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Invasive Candidiasis in Liver Transplant Recipients: a Review

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Abstract

Purpose of Review This review summarizes the literature on invasive candidiasis (IC) in liver transplant recipients (LTRs) regarding diagnostic strategies, treatment, and prophylaxis.

Recent Findings Recent literature on IC has expanded and refined definitions of risk factors for IC in LTRs. We discuss increasing rates of resistance among candida species and new antifungals. Diagnostic modalities continue to decrease time to initiation of empiric antifungals, which may impact outcomes.

Summary A well-documented host of risk factors for IC may allow for targeted prophylaxis, while minimizing exposure to antifungal medications. Further research on minimum effective duration of treatment and prophylaxis is needed to combat resistance.

Keywords Liver transplant · Candida · Infection · Solid organ transplant · Invasive fungal infection · Fluconazole

Introduction

Invasive fungal infections (IFIs) are feared complications in solid organ transplant recipients (SOT). Invasive candidiasis (IC) is the most common IFI in this population, of which liver transplant recipients (LTRs) are at particular risk [1]. Despite advances in diagnosis and medical treatment, IC continues to have a high mortality rate in this population, ranging between 25 and 77% [2•, 3•, 4]. Shifts in the epidemiology of candida species, changes in surgical techniques, and increased pre-transplant morbidity have modified LTR's risk for candida infections. Our aim is to evaluate recent literature regarding IC in LTRs and, in particular, focus on diagnostic modalities, treatment, and prophylaxis.

We included published articles through June 2021, with emphasis on recent literature within the past 3–5 years, and any previous seminal works that shaped current practices. We specifically looked for literature that discussed IC, including candidemia. We excluded articles that were either case reports or series or pertained only to mucocutaneous candidiasis, as this was not the disease state of interest. Particular attention was paid to LTR, though reports with SOT, immunocompromised hosts, and critically ill patients were incorporated.

Epidemiology of Invasive Candidiasis in Liver Transplant Recipients

Candida species are part of commensal flora within the human gastrointestinal (GI) tract and are a frequent colonizer of skin. Translocation of fungi from the GI tract and skin during specific disruptions in homeostasis, as well as derangements in the immune system can allow these florae to cause disease [5, 6, 7•]. Candida and aspergillus species are common etiologies of IFI in SOT recipients, with candida species representing the predominant fungal pathogen, causing up to 80% of IFI [4, 7•, 8]. In the Transplant-Associated Infection Surveillance Network (TRANSNET), 17,000 transplant recipients were diagnosed with 1208 IFIs, 53% of which were IC [9]. Of these, almost half (261 cases, 41%) were in LTR [1].

Incidence of IC ranges from 1.8 to 12% within the first year of transplant in SOT recipients. In the TRANSNET study, the overall 1-year cumulative incidence of IFI was 4.7% for LTRs [1, 9]. Many have noted increasing rates of

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infection due to non-albicans species in recent years [4, 10••, 11, 12••]. This has also coincided with increased resistance of candida species in general, and increased rates of prophylaxis [7•].

The timing of candida infections tends to be early in the first year after liver transplant, probably due to a variety of factors. In a Korean multicenter retrospective cohort of 482 LTRs, Kim et al. found that the median time to IFI diagnosis was 38 days [13••]. Similarly, in a retrospective review of 102 LTRs, Chiereghin et al. found that 85% of fungal infections occurred less than 30 days after transplant [14]. Surgical intervention, disruption of GI flora, and higher levels of immunosuppression in the early post-transplant period contribute to this [5, 15, 16•]. Additional factors that may pre-dispose LTRs to IC are their pre-transplant morbidity especially when transplanted at high Model for End Stage Liver Disease (MELD) scores. Increasing MELD score is associated with increased risk of infectious complications including IFI. At risk MELD score of >20 and >30 for IFI has been reported in the setting of cirrhosis [17•, 18]. High MELD score may be associated with increased rates of infections, such as spontaneous bacterial peritonitis leading to increased (and recurrent) systemic antibiotic use in the pre-transplant period which in turn would predispose to candida overgrowth in the gut. Lastly, candida species is one of the more common nosocomial pathogens, and is associated with infections due to surgical complications, vascular access catheters, drains, and increased antimicrobial use [15, 16•].

A few studies note later onset of IC in LTR as well. Bassetti et al. [2017] found that the median time to candida infections in LTRs was 5 months [4]. In the Swiss Transplant cohort, a study of 3,541 SOT recipients, the overall burden of infection remained elevated during the entire year post-transplant [12••]. While the opportunistic nature of candida infections presents a possible explanation for delayed presentation, further exploration for the reason of this late presentation is needed [19].

Risk Factors for Invasive Candidiasis in Liver Transplant Recipients

Invasive candidiasis in LTR is associated with presence of certain risk factors [20, 21]. Some of these risk factors have evolved over time and changed as practices in transplant have changed. Surgical advancement has resulted in decreased operation time and improved transfusion requirements, and thus risk related to operative variables has decreased [22, 23•]. Progress in medical management of transplantation has led to improved rates of rejection and closer management of immunosuppression, potentially decreasing this as a contributing factor [22].

Liver transplant candidates with cirrhosis are at increased risk for developing IC prior to transplant. This is an indirect metric of a patient's medical condition and the urgency for transplant [4, 24•]. As noted earlier, MELD score can be predictive of IC risk [25–28]. A MELD score of >20 or >30 was associated with 2-fold and 4.3-fold increase in relative risk of IFI [25]. Pre-operative colonization and undetected, subacute infection may lead to early post-operative IC [29••, 30]. Table 1 summarizes the major risk factors identified through numerous epidemiologic studies in the literature over the past decade.

High-risk LTRs usually have at least one risk factor for IC [21]. However, in a recent prospective multicenter trial in Italy by Rinaldi et al., LTRs were divided into high-risk (2 or more risk factors), low-risk (1 risk factor), or no-risk categories. Low-risk individuals received fluconazole prophylaxis and high-risk patients received either echinocandin or amphotericin B, for additional aspergillus coverage [29••, 38]. The addition of this third category of high risk and prophylaxis with echinocandin or amphotericin did not improve the rate of breakthrough IFI, and in fact, most of the breakthrough IFIs (76%) occurred in the high-risk class [29••]. In LTRs with at least one risk factor, the frequency of IFI without antifungal prophylaxis has been reported to be as high as 36% [14, 31]. Low- or no-risk recipients develop invasive fungal disease <4% of the time without prophylaxis [11, 31, 39].

Clinical Presentation

Common manifestations of IC include candidemia, intra-abdominal candidiasis, including peritonitis and abdominal abscess, and biliary tract infection [1, 4, 37••, 40•]. In a prospective trial from Spain assessing rate of candidemia, LTRs had a higher relative risk of IC and about 60% had bloodstream involvement [37]. Candidemia has a higher overall 30-day mortality compared to intraabdominal infections [4, 19, 41••]. In the Swiss Transplant Cohort, intra-abdominal and hepatic infections predominated in LTRs. Fungemia and CNS involvement were noted to be 3% and 2% respectively [12••].

Outcomes

Candida infections in LTRs are associated with poor outcomes, including graft failure, high morbidity, and mortality [2, 27, 42]. IC-related mortality in the liver transplant setting ranges from 20 to 77% [4, 11, 31, 43], with worse outcomes associated with non-albicans species [44]. The

Table 1 Risk factors for invasive candidiasis in liver transplant

Pre-transplant	Intraoperative	Early post-transplant±	Late post-transplant±
*Steroid treatment prior to transplant (*alcoholic hepatitis) [11]	*High blood-products transfusion requirements [4, 11, 13••, 29••, 31, 32, 33••, 34]	Re-operation [4, 11, 15, 31, 33••, 34, 35••, 36••]	Dialysis Renal failure [1, 4, 11, 13••, 15, 29••, 31, 33••, 34, 35••, 36••]
Hospitalization at time of LT [11]	Choledocojejunostomy [3•, 4, 6, 7•, 8, 10, 14]	Dialysis Renal failure [1, 4, 11, 13••, 15, 29, 31, 33••, 34, 35••, 36••]	T-cell depleting medications [7•, 34]
*Re-transplantation [3•, 4–6, 11, 32]	*Prolonged surgery (>8 h) [4, 29••, 32, 33••]	Parenteral nutrition [15, 35••, 37••]	*CMV disease [5, 7•, 8, 9, 10••, 14, 32]
Fulminant hepatic failure Acute liver failure Decompensated cirrhosis [4, 6, 7•, 11, 12••, 13••, 14]	Split liver [11]	Prolonged ICU admission, Prolonged ventilation [10••, 12••, 15]	*Prolonged antibiotic treatment [5, 7•, 8, 16•, 17•, 32]
Recent abdominal surgery (<6 months) [36••]	Living donor [31]	Prolonged hospitalization [10••, 12••, 15]	*Organ rejection requiring treatment [1, 4, 29••, 32]
Colonization with C*andida* species [4, 13••, 15, 31, 33••, 34]		T-cell depleting medications [7•, 34]	Vascular access catheters [15, 19, 35••, 37••]
Prior antifungal therapy [13••]		*CMV disease [5, 7•, 8, 9, 10••, 14, 32]	
MELD > 20 [31] [13••, 17•, 25–27],,		*Prolonged antibiotic treatment [5, 7•, 8, 16•, 17•, 32]	
*Dialysis Renal failure [13••, 32]		*Organ rejection requiring treatment [1, 4, 29••, 32]	
		Vascular access catheters, surgical drains [15, 19, 35••, 37••]	
		Neutropenia [15, 35••]	

Legend: *Risk factor for aspergillosis

±Early post-transplant <30 days post-operative. Late post-transplant >30 days post-operative

TRANSNET study found that mortality from non-albicans candida species was 31.4% versus 22.6% among *C. albicans* infections, and was highest among those with *C. glabrata* infections [1, 30]. A multicenter study from Fernández-Ruiz et al. looked at two discrete periods (2010–2011 and 2016–2018) and found that *C. glabrata* increased from 18.8 to 20.4% of cases respectively [37••]. Rates of *C. glabrata* from this study were significantly higher than in the TRANSNET cohort, suggesting influence of antifungal exposure selecting for these organisms [32].

Diagnosis of IC

Diagnosis of IC in LTRs can be difficult due to lack of typical presentation in immunocompromised hosts, and thus, a high index of suspicion is required to initiate early diagnostics and empiric treatment [5, 35••]. Ideal diagnostic tests should be sensitive enough to detect both candidemia, and deep-seated infections in which candidemia may not be present [45, 46]. Table 2 gives an overview of various diagnostic tools for the diagnosis of IC.

Microbiological culture

The gold standard for diagnosis of IC is identifying candida from a sterile body site, whether on culture or pathology [35••, 52•]. Fungal cultures are the only modality that allows for anti-fungal susceptibility testing [16•]. In general, blood cultures have low microbiological yield in making the diagnosis. In the presence of deep-seated candida infection, blood cultures are positive only 40% of the time [41••, 45, 50••]. Moreover, blood cultures can take anywhere from 2 to 5 days to result, leading to delays in antifungal therapy and poor outcomes for patients [51].

Biomarkers

Fungal biomarkers are useful to augment diagnosis and tend to be more sensitive than culture. Thus, they can allow for early empiric antifungal use with potential impact on mortality [41••, 47]. Earlier initiation of antifungal treatment has been associated with a reduction in mortality of 15% [53]. Thus, early diagnosis and early initiation of effective therapy is critical to improving outcomes.

Serum levels of 1,3-beta-D-glucan (BDG) in blood can be detected via the Fungitell assay (Cape Cod, East Falmouth,

Table 2 Diagnostic tests for Candida

Test	Sensitivity	Specificity	Time to results	Utility	Pitfalls
Blood culture	50–70% [35••, 47, 48•] 17–40% (deep seated infection) [42, 45]		2–5 days [48•]	Able to test isolates for sensitivities.	Low sensitivity in certain situations Slow time to positivity [48•]
Beta-D glucan	56–80% [45, 46, 49]	80% [45]–87% [49]	Variable	100% NPV [42]	Non-specific High false positive rate early after liver transplant [45]
T2Candida	89–90% [35••, 50, 51]	99% [35••, 51]	0.6 days [42]	Strong NPV Rapid time to positivity Advantage for stewardship [35••]	Detects 5 most common species. No information on resistance [48•]
PCR	59–95% [42, 45, 47, 48•]	70% [47]–92% [45]	Approx. 1 h	In vitro detection limits of less than 10 CFU/mL [45]	Lower sensitivity for candidemia [48•] Heterogenous results

MA). BDG is a component of the fungal cell wall of candida and other fungi, including aspergillus, pneumocystis, and others [49, 54]. The Fungitell assay uses colorimetric or turbidimetric methods to quantify the rate of activation of a horseshoe crab coagulation cascade, which is triggered by BDG [45]. The test is not specific for candida, which can affect the utility of the study [35••]. False positive rates are increased in hospitalized patients due to exposure to enteral nutrition, intravenous immunoglobulin, certain beta-lactam antibiotics, *Pseudomonas aeruginosa* bacteremia, cellulose dressings, mucositis, and GI tract breakdown [45, 48•, 54]. Levesque et al. examined 52 LTR admitted to the ICU and obtained serial BDG weekly. Using a quantitative cutoff value of 146 pg/mL, the single test sensitivity was 100%, specificity was 61%, positive predictive value (PPV) 25%, and negative predictive value (NPV) 100%. When two sequential positive tests were obtained, specificity increased to 87% and PPV to 45% [54]. Interestingly, a high false positive rate was noted the first week after surgery [54]. Correct utilization of BDG testing in LTRs, coupled with a high index of suspicion, may allow for earlier initiation of antifungal therapy [25].

The T2 Candida assay can identify the five most common candida species that cause human disease, *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei* [48•]. In a clinical trial of over 1800 patients, Mylonakis et al. found a strong NPV of up to 99.5% with a 5–10% prevalence rate of candidemia. Median time to species identification was 4.4 h, significantly shorter than traditional blood cultures [51, 55•]. In the DIRECT2 trial, a prospective multicenter study by Clancy et al., the T2 Candida assay and companion blood cultures were obtained from patients and the sensitivity of the assay was found to be 89%. However, prior antifungal therapy, neutropenia, and *C. albicans* candidemia were independently associated with T2 Candida positivity [50••]. Invalid results were noted in 7–9% of samples [50••]. Eighteen percent of patients had prior SOT in that study. Additionally, no information about resistance can be obtained from the test [48•, 53].

Molecular testing

PCR testing for candida is available, both commercially and via in-house testing. Most of these assays are run on whole blood [45]. In a meta-analysis of 54 studies, which included nearly 5000 patients, the pooled sensitivity and specificity for proven and probable candida infections were 95% and 92% respectively [56]. FilmArray system (BioFire, Salt Lake City, UT) allows multiplex PCR from blood cultures that result in 1 h [42]. PCR allows for in vitro detection limits of less than 10 colony forming units per 10 mL, needing only a small amount of fungus to be detected [45]. PCR was noted to be more sensitive than BDG and blood cultures in SOT recipients with candidiasis in sterile sites at 89%, though it has reported decreased sensitivity for candidemia [46, 48•].

Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker, Millerica, MA, or Biomeriuex, Durham, NC) allows for rapid identification of candida species from tissue. Identification of organisms based on molecular weight via colony placement on target plate and overlaid with a matrix and shot by a laser. Desorption and ionization of organism molecules fly into a mass spectrometry chamber with different speeds based on molecular weight [42]. Identification with MALDI-TOF allows for subspecies identification more specifically than the T2Candida test and quicker than blood cultures [57] and thus allows for rapid initiation of antifungals [42, 57].

C. auris is an emerging drug-resistant pathogen. Rapid diagnostic testing for *C. auris* is of the utmost importance to facilitate early infection prevention strategies and treatment [58, 59].

DNA sequencing or MALDI-TOF allows for in-house identification of *C. auris* from sterile sites [60].

Treatment of Invasive Candida Infections in LTR

Choice of Antifungals

The choice of antifungal for treatment should be based on local epidemiology as well as patient's prior antifungal exposure [24•]. Guidelines recommend an echinocandin as first-line empiric therapy for candidemia and IC [2•, 16•, 31, 35••]. Non-albicans species generally predominate after fluconazole exposure for prophylaxis; therefore, an echinocandin or amphotericin compound should be considered in cases of prior azole exposure [27]. Generally, if a certain class of antifungal medication was used in the previous 90 days, empiric therapy should be undertaken with alternate class [35••]. As discussed in Prigent et al., resistance to fluconazole developed within 30 days of treatment, making its use as empiric therapy limited after prophylaxis [16•, 33••, 61]. Additional consideration should be paid to whether risk factors for invasive aspergillosis exist and the need for a mold-active azole, rather than fluconazole (see Table 1). Figure 1 depicts the general spectrum of susceptibility of *Candida* species to common antifungals [35••, 62•].

Echinocandins have good in vitro activity against many candida species and a good safety profile. They act by inhibiting cell wall synthesis of BDG in the fungal cell wall [61]. Echinocandins have the added advantage of very few interactions with other medications, unlike azoles. Use of azole antifungals may be limited due to interactions between calcineurin and mTOR inhibitors, used as part of immunosuppressive regimens [15]. Cyclosporine, tacrolimus, and rapamycin are extensively metabolized by the cytochrome 3A4 enzyme, which azoles inhibit, increasing plasma concentrations of these immunosuppressants [16•]. Therefore, it may be prudent to use echinocandins when initiating immunosuppression in the early post-transplant period, until baseline levels of immunosuppressants are established. Echinocandins have low penetration into certain spaces such as urine, central nervous system, and intraabdominal space [61, 63]. This limited penetration into certain spaces could potentially lead to increased resistance to echinocandins, and thus, we suggest using a higher dose in these settings or an alternative agent [61].

Aggressive early interventions, including rapid initiation of empiric treatment within 72 h and source control, improve outcomes for IC [15, 35••]. Source control in intra-abdominal infections is critical to treat this form of candidiasis [52•, 64••]. In candidemia, early intravascular catheter removal in addition to early empiric antifungals reduced all-cause 30-day mortality [37••]. Ophthalmology examination and consideration of echocardiogram are recommended to rule out complicated infections that may [16•, 35••] necessitate longer courses of treatment. Notably, IC in LTRs is associated with surgical complications such as biliary leak, hepatic artery thrombosis, and abdominal abscesses. Correction of these complications will be critical in improving clinical outcomes.

With increasing frequency of non-albicans species and increased exposure to broad spectrum antifungals, susceptibility testing should be undertaken for all sterile site culture isolates, so that appropriate therapy is used [15]. Transitioning from echinocandins to an azole is recommended in

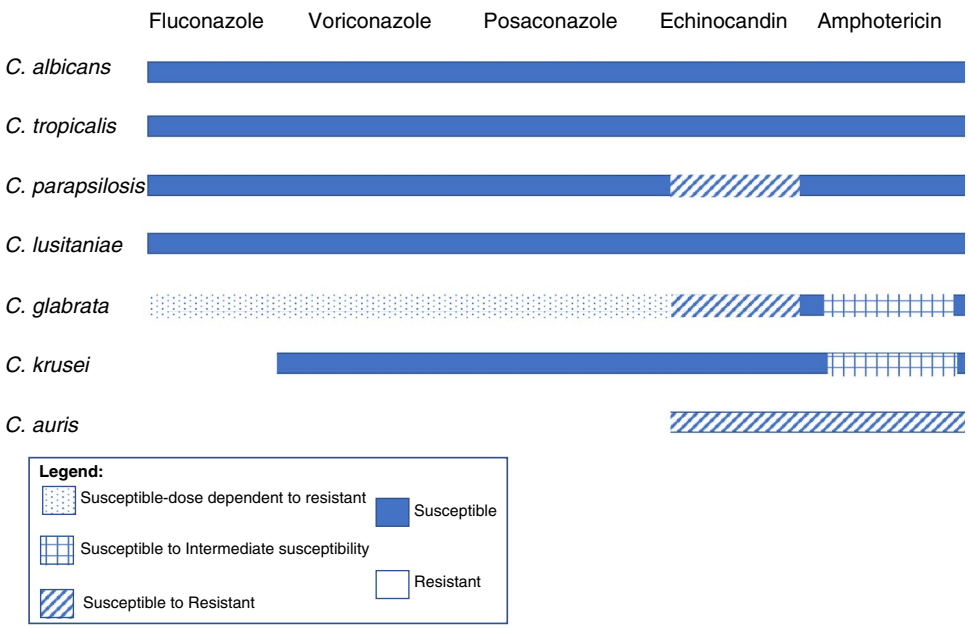

Fig. 1 General susceptibility patterns of Candida species

patients who have clinically stabilized and have a susceptible organism [35••, 65]. Consideration should be given to whether the patient needs mold coverage for aspergillus when selecting an azole [66].

Bassetti et al. [2017] noted that adequate antifungal treatment was prescribed for candidemia at least 95% of the time, yet intraabdominal candidiasis was sufficiently treated only 66% of the time [4]. Clinical complexity should be considered when determining duration of treatment for IFI. Depending on the indication, isolated fungemia from an intravascular catheter (less common source of IC in the liver transplant setting) may be treated sufficiently for 2 weeks from negative cultures, assuming that the catheter has been removed and no other source of infection is identified. Other infections, especially intraabdominal abscesses, may require longer treatment, such as 4–6 weeks. However, in their review of candidiasis in LTR, Righi et al. found that abdominal candidiasis was the most frequent infection type in their adult liver transplant recipient retrospective study and had median treatment duration of 17 days [36••].

Therapeutic drug monitoring (TDM) is recommended for patients receiving azole therapy, in particular voriconazole, posaconazole, and isavuconazole. Righi et al. determined that fluconazole levels equal to or greater than 11 were significantly associated with clinical success [36••]. Though their study ultimately did not justify use of TDM in all fluconazole use, it speaks to more aggressive dosing of fluconazole to adequately treat these infections. TDM should be performed when using posaconazole or voriconazole, but its use outside these drugs remains investigational [35••]. Generally, target trough levels for Posaconazole should be greater than 1.0–1.25mg/L for treatment, and greater than 0.7mg/L for prophylaxis, whereas a target trough level ≥1–2 μg/mL for voriconazole is recommended for treatment [67, 68].

Prophylaxis for Invasive Candidiasis

Due to poor outcomes in LTR with IC, prophylaxis is the preferred strategy; and generally targeted prophylaxis is recommended [35••, 66]. Early analyses have shown that antifungal prophylaxis given to individuals with certain risk factors, now referred to as targeted antifungal prophylaxis (TAP), could effectively decrease the incidence of IFI and mortality related to these infections [33••, 69]. As such, guidelines for management of antifungal prophylaxis in LTR recommend against universal prophylaxis and recommend targeted prophylaxis for higher risk patients [29••, 31]. While practices have changed significantly, Kim et al. found that over 40% of 482 LTRs received systemic antifungal prophylaxis, regardless of risk factors [13••]. Providers can judiciously limit use of antifungals by identifying and giving prophylaxis to high-risk patients. It should be noted that there is a lack of unanimous recommendation for prophylaxis for LTRs, and practices vary widely [27].

TAP helps to limit indiscriminate use of antifungal medications, while still effectively decreasing the risk of IFI [12••, 13••]. TAP after liver transplant has demonstrated efficacy in reducing incidence and mortality due to IFI, particularly when one or more of a set of risk factors are identified (Table 2) [4]. However, studies of prophylaxis failed to show any difference in overall mortality, despite reducing IFI-related mortality [20, 24•, 43, 70].

Timing and Duration of Prophylaxis

Ideally, TAP should start when a risk factor for IC is identified in the peri-transplant time period or even within the first post-transplant year. Duration of prophylaxis varies widely among studies and transplant centers [35••]. Whether using universal or TAP, Singh et al. noted that 49% of centers used prophylaxis just during the index hospitalization, 19% of centers used 1 month of prophylaxis post-transplant, and 8.5% of centers used 3 months of prophylaxis [34]. Using short-term prophylaxis of 10 days in 137 high-risk individuals demonstrated a *Candida* infection breakthrough rate of 2.9% in individuals receiving prophylaxis [11]. Rinaldi et al. had longer prophylaxis durations for low versus high risk categories, 7–14 and 21 days respectively [29••]. Lum et al. used a median duration of 3.5 weeks of prophylaxis; however, the median time to presentation in that study was 77 days, leading those investigators to question whether late onset fungal infections could have different set of risk factors [33••]. General recommendations are that duration of prophylaxis should be from 2 to 4 weeks, or when removal of identified risk factor has occurred [2•, 16•, 31, 35••].

Choice of Antifungal

Despite a variety of antifungals being studied for fungal prophylaxis, fluconazole has been the mainstay for antifungal prophylaxis in LTRs. Fluconazole is active against common candida species but not against *C. glabrata* and aspergillus species. Multiple studies have assessed the utility of fluconazole prophylaxis for LTRs with risk factors for IC and found low rates of breakthrough infection [33••, 65, 71].

Echinocandins and liposomal amphotericin have been used successfully in high-risk patients and have activity against aspergillus species as well [29••, 72]. Studies that have looked at echinocandins versus fluconazole and amphotericin B have not found a statistically significant difference in outcomes for IC prophylaxis [69, 71, 73]. However, in Rinaldi et al, a majority of breakthrough fungal infections (76%) was in the high-risk class (2 or more risk factors) on an echinocandin or polyene [29••]. In the Swiss Transplant

Cohort, though antifungal prophylaxis was infrequently used, echinocandins were used in 22, fluconazole in 20, and amphotericin in 19, while mold-active azoles were used in 11 patients [12••]. Use of these broader agents has potential to increase resistance rates without much appreciable increase in benefit [71, 74].

Occasionally, topical agents, such as clotrimazole troche in oral candidiasis, are used for prophylaxis after solid organ transplant. All patients in the Swiss Transplant Cohort received nystatin prophylaxis for 14 days peri-transplant [12••]. The impact on IC, if any, is unknown, and there are no international consensus guidelines on the role of topical prophylaxis agents [14, 35••, 75•].

Despite careful identification of risk factors and prophylaxis, breakthrough fungal infections may occur in LTRs, especially in those with surgical complications [76••]. In a retrospective analysis of low-risk liver transplant patients by Lavezzo et al., breakthrough infections were noted to be around 2.9% in the prophylaxis group [11]. Rate of breakthrough IFI on TAP has been found to be around 5%, the majority of which are in high-risk patients [29••]. Causes of breakthrough infections are due to host dynamics, fungal changes, and iatrogenic factors [64••]. Higher degree of immunosuppression is associated with breakthrough infections. Antibiotic exposure for at least 14 days prior to infection has been suggested as a risk for breakthrough infections, as changes to host microbiota could predispose to *Candida* infections [64••, 71]. Antifungal resistance can occur rapidly after exposure to short course of prophylactic azole, leading to breakthrough of resistant species [61].

Resistance

The epidemiology of *Candida* subspecies in infections has been changing, due in part to increased fluconazole use over the past decades [73]. Candida species develop resistance primarily through point mutations in hot spot regions of FKS genes. In a 2011 study, Lockhart et al. found that 16% of *Candida* isolates were fluconazole resistant [77]. A majority of this is due to *C. glabrata* infections that have been increasing in frequency in recent years [61]. The mean minimum inhibitory concentration (MIC) for breakthrough isolates in patients receiving fluconazole prophylaxis was significantly higher for all candida species [61, 73, 77]. Increased exposure to azoles and echinocandins has resulted in selective pressure on candida subspecies and selection of resistant organisms to these antifungal classes [4, 78•]. In Lum et al., all patients with infections with *C. glabrata* had prior azole exposure [1, 33••]. Prigent et al. found that echinocandin resistance was present in 8% of treated patients within 1 month of treatment [61]. This rapid development of resistance also mirrored the non-albicans species frequency in this study [61].

Candida auris is a rare but highly drug-resistant candida subspecies infection that is found in nosocomial settings such as ICU and nursing homes [75]. The organism is known to cause persistent colonization of skin and body sites weeks to months after infection [75]. It has been implicated in nosocomial outbreaks in the USA and India, demonstrated via whole genome sequencing [35••, 60, 75•, 79, 80]. *C. auris* has been reported in a case of donor-derived infection in lung transplant associated with poor outcome [81]. Infection control practices are critical to prevent dissemination of the organism [75•, 82•].

Conclusion

Invasive candidiasis remains the most common IFI in the liver transplant setting. Advances in diagnostic modalities can help guide earlier treatment which may impact outcomes. A variety of therapeutic agents are available for treatment though development of resistance remains a concern. Identification of risk factors for IC, especially with increasing complexity of liver transplant candidates and recipients, is important for an effective prophylactic strategy.

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•• Of major importance

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