Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v26i1.475_ENG

REVIEW ARTICLE

Prophylaxis of Fungal Infections in Transplant Patients: What has Changed in Recent Years?

Mariana Araujo Mendes Silva[1*], Fernando Callera[1], Mariella Vieira Pereira Leão[1]

1.Faculdade de Ciências Médicas de São José dos Campos – São José dos Campos/SP – Brasil.

*Corresponding author: mendes.marianaaraujo@gmail.com

Section editor: Ilka de Fátima Santana F Boin

Received: Jun. 29, 2022

Accepted: Jan. 03, 2023

How to cite: Silva MAM, Callera F, Leão MVP. Prophylaxis of Fungal Infections in Transplant Patients: What has Changed in Recent Years? BJT. 2023.26 (01):e0523. https://doi.org/10.53855/bjt.v26i1.475_ENG

ABSTRACT

Objective: The present work aimed to review the invasive fungal infections (IFIs) and antifungal prophylaxis used in the last 20 years in transplant patients to identify the changes that occurred in this period and discuss the most current conducts. **Methods:** This is a systematic review in which the PubMed database was used, in which scientific articles from the last 20 years were selected, covering clinical trials, randomized controlled trials, systematic reviews of the literature and meta-analyses. **Results:** According to the present study, posaconazole and voriconazole are the antifungal drugs of choice for IFI prophylaxis in hematopoietic stem cell transplantation (HSCT). However, as posaconazole is not available in the public health system in Brazil, the most viable option remains voriconazole. Regarding IFI prophylaxis in solid organ transplantation (SOT), it was observed that there are variations depending on the transplanted target organ, and there is no evidence of its need in kidney transplantation. Although azoles are also the most used and bring clear benefits in liver and lung transplantation, some current studies have placed echinocandins on the same level, encouraging their use to prevent IFI in these patients. **Conclusion:** In the last five years, there has been a great shortage of clinical trials comparing different antifungal prophylaxis. New studies are needed to establish the most appropriate protocols for each condition and profile of the transplanted patient.

Descriptors: Hematopoietic Stem Cell Transplantation; Organ Transplantation; Post-Exposure Prophylaxis; Pre-Exposure Prophylaxis; Liver Transplantation; Lung Transplantation.

Profilaxia de Infecções Fúngicas em Pacientes Transplantados: O que Mudou nos Últimos Anos?

RESUMO

Objetivo: O presente trabalho objetivou revisar as infecções fúngicas invasivas (IFIs) e as profilaxias antifúngicas utilizadas nos últimos 20 anos em pacientes transplantados, de forma a identificar as mudanças ocorridas nesse período e discutir as condutas mais atuais. **Métodos:** Trata-se de uma revisão sistemática em que se utilizou a base de dados PubMed, na qual foram selecionados artigos científicos dos últimos 20 anos, abrangendo ensaios clínicos, ensaios controlados randomizados, revisões sistemáticas da literatura e metanálises. **Resultados:** De acordo com o presente estudo, o posaconazol e o voriconazol parecem ser as drogas antifúngicas de escolha na profilaxia de IFI em transplante de células-tronco hematopoiéticas (TCTH). Entretanto, como não há disponibilidade do posaconazol no sistema público de saúde do Brasil, a opção mais viável continua sendo o voriconazol. Com relação à profilaxia de IFI em transplante de órgãos sólidos (TOS), observou-se que existem variações em função do órgão-alvo transplantado, sendo que no transplante renal (TR) nem há evidência da sua necessidade. Apesar dos azóis também serem os mais utilizados e trazerem benefícios evidentes nos transplantes de fígado (TF) e de pulmão (TP), alguns estudos atuais têm colocado as equinocandinas no mesmo patamar, encorajando mais seu uso para prevenção de IFI nesses pacientes. **Conclusão:** Uma vez que nos últimos 5 anos existe grande escassez de ensaios clínicos comparando diferentes profilaxias antifúngicas, novos estudos são necessários a fim de estabelecerem os protocolos mais adequados para cada condição e perfil de paciente transplantado.

Descritores: Transplante de Células-Tronco Hematopoiéticas; Transplante de Órgãos; Profilaxia Pós-Exposição; Profilaxia Pré-Exposição; Transplante de Fígado; Transplante de Pulmão.

INTRODUCTION

It is known that patients who have received solid organ transplantation (SOT), hematopoietic stem cell transplantation (HSCT), or bone marrow transplantation may develop invasive fungal infections (IFIs), with high mortality, prolonged hospitalization days and excessively increasing costs for healthcare facilities.[1] Most transplant recipients require lifelong treatment with potent immunosuppressive drugs. Excessive immunosuppression is associated with a higher incidence of these infections during the immediate postoperative period.[2]

Neofytos et al. evidenced that Candida, Aspergillus, Cryptococcus, and other fungi caused most IFIs in SOT recipient patients. Invasive candidiasis was the most observed IFI, except in lung transplant recipients, in whom invasive aspergillosis was the most common. Organ damage, neutropenia, and corticosteroid administration were also observed to be predictors of death in these patients.[3]

The incidence of IFI in patients receiving HSCT transplantation is also significant, being reported in 5.4% to 16.0% of cases, with prolonged neutropenia and immunosuppression as contributing factors to the increased risk of fungal disease in these patients.[4] The IFIs developed by HSCT transplant recipients also include aspergillosis and candidiasis, followed by a smaller number of scedosporiosis and zygomycosis.[5]

Treatment of an established IFI is often very difficult, and the most effective antifungal agents have toxicities that limit treatment. In this sense, antimicrobial prophylaxis could bring benefits such as reducing mortality and lowering healthcare costs.[6] According to Evans et al., the chances of mortality due to IFIs are lower in patients who have received antifungal prophylaxis compared to those who have not[7] However, protocols for antimicrobial use vary widely among healthcare institutions, and the results of studies supporting specific practices also vary.[8]

Since the high rate of comorbidity in transplant patients raises the risk of developing IFI and may indicate the need for active antifungal prophylaxis in high-risk patients,[9] this study proposes to review the IFIs and the different antifungal prophylaxes proposed in the last 20 years, both for patients undergoing HSCT and SOT, emphasizing the changes that have occurred in this period and the most up-to-date conducts.

METHODS

The PubMed database was used, in which scientific articles from the last 20 years were selected, covering clinical trials, randomized controlled trials, systematic literature reviews, and meta-analyses. The keywords used were: "Invasive Fungal Infections," "Hematopoietic Stem Cell Transplantation," "Organ Transplantation," "Post-Exposure Prophylaxis," "Pre-Exposure Prophylaxis," "Liver Transplant," and "Lung Transplantation." Initially, 879 papers were found, of which 822 were excluded due to incompatibility with the aim of the study.

REVIEW AND RESULTS

Invasive Fungal Infections

IFIs are severe infections associated with high mortality rates, despite the availability of new classes of antifungal agents.[10] The fungi most frequently presented as etiologic agents of IFIs include the genera *Aspergillus* and *Candida*.[11]

Species of the genus *Aspergillus* are filamentous saprophytic fungi commonly found in the soil of subtropical climate regions. Inhalation of asexual spores produced by *Aspergillus* causes a group of diseases collectively called aspergillosis.[12]

Aspergillus fumigatus and other filamentous fungi grow as networks of filamentous hyphae that have characteristics of a classical microbial biofilm. Biofilm growth of *A. fumigatus* occurs *in vivo* at sites of infection, contributing to increased resistance to contemporary antifungal drugs.[13] Although significant advances have been made in diagnosing this disease, obtaining mycological confirmation of infection is still difficult.[14]

On the other hand, the Candida genus is the cause of invasive candidiasis, much in evidence in the context of IFIs, and an important cause of complications and death in hospitalized patients.[15] The most prominent species of this genus is *Candida albicans*. This dimorphic commensal fungus colonizes the vaginal and oral mucosa of healthy individuals and can become a pathogen when the balance between the fungus, mucosa, and host defense mechanisms is disrupted. The pathogenic potential of *Candida* depends on its ability to adhere and produce biofilms on abiotic and living surfaces. The cells in biofilms are much less susceptible to host defenses and the action of antimicrobials.[16]

IFIs are usually challenging to diagnose, especially in critically ill patients, and are responsible for considerable morbidity in immunocompromised individuals, including those with hematologic malignancies or recipients of solid organs or hematopoietic

cell transplants.[17,18] Definitive diagnosis of fungal infection is possible only after histopathological examination or culture of the etiologic agent. Treatment is still challenging because one must assume that the agent isolated in culture is the actual pathogen of the infection.[19]

Antifungal treatment options for most IFIs include formulations of amphotericin B, echinocandins, and triazole antifungal agents. However, each may be associated with limitations that have pathogen resistance and intolerability of the patient.[18] Drugs such as amphotericin B, in its different formulations: lipidic complex, deoxycholate and liposomal, are available in the Brazilian Unified Health System (UHS), the first in suspension for injection and the following in powder for injection. Fluconazole is also available in capsules, oral suspension, and injectable solution; itraconazole, only in oral solution or capsule; and voriconazole, only for hospital use. Posaconazole, on the other hand, is not cited in the Ministry of Health's National List of Essential Medicines (RENAME). Micafungin and caspofungin (both of the echinocandins group) are not mentioned in the RENAME; however, anidulafungin was recently incorporated into the UHS, and its use is reserved for patients with candidemia and other forms of invasive candidiasis.[20,21]

IFI prophylaxis in HSCT

HSCT is one of the possible treatments established for patients with hematological malignancies and those with congenital and acquired disorders of the hematopoietic system.[22] As for the patient profile, one study gathered patients from 3 to 64 years of age, and all had an indication for HSCT, i.e., the profile of patients undergoing this type of procedure is variable.[23]

The development of severe and/or steroid-refractory graft-versus-host disease (GVHD) remains a significant limitation for the success of HSCT.[24] This condition results from complex and dynamic mechanisms that can start with early inflammation due to tissue injury[25]

GVHD is considered the main risk factor for invasive aspergillosis after HSCT,[26] with high mortality in immunocompromised hosts, as well as being the leading cause of late post-HSCT morbidity and mortality.[27]

Ullmann et al., in a randomized, double-blind study on IFI prophylaxis in patients with GVHD, compared oral posaconazole with oral fluconazole. The incidence rate of invasive aspergillosis was 2.3% in patients using posaconazole versus 7.0% in those using fluconazole. In the posaconazole group, the overall mortality rate was 1%, and the adverse event rate was only 36%, while in the fluconazole group, the overall mortality was 3%, and adverse events occurred in 38%.[28] Still comparing these same two drugs, Shen et al., by analyzing 234 patients, observed that the incidence of proven, probable, or possible IFI was 9.4% and 22.2% in the posaconazole and fluconazole groups, respectively ($p = 0.0114$). In addition, the clinical failure rate was also lower in the posaconazole group but without statistical significance ($p = 0.168$).[29]

In contrast, a study by Marks et al. presented a comparison between voriconazole and itraconazole, which concluded that prophylaxis success was significantly higher with voriconazole than with itraconazole (48.7% vs. 33.2%) and that tolerance to prophylaxis for 100 days was higher in patients receiving voriconazole (53.6% vs. 39.0%). Also, the need for other systemic antifungals was higher in patients who used itraconazole (41.9% vs. 29.9%), leading the authors to suggest voriconazole in preference.[30]

Still, on voriconazole, a study by Wingard et al. compared it to fluconazole and obtained the following results: lower rate of IFIs (7.3% vs. 11.2%; $p = 0.12$), fewer *Aspergillus* infections (9 vs. 17; $p = 0.09$) and less frequent need for empirical antifungal therapy (24.1% vs. 30.2%, $p = 0.11$), although fungus-free survival rates were very similar between the two (75% vs. 78%; $p = 0.49$).[31] A randomized clinical trial conducted by Hayashi et al., when selecting adult patients undergoing HSCT with acute grade II to IV GVHD or chronic GVHD requiring corticosteroid treatment, mentioned a higher 3-year overall survival rate with voriconazole prophylaxis than 3-year with itraconazole (67% vs. 49%).[32]

The literature brings not only drugs for IFI prophylaxis in HSCT patients but also alternative measures: one research selected 206 patients to receive granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, or a combination of both, subcutaneously, five days after HSCT. A prophylactic granulocyte-macrophage colony-stimulating factor was associated with lower HSCT-related mortality at 100 days and lower IFI-related mortality at 600 days.[4]

On the use of echinocandins in HSCT, micafungin is a viable prophylactic option in patients with neutropenia. Huang et al. conducted a multicenter, randomized, open-label phase III study in which they compared the efficacy and safety of micafungin with itraconazole in patients with neutropenia undergoing HSCT and demonstrated that it achieved similar efficacy to itraconazole.[33] Another, more recent study retrospectively evaluated the effectiveness of oral prophylaxis with itraconazole/voriconazole in conjunction with intravenous micafungin at doses of 50, 100 or 150 mg. The result demonstrated that micafungin was effective and well tolerated in clinical practice for IFI prophylaxis in HSCT patients, and, furthermore that its combination with itraconazole/fluconazole was beneficial with no reported adverse effects. Furthermore, in a 2019 study, micafungin was also shown to be effective and safe for adult patients undergoing cord blood transplantation.[34,35]

The use of amphotericin B lipid complex has also been studied in HSCT, but prophylactically in high doses, it was associated with nephrotoxicity, which could be aggravated by concomitant use of other nephrotoxic agents.[36]

Some of the studies comparing prophylaxis options in patients undergoing HSCT can be seen in Table 1.

Table 1. Comparative studies on antifungal prophylaxes in patients receiving and/or candidates for hematopoietic stem cell transplantation.

Authors/year	Type of study	Sample	Prophylaxis	Best result	Comments
Ullmann et al. (2007)[28]	Randomized double blind	600 patients	Posaconazole versus fluconazole	Posaconazole	Incidence of invasive aspergillosis: 2.3% versus 7.0%, overall mortality 1% versus 3%, and adverse event rate: 36% versus 38%.
Wingard et. al. (2010)[31]	Randomized double blind	600 patients	Voriconazole versus fluconazole	Voriconazole	Although 6-month fungus-free survival and overall survival did not differ, voriconazole achieved a lower rate of IFIs (7.3% vs. 11.2%; P = 0.12) and fewer *Aspergillus* infections (9 vs. 17; P = 0.09).
Marks et al. (2011)[30]	Randomized prospective	489 patients	Voriconazole versus itraconazole	Voriconazole	Voriconazole can be administered for significantly longer periods, with less need for other systemic antifungals.
Huang et al. (2012)[33]	Randomized open phase III	287 patients	Micafungin versus itraconazole	Micafungin	Overall treatment success rate: 80% versus 73.5% and toxicity cases: 1 versus 29.
Chaftari et al. (2012)[36]	Randomized prospective	46 patients	Posaconazole versus amphotericin B	Posaconazole	Incidence of IFI: 0% versus 5% and mean number of patients with adverse effects: 7 versus 8.
Shen et al. (2013)[29]	Randomized multicentric	234 patients	Posaconazole versus fluconazole	Posaconazole	The incidence of proven, probable or possible IFI was 9.4% (11/117) and 22.2% (26/117) (p = 0.0114) in the posaconazole and fluconazole groups respectively.

Source: Elaborated by the authors.

IFI prophylaxis in SOT

SOT has several purposes depending on the type of solid organ transplanted. SOT recipient patients often have several complex symptoms related to the underlying disease and chronic immunosuppression, and these factors certainly diminish their quality of life.[37]

About the profile of the SOT recipient patient, the age range seems to vary between children and adults, and the presence of malignancies presents itself as a frequent pretransplant condition associated with increased mortality.[38]

The most common agents of fungal infections in SOT-receiving patients include *Candida*, *Aspergillus species*, *and Cryptococcus species*, among others.[3]

Depending on the type of transplanted organ, the prevalence of these agents can change. In renal transplant (RT) recipient patients, the most common complications are from aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis consecutively.[39,40] Whereas in lung transplant (LgT), aspergillosis, more specifically that caused by *A. fumigatus*, is the predominantly most common infection,[41] while in liver transplantation (LvT), infections by *Candida* have a higher prevalence.[42]

Regarding antifungal prophylaxis in RT recipients, there needs to be more literature or evidence on the topic; however, there is content on the use of immunosuppressive drugs in these patients and how to minimize immunosuppression to maintain efficacy in preventing rejection of the organ.[43] In a prospective, multicenter, open-label, randomized, controlled study on the treatment of invasive fungal infections and not prophylaxis in patients with RT, there needs to be more literature or evidence on the topic.[43] In a prospective, multicenter, open-label, randomized, controlled study on the treatment of invasive fungal infections and not prophylaxis, in patients with, the efficacy of micafungin was shown to be similar to that of voriconazole.[44]

In cases of heart transplant (HT) recipients, although the literature reports fungal infection in these patients, there is a great scarcity of studies indicating options for prophylactic agents.[45]

Concerning LvT, a 2015 open-label study showed that micafungin 100 mg was not inferior to standard treatment (fluconazole, liposomal amphotericin B or caspofungin) as antifungal prophylaxis in patients at high risk of IFI. The study patients had similar adverse event and liver function profiles, but the standard treatment showed, albeit in a very similar way, a higher clinical success rate: 99.3% versus 98.6%.[46]

Winston et al. found that both anidulafungin and fluconazole are well tolerated in LvT recipients, reserving the use of anidulafungin in patients at high risk of invasive aspergillosis and in patients who received fluconazole before transplantation.[47]

In addition, a more recent review work managed by Khalid et al. suggested that the efficacy of fluconazole was similar to that of liposomal amphotericin. Still, that fluconazole would be preferred due to its cost-effectiveness and safety profile.[48] Still on LvT,

research by Kang et al. showed that micafungin could be used as an alternative to fluconazole, with no difference between the two in terms of IFI presence, time to IFI development, fungus-free survival, and adverse reactions. The research also found similar clinical success rates of 95.65% and 96.10% in the micafungin and fluconazole groups, respectively.[49]

Concerning LgT, Al Jishi et al., in a single-center retrospective cohort study, investigated the use of echinocandin and concluded that it is an important second-line agent, still preempted by the azoles group, as LgT transplant recipient patients who received antifungal prophylaxis with azoles did not develop disseminated invasive aspergillosis, cryptococcal or endemic fungal infections.[50,51]

The comparative studies mentioned in this subtopic on IFI prophylaxis in patients with SOT can be summarized and visualized in Table 2.

Table 2. Studies on invasive fungal infections in solid organ transplant patients undergoing different prophylaxis or treatment.

Population studied	Authors	Type of study	Sample	Prophylaxis	Result	Comments
RT	Shang et al. (2012)[44]	Randomized prospective	65 patients	Micafungin versus voriconazole (treatment)	Very similar results.	Incidence of fungal infection one to three months post-transplant: 83.6% (26/31) versus 85.3% (29/34).
LvT	Winston et al. (2014)[47]	Randomized double blind	200 patients	Anidulafungin versus fluconazole	Very similar results	Anidulafungin may be beneficial if the patient has an increased risk of *Aspergillus* infection or receives fluconazole before transplantation.
LvT	Saliba et al. (2015)[46]	Open-label, non-inferiority	344 patients	Micafungin versus standard treatment (fluconazole, liposomal amphotericin B or caspofungin)	Standard treatment	Clinical success rate: 99.3% versus 98.6%.
LvT	Kang et al. (2020)[49]	Randomized multicentric	172 patients	Micafungin versus fluconazole	Very similar results	The study groups did not differ significantly in terms of secondary efficacy outcomes.
LgT	Husain et al. (2006)[52]		95 patients	Voriconazole versus targeted prophylaxis (itraconazole ± inhaled amphotericin)	Voriconazole	Better rate of invasive aspergillosis at 1 year. Mortality rate: 0.03/person-year versus 0.16/person-year.
LgT	Al Jishi et al. (2018)[50]	Retrospective cohort	777 patients	Echinocandin and azoles	Azoles	Despite having a lower adverse event profile, echinocandins are still considered second-line agents.

Source: Elaborated by the authors.

DISCUSSION AND CONCLUSION

According to the present study, posaconazole and voriconazole are the antifungal drugs of choice in IFI prophylaxis in HSCT. Similarly, Wang et al., in a recent systematic review and meta-analysis of 69 randomized clinical trials that reported comparisons of 12 treatments with a total of 14,789 patients, concluded that voriconazole would be the best choice for patients undergoing HSCT, thus contrasting with some past studies that gave preference to posaconazole.[53] In any case, as posaconazole is not available in UHS, voriconazole (available for hospital use) is the viable option in Brazil's public health system.[20,28,30–33,54] Micafungin may also be a beneficial option for prophylaxis of IFIs in HSCT patients. It may be used in combination with itraconazole or fluconazole, and this consensus has not changed at present. However, since micafungin is not yet available in UHS, its use is restricted to the private healthcare system.[33–35]

Regarding IFI prophylaxis in SOT, it has been observed that variations depend on the transplanted target organ. There is not enough literature in RT highlighting the need for antifungal prophylaxis.[43] The literature addresses antifungals in RT when discussing the treatment of IFI in patients who develop the disease. In these cases, it is possible to use both micafungin and voriconazole, since they have similar clinical results.[46]

In LvT, azoles were a better option in past studies, while more current studies show similar efficacy of echinocandins. A systematic review and meta-analysis also concluded no difference between echinocandins and other antifungals in advancement against IFIs. Anidulafungin, micafungin and fluconazole stand out here as agents of choice. Still, micafungin is not available on the UHS and anidulafungin is restricted to those with candidemia and other forms of invasive candidiasis. Thus, fluconazole is still the most viable option in the public system.[46–49,55]

In LgT, recent and past studies suggest using azoles as the prophylactic agents. Similarly, a recent study places azoles as first-line antifungal agents in 80% of cases, echinocandins in approximately 18.3%, and amphotericin B in only 1.5%.[50,51] However, a recent systematic review and meta-analysis demonstrated that patients undergoing LgT using voriconazole had an increased risk of developing squamous cell carcinoma, suggesting caution with this particular agent. Furthermore, there is a clear need to choose specific drugs according to the patient, and the various comparative clinical trials demonstrate different strategies.[52,55,56]

Past studies were more wary of the echinocandins (the group in which micafungin, anidulafungin, and caspofungin are included), due to the need for daily parenteral administration and the increasing reports of disruptive infections, thus dampening enthusiasm for the use of these agents. Giannella et al. reported that although echinocandins have a low rate of drug interactions, the need for daily parenteral administration was indeed a problem.[57] However, current studies place echinocandins and azoles on the same level regarding benefits, further encouraging their use for IFI prevention in transplant patients. As for liposomal amphotericin, although this drug does not alter the cytochrome P450 system, its nephrotoxicity has been and continues to be a major concern.[46–50,52]

It is also important to note that there is still no consensus on the need for antifungal prophylaxis in all transplant patients. Several programs do not routinely use antifungals perioperatively in these patients, and one study showed a similar incidence of IFI in the absence of prophylaxis.[52] Thus, new studies, specifically clinical trials and randomized controlled trials, are needed to establish the most appropriate protocols for each condition and patient profile. There needs to be more current data (considering the last five years) on the subject of this study.

CONFLICT OF INTEREST

Nothing to declare.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silva MAM, Callera F and Leão MVP; **Conception and design:** Silva MAM and Leão MVP; **Data analysis and interpretation:** Silva MAM, Callera F and Leão MVP; **Article writing:** Silva MAM, Callera F and Leão MVP; **Critical review:** Silva MAM, Callera F and Leão MVP; **Final approval:** Silva MAM, Callera F and Leão MVP.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

FUNDING

Not applicable.

ACKNOWLEDGEMENTS

We thank librarian Denise Serrano for helping us technically with the preparation of the references and tables.

REFERENCES

1. Menzin J, Meyers JL, Friedman M, Korn JR, Perfect JR, Langston AA, et al. The economic costs to United States hospitals of invasive fungal infections in transplant patients. Am J Infect Control. 2011;39(4):e15-20. https://doi.org/10.1016/j.ajic.2010.06.009
2. Ravaioli M, Neri F, Lazzarotto T, Bertuzzo VR, Di Gioia P, Stacchini G, et al. Immunosuppression modifications based on an immune response assay: Results of a randomized, controlled trial. Transplantation. 2015;99(8):1625-32. https://doi.org/10.1097/TP.0000000000000650
3. Neofytos D, Fishman J, Horn D, Anaissi E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3):220-29. https://doi.org/10.1111/j.1399-3062.2010.00492.x

4. Wan L, Zhang Y, Lai Y, Jiang M, Song, Y Zhou J, et al. Effect of granulocyte-macrophage colony-stimulating factor on prevention and treatment of invasive fungal disease in recipients of allogeneic stem-cell transplantation: A prospective multicenter randomized phase IV trial. J Clin Oncol. 2015;33(34):3999-4006. https://doi.org/10.1200/JCO.2014.60.512

5. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: Results of the VOSIFI study. Haematologica. 2010;95(10):1762-68. https://doi.org/10.3324/haematol.2009.020073

6. Mann PA, McNicholas PM, Chau AS, Patel R, Mendrick C, Ullmann AJ, et al. Impact of antifungal prophylaxis on colonization and azole susceptibility of *Candida* species. Antimicrob Agents Chemother. 2009;53(12):5026-34. https://doi.org/10.1128/AAC.01031-09

7. Evans JD, Morris PJ, Knight SR. Antifungal prophylaxis in liver transplantation: A systematic review and network meta-analysis. Am J Transplant. 2014;14(12):2765-76. https://doi.org/10.1111/ajt.12925

8. Anesi JA, Blumberg EA, Abbo LM. Perioperative antibiotic prophylaxis to prevent surgical site infections in solid organ transplantation. Transplantation. 2018;102(1):21-34. https://doi.org/10.1097/TP.0000000000001848

9. Busca A, Passera R, Maffini E, Festuccia M, Brunello L, Dellacasa CM, et al. Hematopoietic cell transplantation comorbidity index and risk of developing invasive fungal infections after allografting. Bone Marrow Transplant. 2018;53(10):1304-10. https://doi.org/10.1038/s41409-018-0161-1

10. Delsing CE, Gresnigt MS, Leentjens J, Preijers F, Frager FA, Kox M, et al. Interferon gamma as adjunctive immunotherapy for invasive fungal infections: A case series. BMC Infect Dis. 2014;14:166. https://doi.org/10.1186/1471-2334-14-166

11. Armstrong AE, Rossoff J, Hollemo D, Hong DK, Muller WJ, Chaudhury S. Cell-free DNA next-generation sequencing successfully detects infectious pathogens in pediatric oncology and hematopoietic stem cell transplant patients at risk for invasive fungal disease. Pediatr Blood Cancer. 2019; 66(7):e27734. https://doi.org/10.1002/pbc.27734

12. Rokas A, Mead ME, Steenwyk JL, Oberlies NH, Goldman GH. Evolving moldy murderers: *Aspergillus* section *Fumigati* as a model for studying the repeated evolution of fungal pathogenicity. PLoS Pathog. 2020;16(2):e1008315. https://doi.org/10.1371/journal.ppat.1008315

13. Morelli KA, Kerkaert JD, Cramer RA. *Aspergillus fumigatus* biofilms: Toward understanding how growth as a multicellular network increases antifungal resistance and disease progression. PLoS Pathog. 2021;17(8):e1009794. https://doi.org/10.1371/journal.ppat.1009794

14. Herbrecht R, Patterson TF, Slavin MA, Marchetti O, Maertens J, Johnson EM, et al. Application of the 2008 definitions for invasive fungal diseases to the trial comparing voriconazole versus amphotericin B for therapy of invasive aspergillosis: A collaborative study of the mycoses study group (MSG 05) and the European organization for research and treatment of cancer Infectious diseases group. Clin Infect Dis. 2015;60(5),713-20. https://doi.org/10.1093/cid/ciu911

15. 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(24):2472-82. https://doi.org/10.1056/NEJMoa066906

16. Ribeiro FC, Rossoni RD, Barros PP, Santos JD, Fugisaki LRO, Leão MPV, et al. Action mechanisms of probiotics on *Candida* spp. and candidiasis prevention: an update. J Appl Microbiol. 2020;129(2):175-85. https://doi.org/10.1111/jam.14511

17. De Vlieger G, Vanhorebeek I, Wouters PJ, Derese I, Casaer MP, Debaveye Y, et al. The soluble mannose receptor (sMR/sCD206) in critically ill patients with invasive fungal infections, bacterial infections or non-infectious inflammation: A secondary analysis of the EPaNIC RCT. Crit Care. 2019; 23(1):270. https://doi.org/10.1186/s13054-019-2549-8

18. Marty FM, Cornely OA, Mullane KM, Ostrosky-Zeichner L, Maher RM, Croos-Dabrera R, et al. Isavuconazole for treatment of invasive fungal diseases caused by more than one fungal species. Mycoses. 2018;61(7):485-97. https://doi.org/10.1111/myc.12777

19. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: Diagnosis & clinical management. Indian J Med Res. 2014;139(2):195-204.

20. Relação Nacional de Medicamentos Essenciais Rename 2022. Brasília: Ministério da Saúde; 2022. [citado 2022 out 10]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/relacao_nacional_medicamentos_2022.pdf

21. Relatório para Sociedade. Informações sobre recomendações de incorporação de medicamentos e outras tecnologias do SUS. Brasília: Ministério da Saúde; 2022. [citado 2022 out 10]. Disponível em: https://www.gov.br/conitec/pt-br/midias/relatorios/2022/sociedade/20220801_ReSoc_345_Anidulafungina.pdf

22. Srinivasan A, Wang C, Srivastava DK, Burnette K, Shenep JL, Leung W, et al. Timeline, epidemiology, and risk factors for bacterial, fungal, and viral infections in children and adolescents after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2013;19(1):94-101. https://doi.org/10.1016%2Fj.bbmt.2012.08.012

23. Cohen S, Roy J, Lachance S, Delisle JS, Marinier A, Busque L, et al. Hematopoietic stem cell transplantation using single UM171-expanded cord blood: A single-arm, phase 1–2 safety and feasibility study . Lancet Haematol. 2020;7(2):e134-45. https://doi.org/10.1016/S2352-3026(19)30202-9

24. Hill GR, Koyama M. Cytokines and costimulation in acute graft-versus-host disease. Blood. 2020;136(4):418-28. https://doi.org/10.1182/blood.2019000952

25. Hamilton BK. Updates in chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program. 2021;2021(1):648-54. https://doi.org/10.1182/hematology.2021000301

26. Robin C, Cordonnier C, Sitbon K, Raus, N, Lortholar O, Maury S, et al. Mainly post-transplant factors are associated with invasive aspergillosis after allogeneic stem cell transplantation: A study from the surveillance des aspergilloses invasives en France and Société Francophone de Greffe de Moelle et de Thérapie Cellulaire. Biol Blood Marrow Transplant. 2019;25(2):354-61. https://doi.org/10.1016/j.bbmt.2018.09.028

27. Panackal AA, Parisini E, Proschan M. Salvage combination antifungal therapy for acute invasive aspergillosis may improve outcomes: A systematic review and meta-analysis. Int J Infect Dis. 2014;28:80-94. https://doi.org/10.1016/j.ijid.2014.07.007

28. 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 Eng J Med. 2007;356:335-47. https://doi.org/10.1056/NEJMoa061098

29. Shen Y, Huang XJ, Wang JX, Jin J, Hu JD, Yu K, et al. Posaconazole vs. fluconazole as invasive fungal infection prophylaxis in China: A multicenter, randomized, open-label study. Int J Clin Pharmacol Ther. 2013;51(9):738-45. https://doi.org/10.5414/CP201880

30. Marks DI, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. Br J Haematol. 2011;155(3):318-27. https://doi.org/10.1111/j.1365-2141.2011.08838.x

31. 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(24):5111-8. https://doi.org/10.1182/blood-2010-02-268151

32. Hayashi Y, Kanda Y, Nakamae H, et al Voriconazole vs itraconazole for antifungal prophylaxis in patients with GVHD: A randomized trial. Biol Blood Marrow Transplant. 2014;20(2):S91. https://doi.org/10.1016/j.bbmt.2013.12.117

33. Huang X, Chen H, Han M, Zou P, Wu D, Lai Y, et al. Multicenter, randomized, open label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. Biol Blood Marrow Transplant. 2012;18(10):1509-16. https://doi.org/10.1016/j.bbmt.2012.03.014

34. Zhang H. Bridging antifungal prophylaxis with micafungin in hematopoietic stem cell transplantation: A retrospective analysis. Hematology. 2021;26(1):670-74. https://doi.org/10.1080/16078454.2021.1959982

35. Yasu T, Konuma T, Oiwa-Monna M, Mizusawa M, Isobe M, Kato S, et al. Efficacy and safety of micafungin in unrelated cord blood transplant recipients. Ann Hematol. 2019;98(11):2593-600. https://doi.org/10.1007/s00277-019-03790-z

36. Chaftari AM, Hachem RY, Ramos E, Kassis C, Campo M, Jiang Y, et al. Comparison of posaconazole versus weekly amphotericin B lipid complex for the prevention of invasive fungal infections in hematopoietic stem-cell transplantation. Transplantation. 2012;94(3):302-8. https://doi.org/10.1097/tp.0b013e3182577485

37. Gross CR, Kreitzer MJ, Thomas W, Reilly-Spong M, Cramer-Bornemann M, Nyman JA, et al. Mindfulness-based stress reduction for solid organ transplant recipients: A randomized controlled trial. Altern Ther Health Med. 2010;16(5):30-8.

38. Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. Outcomes of solid organ transplant recipients with preexisting malignancies in remission: A systematic review and meta-analysis. Transplantation. 2017;101(3):471-81. https://doi.org/10.1097/TP.0000000000001192

39. Imko-Walczuk BB, Prędota A, Okuniewska A, Jaśkiewicz J, Zegarska B, Placek W, et al. Superficial fungal infections in renal transplant recipients. Transplant Proc. 2014;46(8):2738-42. https://doi.org/10.1016/j.transproceed.2014.09.051

40. Parajuli S, Wick A, Pandeya S, Astor BC, Smith J, Djamali A, et al. The feared five fungal infections in kidney transplant recipients: A single-center 20-year experience. Clin Transplant. 2018;32(7):e13289. https://doi.org/10.1111/ctr.13289

41. Chong PP, Kennedy CC, Hathcock MA, Kremers WK, Razonable RR. Epidemiology of invasive fungal infections in lung transplant recipients on long-term azole antifungal prophylaxis. Clin Transplant. 2015;29(4):311-8. https://doi.org/10.1111/ctr.12516

42. Sganga G, Pepe G, Cozza V, Nure E, Lirosi MC, Frongillo F, et al. Anidulafungin--a new therapeutic option for *Candida* infections in liver transplantation. Transplant Proc. 2012;44(7):1982-5. https://doi.org/10.1016/j.transproceed.2012.06.029

43. Bemelman FJ, de Maar EF, Press RR, van Kan HJ, ten Berge IJ, Homan van der Heide JJ, et al. Minimization of maintenance immunosuppression early after renal transplantation: An interim analysis. Transplantation. 2009;88(3):421-8. https://doi.org/10.1097/tp.0b013e3181af1df6

44. Shang W, Feng G, Sun R, Wang X, Liu W, Zhang S, et al. Comparison of micafungin and voriconazole in the treatment of invasive fungal infections in kidney transplant recipients. J Clin Pharm Ther. 2012;37(6):652-6. https://doi.org/10.1111/j.1365-2710.2012.01362.x

45. Mann S, Tobolowsky F, Purohit S, Henao-Martínez A, Bajrovic V, Ramanan P, et al. Cryptococcal pericarditis in a heart transplant recipient. Transpl Infect Dis. 2020;22(6):e13366. https://doi.org/10.1111/tid.13366

46. Saliba F, Pascher A, Cointault O, Laterre PF, Cervera C, De Waele JJ, et al. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. Clin Infect Dis. 2015;60(7):997-1006. https://doi.org/10.1093/cid/ciu1128

47. Winston DJ, Limaye AP, Pelletier S, Safdar N, Morri MI, Meneses K, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. Am J Transp. 2014;14(12):2758-64. https://doi.org/10.1111/ajt.12963

48. Khalid M, Neupane R, Anjum H, Surani S. Fungal infections following liver transplantation. World J Hepatol. 2021;13(11):1653-62. https://doi.org/10.4254/wjh.v13.i11.1653

49. Kang WH, Song GW, Lee SG, Suh KS, Lee KW, Yi NJ, et al. A multicenter, randomized, open-label study to compare micafungin with fluconazole in the prophylaxis of invasive fungal infections in living-donor liver transplant recipients. J Gastrointest Surg. 2020;24(4):832-40. https://doi.org/10.1007/s11605-019-04241-w

50. Al Jishi Y, Rotstein C, Kumar D, Humar A, Singer LG, Keshavjee S, et al. Echinocandin use in lung transplant recipients. Clin Transplant. 2018;32(12):e13437. https://doi.org/10.1111/ctr.13437

51. Chong PP, Kennedy CC, Hathcock MA, Kremers WK, Razonable RR. Epidemiology of invasive fungal infections in lung transplant recipients on long-term azole antifungal prophylaxis. Clin Transplant. 2015;29(4):311-8. https://doi.org/10.1111/ctr.12516

52. Wang J, Zhou M, Xu JY, Zhou RF, Chen B, Wan Y. Comparison of antifungal prophylaxis drugs in patients with hematological disease or undergoing hematopoietic stem cell transplantation: A systematic review and network meta-analysis. JAMA Netw Open. 2020;3(10):e2017652. https://doi.org/10.1001/jamanetworkopen.2020.17652

53. Gatti M, Rinaldi M, Ferraro G, Toschi A, Caroccia N, Arbizzani F, et al. Breakthrough invasive fungal infections in liver transplant recipients exposed to prophylaxis with echinocandins vs other antifungal agents: A systematic review and meta-analysis. Mycoses. 2021;64(11):1317-27. https://doi.org/10.1111/myc.13362

54. Husain S, Paterson DL, Studer S, Pilewski J, Crespo M, Zaldonis D, et al. Voriconazole prophylaxis in lung transplant recipients. Am J Transp. 2006;6(12):3008-16. https://doi.org/10.1111/j.1600-6143.2006.01548.x

55. Shaikh SA, Zimmerman A, Nolan A, Cooper M, Abrams PL. The incidence of fungal infections in pancreas transplant recipients in the absence of systemic antifungal prophylaxis. Clin Transplant. 2019;33(10):e13691. https://doi.org/10.1111/ctr.13691

56. Tang H, Shi W, Song Y, Han J. Voriconazole exposure and risk of cutaneous squamous cell carcinoma among lung or hematopoietic cell transplant patients: A systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(2):500-7. https://doi.org/10.1016/j.jaad.2018.08.010

57. Giannella M, Ercolani G, Cristini F, Morelli M, Bartoletti M, Bertuzzo V, et al. High dose weekly liposomal amphotericin B antifungal prophylaxis in patients undergoing liver transplantation: A prospective phase II trial. Transplantation. 2015;99(4):848-54. https://doi.org/10.1097/TP.0000000000000393