TECHNICAL NOTE

Prophylaxis of fungal infections in transplant patients

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Fungi are an important cause of infection in patients undergoing solid organ transplantation and bone marrow or hematopoietic stem cell transplantation (BMT/HSCT). The incidence and mortality of fungal infections differ according to the organ and the time since transplantation. In the first 30 days after transplantation, yeast (primarily *Candida spp.*) predominate. After the first month, filamentous fungi, such as *Aspergillus spp.*, are the most frequent agents of infection (1-6).

In BMT/HSCT patients, however, invasive aspergillosis has two peaks of incidence: one at one month post-transplantation and another approximately 90 days after the transplant if the patient develops chronic graft versus host disease (7,8).

Among solid organ transplantation, liver and lung transplant have the highest risk for fungal infection due to underlying diseases, surgical techniques and the graft itself (4,9).

Antifungal prophylaxis use is well established following some transplant types, such as BMT/HSCT and liver (10,11). However, few studies have evaluated heart and pancreas transplants. One of the major challenges is the prevention of filamentous fungal infections, especially by *Aspergillus spp.*, in high-risk patients, such as those who have undergone an allogeneic BMT and developed chronic graft versus host disease or undergone a lung transplantation (12,13).

No potential conflict of interest was reported.

To standardize the use of primary prophylaxis in transplant patients, we analyzed the literature related to the following transplants: liver, kidney, heart, lung, and HSCT. The IDSA (Infectious Diseases Society of America) system was used to determine the levels of evidence.

Recommendations

1. Liver transplantation (11,14-20)

Universal prophylaxis: no (CII)
Targeted prophylaxis: yes (AI)
- Fluconazole 400 mg/day for 21 days

- Criterion 1 – at least one of the following risk factors: fulminant hepatitis, re-transplant requirement, post-tx hemodialysis, or the use of antibodies for rejection treatment.
- Criterion 2 – at least two of the following risk factors: antibiotic prophylaxis for spontaneous bacterial peritonitis (SBP) pre-tx, reoperation, ICU admission in the 30 days before the tx, or antibiotic use in the 30 days before the tx.

2. Kidney transplantation

There are no studies on prophylaxis.
Prophylaxis is not recommended (DII).

3. Lung transplantation (12,21-24)

Universal prophylaxis: yes (AI)
- Inhaled amphotericin B deoxycholate for 3 months (50 mg + 50 ml of distilled water; 10 ml inhalation twice a day)

Table 1 - The incidence and mortality of fungal infections in patients who received a solid organ transplantation or BMT/HSCT (1,4).

Transplant	Incidence	Mortality
Liver	8-15%	50-60%
Lung	15-35%	30-75%
Kidney	3.5-6%	NR
Pancreas	9%	NR
Heart	2.2%	30%
HSCT	3.9% (AI)	50%

NR: not reported.

Targeted prophylaxis: yes, if the recipient or donor has airway colonization by *Aspergillus spp.* pre-tx or post-tx (associated with amphotericin B inhalation).

First choice*: 400 mg itraconazole orally for 3 months (BIII)

Second choice: IV voriconazole (6 mg/kg/day) or oral voriconazole (400 mg/day) for 3 months (CIII)

* Advised serum concentration.

4. Heart transplantation (22)

Prophylaxis not indicated (DII).

5. Hematopoietic stem cell transplant (HSCT)(10,25-28)

Universal prophylaxis: yes (AI)

Fluconazole 400 mg/day IV or oral for 100 days

Targeted prophylaxis: yes, for patients under treatment for GVHD

First option: amphotericin B deoxycholate 1 mg/kg/day (or equivalent doses of a lipidic formulation) for 100 days (CIII)

Second option: itraconazole* 400 mg/day, oral for 100 days (CIII)

Third option: EV voriconazole (6 mg/kg/day) or oral voriconazole (400 mg/day) for 100 days (CIII)

** Advised serum concentration.

Controlled and randomized studies have been registered with other azoles, but they were not standardized in the institution or perhaps they are not available in Brazil.

6. Pancreas transplant (29)

Universal prophylaxis: yes (CII)

Fluconazole 400 mg/day IV or VO for 7 days (surgical prophylaxis)

Targeted prophylaxis: no (DII)

Conflicts of interest: Edson Abdala - speaker for Bago, performs clinical research with Bristol. Sílvia Figueiredo Costa - speaker for Pfizer. Tania Mara Varejão Strabelli - speaker for Novartis, works with Novartis, performs clinical research with Merck.

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AUTHOR CONTRIBUTIONS

Abdala E wrote the manuscript (Portuguese), participated of the discussion of the final recommendations and of the revision of the manuscript. Costa SF presented the recommendation for bone marrow transplantation, helped to write the manuscript, wrote part of English version and revised the literature and the final text. Strabelli TMV presented the recommendation for heart transplantantion, wrote part of English version and revised the final text. Caramori ML presented the recommendation for lung transplantation and discussed the final recommendation. Pierrotti LC, Azevedo LSF, Ibrahim KY, Dulley FL, Varkulja GF, Castro Jr C, Almeida GMD, Souza Marques HH participated of the discussion of the text and of the final recommendations. Shikanai-Yasuda MA coordinated the presentations and discussion of the recommendations, helped to revise the final recommendations and to prepare the manuscript for submission.

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APPENDIX
PROFILAXIA DAS INFECÇÕES FÚNGICAS EM PACIENTES TRANSPLANTADOS

Os fungos são uma importante causa de infecção nos pacientes submetidos a transplante de órgão sólido e medula óssea ou transplante de células tronco hematopoiéticas (TMO/TCTH). A incidência e a letalidade das infecções fúngicas variam, entretanto, de acordo com o tipo de transplante e do período após o transplante. Nos primeiros 30 dias ocorre o predomínio das leveduras particurlamente *Candida* spp. Após o primeiro mês predominam os fungos filamentosos como *Aspergillus* spp (1-6). Nos pacientes submetidos a TMO/TCTH, entretanto, a Aspergilose invasiva apresenta dois picos de incidência um no final do primeiro mês e outro aproximadamente 90 dias depois do transplante caso o paciente desenvolva doença do enxerto versus o hospedeiro (7-8). Dentre os transplantes de órgão sólidos os que apresentam maior risco para o desenvolvimento de infecções fúngicas são o transplante de fígado e de pulmão, por questões ligadas às próprias doenças de base, técnica cirúrgica e enxerto (4,9).

Tabela 1 - Incidência e mortalidade das Infecções Fúngicas na população de pacientes submetidos a transplante de órgãos sólidos e TMO/TCTH [1,4].

Transplante	Incidência	Mortalidade
Fígado	8-15%	50-60%
Pulmão	15-35%	30-75%
Rim	3,5-6%	NR
Pâncreas	9%	NR
Coração	2,2%	30%
TCTH	3,9% (AI)	50%

NR: não relatado.

O uso de profilaxia antifúngica já esta bem consolidada para alguns grupos de transplantes como TMO/TCTH e transplantes hepáticos (10,11). Contudo, ainda há uma escassez de estudo em transplante de coração e pâncreas. O grande dilema, entretanto, é a prevenção de infecções por fungos filamentosos em especial *Aspergillus* spp nos pacientes de alto risco como transplante de medula óssea alogênico com doença do enxerto contra o hospedeiro (DECH) e transplantados de pulmão (12,13).

Com intuito de padronizar o uso de profilaxia primária em pacientes transplantados, foi analisada a literatura referente aos seguintes transplantes: fígado, rim, coração, pulmão e TCTH. Para a determinação dos níveis de evidência foi utilizado o sistema da IDSA (Infectious Diseases Society of America).

Recomendações:

1. Transplante de Fígado (11,14-20)

Profilaxia universal: não (CII)
Profilaxia dirigida: sim (AI)
- Fluconazol 400 mg/dia por 21 dias

- Critério 1 – pelo menos um dos seguintes fatores de risco: hepatite fulminante, re-transplante, hemodiálise pós-transplante, uso de anticorpos para tratamento de rejeição.
- Critério 2 – pelo menos dois dos seguintes fatores de risco: uso de antibiótico profilático para peritonite bacteriana espontânea pré-transplante, reoperação, admissão em unidade de terapia intensiva nos últimos 30 dias antes do transplante, antibióticos nos últimos 30 dias antes do transplante.

2. Transplante de Rim

Não há estudos sobre profilaxia
Profilaxia não indicada (DII)

3. Transplante de Pulmão (12,21-24)

Profilaxia universal: sim (AI)

Anfotericina B deoxicolato via inalatória, por 3 meses (50 mg + 50 ml de água destilada – inalação com 10 ml, 2 vezes por dia)

Profilaxia dirigida: sim, se receptor ou doador com colonização das vias aéreas por *Aspergillus* spp pré-tx ou pós-tx (associada à anfotericina B inalatória)

Primeira opção: Itraconazol* 400 mg oral por 3 meses (BIII)

Segunda opção: Voriconazol EV (6 mg/kg/dia)/Oral (400 mg/dia) por 3 meses (CIII)
*Aconselhável dosagem sérica.

4. Transplante de Coração (22)

Profilaxia não indicada (DII)

5. Transplante de Células Tronco Hematopoéticas (10,25-28)

Profilaxia universal: sim (AI)
Fluconazol 400 mg/dia EV/Oral por 100 dias
Profilaxia dirigida: sim, para pacientes sob tratamento para DECH.
Primeira opção: Anfotericina B deoxicolato 1 mg/kg/dia (ou doses equivalentes de formulações lipídicas) por 100 dias (CIII)
Segunda opção: Itraconazol* oral 400 mg/dia por 100 dias (CIII)
Terceira opção Voriconazol: EV (6 mg/kg/dia)/Oral (400 mg/dia) por 100 dias (CIII)
*Aconselhável dosagem sérica
Obs. Há estudos controlados e randomizados com outros azólicos, porém não são medicamentos padronizados na instituição ou talvez não disponíveis no Brasil.

6. Transplante de Pâncreas (29)

Profilaxia universal: sim (CII)
Fluconazol 400 mg/dia EV/VO por 7 dias (profilaxia cirúrgica)
Profilaxia dirigida: não (DII)