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Invasive *Candida* infection: epidemiology, clinical and therapeutic aspects of an evolving disease and the role of rezafungin

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ABSTRACT

Introduction: Invasive *Candida* Infections (ICIs) have undergone a series of significant epidemiological, pathophysiological, and clinical changes during the last decades, with a shift toward non-albicans species, an increase in the rate of exogenous infections and clinical manifestations ranging from candidemia to an array of highly invasive and life-threatening clinical syndromes. The long-acting echinocandin rezafungin exhibits potent in-vitro activity against most wild-type and azole-resistant *Candida* spp. including *C.auris*.

Areas covered: The following topics regarding candidemia only and ICIs were reviewed and addressed: i) pathogenesis; ii) epidemiology and temporal evolution of *Candida* species; iii) clinical approach; iv) potential role of the novel long-acting rezafungin in the treatment of ICIs.

Expert opinion: Authors’ expert opinion focused on considering the potential role of rezafungin in the evolving context of ICIs. Rezafungin, which combines a potent in-vitro activity against *Candida* species, including azole-resistant strains and *C.auris*, with a low likelihood of drug–drug interactions and a good safety profile, may revolutionize the treatment of candidemia/ICI. Indeed, it may shorten the length of hospital stays when clinical conditions allow and extend outpatient access to treatment of invasive candidiasis, especially when prolonged treatment duration is expected.

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Candidemia; *Candida auris*; fluconazole resistant; Invasive *Candida* infection (ICI); echinocandin; long-acting; non-albicans *Candida* species; rezafungin

1. Introduction

Like many infectious diseases, Invasive *Candida* Infections (ICIs) have undergone a series of significant epidemiological and clinical changes during the last decades [1]. Indeed, while ICIs were trivial mucocutaneous infections before the advent of cancer chemotherapy, nowadays ICIs range from candidemia to an array of highly invasive infections that cause a variety of life-threatening clinical syndromes [2–4].

Moreover, in recent decades, ICIs have exhibited an increasing incidence rate (from approximately 2.18 cases per 100,000 inhabitants per year in the 1990s to 3.22 in the last decade for candidemia [5]), primarily attributed to the expanding population of high-risk and fragile individuals. This population encompasses not only severely immunocompromised hosts such as hemato-oncological neutropenic patients and solid organ transplant recipients, but also critically ill patients and those with multiple comorbidities admitted to Internal Medicine (IM) wards [6–11].

Although ICIs other than ‘candidemia only’ are mostly abdominal infections, all body sites can be affected by *Candida* and many other deep localizations can be observed

[2,3]. Moreover, the increasing availability of drug-delivery or prosthetic devices (e.g. long-term central venous catheters) has resulted in this microorganism being involved in a variety of foreign body infections that significantly added to the complexity of ICI clinical manifestations [12]. As a paradigmatic example, *Candida* spp represented up to 27% of all central-line – associated bloodstream infection (CLABSI) in US adult ICUs (from 0.216 to 0.281 density rates per 1,000 central-line days from 2011 to 2017) [13].

In this scenario, *Candida albicans* remains the most frequent cause of ICI (ranging from approximately 40% to 60% [1,14,15]), but the prevalence of other species, some of which exhibiting alarming features of antimicrobial resistance, has been increasing over time [1,5,16].

Ultimately, ICIs, particularly when manifesting as candidemia, are still associated with unacceptably high crude mortality rates (approximately 40% overall) [5] and significant increases in healthcare costs, underscoring the importance of early diagnosis and treatment [17]. On the other hand, in recent years the antifungal drug arsenal has been enriched with new agents. Among these, rezafungin is a long-acting

Article highlights

- The advances in healthcare, the evolution of patient risk factors and the ability of some *Candida* species to spread within the hospital environment have led to a change in the epidemiology of Invasive *Candida* Infections (ICIs) in the last decades.
- The shift toward *non-albicans* species may be influenced by the different and evolving pathophysiology behind the development of candidemia/ICI.
- Rezafungin is a novel long-acting echinocandin with a potent *in-vitro* activity against most *Candida* spp., including those azole-resistant and *Candida auris*.
- Rezafungin combines the strengths of the echinocandin class with a prolonged elimination half-life, a low likelihood of drug–drug interactions and a robust safety profile.
- Registrative studies showed non-inferiority of rezafungin to caspofungin, with earlier candidemia clearance in patients on rezafungin than those receiving caspofungin.
- Compared to caspofungin, survivors hospitalized in the ICU receiving rezafungin showed a reduction in ICU length of stay.
- Rezafungin may allow earlier hospital discharge and management of complex fungal infections in an outpatient setting, especially when prolonged treatment duration is expected.
- A possible, although not yet quantifiable, reduction in the costs associated with ICIs and length of hospital stay may be obtained with rezafungin.

echinocandin that might have a favorable impact on the treatment of new emerging resistant *Candida* species as well as on healthcare costs [18,19].

Herein, we reviewed the recent changes in the epidemiology and clinical features of ICIs as well as the improvements brought by new tools for the diagnosis of these infections. Finally, we also provided some insights on the potential role of the long-acting echinocandin rezafungin in this complex scenario.

2. Background

This brief paragraph is focused on how *Candida* spp enter the bloodstream and/or cause infections (endogenous vs exogenous route), while a complete review of the pathogenesis of ICIs is out of the scope of this review.

ICIs commonly refer to bloodstream infections caused by *Candida* species. These infections typically occur when *Candida* organisms breach the damaged intestinal barrier, which can be caused by various factors such as cancer chemotherapy, surgery, bacterial toxins, and local vascular perfusion disorders (endogenous route) (Figure 1) [4]. When these microorganisms enter the bloodstream, the resulting candidemia may be cleared by antifungal therapy and intravascular catheter removal or may persist long enough to cause endophthalmitis, pyelonephritis, peritonitis and intra-abdominal infections, meningitis, encephalitis, endocarditis, osteoarthritis, pneumonia, empyema, mediastinitis, and pericarditis [2,3]. The endogenous route mostly applies for *C. albicans*, *Candida tropicalis*, *Candida glabrata* (*Nakaseomyces glabrata*), *Candida lusitanae* (*Clavispora lusitanae*), *Candida parapsilosis* and, to a lesser extent, *Candida krusei* (*Pichia kudriavzevii*) (Table 1).

New advancements in the pathophysiology of *Candida* have shown that this microorganism may also cause infections via an exogenous route, that is through healthcare workers' hands or central line colonization and subsequent spread into the blood (Figure 1). This is especially true for *Candida auris*, *C. parapsilosis*, *Candida lusitanae* (*C. lusitanae*) and *Candida haemulonii*, which often cause nosocomial outbreaks, frequently due to species resistant to antifungals and for which infection control measures are of paramount importance [16,20] (Table 1).

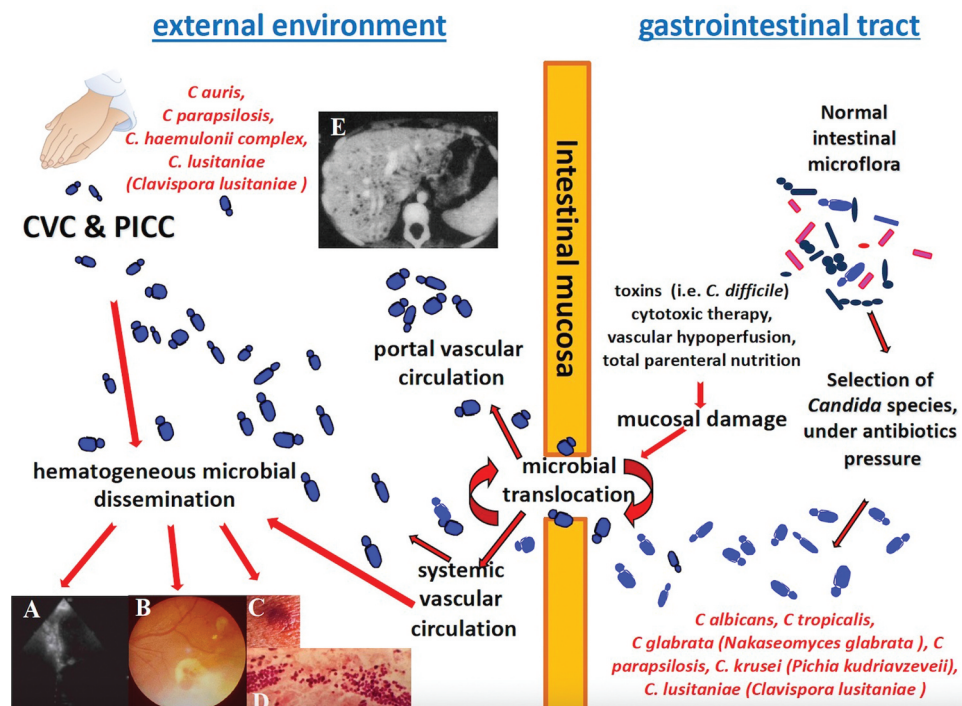


Figure 1. Pathogenesis and hematogenous routes of *Candida* species bloodstream dissemination with possible secondary infections as endocarditis (A), retinitis (B), skin fungal vasculitis (C) with macular/papular lesion (D) and multifocal hepatitis (E). CVC: central venous catheter; PICC: peripherally inserted central catheter.

Table 1. Exogenous versus endogenous route of invasive *Candida* infection: differences in etiologies, epidemiology, and antifungal resistance.

Feature	Endogenous route	Exogenous route
Involved <i>Candida</i> species	<i>C. albicans</i> , <i>C. glabrata</i> (<i>Nakaseomyces glabrata</i>), <i>Candida lusitanae</i> (<i>Clavispora lusitanae</i>), <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. krusei</i>	<i>C. auris</i> , <i>C. haemulonii</i> , <i>C. parapsilosis</i> , <i>Candida lusitanae</i> (<i>Clavispora lusitanae</i>)
Antifungal resistance	Uncommon*	Common
Habitat	Commensal of the gastrointestinal tract	Commensal of the skin
Healthcare-associated infection	Uncommon	Common
Environmental contamination	Uncommon	Common

Note: **C. glabrata* is the species more frequently associated to azole and echinocandin resistance.

Considering *C. parapsilosis* as a possible cause of infection also through the endogenous route is justified by the presence of this species as a causative agent of hepatosplenic candidiasis [21], the most common form of chronic disseminated candidiasis (CDC), which is often associated with negative blood cultures since hematogenous dissemination is limited to the portal vein system [22].

For the purpose of this article, following recently adopted definitions [23], we described the epidemiology, clinical aspects and therapy of candidemia without apparent secondary localizations ('candidemia only') separately from deep-seated ICIs, whether or not associated with *Candida* species isolated from the bloodstream.

3. Epidemiology of candidemia only

Candidemia is one of the most common healthcare-associated invasive fungal infections, with incidence varying according to geographical region, local epidemiology, and outbreak occurrence. A recent report indicates an overall pooled incidence rate of 3.88 cases per 100,000 inhabitants per year (ranging from 1.0 to 10.4). There is an observed increasing trend in incidence rates from the 1990s (median 2.18) compared to subsequent periods (median 4.67 in the year 2000–2010 and 3.22 in the last decade) [5]. This increased incidence may be due to the increase in high-risk populations, such as critically ill and elderly patients and those with multiple comorbidities, along with nosocomial outbreaks.

Although the majority of the candidemia cases are hospital-acquired, with a reported incidence of 0.17–2.7 episodes per 1,000 discharges [24], community-acquired candidemia is an emerging condition driven by the increasing use of long-term intravenous devices such as tunneled intravascular and peripherally-inserted central catheters [3].

While *C. albicans* continues to be the most prevalent *Candida* species in both the adult and pediatric population, there has been a notable shift in species distribution over the past few decades. Specifically, there have been a decrease in the proportion of *C. albicans* and an increase in *C. parapsilosis sensu lato* and *C. glabrata* (*N. glabrata*). This change can be attributed to factors such as the use of antifungal medications, specific risk factors in patients such as immunosuppression, severity of the underlying conditions, chronic respiratory diseases, or nosocomial outbreaks [1,5]. This finding has important clinical implications, as *C. parapsilosis* and *C. glabrata*

(*N. glabrata*) may show decreased susceptibility to echinocandins and azoles, respectively [1].

Mareković and colleagues [1] reported the distribution typical for Southern Europe, with *C. parapsilosis* ranking second and *C. glabrata* (*N. glabrata*) third in frequency. By contrast, in Northern Europe, United States, and Australia, *C. albicans* has been gradually replaced by *C. glabrata* (*N. glabrata*), ranking second in these geographical areas. Likewise, in the FUNGINOS survey conducted in Switzerland, Adam and colleagues observed a significant decrease from 60% to 53% in the proportion of *C. albicans*. At the same time, *C. glabrata* (*N. glabrata*) increased from 18% to 27%, particularly in the age group of 18–40 years and individuals above 65 years old. On the other hand, the frequency of other non-*albicans* *Candida* (NAC) species remained stable throughout the study period [25].

A previous epidemiological study in high-risk patients with hematological malignancies by the Epidemiological Surveillance of Infections in Hemopathies (SEIFEM) group in Italy demonstrated that NACs accounted for 67% of the candidemia episodes (133 overall) and *C. albicans* for 33% only. The most frequent non-*albicans* species were *C. parapsilosis*, *C. glabrata* (*N. glabrata*), *C. krusei* (*P. kudriavzevii*) (intrinsically resistant to fluconazole) and *C. tropicalis*. Strains resistant to at least one azole were 18%, mostly represented by NAC, with only one *C. parapsilosis* strain resistant to amphotericin B (AmB) and none to echinocandins [11].

In IM wards, candidemia is a growing concern, as many more patients have risk factors for candidemia than in the past. In this setting, the most frequent pathogen was *C. albicans* (62%), followed by *C. parapsilosis* (17%), *C. glabrata* (*N. glabrata*) (13%), and *C. tropicalis* (5%), suggesting that the distribution in these patients is the same as in the past, at least in Italy [14].

Furthermore, patients with early-onset candidemia may present with a new risk factor, represented by Chronic Obstructive Pulmonary Disease (COPD) [26], and with significantly higher mortality due to treatment delays.

Clinical infections caused by NAC exceed those caused by *C. albicans* also in the Asia-Pacific region, with a high incidence of *C. tropicalis* [27]. A nation-wide multicenter surveillance of NAC blood isolates was performed at seven university hospitals in Korea between 2010 and 2016: authors found that *C. tropicalis* was the most common NAC species (36.4%), followed by *C. glabrata* (*N. glabrata*) (28.5%), *C. parapsilosis* (24.7%), and *C. krusei* (*P. kudriavzevii*) (2.6%).

Compared the previous 6 years, the proportion of *C. glabrata* (*N. glabrata*) increased (from 21.3% to 28.5%) while that of *C. parapsilosis* decreased (from 36.5% to 24.7%). Fluconazole non-susceptible isolates accounted for 38.6% of isolates [28]. Similar results have been reported in a multi-center prospective observational study carried out in 13 centers from Brunei, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam, where authors showed that *non-albicans* species were the most common isolates from bloodstream infections, with *C. tropicalis* as the predominant species. Overall, the most common species were *C. albicans* (35.9%), *C. tropicalis* (30.7%), *C. parapsilosis* (15.7%), and *C. glabrata* (*N. glabrata*) (13.6%) [29]. Slightly differently, distribution of candidemia in a Malaysian tertiary care hospital revealed predominance of *C. parapsilosis* as the most common agent of candidemia (29.2%), followed by *C. albicans* (20.1%), *C. tropicalis* (18.7%), *C. glabrata* (*N. glabrata*) (6.0%) [30].

Among agents of candidemia, diverse NAC species present some specific features which reflect different pathophysiology (Figure 1) and influence the observed differences in epidemiology.

Indeed, *C. parapsilosis* complex is a biofilm-producing and environmental contaminant species able to colonize central venous catheters (CVCs) and the hands of healthcare workers, causing systemic infections not only by the endogenous but also by the exogenous route (Figure 1). These features may contribute to clonal outbreaks [31] and underline the need of implementing measures to avoid the nosocomial spread of this species [32].

Moreover, the ability of *C. parapsilosis* to produce biofilm seems to be related to an increase in virulence and to a worse outcome when these high-producing biofilm isolates are involved in candidemia [33].

Antifungal susceptibility testing commonly shows borderline susceptibility to echinocandins; importantly, although fluconazole resistance was generally considered to be uncommon, up to one-third and one-quarter of the isolates recently showed resistance to fluconazole or voriconazole, respectively [31]. A recent paper investigating candidemia in SARS-CoV-2 critically ill patients showed that the incidence of candidemia was significantly higher in critically ill COVID-19 patients on VV-ECMO than in critically ill COVID-19 patients who did not meet the criteria for VV-ECMO (16/45, 36% vs 13/93, 14%, respectively), and that *C. parapsilosis* accounted for the majority of the candidemia events [34]. A 6-year retrospective study performed in China showed that *C. parapsilosis* was the predominant pathogen in patients with persistent candidemia [35].

C. tropicalis is the species with the highest mortality rates in patients with candidemia, is increasingly reported in frequency and shows growing resistance to fluconazole [36].

C. glabrata (*N. glabrata*) shows higher echinocandin resistance than other *Candida* species (1.7–3.5%), possibly due to the preferential use of echinocandins for the treatment of these infections, encouraged by increasing azole resistance in this species, ranging from 5.6% to 15.7% [27,37,38]. Furthermore, *C. glabrata* (*N. glabrata*) showed a high propensity to readily mutate *in vivo*, especially in cases of intra-

abdominal infections, where source control may be delayed or drug underexposure may be present [37,39].

Most commonly, *C. tropicalis* and *C. glabrata* (*N. glabrata*) cause candidemia after passing through damaged intestinal barrier (Figure 1).

However, the most alarming agent for candidemia nowadays is *C. auris*, firstly reported in 2009 from the external ear canal of a patient in Japan and belonging to the critical priority group according to the recent WHO fungal priority pathogens list [40,41]. *C. auris* is characterized by several distinct features. Firstly, it has high transmissibility, having the ability to potentially colonize patients indefinitely and exhibiting resistance in the healthcare environment. This is due to prolonged survival on surfaces and its ability to resist common disinfectants [42] (Figure 1). Secondly, the identification of *C. auris* with conventional biochemical and microbiological techniques presents challenges [43]. Thirdly, *C. auris* demonstrates a high rate of antifungal resistance, with almost universal resistance to fluconazole (90%), frequent resistance to AmB (30%), and the potential for resistance to echinocandins (5%), particularly in cases of pre-exposure. The emergence of pan-drug-resistance in *C. auris* is indeed alarming. Isolates resistant to three major classes of antifungal agents have recently been described in the US and other countries [44–46]. A healthcare transmission of pan-resistant and echinocandin-resistant *C. auris* has been reported [47], while a recent study analyzed the genome and drug-resistance profile of 19 isolates of *C. auris* collected over 72 days from a multi-visceral transplant recipient with refractory fungal peritonitis. Authors found that two *C. auris* isolates were resistant to four major classes of antifungal agents (azoles, echinocandins, polyene, and flucytosine) while several other strains exhibited resistance to three major drug classes [48].

Lastly, *C. auris* has an unprecedented capacity to cause nosocomial outbreaks, which are difficult to control in many countries and can persist for extended periods, even years [49,50].

These outbreaks, frequently reported during the COVID-19 pandemic, occurred through environmental reservoirs (sometimes difficult to pinpoint, such as thermometers), extensive colonization in humans detected in axilla, groin, nares, rectum, and high rate of horizontal transmission [51–53]. In Italy, the Liguria region reported a *C. auris* outbreak with at least 277 cases in eight healthcare facilities. The first of these cases was detected in one hospital in July 2019, and cases sporadically continued to occur in the same hospital [54,55]. In February 2020, *C. auris* was detected in an intensive care unit (ICU) dedicated to patients with severe COVID-19 in the same hospital, with a subsequent increase in cases throughout 2020 and 2021. Another 11 cases have occurred in facilities in the neighboring Emilia-Romagna region so far [56]. *C. auris* infections have been described by a number of countries in Asia. Interestingly, the first *C. auris* candidemia was reported from a retrospective analysis of South Korean unidentified *Candida* isolates using rDNA sequencing. Later on, several reports and outbreaks of *C. auris* infections have been described in China, Hong Kong, and Taiwan [57].

While a significantly higher risk for microbiologic recurrence within 60 days of completion of antifungal therapy was observed in *C. auris* patients, the outcome of patients with *C. auris* candidemia was similar to patients with candidemia due to other species [58,59].

Although still considered rare, the emergent *C. haemulonii* species complex (*C. haemulonii sensu stricto*, *Candida duobushaemulonii*, and *Candida haemulonii* var. *vulnera*) has been increasingly reported worldwide over the last 10 years, especially in patients with previous antimicrobial/antifungal therapy, those with malignant tumors, organ transplants, diabetes mellitus, and vascular diseases. Outbreaks in neonatal intensive care units have been reported in Korea and India, highlighting that this species may reach the blood by the exogenous route [60]. Furthermore, the *C. haemulonii* species complex shows increased resistance to the available antifungal drugs such as fluconazole and AmB [61].

Candida lusitanae (*C. lusitanae*), generally considered a low-frequency emerging pathogen, has been associated with peritonitis, meningitis, and urinary tract infections [62] and can cause fatal infections in immunocompromised patients [63]. In this setting, while representing approximately 1.3% of all candidemia episodes among cancer patients, *C. lusitanae* caused up to 28% and 19% of fungemia and breakthrough fungemia caused by uncommon *Candida* species (19/68 and 7/37, respectively), with an overall mortality of 53% [64]. Additionally, *C. lusitanae* has been implicated in nosocomial acquisition [20] and person-to-person transmission [65]. Most importantly, *C. lusitanae* is known for its ability to acquire *in vivo* drug resistance under antifungal treatment and multidrug resistance has also been reported [66]. Very recently, the emergence of *C. lusitanae* isolates with decreased micafungin susceptibility emerged during micafungin monotherapy was shown; furthermore, for the first time, cross-resistance to fluconazole despite no history of drug use was observed [67].

Candida palmioleophila, often misidentified as *Meyerozyma guilliermondii* (*Candida guilliermondii*) or *Candida famata*, is an emerging pathogen in Denmark [68]. Isolates of this species are still susceptible to echinocandins and resistant to azoles, especially fluconazole. Recently, two strains, misidentified as *C. albicans*, were described in the Campania region in Italy [69].

4. Clinical approach to candidemia

The decision whether to initiate antifungal treatment for candidemia depends on several considerations, including epidemiology (community vs. hospital-acquired), setting (ICU, IM), risk factors (immunosuppression, severity of the underlying conditions, chronic respiratory diseases), severity of infection (septic shock), possibility of source control and treatment strategies (empiric, preemptive or targeted strategies, de-escalation) [70–72].

However, one of the main drivers for better outcomes is represented by early antifungal treatment [73,74]. Indeed, a retrospective cohort of 230 patients with candidemia showed that mortality was lower if fluconazole was started on the same day of the index culture than if started later (15%

vs 24% vs 37% vs 41% if started at day 1, day 2 or day 3 or later, respectively) [75]. On the other hand, a > 12-hour delay in antifungal therapy initiation from the time of blood sample collection increased mortality (33.1% vs 11.1%) [76], while receiving antifungal treatment within 72 h from index blood culture had a significant benefit on mortality (27% versus 40%) [73].

Likewise, in patients with septic shock and candidemia, delayed antifungal treatment and failure to achieve source control were independently associated with hospital mortality [74].

The decision to initiate early antifungal therapy should be guided by the use of biomarkers and/or risk factor-based prediction rules. This approach aims to identify patients at the highest risk of developing candidemia and, conversely, to avoid unnecessary antifungal treatment when results are negative. While blood cultures are considered the gold standard for diagnosing candidemia, their overall sensitivity is approximately 50% (ranging from 21% to 71%). Furthermore, blood cultures may require a significant amount of time to yield positive results, potentially leading to delays in initiating appropriate antifungal treatment [77,78].

As additional tools, non-culture-based assays may aid in guiding the diagnosis of candidemia. 1–3 β -D-glucan (BDG) has a pooled sensitivity and specificity of 80% and 82%, respectively, with the most accurate cutoff value >80 pg/mL [79–81]. However, its main advantage is its high negative predictive value (98.7%), allowing early interruption of antifungal therapy if started empirically based on clinical suspicion and/or prediction scores [82]. There are experiences and proposals for different cutoffs in IM Wards [83].

T2Candida is a novel nanodiagnostic panel that uses T2 magnetic resonance (T2MR) and a dedicated instrument (T2Dx Instrument) to detect *Candida* directly in whole blood samples [84,85]. This instrument is able to identify the five most common *Candida* species [*C. albicans*, *C. glabrata* (*N. glabrata*), *C. parapsilosis*, *C. tropicalis*, *C. krusei* (*P. kudriavzevii*)] [86] with an estimated sensitivity and specificity of 91.1% and 99.4%, respectively [87]. Interestingly, T2Candida can detect candidemia in 3–5 hrs., thus reducing the time to a negative result by some days. Along with its high negative predictive value (approximately 100%), T2 *Candida* negative results may suggest that antifungal therapy can be early withdrawn. In fact, stopping antifungal treatment when no longer necessary counteracts the detrimental effects of over-treatment in terms of selective pressure with a shift to resistant *Candida* species, emergence of resistance and increased costs [88,89].

Clinical prediction rules/scores have also been proposed for the identification of patients at high risk of candidemia necessitating early antifungal treatment and include, although not limited to, the Ostrosky-Zeichner or the *Candida* scores [90–93]. Despite differences in sensitivity, they have high negative predictive value, ranging from 97% to 99.4% [78]. Again, this feature allows not to start or early discontinue antifungal treatment when not necessary.

Several updated detailed guidelines for candidemia treatment can support healthcare professionals [70,72,94]. Initial treatment with echinocandins is strongly recommended either in neutropenic or non-neutropenic candidemia patients, in

more severe patients or where biofilm activity is needed [10,94,95]. This recommendation is mainly based on trials comparing caspofungin or micafungin versus AmB (deoxycholate or liposomal, respectively), showing similar effectiveness but fewer adverse events [96,97], or a randomized controlled trial showing non-inferiority of anidulafungin versus fluconazole [98]. A subsequent *post-hoc* analysis focused on *C. albicans* showed that global response was significantly better for anidulafungin than fluconazole and that anidulafungin was associated with significantly faster clearance of blood cultures [99]. Furthermore, in approximately 2,000 patients from seven trials (three including patients with candidemia, four including patients with either candidemia or ICIs), echinocandins were associated with a significantly lower 30-day mortality rate than azoles or AmB [100]. Notwithstanding the lower *in-vitro* activity vs. *C. parapsilosis*, echinocandins were associated with clinical effectiveness [101,102].

The echinocandin armamentarium currently available is being reinforced by the new long-acting, once weekly administered, rezafungin [103], which demonstrated non-inferiority to caspofungin in the treatment of candidemia or ICIs regarding the primary endpoints of day-14 global cure (European Medicine Agency, EMA) and 30-day all-cause mortality (Food and Drugs Administration, FDA) [23].

Compared to echinocandins, azoles may have advantages as a first-line therapy in stable patients if *C. krusei* (*P. kudriavzevii*) or *C. glabrata* (*N. glabrata*) are not considered and in the absence of immunosuppression [10,94].

Interestingly, in patients admitted to IM wards and with septic shock due to candidemia, there are conflicting reports concerning echinocandin effectiveness over fluconazole, perhaps related to methodology, patient clinical complexity, frequencies of septic shock and treatment delays [103–107]. Indeed, the initial echinocandin therapy does not seem to impact the outcome of candidemia patients with septic shock, while the benefit over fluconazole was mainly observed in non-septic patients [108]. Similar results were obtained in a Spanish prospective study showing that both empirical and targeted treatment with fluconazole was not associated with increased 30-day mortality compared to echinocandins [108]. On the other hand, echinocandins were associated with significantly higher survival as a definitive therapy in IM wards [104].

Among azoles, isavuconazole should not be used in treating candidemia because of the excess of mortality observed in the trial vs. caspofungin [106].

AmB deoxycholate or, preferably, lipid and especially liposomal formulations are fungicidal, active against *Candida* biofilm and able to penetrate the blood-brain barrier [95,109]. Despite these promising features, a recent meta-analysis revealed that the initial treatment of candidemia with echinocandins had a reduced mortality rate compared to polyenes [95]. Furthermore, AmB use may be limited by the risk of nephrotoxicity and varying sensitivity of *C. auris*.

Echinocandins are the current preferred treatment options for *C. auris* infections [16]. However, emergence of resistance and pan-fungal resistance have been reported [16,48,55]. Amphotericin B may be an alternative to echinocandins since

it has fungicidal activity and good biofilm penetration. Its main drawbacks include a relatively high rate of resistance in some *C. auris* clades, such as Clade I, potentially explaining the therapeutic failures observed in some clinical cases [110]. Moreover, a case of *in-vivo* development of high-level AmB resistance during therapy was recently reported, and a novel mutation mechanism in the *C. auris* sterol-methyltransferase gene *ERG6* was found [111]. Delayed (or not executed) source control was another risk factor for the development of resistance to antifungals in *C. auris* [49]. While some studies have reported susceptibility to azoles other than fluconazole, there are currently no established breakpoints for interpreting *in vitro* MIC values. In complex cases, especially when dealing with persistent infections or failure of echinocandins, alternative treatment options may be necessary. These may involve the use of combination therapies based on *in-vitro* and *in vivo* experiments such as colistin plus echinocandins [112], isavuconazole plus echinocandins [113,114], posaconazole plus caspofungin [115], isavuconazole plus colistin [116], or novel agents, such as rezafungin (which has *in vitro* activity against strains resistant to other echinocandins), ibrexafungerp, or fosmanogepix may be considered [5,117–120].

The correct choice of the antifungal should be accompanied by the demonstration of negative blood cultures if previously positive, by at least 14 days of effective treatment and by appropriate de-escalation strategies, depending on clinical stability, isolates and guidelines, 3-to-7 days after the beginning of therapy, usually from echinocandins to fluconazole. As a matter of fact, it is safe to stepdown therapy to oral fluconazole or voriconazole as soon as patients are clinically stable and blood cultures are negative [106,121]. Nevertheless, early (day 5) de-escalation to fluconazole was only performed in a minority of cases despite no negative impact on patients' outcome (in only 23% out of 235 eligible patients in a cohort from 3 RCTs including 1023 patients) [122]. Compared to fluconazole, voriconazole is active against *C. guilliermondii*, *C. glabrata* (*N. glabrata*), and *C. krusei* (*P. kudriavzevii*) with reduced susceptibility, or resistance, to fluconazole. The switch to oral azoles may undoubtedly present the advantage of allowing patient discharge, if feasible, while long-acting rezafungin can be a valid alternative in the case of azole resistance.

5. Epidemiology and clinical aspects of ICIs other than candidemia only

The epidemiology of ICIs (with or without concomitant candidemia) is still a difficult and unsolved enigma for the scientific community, due to variability in definitions, difficulties in differentiating colonization from infection and diagnostic issues [123]. Indeed, only 17% of cases of deep-seated candidiasis were detected by blood cultures [124], suggesting that many cases of ICIs could be under diagnosed [125].

ICIs are most commonly observed in the ICU setting, where up to two-thirds of patients have concomitant candidemia, while 80% of patients without candidemia have intra-abdominal candidiasis (IAC) [126,127]. IAC accounts for most deep-seated cases, with approximately 30% occurring in

critical care settings [126,127]. A multinational retrospective study conducted in several European ICUs showed a cumulative incidence of 7.07 episodes per 1,000 ICU admissions (5.52 and 1.84 episodes per 1,000 ICU admissions for candidemia and IAC, respectively). *C. albicans* was the most frequently isolated species (57%), followed by *C. glabrata* (*N. glabrata*) (21%) and *C. parapsilosis* (13%) [15]. Of note, significant between-center variability and increased incidence over time were observed. Understanding ICI epidemiology in IM units is even more challenging, with a recent Italian study showing an overall incidence of 1.89 cases/1,000 hospital admissions [14].

In general, ICIs other than 'candidemia only' include a variety of deep-seated infections that may be caused by fungal seeding in various organs as a consequence of hematogenous spread from a distant infectious focus [21,22,128–133] or by direct contamination during surgery, trauma, or extension from a contiguous infected site [123,130,134]. The majority of ICIs other than candidemia present the classical risk factors for invasive fungal diseases, such as previous or concomitant antibiotic therapy and immunosuppression often mediated by steroid therapy [123,130]. Table 2 reports additional specific factors for each type of ICI [21,22,128,129,132,133,138–141,144–152,154–158]. Along the same line, the spectrum of the *Candida* species involved varies according to the different type of infection. In general, *C. albicans* remains the most common pathogen, followed by *C. glabrata* (*N. glabrata*) and *C. tropicalis* in many deep-seated infections that usually represent a source of secondary candidemia, especially intra-abdominal and urinary tract infections [135,136,138–140,158]. On the other hand, *C. parapsilosis* is the second cause of all intravascular infections, shunt-related meningitis, and the leading cause of trauma or fracture-related *Candida* infections [134,141,144,145]. Of interest, *C. dubliniensis* may be considered an emerging pathogen since it has represented, in recent case series, not only an increasing cause of endophthalmitis and esophagitis, particularly in cases of infection related to intravenous drug addiction, but also a leading cause of *Candida* meningitis not related to intraventricular devices [133,147,148].

Some infections usually manifest with an acute onset, with septic shock being a possible ominous component of the initial clinical picture. It typically occurs in patients with ascending or emphysematous pyelonephritis [140], but also in many intrabdominal infections [135,158] or serious intravascular infections [130–132] such as peripheral vein septic thrombophlebitis [145] or central vein septic thrombosis [146]. In these instances, prompt adequate antifungal therapy, either directed against the offending pathogen or in terms of antimicrobial exposure in the infection sites, and surgical source control (when indicated, as outlined in Table 2) are crucial for patient survival.

Other infections have a very insidious and misleading presentation. A typical example is that of *Candida* meningitis not related to intraventricular devices [133,147,148]: this infection, nowadays more commonly sustained by *C. dubliniensis*, has an indolent course that mimics tubercular meningitis, and seems to be a late complication of a previous, apparently resolved, nosocomial candidemia or a side effect of intravenous drug addiction [133,147,148]. Similarly, *Candida* prosthetic valve endocarditis is a typical biofilm-related infection that may be

acquired during a candidemia episode in the early post cardio-surgery period [132,142]: despite apparent cure with standard antifungal therapy, *Candida* seeding on the prosthetic valve and surrounding endocardium persists and the infection manifests insidiously even after more than 1 year [132,143]. Under these circumstances, both the prompt recognition of the clinical syndrome and a correct approach to the microbiological diagnosis, along with the use of biomarkers, are of paramount importance for optimal management.

Despite being a very rare disease, hepatosplenic candidiasis is the most frequent form of chronic disseminated candidiasis (CDC) and typically occurs in patients with hematological malignancies and long-lasting neutropenia [19,20,153]. CDC is now considered as a fungal immune reconstitution inflammatory syndrome (IRIS), because of the lack of microbiologically active lesions (often documented by negative cultures of liver biopsies and rare documentation of recent candidemia episodes), contrasting with a major inflammatory reaction and high levels of immune activation [153]. Following the hypothesis that CDC may be driven by IRIS, the use of concomitant glucocorticosteroids may be considered for the management of this condition, along with long-term antifungals [22].

In most ICIs other than candidemia, a proper therapeutic approach includes an initial treatment regimen, usually with intravenous fungicidal and effective anti-biofilm agents such as echinocandins and liposomal AmB [94,137]. Being hydrophilic agents, the former may have poor penetration across the blood-brain barrier, in the vitreous, and in the mesothelial cavities. Consequently, in the presence of deep-seated infections involving these body sites, fluconazole, voriconazole or liposomal AmB may be valuable alternatives or add-on therapies [159]. In any case, as soon as clinical improvement, and clearance of a possible concomitant candidemia have been achieved with the initial treatment, intravenous or oral azoles, usually fluconazole or voriconazole, are the agents of choice for maintenance therapy [160]. Various forms of source control are of paramount importance in many instances: surgical or percutaneous drainage or debridement, such as in secondary peritonitis or intrabdominal abscesses [158,161], and device removal with or without replacement, such as in prosthetic valve endocarditis or shunt-related meningitis [94,132,150]. Peripheral vein thrombophlebitis, an infectious process that involves adventitia, intima, and adjacent thrombus, requires debridement or phlebotomy in most instances [144]. On the other hand, in central vein septic thrombosis, which involves almost only the thrombus, anticoagulation, and antifungal therapy allow clinical cure in most cases [145,161].

In certain cases, maintenance antifungal therapy with oral azoles may be prolonged from 2 to 12 months, as in cases of hepatosplenic candidiasis [141], osteomyelitis or disc space infection [154–156]. Likewise, chronic suppressive therapy with oral azoles may be required in selected cases of intravascular device infections (prosthetic valve endocarditis, aortic graft infections, and cardiac implantable electronic device infections), where surgical device removal and replacement cannot be performed [132]. In these cases, other therapeutic options should be considered when oral antifungal treatment is not suitable, as in the case of azole resistance. A reasonable

Table 2. Underlying diseases and conditions, main *Candida* species involved, therapy options and management of different ICIs.

Type of infection	Reference	Underlying diseases/conditions	Main <i>Candida</i> spp. involved	Clinical onset	Initial therapy [^] (§ indicates surgery)	Maintenance therapy [^] (or long term/CS therapy) [total course: wks] ^{^,^}
Primary peritonitis	[135,136]	ESLD, nephrotic syndrome, peritoneal dialysis	<i>C. albicans</i> > <i>C. krusei</i> (<i>Pichia kudriavzevii</i>) > <i>C. glabrata</i> (<i>Nakaseomyces glabrata</i>)	Acute	echino+fluco or L ampho B	fluco [total course: 2–4 wks]
Secondary peritonitis	[135–137]	abdominal trauma or surgery, abnormal biliary tract	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i>	Acute	echino+fluco, fluco or L ampho B §	fluco [total course: 2–4 wks]
Intradominal abscess	[135–137]	abnormalities of bile and pancreas ducts	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i>	acute/subacute	fluco, L-ampho B, echino ±azole §	fluco [total course: 2–4 wks]
Infected pancreas necrosis	[135–137]	chronic pancreatitis, abnormal biliary tract	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	Acute	echino± fluco, L ampho B§	fluco [total course: 2–4 wks]
Ascending pyelonephritis	[138]	older age, female, DM, antibiotic use, urinary tract obstruction & surgery, drainage devices, steroids us	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i>	Acute	fluco or D ampho B, L ampho B or echino in selected cases	fluco [total course: 2 wks]
Renal fungus ball	[139]	same as ascending pyelonephritis	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i>	acute & recurrent	same as ascending pyelonephritis §	fluco [total course: 2 wks]
Emphysematous pyelonephritis	[140]	same as ascending pyelonephritis	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i>	acute/fulminant	same as ascending pyelonephritis §	fluco [total course: 2 wks]
Right sided NVE	[131,132,141,142]	abdominal surgery, IVDA, CIED	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	acute/subacute	echino, L ampho B, fluco	fluco [total course: 6 wks]*
Left sided NVE	[131,132,141,142]	previous NVE, abdominal surgery, IVDA, malignancy	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	acute/subacute	echino±L ampho B §	fluco [total course: 6 months or CS therapy]*
PVE	[131,132,141,143]	post valve replacement candidemia	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	subacute/chronic	L ampho B±echino. §	fluco [total course: 6 months or CS therapy]*
PV-thrombophlebitis	[144,145]	long term vein cannulation, IVDA	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. tropicalis</i>	Acute	echino, L ampho B §	fluco [total course: 2 wks after first negative FUBC]
CV-septic thrombosis	[146]	Long term CVC; abdominal surgery, polytrauma	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	Acute	echino, L ampho B, & anticoagulation §°	fluco [total course: 2 wks after first negative FUBC]
meningitis	[133,147,148]	previous candidemia, SOT, ESLD, IVAD	<i>C. dubliniensis</i> > <i>C. albicans</i> > other spp.	chronic	vorico or fluco, L ampho B	vorico or fluco [total course: 4–6 wks]
Brain abscess	[149]	previous candidemia, SOT, ESLD, IVAD	<i>C. albicans</i> > other spp.	subacute/chronic	L amphoB ±5FC, vorico or fluco, B	vorico or fluco [total course: 6–12 months]
shunt related meningitis	[150]	previous pneumonia or brain infection, steroid use	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	subacute/chronic	vorico or fluco; L ampho B ±5FC §	vorico or fluco [total course: 2–4wks]
Endophthalmitis	[128,129,131]	usual risk factor of candidemia (CVC, TPN, etc), IVDA	<i>C. albicans</i> > <i>C. dubliniensis</i> > <i>C. tropicalis</i>	subacute/chronic	fluco^or vorico, L ampho B	vorico or fluco^ [total course: at least 2–4wks]
Esophagitis	[151,152]	HIV, chronic steroid therapy, alcohol consumption, chronic renal disease	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>) > <i>C. tropicalis</i> & <i>C. dubliniensis</i>	acute/subacute	fluco, posaco & vorico, echino, L ampho B	fluco, vorico or posaco [total course: at least 2–4wks]**

(Continued)

Table 2. (Continued).

Type of infection	Reference	Underlying diseases/conditions	Main <i>Candida</i> spp. involved	Clinical onset	Initial therapy [^] (\$ indicates surgery)	Maintenance therapy [^] (or long term/CS therapy) [total course: wks] ^{^,^}
Hepatosplenic infection	[21,22,153]	prolonged chemotherapy induced granulocytopenia for hematologic malignancy	<i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)> <i>C. tropicalis</i> , <i>C. krusei</i> (<i>P. kudriavzevii</i>)	Acute/subacute	Fluco, vorico, echino, L ampho B	fluco, vorico [total course: 3–12 months]
Osteomyelitis	[154,155]	spinal, abdominal & cardio-thoracic surgery, IVDA	<i>C. albicans</i> > <i>C. tropicalis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	subacute/chronic	L ampho B, fluco or vorico, echino \$ ^{ooo}	fluco [total course: 3–12 months]*
Arthritis (usually disk space infection and bursitis)	[156]	disk space infection: previous candidemia, IVDA. Bursitis: previous candidemia,	<i>C. albicans</i> > <i>C. tropicalis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	subacute/chronic	L ampho B, fluco or vorico, echino \$ ^{ooo}	fluco [total course: 2–12 months]*
Trauma-related fracture	[134]	open fracture	<i>C. parapsilosis</i> > <i>C. albicans</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	chronic	L ampho B, fluco or vorico, echino \$	fluco [total course: 3–12 months]*
Prosthetic joint infection (PJI)	[157]	implant	<i>C. albicans</i> > <i>C. parapsilosis</i> > <i>C. glabrata</i> (<i>N. glabrata</i>)	chronic	L ampho B, fluco or vorico, echino \$	fluco [total course: 3–12 months]*

Note: Legend: \$ indicates surgery or percutaneous drainage for source control (i.e. for secondary peritonitis or abscess) and/or device removal/replacement (i.e. for PVE, shunt-related meningitis or osteosynthesis-related fracture infection).
 CS therapy= chronic suppressive therapy; ESLD= end-stage liver disease; DM= diabetes mellitus; IVDA= intravenous drug addiction; CIED= cardiovascular implantable electronic device; NVE= native valve endocarditis; PVE= prosthetic valve endocarditis; SOT= solid organ transplantation; PV= peripheral vein; 5FC = 5 fluorocytosine; ^ increased exposure to doses of fluco (800 mg, or 12 mg/kg, once daily i.v./oral) may be required for *C. glabrata* or to achieve adequate concentrations at the infection site (e.g. meninges and eye); ^,^ total course of therapy includes initial+maintenance course of therapy; echino=echinocandins; fluco=fluconazole; vorico=voriconazole; posaco=posaconazole; L ampho B=liposomal amphotericin B; D ampho B=desosicholate amphotericin B; *in cases of fluconazole/azole resistance, once weekly dose regimen with rezafungin may be a reasonable option; # = CS therapy may be required in cases where surgical valve replacement cannot be performed; FUBC= follow-up blood culture; surgical debridement is required in a minority of cases; final therapy duration may depend on lesion resolution as determined by repeated ophthalmological examinations, and vitrectomy may be required in some cases; ^{ooo}CS-therapy might be required in cases of recurrent esophagitis; surgery is required in a minority of cases, usually when a foreign body must be removed.

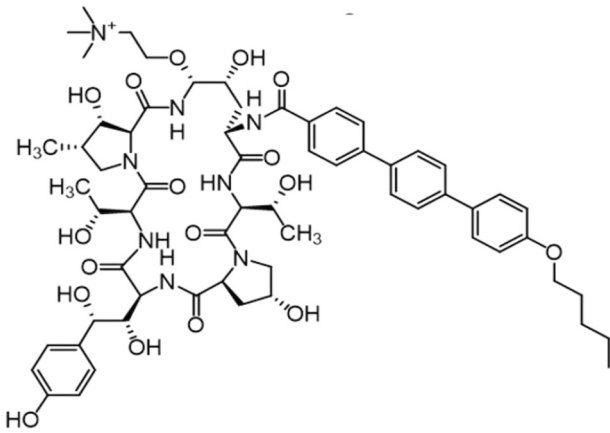


Figure 2. Chemical structure of rezafungin.

approach to the above clinical settings may be the use of the novel long-acting echinocandin rezafungin [162,163].

6. Rezafungin

Rezafungin is a novel echinocandin derived from the precursor anidulafungin with an additional choline ether (Figure 2) [164,165]. Rezafungin shares the same mechanism of action as other echinocandins, which consists in inhibiting fungal cell wall synthesis by blocking the beta 1,3 D-glucan synthetase activity [162].

6.1. In-vitro activity

Rezafungin activity against *Candida* spp. is similar to that of other members of the echinocandin class, exhibiting potent *in-vitro* activity against most wild-type and azole-resistant *Candida* spp [166].

In a wide *in-vitro* study performed on several clinical *Candida* isolates in four different European Laboratories following the EUCAST method, the lowest rezafungin MICs (range, mg/L) were observed for *C. albicans* (0.002–0.125) and the highest for *C. parapsilosis* (0.063–>4). Of note, unexplained laboratory variation was observed for *C. albicans*, including the quality control strains [167].

Additionally, the *in-vitro* activity of rezafungin and comparators (caspofungin, anidulafungin, micafungin, and azoles) was analyzed on a worldwide collection performed on 2,205 invasive fungal isolates including 1,904 isolates from six *Candida* species and recovered from 2016 to 2018 by using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods. Authors found that rezafungin inhibited 99.8% of *C. albicans* isolates (MIC_{50/90}, 0.03/0.06 µg/ml), 95.7% of *C. glabrata* (*N. glabrata*) isolates (MIC_{50/90}, 0.06/0.12 µg/ml), 97.4% of *C. tropicalis* isolates (MIC_{50/90}, 0.03/0.06 µg/ml), 100.0% of *C. kruzei* (*P. kudriavzevii*) isolates (MIC_{50/90}, 0.03/0.06 µg/ml), and 100.0% of *C. dubliniensis* isolates (MIC_{50/90}, 0.06/0.12 µg/ml) at ≤0.12 µg/ml. All (329/329) *C. parapsilosis* isolates (MIC_{50/90}, 1/2 µg/ml) were inhibited by rezafungin at ≤4 µg/ml [168]. Indeed, *C. parapsilosis* was the least susceptible species *in-*

vitro, with MICs up to 4 µg/mL [166], while *C. metapsilosis*, *C. orthopsilosis*, and *C. guilliermondii* showed MICs between 0.5 and 1 µg/mL [162]. Despite the lower *in-vitro* susceptibility for *C. parapsilosis*, treatment failures have not yet been described [103].

Another study determined the *in-vitro* susceptibility of 689 clinical isolates of *Candida* species, including 19 rare *Candida* species, and *Saccharomyces cerevisiae* by using CLSI methods, showing excellent *in-vitro* activity against both wild-type and azole-resistant *Candida* species, as well as against *S. cerevisiae* [169]. For *C. lusitaniae* (*C. lusitaniae*), MICs were 0.25 µg/mL [162].

Overall, rezafungin had species-specific activity similar to other echinocandin, being equally or more active than fluconazole and amphotericin B against the most common *Candida* species, except *C. parapsilosis* [166,167]. Of note, rezafungin seems to be more potent *in-vitro* against *C. auris* than caspofungin and micafungin, with MIC 0.25 µg/mL [16,162,170].

The selection of FKS mutants occurred at a similar low frequency for rezafungin as for anidulafungin and caspofungin. As expected, rezafungin shares with the other echinocandins the reduced activity against strains carrying mutations of the FKS1 and FKS2 genes [16,162]. Interestingly, *fkp1* mutations raised rezafungin MICs notably less than anidulafungin and micafungin MICs in *C. auris* [166].

Rezafungin also exhibits high activity against *Aspergillus* spp., including azole-resistant strains, while it is not active against non-*Aspergillus* molds, *Cryptococcus*, *Trichosporon*, and *Rhodotorula* [162,170].

6.2. Pharmacokinetics

The major difference between rezafungin and the first-generation class of echinocandins is the much lower clearance rate, which prolongs the elimination half-life up to 6 to 10-fold compared to anidulafungin, caspofungin, or micafungin (Table 3).

This gives rezafungin a unique feature within the class of the echinocandins, namely the possibility of being administered once weekly instead of once daily, unlike all other available echinocandins. Rezafungin biotransformation is minimal in humans, and fecal excretion is the major route of elimination [171]. It does not interact with the cytochrome P450 isoenzymes; therefore, it is not prone to drug–drug pharmacokinetic interactions, similarly to the other echinocandins [172]. Specifically, it was recently shown that co-administration of rezafungin did not impact cyclosporine or mycophenolate mofetil pharmacokinetics [173]. Rezafungin is minimally excreted by the renal route, and consequently, in an *ex vivo* bovine blood model, it was not shown to be cleared by continuous veno-venous hemofiltration [174]. Interestingly, a population pharmacokinetic model based on data from a phase 1 study showed that none of several subject descriptors (including sex, infection status, serum albumin, and body surface area) affected the pharmacokinetic behavior of rezafungin in a clinically relevant manner [175,176].

Table 3. Pharmacokinetic parameters of rezafungin vs. older echinocandins.

	Rezafungin	Anidulafungin	Caspofungin	Micafungin
Dose (mg)	400 LD/200 OW	200 LD/100 OD	70 LD/50 OD	100 OD
C _{max} (mg/L)	22.7	7.2	12.1	7.2
Plasma protein binding (%)	99	99	97	99
V _d (L)	35.9	35.2	9.7	25.6
CL (L/h)	0.2	1.0	0.6	1.3
Elimination t _{1/2} (h)	129–133	24–26	9–11	11–17
Excretion in feces (%)	38	30	35	40
Excretion in urine (%)	14	1	41	15

Note: LD: loading dose; OW: once weekly; OD: once daily; V_d: Volume of distribution; CL: clearance.

6.3. Pharmacodynamics

Like first-generation echinocandins, the major pharmacodynamic determinant of rezafungin efficacy is the area under the concentration-time curve (AUC) to the MIC ratio [177,178].

In a neutropenic animal model of disseminated candidiasis caused by *C. tropicalis* and *C. dubliniensis*, free AUC/MIC ratio values ranging from 3 to 25 were associated with stasis, and values ranging from 4.3 to 62 were associated with 1-log kill [179,180]. It was estimated that a dosing regimen of 400 mg loading dose on week 1 followed by 200 mg once weekly may guarantee these AUC/MIC targets against the vast majority (>99%) of *C. tropicalis* and *C. dubliniensis* clinical isolates [179,180]. In a neutropenic mouse model of disseminated candidiasis caused by *C. albicans*, *C. glabrata* (*N. glabrata*) and *C. parapsilosis*, free AUC/MIC ratio values of 2.92, 0.07 and 2.61, respectively, were associated with stasis whereas values two- to four-fold higher than these were associated with 1-log kill [179–181].

Studies on different dosing schedules for the same total weekly dose of rezafungin showed that once weekly dosing may guarantee more effective fungal killing than twice-weekly or once-daily regimens [182]. Monte Carlo simulations conducted with three different intravenous rezafungin regimens (namely, single 400 mg dose; 400 mg week 1 followed by 200 mg weekly for 5 weeks; 400 mg weekly for 6 weeks) showed that the likelihood of attaining PK-PD targets against *C. albicans* and *C. glabrata* (*N. glabrata*) were always $\geq 90\%$. These analyses supported the use of single and once weekly rezafungin regimens for treating patients with candidemia and/or candidiasis due to *C. albicans* or *C. glabrata* (*N. glabrata*) [183].

In a neutropenic mouse model of invasive candidiasis caused by *C. auris*, the free AUC/MIC ratio value for stasis was 1.88, whereas that for 1-log kill was 5.77 [181]. Likewise, in a disseminated immunocompromised mouse model of candidiasis, rezafungin exhibited potent antifungal activity against *C. auris*, with significantly lower renal tissue fungal burden than AmB- and vehicle-treated mice [184].

6.4. Registrative and real-life studies

The STRIVE trial was a phase II trial comparing adults with candidemia and/or ICI randomized to receive either rezafungin 400 mg once weekly or rezafungin 400 mg on week 1 followed by 200 mg once weekly or caspofungin 70 mg as a loading dose, followed by 50 mg daily for ≤ 4 weeks [103].

The primary efficacy endpoint was overall cure at day 14 as demonstrated by mycological eradication and resolution of signs. The overall cure rate was highest for rezafungin 400/200 mg compared to rezafungin 400 mg or caspofungin (76.1% vs 60.5% vs 67.2%, respectively); likewise, the mortality rate was lowest for rezafungin 400/200 mg compared to rezafungin 400 mg or caspofungin (4.4% vs 15.8% vs 13.1%, respectively). Interestingly, candidemia was cleared earlier in patients on rezafungin than those receiving caspofungin. No significant safety issues were observed [103]. The observed discrepancies between the two rezafungin dosing regimens were explained as a possible paradoxical effect at higher concentrations.

The subsequent ReSTORE trial was a multicenter, double-blind, double-dummy, randomized phase III trial including adults with candidaemia or ICI randomly assigned (1:1) to receive either intravenous rezafungin once weekly (400 mg in week 1, followed by 200 mg weekly, for a total of two to four doses) or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg daily) for up to 4 weeks. The primary endpoints were global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14 for the EMA and 30-day all-cause mortality for the FDA. The global cure rate at day 14 was 59% in the rezafungin group, compared to 61% in the caspofungin group, while 30-day mortality was 24% and 21% in the rezafungin and caspofungin groups, respectively, thus showing non-inferiority of rezafungin to caspofungin [23].

A Phase III, multicenter, prospective, randomized, double-blind study is currently ongoing to evaluate the efficacy and safety of rezafungin (400 mg/200 mg once weekly) versus the standard antimicrobial regimen (daily azole prophylaxis with fluconazole or posaconazole and oral trimethoprim-sulfamethoxazole for anti-*Pneumocystis jirovecii* prophylaxis) for the prevention of invasive fungal diseases including *Candida* spp., *Aspergillus* spp., and *P. jirovecii* in subjects undergoing allogeneic blood and bone marrow transplantation. Fungal-free survival at day 90 is the primary outcome [177].

A *post-hoc* analysis of the STRIVE and ReSTORE trials aimed to examine the outcomes of all-cause mortality in patients with candidemia/ICI and day-5 mycological eradication in patients with candidemia. The integrated analysis included 294 patients (139 in the rezafungin arm, 155 patients in the caspofungin arm) and showed that 30-day mortality was 18.7% and 19.4% for the rezafungin and caspofungin groups, respectively. Patients with candidemia exhibited higher

mycological eradication rates at day 5 (80.0% for rezafungin vs 67.8% for caspofungin) [23,103,185].

To date, there are only three reports of successful compassionate use of rezafungin in the treatment of patients with *Candida* spp infections: i) a multidrug-resistant *C. glabrata* (*N. glabrata*) mediastinal infection from vascular graft infection and retained foreign material, where rezafungin was administered for over 1 year, in the absence of adverse effects [163]; ii) a refractory intra-abdominal candidiasis due to *C. krusei* (*P. kudriavzevii*) in a liver transplant recipient, where rezafungin was administered for 12 weeks [186] and iii) a chronic mucocutaneous candidiasis sustained by azole-resistant *C. albicans* in a 19-year-old man with *STAT1*-GOF immunodeficiency, where rezafungin was administered for 5 weeks [187].

6.5. Safety

Rezafungin is characterized by higher chemical stability compared to anidulafungin, which may prevent the formation of reactive metabolites potentially causing toxicity [164,165,172]. A preclinical 2-week repeat-dose comparison study in rats showed some degree of toxicity and hepatotoxicity with anidulafungin, but not with rezafungin [172].

In a phase I, single-center, randomized, double-blind trial assessing the effects of intravenous rezafungin vs. intravenous placebo (with moxifloxacin as positive control) on the QT interval of the electrocardiogram, therapeutic (600 mg), and suprathreshold (1,400 mg) rezafungin doses did not cause any clinically relevant QT interval prolongation [178].

6.6. Economic impact

The health economic burden associated with candidemia/ICIs is largely due to prolonged hospital and ICU stays, contributing to more than half of the total costs [17]. The once-weekly administration of rezafungin may possibly reduce hospitalization costs or length of stay. In this regard, the integrated analysis of the STRIVE and ReSTORE trials showed that, among patients hospitalized in the ICU, survivors receiving rezafungin had a reduction of 7.1 days in ICU length of stay (15.9 vs. 23 days, respectively). Although slightly reduced, this trend was confirmed after adjusting for mechanical ventilation (17.3 vs. 21.4 days in the rezafungin and caspofungin groups, respectively, with a difference of 4.1 days) [185].

7. Expert opinion

Candidemia and ICI are major causes of in-hospital morbidity and mortality, accounting for prolonged ICU/hospital stays and leading to excessive healthcare economic burden [188,189]. The advances in healthcare as well as the evolution of patient risk factors and the ability of some *Candida* species to spread within the hospital environment and cause outbreaks have led to a change in the epidemiology of invasive fungal infections [3–5,38]. As a matter of fact, despite *C. albicans* being still the most common, a continuous increase in non-*albicans* species has been observed in recent years,

along with the emergence of worrisome and drug resistant species such as *C. auris* [16,38,127].

The shift toward non-*albicans* species may be influenced by the different and evolving pathophysiology behind the development of candidemia/ICIs. In fact, while the endogenous route (consisting of *Candida* species passing through an intestinal barrier damaged by a variety of insults) is mostly commonly observed for *C. albicans*, *C. tropicalis*, *C. glabrata* (*N. glabrata*), *C. parapsilosis*, and *C. krusei* (*P. kudriavzevii*), the exogenous route (consisting in healthcare workers' hands, patients' skin or central lines contamination and subsequent spread into the blood) applies, above all, for *C. auris*, *C. parapsilosis*, and *C. haemulonii* [16,22].

Among the increasing proportion of infections caused by non-*albicans* *Candida* species, those caused by the emerging *C. auris* are of particular concern, given its long-lasting ability to colonize patients and the environment and its high rate of resistance to antifungals. Indeed, up to 40% of *C. auris* isolates may be resistant to at least two classes of antifungals, and resistance to echinocandins, although to a lesser extent, may also occur [16]. Prompt and adequate source control as well as the adoption of effective infection control measures are key strategies to manage infected patients and reduce cross-transmission and outbreaks.

C. parapsilosis and *C. auris* share the ability to colonize central lines and cause nosocomial outbreaks. One of the main concerns lies in the fact that up to one-third of the strains are resistant to fluconazole, thus limiting the available therapeutic options to AmB or, as an alternative, to echinocandins [31,190].

Furthermore, some ICIs, such as endovascular infections, in which source control is not feasible, require prolonged treatment, up to weeks or months.

In all the aforementioned conditions, the availability of long-acting rezafungin is of paramount importance [162]. In general terms, the advent of long-acting antimicrobial agents (e.g. dalbavancin) has represented a real revolution in the field of infectious diseases, enabling outpatient treatment of complex infections and allowing therapeutic switch in patients suitable for hospital discharge [189–192]. As for fungal infections, rezafungin combines the strengths of the echinocandin class with a prolonged elimination half-life, a low likelihood of drug–drug interactions and a robust safety profile, thus opening up several possibilities for its future use [16,162].

In particular, it may allow earlier hospital discharge when clinical conditions are favorable and extend outpatient access to treatment of invasive candidiasis, especially when prolonged treatment duration is expected. Rezafungin's high activity against *Candida* spp., including species resistant to azoles or *C. auris*, makes it highly attractive for the treatment of candidemia/ICI. An additional advantage may be the potential effect on hospital stay duration and the costs associated with candidemia/ICI, such as those related to the need of daily infusions and the use of central lines. Unfortunately, there are still limited data available on these interesting aspects and more studies are needed to ascertain the cost-effectiveness of rezafungin over other antifungals. Its pharmacological

characteristics make rezafungin attractive also for the prophylaxis of invasive fungal diseases in high-risk populations [16,177].

8. Conclusion

In the recent years, candidemia and ICIs have undergone an important change in their epidemiology, with a shift toward *non-albicans* species as causative agents. In the meantime, the emergence of *C. auris* as a worrisome agent of nosocomial outbreaks and the growing rate of antifungal resistance in some species highlight the dynamic aspects of this evolving condition, which may result from the different underlying pathophysiology (endogenous vs. exogenous route of infection). In this scenario, the novel long-acting echinocandin rezafungin, which combines a potent *in-vitro* activity against *Candida* species, including azole-resistant strains, with a low likelihood of drug–drug interactions and a good safety profile, may revolutionize the treatment of candidemia/ICI. Indeed, it may allow earlier hospital discharge and management of complex fungal infections in an outpatient setting, with a possible, although not yet quantifiable, reduction in associated costs and length of hospital stay.

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