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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.

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