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Special article

EPICO 3.0. Antifungal prophylaxis in solid organ transplant recipients

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ABSTRACT

Background: Although over the past decade the management of invasive fungal infection has improved, considerable controversy persists regarding antifungal prophylaxis in solid organ transplant recipients.
Aims: To identify the key clinical knowledge and make by consensus the high level recommendations required for antifungal prophylaxis in solid organ transplant recipients.
Methods: Spanish prospective questionnaire, which measures consensus through the Delphi technique, was conducted anonymously and by e-mail with 30 national multidisciplinary experts, specialists in invasive fungal infections from six national scientific societies, including intensivists, anesthetists, microbiologists, pharmacologists and specialists in infectious diseases that responded to 12 questions prepared by the coordination group, after an exhaustive review of the literature in the last few years. The level of agreement achieved among experts in each of the categories should be equal to or greater than 70% in order to make a clinical recommendation. In a second term, after extracting the recommendations of the selected topics, a face-to-face meeting was held with more than 60 specialists who were asked to validate the pre-selected recommendations and derived algorithm.
Measurements and primary outcomes: Echinocandin antifungal prophylaxis should be considered in liver transplant with major risk factors (retransplantation, renal failure requiring dialysis after transplantation, pretransplant liver failure, not early reoperation, or MELD > 30); heart transplant with hemodialysis, and surgical re-exploration after transplantation; environmental colonization by *Aspergillus*, or cytomegalovirus (CMV) infection; and pancreas and intestinal transplant in case of acute graft rejection, hemodialysis, initial graft dysfunction, post-perfusion pancreatitis with anastomotic problems or need for laparotomy after transplantation. Antifungal fluconazole prophylaxis should be considered in liver transplant without major risk factors and MELD 20–30, split or living donor, choledochojejunostomy, increased transfusion requirements, renal failure without replacement therapy, early reoperation, or multifocal colonization or infection with *Candida*; intestinal and pancreas transplant with no risk factors for echinocandin treatment. Liposomal amphotericin B antifungal prophylaxis should be considered in lung transplant (inhalant form) and liver transplant with major risk factors. Antifungal prophylaxis with voriconazole should be considered in lung transplant, and heart transplant with hemodialysis, surgical re-exploration after transplantation, environmental colonization by *Aspergillus*, or CMV infection.
Conclusions: The management of antifungal prophylaxis in solid organ transplant recipients requires the application of knowledge and skills that are detailed in our recommendations and the algorithm developed therein. These recommendations, based on the DELPHI methodology, may help to identify potential patients, standardize their management and improve overall prognosis.

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EPICO 3.0. Profilaxis antifúngica en el paciente trasplantado de órgano sólido

Palabras clave:
Profilaxis
Trasplante de órgano sólido
Equinocandina
Fluconazol
Voriconazol
Anfotericina B liposómica

RESUMEN

Antecedentes: Aunque en la última década se ha observado una mejora en el tratamiento de la infección fúngica invasiva, todavía existen numerosas controversias en la profilaxis antifúngica del paciente trasplantado de órgano sólido.
Objetivos: Identificar los principales conocimientos clínicos y elaborar recomendaciones con un alto nivel de consenso, necesarias para la profilaxis antifúngica del paciente trasplantado de órgano sólido.
Métodos: Se realizó un cuestionario prospectivo español, que valora el consenso mediante la técnica Delphi. El cuestionario se llevó a cabo de forma anónima y por correo electrónico con 30 expertos multidisciplinarios nacionales, especialistas en infecciones fúngicas invasivas de seis sociedades científicas nacionales, que incluían intensivistas, anestesistas, microbiólogos, farmacólogos y especialistas en enfermedades infecciosas que respondieron a 12 preguntas preparadas por el grupo de coordinación, tras una revisión exhaustiva de la bibliografía de los últimos años. El nivel de acuerdo alcanzado entre los expertos en cada una de las categorías debía ser igual o superior al 70% para elaborar una recomendación. En un segundo término, después de extraer las recomendaciones de los temas seleccionados, se celebró una reunión presencial con más de 60 especialistas y se les solicitó la validación de las recomendaciones preseleccionadas y del algoritmo derivado de estas.
Mediciones y resultados principales: Debe considerarse la profilaxis antifúngica con equinocandinas en el trasplante hepático con los principales factores de riesgo (retrasplante, insuficiencia renal postrasplante con necesidad de diálisis, insuficiencia hepática pretrasplante, reintervención quirúrgica no precoz, o MELD > 30); trasplante cardíaco con hemodiálisis, y reexploración quirúrgica postrasplante; colonización ambiental por *Aspergillus*, o infección por citomegalovirus; trasplante de páncreas e intestino si existe rechazo agudo del injerto, hemodiálisis, disfunción inicial del injerto, problemas en la anastomosis con pancreatitis posperfusión, o necesidad de laparotomía postrasplante. Debe considerarse la profilaxis antifúngica con fluconazol en el trasplante hepático sin los principales factores de riesgo y MELD de 20-30, *split* o donante vivo, coledocoyeyunostomía, altos requerimientos transfusionales, fracaso renal sin necesidad de terapia sustitutiva, reintervención precoz o colonización multifocal o infección por *Candida*, y trasplante de páncreas e intestino sin factores de riesgo para el tratamiento con equinocandina. Debe considerarse la profilaxis antifúngica con anfotericina B liposómica en el trasplante pulmonar (vía inhalada) y el trasplante hepático con los principales factores de riesgo. Debe considerarse la profilaxis antifúngica con voriconazol en el trasplante pulmonar y el trasplante cardíaco con hemodiálisis, reexploración quirúrgica postrasplante, colonización ambiental por *Aspergillus* o enfermedad por citomegalovirus.
Conclusiones: El manejo de la profilaxis antifúngica del paciente trasplantado de órgano sólido requiere la aplicación de los conocimientos y destrezas que se detallan en nuestras recomendaciones y en el algoritmo desarrollado. Estas recomendaciones basadas en la metodología Delphi pueden ayudar a identificar a los potenciales pacientes, estandarizar su tratamiento en conjunto y mejorar su pronóstico.

Solid organ transplant (SOT) recipients have a very high risk of invasive fungal infection (IFI), especially by *Candida*, *Aspergillus*, and, to a lesser degree, by *Cryptococcus*, mucorales and other filamentous fungi.[17]

In almost 50% of the IFI cases in SOT recipients, *Candida* is the most prevalent pathogen.[17] Even though the incidence of invasive candidiasis (IC) varies depending on the transplanted organ – certainly high in liver, pancreas and intestinal transplants[17] and very rare in the case of heart transplants[21] –, the rate of global mortality in a period of 12 months associated to IC is 34%.[20] Candidemia is the most common IC clinical presentation, and its incidence rate in SOT recipients is established at around 4%.[13]

On the other hand, the invasive aspergillosis (IA) rate in Europe varies from 0.2% to 3.5%, depending on the type of SOT recipients, being significantly more common in lung transplants.[14] Despite the traditional consideration of IA as a complication associated to immediate post-transplantation, the risk continues high up to three months after the intervention.[5]

The type of SOT recipients conditions the selection of universal prophylaxis versus guided prophylaxis. Nevertheless, the existence of different inter-center protocols and the diverse epidemiology of fungal infections among different programs, makes it difficult to establish definitive recommendations on prophylaxis in SOT recipients.[6,7] In this context, IFI in SOT recipients is an excellent target for the use of antifungal prophylaxis.[28]

The primary goal of this research is to analyze the current situation of antifungal prophylaxis in SOT recipients in hospitals throughout the country, and to obtain a set of therapeutic recommendations for different situations through the DELPHI methodology. For this purpose, a panel including specialists from six scientific societies was formed – Spanish Society of Mycology (AEM), as the promoter; the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); the Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR); the Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC); the Spanish Society of Chemotherapy (SEQ); the Spanish Society of Hospital Pharmacies (SEFH) – all with extensive experience in the treatment of critically-ill patients. They were requested to answer a questionnaire drafted by the seven coordinators responsible for the study, who had previously conducted a thorough review of the existing literature, as performed in the two previous editions of this project.[26,27]

After the group of coordinators elaborated the resulting recommendations, a second round of analysis was conducted in a face-to-face meeting in which the 60 specialists distributed throughout the whole country, who care for solid organ transplant recipients, validated the pre-selected recommendations and the algorithm derived from them through a voting procedure.

The panel was made up of 30 specialists from different geographic locations in the country from six scientific societies involved in the study. The criteria of inclusion were based on their experience in the research of invasive fungal infections (IFI), as well as their expertise in antifungal prophylaxis in SOT recipients.

The Delphi methodology used in this study aimed to optimize the consultation process of the 30 panel members. More specifically, thanks to the Delphi methodology, we were able to identify the groups' opinions; not only those of one individual, but of each of the experts in different areas of information as suggested by the coordinators.

An agreement/disagreement consensus for each question was achieved when scoring equal to or higher than 70% (21 out of 30) in Top 4 (score of 7 or more points) of the total number of experts consulted. The coordinators posed a total of 12 questions (Annex 1) to be assessed by the experts by means of a metric scale.

The study methodology was based on the development of only one phase aimed to discover the level of consensus of all questions. To fulfill this goal, between May 19 and 26, 2014, the 30 specialists (Annex 2) participating in the study anonymously answered the online questionnaire of 12 questions. The coordinators responsible for the systematic research of the literature to elaborate the questions did not answer the questionnaire.

Thereafter, as mentioned above, recommendations were extracted and an algorithm elaborated and validated by the 73 experts in a face-to-face meeting held on September 25, 2014 (Annex 3).

Results

1. Variables considered risk factors for the development of aspergillosis in liver transplant recipients

Answers provided by the coordinators: retransplant, the event of more than one acute rejection requiring the use of steroids or monoclonal antibodies during the first month, post-transplant renal failure, pretransplant fulminant liver failure, dialysis, poor graft function (basically primary graft failure), surgical reintervention, prior renal failure, severe bacterial infection requiring antibiotic therapy for more than 10 days, bile leak and/or primary hepaticojejustonomy, presence of vascular graft complications, transfusion requirement >10 red blood cell units, surgery time >10 h, assisted ventilation >7 days.

Rationale. The existence of different inter-center protocols and the diverse epidemiology of fungal infections among different programs, makes it difficult to establish definitive recommendations on prophylaxis in SOT recipients.[6,7] Although infections by *Candida* are the most common fungal infections in liver transplants, due to the high morbidity and mortality rates caused by *Aspergillus* infection, coverage in high-risk patients is necessary.[2,6–8,22,23] In fact, aspergillosis is a serious and very common complication in liver transplants, whereas re-transplants and dialysis are the main risk factors to acquire infections by *Aspergillus* in this population.[3]

The majority of the panel members (92.9%) agreed on considering retransplant as a risk factor for acquiring an *Aspergillus* infection in liver transplant recipients. In particular, on a scale of 0–10 in which 10 stands for the highest score, 26 out of 28 experts granted this 7 or more points, so a consensual agreement was established (Top 4 ≥70%). In addition, the experts also reached consensus when defining the following items as aspergillosis risk factors: presence of more than one acute rejection requiring the use of steroids or monoclonal antibodies during the first month (24 out of 28 answers with 7 or more points; Top 4: 85.7), post-transplant renal failure (23, 82.1%), pre-transplant fulminant liver failure (23, 82.1%), dialysis (23, 82.1%), surgical re-intervention (20; 71.4%), previous renal failure with creatinine values >2 mg/dl (20; 71.4%), appearance of serious bacterial infection requiring antibiotic therapy for more than 10 days (20; 71.4%), bile leak, bilomas, and/or primary hepaticojejunostomy (20; 71.4%), and the presence of vascular graft complications (20; 71.4%).

In contrast, consensus was not reached (Top 4 <70%) when considering the transfusion requirement >10 red blood cell units as an aspergillosis risk factor (18 out of 28 answers with 7 or more points; Top 4: 64.3%), surgery time >10 h and assisted ventilation for a period superior to 7 days (16; 57.1%).

2. Agreement on antifungals considered prophylactic treatment in high-risk liver transplant recipients

Answers provided by the coordinators: itraconazole, posaconazole, voriconazole, liposomal amphotericin B, amphotericin B lipid complex, anidulafungin, caspofungin, micafungin.

Rationale. A prophylaxis treatment against *Candida* in high-risk liver transplant recipients is recommended. The effectiveness and good tolerability of fluconazole (100–400 mg/during 21–60 days), as well as liposomal amphotericin B (1 mg/kg/during 5 days) has been proven in this field.[2,6–8,22,23] The study by Fortún et al. proves the effectiveness and tolerability of caspofungin in antifungal prophylaxis in high-risk liver transplant recipients.[4]

Most specialists positively assessed the prophylactic administration of caspofungin, anidulafungin and liposomal amphotericin B in high-risk liver transplant recipients. Specifically, on a scale of 0–10 points in which 10 stands for the highest level of agreement, 25 out of 28 experts (89.3%) granted 7 or more points to the administration of caspofungin under these circumstances; in the case of anidulafungin and liposomal amphotericin B, the opinion was shared by 22 participants (78.6%). Thus, a high consensual agreement was reached regarding these three antifungals (Top 4 ≥70%).

In contrast, no consensus was achieved when considering the convenience of prescribing a prophylactic treatment with micafungin (19 out of 28 answers with 7 or more points; Top 4: 67.9%), amphotericin B lipid complex (10; 35.7%), voriconazole (8; 28.6%), itraconazole (8; 28.6%) or posaconazole (6; 21.4%) in this population.

3. Agreement on not administering any type of antifungal prophylaxis in liver transplant recipients in the absence of high-risk factors

Rationale. The incidence rate of aspergillosis in liver transplant recipients is just around 0.5%.[10] In addition, although diverse studies have shown the incidence of infections caused by other filamentous fungi,[19,24] there is not a clear recommendation about prophylaxis against them in SOT recipients. In this context, it should be taken into account that prevention against infections caused by filamentous fungi in SOT recipients is not a general practice, since the preferred measure is protecting transplant areas against massive inoculants, such as those produced during refurbishing works. Moreover, the use of HEPA filters is not necessary, as in the case of neutropenic patients.[2,6–8,22,23]

Only 18 out of 28 expert consultants (64.3%) did not consider necessary the administration of a prophylactic antifungal treatment in patients undergoing a liver transplant with no risk-factors, thus consensus was not established (Top 4 <70%).

4. Variables considered risk-factors for the development of aspergillosis in heart transplant recipients

Answers provided by the coordinators: hemodialysis, surgical re-exploration after transplantation, environmental colonization by *Aspergillus*, cytomegalovirus (CMV) infections, acute rejection.

Rationale. The existence of different inter-center protocols and the diverse epidemiology of fungal infections among different

programs, makes it difficult to establish definitive recommendations on prophylaxis in SOT recipients.[2,6–8,22,23] Re-intervention, CMV infections, post-transplant hemodialysis and environmental colonization by *Aspergillus* are aspergillosis risk-factors in patients undergoing a heart transplant.[15]

The members of the board agreed on considering each and every one of the variables proposed by the coordinators as *Aspergillus* infection risk-factors in patients undergoing a heart transplant. Specifically, on a scale of 0–10, in which 10 stands for the highest level of agreement, 25 out of 28 experts (89.3%) granted 7 or more points to hemodialysis as a risk-factor; an assessment shared by 24 experts (85.7%) regarding re-exploration after transplantation and by 23 specialists (82.1%) regarding environmental colonization by *Aspergillus* spp., CMV infection and acute rejection, were collected. Therefore, a high level of consensus was achieved regarding the proposed variables (Top 4 ≥70%).

5. Agreement on the use of antifungals as a prophylactic treatment in heart transplant recipients

Answers provided by the coordinators: itraconazole, posaconazole, voriconazole, liposomal amphotericin B, amphotericin B lipid complex, anidulafungin, caspofungin, micafungin

Rationale. The medical guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend the administration of voriconazole or echinocandins in high-risk heart transplant recipients.[6,7] Specifically, on a scale of 0–10 points, in which 10 stands for the highest level of agreement, 24 out of 28 experts (85.7%) granted 7 or more points to the administration of caspofungin in this situation; an opinion shared by 22 participants (78.6%) in the case of anidulafungin and micafungin, and by 20 experts (71.4%) in the case of voriconazole, were registered. There was, therefore, a high consensual agreement on the use of the four antifungals mentioned above (Top 4 ≥70%).

In contrast, consensus was not reached when considering the convenience of administering a prophylactic treatment with itraconazole (15 out of 28 answers with 7 or more points; Top 4: 53.6%), posaconazole (15; 53.6%) liposomal amphotericin B (14; 50%), and amphotericin B lipid complex (9; 32.17%) in this population.

6. Agreement on not administering any type of antifungal prophylactic treatment in heart transplant recipients in the absence of risk-factors

Rationale. Antifungal prophylaxis is usually administered only in high-risk heart transplant recipients.[16] Moreover, even though there are several studies which prove the incidence of infectious diseases caused by other filamentous fungi,[19,24] there is not a clear recommendation on prophylaxis against them in SOT recipients. In this context, it should be taken into account that prevention against infections caused by filamentous fungi in SOT recipients is not a general practice, since the preferred measure is protecting transplant areas against massive inoculants, such as those produced during refurbishing works. Moreover, the use of HEPA filters is not necessary, as in the case of neutropenic patients.[2,6–8,22,23]

Most of the expert consultants (85.7%) agreed on the fact that antifungal prophylaxis is not necessary in patients undergoing a heart transplant in the absence of risk factors. Specifically, on a scale of 0–10 in which 10 stands for the highest rate of agreement, 24 out of 28 experts (85.7%) granted 7 or more points, so a consensual agreement was established (Top 4 ≥70%).

7. Variables considered risk factors for the development of aspergillosis in pancreas or intestinal transplant recipients

Answers provided by the coordinators: over-immunosuppression, acute graft rejection, hemodialysis, initial graft dysfunction, anastomotic problems, need for laparotomy after transplantation, cytomegalovirus infection, bacterial infection.

Rationale. The existence of different inter-center protocols and the diverse epidemiology of fungal infections among different programs, makes it difficult to establish definitive recommendations on antifungal prophylaxis in SOT recipients.[6,7] Although infections by *Candida* are the most common fungal infections in pancreas[9] transplants and intestinal[1] transplants, the high morbidity and mortality rates of infections caused by *Aspergillus* in high-risk patients makes its coverage necessary.[2,6–8,22,23]

Most members of the panel (92.9%) agreed on considering over-immunosupression and acute graft rejection as aspergillosis risk factors in patients undergoing pancreas or intestinal transplants.

Specifically, on a scale of 0–10 points in which 10 stands for the highest level of agreement, 26 out of 28 experts granted 7 or more points to both variables, thus, a consensual agreement was reached (Top 4 ≥70%). Moreover, consensus was also reached when considering hemodialysis (25 out of 28 answers with 7 or more points; Top 4: 89.3%), initial graft dysfunction (25; 89.3%), anastomotic problems (23; 82.1%), need for laparotomy after transplantation (23; 82.1%) and CMV infection as *Aspergillus* infection risk factors.

In contrast, consensus was not reached (Top 4 <70%) when considering bacterial infections (18 out of 28 answers with 7 or more points; Top 4: 64.3%) as aspergillosis risk factor in this population.

8. Agreement on the use of antifungals as a prophylactic treatment in high-risk pancreas or intestinal transplant recipients

Answers provided by the coordinators: itraconazole, posaconazole, voriconazole, liposomal amphotericin B, amphotericin B lipid complex, anidulafungin, caspofungin, micafungin.

Rationale. It is recommended to prescribe a prophylactic treatment against *Candida* in pancreas and intestinal transplant recipients. The administration of fluconazole (100–400 mg/d during 21–60 days), as well as liposomal amphotericin B (1 mg/kg/d during 5 days) has proven effectiveness and a good tolerability in this field.[2,6–8,18,22,23]

The majority of specialists positively valued the administration of echinocandins – anidulafungin, caspofungin, micafungin – as a prophylactic treatment in high-risk pancreas or intestinal transplant recipients. Specifically, on a scale of 0–10 points in which 10 stands for the highest level of agreement, 24 out of 28 experts (85.7%) granted 7 or more points to the administration of anidulafungin in this situation; an opinion shared by 22 participants (78.6%) in the case of the administration of caspofungin and micafungin was also registered. Thus, a high consensual agreement was reached regarding these three echinocandins (Top 4 ≥70%).

In contrast, no consensus was reached when considering the convenience of prescribing a prophylactic treatment with liposomal amphotericin B (18 out of 28 answers with 7 or more points; Top 4: 64.3%), amphotericin B lipid complex (10; 35.7%), or an extended azole spectrum voriconazole (14; 50%), posaconazole (9; 32.1%), itraconazole (8; 28.6%) in this population.

9. Agreement on not administering any type of antifungal prophylaxis in pancreas or intestinal transplant recipients in the absence of high-risk factors

Rationale. Despite of the lack of studies in scientific literature designed to evaluate the role of antifungal prophylaxis in intestinal transplant recipients, its administration should be recommended due to the high risk of infection by *Candida* in this population. Likewise, it is recommended to prescribe a prophylactic treatment in pancreas transplant recipients.[2,6–8,18,22,23]

Only 11 out of 28 experts (39.3%) agreed on pointing out that antifungal prophylaxis is not necessary for patients undergoing a pancreas or intestinal transplant in the absence of risk factors, thus consensus was not established (Top 4 <70%) in this case.

10. Agreement on the use of antifungals as a prophylactic treatment in lung transplant recipients

Answers provided by the coordinators: itraconazole, posaconazole, voriconazole, inhalant form of liposomal amphotericin B, amphotericin B lipid complex, anidulafungin, caspofungin, micafungin.

Rationale. Lung transplant recipients benefit from the administration of amphotericin B nebulizer (6 mg/8 h 4 months, and afterwards every 24 h longlife) or voriconazole for no less than 12 months as a prophylactic treatment against *Aspergillus*.[6,7,11,25]

Most members of the panel agreed on the convenience of administering inhaled amphotericin B and voriconazole as a prophylactic treatment in lung transplant recipients.

Specifically, on a scale of 0–10 in which 10 stands for the highest rate of agreement, 24 out of 28 experts (85.7%) granted 7 or more points to the administration of inhaled amphotericin B and voriconazole in this situation, thus consensus was established regarding both therapeutic alternatives (Top 4 ≥70%).

In contrast, there was no consensus when considering a prophylactic treatment with amphotericin B lipid complex (14 out of 28 answers with 7 or more points; Top 4: 50%), posaconazole (13; 46.4%), itraconazole (9; 32.1%) or an echinocandin – caspofungin (12; 42.9%), anidulafungin (11; 39.3%), micafungin (11; 39.3%) – in this population.

11. Agreement on the duration of the prophylactic treatment with trimethoprim-sulfamethoxazole in kidney transplant recipients

Rationale. Kidney transplant recipients only need prophylaxis against *Pneumocystis jirovecii*.[6,7] The most extended prophylactic treatment to prevent infections by *P. jirovecii* is the administration of cotrimoxazole, a drug which also has activity against *Listeria*, *Toxoplasma*, *Nocardia* and *Legionella*, among others. Cotrimoxazole may be administered in different regimens (trimethoprim 160 mg + sulfamethoxazole 800 mg/12 h Saturdays and Sundays, trimethoprim 160 mg + sulfamethoxazole 800 mg/day, 3 days a week, trimethoprim 160 mg + sulfamethoxazole 800 mg/day, etc.).

A consensus was not reached by experts (Top 4 <70%) on the convenience of the three periods of time proposed by the coordinators for the maintenance of prophylaxis with trimethoprim-sulfamethoxazole in kidney transplant recipients: 3 months (18 out of 28 answers with 7 points or more; Top 4: 64.3%), 6 months (17; 60.7%), and 1 year (3; 10.7%).

12. Agreement on the duration of the prophylactic treatment with trimethoprim-sulfamethoxazole in the rest of transplant recipients

Answers provided by the coordinators: 3 months, 6 months, 1 year.

Rationale. Prophylaxis must be initiated after surgery and cover at least the maximum risk period (6–12 months). In this context, it should be remembered that prophylaxis cannot eradicate *P. jirovecii*, so it will only be effective if continuously administered.[6,7,12]

Most members of the panel (71.4%) agreed on pointing out the need to maintain prophylaxis with trimethoprim-sulfamethoxazole for a year in patients who have undergone a solid organ transplant – not renal transplants. Specifically, on a scale of 0–10 in which 10 stands for the highest rate of agreement, 20 out of 28 experts granted 7 or more points, so a consensual agreement was established (Top 4 ≥70%) for a 1 year duration treatment (20 answers in Top 4; 71.4%). As for the rest of the periods proposed by the coordinators, only 10 specialists (35.7%) granted 7 or more points to a 6 month period of prophylaxis and 7 experts granted points to a 3 month period of prophylaxis (25%).

Table 1
Recommendations in SOT patients.

1) Antifungal prophylaxis with echinocandins is recommended under the following circumstances:
A) Liver transplant with at least one of the following major risk factors:
-Re-transplant
-Post-transplant renal failure requiring dialysis
-Pre-transplant fulminant hepatic failure
-Surgical re-intervention (not early)
-MELD > 30
B) Heart transplant and one of the following risk factors:
-Hemodialysis
-Post-transplant surgical re-exploration
-Environmental colonization by *Aspergillus*
-CMV infection.
C) Pancreas and intestinal transplant and one of the following risk factors:
-Acute graft rejection
-Hemodialysis, Cr CL < 50 ml/min
-Initial graft dysfunction
- Post-perfusion pancreatitis with anastomotic problems
-Need for laparotomy after transplantation

2) Antifungal prophylaxis with fluconazole is recommended under the following circumstances:
A) Liver transplant without major risk factors (see RECOMMENDATION 1) with at least one of the following candidiasis risk factors (minor):
-MELD 20–30
-Split or living donor
-(Y Roux) Choledochojejunostomy
-Increased transfusion requirements (more than 40 units of blood derivatives)
-Renal failure not requiring replacement therapy (CCr < 50 ml/min).
- Early re-intervention
-Multifocal colonization or infection by *Candida*
B) Pancreas and intestinal transplant: every patient in the absence of the risk factors described in RECOMMENDATION 1.

3) Antifungal prophylaxis with liposomal amphotericin B is recommended under the following circumstances:
A) Lung transplant (inhaled therapy)
B) Liver transplant (as an alternative to echinocandins) in patients with at least one of the following risk factors:
-Re-transplant
-Post-transplant renal failure requiring dialysis
-Pre-transplant fulminant hepatic failure
-Surgical (non-early) re-intervention
-MELD > 30

4) Antifungal prophylaxis with voriconazole is recommended under the following circumstances:
A) Lung transplant (as an alternative to inhaled liposomal amphotericin B)
B) Heart transplant and one of the following risk factors:
-Hemodialysis
-Post-transplant surgical re-exploration
-Environmental colonization by *Aspergillus*
-CMV infection

5) Does not require antifungal prophylaxis:
A) Kidney transplant
B) Heart transplant in the absence of the risk factors previously described
C) Liver transplant

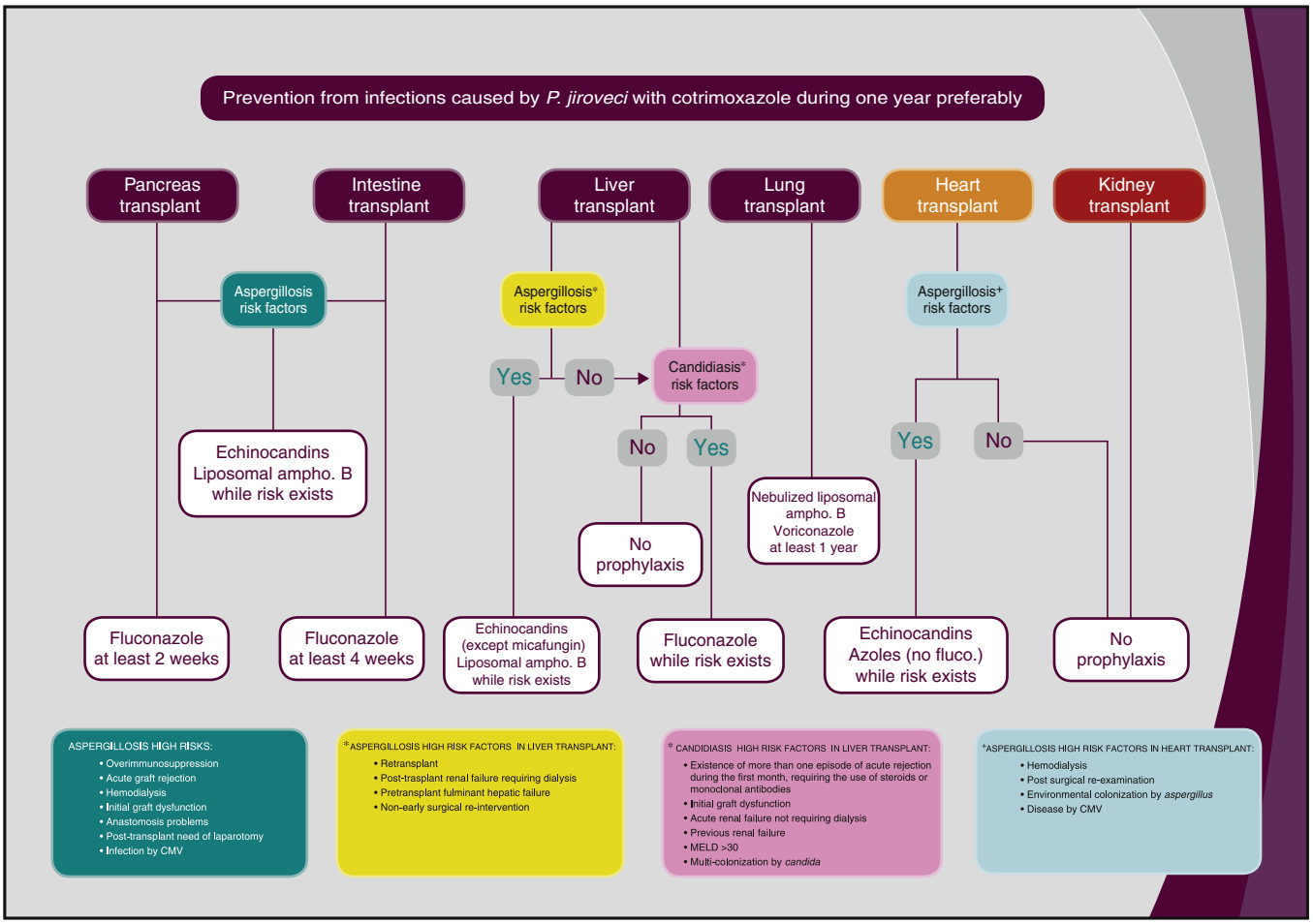

Fig. 1. Antifungal profilaxis algorithm for SOT recipients.

Recommendations and algorithm

Once the results achieved in the Delphi methodology regarding antifungal prophylaxis in solid organ transplant recipients were collected, five recommendations were elaborated and the conclusions are exhibited in Table 1. They are based on the questions which reached a consensus equal or higher than 70%. These recommendations and the algorithm deriving from them (Fig. 1) were validated thereafter during a face-to-face meeting with the hospital experts.

Conflict of interests

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