5	0.25 to 0.5	[44]
	10		0.0041	0.011		[42]
	8		0.25		0.25 to 0.5	[39]
	12	albaconazole	0.015	0.06	≤0.0002 to 0.06	[51]
	5		0.25	0.25	0.06 to 0.25	[50]
	5	MGCD290	4		2 to 8	[28]
	19	MK-3118/ SCY-078	0.5	2	0.5 to 2	[60]
	16	T-2307	0.001	0.002	0.0005 to 0.002	[73]
	25	aminocandin	0.12	0.5	0.03 to 4	[93]
	4	E-1210			2 to > 32	[101]
C. parapsilosis	23	isavuconazole	0.016	0.031	0.004 to 0.25	[44]
	84		≤0.015	0.03	≤0.015 to 0.125	[43]
	17		0.0015	0.011	<0.0004 to 0.017	[42]
	22		0.03	0.06	≤0.008 to 0.06	[39]
	62	albaconazole	≤ 0.0002	≤ 0.0002	≤ 0.0002 to 0.25	[51]
	15	MK-3118/ SCY-078	0.25	0.5	0.25 to 1	[60]
	10	VT-1161	<0.03	<0.03		[67]
	20	T-2307	0.0005	0.0005	0.00025 to 0.002	[73]
	14	aminocandin	1	2	1 to 2	[92]
	25		1	2	0.03 to 2	[93]
	25	E-1210	0.03	0.06	≤0.008 to 0.5	[26]
	26		≤0.008	0.016	≤0.008 to 0.016	[101]
C. tropicalis	25	isavuconazole	0.031	0.063	0.004 to 0.25	[44]
	15		≤0.015	0.06	≤0.015 to 0.125	[43]
	24		0.0046	0.008	<0.0004 to 0.0094	[42]
	14		0.06	0.5	0.03 to 0.5	[39]
	36	albaconazole	≤ 0.0002	0.03	≤ 0.0002 to 64	[51]
	21	MK-3118/ SCY-078	0.25	1	0.06 to 2	[60]
	20	T-2307	0.0005	0.0005	0.00025 to 0.0005	[73]

Candida spp.	N[1]	Antifungal agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	Reference
	22	aminocandin	0.25	0.25	0.06 to 0.5	[92]
	25		0.25	1	0.06 to 2	[93]
	24	E-1210	0.03	0.06	0.008 to 0.06	[26]
	23		0.016	0.03	≤0.008 to 0.03	[101]
C. guilliermondii	15	isavuconazole	0.051	0.11	0.0069 to 0.18	[42]
	8	albaconazole	≤ 0.0002	≤ 0.0002	≤ 0.0002	[51]
	17	T-2307	0.002	0.0039	0.001 to 0.0039	[73]
	25	aminocandin	0.5	1	0.12 to 1	[93]
C. lusitaniae	17	isavuconazole	0.00059	0.0024	<0.0004 to 0.0025	[42]

[1]Number of isolates.