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Review

Evolution in the Management of Invasive Fungal Infections in Liver Transplant Recipients

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Abstract:

Invasive fungal infections (IFI) remain an important cause of morbidity and mortality, especially in hospitalized and immunocompromised or critically ill patients. The incidence of IFIs has been declining in liver transplant recipients (LTR). This is likely due to the evolving immunosuppressive drug regimens, improved surgical techniques and targeted antifungal prophylaxis. However, IFI still contribute to high mortality and are associated with high economic burden due to consumption of costly newer antifungal agents, longer hospital stay and need of intensive supportive care. *Candida* remains the most common fungal infection in LTR. Antifungal prophylaxis in LTR at high risk of developing IFI is widely agreed on, but there is no universal consensus on treatment selection and duration. Fluconazole and

echinocandins are recommended for prophylaxis, but is increasingly associated with resistance. Risk factors for invasive candidiasis (IC) and invasive aspergillosis (IA) continue to evolve, and thus strategies for their prevention should be constantly updated and targeted. What is clear, however, is that antifungal prophylactic strategy should be selected by the transplant centre based on risk factors for IFIs in their patients, local epidemiology, the sensitivity profile of local fungal pathogens, and drug costs. The treatment with echinocandin is recommended for IC, although the risk of breakthrough infections for intra-abdominal candida infections should be recognised. The recommended treatment for IA is voriconazole. Although many non-culture methods are available for the diagnosis of IFI, there is a need for further evaluation of these tests in LTR and antifungal stewardship (AFS).

Keywords
Invasive fungal infections; liver transplant recipients; antifungal prophylaxis; candidiasis; aspergillosis

1. Introduction

Invasive fungal infections (IFI) remain a major cause of morbidity and mortality in immunocompromised patients. The incidence of IFI is increasing. This is directly related to the increasing population of immunocompromised patients. Patients with cancer on chemotherapy and/or bone marrow transplantation, solid organ transplant recipients, critically ill patients in intensive care units, and very low birth weight neonates are at high risk of getting IFI [1-5]. Liver transplantation (LT) has become a life-saving therapeutic option for many patients with end-stage liver disease and with liver failure. A high mortality rate due to infections during the first post-transplant year persists. The incidence of IFI in LTR has declined over the years, which can be explained by advances in surgical techniques, evolving immunosuppressive therapies and an expanded armamentarium of antifungals [1-7]. The *Candida* species remains the most common cause of fungal infections (FI) in LTR [7-9]. With increasing use of prophylactic and empiric antifungal therapy, there are epidemiologic shifts towards more non-*Candida albicans* species and infections due to mold spp. These are associated with high morbidity and mortality [4, 10-15]. Emerging fungal pathogens, such as *Aspergillus*, *Fusarium* and *Zygomycetes*, are changing the clinical spectrum of fungal diagnosis. Numerous risk factors have been identified which are associated with IFI in LTR [14-33]. In this review, we will discuss the evolving epidemiology, diagnostic challenges, antifungal treatment strategies and resistance, role of antifungal stewardship and risk factors associated with IFI in LTR.

2. Incidence and Epidemiology of Invasive Fungal Infection in Liver Transplant Recipients

LTRs have a higher rate of IFI in comparison to other solid organ transplant recipients (SOTR) [1-7]. The overall incidence of FI in LTR varies from centre to centre because of variability in associated risk factors [7, 8]. Although IFI in LTR has declined over the years from 42% to 5-15% in the 21st century, overall mortality rate remains high [1, 2, 9-12, 18, 34]. The declining trend could be explained by the evolving immunosuppressive drug regimens, improvement in surgical

techniques, targeted antifungal prophylaxis and improved diagnostic methods. The risk of IFI is highest in the immediate post-operative period, and 72% of infections occur within the first 30 days post-transplant [2, 3, 35]. *Candida* species accounts for more than 70% of IFIs, followed by the *Aspergillus* species (2-11%). Other rare fungal species such as *Cryptococcus neoformans*, the non-*Aspergillus*filamentous species and the endemic mycosis agents such as histoplasmosis, coccidioidomycosis and blastomycosis have variable incidence depending on the geographic origin of the patient [2, 16, 36, 37]. In 2 multicentre studies, the incidence of invasive candidiasis (IC) was reported to be as high as 68-78%, while the incidence of invasive aspergillosis (IA) and cryptococcosis varied from 8-11% and from 6-7.1%, respectively [2,3]. The incidence of candidemia among SOTR ranges between 2% and 8%, and the overall mortality can be as high as 77% [4, 38, 39]. In a multicentre analysis of IC in LTR, candidemia was found to be an independent risk factor for mortality [40]. Although there are over 160 species of *Candida,* only a few species are recognized to cause disease in humans. In LTR, a study in pediatric patients and meta-analysis data in adult patients showed that *C. albicans* infections account for the majority of fungal infections [9, 12, 18, 40]. More recently, larger multicentre studies of IFI in LTR have revealed a shift in *Candida* epidemiology [2, 3]. Among non-*albicans Candida* spp., *C. glabrata* was the second most common species, followed by *C. krusei, C. parapsilosis* and *C. tropicalis.* The clinical manifestation of IC may be divided into two different categories: candidemia without organ involvement and disseminated candidiasis. Deep organ infections due to *Candida* spp. are generally observed as part of the disseminated candidiasis syndromes, which may be associated with either single- or multi-organ involvement.

IA is the second most common FI in LTR, and associated mortality approaches 100% if untreated [6, 28, 41-43]. The most common infectious *Aspergillus* species are *Aspergillus fumigatus* (73%), *Aspergillus flavus* (14%) and *Aspergillus terreus* (8%) [6]. Although most IFIs occur within 90 days after transplantation [24, 41], more emerging data is showing a shift towards late-onset IA in LTR. The studies by Singh et al, Nagao et al and a study from Spain reported that >40% of patients had late-onset IA [4, 27, 44]. Rabkin et al found IFIs in their patients in the first 120 days following LT [13]. This shift in timing has important implications on choice and timing of antifungal agents to prevent IFI. The precise reasons for the later occurrence of IA in LTR are unclear. Cytomegalovirus (CMV) infection in LTR, which is one of the risk factors for IA, is occurring later in the present era of ganciclovir prophylaxis. This likely accounts for the later occurrence of opportunistic infections. IA in LTR are uniquely predisposed to dissemination of infection beyond the lungs, with >55% of patients having extrapulmonary manifestations. However, the clinical manifestations of IFIs can be non-specific because of immunosuppression and antifungal prophylaxis [45].

3. Risk Factors for Invasive Fungal Infections

The predisposition of IFI in LTR is influenced by the host factors, environment and fungal factors. Host factors include underlying disease and immunosuppressive agents. These agents target different sites in the T cell activation cascade, usually by inhibiting T cell activation or via T cell depletion. The risk of infection after LT is strongly influenced by the net state of immunosuppression [46]. The identification of risk factors for the LTR is very important in order to stratify the antifungal prophylaxis. Among SOTR, the risk factors for LTR are very well described.

Risk factors for IC and IA in LTR are included in Table 1 [14, 16-33]. In the last two decades, multiple pre-, peri- and post-operative risk factors for IFI in LT have been identified [14, 16-33, 47]. Important pre-operative risk factors include severity of liver disease before transplantation, which today would equate to a high MELD score [14, 31, 33] and pre-transplantation or early post-transplantation fungal colonisation [9, 17-20]. Intraoperative risk factors are commonly markers of complex surgeries with long environmental exposure or spillage of intestinal contents, which are frequently colonized with *Candida*. These risk factors include high intraoperative transfusion requirements [14, 19, 20, 25, 31] and biliary complications such as hepatic artery thrombosis, bile leaks or choledochojejunostomy [19, 20, 31, 47]. Similarly, repeated surgical interventions will increase the patients' risk [19, 21-24]. Post-operatively, renal failure and dialysis [21-25] as well as CMV infection [20, 23, 26] are associated with IFI. In clinical practice, risk factors have to be organised to classify patients into specific risk groups. Such an effort has been made by Giannella et al to divide patients into a low-risk group, an intermediate-risk group or a high-risk group [48]. Based on that, patients were administered no prophylaxis, fluconazole prophylaxis or anti-mold prophylaxis according to risk groups and patient-specific features [48].

There are donor-related risk factors for *Candida* infection. *Candida* may contaminate the organ while the donor is still alive, or during the procurement, processing and transplantation processes. Organ preservation fluid may become contaminated with *Candida* species and serve as a conduit for transmission [49-52]. Avoiding the use of organs from patients with active candidiasis, and routinely monitoring the culture of preservation media are important preventative strategies [49-52].

Table 1 Risk factors associated with invasive fungal infections in liver transplant recipients

Risk factors for invasive candidiasis	**Risk factors for invasive aspergillosis**
High MELD score>30, fulminant hepatic failure, antibiotics for spontaneous bacterial peritonitis	Preoperative steroid use
Prolonged and complicated surgery or choledochojejunostomy, requirement of high blood products volumes during surgery	Renal failure requiring haemodialysis after transplant
Donor vessels or organ contaminated with *Candida* spp.	Retransplantation
Multifocal fungal colonization, retransplantation	Presence of *Aspergillus* antigenemia
Renal failure requiring dialysis after transplant	Building works in close vicinity of transplant centre
Bacterial infection, cytomegalovirus infection	Cytomegalovirus infection
High transfusion requirements	Human herpesvirus 6 infection
Biliary complications, hepatic artery thrombosis	Neutropenia
Prolonged ICU stay or prolonged broad-spectrum antibiotics use	

For a targeted antifungal approach in high-risk patients, there should be an analysis of risk factors for different pathogens to ensure optimal coverage [48]. This is especially important as fluconazole shows poor effectiveness for IA [53]. Efforts have been made to identify mold infection-specific risk factors to enable targeted therapy with appropriate antifungals. Studies implicate pre-operative steroid use [15, 27, 30], post-operative renal failure requiring haemodialysis [29, 30, 32, 53], CMV infection [30, 32] as well as retransplantation and reoperation [27-30] as independent risk factors for IA. These risk factors should be taken into consideration when selecting treatment and prophylaxis strategies.

4. Diagnosis of Invasive Fungal Infection

The management of IFI in LTR is hampered by the lack of early diagnostic methods. Traditionally, diagnosis of IFI is based on clinical signs and symptoms, isolation of fungal pathogens from blood cultures, sterile body fluid samples and positive fungal hyphae in biopsy of suspected lesion [54-55]. The current diagnostic methods for fungal infections lack sensitivity and specificity. Survival of patients from these infections depends on early diagnosis. The conventional laboratory methods of culture are often unable to diagnose the infection in its early stages. Having reliable diagnostic tests not only allows early treatment to be targeted, but is cost–effective too. In a few studies, it has been determined that mortality and hospitalization costs increase significantly for each day without appropriate antifungal agents [56-59]. The initiation of antifungal treatment 12 hour after the first positive blood culture sample constitutes an independent determinant of hospital mortality in immunocompromised LTRs [57].

Blood cultures remain the gold standard for the diagnosis of candidemia and should be the initial diagnostic test. Antifungal prophylaxis or empiric therapy may further reduce the sensitivity of blood cultures [60]. The yield of positive blood culture can be optimized by sending adequate volumes of blood and by doing multiple sets. These tests are inexpensive, but the turnaround time for species identification and sensitivity can be longer, which may delay appropriate antifungal treatment.

Alternative non-culture methods in the form of fungal biomarkers and metabolites have been established [61]. Biomarker assays have focused on antigens or nucleic-acid detection methods that are positive in patients with invasive fungal infections. Many serological methods have been evaluated for the diagnosis of fungal infections, and the results of these tests are more rapidly available than those of culture. In some of these infections, such as cryptococcosis and histoplasmosis, the detection of antigen as a marker of invasive infection has become a standard for diagnosis and can also be important in the management of infection. Detection of cryptococcal polysaccharide antigen in CSF and serum by latex agglutination test is routinely done. The test is sensitive, specific and simple to perform. Although the detection of fungal cell wall markers in serum has been widely reported for 1, 3-beta-D-glucan (BDG) and galactomannan (GM) in many studies, the utility data for these biomarkers in LTR remains scarce [54]. BDG is a carbohydrate component of the fungal cell wall and is found in several important fungal genera including *Candida, P. jiroveci* and *Aspergillus.* However, *Mucorales*, *C. neoformans* and *Blastomyces dermatitidis* contain relatively small amounts of cell wall BDG; therefore, these assays may not be completely reliable in patients infected with these organisms. In a meta-analysis of 16 studies involving 594 IFIs, the pooled sensitivity of the BDG test was 77% and the specificity 85% [62, 63].

The BDG test was also included in the EORTC/MSG (European Organisation for Research and Treatment of Cancer/ Mycosis Study Group) diagnostic criteria for IFI in 2008 for all types of patients [54]. The limitations of this approach are its lack of specificity for candidiasis detection, and the false-positive results 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 containing glucans [64-67]. In a cohort of LTR, Levesque et al demonstrated that the high negative predictive value (NPV) of BDG was useful to differentiate *Candida* colonization from IC among high-risk patients [68]. In contrast, Singh et al demonstrated that the GM and BDG tests had limited accuracy for the diagnosis of IFIs in high-risk LTR [69]. Akamatsu et al reported that for pre-emptive treatment of FI based on plasma BDG levels after LT, the sensitivity and specificity of BDG for overall IFI was 58% and 83%, respectively, with a positive predictive value (PPV) of 35% and NPV of 93% [70]. Serial measurements of 1, 3-beta-D- glucan, correlate with outcome but positive results should be interpreted in conjunction with other clinical indicators of infection.

Galactomannan is another most commonly used biomarker. It is an antigen released from *Aspergillus* hyphae upon host tissue invasion and it is relatively specific for *Aspergillus* species. It can be detected in urine, bronchoalveolar lavage fluid (BAL), cerebrospinal fluid and other specimens with enzyme immunoassay [61]. Detection of GM antigen in BAL is more useful because of its very high specificity (>90%) and sensitivity (100%) for the diagnosis of IA. It should be performed whenever possible [71]. One Spanish study found that the sensitivity of GM is 56% for the diagnosis of IA in LTR [72]. However, its sensitivity varies from 30-100%, and similarly wide-ranging specificities from 38–98% have been reported [73-76]. In a meta-analysis of 50 studies involving 5660 patients (of whom 586 were immunocompromised individuals with proven or probable IA), specificity increases from 82% to 91% for the cut-off values of GM at 0.5 and 1.5 respectively [75]. Factors that limit the specificity of this test are immune reactivity with other fungi such as *Penicillium* spp., previous antifungal treatment, and false positive results with antibacterial agents such as beta-lactam antibiotics, particularly piperacillin–tazobactam, amoxycillin, and dietary GM in pasta, cereals and milk [77-80]. The GM detection is also affected by host immune response, with its sensitivity lowered in patients on steroids compared to neutropenic patients [81]. The diagnosis of IA is always difficult in LTR because of its extrapulmonary manifestation and antifungal prophylaxis. If invasive pulmonary aspergillosis is suspected, a high-resolution chest CT is recommended because its sensitivity is higher than chest radiography. Radiological criteria for diagnosis of IA include halo sign, nodular and cavitating lesion, infiltrate or consolidation. In the case of cerebral lesions, urgent or early biopsy should be considered. In general, newer diagnostic assays with high NPV, including BDG or GM assays, should be integrated into clinical decision algorithms to rule out infection and decrease empirical antifungal therapy in high-risk patients with other radiologic or microbiologic signs of IFI.

In LTR, the molecular tests for detection of IFI are less promising for routine diagnosis. PCR-based methods have been developed for the detection of *Candida* spp. and *Aspergillus* spp. in clinical samples [82, 83]. A meta-analysis study of 963 patients of IC reported 95% sensitivity for PCR-based techniques [84]. In a prospective study in which 20% of patients were transplant recipients, the sensitivity and specificity of PCR for the diagnosis of IC were 80% and 70%, respectively [82]. The lack of consensus over specimen type, extraction technique, PCR methodology and interpretation of results has limited the impact of molecular diagnosis [54]. For

PCR to be included in future consensus criteria, there is a need for multi-centre clinical evaluation using a standard protocol. As the diagnosis of infection based on molecular and serologic techniques has evolved over the past decade, this can provide powerful tools for the early diagnosis of IFI in immunosuppressed population.

5. Prevention of Invasive Fungal Infection

The two key strategies for prevention of IFI are antifungal prophylaxis and environmental control of some filamentous fungi and some *Candida* spp., especially for a new emerging multidrug-resistant fungal pathogen *Candida auris.* The latter has a unique ability of skin colonisation and environmental persistence among other *Candida* spp. [85].

5.1 Antifungal Prophylaxis

The most effective preventive strategy for LTR is antifungal prophylaxis. Choice of antifungal prophylaxis should take into account its efficacy, safety, side effects and drug interactions with immunosuppressive agents. Table 2 shows the studies on use of antifungal prophylaxis in LTR. The main issue with antifungal prophylaxis is the lack of universal consensus on choice of antifungals, its duration, and type of antifungal prophylaxis. This has been demonstrated in surveys of transplant centres from Europe and North America. In a European survey of 60 transplant centres, Vandecasteele et al reported that universal antifungal prophylaxis was administered in 35% of centres, while 53% applied prophylaxis in high-risk patients and 12% applied no prophylaxis. Fluconazole is the most commonly administered prophylactic agent [86]. In a similar survey of 67 active liver transplant programs in North America, >90% of centres used antifungal prophylaxis, and most centres (72%) used targeted prophylaxis. The most common antifungal agent used was fluconazole (86%) at variable doses and duration. For mold infections, the most common agent used was echinocandin [87]. These data reflect the variability in the use of antifungal prophylaxis strategies for LTR. The use of universal prophylaxis was primarily directed towards *Candida*, however targeted prophylaxis was also directed towards *Aspergillus.*

Presently, even though risk-specific prophylaxis is a widely accepted practice, there are no clear guidelines on risk stratification [88]. Retrospective and prospective studies indicate that LTR with two or more risk factors are at substantially higher risk for IFI. Since Winston et al first proved the efficacy of fluconazole as prophylaxis for IFI in LTR in 1999 [89], multiple metaanalysis studies have confirmed these results. Antifungal prophylaxis was proven to decrease the incidence of IFI, and of IFI-related deaths. However, it did not show any impact on overall mortality [10-12, 90]. The incidence of IFI (0-4%) in low-risk LTR is too low to warrant systemic prophylaxis [19, 29, 91- 95]. A targeted approach is efficient because it not only reduces IFI, but also reduces the risk of resistance and cost for the healthcare provider [48, 90, 96, 97]. There is no universal consensus on the antifungal choice, doses and duration for prophylaxis in LTR [Table 2]. The various antifungals used for prophylaxis are fluconazole, echinocandins and liposomal amphotericin B (LAmpB) [22, 48, 53, 89, 96, 98-105]. Fluconazole has been most widely used for prophylaxis in LTR. As a result, there is an epidemiological shift from *Candida albicans* to more non-*albicans Candida* species, which include *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei* [106-109] and fluconazole-

resistant strains [110]. While antifungal resistance among *C. albicans* isolates remains low [107], *C. krusei* is always resistant to fluconazole and *C. glabrata* may emerge as breakthrough infection resistant to all triazoles [108, 109]. Several reports of acquired resistance in *C. glabrata* isolates highlight concern over this species because of a broad emergence of co-resistance over time to both azoles and echinocandins [111-113]. Prior echinocandin exposure is the key risk factor for fluconazole mutation, followed by duration of exposure.

Drug interactions between azoles and calcineurin inhibitors (CNI) pose another challenge. Due to genetic variation, the metabolism of azoles by CYP3A4 protein results in variable serum levels. Azoles and CNIs are mutual potentiators. Azoles often inhibit CYP3A4 which degrades most CNIs, while CNIs act on the transport protein, P-glycoprotein. Such interactions concern all triazoles, and can result in hepato- or nephrotoxicity. Consequently, drug levels as well as liver and kidney function tests need to be closely monitored. Fluconazole interactions are dose-dependant and predictable, and can thus be avoided [114]. Nevertheless, the use of fluconazole remains very common, [86] and a meta-analysis of studies by Evans et al confirmed its effectiveness to be equivalent to that of amphotericin B (AmpB) [11]. Alternative azoles such as voriconazole and itraconazole are being studied, and have applications in specific situations [104]. Itraconazole is recommended for treatment of IA [115], however its prophylactic value has been shown to be inferior to that of fluconazole and LAmpB in a meta-analysis [11]. Voriconazole shows a particularly high variation in serum levels, both between and within patients. Thus, drug levels have to be closely monitored [116]. A recent meta-analysis of studies has found that the tolerability of voriconazole was slightly inferior, and the risk of neurotoxicity and visual toxicity were higher than those of alternative drugs. Only the risk of nephrotoxicity proved to be lower than that of alternatives [117]. Hence, voriconazole should be used as prophylaxis for LTR at high risk for IA. Balogh et al reported that the cost of voriconazole prophylaxis equals to only around 5% of the cost of a single episode of IA [53]. Prophylaxis using AmpB variants is another widely accepted practice. AmpB was shown to prevent IC as well as IA in 1995 by Tollemar et al. They also found that prophylaxis costs 5000 USD less than treating proven FI in placebo patients [105]. A meta-analysis in 2014 found that LAmpB showed equal efficacy to fluconazole for IC and better outcomes for prevention of IA [48].

Echinocandins including micafungin, caspofungin and anidulafungin have been evaluated in fewer studies over the past few years. All three have repeatedly shown to be very efficacious, non-inferior alternatives for antifungal prophylaxis [Table 2]. Echinocandins are intriguing because they show a very low risk profile, especially in terms of nephrotoxicity and hepatotoxicity [98,102,118,119]. They are recommended for treatment of IA [115], and may show beneficial results in preventing incidence of IA and fluconazole-resistant *Candida* spp. [98,101,119,120]. Although the need for antifungal prophylaxis in LTR at high risk of developing IFI is widely agreed on, there is no universal consensus on treatment selection. What is clear however, is that an antifungal prophylactic strategy should be selected by the transplant center based on risk factors for IFI in their patients, local epidemiology, sensitivity profile of local fungal pathogens, and drug costs.

Table 2 Antifungal prophylaxis studies and outcome data.

Study author/year /ref no	**Study design**	**Antifungal prophylaxis type**	**Total no of LTR / n Antifungal/dose/ duration**	**IFI incidence**	**Mortality**	**Comments**
Balogh et al 2016 [53]	Retrospective	MELD score >25 or 2+ high-risk factors	314 LTR 174 LTR voriconazole BD PO vs 140 LTR fluconazole or nystatin	0% of IA in high-risk patients	6% vs 10% at 365 days, no conversion to alternate therapy required	Voriconazole prophylaxis is safe, clinically effective and cost-effective in high-risk LTR.
Giannella et al 2016 [48]	Retrospective cohort study	Targeted; 1 RF for IC vs 1 RF for IA / 2+ RF for IC	303 LTR 41 LTR fluconazole 400mg/d vs 80 LTR LAmpB 10mg/kg weekly for median length of 14 days and 18 LTR caspofungin 50mg/d	Total incidence of IFI 6.3%; 22% vs 6.1%	All-cause mortality at 100 days: With IFI 53.6%, Without IFI 9.5%	Targeted approach based on number and type of RF is superior to universal fluconazole prophylaxis.
Fortun et al 2016 [98]	Multicentre retrospective	Targeted	195 LTR 97 LTR caspofungin 50mg/d , 22 days vs 98 LTR fluconazole 200mg/d 24 days	IFI 6% vs 12.2%	Overall mortality 19.5%; 23.7% vs 16.3%; IFI attributable 7.5%	Prophylactic antifungal regimen to high-risk patients might reduce the incidence of IFI and prevent FI related mortality.
Perrella et al 2015 [99]	Randomized controlled trial	Targeted 3+ RF	54 LTR 28 LTR LAmpB 3mg/kg/d vs 26 caspofungin; LD 70mg/d; MD 50mg/d	IFI 0% vs higher rate in oral candidiasis	2 patients died vs 3 but no deaths secondary to IFI	Both treatments show comparable results in terms of prevention of IFI. LAmpB prophylaxis may reduce bacterial infectious episodes, ICU stay and improve IL-10 environment.
Eschenauer et 2014 [96]	Retrospective	Targeted vs universal	145 LTR; voriconazole 200mg BD, PO 30 days (54%), fluconazole 400mg/d PO post-transplant ICU stay (8%), no	IFI 6.9% vs 4.2% (p= 0.34)	10% vs 7% (p=0.26) IFI attributable 10%	Targeted antifungal prophylaxis in LTR was safe, effective and reduced the number of patients exposed to antifungals.

			antifungal (38%) vs 237 LTR universal voriconazole 200mg BD post-transplant ICU stay			
Saliba et al 2014 [100]	Multi-center, randomized, parallel-group, open-label non-inferiority study	LTR at high risk for IFI with 1+ RF	344 LTR 172 LTR micafungin IV 100mg vs 172 LTR standard care: IV fluconazole 200-400mg/d or IV LAmpB 1-3mg/kg/d or caspofungin 50mg/d 21 days, or until hospital discharge	Clinical success 96.5% vs 93.6%	Mortality 16.8% vs 13.4%; 1 death each, possibly attributable to treatment	Micafungin was non-inferior to standard care. Adverse event profiles and liver function were similar, although kidney function was better with micafungin.
Winston et al 2014 [101]	Randomized, double-blind trial	LTR at high risk for IFI with 1+ RF	197 LTR 99 LTR IV fluconazole 400mg/d (creatinine clearance <50ml/min 200mg/d; 400mg/d only on dialysis days) vs IV anidulafungin 100mg/d; Median duration of prophylaxis 21 days	IFI in 8.0%; IA 2% vs 5.1%; IA 0%	Mortality 12% in each group; Breakthrough IFI 5% vs 2%	In LTR at high risk of IFI, anidulafungin and fluconazole have similar efficacy and are both well-tolerated. Anidulafungin may be beneficial in patients at high risk for IA or have received fluconazole prior to transplantation
Sun et al 2013 [102]	Sequential cohort study	Targeted	276 LTR 42/276 LTR 24 LAmpB 5mg/kg median duration 27 days vs 18 micafungin 100mg/d median duration 20 days	IFI within 90 days 8.3% vs 11%	Mortality 29.2% vs 22.2%; Breakthrough IFI 0% vs 4.9%	Targeted prophylaxis in high-risk LTR with micafungin or amphotericin B lipid complex was equally effective in reducing the risk of IFI. Micafungin incurred less cost, had lower rates of early nephrotoxicity and added no risk of hepatic dysfunction.
Reed et al 2007 [103]	Retrospective review	LTR at high risk for IFI with 1+ RF	232 LTR 58 LTR (22/58) AmpB 1mg/kg/d + (36/58) LAmpB	FI 5.17% vs 16.09%	-	*Due to 4-fold higher risk of fungal infection, prophylaxis offered an estimated cost

			5mg/kg/d for 5 days vs 174 LTR no prophylaxis			reduction of 8.73% in high-risk LTR.
Fortun et al 2003 [22]	Sequential cohort analysis	Universal	280 LTR 131 LTR historical group universal fluconazole prophylaxis vs 149 LTR on LAmpB 10-15 days	IFI in 17% & IA in 10% vs IFI in 6% & IA in 4%	Mo rtality at 12 months 18% vs 10%	Pre-emptive LAmpB prophylaxis is a protective factor in the development of IFI in patients with >4 RF (OR 0.1 (CI 0.02-0.8)). It is effective for prevention of IA.
Winston et al 2002 [104]	Randomized controlled trial	LTR	188 LTR 97 itraconazole solution 200mg/12h vs 91 LTR fluconazole 400mg/d PO or IV; both for 10 weeks post-transplant	Proven IFI in 7% vs 3%	Mortality 0.5% of total population	Oral itraconazole solution 200mg/12hours has adequate bioavailability for effective antifungal prophylaxis. It decreases fungal colonization and is associated with low incidence of IFI. It is well-tolerated and has no significant hepatotoxicity.
Winston et al 1999 [89]	Randomized, double blind, placebo-controlled trial	LTR	212 LTR 108 LTR placebo vs 104 LTR fluconazole 400mg OD for 10 weeks post-transplant	IFI in 23% vs 6%, fungal colonisation increased from 60 to 90% vs decreased from 70 to 28%	14% with 13% attributable to FI vs 11% with 2% attributable to FI	Prophylactic treatment is related to lower IFI and fungal colonization rates and did not show any hepatotoxicity. However, overall survival could not be improved.
Tollemar et al 1995 [105]	Randomized, placebo-controlled study	LTR	77 LTR 40 LAmpB 1mg/kg/d vs 37 placebo; for 5 days each	IFI: 0% vs 16% of which IA 2.5%	Survival at 30 days 92% for Ambisome vs 94% placebo	Low-dose LAmpB prophylaxis was effective and generally well-tolerated. *Prophylaxis with LAmpB was 5000 USD less expensive than treatment of proven IFI among placebo patients.
IC, invasive candidiasis; IFI, Invasive fungal infection; LTR, Liver transplant recipients; RF, Risk factor; AmpB, Amphotericin B; LAmpB, Liposomal amphotericin B						

5.2 Emerging Antifungal Resistance

Most antifungal resistance are due to mutations. The drivers of resistance include the prolonged use of antifungals, subtherapeutic drug levels at sites of infection or colonization, and suboptimal infection control during outbreaks. Diagnosis of antifungal-resistant *Candida* infections is critical to the successful management of patients with these infections. Antifungal resistance in *Candida* spp. represents a rising problem, even though it varies widely across different countries and species. The overall rate of fluconazole resistance is approximately 5% in *C. albicans* [40]. Studies in LTR reported that the overall rates of fluconazole resistance are as high as 57%. This is attributed to the high rates of non-*albicans Candida* strains and previous antifungal prophylaxis [17]. *C. glabrata* is intrinsically less susceptible to azoles and AmpB. *C. glabrata* may emerge as a breakthrough infection resistant to all triazoles [108,109]. *C. krusei* is always resistant to fluconazole. Increasing echinocandin administration is associated with an increase in resistant *Candida* strains. Echinocandin resistance is reported in less than 2% of *Candida* isolates worldwide [24]. Shields et al investigated abdominal IC as a hidden reservoir for echinocandin-resistant strains, particularly in patients with prolonged echinocandin exposure and breakthrough infections [121]. They reported that 24% of patients were infected with abdominal IC. Those treated with an echinocandin were infected with FKS-mutant *Candida*, which is an echinocandin-resistant gene variation, 50% of these were breakthrough infections, with 83% being *C. glabrata* [121]. The mortality rate for FKS-mutant IC was 100%. In another study of 30 LTRs receiving echinocandin prophylaxis, 8% developed resistance within 1 month [122]. There is growing evidence to suggest that patients who have drug-resistant candidemia have poorer outcomes than patients with antifungal-susceptible candidemia [123]. Although multidrug resistance is uncommon, increasing reports of multidrug resistance to the azoles, echinocandins and polyenes have occurred in several *Candida* species, most notably *C glabrata* and more recently, newly emerging fungal pathogen *C. auris*.

The epidemiology of resistance in filamentous fungi is characterized by secondary resistance to azoles by *A. fumigatus* and by an intrinsic antifungal-resistant pattern of emerging species showing high minimum inhibitory concentrations (MICs) to major antifungals [124]. Triazole resistance in *Aspergillus spp*. can evolve during therapy, but resistant isolates are also detected in azole-naive patients [125].

6. Antifungal Treatment for Invasive Fungal Infection

The management of IFIs relies, in part, on the accurate selection of an antifungal agent for the infection. While selecting antifungal for prophylaxis and treatment, it is important to consider the antifungals spectrum of activity, pharmacokinetics, pharmacodynamics, toxicity profile, and distribution to the infection site. For severely immunocompromised patients, a fungicidal agent may be preferred over a fungistatic agent. Triazoles and to a lesser extent, other antifungals, are also subjected to drug-drug interactions. This needs to be considered when selecting a particular antifungal agent for use. Voriconazole concentration is affected by polymorphisms in the major metabolic enzyme, cytochrome P450 2C19. Therapeutic drug monitoring is required when treating patients with itraconazole, voriconazole or posaconazole. When the IFI involves a

pharmacologically protected site such as the central nervous system (CNS) or eye, 5-fluorocytosine, fluconazole, or voriconazole are generally preferred [5,125,126]. LAmpB and echinocandin penetration is typically inadequate for IFI of the CNS or eye.

For IC, after using fluconazole or LAmpB for several years, echinocandin is now the new recommended treatment. The latest guidelines recommend echinocandins (caspofungin, micafungin or anidulafungin) as the first line for empirical, pre-emptive or proven treatment of IC [5, 87]. Fluconazole is considered as an oral alternative if the patient is not critically ill, or has been evaluated or tested to be unlikely for fluconazole-resistant *Candida* infection. LAmpB should be considered if the first two are contraindicated as a first-line treatment [87].

IA is preferably treated with the triazole voriconazole [5,115]. Alternative treatments include LAmpB and isavuconazole. Primary echinocandin therapy is not recommended, although they are effective in salvage therapy or in combination with voriconazole. This combination is especially effective in pulmonary IA. Historically, CNS infections with aspergillosis were associated with 100% mortality. Voriconazole has improved the prognosis of patients suffering from breakthrough CNS aspergillosis [5,115,126,127]. Despite being the third most common type of IFI, there has been, until recently, a lack of recommendations on diagnosis and the best management for mucormycosis.

7. Role of Antifungal Stewardship (AFS)

IFI in LTR is associated with a high economic burden because of the consumption of costly newer antifungal agents, longer hospital stay and the need for intensive supportive care. To overcome these in LTR, there is a need for validation of reliable, rapid diagnostic tests to initiate optimal use of antifungals. In LTR, antifungal prophylaxis is selected in the early post-transplant period, during which the incidence of IC peaks. However, there is no consensus on the duration and choice of antifungal agent [45]. In LTR, 10 patients receive unnecessary antifungals to prevent one case of FI. A reduction of the unnecessary use of antifungals via AFS is critical to limit multidrug resistance emergence and drug cost. AFS is a co-ordinated intervention to promote the optimal selection, dosage and length of antifungal therapy. Some principles of AFS are shared with the much-established antibiotic stewardship (ABS) programmes [128]. ABS reduces the overuse of antibiotics. This relieves the pressure for fungal overgrowth and hence, the risk of IFIs. [129]. Although a reduction in healthcare costs is a secondary goal of ABS [128], it is a common justification for stewardship [130] due to the high costs of antifungals. The AFS team should adapt practice guidelines according to local epidemiology of fungal infections. The AFS programme must help clinicians overcome the knowledge barriers they routinely face in managing IFI in LTR. Multi-disciplinary team engagement and consensus building with end-users are vital for success. The antifungal use and diagnostic guidelines should be made available to multidisciplinary staff. There are a variety of challenges for implementing AFS programmes. This includes the lack of dedicated personnel, guidance and investment in new diagnostic and prescription tools, as well as misperception by some physicians.

8. Conclusions

The risk factors for IC and IA continue to evolve. Thus, the strategies for their prevention should be constantly updated and targeted to both the individual patient's risk factors and the local

epidemiology. IFI in LTR is also associated with a high economic burden because of the consumption of costly newer antifungal agents, longer hospital stay and the need for intensive supportive care. To overcome these in LTR, there is a need for validated, rapid diagnostic tools and antifungal stewardship.

Author Contributions

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Competing Interests

The authors have declared that no competing interests exist.

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