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Fungal infections following liver transplantation

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Abstract

With increasing morbidity and mortality from chronic liver disease and acute liver failure, the need for liver transplantation is on the rise. Most of these patients are extremely vulnerable to infections as they are immune-compromised and have other chronic co-morbid conditions. Despite the recent advances in practice and improvement in diagnostic surveillance and treatment modalities, a major portion of these patients continue to be affected by post-transplant infections. Of these, fungal infections are particularly notorious given their vague and insidious onset and are very challenging to diagnose. This mini-review aims to discuss the incidence of fungal infections following liver transplantation, the different fungi involved, the risk factors, which predispose these patients to such infections, associated diagnostic challenges, and the role of prophylaxis. The population at risk is increasingly old and frail, suffering from various other co-morbid conditions, and needs special attention. To improve care and to decrease the burden of such infections, we need to identify the at-risk population with more robust clinical and diagnostic parameters. A more robust global consensus and stringent guidelines are needed to fight against resistant microbes and maintain the longevity of current antimicrobial therapies.

Key Words: Invasive fungal infections; Liver transplantation; Candidiasis; Antifungal prophylaxis; Aspergillosis; *Cryptococcus*

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Core Tip: Fungal infections post liver transplant remains the predominant source of morbidity and mortality despite the incidence being low. This is because of evasive clinical features coupled with difficulty to isolate and culture these pathogens. Therefore, appropriate patients are selected for prophylactic regimen based on specific risk factors to curb the rise of drug-resistant species. Traditional regimens include fluconazole or liposomal amphotericin with a shift towards echinocandins based on recently published and promising data.

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INTRODUCTION

Liver transplantation is one of the principal treatment modalities for the treatment of many hepatic diseases, mainly but not limited to chronic and end-stage liver disease. Despite advances in the field of transplantation, invasive fungal infections remain a major source of morbidity and mortality. This is attributed to delay in diagnosis, nonspecific clinical features[1], fastidious nature of these organisms, lack of consensus on prophylactic regimens, and rise of antifungal resistant species.

Moreover, with an increase in the number of grafts being offered, there is a trend towards recipients being older, debilitated, and having more non hepatic comorbidities which contributes to the burden and subsequently leads to a higher rate of fungal infections[2].

In this article, we aim to discuss the incidence and trend of invasive fungal infections (IFI) in liver transplant (LT) patients, associated risk factors, diagnostic challenges, and data on prophylaxis.

IFI DEFINITION

IFIs, according to the Invasive Fungal Infections Cooperative Group in Europe and the Mycoses Study Group in the United States, are divided into 3 categories: proven, probable and possible.

Proven IFI is defined as a positive fungal culture or histological proof of fungal or hyphal elements in a sterile site biopsy. This also includes positive cryptococcal antigen in cerebrospinal fluid.

Probable and possible IFIs have a wider definition and inclusion criteria. This is based on several host factors along with various clinical and mycological criteria[3].

Some studies evaluating prophylactic regimens, in this regard have been a focus of criticism as their IFI's were considered colonization rather than infection[4].

INCIDENCE AND RESPONSIBLE FUNGI

The incidence of IFI after LT has decreased in recent years and this is attributable to advancement and improvement in surgical techniques along with more aggressive post-operative care. Previously, in one study by Fung *et al*[5], the incidence of IFI after LT was reported to be 6.6% with a mortality of 54.5%. The ninety-day cumulative mortality after invasive candidiasis has been reported to be 26% and 1-year survival after invasive aspergillosis is about 59% according to TRANSNET in 2010[6].

More recently, according to some cohort studies, the overall incidence of IFI after solid organ transplant is about 1%-4%[7-9]. 1-year cumulative probability of IFI in LT was 1.8%[7]. This shows a promising trend and is related to improve surgical techniques and timely recognition of risk factors that make certain patients more susceptible to IFIs.

However, in underdeveloped nations, it remains higher at 14.7% with an in-hospital mortality rate of 77% [10]. A future streamlined approach to the problem with specific guidelines might be one of the ways to improve these numbers.

The three major fungi involved are *Candida* spp., *Cryptococcus*, and *Aspergillus* spp. *Candida* predominates with 81% followed by *Aspergillus* (16%) and *Cryptococcus* (3%). Non-*Albicans Candida* accounted for 68% of all *Candida* infections [11]. The rise of resistant non-*Albicans Candida* especially *C. parapsilosis* was felt to coincide with the increased use of fluconazole [11]. *C. parapsilosis* is associated with increased mortality in these patients. This increase in resistant fungal species indicates a dire need for a patient-specific prophylactic regimen based on risk factors *vs* a universal approach.

The distribution of the fungal species remains similar in the East with *Candida* representing 64.1% and *Aspergillus* 35.8% of the IFIs in LT patients.

Despite the highly variable clinical presentation, these pathogens most commonly affect the respiratory system followed by renal and gastrointestinal tract [10]. According to a retrospective study in 2015 by Eschenauer and colleagues, intra-abdominal candidiasis (73%) was the most common IFI [12]. The common clinical manifestations of various fungal organisms are shown in Table 1.

TIMING FROM TRANSPLANT TO INFECTION

There has been a shift in the time duration between the developments of IFIs after LT. It was initially thought to occur in the early post-operative phase most commonly within the first couple of months.

Grauhan *et al* [13] in 1994 reported a median time from LT to IFI of 2 mo.

According to Husain *et al* [14] in 2003, the median time to infection for invasive candidiasis was 13.5 d with 72% of the IFIs happening within the first month after LT.

Aspergillus tends to present later as compared to *Candida*. Results from one study by Singh and colleagues in 2003 reported 55% of their *Aspergillus* IFI occurring after 90 d [15] and Gravalda *et al* [16] also described 43% of their IFIs as late onset *Aspergillus*.

In transplant centers with a higher risk of *Aspergillus* based on epidemiology, this delayed time to presentation is important to consider while deciding on the length of prophylactic regimen in high-risk patients. Moreover, clinicians need to be mindful of this time frame while diagnosing an already difficult-to-diagnose disease.

RISK FACTORS

Multiple factors have been observed over time to be associated with the development of fungal infections in LTs. Identifying patients that are at high risk for developing IFI can be of immense help as that can aide in decreasing the diagnostic delay and assure appropriate prophylaxis. By adopting this targeted method of prophylaxis *vs* universal approach, we can also potentially reduce the incidence of drug-resistant fungi, lower the morbidity due to side effects and interactions of these medications particularly with immunosuppressants, and mitigate the overall cost.

Many scientists over the past few decades have worked on identifying these attributes. These can be categorized into pre-operative, operative, and post-operative factors as shown in Table 2. Risk factors for *Aspergillus* specifically seem to depend more on post-operative factors as highlighted in Figure 1.

Collins *et al* [17] in 1994 identified the following as potential risk factors: renal insufficiency, length of transplant operation, rate of re-transplantation, abdominal or intra-thoracic reoperation, and cytomegalovirus infection.

Other studies showed that model for end-stage liver disease (MELD) scores > 25, post-transplant acute kidney injury (Cr > 2 or risk, injury, failure, loss of kidney function, and end-stage n criteria I- or F-) and pre-transplant fungal colonization seem to be the culprits identified with IFIs [11,18].

One of these was an important and common risk factor of daily prophylactic fluconazole dose of < 200 mg, which was thought to cause a rise in drug-resistant non-*Albicans Candida* spp [11].

Although very rare, a French study also identified contamination during organ procurement as a risk factor with a 1.33% prevalence of *Candida* spp. in preservation fluid. This was associated with a higher rate of IFI and impaired survival [19].

Alongside predictable risk factors like diabetes and hemodialysis dependence, Verma *et al* [10] pointed out prior antibiotic use, cerebral and respiratory organ failures, chronic liver failure (CLIF) organ failure/CLIF-consortium acute-on-chronic liver

Table 1 Common clinical manifestations of invasive fungal infection

	Clinical manifestations
Candida	Intra-abdominal abscesses
	Recurrent cholangitis
	Peritonitis
	Fungemia
Aspergillus	Invasive pulmonary <i>Aspergillosis</i>
	Brain abscess
	Endophthalmitis
	Osteomyelitis
Cryptococcus	Endocarditis
	CNS infection
	Focal lesions on imaging
	Meningeal enhancement

CNS: Central nervous system.

Table 2 Risk factors for invasive fungal infections

	Risk factors
Pre-operative	SBP prophylaxis with fluoroquinolone
Operative	Retransplantation
	Long transplantation time
	Long transplantation time
	Class 2 partial or complete match
Post-operative	Donor from male
	Post-transplant HD
	High number of RBC units transfused
	Post-transplant bacterial infection
	Cytomegalovirus infection
	Use of muromonab-CD3
	Aspergillus antigenemia

SBP: Spontaneous bacterial prophylaxis; HD: Hemodialysis; RBC: Red blood cells.

failure as predictors of IFIs. Non-survivors in their study also had higher levels of 1.3-beta D glucan (BDG) levels. BDG levels have been studied as a diagnostic marker and look promising.

There has been a general shift in the trend of risk factors over the last 2 decades, which is attributable to better surgical techniques. Singh *et al*[20] studied 190 liver transplants during 1990 and 2000 and demonstrated improvement in length of operation, intraoperative transfusion requirements, use of roux-en-Y biliary anastomosis, re-transplantation, rate of rejection over time, and cold ischemic time. This led to a decrease in the incidence of invasive candidiasis in this study population from 9%-1.7% without any use of antifungal prophylaxis.

In 2015, Eschenauer and colleagues identified bile leaks within the first 30 d post-transplant and living donor liver transplants as new independent risk factors for IFIs. This is because *Candida* has an affinity for growth in the biliary tract. Moreover, living donor liver transplants are highly technical procedures that are not commonly

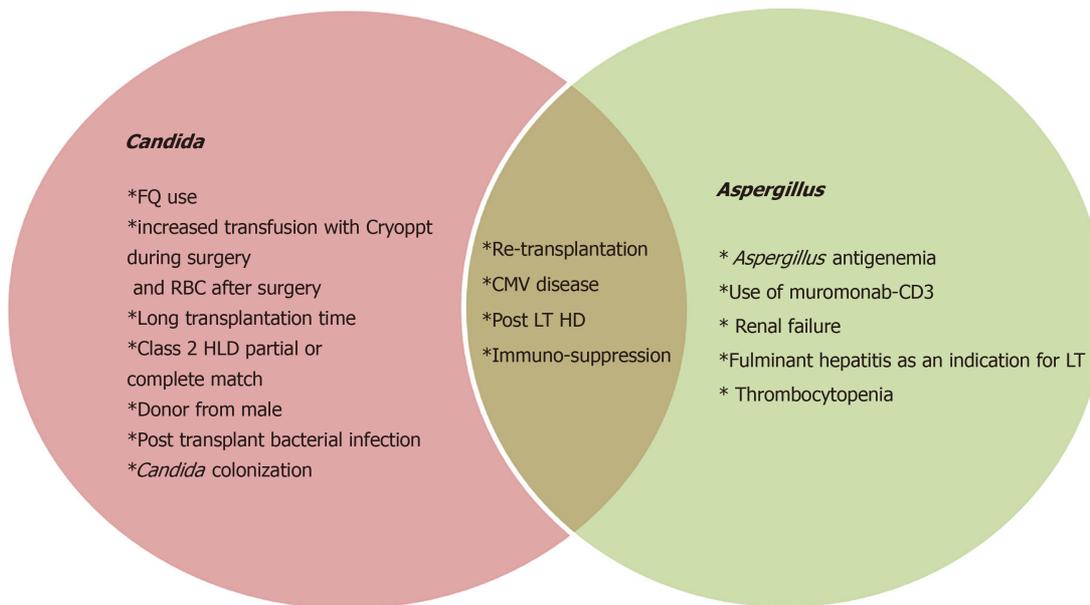


Figure 1 Risk factors for *Candida* and *Aspergillus*. FQ: Fluoroquinolone; HLA: Human leukocyte antigen; CMV: Cytomegalovirus; HD: Hemodialysis; LT: Liver transplant.

performed in the United States. The increased length and complexity of these procedures along with higher disruption of the biliary tract is responsible for these findings. The authors recommended instituting antifungal prophylaxis in all living donor liver transplants[12].

A small study recently in 2020 by Jorgenson *et al*[21] studied the effects of pre-transplant roux-en Y gastric bypass on liver transplant outcomes. There were increased rates of fungal infection in patients with bariatric surgery before transplant and might be associated with loss of defense provided by gastric acid. This study is limited by its retrospective nature and its size.

DIAGNOSTIC CHALLENGES

In general, fungal infections do not present themselves vividly and are increasingly difficult to grow in culture media. It makes it even more challenging in patients who have chronic liver disease, are immunosuppressed, or have other underlying comorbidities. They are difficult to detect clinically and also objectively in laboratories. Hence, prevention becomes essential, and it has significantly improved in the last decade with the advancement in surgical techniques, intense pre-operative evaluation, and appropriate use of antifungal prophylactic agents in high-risk patients.

Distinguishing between colonization and true infection can be challenging for the clinician. Apart from 'proven IFI' as discussed above, the other two categories are vague and have plenty of variable factors. In these clinical scenarios, the use of newer diagnostic tools like BDG and galactomannan (GM) can be helpful. Polymerase chain reaction fungal assays are promising but not yet approved by the Food and Drug Administration.

BDG has been studied and looks promising as a diagnostic marker in serum. In a study from 2017, with 271 transplant patients, weekly BDG was tested and monitored for IFIs. 95% of the patients with IFI had positive BDG and a very promising negative predictive value of 96% was seen. The sensitivity of BDG was 75% and specificity was 65%, making it a very good tool to rule out IFIs[22].

The GM test is an enzyme-linked immunosorbent assay that detects the GM antigen released by *Aspergillus* hyphae when they invade host cells.

The patient's epidemiological risk factors should be considered strongly which would help guide better towards increasing clinical suspicion and ordering appropriate tests and guided treatments. Objective risk factors such as the MELD score, the overall duration of need for total parenteral nutrition, length of the operative procedure, and removal of abdominal drains and other catheters or lines should be evaluated[23].

PROPHYLAXIS

Fungal infections in liver transplant recipients are mostly attributed to *Aspergillus* and *Candida*. Three agents are mainly used in prophylaxis—fluconazole, liposomal amphotericin B, and itraconazole. The studies involving these agents have been confounded by the difficulty of differentiating colonization and a true infection, the variability between patient selection, therapeutic agent(s) used in comparison with placebo or each other, and variable duration of treatment.

Data on the effectiveness of antifungal prophylaxis in LT over the past 10 years have been summarized in the [Table 3](#) below.

There have been three meta-analyses as summarized in [Table 3](#). Playford *et al*[24] and Cruciani *et al*[25] published two in 2006, with 10 and 6 studies respectively. These summarized that universal fungal prophylaxis leads to a reduction in proven IFIs without any mortality benefit. This universal approach leads to a significantly higher proportion of episodes of non-*Albicans Candida* infection.

In 2014, Evans *et al*[26] published a meta-analysis of studies on prophylaxis to prevent IFIs after LT and concluded that the odds of proven IFI and IFI related mortality were lower in patients receiving antifungal prophylaxis, even if the overall mortality did not change. It was also demonstrated that the efficacy of fluconazole compared to liposomal amphotericin was similar with the latter having the benefit of not altering the cytochrome P450 system and therefore not affecting the calci-neurin inhibitor levels. However, fluconazole is favored because of its cost-effectiveness and safety profile. This meta-analysis did not reveal any information on echinocandins, however, it was different from their counterparts in that they did a mixed treatment comparison and was more recent of the few meta-analyses already on the subject matter.

Studies since 2014 (after the last meta-analysis) on prophylaxis are summarized in [Table 4](#).

In 2015, Eschenauer and colleagues performed a retrospective study involving liver transplant patients that were divided into three main groups. Group 1 included 145 patients who received targeted prophylaxis with either voriconazole in 54%, fluconazole in 5% or no antifungal which was the case of 38% of these patients. This was compared to a group of 237 patients, who received universal prophylaxis with voriconazole. These regimens were continued for a median time of 11 d in the targeted group and for 6 d in the universal group, with a significant *P* value. There was no statistical difference between incidence of IFI between both groups (6.8% in targeted and 4.2% in universal). Similarly, the *P* value was not statistically significant for the mortality rates over 100 d from IFIs in both groups (10% for targeted and 7% for universal group). They, therefore concluded that targeted approach to antifungal use in liver transplant patients was a safe, cost effective strategy and prevented unnecessary side effects[12].

With regards to echinocandins, Saliba *et al*[27] in 2015 compared micafungin *vs* standard treatment and found them equally effective. Standard therapy was center-specific and included IV fluconazole, liposomal amphotericin, or IV caspofungin.

Similarly, in a study from Spain in 2016, caspofungin was compared to fluconazole in high-risk patients and similar efficacy was reported to prevent global IFIs. In this study caspofungin was related to decrease in breakthrough IFIs and also led to a lower rate of invasive aspergillosis[28].

Echinocandins should be considered as prophylactic agents, where appropriate, especially in areas of increased prevalence of drug-resistant non-*Albicans Candida*. Unfortunately, these too come with a higher price tag compared to fluconazole which can affect their use, especially in non-affluent countries.

According to the Infectious Disease Society of America guidelines, patients who meet 2 or more of the following risk factors to be considered for prophylaxis: creatinine more than 2 mg/dL, need for re-transplantation, choledochojejunostomy, more than 11 h of operative time, need to transfuse with ≥ 40 units of blood products, evidence of fungal colonization in immediate pre and post-operative days. Suggested duration of antifungal use is 14-21 d.

However, since the current data suggest that the incidence and risk of fungal infection overall in the general liver transplantation population is low, these agents should be utilized for higher-risk patients as unguided use is associated with drug-resistant non-*Albicans Candida* infection and higher mortality in these patients[23].

Table 3 Effectiveness of antifungal prophylaxis in liver transplant

Ref.	Trials	Patients	Regimens	Infection reduction (95%CI)	Comments
Cruciani <i>et al</i> [25], 2006	6	698	AmB <i>vs</i> Pla (1) Flu <i>vs</i> non-systemic AF (1) Flu <i>vs</i> Pla (2) Itra <i>vs</i> Pla(1) Amb-Itra <i>vs</i> Flu-itra <i>vs</i> Pla (1)	Total proven fungal infections RR 0.31 (0.21-0.46), IFI RR 0.33 (0.18-0.59)	Patients receiving prophylaxis had higher number of non- <i>Albicans</i> proven fungal infections. Mostly <i>C. glabrata</i> .
Playford <i>et al</i> [24], 2006	7	793	Flu <i>vs</i> Pla (2) Flu <i>vs</i> non-systemic AF (2) Itra <i>vs</i> Pla (2) AmB <i>vs</i> Pla (1)	Proven IFI RR 0.39 (0.18-0.85), fungal colonization RR 0.51 (0.41-0.62), fungal colonization with <i>C. glabrata</i> / <i>C. krusei</i> , RR 1.57 (0.76-3.24)	Formulated algorithm in which patients with < 2 RF deemed low risk (4% incidence) for IFI and those with ≥ 2 at high risk (25% incidence) for IFI.
Evans <i>et al</i> [26], 2014	14	1633	Flu <i>vs</i> Pla/nonabs AF (4) Itra <i>vs</i> Pla (1) AmB <i>vs</i> Pla (1) 3 arm study with Pla/AmB/Flu (1) Flu <i>vs</i> AmB (3) Liposomal + Flu <i>vs</i> standard AmB + Flu Itra <i>vs</i> Flu (2) Micafungin <i>vs</i> standard care (1) Clo <i>vs</i> Nys (1)	Proven IFI OR 0.37 (0.19-0.72), <i>P</i> = 0.003, Bayesian MTC, AmB <i>vs</i> Pla OR 0.21 (0.05-0.71), Flu <i>vs</i> Pla OR 0.21 (0.06-0.57)	Benefit of AmB is of similar magnitude to that previously described for fluconazole.

AmB: Amphotericin-B; Pla: Placebo; Flu: Fluconazole; AF: Antifungal; Itra: Itraconazole; Nonabs AF: Nonabsorbable antifungal; Nys: Nystatin; Clo: Clotrimazole.

CONCLUSION

Fungal infections following liver transplantation remain an influential cause of morbidity and mortality in these patients, despite the low incidence. Identification of high-risk patients based on risk factors discussed above and starting an appropriate prophylactic antifungal regimen based on epidemiology, calcineurin inhibitor use, and renal function is the first step in avoiding dealing with this evasive disease.

Prophylactic antifungals are generally well tolerated but can lead to drug-resistant *Candida* spp., hence the importance of selecting the appropriate patient and agent. Using BDG as a negative predictive tool and having a high degree of suspicion, even if the time from transplant exceeds 2 mo, can prevent diagnostic delays.

Further randomized controlled trials comparing azoles, amphotericin, and echinocandins are needed to develop an updated standard of care.

Table 4 Studies since 2014 (after the last meta-analysis) on prophylaxis for liver transplant

Ref.	Design	Regimen	Outcomes
Antunes <i>et al</i> [29], 2014	Single center. Retrospective (<i>n</i> = 461)	High risk group: AmB <i>vs</i> nystatin; Low risk group: nystatin	Higher IFI in high risk patients who did not receive AmB
Winston <i>et al</i> [30], 2014	Randomized, double-blind. 2010-2011 (<i>n</i> = 200)	Group 1: Andulafugin; Group 2: Flu	1:1 randomized. Similar cumulative IFI occurrence and equal 3 mo mortality
Saliba <i>et al</i> [27], 2015	Randomized, open label. 2009-2012 (<i>n</i> = 347)	Micafungin <i>vs</i> center specific standard care (Flu/AmB/Caspo)	Micafungin was non-inferior to standard of care
Giannella <i>et al</i> [31], 2015	Prospective, non-randomized. 2009-2013. Safety of high dose AmB (<i>n</i> = 76)	Amb 10 mg/kg Q weekly until hospital discharge for a minimum of 2 wk	10 patients discontinued therapy. (6 for AmB related AEs and 4 for IFI)
Eschenauer <i>et al</i> [12], 2015	Single center study. 2008-2012. Effectiveness of targeted prophylaxis (<i>n</i> = 381)	Universal ppx: Vori. Targeted: Group1: Vori, 30 d. Group 2: Flu during icu sta. Group3: No ppx	Cumulative IFI occurrence 5.2% (targeted <i>vs</i> universal group). Similar 100 day mortality between targeted and universal ppx gp. 40% breakthrough IFI
Balogh <i>et al</i> [32], 2016	Single center study. 2008-2014 (<i>n</i> = 314)	Voriconazole <i>vs</i> oral nystatin or Flu	No episodes of IA occurred. No difference in graft and patient survival curves between the two groups
Perrella <i>et al</i> [33], 2016	Single center study. 2006-2012. Comparative observational study for targeted prophylaxis (<i>n</i> = 54)	Group 1: AmB 3 mg/kg/day; Group2: Caspofungin 70 mg loading→50 mg/day	No episodes of IFI in both groups
Fortún <i>et al</i> [28], 2016	Multicenter. 2005-2012. Comparative observational study for targeted prophylaxis (<i>n</i> = 195)	Group 1: Caspofungin 50 mg/d; Group 2: Flu median 200 mg/day	Similar 6 m IFI occurrence [5.2% b (G1) <i>vs</i> 12.2% (G2)]. Reduced risk of IA in LT receiving caspofungin. Similar overall mortality
Chen <i>et al</i> [34], 2016	Single center study. 2005-2014. Effectiveness of targeted prophylaxis (<i>n</i> = 402)	Group 1: Anidulafungin 100 mg/day or micafungin 100 mg/day; Group 2: No prophylaxis	High risk patients MELD > 20; Similar IFI occurrence lower cumulative mortality in group 1 (<i>P</i> = 0.001)
Giannella <i>et al</i> [35], 2016	Retrospective, single center. 2010-2014. Evaluation of RF for a targeted prophylaxis (<i>n</i> = 303)	Group 1: No RF. No prophylaxis; Group 2: 1RF IC, Flu; Group3: High risk, anti mould agent	Antifungal prophylaxis administered to 45.9% patients. Cumulative IFI prevalence 6.3%. Flu independently associated with IFI development
Lavezzo <i>et al</i> [36], 2018	Single center study. 2011-2015. Effectiveness of targeted prophylaxis	Group 1 high risk: AmB; Group 2 low risk: No prophylaxis	Overall IFI prevalence 2.8%. 1 yr mortality higher in prophylaxis group (<i>P</i> = 0.001). 1 yr mortality higher in IFI patients (<i>P</i> < 0.001)
Jorgenson <i>et al</i> [37], 2019	Single center study. 2009-2016. Effectiveness of fixed dose prophylaxis (<i>n</i> = 189)	Group 1: Flu 400 mg/day for 14 d for high risk patients; Group 2: unsupervised antifungal protocols	Reduction in 1 yr IFI among high risk group (12.5% <i>vs</i> 26.6%). Similar 1 yr patient and graft survival
Kang <i>et al</i> [38], 2020	Multicenter, randomized, open label. Living donor LT. 2012-2015 (<i>n</i> = 144)	Group 1: Micafungin 100 mg/d; Group 2: Flu 100-200 mg/day	Group 1 <i>vs</i> Group 2: 69 <i>vs</i> 75 pts. IFI occurrence in 3 wk: 1/69 <i>vs</i> 0/75. Micafungin was noninferior to Flu

AmB: Amphotericin-b; Flu: Fluconazole; Caspo: Caspofungin; AE: Adverse effects; Vori: Voriconazole; ppx: Prophylaxis; gp: Group; IA: Invasive aspergillosis; IC: Invasive candidiasis.

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