



## Revista Iberoamericana de Micología

[www.elsevier.es/reviberoammicol](http://www.elsevier.es/reviberoammicol)



### Review

# Antifungal activity of rezafungin in invasive candidiasis: From bench to bed

Guillermo Quindós <sup>a,b,\*</sup>, Carolina Garcia-Vidal <sup>c,d</sup>, Xabier Martin-Martitegui <sup>e</sup>,  
Rafael Zaragoza <sup>f</sup>

<sup>a</sup> Department of Immunology, Microbiology and Parasitology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Bizkaia, Spain

<sup>b</sup> Instituto de Investigación Sanitaria Biobizkaia, Barakaldo, Spain

<sup>c</sup> Infectious Disease Department, Hospital Clinic of Barcelona-IDIBAPS, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), Barcelona, Spain

<sup>d</sup> CIBER Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain

<sup>e</sup> Haematology Service, Hospital Universitario Cruces, Barakaldo, Spain

<sup>f</sup> ICU, Hospital Universitario Dr. Peset, Valencia, Spain

### ARTICLE INFO

#### Article history:

Received 12 September 2025

Accepted 5 February 2026

#### Keywords:

Antifungal activity  
Rezafungin  
Invasive candidiasis  
Mycoses  
Therapy

### ABSTRACT

Invasive mycoses present significant medical challenges, with new populations at risk and the emergence of antifungal resistance. Therapeutic options for antifungal treatment are limited and further complicated by drug–drug interactions, toxicity, and constraints in administration routes. Despite the urgent need for more antifungal drugs, few new antifungal drugs have been introduced over the past decades. Nevertheless, there is hope on the horizon, with new antifungal drugs approved or in late-stage clinical trials.

In this review, we critically examine the antifungal activity of rezafungin, a new-generation echinocandin with distinctive PK/PD properties, including high stability that enables once-weekly dosing, as well as elevated peak concentrations ( $C_{max}$ ) and area under the curve (AUC) values, and its therapeutic utility in the treatment of invasive candidiasis. We focus on its mechanism of action, as well as on its broad spectrum of activity against emergent species of *Candida* and other pathogenic fungi. Additionally, we highlight its utility in the treatment of candidemia and other forms of invasive candidiasis in various medical settings, and the potential future roles of rezafungin and the unmet needs in this field.

© 2026 The Authors. Published by Elsevier España, S.L.U. on behalf of Asociación Española de Micología. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Actividad antifúngica de la rezafungina en la candidiasis invasiva: del laboratorio a la práctica clínica

### RESUMEN

Las micosis invasoras son un desafío médico importante, con nuevas poblaciones en riesgo y la aparición de resistencia a los fármacos antifúngicos. Las opciones terapéuticas para el tratamiento antifúngico son limitadas y se complican por las interacciones farmacológicas, toxicidad y restricciones en las vías de administración de estos medicamentos. A pesar de la urgente necesidad de nuevos fármacos antifúngicos, se han producido pocas novedades en las últimas décadas. No obstante, hay luz y esperanza en el horizonte, con la aprobación de algunos fármacos antifúngicos o que están en etapas avanzadas de ensayos clínicos.

En esta revisión examinamos la actividad antifúngica de la rezafungina, una equinocandina de nueva generación que presenta características diferenciales en sus propiedades farmacocinéticas, entre las que destacan su elevada estabilidad, que permite una administración semanal, y los altos valores de concentración máxima ( $C_{max}$ ) y área bajo la curva (AUC) alcanzados, y con gran utilidad terapéutica en el

#### Palabras clave:

Actividad antifúngica  
Rezafungina  
Candidiasis invasiva  
Micosis  
Tratamiento

\* Corresponding author.

E-mail address: [Guillermo.Quindos@ehu.eus](mailto:Guillermo.Quindos@ehu.eus) (G. Quindós).

<https://doi.org/10.1016/j.riam.2026.02.001>

1130-1406/© 2026 The Authors. Published by Elsevier España, S.L.U. on behalf of Asociación Española de Micología. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

tratamiento de la candidiasis invasora. Nos centramos en su mecanismo de acción y farmacocinética, así como en su amplio espectro de actividad antifúngica contra especies emergentes de *Candida* y otros hongos patógenos. Además, destacamos su utilidad en el tratamiento de la candidemia y de otras formas de candidiasis invasora en diversos entornos médicos, las posibles indicaciones futuras de la rezafungina y las necesidades aun no cubiertas.

© 2026 Los Autores. Publicado por Elsevier España, S.L.U. en nombre de Asociación Española de Micología. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Background and perspective

The incidence of invasive mycoses is increasing in association with a growing at-risk population. The estimated annual incidence of invasive mycoses is 6.5 million, with about 3.8 million deaths, of which approximately 2.5 million are directly attributable to the fungal infection.<sup>28,49,74</sup> Fungi are ubiquitous organisms capable of surviving in a vast array of conditions. While the number of different fungi is estimated to be around 12 million, approximately 200 species are considered frequent human pathogens.<sup>144</sup> Furthermore, climate change is favouring the emergence of new resistant fungal species as human pathogens, such as *Candidozyma auris* (formerly *Candida auris*) and azole-resistant *Aspergillus*.<sup>45,47</sup> Moreover, the selective pressure of antifungal prophylaxis, along with advances in molecular testing, may be contributing to the emergence and discovery of formerly less common fungal pathogens that are often resistant to currently available antifungal treatments.<sup>4,82</sup> The spectrum of patients affected by invasive mycoses has expanded significantly in recent years, now including not only individuals with severe immunodeficiencies but also other patient populations. Most invasive mycoses occur in individuals with profound immunodeficiency and are more common in males.<sup>30</sup> These infections contribute substantially to increased clinical risk, and are influenced by economic and social determinants, thereby exacerbating existing health disparities.<sup>61</sup> Candidiasis, caused by *Candida albicans* and increasingly by other *Candida* species, remains one of the most frequent and significant invasive mycoses. This mycosis is typically endogenous, associated with immunodeficiencies, severe diseases, and serious predisposing factors (e.g., intensive care unit – ICU-stay, use of central venous catheters, broad-spectrum antibiotics, or abdominal surgery). The signs and symptoms of invasive candidiasis are non-specific, with candidaemia being the most common type, potentially leading to disseminated candidiasis affecting multiple organs. Diagnosis is complex, often requiring conventional culture techniques supplemented by non-culture-based assays. Furthermore, the expanding immunodeficient population presents a growing challenge with new risk factors.<sup>24,60,73,74,88,143</sup>

Patient mortality remains high, with all-cause mortality exceeding 40% among cases. In invasive mycoses caused by antifungal-resistant fungi, mortality increases further and may exceed 80%.<sup>55,115</sup> The attributable mortality from candidaemia and disseminated infections is approximately 30%. The 30-day mortality rate in patients with invasive candidiasis in European hospitals, including ICUs, is 27–42%.<sup>13,44,95</sup> Additionally, the intensive care population may develop new symptoms related to other diseases, such as influenza- and COVID-19-associated mycoses, that pose further threats to the current therapeutic armamentarium.<sup>47,101,102,117</sup>

The epidemiology of invasive candidiasis is continuously evolving and varies across different geographical regions and patient populations.<sup>73,74,109,88,110</sup> Advances in healthcare have led to a persistent increase in the immunosuppressed patient population. A significant challenge in the management of patients with invasive candidiasis is determining the optimal timing of antifungal treatment. Early and appropriate initiation of antifungal therapy has

been shown to significantly impact patient outcomes; however, treatment is often initiated too late due to, for example, the presence of diagnostic challenges.<sup>123</sup> Early antifungal treatment and removal of the central venous catheter are crucial for reducing mortality, with broad-spectrum antifungal prophylaxis decreasing prevalence and improving survival in patients with traditional risk factors.<sup>24,52,142,143</sup>

Available treatment options for invasive candidiasis include echinocandins (anidulafungin, caspofungin, or micafungin), azoles (fluconazole, itraconazole, isavuconazole, posaconazole, or voriconazole), and polyenes (amphotericin B). Data from direct comparisons and meta-analyses indicate that echinocandins show higher success rates than azoles and similar efficacy to amphotericin B, but with a better safety profile. Global candidiasis guidelines recommend echinocandins as first-line treatments for candidaemia and invasive candidiasis because they have a broad anti-*Candida* spectrum, are relatively well tolerated, and exhibit limited drug–drug interactions.<sup>22,99</sup> Among these, anidulafungin has demonstrated superior efficacy over fluconazole in treating invasive candidiasis.<sup>112</sup> Nevertheless, as classical echinocandins (anidulafungin, caspofungin, micafungin) require daily intravenous infusions, any other echinocandin with an improved pharmacokinetic profile could reduce the frequency of administration.<sup>52</sup>

Despite established treatments, there is an unmet need for new antifungal drugs and treatment strategies due to increased antifungal resistance and the rising incidence of candidiasis caused by non-*C. albicans* species, such as *C. auris*, *Nakaseomyces glabratus* (formerly *Candida glabrata*), or *Candida parapsilosis*.<sup>10</sup> Fluconazole resistance is a concern in these species of *Candida*, although acquired echinocandin resistance is infrequent. New antifungal drugs and/or novel treatment strategies are also needed to help reduce the risk of nosocomial infections associated with prolonged hospital stays. This may occur when the step-down from daily parenteral echinocandin to oral fluconazole treatment, as recommended by guidelines, is not suitable due to the limited antifungal activity of fluconazole against some species. Antifungal drugs with antibiofilm activity are important in these patient populations with numerous risk factors for biofilm formation (presence of catheters and other biomedical devices), which is a key virulence factor in the pathogenicity of *Candida* and is associated with increased resistance.<sup>23</sup>

Patients requiring long courses of antifungal therapy frequently exhibit drug-related adverse effects, which may be cumulative. The nephrotoxicity, acid-base, and electrolyte disturbances of currently available amphotericin B formulations are well known and obviate attempts for long-term therapy. The triazole class is frequently prescribed to those patients requiring long courses of treatment, but drug–drug interactions are extensive. Fluconazole has poor efficacy in the treatment of several invasive infections and itraconazole absorption is limited by food and gastric pH. Voriconazole is associated with photosensitivity reactions, being rash frequent in addition to hepatotoxicity, and posaconazole may cause drug-induced hypertension, necessitating therapeutic drug monitoring. For these reasons, there is a significant need for new

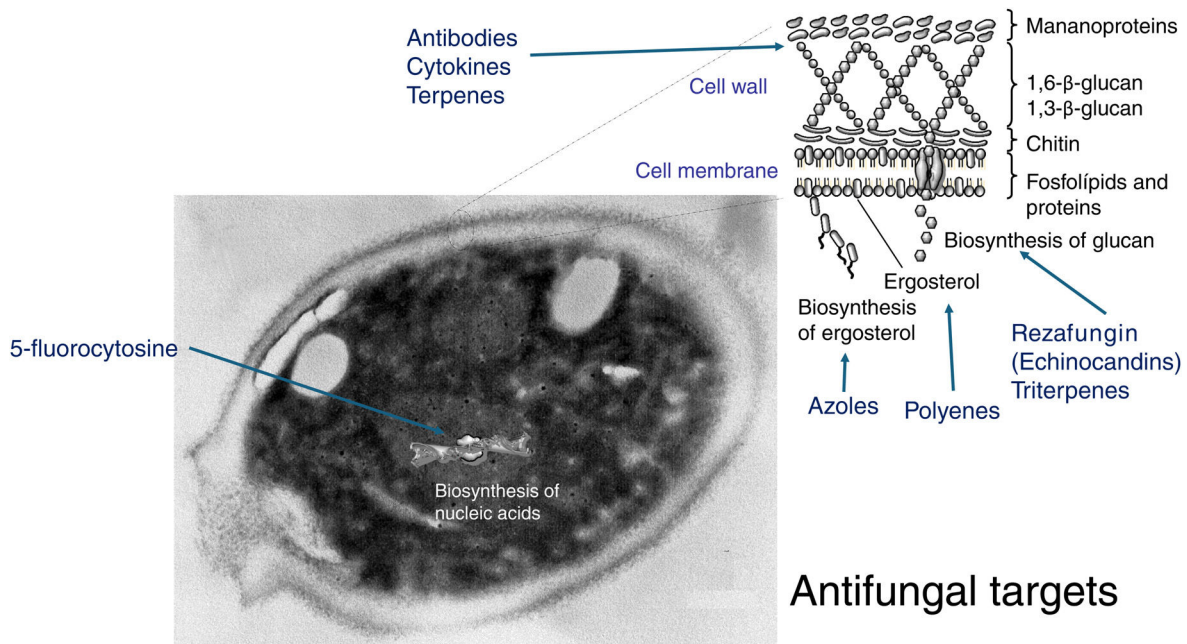


Fig. 1. Antifungal mechanisms of action. Modified from 108.

antifungal drugs. However, very few have been introduced as therapeutic tools against mycoses over the last decades. Fortunately, several new antifungal classes are finally in late-stage clinical development.<sup>55,93,94</sup>

Rezafungin (Rezzayo – Mundipharma –, formerly SP3025 and CD101 – Cidara Therapeutics–) is considered the first member of a second generation of echinocandins with enhanced pharmacokinetics. Following ReSTORE pivotal phase III clinical study, rezafungin has been approved by the European Medicines Agency (EMA) with input from national authorities, such as the Agencia Española de Medicamentos y de Productos Sanitarios (AEMPS), and Food and Drug Administration (FDA).<sup>5,37,41</sup> Rezafungin exhibits activity against multiple species of *Candida*, including wild-type, azole-resistant, and some echinocandin-resistant isolates. Rezafungin has distinct pharmacokinetic-pharmacodynamic (PK/PD) properties compared to other echinocandins, such as prolonged half-life and stable molecular structure that allows weekly dosing, high front-loaded therapeutic drug exposures with a high area under the concentration-time curve (AUC), a significant post-antifungal effect, and widespread distribution and penetration at infection sites. High initial plasma concentrations of rezafungin have the potential to rapidly clear *Candida* from infection sites and may prevent the development of antifungal resistance.<sup>23</sup> Rezafungin has been developed for the treatment of invasive candidiasis, including candidaemia, and its use in the prophylaxis against invasive mycoses in haematopoietic stem cell transplant recipients is currently under investigation. Thus, the recent global guideline for the diagnosis and management of candidiasis published by the European Confederation of Medical Mycology (ECMM) in cooperation with the International Society of Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM) recommends echinocandins – including the novel agent rezafungin – as the first-line therapy for candidaemia and for certain forms of invasive candidiasis, such as intra-abdominal candidiasis, due to their broad-spectrum activity and favourable safety profile.<sup>24</sup>

In this review, we extensively discuss about this promising drug, rezafungin, designed for once-weekly dosing. We also highlight its potential future roles, the clinical trials currently evaluating it, and its spectrum of antifungal activity. We have conducted a

literature search including a PubMed search for rezafungin (old and new names), as well as searching the reference lists for additional studies, over the last 10 years. The final section of the manuscript includes three different clinical perspectives: the usefulness of rezafungin in patients from Infectious Diseases, Intensive Care Medicine and Haematology services.

### Antifungal activity of rezafungin

#### Mechanism of action

Rezafungin derives from anidulafungin and has been developed creating structural changes in order to reduce pharmacological and stability problems of first generation echinocandins.<sup>142</sup> Rezafungin, as the other echinocandins, non-competitively inhibits the biosynthesis of a major fungal cell wall carbohydrate, 1,3-β-D-glucan, by binding to the catalytic subunit of 1,3-β-D-glucan synthase enzyme complex, encoded by FKS1 and FKS2 genes (Fig. 1).<sup>108</sup>

#### Pharmacokinetics/Pharmacodynamics (PK/PD)

Rezafungin has been designed to optimise PK/PD properties and reduce hepatotoxicity by reducing its degradation while maintaining the potent antifungal activity and safety profile of the echinocandins.<sup>97</sup> Rezafungin has a cyclic depsipeptide core and an N-linked acyl lipid side chain, responsible for its antifungal activity. The hemiaminal region of the echinocandin cyclic nucleus has been replaced with a choline aminal ether that reduces the chemical degradation and enhances stability and solubility of rezafungin (Fig. 2). This echinocandin has minimal CYP450 interactions and is chemically stable to biotransformation in liver microsomes or hepatocytes, reducing the risk of hepatotoxicity.<sup>14,46,97,113,127</sup> Rezafungin mean half-life is of approximately 80 h after the first dose of 400 mg, and 150 h after the second or third doses of 200 mg, indicating linear pharmacokinetics. This property allows a weekly administration of rezafungin, a better tissue penetration and improved safety in comparison with other echinocandins. Mean plasma C<sub>max</sub> and AUC have been shown to increase with the dosage. Following single or multiple intravenous doses of

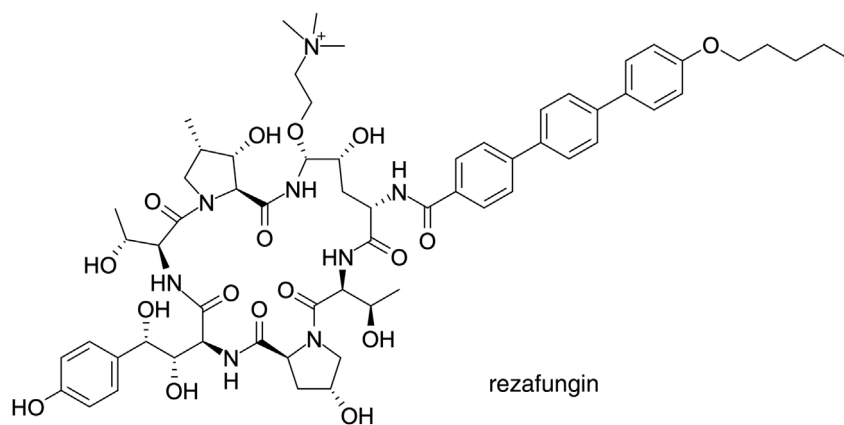


Fig. 2. Chemical structure of rezafungin (Wikipedia commons).

rezafungin in healthy adults, rezafungin exposure increases in a dose-dependent manner over the dose range of 50–400 mg. Steady-state is reached after the first 400 mg loading dose, with comparable AUC values maintained with subsequent 200 mg doses. In healthy volunteers who received a single dose of radiolabelled rezafungin, parent rezafungin made up approximately 77% of the total circulating rezafungin exposure, with individual metabolites each making up less than 10% of exposure. Rezafungin is excreted predominantly (approximately 74%) in the faeces, mainly as unchanged drug. The remainder (26%) is excreted in the urine, largely as inactive metabolites. The proportion of the dose recovered in urine as unchanged rezafungin is less than 1% at all dose concentrations, which evinces that renal clearance makes only a minor contribution to overall rezafungin elimination.<sup>37,43,65</sup> Consistent with other approved echinocandins, rezafungin has a low potential for clinically meaningful drug–drug interactions. In healthy subjects, no relevant pharmacokinetic interactions were observed when dosing rezafungin concomitantly with several other drugs concurrently used: Rezafungin had minimal or no effect on drug interactions with cytochrome P450 enzymes (CYP2B6, CYP3A4, CYP1A2, CYP2C8) and transporter proteins (P-gp, OCT-1, OCT-2, MATE1, MATE-2, OATP, and BCRP).<sup>7,8,14,37,38,40,43,113,116,121</sup>

Achieving and maintaining therapeutic drug concentrations in the case of antifungal drugs is a significant challenge in special patient populations, such as those with organ dysfunctions (liver or kidney failures) or obesity, severe immunodeficiency or neutropenia, paediatric or elderly patients, among others. Echinocandins exert a concentration-dependent fungicidal activity against *Candida* cells, reflecting their PK/PD profiles. Consequently, higher drug concentrations than MIC values are necessary for the optimal treatment of invasive candidiasis. This could explain the higher activity of rezafungin. The PK/PD properties of antifungal drugs can be affected by various factors, including the following: organ dysfunction (hepatic impairment/liver failure and renal insufficiency), extracorporeal membrane oxygenation (ECMO), obesity (high body mass index), extreme ages (frailty, changes in body composition, diminished homeostatic control, low tolerance for adverse drug reactions, multiple comorbidities in the elderly, etc.), polypharmacy (use of immunosuppressants and corticosteroids), and critical illness (organ dysfunction and physiological factors such as a hyperdynamic state, third spacing, and hypoalbuminaemia). Dose adjustments may be necessary for some echinocandins in these populations (Table 1). Rezafungin appears to be suitable for these special patient populations without the need for dose modifications.<sup>7,8,23,123</sup>

Echinocandins are utilised in the outpatient setting (hospital-at-home) for a wide range of clinical conditions, particularly when

there is fluconazole resistance or when azole therapy is contraindicated. The once-weekly dosing regimen of rezafungin facilitates its use in the outpatient setting, which is particularly important for many of the special patient populations discussed here (e.g., the elderly and obese patients), both for optimising quality of life and reducing complications related to hospital stays.<sup>21</sup> Rezafungin may be a suitable option for patients with severe immunodeficiencies without the need for dose adjustment or concerns over drug–drug interactions. However, data concerning the use of rezafungin in this patient population remains scarce. Experience with other echinocandins (though not rezafungin) also suggests that clinical outcomes for neutropenic patients are generally less favourable. Nevertheless, there is insufficient information on rezafungin in children, HIV-infected people, patients on ECMO, among others.<sup>23,24,123</sup>

#### Spectrum of antifungal activity

In vitro susceptibility testing of rezafungin has been conducted in several studies for both wild-type and resistant fungal isolates, using reference methodologies and guidelines from the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These studies have shown excellent concordance in testing. The minimum inhibitory concentration 50 and 90 (MIC<sub>50</sub> and MIC<sub>90</sub>) values for rezafungin are comparable to those of anidulafungin, caspofungin, and micafungin.<sup>19</sup>

Table 2 shows the activity of rezafungin against the fungi included in the World Health Organization's fungal priority pathogens list.<sup>71,136</sup> Rezafungin is highly active against nine of the twenty pathogenic fungi listed. Notably, rezafungin is highly effective against three of the four critically prioritised fungi: *Aspergillus fumigatus*, *C. albicans*, and *C. auris*. Rezafungin was inactive against three of these twenty fungi, and data are scarce for the remaining eight. However, based on the in vitro activity of other echinocandins, it is likely that rezafungin is not active against them. It is important to underscore that the fungi within the genera *Candida* and *Aspergillus* against which rezafungin is active cause more than 90% of invasive mycoses, according to most estimates.<sup>28</sup>

Rezafungin has potent in vitro activity against a broad range of *Candida* species. Most *C. albicans* isolates are inhibited by rezafungin concentrations of  $\leq 0.125$  mg/L, and most *C. auris* isolates are inhibited by  $\leq 0.5$  mg/L.<sup>12,54,55,141</sup> In most studies, rezafungin MIC<sub>90</sub> values were 0.03 mg/L for *Pichia kudriavzevii* (formerly *Candida krusei*) and *Pichia anomala* (formerly *Candida pelliculosa*), 0.06 mg/L for *C. albicans* and *N. glabratus*, 0.125 mg/L for *Cyberlindnera fabianii* (formerly *Candida fabianii*), *Kluyveromyces marxianus* (formerly

**Table 1**  
Properties and pharmacokinetic-pharmacodynamic parameters of rezafungin and other echinocandins.<sup>23,34-37,41,65,93,95,129</sup>

Parameter	Echinocandin			
	Rezafungin	Anidulafungin	Caspofungin	Micafungin
Mechanism of action	Inhibition of 1,3-β-D-glucan biosynthesis			
Formulation	Powder for reconstitution for intravenous infusion			
Dose (mg)	Loading dose: 400 Weekly dose: 200	Loading dose: 200 Daily dose: 100	Loading dose: 70 Daily dose: 50	Daily dose: 100 (50–150)
C <sub>max</sub> (mg/L)	19.2–22.7	7.2	12.1	7.2
Plasma protein binding (%)	96–99	99	97	99
Volume of distribution (L)	39–95	35.2	9.7	25.6
Distribution	Extensive tissue distribution (except brain)			
Clearance (L/h)	0.19–0.35	0.87–1.39	0.55–0.78	0.90–1.27
Terminal half-life t <sub>1/2</sub> (h)	123–181	24–26	9–11	11–17
Excretion in faeces (%)	38–74	30	35	40
Excretion in urine (%)	14–26 (inactive metabolites) and <1% unchanged rezafungin	1	41	15
Drug interactions	Minimal (negligible interactions with CYP450 isoenzymes)			
Need for dose adjustment in special populations <sup>a</sup>				
Liver failure	No	No	Yes, in moderate failure	Not in severe impairment
Renal failure	No	No	No <sup>b</sup>	No <sup>b</sup>
Obesity	No	No?	Yes	Yes?
Older patients	No	No	Yes?	No
ICU patients	No	No	No	No

<sup>a</sup> Data are limited. Moreover, data on rezafungin in children, patients on extracorporeal membrane oxygenation, patients with severe immunocompromise or neutropenia, HIV-infected individuals, and other special groups are not yet available.

<sup>b</sup> Dose escalation may be needed in some patients undergoing continuous veno-venous haemodiafiltration or plasma exchange therapy due to filter adsorption.

**Table 2**  
Activity of rezafungin against the fungi included in the World Health Organization fungal priority pathogens list <sup>136</sup>.

Priority	Fungal species	Rezafungin activity
Critical priority	<i>Aspergillus fumigatus</i>	Very active
	<i>Candida albicans</i>	Very active
	<i>Candidozyma auris</i>	Very active
	<i>Cryptococcus neoformans</i>	Inactive
High priority	<i>Nakaseomyces glabratus</i>	Very active
	<i>Candida parapsilosis</i>	Very active
	<i>Candida tropicalis</i>	Very active
	Eumycetoma causative agents	Inactive?
	<i>Fusarium</i>	Inactive
	<i>Histoplasma</i>	Inactive?
	Mucorales	Inactive
Medium priority	<i>Pichia kudriavzevii</i>	Very active
	<i>Coccidioides</i>	Inactive?
	<i>Cryptococcus gattii</i>	Inactive
	<i>Lomentospora prolificans</i>	Inactive
	<i>Paracoccidioides</i>	Inactive?
	<i>Pneumocystis jirovecii</i>	Very active
	<i>Scedosporium</i>	Inactive
	<i>Talaromyces marneffeii</i>	Inactive

**Table 3**  
In vitro susceptibility to rezafungin of medically relevant *Candida* (or formerly *Candida*) species <sup>11,33,16-18,32,82</sup>.

Standard for antimicrobial susceptibility testing	Species of <i>Candida</i> (or formerly within the genus <i>Candida</i> )						
	<i>Candida albicans</i>	<i>Candidozyma auris</i>	<i>Nakaseomyces glabratus</i>	<i>Meyerozyma guilliermondii</i>	<i>Pichia kudriavzevii</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>
<b>Susceptible category – Clinical breakpoints (mg/L)</b>							
CLSI	≤0.25	≤0.5	≤0.5	–	≤0.25	–	≤0.25
EUCAST	≤0.08	–	≤0.016	–	≤0.03	≤4	≤0.03
FDA	≤0.125	–	≤0.125	–	–	≤2	≤0.125
<b>MIC ranges (mg/L)</b>							
CLSI	≤0.008–1	0.25–0.5	≤0.008–4	0.5–1	≤0.008–1	≤0.008–≥8	≤0.008–2
EUCAST	0.0005–0.004	0.125–0.25	0.04–0.5	0.25–0.5	0.008–0.016	0.25–2	0.002–0.016

CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; FDA: Food and Drug Administration; MIC: minimum inhibitory concentration.

*Candida kefyr*, *Yarrowia lipolytica* (formerly *Candida lipolytica*), and *Candida tropicalis*, 0.25 mg/L for *Candida dubliniensis* and *Clavispora lusitanae* (formerly *Candida lusitanae*), 0.5 mg/L for *C. auris*, *Candida metapsilosis* and *Saccharomyces cerevisiae*, and 1 mg/L for *Candida orthopsilosis* and *Meyerozyma fermentati* (formerly *Candida fermentati*). *C. parapsilosis* and *Meyerozyma guilliermondii* (formerly *Candida guilliermondii*) exhibited an intrinsic reduced susceptibility phenotype, being inhibited by  $\leq 4$  mg/L of rezafungin (Table 3). This observation is similar to those previously reported for other echinocandins, and it is attributed to a polymorphism in the *FKS* genes of *C. parapsilosis*, although consistent treatment failures have not been reported.<sup>11,12,16,18,32,54,55,102,118,131,141,145</sup>

Rezafungin exhibits the same or slightly better activity as other echinocandins on *Candida* isolates harbouring *FKS* hot spot mutations, which may lead to echinocandin resistance, with higher MICs than those of wild-type isolates without *FKS* mutations.<sup>10,11,46,54,76,103,111</sup> The in vitro antifungal spectrum is so similar that Winkler et al.<sup>140</sup> have proposed that other echinocandins, particularly anidulafungin, could be used to predict, by using the CLSI microdilution method and interpretive criteria, the in vitro susceptibility to rezafungin of clinical isolates within the five most common *Candida* species (some of which have since been reclassified into different genera): *C. albicans*, *N. glabratus*, *P. kudriavzevii*, *C. parapsilosis*, and *C. tropicalis*.

There were no MIC increases over time for *Candida* species, and an extended post-antifungal effect against *C. albicans*, *C. parapsilosis*, and *N. glabratus* has been reported, similar to that of micafungin.<sup>17</sup> The existence of this inhibition of fungal growth after the drug is stopped and its magnitude largely depend on the fungal species and the class of antifungal drug. It should be noted that echinocandins have the longest post-antifungal effect, followed by polyenes and azoles, and this property can have a positive effect on the eradication of fungal burden.<sup>58</sup>

The potential to develop in vitro rezafungin resistance is low for common *Candida* species. The median frequency of spontaneous mutations conferring reduced susceptibility to rezafungin ranged from  $1.4 \times 10^{-8}$  to  $3.9 \times 10^{-9}$ . Serial passage results showed that around 20 passages were required to develop resistance.<sup>79</sup> As previously mentioned, mechanisms of resistance or tolerance to rezafungin are similar to those described for other echinocandins and are primarily associated with mutations in the hot spots of the *FKS* genes.<sup>75</sup> However, while higher concentrations of rezafungin, caspofungin and other echinocandins were required to inhibit the in vitro growth of *Candida* isolates with resistance mechanisms (e.g., *FKS1* and *FKS2* mutations), dose adjustments of rezafungin were not necessary for achieving mycological cure in patients with resistant isolates in clinical trials.<sup>80,122,124</sup> Moreover, rezafungin is active against early and mature *Candida* biofilms. Rezafungin concentrations of 0.25–1.0 mg/L reduced biofilm size and prevented the development of mature biofilms.<sup>20</sup> In time–kill studies of *C. auris*, rezafungin concentrations of  $\geq 1$  to  $\geq 8$  mg/L using RPMI-1640 medium with 50% human serum killed the yeasts in the first 8–12 h at clinically achievable trough concentrations.<sup>70</sup>

Rezafungin has demonstrated efficacy in murine models of neutropenic and other immunocompromised invasive candidiasis, showing potent activity against isolates of *C. albicans*, including azole-resistant strains, *N. glabratus*, and *C. parapsilosis*. In these animal models, rezafungin exhibits concentration-dependent fungicidal activity with similar or better efficacy than other echinocandins, even against azole-resistant isolates of *C. dubliniensis*, *C. tropicalis*, and *C. auris*.<sup>12,76,77,90,97,148</sup> The AUC/MIC ratio required to achieve efficacy endpoints was lower for rezafungin compared to other echinocandins.<sup>76,77</sup> Rezafungin was more potent than amphotericin B and micafungin against *C. auris* in immunosuppressed mice, reducing fungal burden in kidneys.<sup>53</sup> Rezafungin achieved higher hepatic concentrations compared to micafun-

gin, resulting in improved survival of mice with intra-abdominal candidiasis.<sup>148</sup> Rezafungin also demonstrated benefits in the prophylaxis of immunosuppressed mice models of *C. albicans* infection. The reduction of *Candida* colony-forming units was greater with increasing drug concentrations (5, 10, or 20 mg/kg) and when the drug was administered closer to the time of infection (day –1, –3, or –5). Mice that received 20 mg/kg of the drug, which is the human equivalent in mice, had *C. albicans* cleared.<sup>89</sup>

The activity of rezafungin against *Aspergillus* is comparable to that of other echinocandins.<sup>55</sup> Rezafungin minimum effective concentration (MEC) ranges of  $\leq 0.015$ – $0.125$  mg/L and  $\leq 0.015$ – $2$  mg/L have been reported against *A. fumigatus* wild-type and azole-resistant species, respectively. Moreover, rezafungin is active with MECs of  $\leq 0.008$ – $0.03$  mg/L against *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* clinical isolates. Rezafungin also had activity against some cryptic species of *Aspergillus*, including *Aspergillus calidoustus*, *Aspergillus lentulus*, *Aspergillus thermomutatus*, and *Aspergillus udagawae*.<sup>103,137,138</sup> In a disseminated infection mouse model of aspergillosis using *A. fumigatus*, similar survival rates were shown with rezafungin compared to amphotericin B treatment.<sup>89,90</sup> In vivo efficacy has also been demonstrated in a murine model of disseminated aspergillosis with an azole-resistant *A. fumigatus* isolate harbouring a TR34/L98H CYP51A mutation.<sup>137,138</sup> However, additional studies are warranted to determine whether this preclinical research translates to clinical experience, and if rezafungin has the potential to prevent and treat invasive aspergillosis. Rezafungin, like other echinocandins, is less active or inactive against non-*Aspergillus* filamentous fungi isolates, such as *Fusarium*, *Lomentospora* or *Scedosporium*, and basidiomycete yeasts, such as *Cryptococcus*, *Trichosporon*, and *Rhodotorula*, with MICs  $> 8$  mg/L, but in vitro data are lacking for most of the rare and emerging moulds and yeasts.<sup>46</sup>

Echinocandins are not commonly used in pneumocystosis therapy. However, the efficacy of rezafungin has been investigated in the prevention of *Pneumocystis murina* infection in an immunosuppressed mouse model of *Pneumocystis* pneumonia. A rezafungin dose of 20 mg/kg was comparable to trimethoprim–sulfamethoxazole in clearing the trophic forms and asci of *P. murina*. Rezafungin prophylaxis for at least four weeks also prevented the reactivation of pneumocystosis six weeks after discontinuation. Although other echinocandins reduce the number of asci forms, trophic forms do not contain 1,3- $\beta$ -D-glucan and are not inhibited by anidulafungin, caspofungin, or micafungin, leading to reactivation of infections after discontinuation of prophylaxis. The higher efficacy of rezafungin may be due to its long-acting pharmacokinetics, as *Pneumocystis* depends on sexual reproduction and the development of asci that contain 1,3- $\beta$ -D-glucan.<sup>26,55,89</sup>

### Therapeutical efficacy of rezafungin

EMA has approved the use of rezafungin for the treatment of invasive candidiasis in adults.<sup>5,37</sup> The United States Food and Drug Administration (FDA)<sup>41,121</sup> has also approved its use for treating candidemia and invasive candidiasis in individuals over 18 years old who have no alternative treatment options. These approvals are based on the results obtained from the phase 2 STRIVE (NCT02734862) and phase 3 ReSTORE (NCT03667690) clinical trials, which showed that weekly administration of rezafungin was statistically as active and effective as daily treatment with caspofungin. Moreover, rezafungin was well tolerated and had a safety profile very similar to that of caspofungin.<sup>56,122,124,128–130</sup>

The STRIVE study was a two-part phase 2 trial of rezafungin, comparing two dosing regimens (400 mg once weekly, and 400 mg in week 1 followed by 200 mg once weekly) with a standard caspofungin therapy (70 mg intravenous once, followed by 50 mg daily).

Efficacy was assessed in the modified intention-to-treat population, which included 76, 46, and 61 patients in the high-dose and low-dose rezafungin regimens, and caspofungin treatment groups, respectively. Overall, cure rates at day 14 were comparable between the three treatment arms (60.5% vs. 76.1% vs. 67.2%, respectively). The highest cure rates and lowest mortality were observed with the low-dose rezafungin regimen. Apparent differences between the two rezafungin groups raised the discussion of paradoxical growth with higher concentrations of rezafungin. Both in vitro and animal studies of other echinocandins have reported this phenomenon, where the fungal burden increases at doses above a certain threshold.<sup>84</sup> However, the differences with rezafungin occurred on day 5, when both treatment arms had received a similar 400 mg dose. Therefore, the hypothesis of a paradoxical growth effect appears to be improbable.<sup>126</sup>

There were no serious or severe adverse events (all were transient and resolved), withdrawals due to adverse events, or deaths. Mild transient infusion reactions such as flushing, nausea, and chest tightness were observed with the third 400 mg dose in the multiple-dose study.<sup>116</sup> No clinically meaningful laboratory abnormalities were noted. A randomised, double-blind, phase 1 study was conducted in healthy volunteers to evaluate the cardiac effects of single doses of intravenous rezafungin.<sup>38</sup> Unlike anidulafungin, rezafungin did not prolong the QT interval and had no apparent effect on repolarization or QRS duration at doses up to 1400 mg. Echocardiograms showed no change in ejection fraction or other cardiac parameters compared with baseline. Although an increase in PR interval was seen in the 1400 mg dose group, it was considered not clinically relevant. According to the results from the STRIVE study, 400 mg of rezafungin in the first week, followed by 200 mg weekly, was the most effective dosing regimen in the phase 3 randomised double-blind ReSTORE study.<sup>128</sup>

The ReSTORE trial was a multicentre, randomised, double-blind study examining the aforementioned rezafungin dosage 400 mg/200 mg once-weekly protocol to treat candidemia and/or invasive candidiasis. The active comparator was intravenous caspofungin followed by optional fluconazole step-down. The primary endpoints were all-cause mortality at day 30 and global cure at day 14, measured by clinical, radiological, and mycological indices. Patients included in the ReSTORE study had to present one or more systemic symptoms (fever, hypothermia, hypotension, tachycardia, tachypnoea) and a mycological diagnosis of candidemia and/or invasive candidiasis. However, patients with osteomyelitis, endocarditis, meningitis, endophthalmitis, chorioretinitis, central nervous system infections, chronic disseminated candidiasis or urinary tract candidiasis were excluded from the study. The patients were randomly assigned to two different groups. In one group, the patients received intravenous rezafungin in loading dose of 400 mg on day 1, followed by 200 mg on day 8, and then 200 mg once weekly (total of two to four doses). In the other group, the patients received caspofungin in loading dose of 70 mg on day 1, followed by 50 mg once daily for a total treatment duration of two to four weeks. After three days of intravenous treatment, patients could switch to oral treatment (placebo for patients randomised to rezafungin, and fluconazole for those randomised to caspofungin) if certain criteria were met (v.g., fluconazole-susceptible *Candida* isolate, all symptoms of candidiasis resolved, or a recent blood culture negative for *Candida*). Randomisation was stratified by diagnosis (candidemia only vs. invasive candidiasis) and by Acute Physiology and Chronic Health Evaluation II (APACHE II) score or absolute neutrophil count (APACHE II  $\geq 20$  and neutrophils  $< 500$  cells/ $\mu$ L vs. APACHE II  $< 20$  and neutrophils  $\geq 500$  cells/ $\mu$ L).

The primary efficacy endpoint was the global response, determined based on clinical, mycological, and radiological responses, confirmed by an independent committee on day 14. These responses were also analysed separately as secondary endpoints.

Other secondary efficacy endpoints included all-cause mortality on day 30 (the primary endpoint for FDA evaluation) and global response on days 5, 30, end of treatment, and follow-up (days 52–59). When the lower limit of the 95% confidence interval (CI 95%) in relation to the difference in cure rates on day 14 (rezafungin vs. caspofungin) was greater than  $-20\%$ , non-inferiority was inferred. The modified intention-to-treat population was defined as all subjects with confirmed candidiasis, based on a blood culture or a culture from a normally sterile site obtained four or fewer days before randomisation; those patients received one or more doses of the investigational drug. A total of 199 patients were included in the study, with 100 patients randomised to rezafungin and 99 to caspofungin. Eight patients from the rezafungin group were excluded from the modified intention-to-treat population due to the absence of documented candidiasis ( $n=6$ ) and for not having received the treatment ( $n=2$ ). With regard to the caspofungin group, five patients were excluded from the study: in four cases there was a lack of documented infection, and in one case the patient did not receive the treatment. Thus, 187 patients were included in the modified intention-to-treat population: 93 in the rezafungin group and 94 in the caspofungin group. No notable differences were observed between the treatment arms in baseline demographic characteristics. The majority of patients (70% vs. 68.7%) had a diagnosis of candidaemia. The APACHE II score was  $< 20$  for 84% and 81.8%, and neutrophils were  $\geq 500$  cells/ $\mu$ L in 88% and 93.9% of patients, respectively.

The primary endpoint for EMA was the global response confirmed by an independent committee on day 14. The study demonstrated the non-inferiority of rezafungin, with a treatment difference of  $-1.5\%$  (95% CI:  $-15.4$  to  $12.5$ ), with mortality rate values at day 30 of 23.7% and 21.3% in the rezafungin and caspofungin groups, respectively. Non-inferiority of rezafungin in all-cause mortality was demonstrated, with a treatment difference of 2.4% (95% CI:  $-9.7$  to  $14.4$ ). The analyses of secondary and exploratory endpoints were consistent with the primary analysis: Mycological eradication rates were similar between treatment groups, and the clinical response rate on day 5 was lower in the rezafungin group than in the caspofungin group (63.4% vs. 74.5%), being similar at subsequent visits (Table 4). Response rates for *N. glabratus*, *C. tropicalis*, and *C. parapsilosis* were higher in the rezafungin group (66.7%, 70%, and 75%) than in the caspofungin group (56%, 58.8%, and 64.7%).<sup>80</sup>

The subgroup analysis for all-cause mortality showed that, on day 30, mortality rates in patients over 65 years were lower in the rezafungin group (14%) than in the caspofungin group (31.7%). Similar results were seen in patients with candidemia alone and in those with end-organ invasive candidiasis.<sup>128</sup> An integrated analysis of the STRIVE and ReSTORE trials has further supported the efficacy of rezafungin in invasive candidiasis. The 30-day all-cause mortality was 18.7% for rezafungin and 19.4% for caspofungin (difference  $-1.5$ , 95% CI  $-10.7$  to  $7.7$ ), in the modified intention-to-treat population analysis (139 patients for rezafungin, 155 for caspofungin). Mycological eradication rates on day 5 in patients with positive blood cultures were 75.5% and 54.9%, respectively (difference 19.2, 95% CI 3.0–35.5). The rezafungin 400 mg/200 mg protocol showed the greatest overall cure, with the highest clinical and mycological cure rates and the lowest rate of all-cause mortality at day 30 across all treatment arms. More patients in the rezafungin group had negative blood cultures at 24 hours than in the caspofungin group (60% vs. 49.1%, respectively), suggesting that rezafungin may be associated with a shorter time to achieve negative blood cultures than caspofungin in patients suffering from invasive candidiasis.<sup>129</sup> Candidemia cleared more rapidly in the rezafungin-treated patients, possibly reflecting greater fungicidal activity with front-loaded drug exposure, and demonstrated high rates of early treatment efficacy in patients with candidemia. Clin-

**Table 4**  
Global response on the efficacy of rezafungin in adults recruited in the ReSTORE study [5,37,41,128](#).

Endpoint	Response	Rezafungin (N=93)	Caspofungin (N=94)	Difference (95% CI)
At day 5	Clinical cure <sup>a</sup>	55 (59.9%)	49 (52.1%)	3.8% (-10.5 to 17.9)
	Clinical cure	59 (63.4%)	70 (74.5%)	-11.0% (-24.0 to 2.3)
	Mycological eradication	64 (68.8%)	58 (61.7%)	7.1% (-6.6 to 20.6)
At day 14	Clinical cure <sup>a</sup>	55 (59.1%)	57 (60.6%)	-1.5% (-15.4 to 12.5)
	Clinical cure	62 (66.7%)	63 (67.0%)	-0.4% (-13.8 to 13.1)
	Mycological eradication	63 (67.7%)	62 (66.0%)	1.8% (-11.7 to 15.2)
At day 30	Clinical cure <sup>a</sup>	46 (49.5%)	46 (48.9%)	0.5% (-13.7 to 14.7)
	Clinical cure	51 (54.8%)	52 (55.3%)	-0.5% (-14.6 to 13.7)
	Mycological eradication	56 (60.2%)	53 (56.4%)	3.8% (-10.3 to 17.8)
At the end of treatment	Clinical cure <sup>a</sup>	56 (60.2%)	59 (62.8%)	-2.6% (-16.4 to 11.4)
	Clinical cure	65 (69.9%)	64 (68.1%)	1.8% (-11.5 to 15.0)
	Mycological eradication	63 (67.7%)	63 (67.0%)	0.7% (-12.7 to 14.1)
At follow-up	Clinical cure <sup>a</sup>	42 (45.2%)	39 (41.5%)	3.7% (-10.5 to 17.7)
	Clinical cure	46 (49.5%)	44 (46.8%)	2.7% (-11.6 to 16.8)
	Mycological eradication	48 (51.6%)	49 (52.1%)	-0.5% (-14.7 to 13.7)

<sup>a</sup> Evaluated by the Independent Committee. CI: confidence interval.

ical cure rates were also highest with rezafungin 400 mg/200 mg protocol when differentiating between *C. albicans* and other *Candida* species.<sup>122,124</sup>

Soriano et al.<sup>124</sup> conducted a post hoc analysis using pooled data from the STRIVE/ReSTORE trials to determine clinical and mycological cure in the treatment of invasive candidiasis with rezafungin or caspofungin, based on the *Candida* species causing the infection and the in vitro antifungal susceptibility of the *Candida* isolates obtained from the patients. This analysis included data from patients with a documented candidiasis within 96 h of randomisation who also received one or more doses of the study drug. A total of 294 patients were included, 139 treated with rezafungin and 155 with caspofungin. Global cure rates at day 14 were similar between both treatment groups in infections caused by *C. albicans* (61% – rezafungin– vs. 65.2% – caspofungin–) and *C. tropicalis* (70.4% vs. 63.6%). However, cure rates were higher with rezafungin for invasive candidiasis caused by *N. glabratus* (71.1% vs. 60%) and *C. parapsilosis* (78.6% vs. 55.6%). All-cause mortality at day 30 was similar in both treatment arms in infections caused by *C. albicans* (22% – rezafungin – vs. 18.8% – caspofungin–) and *N. glabratus* (15.8% vs. 11.4%), but higher in patients with invasive infections by *C. tropicalis* (18.5% – rezafungin – vs. 31.8% – caspofungin–) and *C. parapsilosis* (7.1% vs. 29.6%) treated with caspofungin. In cases of invasive candidiasis caused by *C. albicans* and *C. parapsilosis*, both rezafungin and caspofungin had similar mycological cure rates at days 5 and 14, although rezafungin achieved higher mycological cure rates in candidiasis caused by *N. glabratus* and *C. tropicalis*. Front-loaded dosing may maximise the effect of rezafungin due to its low clearance and long half-life, as well as the concentration-dependent fungicidal activity of echinocandins.<sup>122</sup>

Of interest, there was no correlation between clinical and microbiological outcomes, and the MICs of the isolates causing the infections in either treatment group. Moreover, only three isolates of the 313 isolates from the 294 pooled patients, tested by the EUCAST method, were non-susceptible to rezafungin: one *C. albicans* isolate in the caspofungin group, and two *N. glabratus* isolates, one in the rezafungin group and one in the caspofungin group. Only the *N. glabratus* isolate from the patient treated with rezafungin had an *FKS* mutation. However, as the MIC of rezafungin or caspofungin increased, no clear trends were observed in the overall cure rates or mycological eradication rates at day 14 in any patient, regardless of the *Candida* species.

In the patient infected with a *N. glabratus* isolate carrying a *FKS* mutation (*FKS2* HS1 F659V) and treated with rezafungin, although global cure was not achieved at day 14, mycological cure was sup-

posed at this time point and the patient was alive at day 30. Data on the effectiveness of rezafungin in patients with *FKS* mutations conferring echinocandin resistance are limited; however, this patient and two patients with *N. glabratus* candidiasis under the rezafungin expanded-access programme have been classified as having achieved mycological cure.<sup>3</sup> Rezafungin reaches high plasma concentrations early in therapy and may be better positioned to treat invasive candidiasis caused by *Candida* isolates with higher MICs. This is of particular importance given the shift in the epidemiology of infections caused by *N. glabratus*, *C. parapsilosis*, and other *Candida* species, with a reduced susceptibility to antifungal treatment of the aetiological isolates.<sup>80</sup>

The most relevant safety data regarding the use of rezafungin in adult patients with candidaemia or invasive candidiasis come from the pooled data of the STRIVE and ReSTORE studies. In total, 409 subjects were exposed to at least one dose of rezafungin, with data of 151 patients exposed to the recommended dose available. The median duration of the treatment was 14 days (range: 1–28). In the pooled population, 27.8% of patients randomised to rezafungin and 35.5% of those randomised to caspofungin, switching from intravenous to oral therapy. The rate of adverse events was higher in the rezafungin group than in the caspofungin group (92.1% vs. 83.1%), as were treatment-related adverse events (14.3% vs. 10.8%) and serious adverse events (55% vs. 48.8%). Treatment-related serious adverse events occurred in 2% of the patients in the rezafungin group and 3% in the caspofungin group. The most frequent adverse events were hypokalaemia (14.6% vs. 10.2%), pyrexia (11.9% vs. 6.6%), and diarrhoea (11.3% vs. 10.2%). Adverse events leading to treatment discontinuation occurred in 2% of patients in the rezafungin group and 2.4% in the caspofungin group. The most common serious adverse event was septic shock (6% in both treatment groups). Adverse events of special interest included infusion-related reactions, phototoxicity, tremor, and neuropathy.

Infusion-related reactions may occur with other echinocandins as well. The formulation of rezafungin contains relatively high concentrations of polysorbate, as do the formulations of other echinocandins. Infusion-related reactions may mimic anaphylactic reactions; however, they differ in that they usually resolve spontaneously and do not occur or recur when the drug is administered at slower infusion rates. Distinguishing infusion-related reactions from true anaphylaxis is crucial when using potentially life-saving agents, as an incorrect diagnosis of anaphylaxis may lead to unjustified discontinuation of therapy, whereas treatment can often be safely continued by reducing the infusion rate. The risk of infusion-related reactions can be minimised by adhering to,

and not exceeding, the infusion rates recommended in the product information.

The proportion of patients under 65 years of age was higher in the combined rezafungin group (90.8% vs. 77.6%). In patients aged 65 years or older, the incidence of adverse events leading to study discontinuation was 10.9% in the rezafungin group and 27.9% in the caspofungin group. Considering the safety results in special populations, it was concluded that dose adjustment is not necessary in patients aged 65 years or older with hepatic impairment, renal impairment, or based on weight. The number of neutropenic patients included in the pivotal study with rezafungin was small (7.4%). These patients often receive prophylactic antifungal treatment, making their recruitment in clinical trials challenging. However, there are no data suggesting a different response to rezafungin in these patients.<sup>23</sup>

Moreover, Honoré et al.<sup>56</sup> conducted a post hoc, pooled, exploratory analysis of the length-of-stay in hospital and ICU in the STRIVE and ReSTORE studies. They observed that patients treated with rezafungin had a shorter length-of-stay in hospital compared to those treated with caspofungin across all studied parameters, including total length-of-stay in hospital, ICU length-of-stay, and ICU length-of-stay in patients with mechanical ventilation.

Long-term therapy with echinocandins is necessary to treat some infections caused by azole-resistant *Candida* isolates, such as endocarditis or osteomyelitis, or certain aspergillosis, either in combination with other antifungal drugs or not. Daily intravenous treatment for these patients is associated with a poorer quality of life and a higher risk of health care-associated complications. The ReSTORE study did not include patients with forms of invasive candidiasis that typically require prolonged antifungal treatments, such as candidiasis associated with biofilm development (prosthetic candidiasis) or candidiasis located in organs or tissues in which echinocandins penetration is limited, such as the candidiasis of the central nervous system or the urinary tract.<sup>25,128</sup> However, there is a growing number of anecdotal case reports and small case series describing the successful and long-term use of rezafungin in difficult-to-treat cases of invasive candidiasis, such as natural valve and prosthetic valve endocarditis, osteomyelitis, prosthetic joint infection, or spondylodiscitis,<sup>4,21,42,50,64,72,92,104,132,134</sup> but more information on its efficacy against these forms of invasive candidiasis, or those caused by uncommon *Candida* species, would be desirable.

There are no direct comparisons of rezafungin with azoles or polyenes, nor with other echinocandins besides caspofungin. Available meta-analyses suggest rezafungin is as effective as other echinocandins. However, this conclusion is based mainly on the results of the phase 2 STRIVE study of rezafungin, with the results of the phase 3 ReSTORE study not being considered. Therefore, any interpretation should be treated with caution. Unlike the other echinocandins (anidulafungin, caspofungin and micafungin), which are administered by daily intravenous infusion, rezafungin is administered by weekly intravenous infusion. This weekly dosing regimen could offer a significant clinical advantage to these patients. In line with the results of the ReSTORE study, physicians would have considered that 16% of the patients could have been discharged a median of five to six days earlier if they did not require daily antifungal treatment.<sup>56</sup> In addition to the potential reduction in hospital stay duration and treatment burden, administration of antifungal medication on a weekly basis reduces the total volume of infusion needed, thereby decreasing the risk of intravenous fluid overload, which can be significant in certain patients, such as those with renal impairment or requiring dialysis.<sup>23,56</sup> Unlike other echinocandins, which are also indicated for use in paediatric populations, the use of rezafungin is limited to adult patients.<sup>5</sup>

Additionally, there are ongoing studies in the recruitment phase regarding the utility of rezafungin.<sup>142</sup> A multicentre, open-label

phase 1 study (NCT05534529) aims to evaluate the PK/PD, safety, and tolerability of a single intravenous dose of rezafungin in children receiving antifungal drugs for prophylactic treatment, or to treat confirmed or probable invasive mycoses. However, it should be noted that recruitment to this study has been halted for strategic reasons.

Another phase 2, proof-of-concept, multicentre, open-label, randomised study (NCT05835479) aims to evaluate the efficacy, safety, and tolerability of rezafungin with cotrimoxazole compared to cotrimoxazole monotherapy in adult patients with HIV suffering from *Pneumocystis jirovecii* pneumonia. A combination approach for the treatment of this fungal infection may be very promising, as the combination of an echinocandin and trimethoprim-sulfamethoxazole not only covers all stages of the *Pneumocystis* life cycle, but may also allow for dose reduction of trimethoprim-sulfamethoxazole, thereby reducing its associated toxicity and improving tolerability.<sup>67</sup>

Finally, a phase 3 study (NCT04368559, ReSPECT) is comparing the efficacy and safety of intravenous prophylaxis with rezafungin (for preventing invasive mycoses, including *P. jirovecii* pneumonia) with the standard treatment – fluconazole or posaconazole – for patients who have undergone allogeneic bone marrow transplants. Rezafungin 400 mg/200 mg once weekly is compared with a standard regimen containing daily azole prophylaxis with fluconazole or posaconazole and anti-*P. jirovecii* prophylaxis with oral trimethoprim-sulfamethoxazole. Fungal-free day 90 survival will be evaluated as the primary outcome.

### Infectologist's point of view

The incorporation of rezafungin into the therapeutic toolbox for treating invasive fungal infections is of significant importance to infectious disease specialists for several reasons. Firstly, rezafungin offers an optimal PK/PD profile that facilitates the rapid clearance of candidaemia, a feature inherently associated with improved patient outcomes. In the ReSTORE trial, the overall mortality was approximately 20%, which is notably low for this patient population. A recent European, multicentre, observational case-control study compared mortality in patients with candidaemia to that in matched controls. Matching was based on age, primary underlying disease, ICU versus non-ICU hospitalisation, and major surgery within two weeks prior to the index event. The overall mortality rate among patients with candidaemia was 40%, with an attributable mortality of 18.2%, compared to 22% in the control cohort. These findings suggest that clinical trials, such as ReSTORE, which involve patients with a baseline mortality close to 20%, may have limited power to assess antifungal efficacy in terms of mortality endpoints.

Nevertheless, several studies underscore the prognostic significance of early *Candida* eradication. A retrospective US study of 827 patients demonstrated that early mycological clearance ( $\leq 3$  days), defined by the timing of the last positive blood culture, was significantly associated with lower in-hospital ( $p = 0.005$ ) and 30-day mortality ( $p = 0.009$ ).<sup>81</sup> Additionally, a subgroup analysis of the ReSTORE trial reported higher rates of mycological eradication by day 5 with rezafungin (77.4%) compared to caspofungin (68.2%), with early clearance correlating with numerically lower mortality.<sup>129</sup> Early mycological clearance may also play a conceptual role in preventing the development of antifungal resistance, although further data are needed.

Moreover, early eradication of candidiasis has been associated with reduced healthcare costs. The same retrospective study found that early clearance was linked to significantly shorter hospital stays and decreased overall costs ( $p < 0.001$ ). Candidaemia poses a substantial economic burden, primarily driven by

extended hospitalisation and antifungal therapy costs, with per-patient expenditures ranging from \$48,487 to \$157,574.<sup>51,59,135</sup> Rezafungin has demonstrated other potential cost-saving advantages. Data from the STRIVE and ReSTORE studies indicated that patients treated with rezafungin had shorter hospital and ICU stays compared to those receiving daily echinocandins, resulting in substantial cost savings. These findings support the clinical and economic value of early, aggressive therapy aimed at rapid fungal clearance. Nevertheless, additional country-specific analyses are needed to identify the optimal timeframe for clearance that maximises both clinical and economic outcomes.

Beyond its PK/PD advantages, rezafungin's long half-life and weekly dosing schedule offer clear logistical and clinical benefits. In the Candida III cohort study conducted by the European Confederation of Medical Mycology (ECMM),<sup>31</sup> which included 621 patients across 64 hospitals in 20 countries, hospitalisation was extended by a median of 14 days in 16% of patients solely to complete parenteral antifungal therapy. An additional 4% required outpatient parenteral antifungal treatment. These data suggest that approximately one in five patients with candidaemia could benefit from the use of rezafungin to expedite hospital discharge.

Apart from ICU or haematologic patients, who will be discussed separately, the majority of “other” patients with candidaemia are elderly, with high comorbidity burdens and extensive use of concomitant medications.<sup>91</sup> The administration of rezafungin on a weekly basis, in conjunction with minimal drug–drug interactions and a favourable safety profile, renders it particularly suitable for this population, including patients with chronic or difficult-to-treat infections. Long-term echinocandin therapy is often required for treating azole-resistant *Candida* infections – such as endocarditis, osteomyelitis, and some forms of aspergillosis – either as monotherapy or in combination with other agents. Daily intravenous administration in these cases is associated with reduced quality of life and an increased risk of healthcare-associated complications. While the ReSTORE study did not include patients with forms of invasive candidiasis that typically require prolonged antifungal therapy, such as biofilm-associated infections (e.g., prosthetic valve endocarditis) or infections in sites with poor echinocandin penetration (e.g., central nervous system, urinary tract), an increasing number of case reports and small series have documented successful long-term use of rezafungin in such settings. These include natural and prosthetic valve endocarditis, osteomyelitis, prosthetic joint infections, and spondylodiscitis.<sup>4,21,42,50,64,72,92,104,132,134</sup> However, further evidence is needed to assess its efficacy in these complex clinical scenarios and in infections caused by uncommon *Candida* species.

### Intensivist's point of view

Critically ill patients are at risk of candidaemia and invasive candidiasis, with one-third to half of all candidaemia cases occurring in the ICU. Outcomes remain poor, with an estimated crude mortality rate of 40–55% in the ICU for invasive candidiasis.<sup>48,107</sup> Complicated intra-abdominal infections are the second leading cause of sepsis-related mortality and present a significant challenge for physicians, accounting for nearly 60% of all surgical patients with sepsis. Treatment focuses on effective intra-abdominal source control and appropriate antimicrobial therapy to reduce mortality. However, despite advancements in prevention, diagnosis, and treatment, mortality rates remain high, ranging from 20% to 60%.<sup>13,87</sup>

Classical echinocandins are established as first-line treatment for candidaemia<sup>146</sup> and invasive candidiasis, even in the most recent guidelines.<sup>24</sup> However, treatment must be individualised due to certain limitations that can influence the efficacy of the treatment and, consequently, the patient's prognosis. These

limitations<sup>62</sup> are mainly related to the speed of action of echinocandins, the avoidance of inappropriate empirical treatment, their activity against non-*C. albicans* species resistant to azoles, especially *C. parapsilosis*, *N. glabratus*, and *C. auris*, and the PK/PD properties with poor penetration into peritoneal fluid.<sup>87,147</sup> Therefore, new agents and/or dosing strategies are needed for critically ill patients with candidaemia and/or invasive candidiasis.

Rezafungin was developed to treat candidaemia and invasive candidiasis among other indications. Due to its special properties, which overcome the previously described limitations, the new European guidelines<sup>24</sup> strongly recommend the use of rezafungin for candidaemia, and do it moderately (at the same level as classical echinocandins) for intra-abdominal candidiasis. In the following paragraphs, we will describe the principal characteristics of rezafungin, focusing on the current limitations of echinocandins.

### *The timely initiation of appropriate antifungal therapy and its early benefits in reducing the time taken for a blood culture to turn negative*

It has been widely studied that timely initiation of appropriate antifungal therapy is essential; delay or inadequate treatment absolutely increases mortality.<sup>48,68,107</sup> Another important factor, less studied until now, is the benefit of reducing the time to negative blood culture. Both phase 2 and phase 3 trials suggested that rezafungin was associated with better time to negative blood culture and day 5 outcomes, including global (ReSTORE) or overall (STRIVE) cure and mycological eradication rates.<sup>128,130</sup> A pooled analysis of STRIVE and ReSTORE also confirmed these findings and suggested a potentially faster time to negative blood culture, especially in patients with a positive blood culture close to randomisation.<sup>129</sup> This may be particularly relevant in critically ill patients.

A post hoc, pooled, patient-level analysis of STRIVE and ReSTORE investigated the efficacy and safety of rezafungin compared with caspofungin in the subgroup of patients with candidaemia and/or invasive candidiasis who were in the ICU at randomisation. Of 294 patients in STRIVE/ReSTORE, 113 were in the ICU at randomisation (rezafungin  $n=46$ ; caspofungin  $n=67$ ).<sup>56</sup> The results provide further support for potential early treatment benefits with the rezafungin dosing regimen, as demonstrated by a reduced time to negative blood culture compared to caspofungin treatment and numerically higher mycological eradication rates on day 5.

The median time to negative blood culture was 18 hours (interquartile range, 12.6–43) in the rezafungin group, as opposed to 38 hours (interquartile range, 15.9–211.3) in the caspofungin group (stratified log-rank  $p=0.001$ ; nominal, not adjusted for multiplicity). Interestingly, the approximately 20-h difference in median time to negative blood culture between treatments was greater in the present subgroup of critically ill patients than in the individual trials (3-h treatment difference, approximately).<sup>128,130</sup> Furthermore, the mean time from the first positive blood sample to the initiation of any antifungal treatment for candidaemia/invasive candidiasis, and the time to the first dose of randomised treatment, were both longer for patients who received rezafungin than for those who received caspofungin. This is consistent with the data reported for the ReSTORE trial.<sup>128</sup> There was a similar trend in favour of rezafungin in the proportions of patients achieving negative blood cultures at 24 and 48 h in the ICU versus the overall population, although treatment differences between the groups were slightly greater in patients in the ICU versus the overall population.<sup>129</sup>

Mycological eradication rates on day 5 and 14 were 78.3% and 71.7% for rezafungin versus 59.7% and 65.7% for caspofungin, respectively. Safety profiles were similar between groups. Overall, the treatment of 17.4% of the patients under rezafungin

regimen and that of 29.9% of those under caspofungin was discontinued due to treatment-emergent adverse events. Finally, day 30 all-cause mortality rate was numerically higher, though not statistically significant, with rezafungin, but the mortality attributable to candidaemia/invasive candidiasis appeared to be similar in both treatment groups.

#### Activity against non-*C. albicans* species resistant to azoles and echinocandins

The increasing problem of azole and echinocandin resistance, particularly in relation to *N. glabratus* and *C. auris*, is a cause for concern.<sup>62</sup> In the ICU setting, antifungal-resistant isolates spread among patients; outbreaks of azole-resistant *C. parapsilosis* with similar genotypes and intra-hospital spread of azole-resistant *N. glabratus* have also been reported.<sup>10,18,33</sup> The lack of activity against these strains is worrying.

As previously mentioned, Soriano et al.<sup>124</sup> conducted a post hoc analysis using pooled data from the STRIVE/ReSTORE trials to determine clinical and mycological cure in the treatment of invasive candidiasis with rezafungin or caspofungin, based on the *Candida* species causing the infection and the in vitro antifungal susceptibility of the *Candida* isolates obtained from patients. Although global cure rates at day 14 were similar between both treatment groups for infections caused by *C. albicans* (61% – rezafungin – vs. 65.2% – caspofungin–) and *C. tropicalis* (70.4% vs. 63.6%), it is notable that cure rates were higher with rezafungin for candidiasis caused by *N. glabratus* (71.1% vs. 60%) and *C. parapsilosis* (78.6% vs. 55.6%).

Regarding mortality, all-cause mortality at day 30 in candidiasis caused by *C. albicans* (22% – rezafungin – vs. 18.8% – caspofungin–) and *N. glabratus* (15.8% vs. 11.4%) was similar in both treatment arms, but higher in those patients treated with caspofungin for invasive infections by *C. tropicalis* (18.5% – rezafungin – vs. 31.8% – caspofungin–) and *C. parapsilosis* (7.1% vs. 29.6%). Differences were also observed in mycological cure rates at days 5 and 14, where rezafungin achieved higher mycological cure rates for candidiasis caused by *N. glabratus* and *C. tropicalis*. Outcomes by *Candida* species were not associated with treatment-specific MICs.

Results from the ReSTORE rezafungin phase 3 clinical study also included in vitro results against *Candida*, but no patients with *C. auris* infections were included. In a mini-review of in vitro data for *Candida* species, including *C. auris*, isolated during clinical trials of three new antifungal drugs, fosmanogepix, ibrexafungerp, and rezafungin, recently published, rezafungin showed a good activity against this fungal species.<sup>32</sup> Furthermore, it has been demonstrated that *FKS1* mutations raised rezafungin MICs by a smaller amount than anidulafungin and micafungin MICs in *C. auris*.<sup>54</sup>

#### The PK/PD properties of echinocandins with poor penetration into peritoneal fluid

Intra-abdominal candidiasis should be addressed separately from candidaemia due to the peculiarity of the required penetration of antifungal drugs into the peritoneal cavity. Intra-abdominal concentrations may be further restricted in critically ill patients where pathophysiological factors alter normal drug distribution. However, echinocandins are recommended as first-line treatment in guidelines.<sup>24</sup> Controversial results about caspofungin concentrations in critically ill patients are found in the literature. Echinocandins are highly bound to albumin (>95%), thus, considering that only the unbound fraction is active and passively diffuses to the extravascular space, penetration into the peritoneal fluid is highly compromised. Moreover, the percentage of reduction in echinocandins peritoneal concentrations with respect to serum concentrations was reported to be approximately 33%.<sup>7,8,34–36</sup> Given that drug concentrations in peritoneal fluid are

often suboptimal, there is a genuine risk of promoting the emergence of antifungal resistance in *Candida* isolates responsible for intra-abdominal candidiasis, making intra-abdominal microbiota a reservoir of non-susceptible isolates, as occurs with bacteria. Mean peritoneal concentrations of the three classical echinocandins were reported to be always below the mutant prevention concentrations. For all these reasons, abdominal candidiasis has been pointed out as a hidden reservoir of echinocandin resistance.<sup>87</sup> The likelihood of achieving effective exposures with current dosing regimens of first-generation echinocandins (anidulafungin, caspofungin, and micafungin) is also unclear, especially regarding resistant *Candida* species. It is clear that new agents and/or dosing strategies are needed for critically ill patients with candidaemia and/or invasive candidiasis. However, considering the published evidence, these data suggest that higher doses – an approach proposed by some authors – may be required to achieve adequate PK levels in peritoneal fluid. Furthermore, liposomal amphotericin B is advocated as first-line therapy in patients with sepsis/septic shock presenting with candidaemia or endophthalmitis, or with prior exposure to echinocandins and/or fluconazole, or with infections by *N. glabratus*.<sup>87</sup> Rezafungin's long half-life (~5–6 days) and high front-loaded dosing allow for extended-interval dosing and high plasma drug concentrations early in therapy. This is due to the concentration-dependent efficacy of echinocandins for intra-abdominal candidiasis, which overcomes the limitations of previous echinocandins.

To sum up, due to the special characteristics of rezafungin, this new antifungal drug should be considered as first-line therapy in these circumstances over classical echinocandins in the ICU setting.

#### Haematologist's point of view

Patients with haematological malignancies are at high risk of invasive candidiasis, primarily due to an inadequate immune response. Neutropenia is a major risk factor for the development of invasive candidiasis. Neutropenia may be caused by the underlying haematologic disease itself, may be a side effect of anti-tumour treatment (cytotoxic drugs or radiotherapy), occur in the context of haematopoietic transplantation (both during the pre-engraftment period and in cases of graft-versus-host disease), or be a side effect of adjuvant medication, including antimicrobial drugs. Neutropenia is also a marker of chemotherapy intensity. Patients with chemotherapy-induced neutropenia associated with infection (known as febrile neutropenia) also exhibit other common risk factors for invasive candidiasis: use of broad-spectrum antibiotics, need for intravascular catheter cannulation for drug administration, development of post-chemotherapy mucositis, need for parenteral nutrition, or admission to critical care units. In this context, patients diagnosed with haematologic malignancies, especially those with acute leukaemia or haematopoietic transplant recipients, have been classically considered at high risk for developing invasive candidiasis.<sup>73,83</sup>

The incidence and mortality of invasive candidiasis in patients with haematologic malignancies have decreased in recent years.<sup>78</sup> The first milestone associated with this change was the universalisation, in the early 1990s, of fluconazole as a prophylactic strategy in patients with high-risk haematologic malignancies, aiming to reduce the previously unacceptable incidence and mortality rates secondary to invasive candidiasis.<sup>85,86,120</sup> Moreover, the approval of new antifungal drugs and their early use in patients with high-risk febrile neutropenia have achieved better infectious control and a decrease in mortality associated with invasive candidiasis.<sup>125</sup> Despite this, reported mortality rates in invasive candidiasis in haematologic patients vary between 17% and 45%, with significant differences depending on the underlying haematologic disease and

whether the patient is a recipient of a haematopoietic stem cell transplant.<sup>44,98,105</sup>

Although various studies highlight that invasive candidiasis is currently a less significant problem than in the past, new challenges have emerged in recent years in the context of patients with haematological malignancies. The widespread use of fluconazole and posaconazole for antifungal prophylaxis in high-risk haematologic patients is associated with a decreased incidence of invasive candidiasis due to *C. albicans*, which has led to an epidemiological shift in the distribution of *Candida* species causing invasive candidiasis in these patients. It has been described an increase in breakthrough invasive candidiasis and a current predominance of *Candida* species other than *C. albicans*, including former *Candida* species (*C. parapsilosis*, *N. glabratus*, *P. kudriavzevii*), reaching between 66.9% and 90% of the isolates reported in various studies.<sup>105,106</sup> These species are associated with both intrinsic and extrinsic azole resistance. Although this epidemiological change does not seem to negatively impact haematological patients' mortality, the epidemiological evolution could prompt a re-evaluation of our prophylactic approaches.<sup>69</sup>

Simultaneously, in the last 30 years, the diagnosis and treatment of haematological malignancies have undergone extraordinary progress. The introduction of imatinib for the treatment of chronic myeloid leukaemia in 2001 paved the way for precision medicine, leading to a novel landscape of therapeutic strategies directed against specific targets, aiming to improve patient survival while minimising the toxicity associated with classical chemotherapy drugs.<sup>29,114</sup> Among the different groups of treatments, monoclonal, conjugated and bispecific antibodies, checkpoint inhibitors, small molecule inhibitors and, more recently, CAR-T therapy, stand out.<sup>1,6,96,100</sup> All these drug groups target specific cell lines or signalling pathways and have changed the natural history of various haematological malignancies, such as diffuse large B-cell lymphoma or chronic lymphocytic leukaemia. However, these treatments are associated with different toxicities on the immune system, which, together with their general reservation for patients in a relapsed or refractory status, has led to the emergence of new risk profiles for invasive mycoses in patients with haematologic malignancies.<sup>9,63,119</sup>

Rezafungin, a next-generation echinocandin, has potent in vitro activity against most *Candida* species, including azole-resistant *Candida* species. Rezafungin combines the high efficacy of echinocandins with a prolonged half-life, a low rate of drug–drug interactions, and a favourable safety profile.<sup>95</sup> The clinical efficacy of rezafungin in the treatment of candidemia and invasive candidiasis was established in the randomised, controlled Phase 2 STRIVE and Phase 3 ReSTORE trials, which demonstrated that rezafungin is non-inferior to caspofungin for all-cause mortality.<sup>128,130</sup> However, the number of neutropenic patients included in these studies is low, with only 7.4% of the total patients. Additionally, haematological patients are underrepresented in these trials, partly due to the prophylactic antifungal treatment they usually receive, which is an exclusion criterion in most clinical trials. Nevertheless, there are no data suggesting a different response to rezafungin in these patients in terms of efficacy and safety, and no differences in response rate and serious treatment-related adverse effects were detected.

Rezafungin is of particular interest for the treatment of invasive candidiasis in haematological patients. Firstly, rezafungin can be safely administered in patients with renal impairment, as it is non-renal excreted, making it particularly useful in the context of renal insufficiency, a relatively frequent situation in haematological patients secondary to the administration of certain cytotoxic drugs such as cisplatin, methotrexate, melphalan, cyclophosphamide, or as a consequence of different immunosuppressive drugs such as calcineurin inhibitors (cyclosporine or tacrolimus).<sup>93,116</sup> Rezafungin has potential clinical use in the treatment of invasive candidiasis

in patients under immunosuppressive treatment after allogeneic transplantation. It can also be safely administered in patients with hepatic insufficiency.<sup>57</sup> Furthermore, rezafungin does not affect the QTc interval. This makes its use in managing invasive candidiasis in patients receiving chemotherapy treatments that prolong the QT interval, such as arsenic trioxide or tyrosine kinase inhibitors like dasatinib or nilotinib, particularly interesting.<sup>2,38,39,66</sup>

Secondly, an important issue with new targeted therapies is drug-to-drug interactions. Rezafungin is neither a substrate, inhibitor, nor inducer of cytochrome P450 enzymes. Additionally, interactions of rezafungin with various drugs, such as venetoclax, have been studied. Co-administration of rezafungin and venetoclax caused a reduction in its AUC or  $C_{max}$ , but did not result in a clinically significant reduction in drug exposure.<sup>40</sup> Venetoclax, an oral inhibitor of the anti-apoptotic BCL-2 protein, can be used for the treatment of acute myeloid leukaemia in combination with azacitidine as induction therapy in patients ineligible for intensive chemotherapy. This is a high-risk scenario for the development of invasive candidiasis, so the absence of interactions could potentially allow us to treat an infection without antifungal adjustment, thus not compromising our patient's clinical outcomes.

Finally, given the prolonged half-life of rezafungin that allows a weekly administration along with a favourable drug–drug interaction profile, its potential usefulness as antifungal prophylaxis in high-risk haematologic patients is under study. Current guidelines recommend the use of fluconazole or voriconazole/posaconazole as first-line antifungal prophylaxis for allogeneic haematopoietic stem cell transplant recipients. Additionally, prophylactic posaconazole is recommended for patients with graft-versus-host disease.<sup>27,83</sup> Azole prophylaxis decreases the incidence of invasive fungal infection in allogeneic haematopoietic stem cell transplant recipients.<sup>85,86,120,133,139</sup> However, there are still some concerns, primarily regarding drug-to-drug interactions, toxicity, safety, and tolerability.<sup>15</sup> Echinocandins are not routinely recommended as prophylactic strategies because they must be infused daily, and there is a lack of trials supporting their efficacy in this setting. In this context, the ReSPECT clinical trial, a multicentre, randomised, double-blind, phase 3 clinical trial, will evaluate the efficacy of rezafungin versus the standard of care (fluconazole or posaconazole plus trimethoprim–sulfamethoxazole) as a prophylactic strategy in adults undergoing allogeneic stem cell transplantation. The primary endpoint of fungal-free survival at day 90 aims to assess efficacy during the acute phase of allogeneic haematopoietic stem cell transplantation. This trial will be the first to evaluate the efficacy of an echinocandin in preventing invasive fungal infection in patients undergoing allogeneic haematopoietic stem cell transplantation and will open the door to investigating the potential benefits of antifungal prophylaxis with rezafungin in different settings.

## Conclusions

Rezafungin has the potential to complement the existing antifungal toolbox and address many needs in the care of invasive mycoses, improving patient outcomes. The strengths of the echinocandins, combined with the prolonged half-life and robust safety profile of rezafungin, open several possibilities for future use.<sup>23</sup> The greatest promise of rezafungin lies in its prolonged half-life, favourable safety profile, and high initial drug exposure, which can reduce fungal burden and prevent or limit the development of resistance. As outlined in a recent European guideline,<sup>24</sup> the primary intended use of rezafungin is the targeted treatment of invasive candidiasis, with a particular emphasis on candidaemia. Furthermore, the weekly intravenous infusion of rezafungin has the potential to facilitate earlier hospital discharge and extended

outpatient treatment, which will be of particular benefit to those with candidaemia without focal invasive candidiasis. A key benefit would be the treatment of candidiasis in cases requiring prolonged therapy, such as intra-abdominal candidiasis. For patients requiring daily echinocandin therapy, rezafungin can ease healthcare burdens, and for patients with resistant or refractory infections, the unique pharmacokinetic parameters of rezafungin may offer significant benefits. Patient populations that may benefit include those with abdominal surgery and anastomotic leak. However, the potential benefit of its use in forms of invasive candidiasis, such as endocarditis, endophthalmitis and other fungal sanctuary infections, requires more data as current information is limited to anecdotal cases or small case series.<sup>3,4,21,42,50,52,64,72,92,104,132,134</sup> The use of rezafungin as a prophylactic agent to prevent invasive candidiasis, aspergillosis, and pneumocystosis, given the activity of rezafungin against *Candida*, *Aspergillus*, and *Pneumocystis*, could surpass current multidrug regimens in onco-haematology patients. Weekly dosing with limited drug–drug interactions may also be attractive for prophylaxis during the early phase of solid organ transplantation (e.g., liver). Furthermore, the theoretical risk of in vivo resistance development (*FKS* mutant selection) resulting from prolonged drug exposure with subtherapeutic concentrations for at least part of the treatment period is a valid concern. However, there have been no signals thus far, either in vitro or clinical studies, indicating a clinical impact of echinocandin resistance.

The availability of rezafungin with its prolonged antifungal action may represent a significant change in the pharmacological treatment of candidiasis and other invasive mycoses, as it combines the strengths of echinocandins with a prolonged half-life, a low likelihood of drug–drug interactions, and a robust safety profile. These properties may allow for earlier hospital discharge of patients with favourable clinical conditions and enable outpatient treatment when prolonged treatment duration is expected. When ongoing clinical trials are completed, and considering the results of STRIVE and ReSTORE clinical studies, rezafungin may also emerge as an outpatient parenteral antimicrobial therapy for long-term antifungal treatment of candidiasis and potentially other mycoses, such as aspergillosis, as well as for outpatient parenteral antimicrobial prophylaxis.<sup>21</sup> The authors acknowledge the limitations of this review manuscript as it is not a systematic review or meta-analysis, and there is potential for bias in the selection of data and scientific articles by the authors. Additionally, clinical and microbiological data are continuously expanding and are limited or non-existent in some areas, and patients will be evaluated in future studies.

To conclude, the spectrum of invasive mycoses may change in the coming decades, associated with advances in medicine, the increase in the population at risk of mycoses, and climate changes, which may induce the emergence of new fungal pathogens and antifungal resistance. It is also likely that the treatment of invasive mycoses will evolve. We hope that rezafungin will fill important gaps in the current therapeutic options and contribute to improving patient survival due to its PK/PD advantages, limited drug–drug interactions, and good tolerability. However, further research is required to address the knowledge that will be filled once rezafungin is used in real-world clinical scenarios.

### Conflict of interest

GQ has received funding and has participated in Advisory Boards or Speaker services for Astellas Pharma, Evidenze, Gilead, Merck, Sharp & Dohme (MSD), Palau Pharma (Noucor), Pfizer, and Scynexis.

RZ has not specific conflicts of interest related to the current manuscript but declare the following: RZ has received funding and has participated in Advisory Boards and/or Speaker services for Gilead, Pfizer and Mundipharma.

CG has received funding and participated in sponsored talks for Pfizer, MSD, Gilead, Shionogi, AdvanzPharma, bioMérieux, Viatris and Mundipharma; in Advisory Boards for Advanz Pharma and Pfizer; and has received grants from Gilead and Mundipharma.

XMM has no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

### Acknowledgments

This study was supported by the Department of Education, Universities, and Research of the Basque Government (GIC21/24 IT1607-22) and by Mundipharma.

### References

1. Abbasi S, Totmaj MA, Abbasi M, Hajazimian S, Goleij P, Behrooz J, et al. Chimeric antigen receptor T (CAR-T) cells: novel cell therapy for hematological malignancies. *Cancer Med*. 2023;12:7844–58. <http://dx.doi.org/10.1002/cam4.5551>.
2. Abu Rmilah AA, Lin G, Begna KH, Friedman PA, Herrmann J, Risk of QTc prolongation among cancer patients treated with tyrosine kinase inhibitors. *Int J Cancer*. 2020;147:3160–7. <http://dx.doi.org/10.1002/ijc.33119>.
3. Adeel A, Qu MD, Siddiqui E, Levitz SM, Ellison RT III. Expanded access use of rezafungin for salvage therapy of invasive *Candida glabrata* infection: a case report. *Open Forum Infect Dis*. 2021;8. <http://dx.doi.org/10.1093/ofid/ofab431>, ofab431.
4. Adelman MW, Andes DR. Case commentary: extending our therapeutic range against multidrug-resistant *Candida*. *Antimicrob Agents Chemother*. 2024;68. <http://dx.doi.org/10.1128/aac.00847-24>, e0084724.
5. AEMPS. Agencia Española de Medicamentos y de Productos Sanitarios. Informe de Posicionamiento Terapéutico de rezafungina (Rezzayo®) en el tratamiento de la candidiasis invasiva en adultos; 2024. Available from: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2024/IPT-324-Rezzayo-rezafungina.pdf>
6. Ahn IE, Brown JR. Targeting Bruton's tyrosine kinase in CLL. *Front Immunol*. 2021;12:687458. <http://dx.doi.org/10.3389/fimmu.2021.687458>.
7. Albanell-Fernández M. Echinocandins pharmacokinetics: a comprehensive review of micafungin, caspofungin, anidulafungin, and rezafungin population pharmacokinetic models and dose optimization in special populations. *Clin Pharmacokinet*. 2025;64:27–52. <http://dx.doi.org/10.1007/s40262-024-01461-5>.
8. Andes D, Brüggemann RJ, Flanagan S, Lepak AJ, Lewis RE, Ong V, et al. The distinctive pharmacokinetic profile of rezafungin, a long-acting echinocandin developed in the era of modern pharmacometrics. *J Antimicrob Chemother*. 2025;80:18–28. <http://dx.doi.org/10.1093/jac/dkaf415>.
9. Andreescu M. Risk of severe infections secondary to the use of targeted therapies in hematological malignancies. *Cureus*. 2024;16:e2050. <http://dx.doi.org/10.7759/cureus.52050>.
10. Arendrup MC, Arıkan-Akdagli S, Jørgensen KM, Barac A, Steinmann J, Toscano C, et al. European candidaemia is characterised by notable differential epidemiology and susceptibility pattern: Results from the ECMM Candida III study. *J Infect*. 2023;87:428–37. <http://dx.doi.org/10.1016/j.jinf.2023.08.001>.
11. Arendrup MC, Meletiadis J, Zaragoza O, Jørgensen KM, Marcos-Zambrano LJ, Kanioura L, et al. Multicentre determination of rezafungin (CD101) susceptibility of *Candida* species by the EUCAST method. *Clin Microbiol Infect*. 2018;24:1200–4. <http://dx.doi.org/10.1016/j.cmi.2018.02.021>.
12. Balázs D, Tóth Z, Locke JB, Borman AM, Forgács L, Balla N, et al. In vivo efficacy of rezafungin, anidulafungin, caspofungin, and micafungin against four *Candida auris* clades in a neutropenic mouse bloodstream infection model. *J Fungi (Basel)*. 2024;10:617. <http://dx.doi.org/10.3390/jof10090617>.
13. Bassetti M, Giacobbe DR, Vena A, Trucchi C, Ansaldi F, Antonelli M, et al. Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project. *Crit Care*. 2019;23:219. <http://dx.doi.org/10.1186/s13054-019-2497-3>.
14. Bassetti M, Stewart A, Bartalucci C, Vena A, Giacobbe DR, Roberts J. Rezafungin acetate for the treatment of candidemia and invasive candidiasis: a pharmacokinetic evaluation. *Expert Opin Drug Metab Toxicol*. 2025;21:125–32. <http://dx.doi.org/10.1080/17425255.2024.2424899>.
15. Benitez LL, Carver PL. Adverse effects associated with long-term administration of azole antifungal agents. *Drugs*. 2019;79:833–53. <http://dx.doi.org/10.1007/s40265-019-01127-8>.
16. Carvalhaes CG, Klauer AL, Rhomberg PR, Pfäller MA, Castanheira M. Evaluation of rezafungin provisional CLSI Clinical Breakpoints and Epidemiological Cutoff Values tested against a worldwide collection of contemporaneous invasive fungal isolates (2019–2020). *J Clin Microbiol*. 2022;60:e0244921. <http://dx.doi.org/10.1128/jcm.02449-21>.

17. Carvalhaes CG, Rhomberg PR, Pfaller MA, Locke JB, Castanheira M. Evaluation of the post-antifungal effect of rezafungin and micafungin against *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*. *Mycoses*. 2022;65:1040–4, <http://dx.doi.org/10.1111/myc.13490>.
18. Castanheira M, Deshpande LM, Kimbrough JH, Winkler M. Activity of rezafungin against echinocandin non-wild type *Candida glabrata* clinical isolates from a global surveillance program. *Open Forum Infect Dis*. 2025;12, <http://dx.doi.org/10.1093/ofid/ofae702>, ofae702.
19. Ceballos-Garzon A, Holzapfel M, Welsch J, Mercer D. Identification and antifungal susceptibility patterns of reference yeast strains to novel and conventional agents: a comparative study using CLSI EUCAST and Sensititre YeastOne methods. *JAC Antimicrob Resist*. 2025;7, <http://dx.doi.org/10.1093/jacamr/dlaf040>, dlaf040.
20. Chandra J, Ghannoum MA. CD101, a novel echinocandin, possesses potent antibiofilm activity against early and mature *Candida albicans* biofilms. *Antimicrob Agents Chemother*. 2018;62:e01750–1817, <http://dx.doi.org/10.1128/AAC.01750-17>.
21. Clarke F, Grenfell A, Chao S, Richards H, Korman T, Rogers B. Use of echinocandin outpatient parenteral antimicrobial therapy for the treatment of infection caused by *Candida* spp.: utilization, outcomes and impact of a change to weekly dosing. *J Antimicrob Chemother*. 2024;79:2896–900, <http://dx.doi.org/10.1093/jac/dkac302>.
22. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID\* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18 Suppl. 7:19–37, <http://dx.doi.org/10.1111/1469-0691.12039>.
23. Cornely OA, Dupont H, Mikulska M, Rautemaa-Richardson R, García-Vidal C, Thompson GR III, et al. Rezafungin in special populations with candidaemia and/or invasive candidiasis. *J Infect*. 2025;90:106435, <http://dx.doi.org/10.1016/j.jinf.2025.106435>.
24. Cornely OA, Sprute R, Bassetti M, Chen SC, Groll AH, Kurzai O, et al. Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect Dis*. 2025, [http://dx.doi.org/10.1016/S1473-3099\(24\)00749-7](http://dx.doi.org/10.1016/S1473-3099(24)00749-7), S1473-3099(24)00749-7.
25. Cuervo G, García-Vidal C, Puig-Asensio M, Vena A, Meije Y, Fernández-Ruiz M, et al. Echinocandins compared to fluconazole for candidemia of a urinary tract source: a propensity score analysis. *Clin Infect Dis*. 2017;64:1374–9, <http://dx.doi.org/10.1093/cid/cix033>.
26. Cushion MT, Ashbaugh A. The long-acting echinocandin, rezafungin, prevents *Pneumocystis pneumonia* and eliminates *Pneumocystis* from the lungs in prophylaxis and murine treatment models. *J Fungi (Basel)*. 2021;7:747, <http://dx.doi.org/10.3390/jof7090747>.
27. Dadwal SS, Hohl TM, Fisher CE, Boeckh M, Papanicolaou G, Carpenter PA, et al. American Society of Transplantation and Cellular Therapy series. 2: Management and prevention of aspergillosis in hematopoietic cell transplantation recipients. *Transplant Cell Ther*. 2021;27:201–11, <http://dx.doi.org/10.1016/j.jtct.2020.10.003>.
28. Denning DW. Global incidence and mortality of severe fungal disease. *Lancet Infect Dis*. 2024;24:e428–38, [http://dx.doi.org/10.1016/S1473-3099\(23\)00692-8](http://dx.doi.org/10.1016/S1473-3099(23)00692-8).
29. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355:2408–17, <http://dx.doi.org/10.1056/NEJMoa062867>.
30. Egger M, Hoenigl M, Thompson GR III, Carvalho A, Jenks JD. Let's talk about sex characteristics – as a risk factor for invasive fungal diseases. *Mycoses*. 2022;65:599–612, <http://dx.doi.org/10.1111/myc.13449>.
31. Egger M, Salmanton-García J, Barac A, Gangneux JP, Guegan H, Arsic-Arsenijevic V, et al. Predictors for prolonged hospital stay solely to complete intravenous antifungal treatment in patients with candidemia: results from the ECMM Candida III Multinational European Observational Cohort Study. *Mycopathologia*. 2023;188:983–94, <http://dx.doi.org/10.1007/s11046-023-00776-4>.
32. Espinel-Ingroff A, Wiederhold NP. A mini-review of in vitro data for *Candida* species, including *C. auris*, isolated during clinical trials of three new antifungals: fosmanogepix, ibrexafungerp, and rezafungin. *J Fungi (Basel)*. 2024;10:362, <http://dx.doi.org/10.3390/jof10050362>.
33. EUCAST. Rezafungin Rationale Document from the AFST. Available from: [https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Rationale\\_documents/Rezafungin\\_RD.v1.0\\_final.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Rezafungin_RD.v1.0_final.pdf).
34. European Medicines Agency. Cancidas (caspofungin). Available from: <https://www.ema.europa.eu/en/documents/product-information/cancidas-epar-product-information.en.pdf>.
35. European Medicines Agency. Ecalta (anidulafungin). Available from: <https://www.ema.europa.eu/en/documents/product-information/ecalta-epar-product-information.en.pdf>.
36. European Medicines Agency. Mycamine (micafungin). Available from: <https://www.ema.europa.eu/en/documents/product-information/mycamine-epar-product-information.en.pdf>.
37. European Medicines Agency. Rezzayo (rezafungin). Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/rezzayo>.
38. Flanagan S, Goodman DB, Jandourek A, O'Reilly T, Sandison T. Lack of effect of rezafungin on QT/QTc interval in healthy subjects. *Clin Pharmacol Drug Dev*. 2020;9:456–65, <http://dx.doi.org/10.1002/cpdd.757>.
39. Flanagan S, Ong V, Marbury T, Jandourek A, Gandhi RG, Sandison T. Phase I study of the pharmacokinetics and safety of rezafungin in subjects with moderate/severe hepatic impairment and matched control subjects. *Pharmacotherapy*. 2024;44:435–43, <http://dx.doi.org/10.1002/phar.2943>.
40. Flanagan S, Walker H, Ong V, Sandison T. Absence of clinically meaningful drug–drug interactions with rezafungin: outcome of investigations. *Microbiol Spectr*. 2023;11:e0133923, <http://dx.doi.org/10.1128/spectrum.01339-23>.
41. Food and Drug Administration. Rezzayo. Available from: <https://www.fda.gov/media/180688/download>.
42. Forriester NM, McCarty TP, Pappas PG. New perspectives on antimicrobial agents: rezafungin. *Antimicrob Agents Chemother*. 2025;69:e0064623, <http://dx.doi.org/10.1128/aac.00646-23>.
43. Fung S, Shirley M. Rezafungin: a review in invasive candidiasis. *Drugs*. 2025;85:415–23, <http://dx.doi.org/10.1007/s40265-024-02134-0>.
44. Gamaletsou MN, Walsh TJ, Zaoutis T, Pagoni M, Kotsopoulou M, Voulgarelis M, et al. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. *Clin Microbiol Infect*. 2014;20:050–7, <http://dx.doi.org/10.1111/1469-0691.12312>.
45. García-Bustos V, Cabañero-Navalon MD, Ruiz-Gaitán A, Salavert M, Tormo-Mas MÁ, Pemán J. Climate change, animals, and *Candida auris*: insights into the ecological niche of a new species from a One Health approach. *Clin Microbiol Infect*. 2023;29:858–62, <http://dx.doi.org/10.1016/j.cmi.2023.03.016>.
46. García-Effron G. Rezafungin: mechanisms of action, susceptibility and resistance: similarities and differences with the other echinocandins. *J Fungi (Basel)*. 2020;6:262, <http://dx.doi.org/10.3390/jof6040262>.
47. García-Vidal C, Alastruey-Izquierdo A, Aguilar-Guisado M, Carratalà J, Castro C, Fernández-Ruiz M, et al. Executive summary of clinical practice guideline for the management of invasive diseases caused by *Aspergillus*: 2018 update by the GEMICOMED-SEIMC/REIPI. *Enferm Infect Microbiol Clin (Engl Ed)*. 2019;37:535–41, <http://dx.doi.org/10.1016/j.eimc.2018.03.018>.
48. Garnacho-Montero J, Díaz-Martín A, Cantón-Bulnes L, Ramírez P, Sierra R, Arias-Verdú D, et al. Initial antifungal strategy reduces mortality in critically ill patients with candidemia: a propensity score-adjusted analysis of a multicenter study. *Crit Care Med*. 2018;46:384–93, <http://dx.doi.org/10.1097/CCM.0000000000002867>.
49. Giannella M, Lantermier F, Dellièrre S, Groll AH, Mueller NJ, Alastruey-Izquierdo A, et al. ECCMID study groups on Invasive Fungal Infection and Infection in Immunocompromised Hosts. Invasive fungal disease in the immunocompromised host: changing epidemiology, new antifungal therapies, and management challenges. *Clin Microbiol Infect*. 2025;31:29–36, <http://dx.doi.org/10.1016/j.cmi.2024.08.006>.
50. Grasselli Kmet N, Luzzati R, Monticelli J, Babich S, Conti J, Bella SD. Salvage therapy of complicated *Candida albicans* spondylodiscitis with Rezafungin. *Eur J Clin Microbiol Infect Dis*. 2025, <http://dx.doi.org/10.1007/s10096-025-05117-5>.
51. Grau S, Pozo JC, Romá E, Salavert M, Barrueta JA, Peral C, et al. Cost-effectiveness of three echinocandins and fluconazole in the treatment of candidemia and/or invasive candidiasis in nonneutropenic adult patients. *Clinicoecon Outcomes Res*. 2015;7:527–35, <http://dx.doi.org/10.2147/CEOR.S91587>.
52. Gressens SB, Rouzard C, Lamoth F, Calandra T, Lantermier F, Lortholary O. Duration of systemic antifungal therapy for patients with invasive fungal diseases: a reassessment. *Mol Aspects Med*. 2025;103:101347, <http://dx.doi.org/10.1016/j.mam.2025.101347>.
53. Hager CL, Larkin EM, Long LA, Ghannoum MA. Evaluation of the efficacy of rezafungin, a novel echinocandin, in the treatment of disseminated *Candida auris* infection using an immunocompromised mouse model. *J Antimicrob Chemother*. 2018;73:2085–8, <http://dx.doi.org/10.1093/jac/dky153>.
54. Helleberg M, Jørgensen KM, Hare RK, Dattu R, Chowdhary A, Arendrup MC. Rezafungin in vitro activity against contemporary Nordic clinical *Candida* isolates and *Candida auris* determined by the EUCAST reference method. *Antimicrob Agents Chemother*. 2020;64:e02438–19, <http://dx.doi.org/10.1128/AAC.02438-19>.
55. Hoenigl M, Arastehfar A, Arendrup MC, Brüggemann R, Carvalho A, Chiller T, et al. Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease. *Clin Microbiol Rev*. 2024;37:e0007423, <http://dx.doi.org/10.1128/cmr.00074-23>.
56. Honoré PM, Girardis M, Kollef M, Cornely OA, Thompson GR III, Bassetti M, et al. Rezafungin versus caspofungin for patients with candidaemia or invasive candidiasis in the intensive care unit: pooled analyses of the ReSTORE and STRIVE randomised trials. *Crit Care*. 2024;28:348, <http://dx.doi.org/10.1186/s13054-024-05117-5>.
57. Huguet J, Ong V, Sandison T, Melara RM, Marbury TC, Jandourek A, et al. 982. Effect of hepatic impairment on the safety and pharmacokinetics of rezafungin. *Open Forum Infect Dis*. 2021;8 Suppl. 1:582–3, <http://dx.doi.org/10.1093/ofid/ofab466.1176>.
58. Jauregizar N, Quindós G, Gil-Alonso S, Suárez E, Sevilano E, Eraso E. Postantifungal effect of antifungal drugs against *Candida*: what do we know and how can we apply this knowledge in the clinical setting? *J Fungi (Basel)*. 2022;8:727, <http://dx.doi.org/10.3390/jof8070727>.
59. Jeck J, Jakobs F, Kurte MS, Cornely OA, Kron F. Health-economic modelling of cost savings due to the use of rezafungin based on a German cost-of-illness study of candidiasis. *JAC Antimicrob Resist*. 2023;5, <http://dx.doi.org/10.1093/jacamr/dlad079>, dlad079.
60. Jenks JD, Aneke CI, Al-Obaidi MM, Egger M, García L, Gaines T, et al. Race and ethnicity: risk factors for fungal infections? *PLoS Pathog*. 2023;19:e1011025, <http://dx.doi.org/10.1371/journal.ppat.1011025>.

61. Jenks JD, Gangneux JP, Schwartz IS, Alastruey-Izquierdo A, Lagrou K, Thompson GR III, et al. Diagnosis of breakthrough fungal infections in the clinical mycology laboratory: an ECMM consensus statement. *J Fungi (Basel)*. 2020;6:216. <http://dx.doi.org/10.3390/jof6040216>.
62. José P, Alvarez-Lerma F, Maseda E, Olaechea P, Pemán J, Soriano C, et al. Invasive fungal infection in critically ill patients: hurdles and next challenges. *J Chemother*. 2019;31:64–73. <http://dx.doi.org/10.1080/1120009X.2018.1557799>.
63. Kampouri E, Little JS, Rejeski K, Manuel O, Hammond SP, Hill JA. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. *Transpl Infect Dis*. 2023;25 Suppl. 1:e14157. <http://dx.doi.org/10.1111/tid.14157>.
64. Keck JM, Dare RK, Jenkins MB, Rico JC, Grisham L, McDonald J, et al. It's here, it's there, there's fungi everywhere: a case series utilizing rezafungin for invasive candidiasis. *Infect Dis Ther*. 2025. <http://dx.doi.org/10.1007/s40121-025-01120-7>.
65. Kessel B, Baker DE. Formulary drug review: rezafungin. *Hosp Pharm*. 2024;59:245–53. <http://dx.doi.org/10.1177/00185787231206523>.
66. Khatib R, Sabir FRN, Omari C, Pepper C, Tayebjee MH. Managing drug-induced QT prolongation in clinical practice. *Postgrad Med J*. 2021;97:452–8. <http://dx.doi.org/10.1136/postgradmedj-2020-138661>.
67. Koehler P, Prattes J, Simon M, Haensel L, Hellmich M, Cornely OA. Which trial do we need? Combination treatment of *Pneumocystis jirovecii* pneumonia in non-HIV infected patients. *Clin Microbiol Infect*. 2023;29:1225–8. <http://dx.doi.org/10.1016/j.cmi.2023.05.004>.
68. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to *Candida* infection: importance of empiric therapy and sourcecontrol. *Clin Infect Dis*. 2012;54:1739–46. <http://dx.doi.org/10.1093/cid/cis305>.
69. Kontoyiannis DP, Reddy BT, Hanna H, Bodey GP, Tarrand J, Raad II. Breakthrough candidemia in patients with cancer differs from de novo candidemia in host factors and *Candida* species but not intensity. *Infect Control Hosp Epidemiol*. 2002;23:542–5. <http://dx.doi.org/10.1086/502104>.
70. Kovács R, Tóth Z, Locke JB, Forgács L, Kardos G, Nagy F, et al. Comparison of in vitro killing activity of rezafungin, anidulafungin, caspofungin, and micafungin against four *Candida auris* clades in RPMI-1640 in the absence and presence of human serum. *Microorganisms*. 2021;9:863. <http://dx.doi.org/10.3390/microorganisms9040863>.
71. Kriegl L, Egger M, Boyer J, Hoenigl M, Krause R. New treatment options for critically important WHO fungal priority pathogens. *Clin Microbiol Infect*. 2024. <http://dx.doi.org/10.1016/j.cmi.2024.03.006>. S1198–743X(24)00118–6.
72. Lahouati M, Tinévez C, Gabriel F, Xuereb F, Lefranc M, Dauchy FA. Efficacy of rezafungin in a case of *Candida* spondylodiskitis. *J Bone Jt Infect*. 2024;9:213–5. <http://dx.doi.org/10.5194/jbji-9-213-2024>.
73. Lass-Flörl C, Kanj SS, Govender NP, Thompson GR III, Ostrosky-Zeichner L, Govrins MA. Invasive candidiasis. *Nat Rev Dis Primers*. 2024;10:20. <http://dx.doi.org/10.1038/s41572-024-00503-3>.
74. Lass-Flörl C, Steixner S. The changing epidemiology of fungal infections. *Mol Aspects Med*. 2023;94:101215. <http://dx.doi.org/10.1016/j.mam.2023.101215>.
75. Lee Y, Robbins N, Cowen LE. Molecular mechanisms governing antifungal drug resistance. *NPJ Antimicrob Resist*. 2023;1:5. <http://dx.doi.org/10.1038/s44259-023-00007-2>.
76. Lepak AJ, Zhao M, Andes DR. Determination of pharmacodynamic target exposures for rezafungin against *Candida tropicalis* and *Candida dubliniensis* in the neutropenic mouse disseminated candidiasis model. *Antimicrob Agents Chemother*. 2019;63:e01556–19. <http://dx.doi.org/10.1128/AAC.01556-19>.
77. Lepak AJ, Zhao M, Andes DR. Pharmacodynamic evaluation of rezafungin (CD101) against *Candida auris* in the neutropenic mouse invasive candidiasis model. *Antimicrob Agents Chemother*. 2018;62:e01572–18. <http://dx.doi.org/10.1128/AAC.01572-18>.
78. Lewis RE, Cahyame-Zuniga L, Leventakos K, Chamilos G, Ben-Ami R, Tamboli P, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with hematological malignancies: a 20-year autopsy study. *Mycoses*. 2013;56:638–45. <http://dx.doi.org/10.1111/myc.12081>.
79. Locke JB, Almaguer AL, Zuill DE, Bartizal K. Characterization of in vitro resistance development to the novel echinocandin CD101 in *Candida* species. *Antimicrob Agents Chemother*. 2016;60:6100–7. <http://dx.doi.org/10.1128/AAC.00620-16>.
80. Locke JB, Pillar CM, Castanheira M, Carvalhaes CG, Andes D, Aram JA, et al. Outcomes by *Candida* spp. in the ReSTORE Phase 3 trial of rezafungin versus caspofungin for candidemia and/or invasive candidiasis. *Antimicrob Agents Chemother*. 2024;68:e0158423. <http://dx.doi.org/10.1128/aac.01584-23>.
81. Lodise TP, Garey KW, Aram JA, Nathanson BH, Redell M. Association between duration of candidemia and clinical and healthcare resource utilization outcomes among hospitalized adult patients with candidemia who received empiric treatment with an echinocandin across United States hospitals. *Clin Infect Dis*. 2025. <http://dx.doi.org/10.1093/cid/ciaf472> [in press].
82. Logan A, Wolfe A, Williamson JC. Antifungal resistance and the role of new therapeutic agents. *Curr Infect Dis Rep*. 2022;24:105–16. <http://dx.doi.org/10.1007/s11908-022-00782-5>.
83. Maertens JA, Girmenia C, Brüggemann RJ, Duarte RF, Kibbler CC, Ljungman P, et al. European Conference on Infections in Leukaemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and; European Conference on Infections in Leukaemia (ECL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN). European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother*. 2018;73:3221–30. <http://dx.doi.org/10.1093/jac/dky286>.
84. Mariné M, Pastor FJ, Sahand IH, Pontón J, Quindós G, Guarro J. Paradoxical growth of *Candida dubliniensis* does not preclude in vivo response to echinocandin therapy. *Antimicrob Agents Chemother*. 2009;53:5297–9. <http://dx.doi.org/10.1128/AAC.00980-09>.
85. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood*. 2000;96:2055–61.
86. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. *J Infect Dis*. 2000;181:309–16. <http://dx.doi.org/10.1086/315193>.
87. Maseda E, Martín-Loeches I, Zaragoza R, Pemán J, Fortún J, Grau S, et al. Critical appraisal beyond clinical guidelines for intraabdominal candidiasis. *Crit Care*. 2023;27:382. <http://dx.doi.org/10.1186/s13054-023-04673-6>.
88. McCarty TP, White CM, Pappas PG. Candidemia and invasive candidiasis. *Infect Dis Clin North Am*. 2021;35:389–413. <http://dx.doi.org/10.1016/j.idc.2021.03.007>.
89. Miesel L, Cushion MT, Ashbaugh A, Lopez SR, Ong V. Efficacy of rezafungin in prophylactic mouse models of invasive candidiasis, aspergillosis, and *Pneumocystis* pneumonia. *Antimicrob Agents Chemother*. 2021;65:e01992–20. <http://dx.doi.org/10.1128/AAC.01992-20>.
90. Miesel L, Lin KY, Ong V. Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: insights on the PK/PD pharmacometrics of rezafungin efficacy. *Pharmacol Res Perspect*. 2019;7:e00546. <http://dx.doi.org/10.1002/prp2.546>.
91. Monzó-Gallo P, Chumbita M, Lopera C, Aiello TF, Peyrony O, Bodro M, et al. Real-life epidemiology and current outcomes of hospitalized adults with invasive fungal infections. *Med Mycol*. 2023;61. <http://dx.doi.org/10.1093/mmy/myad021>, myad021.
92. Mori G, Gottardi M, Guffanti M, Castagna A, Lanzafame M. Treatment of *Candida glabrata* native valve endocarditis with rezafungin: a case report. *JAC Antimicrob Resist*. 2024;6. <http://dx.doi.org/10.1093/jacamr/dlae042>, dlae042.
93. Neoh CF, Jeong W, Kong DC, Slavin MA. The antifungal pipeline for invasive fungal diseases: what does the future hold? *Expert Rev Anti Infect Ther*. 2023;21:577–94. <http://dx.doi.org/10.1080/14787210.2023.2203383>.
94. Nicolaysen A. Nephrotoxic chemotherapy agents: old and new. *Adv Chronic Kidney Dis*. 2020;27:38–49. <http://dx.doi.org/10.1053/j.ackd.2019.08.005>.
95. Oliva A, De Rosa FG, Mikulska M, Pea F, Sanguinetti M, Tascini C, et al. Invasive *Candida* infection: epidemiology, clinical and therapeutic aspects of an evolving disease and the role of rezafungin. *Expert Rev Anti Infect Ther*. 2023;21:957–75. <http://dx.doi.org/10.1080/14787210.2023.2240956>.
96. Omer MH, Shafqat A, Ahmad O, Alkattan K, Yaqinuddin A, Damlaj M. Bispecific antibodies in hematological malignancies: a scoping review. *Cancers (Basel)*. 2023;15:4550. <http://dx.doi.org/10.3390/cancers15184550>.
97. Ong V, Hough G, Schlosser M, Bartizal K, Balkovec JM, James KD, et al. Preclinical evaluation of the stability, safety, and efficacy of CD101, a novel echinocandin. *Antimicrob Agents Chemother*. 2016;60:6872–9. <http://dx.doi.org/10.1128/AAC.00701-16>.
98. Pagano L, Dragonetti G, Cattaneo C, Marchesi F, Veggia B, Busca A, et al. Changes in the incidence of candidemia and related mortality in patients with hematologic malignancies in the last ten years. A SEIFEM 2015–B report. *Haematologica*. 2017;102:e407–10. <http://dx.doi.org/10.3324/haematol.2017.172536>.
99. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–50. <http://dx.doi.org/10.1093/cid/civ933>.
100. Parakh S, King D, Gan HK, Scott AM. Current development of monoclonal antibodies in cancer therapy. *Recent Results Cancer Res*. 2020;214:1–70. [http://dx.doi.org/10.1007/978-3-030-23765-3\\_1](http://dx.doi.org/10.1007/978-3-030-23765-3_1).
101. Pemán J, Cantón E, Quindós G, Eraso E, Alcoba J, Guinea J, et al. Epidemiology, species distribution and in vitro antifungal susceptibility of fungaemia in a Spanish multicentre prospective survey. *J Antimicrob Chemother*. 2012;67:1181–7. <http://dx.doi.org/10.1093/jac/dks019>.
102. Pemán J, Ruiz-Gaitán A, García-Vidal C, Salavert M, Ramírez P, Puchades F, et al. Fungal co-infection in COVID-19 patients: should we be concerned? *Rev Iberoam Micol*. 2020;37:41–6. <http://dx.doi.org/10.1016/j.riam.2020.07.001>.
103. Pfaller MA, Carvalhaes C, Messer SA, Rhomberg PR, Castanheira M. Activity of a long-acting echinocandin, rezafungin, and comparator antifungal agents tested against contemporary invasive fungal isolates (SENTRY Program, 2016–2018). *Antimicrob Agents Chemother*. 2020;64. <http://dx.doi.org/10.1128/AAC.00099-20>, e00099-20.
104. Ponta G, Morena V, Strano M, Molteni C, Pontiggia S, Cavalli EM, et al. Safety of rezafungin as a long-term treatment option in two patients with complicated fungal infections: two cases from Lecco Hospital (Italy). *Antimicrob Agents Chemother*. 2024;68:e0075024. <http://dx.doi.org/10.1128/aac.00750-24>.
105. Posteraro B, De Carolis E, Criscuolo M, Ballanti S, De Angelis G, Del Principe MI, et al. Candidaemia in hematological malignancy patients from a SEIFEM

study: epidemiological patterns according to antifungal prophylaxis. *Mycoses*. 2020;63:900–10, <http://dx.doi.org/10.1111/myc.13130>.

106. Puerta-Alcalde P, Monzó-Gallo P, Aguilar-Guisado M, Ramos JC, Laporte-Amargós J, Machado M, et al. Breakthrough invasive fungal infection among patients with haematologic malignancies: a national, prospective, and multicentre study. *J Infect*. 2023;87:46–53, <http://dx.doi.org/10.1016/j.jinf.2023.05.005>.

107. Puig-Asensio M, Pemán J, Zaragoza R, Garnacho-Montero J, Martín-Mazuelos E, Cuenca-Estrella M, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. *Crit Care Med*. 2014;42:1423–32, <http://dx.doi.org/10.1097/CCM.0000000000000221>.

108. Quindós G, Gil-Alonso S, Marcos-Arias C, Sevillano E, Mateo E, Jau-regizar N, et al. Therapeutic tools for oral candidiasis: current and new antifungal drugs. *Med Oral Patol Oral Cir Bucal*. 2019;24:e172–80, <http://dx.doi.org/10.4317/medoral.22978>.

109. Quindós G, Marcos-Arias C, San-Millán R, Mateo E, Eraso E. The continuous changes in the aetiology and epidemiology of invasive candidiasis: from familiar *Candida albicans* to multi-resistant *Candida auris*. *Int Microbiol*. 2018;21:107–19, <http://dx.doi.org/10.1007/s10123-018-0014-1>.

110. Quindós G. Epidemiology of candidaemia and invasive candidiasis. A changing face. *Rev Iberoam Micol*. 2014;31:42–8, <http://dx.doi.org/10.1016/j.riam.2013.10.001>.

111. Raposa J, Vazquez JA. New pharmacotherapeutic strategies for drug-resistant *Candida* infections: a review. *Expert Opin Pharmacother*. 2025;1–11, <http://dx.doi.org/10.1080/14656566.2024.2433605>.

112. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med*. 2007;356:2472–82, <http://dx.doi.org/10.1056/NEJMoa066906>.

113. Roepcke S, Passarell J, Walker H, Flanagan S. Population pharmacokinetic modeling and target attainment analyses of rezafungin for the treatment of candidemia and invasive candidiasis. *Antimicrob Agents Chemother*. 2023;67:e0091623, <http://dx.doi.org/10.1128/aac.00916-23>.

114. Rosenquist R, Bernard E, Erkers T, Scott DW, Itzykson R, Rousselot P, et al. Novel precision medicine approaches and treatment strategies in hematological malignancies. *J Intern Med*. 2023;294:413–36, <http://dx.doi.org/10.1111/joim.13697>.

115. Salmanton-García J, Cornely OA, Stemler J, Barać A, Steinmann J, Siváková A, et al. Attributable mortality of candidemia – results from the ECMM Candida III multinational European Observational Cohort Study. *J Infect*. 2024;89:106229, <http://dx.doi.org/10.1016/j.jinf.2024.106229>.

116. Sandison T, Ong V, Lee J, Thye D. Safety and pharmacokinetics of CD101 IV, a novel echinocandin, in healthy adults. *Antimicrob Agents Chemother*. 2017;61:e01627–16, <http://dx.doi.org/10.1128/AAC.01627-16>.

117. Schauwvlieghe AFAD, de Jonge N, van Dijk K, Verweij PE, Brüggemann RJ, Biemond BJ, et al. The diagnosis and treatment of invasive aspergillosis in Dutch haematology units facing a rapidly increasing prevalence of azole-resistance: a nationwide survey and rationale for the DB-MSG 002 study protocol. *Mycoses*. 2018;61:656–64, <http://dx.doi.org/10.1111/myc.12788>.

118. Seiler GT, Ostrosky-Zeichner L. Investigational agents for the treatment of resistant yeasts and molds. *Curr Fungal Infect Rep*. 2021;15:104–15, <http://dx.doi.org/10.1007/s12281-021-00419-5>.

119. Shah M, El Chaer F, Ho DY, El Boghdady Z. Managing infectious challenges in the age of molecular-targeted therapies for adult hematological malignancies. *Transpl Infect Dis*. 2024;26:e14283, <http://dx.doi.org/10.1111/tid.14283>.

120. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. *J Infect Dis*. 1995;171:1545–52, <http://dx.doi.org/10.1093/infdis/171.6.1545>.

121. Smith HL, Bensman TJ, Mishra S, Li X, Dixon CA, Sheikh J, et al. Regulatory considerations in the approval of Rezafungin (Rezzayo) for the treatment of candidemia and invasive candidiasis in adults. *J Infect Dis*. 2024;230:505–13, <http://dx.doi.org/10.1093/infdis/jiae146>.

122. Soriano A, Honoré PM, Cornely OA, Chayakulkeeree M, Bassetti M, Haihui H, et al. Treatment outcomes among patients with a positive *Candida* culture close to randomization receiving rezafungin or caspofungin in the ReSTORE study. *Clin Infect Dis*. 2024;79:672–81, <http://dx.doi.org/10.1093/cid/ciae363>.

123. Soriano A, Honoré PM, Puerta-Alcalde P, García-Vidal C, Pagotto A, Gonçalves-Bradley DC, et al. Invasive candidiasis: current clinical challenges and unmet needs in adult populations. *J Antimicrob Chemother*. 2023;78:1569–85, <http://dx.doi.org/10.1093/jac/dkad139>.

124. Soriano A, Locke JB, Cornely OA, Roilides E, Ramos-Martínez A, Honoré PM, et al. Clinical and mycological outcomes of candidaemia and/or invasive candidiasis by *Candida* spp. and antifungal susceptibility: pooled analyses of two randomized trials of rezafungin versus caspofungin. *Clin Microbiol Infect*. 2025;31:250–7, <http://dx.doi.org/10.1016/j.cmi.2024.11.029>.

125. Sprute R, Nacov JA, Neofytos D, Oliverio M, Prattes J, Reinhold I, et al. Antifungal prophylaxis and pre-emptive therapy: when and how? *Mol Aspects Med*. 2023;92:101190, <http://dx.doi.org/10.1016/j.mam.2023.101190>.

126. Stevens VM, Mueller SW, Reynolds PM, MacLaren R, Kiser TH. Extrapolating antifungal animal data to humans: is it reliable? *Curr Fungal Infect Rep*. 2020;14:50–62, <http://dx.doi.org/10.1007/s12281-020-00370-x>.

127. Syed YY. Rezafungin: first approval. *Drugs*. 2023;83:833–40, <http://dx.doi.org/10.1007/s40265-023-01891-8>.

128. Thompson GR III, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet*. 2023;401:49–59, [http://dx.doi.org/10.1016/S0140-6736\(22\)02324-8](http://dx.doi.org/10.1016/S0140-6736(22)02324-8).

129. Thompson GR III, Soriano A, Honoré PM, Bassetti M, Cornely OA, Kollef M, et al. Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials. *Lancet Infect Dis*. 2024;24:319–28, [http://dx.doi.org/10.1016/S1473-3099\(23\)00551-0](http://dx.doi.org/10.1016/S1473-3099(23)00551-0).

130. Thompson GR, Soriano A, Skoutelis A, Vazquez JA, Honoré PM, Horcajada JP, et al. Rezafungin versus caspofungin in a phase 2, randomized, double-blind study for the treatment of candidemia and invasive candidiasis: The STRIVE trial. *Clin Infect Dis*. 2021;73:e3647–55, <http://dx.doi.org/10.1093/cid/ciaa1380>.

131. Tóth Z, Forgács L, Locke JB, Kardos G, Nagy F, Kovács R, et al. In vitro activity of rezafungin against common and rare *Candida* species and *Saccharomyces cerevisiae*. *J Antimicrob Chemother*. 2019;74:3505–10, <http://dx.doi.org/10.1093/jac/dkz390>.

132. Trapani F, Viceconte G, Morena V, Tiseo G, Mori G, Kölling B, et al. Long-term safety and effectiveness of rezafungin treatment in candidemia and invasive candidiasis: results from an early access program in Italy and Germany. *Open Forum Infect Dis*. 2025;12, <http://dx.doi.org/10.1093/ofid/ofaf034>.

133. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356:335–47, <http://dx.doi.org/10.1056/NEJMoa061098>.

134. Viceconte G, Buonomo AR, Esposito N, Cattaneo L, Somma T, Scirocco MM, et al. Salvage Therapy with rezafungin for *Candida parapsilosis* spondylodiscitis: a case report from expanded access program. *Microorganisms*. 2024;12:903, <http://dx.doi.org/10.3390/microorganisms12050903>.

135. Wan Ismail WNA, Jasmi N, Khan TM, Hong YH, Neoh CF. The economic burden of candidemia and invasive candidiasis: a systematic review. *Value Health Reg Issues*. 2020;21:53–8, <http://dx.doi.org/10.1016/j.vhri.2019.07.002>.

136. WHO. WHO fungal priority pathogens list to guide research, development and public health action; 2022. Available from: <https://www.who.int/publications/i/item/9789240060241>

137. Wiederhold NP, Locke JB, Daruwala P, Bartizal K. Rezafungin (CD101) demonstrates potent in vitro activity against *Aspergillus*, including azole-resistant *Aspergillus fumigatus* isolates and cryptic species. *J Antimicrob Chemother*. 2018;73:3063–7, <http://dx.doi.org/10.1093/jac/dky280>.

138. Wiederhold NP, Najvar LK, Jaramillo R, Olivo M, Wickes BL, Catano G, et al. Extended-interval dosing of rezafungin against azole-resistant *Aspergillus fumigatus*. *Antimicrob Agents Chemother*. 2019;63:e01165–19, <http://dx.doi.org/10.1128/AAC.01165-19>.

139. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010;116:5111–8, <http://dx.doi.org/10.1182/blood-2010-02-268151>.

140. Winkler ML, Deshpande L, Kimbrough JH, Karr M, Rhomberg P, Klauer AL, et al. Anidulafungin is a useful surrogate marker for predicting in vitro susceptibility to rezafungin among five *Candida* species using CLSI methods and interpretive criteria. *J Clin Microbiol*. 2025;63:e0112924, <http://dx.doi.org/10.1128/jcm.01129-24>.

141. Winkler ML, Rhomberg P, Klauer AL, Edeker S, Castanheira M. The in vitro activity of rezafungin against uncommon species of *Candida*. *Mycoses*. 2024;67:e70001, <http://dx.doi.org/10.1111/myc.70001>.

142. Wolfruber S, Salmanton-García J, Kuate MPN, Henigl M, Brunelli JGP. Antifungal pipeline: new tools for the treatment of mycoses. *Rev Iberoam Micol*. 2024;41:68–78, <http://dx.doi.org/10.1016/j.riam.2024.11.001>.

143. Wolfruber S, Sedik S, Klingspor L, Tortorano A, Gow NAR, Lagrou K, et al. Insights from three pan-European multicentre studies on invasive *Candida* infections and outlook to ECMM *Candida* IV. *Mycopathologia*. 2024;189:70, <http://dx.doi.org/10.1007/s11046-024-00871-0>.

144. Wu B, Hussain M, Zhang W, Stadler M, Liu X, Xiang M. Current insights into fungal species diversity and perspective on naming the environmental DNA sequences of fungi. *Mycology*. 2019;10:127–40, <http://dx.doi.org/10.1080/21501203.2019.1614106>.

145. Yang S, Wan F, Zhang M, Lin H, Hu L, Zhou Z, et al. In vitro activity of rezafungin in comparison with anidulafungin and caspofungin against invasive fungal isolates (2017–2022) in China. *J Fungi (Basel)*. 2024;10:397, <http://dx.doi.org/10.3390/jof10060397>.

146. Zaragoza R, Ferrer R, Linares P, Maseda E, Rodríguez A, Grau S, et al. EPICO 4.0. 'Total quality' in the management of invasive candidiasis in critically ill patients by analysing the integrated process. *Rev Iberoam Micol*. 2017;34:143–57, <http://dx.doi.org/10.1016/j.riam.2017.03.008>.

147. Zaragoza R, Maseda E, Pemán J. Tratamiento antifúngico individualizado en el paciente crítico con infección fúngica invasora. *Rev Iberoam Micol*. 2021;38:68–74, <http://dx.doi.org/10.1016/j.riam.2021.04.006>.

148. Zhao Y, Perlini DS. Review of the novel echinocandin antifungal rezafungin: animal studies and clinical data. *J Fungi (Basel)*. 2020;6:192, <http://dx.doi.org/10.3390/jof6040192>.