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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	

north-western Europe. Another *Cryptococcus* species, *C. gattii*, has emerged in the Pacific Northwest [21] and in Europe [22]. The incidence of cryptococcosis is higher in kidney and heart transplantation. Patients who receive high doses of corticosteroids or monoclonal antibodies such as alemtuzumab and infliximab seem to have the highest risk of developing disseminated cryptococcosis [23]. The mortality of cryptococcosis ranges from 14 to 27% [1,20]. Cryptococcosis is typically a late-occurring infection; the time to onset usually ranges from 16 to 21 months post-transplantation. More than half of SOT recipients have disseminated disease or CNS involvement and as many as 33% have fungaemia [24].

The incidence of infections by other filamentous fungi in transplant recipients has increased in recent years [25]. Most are caused by Mucorales (mucormycosis or zygomycosis), although infections by *Fusarium* spp. and *Scedosporium* spp. are also recorded. Recent American and European series of fungal infections in SOT reported a frequency of mucormycosis lower than 3% among all patients with fungal infection [1,26,27]. Renal insufficiency, diabetes and previous administration of voriconazole or caspofungin have been described as independent risk factors for mucormycosis [28]. The most common site of mucormycosis in SOT patients is the lungs, with a mortality of 45–50% [28,29]. Mortality can reach 73% in cerebral forms [30]. Infections by *Scedosporium apiospermum* account for 25% of invasive infections caused by filamentous fungi other than *Aspergillus* in some series, especially in single lung transplantation recipients and cystic fibrosis transplant patients [31].

Diagnosis

To date, blood culture (BC) has been the reference procedure for the diagnosis of invasive candidiasis. However, its sensitivity for detecting *Candida* is only 50–75% and the guidelines for diagnosis and management of *Candida* infections by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend alternative techniques [32]. If candidaemia is not present, the diagnosis of invasive candidiasis is even more difficult and requires staining techniques and sample cultures [33,34].

Alternative procedures based on the detection and quantification of fungal biomarkers and metabolites have been developed to improve and anticipate the detection of candidaemia and other forms of invasive candidiasis. However, most of these techniques have been tested in immunocompetent patients and their performance decreases in transplant recipients and other immunosuppressed patients [35].

Two serological diagnostic methods (the combined detection of mannan and anti-mannan antibodies and the quantification of the 1,3,β-D glucan (BDG)) are recommended in the ESCMID guidelines for candidaemia detection in adults. Mannan and anti-mannan detection is considered specific for identification of *Candida* spp. in serum samples, and BDG quantification is a panfungal diagnostic method. Both techniques seem to be useful for ruling out infection when serial determinations (twice-weekly) are performed [32].

BDG detection has shown good sensitivity and specificity in the general population for IFD diagnosis [36], higher even than blood cultures and superior to that of mannan quantification [36–38]. The BDG test was also included in the EORTC/MSG (European Organisation for Research and Treatment of Cancer/Mycosis Study Group) diagnostic criteria for invasive fungal infections in 2008, for all types of patients [39]. The sensitivity for glucan detection was >65% in most studies with a cut-off value of 80 pg/mL, with specificity rates >80% and negative predictive values >85%. The test is still to be validated in children. In transplant recipients, serial detection of BDG in serum has revealed a sensitivity for invasive candidiasis of 56% and a specificity of 73% [34]. Using a positive cut-off of 60pg/mL, the sensitivity of BDG in a study of lung transplantation patients who suffered from IFD was 64%, but the specificity was 9% [40]. The limitations of this approach are due to its lack of specificity for candidiasis detection [41]: false-positive results have been described in patients with *Pseudomonas aeruginosa* bacteraemia and in patients receiving treatment with fungus-derived antibiotics, intravenous immunoglobulins or albumin and with exposure to gauze or other materials that contain glucans [37,42,43].

Finally, several promising PCR-based methods have been developed for the detection of *Candida* spp. in clinical samples. A published meta-analysis including 963 cases of invasive candidiasis reported 95% sensitivity for PCR-based techniques [44]. In a prospective study in which 20% of patients were transplant recipients, the sensitivity and specificity of PCR for the diagnosis of invasive candidiasis were 80% and 70%, respectively [34].

The current guidelines issued by ESCMID and EORTC/MSG do not recommend PCR-based methods because no standardization processes or third party validations have been carried out to evaluate their accuracy. However, several studies have shown a high performance of these methods for detection of *Candida* infections, mainly in the ICU population. DNA amplification seems to be more useful than other techniques for early detection of candidiasis and species identification [45]. Recent studies show DNA-based methods to have a sensitivity >90% in ICU patients with invasive candidiasis after abdominal surgery, even in cases with negative BC [46]. No specific data are available for the SOT population.

Identification of *Candida* species is also important, because antifungal susceptibility is needed to achieve better outcomes.

Several tests have been developed for the characterization of yeast isolates. Chromogenic isolation media demonstrate better detection rates of yeasts than traditional media; this test may also be more cost-effective than the germ tube test [47]. However, all these rapid methods for *Candida* species identification require subcultures rather than direct assessment in positive BCs [48]. The Yeast Traffic Light PNA FISH kit test is fast and has good sensitivity for the rapid identification of the five *Candida* species found most frequently in positive blood cultures (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*) [49]. The matrix-assisted laser desorption ionisation–time of flight mass spectrometry assay (MALDI-TOF) can also be used for the identification of *Candida* spp. in clinical microbiology laboratories [50].

The diagnosis of IA is problematic because of the risk of colonization and contamination and the low predictive value of respiratory sample cultures (mainly sputum). However, in a Spanish study [51] the isolation of *A. fumigatus* from respiratory tract specimens in heart transplant recipients in cases of high suspicion was highly predictive of invasive aspergillosis. The EORTC/MSG published consensus guidelines for the diagnosis of IFD [39]. Three diagnostic criteria were established to define proven, probable or possible infection: (i) patient characteristics, including the immunosuppressive-host condition (such as the use of T-cell immunosuppressants, specific monoclonal antibodies, prolonged use of corticosteroids or a recent history of neutropenia); (ii) clinical-radiological presentation; and (iii) microbiological or histological reports.

Although radiological criteria include the appearance of dense, well-circumscribed lesions, cavitations or endobronchial lesions, other radiological lesions not included in the EORTC/MSG consensus, such as the presence of a new or progressive infiltrate or consolidation, can also be taken into consideration for lung transplant patients [52]. The most common radiological findings of pulmonary aspergillosis in SOT recipients are multiple nodules or masses, which commonly appear in the early post-transplant period [53]. Other radiographic findings include focal areas of consolidation and nodular lesions with cavitation. The halo sign, typically suggestive of pulmonary aspergillosis in neutropenic patients, shows a low sensitivity in SOT recipients, because it is often absent [54].

Together with computed tomography, the detection of galactomannan (GM) is one of the non-culture-based tests that most contributes to the diagnosis of IA [55]. One Spanish study found a sensitivity of 56% in the diagnosis of IA in liver recipients [56], but another showed a low diagnostic effectiveness in the heart transplant population [11]. A meta-analysis found the sensitivity of GM in SOT recipients to be 30% [57]. The specificity of GM is reduced by the potential false-positives, which are usually associated with the use of β-lactams [58]. A high frequency of false-positives for GM during the first week after liver transplantation was observed, a finding that was associated with β-lactam prophylaxis [59,60]. Therefore, GM should not be used for routine diagnosis or treatment monitoring.

One potential advance in the diagnosis of IA is the use of GM detection in bronchoalveolar lavage (BAL). A study performed at Pittsburgh assessed the role of GM quantification in BAL of 116 lung recipients [61]. Based on a cut-off of 0.5, the authors found a sensitivity of 60% and a specificity of 95%; when the cut-off was raised to 1.0, the sensitivity was the same and the specificity was 98% [61]. Another study with lung recipients in Florida reported sensitivity and specificity of GM in BAL of 100% and almost 91%, respectively, using an index $>$1.0 as cut-off [62].

PCR-based methods to detect *Aspergillus* DNA have not been externally validated for blood, tissue or BAL fluid. The differences in the primers, extraction/amplification protocols and reagents used make the validation of results between laboratories difficult. The results of a multicentre project (EAPCRI, European Aspergillus PCR Initiative) that standardizes these procedures and recommendations will be available soon [63]. As for the transplant population, a study of liver transplant patients reported favourable results after applying PCR-based techniques to detect *Aspergillus* mitochondrial DNA in patients with positive GM titres in serum. PCR was positive in 8/13 patients with probable or possible IA and in none of 12 patients without IA but with a false-positive GM [64].

The sensitivity and specificity of pan-*Aspergillus* PCR in BAL for diagnosing IA were 100% and 88%, respectively, in a study performed in lung transplant recipients; additionally, the *Aspergillus* PCR identified one patient with IFD not diagnosed by GM [65]. Although the EORTC/MSG consensus document does not include PCR as a microbiological criterion, the International Society for Heart and Lung Transplantation does include this technique together with compatible symptoms and radiological imaging for the diagnosis of probable IFD in lung/heart transplant patients [61]. We consider that PCR techniques warrant further studies with a view to their validation in SOT but should not be used for routine daily diagnosis or treatment monitoring until standardization is performed.

The sensitivity and specificity of the detection of cryptococcal antigen in serum and cerebrospinal fluid (CSF) in cryptococcal meningitis are very high, around 80% and 90%, respectively [66]. Therefore, false-negatives for serum antigen detection can be observed in SOT recipients even in the context of disseminated disease [67]. Serum cryptococcal antigen titres are higher in extrapulmonary, disseminated and neurological disease [68,69]. Together with blood cultures, these techniques are the main diagnostic tools in patients

with suspected cryptococcosis, including the transplant population [69,70]. Diagnosis can also be established by India ink staining of yeasts (usually in CSF) or by culture of sterile samples.

Pulmonary disease caused by *Cryptococcus* often appears as nodular opacities on CT scans and less often as effusions or consolidations [69]. Apart from meningeal disease, cryptococcomas or intraparenchymal mass lesions with hydrocephalus may be observed in cranial MRI or CT scans of transplant patients with neurological involvement [70].

The radiological appearance of *Aspergillus* or other mould infections of the central nervous system (CNS) is variable. Several patterns have been described, depending upon the patients' immune status [71].

Recommendations for the diagnosis of IFD in SOT

- Positive blood cultures that yield yeasts or, in some cases, filamentous fungi (*Scedosporium* spp. and *Fusarium* spp.) are considered diagnostic of IFD (AIII).
- A proven diagnosis of IFD can also be based on the observation of tissues with invasive fungal structures or through isolation from sterile tissue or fluid samples (not obtained through drains) (AIII).
- BDG quantification is recommended to rule out *Candida* infection in adult patients with risk factors and/or symptoms (CIII)
- Detection of GM antigen in plasma or serum should not be used for the routine diagnosis or treatment monitoring of IA in SOT recipients (DIII).
- Detection of GM antigen in BAL (AII) or CSF (BIII) is useful for the diagnosis of IA (AII) and should be performed whenever possible.
- Special considerations for lung transplantation:
    - In the case of a positive sputum culture for *Aspergillus* spp., a bronchoscopy and high-resolution chest CT scan should be performed to rule out tracheobronchial and/or invasive disease (BIII).
    - In the case of a positive GM in BAL, a high-resolution chest CT scan should be performed to rule out invasive disease (AIII).
- If invasive pulmonary aspergillosis is suspected, a high-resolution chest CT is recommended, because its sensitivity is higher than the chest radiograph (AII).
- Therapeutic response should be monitored by clinical follow-up, and periodical high-resolution CT should be considered every 7–10 days during the first weeks of therapy in adults (AIII).
- PCR should not be used for routine diagnosis or treatment monitoring of IA in SOT recipients (DIII).
- The detection of mould nucleic acid by PCR in BAL or sputum of a transplant patient should be considered, particularly in lung/heart transplant patients due to the subsequent risk of invasive infection (BII). In any case, these procedures should be considered experimental, and the results need to be validated.
- The detection of β-D-glucan in serum may be helpful in the diagnosis of IFD (other than cryptococcosis and mucormycosis), together with the clinical-radiological criteria and the immunosuppressive-host criteria, although false-positive results have been reported (B-II). The detection of cryptococcal antigen in serum or CSF and the detection of positive blood cultures, skin cultures (in the case of compatible lesions) and urine cultures are the main diagnostic techniques for patients with suspected cryptococcosis (AII).
- If cranial fungal infection is suspected, CT (BII) or MRI (AII) is recommended.
- MRI is more sensitive than CT for detecting cryptococcomas [70] (A-II).
- For sinonasal fungal infection, CT and MRI is recommended (AIII).
- For skin and soft tissue fungal infections, MRI is the recommended imaging technique (AIII).
- Ultrasound (BIII), CT or MRI (AII) are the recommended techniques for fungal abscesses in the liver, kidney or spleen.
- CT is more sensitive than ultrasound for detecting liver microabscesses (BIII).

Prevention

Correct identification of patients at increased risk of fungal infection is key to IFD prevention. The selection of universal prophylaxis vs. targeted prophylaxis is based on the type of transplant. Choice of prophylaxis must bear in mind the effectiveness, safety, side-effects and drug interactions of the antifungal agent selected.

Due to the lack of clinical trials and to the epidemiological differences in IFD in different transplant programmes, there are no definitive recommendations for the prevention of IFD in SOT. The reduction in the incidence of IFD needs to be analysed together with other measures that may be more important than the use of prophylaxis with antifungals, such as optimization of surgical procedures, the proper handling of immunosuppression and environmental control of certain filamentous fungi [72]. Invasive candidiasis is the most frequent infection in SOT, but invasive aspergillosis carries a higher morbidity and mortality and, given that they share risk factors,

prevention strategies for these entities must be combined in certain transplant populations.

It is generally accepted that universal prophylaxis should not be routinely used for *Candida* spp. infection in renal, heart and lung transplantation. Nevertheless, its use with fluconazole is a common practice in recipients undergoing intestinal (small bowel) or pancreas transplantation, given the prominence of perioperative *Candida* spp. in this type of transplant [73]. The duration of prophylaxis depends on the persistence of risk factors, but is recommended for at least 1 or 2 weeks in pancreas transplant recipients and for at least 4 weeks in intestinal transplant recipients (see Table 3 for details) [74]. There is a group of high-risk pancreas or intestinal transplant patients who also need antifungal prophylaxis for invasive aspergillosis when the attending centre has an incidence of IA of >5%/year in transplant patients. These are patients who suffer from acute rejection and poor initial allograft function, who require haemodialysis or new laparotomy after transplantation, or who present bacterial or CMV co-infection, anastomotic problems or over-immunosuppression [75] (Table 3). Patients who cannot receive fluconazole due to gastrointestinal intolerance or drug interactions may also benefit from a broad-spectrum non-azole antifungal prophylaxis (Table 3).

In the liver transplantation setting there is a high-risk category of recipients who share risk factors for invasive candidiasis and aspergillosis. In the absence of antifungal prophylaxis, IFD occurs in 36% of this population [76]. The risk factors are summarized in Table 2. These high-risk liver transplant recipients should receive antifungal prevention active against *Candida* spp. and *Aspergillus* spp. [74,77] (Table 3). The duration of prophylaxis is not clearly determined, but treatment for 3 or 4 weeks or until resolution of risk factors seems appropriate [78]. The drug of choice remains controversial. Amphotericin-B lipid formulations have been used in at least six studies, showing a significant reduction of IFD; however, the number of patients enrolled was too low to confirm a reduction in mortality [76,79–83]. As renal failure is one of the main risk factors for IFD, the nephrotoxicity associated with the treatment of lipid formulations of amphotericin B represents a limitation for its use. Echinocandins are not nephrotoxic, are unlikely to be hepatotoxic, and have few drug–drug interactions with immunosuppressive agents. In addition, promising results have recently been published using echinocandins in preventive studies focusing on high-risk liver transplant recipients [84–86]. A prospective, multicentre, non-comparative study with caspofungin showed an effectiveness of 88.7% in the ITT analysis, although the hepatotoxicity that appeared in some patients could limit its use [85].

In an international clinical trial, more than 345 liver transplant patients at high risk of IFD were randomized to micafungin or the centre-specific standard of care (fluconazole, liposomal-AmB or caspofungin). Micafungin was found to be non-inferior to the standard of care in preventing IFD in high-risk liver transplant patients and showed similar safety outcomes. At the end of prophylaxis, clinical success rates were 98.6% for micafungin and 99.3% for the centre-specific standard of care in the per protocol set, and were confirmed in the full analysis set (96.5% vs. 93.6%) [87,88].

Although some transplant groups perform universal prophylaxis with fluconazole in the liver transplant population, there are several doubts about this strategy. In the absence of risk factors, the frequency of IFD is <4% [86,89,90]. Universal antifungal prophylaxis for liver transplant recipients has been associated with increased hepatotoxicity and interactions with immunosuppressive drugs. Additionally, the appearance of non-*albicans Candida* spp. and increasing rates of resistance have limited the use of fluconazole [91,92].

In heart transplant recipients *Aspergillus* spp. cause the most infections, which occur earlier than *Candida* spp. infections. Given the absence of clinical trials, there is no clear agreement among the various groups for recommending antifungal prophylaxis in these patients; most of them choose to apply the prevention only to patients at high risk of IFD. One Spanish study confirmed that the frequency of IA was independently associated with the need for reoperation, CMV disease, haemodialysis requirement and the presence of another clinical case of IA during the previous 2 months at the same centre; the use of itraconazole was a protective factor [16]. Therefore, it seems sensible to use antifungal prophylaxis for heart transplant patients with acute rejection, haemodialysis, re-exploration after transplantation, CMV disease or excessive *Aspergillus* spp. in the air of the centre [16] (Table 3).

Universal prophylaxis against *Aspergillus* is generally accepted in lung transplant recipients, although the strategies used vary widely from centre to centre [93]. The efficacy and advantages of using nebulized lipid formulations of amphotericin B as antifungal prophylaxis in lung transplant recipients have been demonstrated; however, the duration is not well established [15,94–97]. Moreover, it has recently been shown that amphotericin B does not cause changes in the lipid content of pulmonary surfactant, thus adding a safety benefit [98]. The duration is usually limited to the first 3–6 months after transplantation, but some groups recommend continuation, especially if risk factors persist [94,99]. The implementation of this prophylaxis protocol has been associated with an incidence of IA of 4.8% [99].

The main advantages of nebulized prophylaxis are: lack of drug–drug interactions due to the absence of systemic administration, the cost-effectiveness relationship and the ability to achieve high levels of lung antifungal concentrations without systemic side-effects [100]. One disadvantage is local irritation

TABLE 3. Antifungal prophylaxis in SOT

Transplant type	Target population	Antifungal Drug Election Alternative	Duration
Kidney	No prophylaxis (B–III)		
Liver	High-Risk Liver Transplant Recipients: *Major:* Retransplantation, fulminant hepatic failure, MELD ≥30 Renal failure requiring replacement therapy *Minor:* MELD score 20–30, Split, Living-donor, choledochojejunostomy (Roux-en-Y), High transfusion requirement (≥40 units of cellular blood products), Renal failure not requiring replacement therapy (CrCl <50 mL/min), Early reintervention, multifocal colonization/infection by *Candida* spp.	If one major or two minor criteria: Micafungin (A–II) Caspofungin (A–II) Lip-AB IV (A–II) AB lipid complex IV (A–II) Anidulafungin (B–III)	2–4 weeks or until resolution of risk factors
Pancreas	*All recipients*	Fluconazole (A–III)	1–2 weeks
Pancreas-kidney	High-Risk Pancreas Transplant Recipients: (see text) Enteric drainage Haemodialysis, Cr CL<50 ml/min, Acute Rejection and poor initial allograft function, Laparotomy after transplantation, Vascular thrombosis, Postperfusion pancreatitis anastomotic problems	Caspofungina (A–III) Micafungin (A–III) Anidulafungin (A–III) Lip-AB IV (A–III)	Determined by the presence of risk factors
Intestinal	All recipients	Fluconazole (A–III)	3–4 weeks or Until healing of anastomosis and absence of rejection
	High-Risk Intestinal Transplant Recipients: (see text) Acute Rejection and poor initial allograft function, Haemodialysis, Laparotomy after transplantation, anastomotic problems	Lip-AB IV (A–III) Caspofungina (A–III) Micafungin (A–III) Anidulafungin (A–III) AB lipid complex IV (A–III)	High-Risk Intestinal Transplant Recipients: Determined by the presence of risk factors Until healing of anastomosis and absence of rejection
Lung/ Lung-heart	All recipients Recommended strategy OR Guided Prophylaxis Induction with Alemtuzumab or Thymoglobulin Acute rejection Single-lung transplant *Aspergillus* spp. Colonization PRE or during first year POST transplant Acquired hypogammaglobulinemia (IgG <400 mg/dL)	Nebulized Lip-AB 25 mg (A–II) Until resolution of bronchial suture: 3 times a week 2 to 6 month: once a week >6 month: once every 2 weeks Guided Prophylaxis: Load 25 mg 3 times a week for 2 weeks, then once a week.	Nebulized Lip-AB: Indefinite or for a minimum of 12 m or Guided Prophylaxis determined by the presence of risk factors
		Nebulized Amphotericin B lipid complex 50 mg (B–II)# Load once every 2 days for 2 weeks, then 50 mg once a week	Nebulized Amphotericin B lipid complex: A minimum of 12 m or Guided Prophylaxis determined by the presence of risk factors
		Voriconazole (B–II) PO. Load 400 mg q12 h, then 200 mg q12 h	Voriconazole: Determined by the presence of risk factors, minimum 4 m
Heart	No prophylaxis High-Risk Heart Transplant Recipients: Acute Rejection Hemodialysis, Re-exploration after transplantation, *Aspergillus* spp. heavy colonization of air.	Itraconazole (A–II) Voriconazole (B–III) Posaconazole (B–III) Equinocandins (B–III)	At least 3 months
Late Invasive Aspergillosis	High-Risk Late Invasive Aspergillosis Chronic rejection, allograft dysfunction due to VHC (liver transplant), hemodialysis	Nebulized Lip-AB B (A–III) Load 25 mg 3 times a week for 2 weeks, then once a week. Nebulized Amphotericin B lipid complex (B–III) Load once every 2 days for 2 weeks, then 50 mg once a week Voriconazole (B–*III*)	Determined by the presence of risk factors

Cr CL, creatinine clearance; CMV, Cytomegalovirus. Caspofungin: load 70 mg IV q24 h for one day, then 50 mg IV q24 h. Micafungin: 100 - 150 mg IV daily. Anidulafungin: 200 mg IV 1 day and then 100 mg IV daily. Fluconazole: 4–6-mg/kg daily. Itraconazole: 400 mg PO daily. Voriconazole: 6 mg/kg IV q12 h IV 1 day and then 4 mg/kg IV q12 h or 400 mg PO BID then 200 mg PO q12. Lip-AB IV 1–2 mg/kg/day. AB lipid complex 1 mg/kg/day. # Nebulized Amphotericin B deoxycholate 6 mg/8 h when patient is intubated

with secondary effects such as cough or bronchospasm. These effects occur in fewer than 10% of patients, and the use of salbutamol or halving the drug concentration can improve the symptoms. Other disadvantages are the need for the patient or family members to know how to administer them and the need for appropriate equipment. The possibility of irregular distribution of the drug in the lung is another potential limitation [101].

Alternatively, antifungal prophylaxis can be performed with azoles such as itraconazole or voriconazole. Husain *et al.* [102] studied the effectiveness and safety of voriconazole as universal prophylaxis in lung transplant patients; the overall incidence of IA was 1.5% in the universal prophylaxis group receiving voriconazole, compared with 23.5% in the targeted prophylaxis group [102]. However, an increase in liver enzymes was observed in 37–60% of patients receiving voriconazole and 14% had to discontinue the drug due to adverse effects [102]. Other studies have confirmed this associated hepatotoxicity [103,104]. What is more, skin cancer has been reported in lung recipients with the prolonged use of voriconazole [105–107], and also in patients experiencing chronic phototoxicity [108].

There is no agreement about the prevention strategy for late IA (>90 days post-transplant). This is a significant problem, because half of the IA cases at some centres occur late. In general, patients with high risk of late IA are those with chronic rejection, allograft dysfunction due to HCV (liver transplant), haemodialysis and over-immunosuppression and transplant-related neoplasms. In these situations, prophylaxis should be considered [9,74].

As voriconazole cannot be given to children below 2 years old, liposomal amphotericin B is the preferred mould-active preventive antifungal agent in this age. Among echinocandins, caspofungin and micafungin are authorized for administration to children <2 years of age, whereas anidulafungin is currently under study for patients <18 years. In general, there are no randomized or large cohort studies in paediatric SOT recipients; therefore, the therapeutic recommendations for these patients are largely based on efficacy studies in adults combined with safety studies in children.

Recommendations for the prevention of IFD in SOT

The recommendations for the prevention of IFD are described in Table 3.

Treatment

Invasive candidiasis

There are no randomized or cohort studies of the treatment of invasive candidiasis in SOT recipients; therefore, the therapeutic recommendations for these patients are based on different randomized studies of heterogeneous patient groups, which include a low proportion of SOT patients [109]. For this reason, most recommendations are evidence level III.

The usual treatment for *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 the azoles should be considered [78,110].

Administration of certain antifungals is limited in solid organ recipients. Amphotericin B deoxycholate should not be used in SOT due to its nephrotoxicity, especially in patients receiving calcineurin inhibitors. All the azoles interact with these inhibitors because their metabolism depends on cytochrome P450; therefore, it is very important to determine plasma levels of both azoles and immunosuppressive agents. Echinocandins (caspofungin, anidulafungin and micafungin) have shown high success rates for the treatment of invasive candidiasis [111]; they generally have fewer side-effects, less nephrotoxicity and fewer drug–drug interactions in SOT recipients than the other antifungals mentioned. Additionally, they are active against *Candida* strains that are resistant to azoles.

The usefulness of echinocandins for treating *C. parapsilosis* is controversial because minimal inhibitory concentrations are higher than those of other *Candida* species [112]. Some studies have observed similar outcomes when comparing different echinocandins vs. amphotericin B or fluconazole [111,113,114]. However, if the catheter cannot be removed, a lipid formulation of amphotericin B or an echinocandin should be used [112,115].

The first measure to be adopted, whenever possible, is the removal of central venous catheters. This measure has been associated with lower mortality in neonates and non-neutropenic patients [116]. Appropriate ophthalmological examination is also recommended in patients with candidaemia.

In non-neutropenic transplant recipients who have not recently received azoles and do not present moderate-to-severe infection or significant liver damage, several guidelines recommend the use of fluconazole for invasive candidiasis (12 mg/kg first dose, followed by 6 mg/kg/day) [110]. In children <12 years, the dose of fluconazole is 12 mg/kg/day (possibly with a loading dose of 25 mg/kg). However, we prefer the use of echicocandins [75]. It should be noted that even when the patient has no signs of clinical severity, most cases of invasive candidiasis occur in the immediate post-transplant period, mostly in the intensive care unit. Moreover, SOT patients sometimes suffer from renal failure or require haemodialysis. In this situation, the dosage of immunosuppressants is itself complicated. Treatment with azoles, particularly at these high doses, entails toxicity problems and drug–drug interactions with immunosuppressants and their

levels must be measured. It is also important to assess voriconazole levels in the case of neurological manifestations and posaconazole levels in the case of diarrhoea or mucositis, which will significantly reduce absorption.

Transplant recipients are frequently affected by candiduria, especially kidney and pancreas recipients. Treatment of asymptomatic candiduria is generally discouraged unless the patient is undergoing a urological procedure. In symptomatic patients, urinary catheters should be withdrawn or replaced and candiduria should be treated for 7–14 days [110]. The treatment of significant candiduria due to a fluconazole-resistant species is difficult, as neither echinocandins nor lipid formulations of amphotericin B achieve satisfactory levels in the urinary tract.

Recommendations for the treatment of invasive candidiasis in SOT [78,112].

- Candidaemia:
  - In non-neutropenic transplant recipients, initial treatment with echinocandins is strongly recommended (AIII). Alternatively, liposomal amphotericin B can be used despite the risk of nephrotoxicity, especially in kidney transplant recipients (AIII). Fluconazole would be marginally recommended (CIII). Similar recommendations can be given for children with SOT.
  - Neutropenia is uncommon in SOT; however, if candidaemia occurs in this context initial treatment with echinocandins or liposomal amphotericin B as fungicidal agents is mandatory (AIII).
  - Once the *Candida* spp. is isolated, it is important to perform an antifungal susceptibility test. If *C. parapsilopsis* is isolated, fluconazole (BIII) or liposomal amphotericin B (AIII) could be used as an alternative.
  - All central venous catheters must be removed (though not over a guidewire) (AII). When catheter removal is not possible, and if the patient is in an unstable condition, antifungal-lock therapy with a lipid-based amphotericin B formulation or echinocandin could be considered (CIII). Azoles or amphotericin B deoxycholate should be avoided (DIII).
  - To specify the duration of treatment a fundoscopic examination is mandatory. Resolution of candidaemia should be established by performing at least one blood culture per day until culture results are negative (AIII).
  - In patients with a central venous catheter, the possibility of a thrombus has to be ruled out (AIII).
  - For uncomplicated candidaemia, treatment for 14 days after resolution is recommended (AIII). Patients with metastatic complications require longer therapy (AIII).
  - To simplify treatment, switching to oral fluconazole could be considered after 10 days of IV therapy when *Candida* spp. are susceptible, the patient is stable, tolerates oral administration and the drug–drug interactions on CYP3A4 metabolism can be managed (BIII).
  - If *C. glabrata* or *C. krusei* is isolated the use of echinocandin (BIII) or liposomal amphotericin B as an alternative should be considered (BIII).
- Urinary Tract Infections (UTIs):
  - Asymptomatic candiduria should not be treated, unless the patient is undergoing a urological procedure or is neutropenic (AIII). Treatment of symptomatic patients with candiduria (cystitis) or pyelonephritis is required (AIII). In symptomatic UTI SOT recipients with candidaemia the candidaemia recommendations described in the section above should be followed.
  - Removal of the urinary catheter is advisable (AIII).
  - An imaging technique should be considered to rule out abscess, fungus ball or urological abnormality (AIII).
  - When a urinary fungus ball is diagnosed, surgical removal is strongly recommended (AIII).
  - For patients with UTI due to a fluconazole-susceptible *Candida* spp. treatment with fluconazole is strongly recommended (AIII). For recipients with fluconazole-resistant organisms, lipid formulations of amphotericin B ± oral flucytosine are the treatment of choice (AIII).
  - Echinocandins achieve poor urinary levels; therefore, these antifungals are precluded for the treatment of UTI (DIII).
  - Amphotericin B deoxycholate bladder irrigation (50 mg amphotericin B per litre of sterile water) continuously for 5–7 days may be an efficacious treatment. Liposomal amphotericin B may be effective as adjunctive therapy for a urinary fungus ball (BIII).
- In lung transplant recipients with anastomotic tracheobronchitis due to *Candida* spp. the recommended treatment is nebulized liposomal amphotericin B 25 mg three times a week, or nebulized amphotericin B lipid complex every other day plus removal of the debris by repeated bronchoscopies (AIII). Echinocandins may be more effective than azoles for *Candida* spp. growing in the biofilms of the anastomoses (BIII).
- In *Candida* endocarditis, either native or prosthetic, surgery within a week or even earlier is recommended (AII). The treatment of choice is liposomal amphotericin B (5 mg/kg/24 h) ± flucytosine 25 mg/kg/6 h for 6–8 weeks (BII), followed by fluconazole (BII) for sequential treatment in stable

patients [78,111]. Patients who are inoperable need suppression of the infection with combined fluconazole 400–800 mg [117] (CII). In view of reports of the efficiency of caspofugin ± flucytosine, this regimen can be recommended as initial treatment (BII) [118].

- In ocular candidiasis, echinocandins diffuse poorly to the retina; therefore, liposomal amphotericin B either alone or combined with flucytosine is recommended when the susceptibility of the isolate is unknown (AII). In susceptible isolates fluconazole or voriconazole are the drugs of choice (AII). In the case of vitreal involvement, vitrectomy and intravitreal injection of amphotericin B are recommended in addition to systemic therapy (AII).
- For detailed recommendations for treatment of *Candida* diseases, readers should refer to Cornely *et al.* [112], ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients.

Invasive Aspergillosis

The emergence of lipid amphotericin B formulations in the 1990s improved the prognosis of IA in the SOT population. However, no new studies with these drugs have been published since then and it is difficult to assess the therapeutic response.

The CLEAR (Collaborative Exchange of Antifungal Research) study analysed 721 immunosuppressed patients with IFD treated with amphotericin B lipid complex. The study included 109 solid organ recipients with IA, of whom 54% had a favourable response [119].

Voriconazole is authorized for the treatment of IA in solid organ recipients based on the results of a small-scale, non-comparative, open-label European trial [120] and on a trial that compared voriconazole and amphotericin B deoxycholate as initial treatment in patients with haematological malignancy [121]; however, the latter study included only 11 solid organ recipients. Although the experience of SOT groups with voriconazole is considerable, few data have been published to date [122–124].

Historically, the mortality of IA when the CNS is affected has been close to 100%. Voriconazole has improved the prognosis of patients suffering from this disease, due to its penetration into the CNS. Schwartz *et al.* [125] confirmed a partial or complete response in 35% of patients with CNS involvement in combination with neurosurgical management.

Caspofungin is the only echinocandin approved by the FDA and EMA for the treatment of refractory IA. In a study of 12 thoracic organ recipients, caspofungin demonstrated an efficacy of 86% [126]. Maertens *et al.* [127] recently confirmed a favourable response in six of nine solid organ recipients. In an observational study of 19 SOT recipients, Winkler *et al.* [128] found a favourable response with caspofungin used as first-line treatment in 78% of patients receiving monotherapy and in 70% of those receiving combination therapy.

The role of combination therapy in solid organ recipients with IA has not been defined. One multicentre study analysed the outcomes of 40 patients who received voriconazole and caspofungin as initial treatment for IA [129], and compared this group with a historic cohort who received a lipid formulation of amphotericin B. Multivariate analysis revealed that combination therapy reduced 90-day mortality in the subgroup of patients with renal insufficiency and IA caused by *A. fumigatus* [129].

To date, the published experience with posaconazole or micafungin for treating SOT recipients with IA is limited, but the few outcomes described are satisfactory [130–132]. Few data are available for anidulafungin [84].

Recommendations for the treatment of invasive aspergillosis in SOT [75,133].

- General principles:
  - Antifungal therapy should be initiated early in SOT patients with high suspicion of IA (AIII).
  - Treatment should be individualized according to type of transplant, SOT recipient, type of IA and immunosuppression used (AIII).
  - Diagnostic evaluation is mandatory in order to confirm the IA (AIII)
  - It is important to reduce immunosuppression as an adjunct to antifungal treatment, but without jeopardizing graft viability. Probably the most important strategy is the reduction of the corticosteroid dose (BIII). There is an added risk of steroid myopathy with combination treatment of voriconazole and methylprednisolone at doses above 20 mg/day (BIII).
- The preferred treatment for IA as a primary approach is voriconazole (4 mg/kg/12 h with a loading dose of 6 mg/kg or 200 mg/12 h PO with a loading dose of 400 mg/12 h PO) (AIII) or liposomal amphotericin B (3 mg/kg/day) (AIII). In children, the dose of voriconazole is 8 mg/kg/12 h IV with a loading dose of 9 mg/kg.
- If voriconazole is used in severely ill patients, a parenteral formulation is recommended in order to ensure bioavailability. If renal impairment is present or if the patient is clinically stable, the drug can be administered orally. Monitoring plasma levels is recommended in order to maintain the range between 2 and 4 mg/L (AII). The potential hepatotoxicity should be considered, especially in liver transplantation, and drug–drug interactions with immunosuppressants (AIII).

- In patients for whom administration of voriconazole is problematic (due to risk of liver toxicity, severe drug–drug interaction, intolerance or allergy to azoles), liposomal amphotericin B is recommended (AIII). Physicians should be aware of the increased risk of nephrotoxicity (AIII).
- If the patient has severe disease (pneumonia or disseminated disease), initial treatment with a combination of antifungals should be considered, at least to ensure therapeutic concentrations of voriconazole (AIII). Elective treatment with voriconazole plus caspofungin is a possibility [129] (loading dose 70 mg/24 h followed by 50 mg/24 h) or voriconazole plus anidulafungin (loading dose 200 mg/24 h, then 100 mg/24 h) (A-III). In children, caspofungin is given with a dose of 50 mg/m^2 with a loading dose of 70 mg/m^2. In patients for whom administration of voriconazole is problematic (see above), liposomal amphotericin B plus caspofungin may be an alternative (BIII).
- The therapeutic response should be monitored periodically by a clinical follow-up and a high-resolution CT scan. Performance of a CT scan every 7–10 days during the first weeks should be considered (AIII). It should be noted that neither a cavitation of lesions indicating necrosis nor a slight increase in lesion volume (especially in the context of recovery after absolute neutropenia) indicates adverse outcome (AIII).
- Rescue treatment is the treatment of infected patients who are refractory or intolerant to initial therapy. The point in time when treatment is considered a failure is not well defined. The following results are associated with poor outcome and may be considered as therapeutic failures in the absence of clinical improvement: (i) dissemination of the clinical symptoms during treatment, (ii) new or increased lesions in the CT scan performed 7–10 days after treatment onset (in the absence of recovery from absolute neutropenia), (iii) no decrease in lesion size in the CT scan performed at 15–21 days, or (iv) intolerance to elective therapy. In the presence of these findings, a switch to a different kind of antifungal to the one used for the initial treatment is recommended (AIII).
- In the case of rescue treatment due to failure of the treatment of choice, a combination of antifungals is strongly recommended (AIII). The recommendations are the same as those discussed above in the severe IA section (pneumonia or disseminated disease).
- In the case of rescue therapy due to intolerance of the treatment of choice, a change to voriconazole or liposomal amphotericin B should be considered if it is not contraindicated (AIII). Other antifungal agents with confirmed effective use as rescue therapy include: amphotericin B lipid complex 5 mg/kg/day (BII), posaconazole 400 mg/12 h (BIII), caspofungin loading dose 70 mg/24 h followed by 50 mg/24 h (BIII) and micafungin 150–200 mg/24 h (BIII).
- Surgery is recommended in patients with massive haemoptysis, endocarditis, sinus disease or infection of the pericardium and large vessels. The benefit of surgery is doubtful when there is bone involvement [134].
- In endocarditis, given the poor prognosis of medical treatment alone, surgery is recommended as well as replacement of valves or affected tissues (BIII) [135] (Table 4).
- Although the duration of treatment has not been established, it should be maintained until radiological signs disappear, which is usually a minimum of 6–12 weeks. Treatment with oral voriconazole could be extended for a few weeks in order to treat possible residual microfoci of aspergillosis.
- Special considerations for lung transplantation:
- Colonization must be treated to prevent invasive disease (AIII). The recommended treatment is nebulized liposomal amphotericin B 25 mg/24 h for 7 days, then 25 mg/72 h, or nebulized amphotericin B lipid complex 50 mg/24 h once every 2 days plus removal of the debris by repeated bronchoscopies In the case of intolerance or difficulties inhaling lipid formulations of amphotericin B, voriconazole

TABLE 4. Surgery criteria for invasive *Aspergillosis* in SOT

Organ involvement	Recommendation
Injuries close to large vessels and/or pericardium	Resection of the lesion
Pericardium involvement	Pericardiectomy
Chest wall invasion by lung injury	Chest injury and chest wall resection is needed (possible later reconstruction)
Empyema	Chest tube drainage is required or even surgical drainage and thoracotomy (whether organized or infiltrative)
Haemoptysis secondary to a pulmonary lesion	Cavity resection vs. embolization
Skin and soft tissue involvement	Debridement and resection with wide margins
Endocarditis	Remove all devices Vegetation and infected valve resection is required
Osteomyelitis	Debridement and cleaning of the affected tissue, with subsequent possibility of reconstruction is required (musculoskeletal grafts or bone grafts)
Sinusitis	Cleaning, curettage and resection of affected tissue is needed
Central nervous system involvement	Resection and withdrawal of affected tissue and space-occupying lesions is required
Endophthalmitis/panophthalmitis	Vitrectomy, evisceration or enucleation, as required

should be considered (loading dose 400 mg/12 h PO, then 200 mg/12 h PO) (BIII).

- In the case of nodular or ulcerative tracheobronchitis, voriconazole plus nebulized lipid formulations at the same doses as those used for colonization episodes are recommended (AIII). Bronchoscopy is also recommended to evaluate the extension of disease and to clear necrotic debris and fungus balls (this should be repeated every week or every 2 weeks). A high-resolution CT scan should also be performed to rule out parenchymal extension (AIII).
- Long-term treatment with voriconazole may induce liver toxicity and may be associated with development of cutaneous squamous cell carcinoma with high clinical aggressiveness [105,106,136] (BIII).

Cryptococcosis

The treatment of cryptococcal infection varies according to the localization of the disease. For cryptococcal meningitis, the essential drug is amphotericin B. Several studies have shown better results using high doses of amphotericin B in this situation [137,138]. The use of lipid formulations has been associated with lower rates of mortality [139,140]. Several studies have shown that the combination of flucytosine with amphotericin B for induction treatment is associated with better response rates than amphotericin B alone, a greater speed in the sterilization of cultures and a better clinical outcome [141–143]. Although it is not clear that this beneficial effect also occurs with the combination of lipid amphotericin B [144], this combination therapy is recommended in SOT patients whenever possible [23] in order to avoid nephrotoxicity. Nevertheless, a recent multinational study of 83 transplant recipients and the review of 168 cases published in the literature confirmed that only one-third of patients received concomitant 5-flucytosine, and it was not associated with poorer sterilization of CSF cultures at 2 weeks. In this study, induction treatment was based on a lipid formulation of amphotericin B in 50% of the patients, and induction with fluconazole was reserved for the mildest and extrameningeal forms [145].

The combination of flucytosine with fluconazole has also produced favourable results, but not as good as the combination with amphotericin B in some studies [146,147]. The consolidation treatment is usually performed with fluconazole (200–400 mg/day) [148]. Other azoles such as voriconazole or posaconazole have been used in refractory cases with good response, but there are no studies that demonstrate superiority over fluconazole [149,150]. Some authors recommend lifelong treatment. Singh *et al.* [145] confirmed that the median maintenance treatment was 6 months (55% of patients); however, in 25% of patients it was maintained for up to 1 year. In comparison to *C. neoformans*, infection by *C. gatii* is associated with more neurological sequelae, a greater need for surgery and a poorer response; this is probably because of the reduced activity of fluconazole, the greater frequency of cryptococcoma and the use of corticosteroids in the presence of marked perilesional oedema. Extended spectrum azoles may be an alternative for the maintenance phase. Cryptococcoma must be removed by surgical resection if they are easily located. In patients with cryptococcosis, intracranial hypertension must be managed appropriately with repeated lumbar punctures or placement of a CSF shunt when necessary [151–153].

An estimated 5–11% of SOT recipients with cryptococcal disease may develop immune reconstitution inflammatory syndrome (IRIS) due to rapid reduction of immunosuppressive therapy, typically between 4 and 6 weeks after initiation of antifungal therapy [145]. The development of IRIS in kidney transplant patients seems to favour the emergence of chronic graft dysfunction [154].

There are no specific recommendations for the treatment of pulmonary cryptococcosis in SOT recipients, which is similar to the case of HIV patients [155]. Lower mortality has been observed when using lipid formulations of amphotericin B rather than conventional amphotericin B in severe cases [18].

For disseminated infection, the recommendations are the same as for the treatment of CNS infection. If flucytosine is not added during the induction phase, the recommendation is to extend induction treatment for 4–6 weeks. The use of conventional amphotericin B is discouraged, because there is a high risk of nephrotoxicity in these patients.

In children cryptococcosis is rare, and there are no specific recommendations in this population.

Recommendations for the treatment of cryptococcosis in SOT.

- For meningoencephalitis, disseminated disease or diffused pulmonary infiltrates and acute respiratory failure, the recommended therapy is as follows [23,156]:
  - Liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day (AII) plus flucytosine 25 mg/kg/6 h (BII); (monitoring to maintain levels of 30–80 mg/L 2 h post-dose) for 2 weeks as induction therapy.
  - Fluconazole 400–800 mg/day for 8 weeks as consolidation (AII).
  - Fluconazole 200 mg/day for 6–12 months as maintenance (AII).

- For management of increased intracranial pressure [23]:
  - Initial opening pressure must be recorded and if >25 mmHg a large volume tap should be performed to reduce the intracranial pressure to <20 mmHg (AII).
  - Lumbar pressure should be performed daily until opening pressure is <25 mmHg (AIII).
- For focal pulmonary and incidentally detected pulmonary disease in otherwise asymptomatic patients, the recommended treatment is fluconazole 400 mg/24 h (6 mg/Kg/24 h) for 6–12 months (AII).
- Whenever possible, a gradual reduction in the net state of immunosuppression should be performed during therapy (AIII).
- There is no proven therapy for IRIS. Corticosteroids in doses equivalent to 0.5–1 mg/kg of prednisone may be considered for major complications related to inflammation in the CNS and severe manifestations in pulmonary or other sites [157] (BII).

Other filamentous fungi

There are no specific recommendations for the management of these infections in SOT, and the same applies to other immunocompromised patients. Diagnosis and treatment guidelines for the rarer IFD (mucormycosis, fusariosis, scedosporiosis and others) are being prepared by ESCMID.

As with other immunosuppressed patients, management of mucormycosis in SOT recipients is based on three approaches: (i) antifungal treatment with high-dose liposomal amphotericin B; (ii) surgical resection, if possible; and (iii) reduced immunosuppression. As first-line therapy in both adults and children with mucormycosis, liposomal amphotericin B at doses of 5 mg/kg/day or more is administered. Posaconazole is a second-line treatment if amphotericin B is contraindicated [130,158]. For CNS mucormycosis, liposomal amphotericin B is preferred. As adjunctive therapy, recombinant cytokines such as granulocyte colony-stimulating factor and granulocyte macrophage-colony stimulating factor can be given to restore immunosuppression. Iron chelators such as deferasirox [159] have not been shown to assist clinically. Echinocandins can be used in combination with amphotericin B [160]. High doses of lipid amphotericin B (10–15 mg/kg/day) have been used in refractory forms and/or in cases of CNS involvement, although their efficacy has not been compared in humans at doses of 5 mg/kg/day and they are more toxic. Promising results have nevertheless been obtained with 10 mg/kg/day in a pilot multicentre study [161].

Good results have been reported with posaconazole in patients who have previously received amphotericin B [130,158]; however, the combination of posaconazole and amphotericin B has not proven beneficial in the prevention of murine experimental mucormycosis [162]. Reed *et al.* [160]

TABLE 5. Emerging fungal infections in SOT

Microorganism	Treatment	Comments
Zygomycetes	Lip-AB high dose (up to 15 mg/kg q24 h if tolerated); most data document maximum benefit achieved at 7.5 mg/kg q24 h Lip-AB 5 mg/kg q24 h + caspofungin Posaconazole as alternative	Surgical resection if amenable Reduction of immunosuppression Control of predisposing metabolic conditions Correction of neutropenia
Fusarium	*F. solani* and *F. verticillioides* Lip-AB 5–15 mg/kg q24 h *F. oxysporon* more susceptible to extended-spectrum triazoles	Surgical resection of localized skin disease Removal of infected foreign bodies such as intravascular catheters Correction of neutropenia
Scedosporium	*S. apiospermum*: *voriconazole* *S. prolificans*: Resistant to all antifungal agents. Surgical debridement is mandatory. Combination antifungal options: Echinocandin + AmB or voriconazole Voriconazole + terbinafine	Surgical resection or debridement is highly recommended Drainage of abscesses and resection of any infected foreign body Correction of neutropenia when present
Paecilomyces	Voriconazole Posaconazole	Surgical excision or debridement is recommended
Penicillium	Lip-AB 2 mg/Kg q24 h followed by maintenance with itraconazole 400 mg q24 h	
Scopulariopsis	Posaconazole or voriconazole + terbinafine Posaconazole or voriconazole + caspofungin	Debridement of infected tissue Removal of involved foreign bodies
Trichoderma	Lipid AmB + voriconazole or posaconazole until susceptibility data are available	Removal of infected peritoneal dialysis catheters Surgical drainage/removal of localized lesions such as pulmonary mycetomas, sinus collections, abdominal and brain abscesses
Phaeohyphomycosis	Voriconazole Posaconazole Itraconazole Fluconazole 800 mg q24 h Extended-spectrum triazoles	Surgical debridement is recommended *In vitro* synergy: Lipid AmB + flucytosine Itraconazole + flucytosine Identification in urine in kidney transplant recipients generally does not require treatment
Sporothrix	AmB until response, followed by itraconazole (total of 12 months)	Itraconazole may be considered for cutaneous disease
Malassezia	Fluconazole 400–800 mg q24 h Lip-AB B 3–5 mg/kg q24 h	Removal of intravenous catheters

Lip-AB, lipid amphotericin B; Lipid AmB, lipid formulations amphotericin B.

TABLE 6. Drug Interactions of Azoles

Azoles Drug A (FLU, ITRA, VOR, POS) Drug B	Effect	Recommendation
Antacid	↓↓ ITRA conc	Avoid/ Use Alternative ITRA
H2 antagonist	Cimetidine POS ↓↓ conc	
Cimetidine		Avoid/ Use Alternative combination Cimetidine /POS
Famotidine		If necessary use Famotidine or Ranitidine
Ranitidine		
Antacids/ITRA	↓ absorption of A	Consider therapy modification
Aluminum Hydroxide	↓ A conc	Apply primarily to itraconazole capsules
Calcium Carbonate		Oral suspension may be less sensitive to the effects of gastric acidity
Magaldrate		
Magnesium Carbonate		Administer itraconazole at least 1 h after and 2 h before administration of any antacids
Magnesium Hydroxide		
Magnesium Trisilicate Sodium Bicarbonate		
Antiepileptic drugs	↓↓ A conc	Avoid/ Use Alternative
Carbamazepine	↑↑ B conc	Consider use other non-azole antifungal drug
Fosphenytoin	A, B; increase ++ metabolism CYP3A4	Partial Seizures: Consider Valproic acid, Gabapentin, Pregabalin, Lacosamide
Oxcarbazepine	A, B ↓↓ CNI, mTOR inhibitors conc [a]	
Phenytoin		Acute repetitive seizures or status epilepticus: Consider IV *Lorazepam*
Barbiturates	↓↓ A conc	*Avoid/ Use Alternative*
Secobarbital	B increase ++ metabolism CYP3A4	
Pentobarbital	B ↓↓ CNI, mTOR inhibitors conc [a]	
Phenobarbital		
Benzodiazepines	↑ B conc	Avoid/Use Alternative or
Alprazolam		*Consider therapy modification*
Bromazepam		Consider Lorazepam, Oxazepam, or Temazepam or
Chlordiazepoxide		Decrease benzodiazepine dose
Clobazam		
Clonazepam		
Clorazepate		
Diazepam		
Estazolam		
Flurazepam		
Midazolam		
Nitrazepam		
Triazolam		
Zolpidem		
Busulfan	May ↑ B conc	Monitor adverse events
Calcium Channel Blockers (CCB)	↑ conc Verapamil, diltiazem, nicardipine	Consider Avoid/ Use Alternative
Amlodipine	amlodipine ++	*If clearly indicated:*
Diltiazem	B, A; inhibition metabolism CYP3A4:	Consider use other non-azole antifungal drug
Felodipine	↑ CNI, mTOR inhibitors conc [b]	CCB dose reduction is needed
Isradipine	Nifedipine, isradipine	Monitor toxic effects CCB
Nicardipine	No effect metabolism CYP3A4	Consider avoid mTOR inhibitors
Nifedipine		*or*
Nisolpidine		*Consider Nifedipine, isradipine*
Verapamil		TDM CNI closely
Cilostazol	↑ B conc	Reduce Cilostazol doses to 50 mg q12 h
Clopidogrel	↓ B efficacy VOR, FLU	*Avoid VOR, FLU / Use Alternative*
Colchicine	↑↑ B serum conc	Reduce colchicine dose
	CNI ↑ B conc	
Cyclosporine	↑ B conc	Consider therapy modification
		Reduce B dose mandatory:
		FLU: Dose dependent. By 20- 50%;
		VORI: by ½;
		POS: by ¼.
		Monitor TDM Cyclosporine closely
Diclofenac	VORI ↑ B conc	Consider therapy modification
		Consider using a lower dose of diclofenac. Max 50 mg q12 h
Digoxin	ITRA, POSA ↑ B conc	Monitor for increased serum conc/effects Digoxin
	Tacrolimus ↑ B conc	
Docetaxel	↑ B conc	Use Itraconazole with Caution and if Clearly Indicated
		Monitor for toxic and increased effects of Docetaxel
		Consider therapy modification
		Consider use a non azole antifungal
Eletriptan	ITRA, VORI, POSA ↑ B conc	Avoid combination
		Consider sumatriptan
Ergot alkaloids	↑ B conc	Avoid ITR, VOR, POS / Use Alternative
		Consider use other non-azole antifungal drug
		FLU: Decrease doses of Ergot alkaloids.
		Monitor for increased toxicity
Fentanyl	↑ B conc	Avoid VOR, POS, ITRA / Use Alternative
	Cyclosporine ↑ B conc	*Consider therapy modification* FLU, ITRA,
		Decrease dose fentanyl
		Monitor adverse events fentanyl
Haloperidol	ITRA, VORI, POSA ↑ B conc	Consider Avoid Combination/ Use Alternative
	B Moderate Risk QTc-Prolonging Agents	*Use only if Clearly Indicated*
Highest Risk QTc-*Prolonging Agents* / *QTc-Prolonging Agents*	A Enhance the QTc-prolonging effect of B	Consider Avoid Combination/ Use Alternative
	CNI Enhance the QTc-prolonging effect of B	Risk of torsades de pointes or potentially life-threatening ventricular tachyarrhythmias
Amiodarone		Consider use other non-azole antifungal drug
Artemether		Combinations should only be undertaken with caution and should be avoided when possible
Astemizole		
Cisapride		

Table 6 (*Continued*)

Azoles Drug A (FLU, ITRA, VOR, POS) Drug B	Effect	Recommendation
Citalopram		
Disopyramide		
Dronedarone		
Escitalopram		
Flupentixol		
Halofantrine		
Procainamide		
Quinidine		
Quinine		
Saquinavir		
Sotalol		
Sparfloxacin		
Telithromycin		
Terfenadine		
Isoniazid	↓ ITRA conc ↑ VOR conc	Avoid ITRA or Use only if Clearly Indicated Risk failure antifungal treatment Consider therapy modification TDM itraconazole and increase dose *VOR:* Risk toxicity *TDM VOR*
Ibuprofen	VOR ↑ B conc by two fold	*Consider therapy modification or other analgesic*
Lomitapide	↑ B conc	*Avoid*
Macrolides	↑ A conc	Avoid Erythromycin/Use Alternative
Erythromycin	↑ B conc	Consider therapy modification
Clarithromycin	A, B Synergism inhibition metabolism CYP3A4:	*Use ONLY if Clearly Indicated*
Azithromycin	↑↑ CNI, mTOR conc [b]	Consider use *azithromycin* Consider use other non-azole antifungal
Metoclopramide	Metoclopramide ↓ POS conc	Consider therapy modification Increase dose POS. TDM
mTOR	↑ mTOR conc [b]	Avoid Combination VOR, POS/ Use Alternative
Sirolimus		*Consider therapy modification FLU, ITRA*
Everolimus		FLU, ITRA: Reduce mTOR dose by ½; TDM closely mTOR
Oral hypoglycemic	↑ B conc	Consider therapy modification
Glimepiride	Increased risk of hypoglycemia	Monitor glycaemia closely
Glipizide		*Metformin* NO interactions with azole antifungals
Glyburide		
PDE5 inhibitor	↑ B conc	Consider therapy modification
Sildenafil		Decrease dose PDE5 inhibitor
Tadalafil		Monitor patients for effects such as hypotension, headache, visual changes, and priapism
Vardenafil		
Proton Pump Inhibitors	↓↓ ITRA	Consider therapy modification VOR/POS/ITRA
Omeprazole	↓↓ POS conc by 50%	*ITRA* Avoid *ITRA* capsules. Use ITRA Oral solution or ITRA with an acidic beverage (eg, cola)
Lansoprazole	↑ VOR conc	*POS* Increase dose of POS. TDM POS
Pantoprazole	↑ B conc B, A; ↑ CNI, mTOR inhibitors conc [b]	*VOR:* Omeprazole ≥40 mg/day or greater: Reduce omeprazole dose by ½ when initiating VOR. TDM VOR. *Consider use* Lansoprazole Pantoprazole (less interaction)
Ranolazine	↑↑ B conc	Avoid Combination / Use Alternative Contraindicated by manufacturer
Red Yeast Rice	↑ B conc	Avoid Conc of Lovastatin and related compounds found in Red Yeast Rice may be increased.
Rifabutin	Rifabutin AUC increased by 80% ↓↓ A conc B increase ++ metabolism CYP3A4 ↓↓↓ CNI, mTOR inhibitors[a]	Avoid Combination/ Use Alternative OR Consider therapy modification *Use ONLY if Clearly Indicated* Monitor adverse events of rifabutin If necessary, doses of rifabutin may be decreased +++
Rifampin	↓↓↓ A conc ↑ B conc B increase ++ metabolism CYP3A4 ↓↓↓ CNI, mTOR inhibitors[a]	Avoid Combination/ Use Alternative If necessary, consider rifabutin
Rituximab	ITRA inhibits action of B	Avoid or Use only if Clearly Indicated
Statins	↑ B conc	Avoid Combination/ Use Alternative
Lovastatin	CNI ↑ A conc	Use pravastatin, atorvastatin
Simvastatin		Careful monitoring for myopathy
Tacrolimus	↑ Tacrolimus conc [b]	Consider therapy modification Reduce tacrolimus dose mandatory: FLU: By 40–50%; VORI, POS: by ⅓ Monitor TDM closely
Theophylline	↑ B conc	*Consider therapy modification*
Venlafaxine	↑ B conc	*Consider therapy modification*
Vinca Alkaloids	VOR, POS, ITRA ↑ B conc	Avoid. Consider therapy modification.
Vinblastine	Enhanced neurotoxicity	Consider use other non-azole antifungal drug
Vincristine		Stop azole 1 day before until 1 day after chemotherapy If combination: Dose adjustment of vinca alkaloid should be considered prior to use Monitor adverse events *Vinca Alkaloids*
Warfarine	INR could increase	Monitor INR closely

[a]Risk Acute Rejection.
[b]Risk toxicity Calcineurin inhibitor, mTOR.
FLU: Fluconazole. ITRA: Itraconazole. VOR: Voriconazole. POS: Posaconazole. CNI: Calcineurin inhibitors. TDM: Therapeutic Drug Monitoring.
[®]Note: Readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician. The recommendations enclosed in this table should not be used to replace or overrule a physician's judgment. Data from: (i). Johns Hopkins ABX Guide. http://www.hopkinsguides.com/hopkins/ub/index/Johns_Hopkins_ABX_Guide/All_Topics/A (ii). Sanford Guide Web Edition 2: http://webedition.sanfordguide.com (iii). Lexicomp. Lexi-Interact™ Online. Lexi-Interact™. http://www.uptodate.com/crlsql/interact/frameset.jsp.

recently reported their preliminary experience with combinations of caspofungin and lipid formulations of amphotericin B used to treat mucormycosis. A triple therapy using lipid amphotericin B, micafungin and deferasirox was effective in a murine model of mucormycosis [163], but not in patients [164].

Management of infections by *Scedosporium* spp. is also based on correction of underlying factors. Surgery can improve outcome, especially in the treatment of processes such as sinusitis, keratitis, arthritis, osteomyelitis and brain abscess. Voriconazole is the treatment of choice, especially in infections by *S. apiospermum* [165]. In contrast, *S. prolificans* is resistant to most antifungals [166]. A recent multicentre study confirmed the usefulness of voriconazole in the treatment of 107 patients with severe infections caused by *Scedosporium* spp., some of whom were transplant recipients [165]. The study showed that 57% of patients responded to voriconazole, and that the response was significantly better in infections caused by *S. apiospermum* (64%) than in those caused by *S. prolificans* (44%). *S. prolificans* is uniformly resistant to all common antifungals such as amphotericin B, flucytosine, fluconazole and itraconazole. *In vitro* studies revealed a synergy between terbinafine and several azoles (voriconazole and itraconazole). There is some clinical experience with these combinations [167].

Infection by *Fusarium* spp. is exceptional in solid organ recipients. It should be treated with high doses of lipid amphotericin B (mainly in infections by *F. solanii* and *F. verticillioides*) or voriconazole, together with withdrawal of infected catheters and resection of necrotic material [168–170].

TABLE 7. Drug Interactions of Azoles with Antiretroviral and anti-HCV drugs

Azoles Drug A (FLU, ITRA, VOR, POS) Drug B	Effect	Recommendation
Protease inhibitors	FLU: No interaction except Tipranavir:	FLU: No dose modification. Consider Avoid FLU/ Tipranavir
Atazanavir/Ritonavir	↑ conc FLU; Tipranavir: ↑ CNI, mTOR inhibitors[a]	Consider Avoid Comb VOR, ITRA/Protease inhibitors
Darunavir/Ritonavir (DRV/r)	ITRA: B ↑ conc ITRA	*If Combination clearly needed:*
Fosamprenavir	VOR: B ↑ or ↓ conc VOR	Consider other antifungal drug class *OR*
Lopinavir/ritonavir	POS: B no ↑ or minimum ↓ conc POS	Consider POS (less interactions)
Tipranavir	ITRA, VOR, POS: ↑ B conc	Monitor side effects/toxicity Protease inhibitors
Telaprevir	B, A; inhibition metabolism CYP3A4:	TDM POS (if it possible)
Boceprevir	↑ CNI, mTOR inhibitors[a]	Reduce dose CNI ++ mandatory, TDM closely
		Check for individual characteristics
NNRTI	NNRTI Inducer metabolism CYP3A4	
Efavirenz	↓ CNI, mTOR inhibitors [b]	
Etravirine	Except Rilpivirine	
Nevirapine	A inhibition metabolism CYP3A4	
Rilpivirine	↑ CNI, mTOR inhibitors[a]	
Efavirenz	↓↓ POS, VOR, ITRA conc	Avoid Combination POS, ITRA - Efavirenz/ Use Alternative
	↑ B conc	*If Combination clearly needed*
		Consider VOR at 400 mg q12 h and efavirenz at 300 mg daily.
		Monitor for increased effects/toxicity of efavirenz
		TDM VOR
		Increase dose CNI, TDM closely
Etravirine	↑↑ B conc; ↓ ITRA	Consider therapy modification
		No preemptive dose adjustment azoles except *ITRA*
		No preemptive dose adjustment Etravirine
		Monitor for increased effects/toxicity of etravirine
		Consider Avoid mTOR inhibitors,
		Increase dose CNI, TDM closely
Nevirapine	FLU, ITRA, VOR ↑↑ B conc	Avoid Combination ITRA, - Nevirapine/ Use Alternative
		Consider therapy modification
		Avoid mTOR inhibitors, TDM CNI closely
Rilpivirine	VOR, FLU enhance the QTc-prolonging effect of B	Moderate risk
		Close monitoring for evidence of excessive QT prolongation and/or torsades de pointes
	CNI Enhance the QTc-prolonging effect of B	
NRTI	B may ↓ absorption of A	Consider therapy modification
Didanosine (ddI)		Concomitant ddI buffered formulations and azoles at least 2 h apart
		Enteric-coated ddI capsules should not interact
Entry and Integrase Inhibitors		
Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Quad ®	↑↑ VOR, ↑ ITRA conc	Avoid combination VOR, ITRA / Use Alternative
	VOR ↑↑, ITRA ↑ Elvitegravir, Cobicistat conc	*Consider therapy modification*
	VOR, ITRA, Elvitegravir, Cobicistat inhibition metabolism CYP3A4:	*If clearly indicated consider POS*
		Decrease dose CNI, TDM closely
	↑ CNI conc, mTOR inhibitors[a]	
Maraviroc	A ↑↑ B conc VOR, POS ++ FLU + mTOR inhibitors ↑ B conc	Consider therapy modification
		Doses of Maraviroc should be decreased if you considered combination
		If POS use Consider MVC 150–300 mg twice daily.
		Consider avoid mTOR inhibitors

Note: Readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician. The recommendations enclosed in this table should not be used to replace or overrule a physician's judgment. (i). University of Liverpool: http://www.hiv-druginteractions.org (ii). Johns Hopkins ABX Guide. http://www.hopkinsguides.com/hopkins/ub/index/Johns_Hopkins_ABX_Guide/All_Topics/A (iii). Sanford Guide Web Edition 2: http://webedition.sanfordguide.com (iv). Lexicomp®. Lexi-Interact™ Online. Lexi-Interact™. http://www.uptodate.com/crlsql/interact/frameset.jsp.
FLU: Fluconazole. ITRA: Itraconazole. VOR: Voriconazole. POS: Posaconazole. CNI: Calcineurin inhibitors
[a]Risk toxicity Calcineurin inhibitor, mTOR.
[b]Risk Acute Rejection.

For the treatment of other emerging and rare fungal infections, see Table 5.

Recommendations for the treatment of other filamentous fungi in SOT.

- The treatment of mucormycosis is based on three approaches: prompt diagnosis and initiation of therapy, correction of predisposing conditions as well as reduction of immunosuppression, and combined medical-surgical treatment (AII).
- The antifungal treatment of choice is liposomal amphotericin B at doses of 5 mg/kg/24 h or more (B-II). The alternative treatment is posaconazole (BIII).
- For the treatment of *Fusarium* spp. the recommendation is liposomal amphotericin B (BIII) or voriconazole (BIII), along with the removal of infected catheters and foreign bodies, and the resection of necrotic material.
- The management of infections caused by *Scedosporium* spp. is based on the correction of risk factors, surgical resection of necrotic material and the removal of any infected foreign bodies. The antifungal drug recommended is voriconazole, especially for infections due to *S. apiospermum* (BII).

Treatment interactions

Drug–drug interactions should be evaluated very carefully in solid organ recipients. If voriconazole is administered, the calcineurin inhibitor dose should be reduced by 50–60% [171]. Co-administration of voriconazole and sirolimus is formally contraindicated, although some authors have applied this combination by reducing the dose of sirolimus by 75–90% [172]. If the patient receives posaconazole, then the dose of tacrolimus or cyclosporine A should be reduced by 60–75% and 14–29%, respectively [173]. Few drug–drug interactions affect the echinocandins: caspofungin presents the highest rate, and anidulafungin the lowest. Other drugs such as rifampicin, nevirapine, efavirenz, carbamazepine, dexamethasone and phenytoin decrease caspofungin concentrations. Caspofungin administration reduces the concentration of tacrolimus by 20% [174]. Micafungin can increase sirolimus concentrations by 20% [175]. Pharmacokinetic studies of anidulafungin have shown that there is no need to adjust the dose when administered with other immunosuppressive drugs [176] (see Tables 6 and 7).

Transparency Declaration

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