



Efficacy of Rezafungin in Prophylactic Mouse Models of Invasive Candidiasis, Aspergillosis, and *Pneumocystis* Pneumonia

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ABSTRACT Antifungal prophylaxis is recommended to prevent invasive fungal disease caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* in patients at risk for opportunistic infections, such as allogeneic blood or marrow transplant recipients, patients with hematological disease undergoing chemotherapy, or patients on immunosuppressive therapies. Current approaches to antifungal prophylaxis require multiple agents to cover these key fungi. Rezafungin, a novel echinocandin designed for next-generation properties (e.g., greater stability and long-acting pharmacokinetics for once-weekly dosing), has demonstrated *in vitro* activity against *Candida* and *Aspergillus* spp. and efficacy against *Pneumocystis* spp. biofilms. Rezafungin was evaluated in *in vivo* studies of prophylactic efficacy using immunosuppressed mouse models of invasive candidiasis, aspergillosis, and *Pneumocystis* pneumonia. Rezafungin reduction of *Candida* CFU burden was generally greater with increasing drug concentrations (5, 10, or 20 mg/kg) and when rezafungin was administered closer to the time of fungal challenge (day -1 , -3 , or -5). Similarly, in the aspergillosis model, survival rates increased with drug concentrations and when rezafungin was administered closer to the time of fungal challenge. Against *Pneumocystis murina*, rezafungin significantly reduced trophic nuclei and asci counts at all doses tested. Rezafungin prevented infection at the two higher doses compared to vehicle and had comparable activity to the active control trimethoprim-sulfamethoxazole at human equivalent doses for prevention. These findings support phase 3 development of rezafungin and the potential for single-agent prophylaxis against invasive fungal disease caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii*.

KEYWORDS *Aspergillus*, *Candida*, *Pneumocystis*, antifungal agents, antifungal therapy, echinocandin, prophylaxis

Antifungal prophylaxis is an important strategy against invasive fungal disease (IFD) in patients at risk for opportunistic infections, such as recipients of allogeneic blood or marrow transplantation or solid organ transplantation, as well as patients with hematological disorders undergoing chemotherapy (1–6). For such patient populations, antifungal prophylaxis is recommended to prevent infections caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* (7–9). An ideal antifungal prophylaxis regimen would provide fitting coverage of the most prevalent opportunistic pathogens without obstructing or complicating therapy due to toxicity, intolerability, or drug-drug interactions (DDIs).

While recommendations and clinical trial data are available to guide antifungal prophylaxis (7, 10–14), there is no single approach as prophylaxis must be customized to the needs of a given patient, as well as local fungal epidemiology and susceptibility.

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Current strategies to protect against these most commonly encountered pathogens generally enlist an azole (one with mold activity if there is risk of *Aspergillus*) and trimethoprim-sulfamethoxazole (SXT) for *Pneumocystis jirovecii* pneumonia (PCP) (7, 9, 10). Considerations when personalizing azole therapy include pharmacokinetic variability, oral tolerability, and safety (such as liver toxicity and effects on the QT interval), as well as DDIs (15, 16). For SXT, personalizing therapy may include modifications to antifungal prophylaxis and/or primary treatment to mitigate SXT-associated fever, rash resembling GVHD, nephrotoxicity, or myelosuppression (8). Unmet needs in the current approach to antifungal prophylaxis may lead to gaps in protection against IFD or complications in treatment of primary disease, such as when dosing is disrupted or when adverse effects (AEs) and DDIs occur.

With the advent of newer therapies for treatment of primary disease, many of which introduce new or increased risks of IFD and DDIs with antifungal agents, patient-level considerations have expanded in scope and complexity. Recent examples include the increased incidence of PCP observed with Bruton's tyrosine kinase inhibitors (ibrutinib and acalabrutinib) and IFD associated with immune checkpoint inhibitors (17–21). Arguably, the greatest impact of newer treatments on antifungal prophylaxis may be from DDIs caused by CYP interactions or other mechanisms that may contraindicate concomitant use (16, 22). The AEs of newer treatments or their management with corticosteroids or other immunosuppressants may also increase infection risk (23–26). Additional experience with newer treatments will help to guide antifungal prophylaxis management. At the same time, newer antifungal options and strategies are needed to support the continuous advancements in treatment of hematologic diseases and in immunosuppressive therapies.

Rezafungin is a novel echinocandin in development for the treatment and prevention of invasive candidiasis, with a phase 3 treatment trial (ReSTORE NCT03667690) and a phase 3 prophylaxis trial (ReSPECT NCT04368559) under way. While the current approach to antifungal prophylaxis requires multiple agents to cover the key target pathogens, rezafungin has demonstrated *in vitro* activity against *Candida* and *Aspergillus* species, including azole-resistant strains of *Aspergillus fumigatus*, as well as efficacy against *Pneumocystis* biofilms (27–34). Rezafungin is distinguished by a long half-life and front-loaded, high plasma drug exposures that allow for the once-weekly intravenous dosing regimen in clinical development. Rezafungin administered once weekly has demonstrated safety and tolerability consistent with that of its echinocandin class. Preclinical evaluation demonstrated rezafungin chemical and metabolic stability and lack of hepatotoxicity, in contrast to anidulafungin (35, 36). Phase 1 trials of rezafungin showed a lack of effect on the QT interval and low risk of DDIs with commonly used drugs (37, 38). To further contribute to these data, this series of *in vivo* studies evaluated the efficacy of rezafungin in prophylactic mouse models of invasive fungal infections caused by *Candida*, *Aspergillus*, and *Pneumocystis* in immunosuppressed mice.

(Data from these studies were preliminarily presented at the 2017 European Hematology Association meeting [Madrid, Spain].)

RESULTS

Prevention of *Candida* infection. Rezafungin prophylaxis in an immunosuppressed mouse model of invasive candidiasis demonstrated decreases in the *Candida* CFU burden, an effect that increased with rezafungin concentrations and when prophylaxis administration occurred closer to challenge (day –1 > day –3 > day –5; Fig. 1). *C. albicans* was completely cleared in all animals given rezafungin 20 mg/kg, except for one animal that had prophylaxis administered on day –3. At the lower doses (10 and 5 mg/kg), bioburden reduction when prophylaxis was administered on day –5 (similar to day –15 for humans as described in Materials and Methods) was not significantly different than vehicle. However, when prophylaxis administration occurred closer to challenge, on day –3 or day –1, the 10-mg/kg rezafungin groups had no

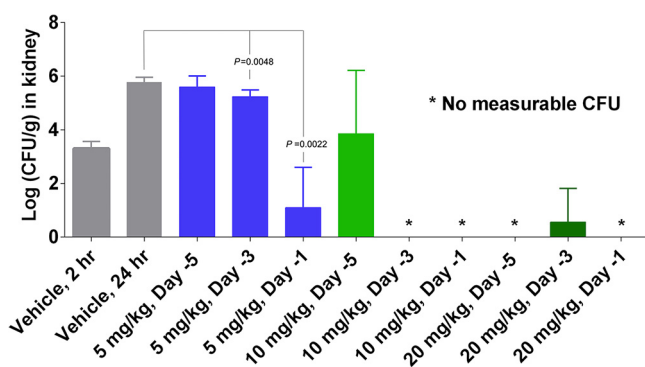


FIG 1 Clearance and significant decreases in kidney CFU burden of *Candida* (*C. albicans*, MIC = 0.03 μ g/ml) in mice after administration of rezafungin prophylaxis.

measurable CFU, and the 5-mg/kg groups showed significantly lower fungal burden than did the vehicle control, indicating a dose response as well as correlation with timing of prophylaxis administration (day -1 > day -3 > day -5).

Prevention of *Aspergillus* infection. Rezafungin prophylaxis against *A. fumigatus* in the immunosuppressed mouse model of invasive aspergillosis demonstrated protection at doses of 10 and 20 mg/kg, with all animals in these groups surviving the 14-day postchallenge period regardless of when prophylaxis was administered (Fig. 2, right). In the group given the lowest dose tested (rezafungin 5 mg/kg), survival increased when prophylaxis administration occurred closer to challenge (day -1 > day -3 > day -5; Fig. 2, left).

Prevention of PCP. Rezafungin prophylaxis in the immunosuppressed mouse model of PCP demonstrated significantly reduced trophic nuclei counts in all rezafungin-treated groups compared to the vehicle control, except at the lowest and least frequently administered dose (0.2 mg/kg 1 \times /week). Three of the rezafungin groups—both 20-mg/kg regimens (20 mg/kg 1 \times or 3 \times /week) and the 2-mg/kg regimen (3 \times /week)—were comparable to the active control SXT, with no trophic nuclei microscopically detected (Fig. 3a). Similarly, asci counts in all rezafungin-treated groups were significantly reduced compared to the vehicle control. The efficacy observed in all but the 0.2-mg/kg 1 \times /week dose group was comparable to that of SXT, with no asci microscopically detected (Fig. 3b).

DISCUSSION

In this series of *in vivo* experiments, the novel echinocandin rezafungin was efficacious in preventing infection caused by *Candida*, *Aspergillus*, and *Pneumocystis* in immunosuppressed mice. Although the interpretation of these findings is limited to the extent that preclinical research may translate to clinical experience, the clinical efficacy demonstrated by currently available, once-daily echinocandins against all three of the fungal pathogens studied supports the predictive value of these *in vivo* data. The

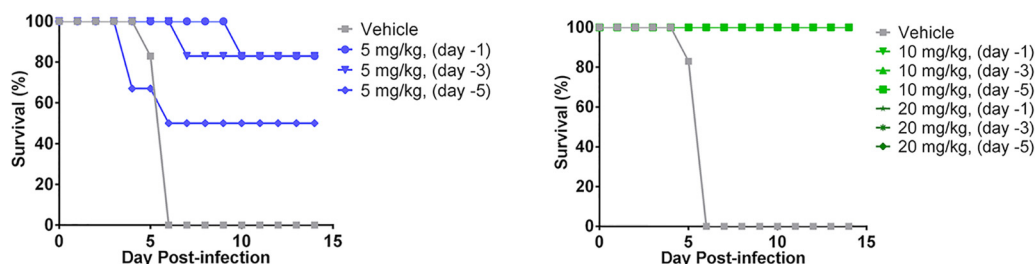


FIG 2 Survival rates in mice challenged with *Aspergillus* (*A. fumigatus*, MEC = 0.0078 μ g/ml) after administration of rezafungin prophylaxis. (Left) 5 mg/kg; (right) 10 or 20 mg/kg. $P < 0.05$ for all dosing arms, except for 5 mg/kg, day -5 ($P = 0.182$).

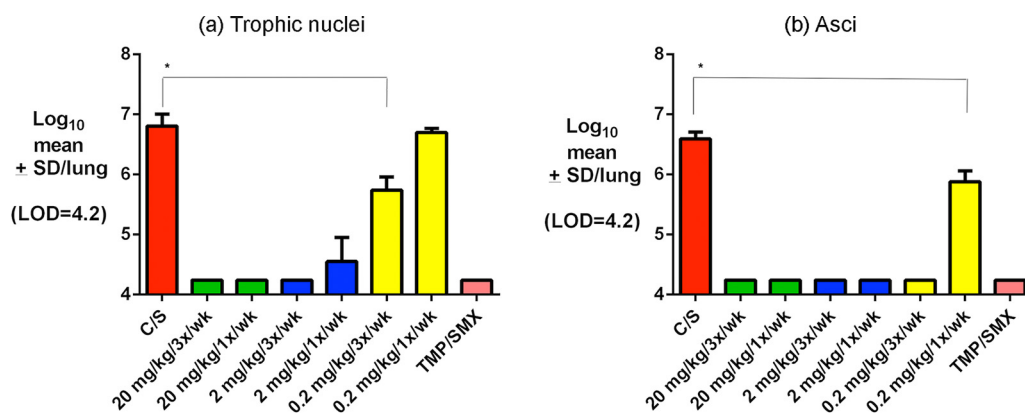


FIG 3 Clearance and significant decreases in kidney burden of *Pneumocystis* (*P. murina*; both trophic [a] and asci [b] forms) in mice after administration of rezafungin prophylaxis compared to active control SXT. *, $P < 0.05$ versus the control. The limit of microscopic observation on this scale is \log_{10} of 4 (the value indicating that no nuclei or asci were observed).

role of preclinical models notwithstanding, these results contribute to the development of rezafungin and the future of antifungal prophylaxis for patients at risk for IFD. To our knowledge, rezafungin is the first echinocandin to report prophylactic efficacy against *Pneumocystis*, as well as against *Candida* and *Aspergillus*.

Safe and efficacious antifungal prophylaxis is important and yet increasingly challenging to provide in a growing number of immunosuppressed conditions and patient populations at risk of developing IFD. The current mainstays of prophylaxis against these key pathogens (azoles and SXT) are generally efficacious but limited by DDIs and/or toxicity that can impede prophylaxis, as well as the treatment of primary disease (39, 40). Alternative therapies for prophylaxis are lacking. Pentamidine, dapsone, and atovaquone, as options for PCP prophylaxis, each have tolerability issues, limitations in efficacy, or administration challenges in the case of inhaled pentamidine (41). Liposomal amphotericin B at intermittent or low doses has been used for prophylaxis of *Candida* and *Aspergillus* but is hampered by a side-effect profile that includes nephrotoxicity and electrolyte abnormalities. In contrast, the relative tolerability and lack of DDIs with echinocandins present an attractive safety profile (41, 42). While all three echinocandins have been studied in various patient populations (13, 43–48), only micafungin is indicated for use as antifungal prophylaxis, specifically, of *Candida* infections in adult and pediatric patients undergoing hematopoietic stem cell transplantation (12, 49, 50). In a retrospective study in patients with hematological disease who received antifungal prophylaxis, micafungin was selected in 26% of 104 cases for safety- or tolerability-related reasons (e.g., liver dysfunctions, severe mucositis, DDIs of other antifungals, and long QT syndrome) (51). The safety of rezafungin is consistent with that of the echinocandin class, as observed in the phase 2 STRIVE trial of once-weekly rezafungin compared to caspofungin in the treatment of candidemia and invasive candidiasis (35, 52) and in phase 1 trials that confirmed rezafungin lack of effect on the QT interval and low DDI potential (37, 38).

The efficacy findings reported here also underscore the distinctive pharmacokinetics of rezafungin. Its long half-life and front-loaded drug exposure allow for once-weekly dosing of rezafungin, as studied in the completed phase 2 and ongoing phase 3 clinical trials. Furthermore, rezafungin demonstrates extensive distribution and tissue penetration, as shown by Zhao et al. (53), who observed 4-fold-higher rezafungin concentrations within lesions than for micafungin at the same dosage in a mouse intra-abdominal abscess model. Rezafungin is distributed to lung epithelial lining fluid and has demonstrated high *in vivo* exposures in the lung and other organs commonly infected by IFD, ~4-fold higher than in plasma (54–56). These pharmacokinetics, together with the *in vivo* efficacy of rezafungin demonstrated here, suggest a potential to replace

poorly tolerated combination regimens for prophylaxis in patients at risk for IFD, many of whom are burdened by polypharmacy and increasingly longer periods of infection risk.

The current set of *in vivo* studies on rezafungin contribute important findings to the published literature on this novel echinocandin and on approaches to antifungal prophylaxis. The efficacy of rezafungin in preventing infections caused by *Candida*, *Aspergillus*, and *Pneumocystis* in immunosuppressed mice demonstrate the potential of rezafungin as prophylaxis for patients at high risk of infection and support its ongoing clinical development.

MATERIALS AND METHODS

These studies were performed in accordance with the *Guide for the Care and Use of Laboratory Animals*, 8th ed. (National Academies Press, Washington, DC), in AAALAC-accredited ABSL-2 laboratories (with the exception of *P. murina*-infected mice) under the supervision of veterinarians. In addition, all procedures were conducted in compliance with the Institutional Animal Care and Use Committee at the respective sites.

Test agents were supplied by Cidara Therapeutics, Inc. (San Diego, CA), except for SXT (Sulfatrim H pediatric oral suspension; Actavis, Baltimore, MD), and amphotericin B (Sigma), which were purchased.

Invasive candidiasis prophylaxis mouse model. Female ICR mice (Envigo Laboratories) weighing ~0.02 kg were immunosuppressed using two intraperitoneal (i.p.) injections of cyclophosphamide, with a first injection of 150 mg/kg administered 4 days before challenge (day -4) with *Candida albicans* (American Type Culture Collection [ATCC] SC5314; Manassas, VA; $4.5 \log_{10}$ CFU/mouse intravenous [i.v.]) and a second injection of 100 mg/kg administered 1 day before challenge (day -1). Prior to *C. albicans* challenge, mice ($n = 5/\text{group}$; 9 groups) were treated with one subcutaneous (s.c.) dose of either rezafungin 5, 10, or 20 mg/kg on either day -5 (which is similar to day -15 for humans, based on a 2- to 3-fold faster clearance in mice), day -3, or day -1. In three additional groups, mice were given either rezafungin at 5 mg/kg s.c., micafungin at 5 mg/kg i.p., or s.c. vehicle control on day 0 administered immediately following *C. albicans* challenge. Treated mice were sacrificed at 24 h postchallenge, and the kidneys were harvested for bioburden enumeration (CFU/g of tissue).

Invasive aspergillosis prophylaxis mouse model. Female ICR mice (BioLasco Taiwan/Charles River) weighing ~0.02 kg were immunosuppressed using three i.p. injections of cyclophosphamide, with the first injection (6 mg/mouse) administered 3 days before challenge (day -3) with *Aspergillus fumigatus* (ATCC 13073; Rockville, MD; 1.85×10^4 CFU/mouse i.v.) and the second and third injections (2 mg/mouse) administered 1 day before (day -1) and 4 days after (day 4) challenge. Prior to *A. fumigatus* challenge, mice ($n = 6/\text{group}$; 9 groups) were treated with one s.c. rezafungin dose of either 5, 10, or 20 mg/kg on either day -5 (similar to day -15 for humans as noted above, day -3, or day -1). In two additional groups, mice were given either rezafungin at 5 mg/kg s.c. or amphotericin B at 3 mg/kg i.p. on day 0 administered 1 h after challenge with *A. fumigatus*. Mortality was observed for 14 days.

PCP prophylaxis mouse model. Male C3H/H3N mice (Charles River) weighing ~0.02 kg were immunosuppressed using dexamethasone (4 mg/liter) added to drinking water acidified with sulfuric acid (1 ml/liter) to prevent secondary microbial infections. Prophylaxis was administered at the same time as inoculation with *Pneumocystis murina* (Cincinnati VAMC Veterinary Medical Unit, Cincinnati, OH; $2 \times 10^6/50 \mu\text{l}$ intranasally), the standard for this *Pneumocystis* infection model, given the slower growth of *Pneumocystis* relative to other fungi. Eight groups of mice ($n = 10/\text{group}$) received either negative control (control steroid, no treatment), positive control (SXT at 50/250 mg/kg $3 \times/\text{week}$ i.p.), or rezafungin (0.2, 2, or 20 mg/kg i.p. $1 \times$ or $3 \times/\text{week}$) for 6 weeks. Mice were sacrificed after 6 weeks, and the lungs were prepared for fungal count measurement (CFU/g of tissue) of both trophic and asci (cyst) forms by rapid Wright-Giemsa and cresyl echt violet stains, respectively (57).

Statistical analysis. Statistical analyses were conducted according to the respective study protocols as follows. In the study of invasive candidiasis, CFU counts for each mouse were log transformed, and *P* values were calculated in Microsoft Excel by using a two-sample Student *t* test assuming unequal variance with comparisons made between treatment groups and the 24-h vehicle control group. In the study of invasive aspergillosis, a Fisher exact test (two tailed) was conducted on the survival curves. In the study of *Pneumocystis* prophylaxis, nuclei and asci counts for each lung were log transformed and analyzed by analysis of variance. Individual groups were compared by using Dunn's test for multiple comparisons (GraphPad Prism, v6).

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REFERENCES

- Drgona L, Khachatryan A, Stephens J, Charbonneau C, Kantecki M, Haider S, Barnes R. 2014. Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of *Aspergillus* and *Candida* species. *Eur J Clin Microbiol Infect Dis* 33:7–21. <https://doi.org/10.1007/s10096-013-1944-3>.
- Marr KA. 2008. Primary antifungal prophylaxis in hematopoietic stem cell transplant recipients: clinical implications of recent studies. *Curr Opin Infect Dis* 21:409–414. <https://doi.org/10.1097/QCO.0b013e328307c7d9>.
- Cornely OA, Kontoyiannis DP. 2018. How to prophylax against invasive fungal infections in adult ALL? An unmet need. *Mycoses* 61:646–649. <https://doi.org/10.1111/myc.12786>.
- Aslam S, Rotstein C, AST Infectious Disease Community of Practice. 2019. *Candida* infections in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 33:e13623. <https://doi.org/10.1111/ctr.13623>.
- Fishman JA, Gans H, AST Infectious Diseases Community of Practice. 2019. *Pneumocystis jirovecii* in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 33:e13587. <https://doi.org/10.1111/ctr.13587>.
- Husain S, Camargo JF. 2019. Invasive aspergillosis in solid-organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 33:e13544. <https://doi.org/10.1111/ctr.13544>.
- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. 2011. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 52:427–431. <https://doi.org/10.1093/cid/ciq147>.
- Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, Hauser PM, Lagrou K, Melchers WJ, Helweg-Larsen J, Matos O, Bretagne S, Cordonnier C, 5th European Conference on Infections in Leukaemia (ECIL-5), 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). 2016. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 71:2397–2404. <https://doi.org/10.1093/jac/dkw157>.
- Ullmann AJ, Aguado JM, Arikian-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Muñoz P, Verweij PE, Warris A, Ader F, Akova M, Arendrup MC, Barnes RA, Beigelman-Aubry C, Blot S, Bouza E, Bruggemann RJM, Buchheidt D, Cadranel J, Castagnola E, Chakrabarti A, Cuenca-Estrella M, Dimopoulos G, Fortun J, Gangneux JP, Garbino J, Heinz WJ, Herbrecht R, Heussel CP, Kibbler CC, Klimko N, Kullberg BJ, Lange C, Lehrnbecher T, Löffler J, Lortholary O, Maertens J, Marchetti O, Meis JF, Pagano L, Ribaud P, Richardson M, Roilides E, Ruhnkne M, Sanguinetti M, Sheppard DC, Sinko J, Skiada A, et al. 2018. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 24(Suppl 1):e1–e38. <https://doi.org/10.1016/j.cmi.2018.01.002>.
- Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, Cooper B, Dubberke ER, Engemann AM, Freifeld AG, Greene JN, Ito JI, Kaul DR, Lustberg ME, Montoya JG, Rolston K, Satyanarayana G, Segal B, Seo SK, Shoham S, Taplitz R, Topal J, Wilson JW, Hoffmann KG, Smith C. 2016. Prevention and treatment of cancer-related infections, version 2.2016. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw* 14:882–913. <https://doi.org/10.6004/jnccn.2016.0093>.
- Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Kruger W, Mousset S, Neuburger S, Neumann S, Penack O, Silling G, Vehreschild JJ, Einsele H, Maschmeyer G, Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation). 2016. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. *Ann Hematol* 95:1435–1455. <https://doi.org/10.1007/s00277-016-2711-1>.
- Epstein DJ, Seo SK, Huang YT, Park JH, Klimek VM, Berman E, Tallman MS, Frattini MG, Papanicolaou GA. 2018. Micafungin versus posaconazole prophylaxis in acute leukemia or myelodysplastic syndrome: a randomized study. *J Infect* 77:227–234. <https://doi.org/10.1016/j.jinf.2018.03.015>.
- Fisher BT, Zaoutis T, Dvorak CC, Nieder M, Zerr D, Wingard JR, Callahan C, Villaluna D, Chen L, Dang H, Esbenschade AJ, Alexander S, Wiley JM, Sung L. 2019. Effect of caspofungin versus fluconazole prophylaxis on invasive fungal disease among children and young adults with acute myeloid leukemia: a randomized clinical trial. *JAMA* 322:1673–1681. <https://doi.org/10.1001/jama.2019.15702>.
- Winston DJ, Bartoni K, Territo MC, Schiller GJ. 2011. Efficacy, safety, and breakthrough infections associated with standard long-term posaconazole antifungal prophylaxis in allogeneic stem cell transplantation recipients. *Biol Blood Marrow Transpl* 17:507–515. <https://doi.org/10.1016/j.bbmt.2010.04.017>.
- Kohl V, Müller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, Scheid C, Hallek M, Rüping MJGT. 2010. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. *Antimicrob Agents Chemother* 54:207–212. <https://doi.org/10.1128/AAC.01027-09>.
- Lindsay J, Teh BW, Micklethwaite K, Slavina M. 2019. Azole antifungals and new targeted therapies for hematological malignancy. *Curr Opin Infect Dis* 32:538–545. <https://doi.org/10.1097/QCO.0000000000000611>.
- Maschmeyer G, De Greef J, Mellingshoff SC, Nosari A, Thiebaut-Bertrand A, Bergeron A, Franquet T, Blijlevens NMA, Maertens JA, European Conference on Infections in Leukemia (ECIL). 2019. Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology: a position paper by the European Conference on Infections in Leukemia (ECIL). *Leukemia* 33:844–862. <https://doi.org/10.1038/s41375-019-0388-x>.
- Reinwald M, Silva JT, Mueller NJ, Fortun J, Garzoni C, de Fijter JW, Fernandez-Ruiz M, Grossi P, Aguado JM. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). *Clin Microbiol Infect* 24(Suppl 2):S53–S70. <https://doi.org/10.1016/j.cmi.2018.02.009>.
- Chamilos G, Lionakis MS, Kontoyiannis DP. 2018. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. *Clin Infect Dis* <https://doi.org/10.1093/cid/cix687>.
- Los-Arcos I, Aguilar-Company J, Ruiz-Camps I. 2019. Risk of infection associated with new therapies for the treatment of lymphoproliferative syndromes. *Med Clin (Barc)* 154:101–107. <https://doi.org/10.1016/j.medcli.2019.07.026>.
- Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, Redelman-Sidi G. 2018. Serious infections in patients receiving ibrutinib for

- treatment of lymphoid cancer. *Clin Infect Dis* 67:679–692. <https://doi.org/10.1093/cid/ciy175>.
22. Butts A, Reitler P, Ge W, Fortwendel JR, Palmer GE. 2018. Commonly used oncology drugs decrease antifungal effectiveness against *Candida* and *Aspergillus* species. *Antimicrob Agents Chemother* 62:e00504-18. <https://doi.org/10.1128/AAC.00504-18>.
 23. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. 2016. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis* 63:1490–1493. <https://doi.org/10.1093/cid/ciw539>.
 24. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. 2014. Opportunistic infections in patients treated with immunotherapy for cancer. *J Immunother Cancer* 2:19–19. <https://doi.org/10.1186/2051-1426-2-19>.
 25. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomaso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA, National Comprehensive Cancer Network. 2018. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 36:1714–1768. <https://doi.org/10.1200/JCO.2017.77.6385>.
 26. Redelman-Sidi G, Michielin O, Cervera C, Ribí C, Aguado JM, Fernandez-Ruiz M, Manuel O. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). *Clin Microbiol Infect* 24(Suppl 2):S95–S107. <https://doi.org/10.1016/j.cmi.2018.01.030>.
 27. Toth Z, Forgacs L, Locke JB, Kardos G, Nagy F, Kovacs R, Szekely A, Borman AM, Majoros L. 2019. *In vitro* activity of rezafungin against common and rare *Candida* species and *Saccharomyces cerevisiae*. *J Antimicrob Chemother* 74:3505–3510. <https://doi.org/10.1093/jac/dkz390>.
 28. Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. 2017. Activity of a long-acting echinocandin (CD101) and seven comparator antifungal agents tested against a global collection of contemporary invasive fungal isolates in the SENTRY 2014. *Antimicrob Agents Chemother* 61:e02045-16. <https://doi.org/10.1128/AAC.02045-16>.
 29. Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. 2017. CD101, a long-acting echinocandin, and comparator antifungal agents tested against a global collection of invasive fungal isolates in the SENTRY 2015 Antifungal Surveillance Program. *Int J Antimicrob Agents* 50:352–358. <https://doi.org/10.1016/j.ijantimicag.2017.03.028>.
 30. Berkow EL, Lockhart SR. 2018. Activity of CD101, a long-acting echinocandin, against clinical isolates of *Candida auris*. *Diagn Microbiol Infect Dis* 90:196–197. <https://doi.org/10.1016/j.diagmicrobio.2017.10.021>.
 31. Pfaller MA, Messer SA, Rhomberg PR, Jones RN, Castanheira M. 2016. Activity of a long-acting echinocandin, CD101, determined using CLSI and EUCAST reference methods, against *Candida* and *Aspergillus* spp., including echinocandin- and azole-resistant isolates. *J Antimicrob Chemother* 71:2868–2873. <https://doi.org/10.1093/jac/dkw214>.
 32. Wiederhold NP, Najvar LK, Jaramillo R, Olivo M, Wickes BL, Catano G, Patterson TF. 2019. Extended-interval dosing of rezafungin against azole-resistant *Aspergillus fumigatus* isolates and cryptic species. *J Antimicrob Chemother* 63:e01165-19. <https://doi.org/10.1128/AAC.01165-19>.
 33. Wiederhold NP, Locke JB, Daruwala P, Bartizal K. 2020. Rezafungin (CD101) demonstrates potent *in vitro* activity against *Aspergillus*, including azole-resistant *Aspergillus fumigatus* isolates and cryptic species. *J Antimicrob Chemother* 73:3063–3067. <https://doi.org/10.1093/jac/dky280>.
 34. Cushion MT, Locke JB, Ong V, Bartizal K. 2018. Novel once-weekly echinocandin rezafungin (CD101) prevention and treatment of pneumocystis biofilms, abstr. EBMT, Lisbon, Portugal.
 35. Ong V, Hough G, Schlosser M, Bartizal K, Balkovec JM, James KD, Krishnan BR. 2016. Preclinical evaluation of the stability, safety, and efficacy of CD101, a novel echinocandin. *Antimicrob Agents Chemother* 61:e00701-16. <https://doi.org/10.1128/AAC.00701-16>.
 36. Sandison T, Ong V, Lee J, Thye D. 2017. Safety and pharmacokinetics of CD101 IV, a novel echinocandin, in healthy adults. *Antimicrob Agents Chemother* 61:e01627-16. <https://doi.org/10.1128/AAC.01627-16>.
 37. Flanagan S, Goodman DB, Jandourek A, O'Reilly T, Sandison T. 2019. Lack of effect of rezafungin on QT/QTc interval in healthy subjects. *Clin Pharmacol Drug Dev* 9:456–465. <https://doi.org/10.1002/cpdd.757>.
 38. Ong V, Sandison T, Flanagan S. 2019. No relevant pharmacokinetic (PK) interaction between rezafungin and nine probe drugs: results from a drug-drug interaction (DDI) study. *Biol Blood Marrow Transpl* 25:S357. <https://doi.org/10.1016/j.bbmt.2018.12.579>.
 39. Moriyama B, Henning SA, Leung J, Falade-Nwulua O, Jarosinski P, Penzak SR, Walsh TJ. 2012. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. *Mycoses* 55:290–297. <https://doi.org/10.1111/j.1439-0507.2011.02158.x>.
 40. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, Wong SL, Menon RM, Konopleva MY, Salem AH. 2017. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Ther* 39:359–367. <https://doi.org/10.1016/j.clinthera.2017.01.003>.
 41. Epstein D, Seo SK, Brown JM, Papanicolaou G. 2017. Echinocandin prophylaxis in patients undergoing hematopoietic cell transplantation and other treatments for hematologic malignancies. *J Antimicrob Chemother* 73(Suppl 1):i60–i72. <https://doi.org/10.1093/jac/dkx450>.
 42. Niwa T, Imagawa Y, Yamazaki H. 2014. Drug interactions between nine antifungal agents and drugs metabolized by human cytochromes P450. *Curr Drug Metab* 15:651–679. <https://doi.org/10.2174/1389200215666141125121511>.
 43. Cattaneo C, Monte S, Algarotti A, Audisio E, Borlenghi E, Campiotti L, Cerqui E, Fanizza C, Giuliani R, Mico C, Rocconi R, Salvi A, Salvi F, Verga L, Levis A, Lambertenghi Dellilieri G, Pogliani EM, Tognoni G, Rambaldi A, Rossi G. 2011. A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study). *J Antimicrob Chemother* 66:2140–2145. <https://doi.org/10.1093/jac/dkr271>.
 44. Mattiuzzi GN, Alvarado G, Giles FJ, Ostrosky-Zeichner L, Cortes J, O'Brien S, Verstovsek S, Faderl S, Zhou X, Raad II, Bekele BN, Leitz GJ, Lopez-Roman I, Estey EH. 2006. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. *Antimicrob Agents Chemother* 50:143–147. <https://doi.org/10.1128/AAC.50.1.143-147.2006>.
 45. Ostrosky-Zeichner L, Shoham S, Vazquez J, Reboli A, Betts R, Barron MA, Schuster M, Judson MA, Revankar SG, Caeiro JP, Mangino JE, Mushatt D, Bedimo R, Freifeld A, Nguyen MH, Kauffman CA, Dismukes WE, Westfall AO, Deerman JB, Wood C, Sobel JD, Pappas PG. 2014. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. *Clin Infect Dis* 58:1219–1226. <https://doi.org/10.1093/cid/ciu074>.
 46. Saliba F, Pascher A, Cointault O, Laterre PF, Cervera C, De Waele JJ, Cillo U, Langer RM, Lugano M, Goran-Ericzon B, Phillips S, Tweddle L, Karas A, Brown M, Fischer L, TENPIN Liver Transplant European Study Into the Prevention of Fungal Infection Investigators. 2015. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clin Infect Dis* 60:997–1006. <https://doi.org/10.1093/cid/ciu1128>.
 47. Bruggemann RJ, Van Der Velden WJ, Knibbe CA, Colbers A, Hol S, Burger DM, Donnelly JP, Blijlevens NM. 2015. A rationale for reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients. *J Antimicrob Chemother* 70:1166–1174. <https://doi.org/10.1093/jac/dku477>.
 48. Winston DJ, Limaye AP, Pelletier S, Safdar N, Morris MI, Meneses K, Busuttill RW, Singh N. 2014. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *Am J Transplant* 14:2758–2764. <https://doi.org/10.1111/ajt.12963>.
 49. Astellas Pharma US. 2019. Mycamine (micafungin sodium). Package insert. Astellas Pharma US, Inc, Northbrook, IL.
 50. El-Cheikh J, Venton G, Crocchiolo R, Fürst S, Faucher C, Granata A, Oudin C, Coso D, Bouabdallah R, Vey N, Duran S, Fougereau E, Berger P, Chabannon C, Blaise D. 2013. Efficacy and safety of micafungin for prophylaxis of invasive fungal infections in patients undergoing haplo-identical hematopoietic SCT. *Bone Marrow Transplant* 48:1472–1477. <https://doi.org/10.1038/bmt.2013.87>.
 51. Villaescusa T, Vazquez L, Bergua JM, Garcia J, Romero A, Olave MT, Garcia Belmonte D, Queipo de Llano MP, Hospital Virgen de la Concha. 2020. Micafungin as antifungal prophylaxis in non-transplanted haematological patients. *Rev Esp Quimioter* 33:44–48. <https://doi.org/10.37201/req/0672019>.
 52. Thompson GR, III, Soriano A, Skoutelis A, Vazquez JA, Honore PM, Horcajada JP, Spapen H, Bassetti M, Ostrosky-Zeichner L, Das AF, Viani RM, Sandison T, Pappas PG. 2020. 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* ciaa1380. <https://doi.org/10.1093/cid/ciaa1380>.
53. Zhao Y, Prideaux B, Nagasaki Y, Lee MH, Chen PY, Blanc L, Ho H, Clancy CJ, Nguyen MH, Dartois V, Perlin DS. 2017. Unraveling drug penetration of echinocandin antifungals at the site of infection in an intra-abdominal abscess model. *Antimicrob Agents Chemother* 61:e01009–17. <https://doi.org/10.1128/AAC.01009-17>.
54. Brown JM, Lakota EA, Flanagan S, Sandison T, Ong V, Rubino CM. 2019. Pharmacokinetic-pharmacodynamic analyses of dose selection for rezafungin prophylaxis against invasive fungal infections in bone marrow transplantation. *Biol Blood Marrow Transpl* 25:S358–S359. <https://doi.org/10.1016/j.bbmt.2018.12.581>.
55. Ong V, Flanagan S, Sandison T, Bartizal K, Satta A, Sharp A, Thommes P, Murphy T. 2018. CD101 lung epithelial lining fluid (ELF) concentrations substantiate its use for prophylaxis treatment as evident in mouse disseminated and pulmonary aspergillosis models, abstr. *Advances against Aspergillosis*, Lisbon, Portugal.
56. Ong V, James KD, Smith S, Krishnan BR. 2017. Pharmacokinetics of the novel echinocandin CD101 in multiple animal species. *Antimicrob Agents Chemother* 61:e01626–16. <https://doi.org/10.1128/AAC.01626-16>.
57. Cushion MT, Linke MJ, Ashbaugh A, Sesterhenn T, Collins MS, Lynch K, Brubaker R, Walzer PD. 2010. Echinocandin treatment of *Pneumocystis pneumonia* in rodent models depletes cysts leaving trophic burdens that cannot transmit the infection. *PLoS One* 5:e8524. <https://doi.org/10.1371/journal.pone.0008524>.