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Invasive fungal infections in solid organ transplant recipients

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Abstract

Solid organ transplant (SOT) recipients have a significant risk of invasive fungal diseases (IFD) caused mainly by Candida spp. and Aspergillus spp. Candida spp. is the most frequent agent of IFD in the transplant recipient. The absence of clinical trials and the epidemiological differences in IFD in different transplant programmes mean that there are no definitive recommendations for the diagnosis, treatment and prevention of IFD in SOT, so most of the evidence must be based on clinical experience.

Keywords: Drug interactions, invasive aspergillosis, invasive candidiasis, solid organ transplantation, Transplant infectious disease
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Hot Topics

- Solid organ transplant (SOT) recipients have a significant risk of invasive fungal diseases (IFD) caused mainly by *Candida* spp. and *Aspergillus* spp.
- *Candida* spp. is the most frequent agent of IFD in the transplant recipient
- The absence of clinical trials and the epidemiological differences in IFD in different transplant programmes mean that there are no definitive recommendations for the diagnosis and prevention of IFD in SOT
- Universal prophylaxis against IFD should not be routinely used in renal, liver and heart transplantation. Guided prophylaxis in high-risk recipients will depend on the risk factors associated with each type of transplant
- Standard treatment of *Candida* infections in transplant recipients is no different from that administered to non-neutropenic patients, although some aspects related to drug–drug interactions and potential toxicities associated with the use of azoles should be considered
- Invasive aspergillosis (IA) in SOT is more a syndrome than an infection. Treatment should be individualized according to type of transplant, SOT recipient, type of IA and immunosuppression used
- Drug–drug interactions involving antifungal drugs should be evaluated very carefully in SOT

Introduction

Transplant patients have a significant risk of invasive fungal disease (IFD). IFDs caused by opportunistic fungi are universally distributed and are caused mainly by *Candida* spp., *Aspergillus* spp., and to a lesser extent, by *Cryptococcus* spp., fungi belonging to the Mucorales order, and other filamentous fungi [1]. IFDs caused by endemic fungi are usually reactivations but may occasionally occur as primary infections in transplant patients who live in or visit highly endemic areas.

Candida spp. is the most frequent agent of IFD in the transplant recipient, accounting for half of all cases in this population. The incidence of invasive candidiasis has been estimated at around 2% in American series of solid organ transplantation (SOT), also including paediatric patients [1]. The rate varies according to the organ transplanted: it is particularly high in abdominal SOT such as intestinal, pancreas and liver transplantation [1] and extremely uncommon after heart transplantation [2]. A Spanish study of bloodstream infections among transplant recipients found the incidence of global candidaemia to be 4% [3]. The main risk factors for invasive candidiasis are displayed in Table 1. Most cases of candidiasis occur during the first months after surgery. The main portal of entry is the gastrointestinal tract, followed by endovascular catheters and the urinary tract. Graft-transmitted candidiasis, which ends most often in fungal arteritis, has also been described in kidney transplantation and related to organ contamination during recovery in the donor [4]. *Candida* infections can manifest as peritonitis, empyema, candidaemia, urinary tract infection, surgical anastomosis infection or oesophagitis. Candidaemia is the most common clinical presentation among the invasive forms [1,5]. The overall mortality of invasive candidiasis at 12 months is reported to be 34% [1,6].

The incidence of invasive aspergillosis (IA) ranges from 0.1 to 2.4% [1,7,8] in American series of adult and paediatric SOT recipients. European studies have shown an incidence between 0.2 and 3.5%, depending on the type of transplant [9–11]. IA incidence is highest among lung transplant recipients. Historically, IA was considered as a complication of the immediate post-transplant period, but the RESITRA study has shown that its incidence remains high after this period [9]. Risk factors for the condition (Table 2) depend on the type of transplant [12–16]. The most common clinical form of IA is invasive pulmonary disease, in which case presentation is usually acute and invasive. Aspergillosis can also cause invasive tracheobronchitis in single, ulcerative or nodular forms in lung transplant patients and may affect the bronchial anastomosis, with dehiscence of the suture in the most severe cases. Mortality due to IA in lung transplantation depends on the clinical presentation; mortality for patients with tracheobronchitis is around 25%, but for patients who develop invasive pulmonary disease it rises to 67–82% [17].

The incidence of cryptococcosis ranges between 0 and 1.5% in American and European series of SOT [1,18,19], and it is the third most common infection after candidiasis and IA [1]. The antifungal activity of calcineurin inhibitors may explain this low incidence [20]. *Cryptococcus neoformans* var. *grubii* has no particular geographical predilection and causes the most infections. *C. neoformans* var. *neoformans* is prevalent in

TABLE 1. Risk factors for invasive candidiasis

Transplant type	Target population
Liver	**High-risk liver transplant recipients:** **Major:** MELD score >30 Re-transplantation, fulminant hepatic failure, Renal failure requiring replacement therapy, **Minor:** MELD score 20–30, split, living-donor >40 transfusion blood products, choledochojejunostomy (Roux-en-Y) Renal failure not requiring replacement therapy (CrCl <50 mL/min) Early re-intervention, multifocal colonization/infection by *Candida* spp.
Pancreas	Post-perfusion pancreatitis, acute rejection and poor initial allograft function Vascular thrombosis, enteric drainage, anastomotic problems, haemodialysis Laparotomy after transplantation
Intestinal	Acute rejection and poor initial allograft function, haemodialysis, laparotomy after transplantation, anastomotic problems, over-immunosuppression
Heart	Acute rejection, haemodialysis, re-exploration after transplantation

Cr CL, creatinine clearance; MELD, model for end-stage liver disease; over-immunosuppression (high immunosuppression drug levels, under corticoid bolus).

TABLE 2. Risk factors for invasive aspergillosis

	Early IA	Late IA (>3 months post-transplant)
Liver transplant	Re-transplantation Kidney failure, especially post-transplant Haemodialysis Fulminant hepatic failure Complicated surgery or reoperation	More than 6 g of accumulative prednisone in the third month after transplantation Post-transplant renal failure Post-transplant haemodialysis Leukopenia (<500/mm^3) Chronic graft dysfunction
Lung transplant	Bronchial anastomotic ischaemia or bronchial stent placement Acute rejection Single-lung transplant *Aspergillus* spp. colonization before or during first year post-transplant	Chronic graft dysfunction
Heart transplant	*Aspergillus* spp. colonization of the respiratory tract Re-operation Post-transplant haemodialysis Hypogammaglobulinaemia (IgG < 400 mg/dl)	ICU readmission Kidney transplantation >2 acute rejection episodes
Kidney transplant	Graft lost and haemodialysis Post-transplant haemodialysis Prolonged high corticosteroid doses	
	CMV infection Over-immunosuppression	