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REVIEW

Management of *Candida* infections in liver transplant recipients: current perspectives

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Abstract: Liver transplantation has emerged as a widely accepted lifesaving therapeutic option for many patients with a variety of liver diseases. Improved surgical and medical management has led to significant improvements in post-transplant survival rates with a 1 year and 5 year patient survival of 87% and 73%, respectively. A high mortality rate due to infections during the first post-transplant year persists. Invasive candidiasis is recognized as a significant problem associated with high morbidity and mortality. Recent surveillance data has helped to understand the changes in the epidemiology and the evolving trends in the use of antifungal agents for prophylaxis and treatment combined with the challenges of managing these invasive fungal infections, which has led the transplant community to explore the best management strategies. The emergence of resistant fungi and excess costs in managing these invasive fungal infections has added to the complexities of management. In this context, current perspectives in the management of *Candida* infections in liver transplant recipients will be reviewed.

Keywords: *Candida* infections, management, liver transplant

Introduction

The field of liver transplant has progressed remarkably since the first attempt at orthotopic human transplant in 1963 by Thomas Starzl in the US. Better understanding and improved outcomes have led to wider indications for liver transplant leading to an increased group of immunocompromised hosts who are now living longer and are at increased risk of infective and noninfective complications. Infections have been recognized as a frequent complication with bacterial pathogens playing a major role in the immediate postoperative period followed by viral and fungal organisms.[1–5] Among fungal infections, *Candida* spp. and *Aspergillus* spp. are the most common pathogens and are described as the most devastating complications contributing to significant morbidity and mortality.[6] Recognizing the factors which lead to these infections and developing appropriate and timely strategies to prevent, diagnose, and manage these invasive fungal infections (IFIs) will be an ongoing challenge faced by transplant teams. A survey on antifungal management practices has revealed the difficulties in making uniform recommendations as there are variations in practice at different transplant centers.[7] Local epidemiological data should guide decisions on choice of antifungal agents and help formulate local guidelines.[8] The epidemiological changes, recognized risk factors, clinical features, and management approaches currently available in managing *Candida* infections in liver transplant recipients will be discussed.

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Epidemiology

Surveillance reports suggest changes in the epidemiology of *Candida* infections among liver transplant recipients. The overall incidence of *Candida* infections has decreased compared to the early transplant years, but *Candida* spp. continue to be the most common pathogen.[9] However, even with evolution of transplant practices, IFIs carry a high mortality rate.[10] Increasing incidence of infections due to non-albicans *Candida* spp. and a shift toward late occurrences, well beyond the traditional risk period, are being reported.

The incidence of *Candida* infections has decreased from 30%–50% in the early years of transplant history to approximately 10% in the early 21st century, to the current estimates of <5%.[11,12] The majority of earlier reports are from single-center studies with relatively small sample sizes, although recently multicenter collaborations have given us a better overview.

In an early six-center study of invasive candidiasis (IC) in liver transplant recipients, Husain et al compared 35 patients with IC with 69 patients without IC.[13] No denominator data are provided so the incidence could not be calculated. Candidemia accounted for 40% of IC, and peritonitis another 40%. The median time to infection was 13.5 days (range 1–4,109 days); 78% of infections occurred in the first 3 months after transplant. In this series, the species identified were *C. albicans* (65%), *Candida glabrata* (21%), *Candida tropicalis* (9%), *Candida parapsilosis* (3%), and *Candida guilliermondii* (3%).

More recently, larger multicenter studies on IFIs in solid organ transplant patients have revealed subtle changes in *Candida* epidemiology. The Transplant-Associated Infection Surveillance Network surveyed multiple US centers to understand IFIs in solid organ transplant recipients.[12] The Prospective Antifungal Therapy Alliance (PATH Alliance) is another study that aimed to collect data on IFIs in the US; a subset of the study, focusing on solid organ transplant recipients, was published by Neofytos et al.[14]

In the PATH Alliance report, IC was the most frequently identified IFI overall, accounting for 59% of IFIs. Among the liver transplant recipients, *Candida* accounted for 78.7% of IFIs, with *C. albicans* contributing to 45% of all the *Candida* spp. identified.[14] In terms of median day of diagnosis, IC tended to be an early complication, generally diagnosed within the first 6 months of transplant. Among liver transplant recipients, IC was diagnosed at a median of 155 days after transplant, although the range was large (0–5,626 days). This contrasts with invasive aspergillosis, which was generally a later complication.[14]

According to Transplant-Associated Infection Surveillance Network data, *Candida* was also the most common IFI in organ transplant recipients – with a 12-month cumulative incidence of 1.9%, it far surpassed other fungal pathogens as a cause of IFI.[12] Candidemia was identified as the most common type of IC in this series. Among liver transplant recipients, candidiasis accounted for 68% of IFIs over the 3-year surveillance period. In this study, the median time to diagnosis of IC was 103 days.

It is noteworthy that in the more recent studies (Transplant-Associated Infection Surveillance Network and PATH Alliance) the median times to the diagnosis of IC were greater than that in the earlier study of Husain et al.[13] Although the accuracy of larger numbers might be contributory, improvements in surgical technique have probably played an important role in reducing infective complications.[8] The role played by antifungal prophylaxis (particularly newer agents such as the echinocandins) in delaying the time to IC has not been fully investigated. Singh et al have shown that more liver transplant centers are practicing prophylaxis, with caspofungin being one of the more popular agents.[7] The duration of prophylaxis varied, but few centers used them for >3 months.

Risk factors and the timing of *Candida* infections

Liver transplant recipients have multiple risk factors for *Candida* infections and the vulnerability and incidence are influenced by host, environment, and fungal factors. Host factors include immunosuppressants (eg, dose and duration), breaches in the anatomical barriers (eg, from the surgical procedure), environmental exposures (health care related or community acquired), and fungal factors (eg, resistance to prophylaxis used).[15] Main risk factors of liver transplant recipients for IC identified are retransplantation, creatinine level ≥2.0 mg/dL, choledochojejunostomy, intraoperative use of 40 units of blood products, prolonged intraoperative time (>11 hours), and fungal colonization.

Despite these many risk factors, it is thought that other factors have probably contributed to lower rates of IC documented in modern-day practice. These include refinements in surgical technique, improved understanding of immunosuppression, improved cytomegalovirus prevention strategies, and antifungal prophylaxis. However, routine antifungal prophylaxis without risk stratification has been implicated for the increasing trends in non-albicans *Candida* spp. and resistant *Candida* spp.[13,16,17]

Candida spp. frequently colonize several anatomical sites, which include the skin, oral cavity, gastrointestinal tract, and the vagina, and constitute the most common fungal pathogens

to affect humans. Nosocomial infections due to *Candida* spp. have increased in vulnerable patients, critically ill patients in the medical and surgical intensive care units, and solid organ transplant and hematopoietic stem cell transplant recipients. There is a global increase in the frequency of candidemia and IC.[18] Crude mortality rates of *Candida* bloodstream infection in intensive care unit patients were higher (42.6%) compared to the more prevalent Gram-positive (25.3%) and Gram-negative bloodstream infection (29.1%).[19]

Altered host immunity is recognized as the principal factor for the opportunistic pathogen; however, adherence of the microbe to host cell and biofilm formation, secretion of hydrolytic enzymes which leads to tissue invasion, ability to switch from yeast and filamentous forms which leads to invasion, and switching phenotypes are a few of the many virulence factors which are being explored in *Candida* spp.[20–22]

Among liver transplant recipients, *C. albicans* is the most common isolate followed by other species of *Candida*. An increase in the proportion of non-albicans *Candida* spp. has been noted over the last 2 decades. In studies published from 1995–2003, *C. albicans* accounted for 55% of proven infections; in studies published from 2004–2007, *C. albicans* accounted for 45% of proven and probable IFIs. Among the non-albicans *Candida* spp, *C. glabrata* was the dominant species followed by *Candida krusei*, *C. parapsilosis*, and *C. tropicalis*.[14,17] *C. glabrata* and *C. krusei* were commonly isolated from patients who had received antifungal therapy.[14] Fluconazole resistance in *C. albicans*, *C. tropicalis*, and *C. parapsilosis* was low (<1%).[23]

The temporal association of infections occurring in organ transplant recipients following the initiation and continuation of immunosuppressants is well described, and the clinical timetable for infections has helped clinicians in generating differential diagnosis while evaluating infections in post-transplant patients. It has also been used as a tool to formulate preventive strategies.[24] Evolving trends suggest a change in the timing of these infections; recent data show IC are occurring later than the traditional timeline of 1 month for nosocomial fungal infection.[25] The impact of cytomegalovirus and fungal prophylaxis contributing to the shift in the timelines of these fungal infections has been suggested.[26]

Clinical aspects of *Candida* infections

Mucocutaneous candidiasis and IC represent different ends of the spectrum of infections caused by *Candida*.[27] Mucocutaneous candidiasis involves the skin and its appendages and the mucous membranes of the oropharynx, esophagus, non-esophageal gastrointestinal tract, respiratory tract, and genitourinary tract. IC includes candidemia (*Candida* spp. isolated from blood cultures) and organ involvement (tissue sites infection).

Abdominal organ transplant recipients in general, and liver transplant recipients in particular, exhibit unique susceptibility to *Candida* infections.[15] In the PATH Alliance study, which evaluated 429 adult solid organ transplants with IFIs, IC manifested as candidemia, abdominal infection, lung infection, and skin involvement.[14] Among liver transplant recipients, postoperative infections such as intraabdominal (peritonitis, biliary tract, abdominal abscess, enteritis), skin and soft tissue infections, and infected bilomas are complications associated with *Candida* infections which are unique, difficult to manage, and associated with significant morbidity and mortality.[28–31]

Recognizing infections in transplant recipients is difficult; clinical signs and symptoms are often not specific and might be muted.[3,11] One-third of patients with infected hepatic fluid collections (bilomas) were asymptomatic.[28] Fever is a non-specific symptom. At the same time, differentiating infective from noninfective causes requires thorough clinical evaluation, diagnostic procedures, and radiologic imaging to arrive at an appropriate diagnosis. For example, allograft rejection, drug fevers, postoperative hematoma, and tissue infarcts can mimic infections and lead to diagnostic dilemmas.[32]

Diagnosis of *Candida* infections

Candida spp. are known colonizers of humans – interpreting a positive culture from a nonsterile site is notoriously difficult.

Guidelines do exist to help categorize patients with IFIs with varying levels of probability. The revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/IFI Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group were formulated primarily to "facilitate the identification of reasonably homogeneous groups of patients" for research purposes.[33] In an earlier edition of the guidelines, the authors stress that the guidelines "should not be taken as strict rules for making or excluding the diagnosis of an IFI in clinical settings".[34]

Diagnosis of candidemia and IC has traditionally been based on clinical suspicion, suggestive signs and symptoms, and cultures of blood, imaging, and biopsy of the suspected lesion for cultures and histopathology. They remain as important as ever, but nonculture techniques in the form of biomarkers may improve our ability to diagnose candidemia

and IC. The latest European guidelines on diagnostic procedures of choice for the diagnosis of candidemia put 1→3-β-D-glucan (BDG) and the mannan/antimannan assays in the "recommended" category.[35] Data for their use in liver transplant recipients, however, remain scarce.

Blood cultures are crucial for the diagnosis of candidemia. Although blood cultures are said to be insensitive with an approximately 50% yield, their yield may be optimized with adherence to consensus recommendations, eg, by sending adequate volumes of blood and doing multiple sets.[35] In addition, the time taken for species identification following positive blood cultures can be quite prolonged, leading to a delay in effective antifungal therapy. Cultures, however, are relatively inexpensive and allow for drug sensitivity testing. Peptide nucleic acid fluorescence in situ hybridization and matrix-assisted laser desorption ionization-time of flight mass spectroscopy are techniques developed to decrease the time to species identification and have been successfully applied to *Candida* as well as bacteria.[36,37]

BDG is a component of the cell wall of many types of fungi. Measurement of BDG in serum has been associated with candidemia and aspergillosis. BDG, however, is not released by *Cryptococcus* or *Mucormycosis*. BDG measurement may be considered an aid in the diagnosis of fungemia; in particular, candidemia and IC. In a series focusing only on patients in the intensive care unit, Posteraro et al drew blood for cultures and BDG at the onset of sepsis. In their series, 13 of 14 patients with candidemia or IC were positive for BDG. There were few false positives; hence, the test in the hands of these investigators had sensitivity and specificity in excess of 93%, a positive predictive value of 75%, and a negative predictive value of 98.6%.[38]

Other investigators, however, have found much higher false positive rates. When Pickering et al tested and compared serum and plasma samples from 36 healthy blood donors with 15 patients with candidemia, all the samples from the blood donors were negative for BDG and 13 of 15 candidemic patients were positive for BDG. However, 14 of 25 patients with bacteremia were also positive for BDG. They concluded that the test was likely more useful for excluding an IFI.[39]

There are few studies addressing specifically the role of BDG after liver transplantation. Chen et al planned and drew blood for procalcitonin and BDG in 55 patients with suspected catheter-related bloodstream infections after orthotopic liver transplantation. Unfortunately, they had only one case of fungemia; hence, conclusions about the role of BDG in liver transplant patients cannot be drawn from their study.[40]

Yamanouchi et al measured BDG levels regularly after living donor liver transplantation. Seventy-one patients had 89 episodes of elevated BDG; 47% of the cases of raised BDG occurred in the first 5 days post-transplant.[41] This is not surprising as false positive BDG elevation has been associated with the infusion of albumin and globulins, with hemodialysis, and even with surgical gauze – all of which are not uncommon in liver transplant patients in the early postoperative period. Patients with elevated levels of BDG were more likely to have a positive fungal culture, but only one of these was a positive blood culture. The most significant finding in this study, however, was the higher mortality rate in patients with raised BDG levels after the 15th postoperative day.

Although mannan/antimannan assays have also been recommended for the diagnosis of candidemia, hardly any study has used them in the field of liver transplant. In a landmark paper that showed that using immunoassays detecting both the mannan antigen and the antimannan antibody improved the sensitivity of the assay, Sendid et al included only one patient whose underlying condition was "liver transplantation".[42] In another publication, the same group suggested that regular monitoring of mannanemia and antimannan antibodies in patients at risk of candidiasis might facilitate its early diagnosis.[43]

Antifungal susceptibility is generally predicted on the basis of species and local epidemiology. However, given the increasing use of antifungals and emerging resistant *Candida* spp., it is reasonable to request antifungal susceptibility testing of isolates when resistant fungi or treatment failure is suspected.[23]

Prevention of *Candida* infections

Liver transplant recipients are at a constant threat of infections depending on their net state of immunosuppression. Preventing infections is a multipronged approach and requires the collaborative effort of teams managing these immunocompromised hosts.

Donor-derived *Candida* infections

A wide range of infections have been transmitted from donors to transplant recipients and are increasingly being recognized to be associated with significant post-transplant morbidity and mortality.[44,45] The Organ Procurement and Transplant Network in the US is the currently available database of the estimated donor-derived infectious disease transmissions among solid organ transplants. Thirty fungal infections including *Candida* spp. were reported between

2005–2009 that were potentially donor derived.[44] Most cases occurred in kidney and liver recipients with contaminated preservation fluid being implicated as the source.[46] Preventive strategies include monitoring and culturing the organ preservation media and avoiding organs from patients with active infections. Potential donors, especially the cadaveric donors, are ill days to weeks before their organs are procured, and are cared for in the intensive care units, and are at risk for IFIs. The evaluation of potential deceased donors for infections includes blood and urine cultures, which the authors suggest for potential donors with problems like fever or leukocytosis.

Immunization

Vaccination is one of the effective strategies to prevent infections. In solid organ transplants, just like in other immunocompromised hosts, the risk of acquiring and also the ability to mount protective immune response depends on the net state of immunosuppression.[3] The American Society of Transplantation has published guidelines which include vaccination of solid organ transplant candidates/recipients and also household members and health care workers who are potential sources of transmitting infections.[47] Currently, there are no known approved vaccines against fungal infections.[48] There are ongoing efforts to develop antifungal vaccines; two Phase I clinical trials against *Candida* spp. have been evaluated.[49,50] There are concerns with regards to the preclinical studies of the antifungal research as the majority use mouse models, which have different innate immune response when compared to humans.[48] New developments looking at a conjugate vaccine that elicits antibodies to BDG against *C. albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* and inducing immunity by vaccinating with heat-killed *Saccharomyces cerevisiae* are two of the pan fungal vaccination options that are being pursued and may be anticipated in the future to help prevent IFIs.[51,52]

Prophylaxis

Current consensus and recommendation is for antifungal prophylaxis in liver transplant candidates at high risk for candidiasis. This is a practice well supported by the data. Cruciani et al found that prophylaxis reduced colonization, total proven fungal infections (including invasive infections), and mortality attributable to fungal infection.[17] A Cochrane review found that fluconazole reduced the incidence of IFIs without a mortality benefit and suggested that individuals at greatest risk be selected for prophylaxis.[53] As the likelihood of IC is greatest in the early post-transplant period, this is the period generally chosen for antifungal prophylaxis.[12] There is less consensus, however, on the agent of choice, as shown in a survey of transplant units.[7] Although certain units practice universal prophylaxis, it has been shown that this has not affected overall mortality; furthermore, there is a risk of developing infection with non-albicans *Candida* spp.[16–18] Hence, perhaps in line with the Cochrane review, the practice of "targeted prophylaxis" seems to be most popular, with patients defined as being at risk selected for prophylaxis. Although "risk" is not easy to define, Pappas et al found that in patients without any, or only one, of the following risk factors prophylaxis could safely be withheld: choledochojejunostomy anastomosis, retransplantation, intraoperative administration of ≥40 units of blood products or return to the operating room for intraabdominal bleeding, return to the operating room for anastomotic leak or vascular insufficiency, preoperative serum creatinine of ≥2 mg/dL, and perioperative *Candida* colonization.[16] In clinical practice, the presence of at least two of these risk factors would usually indicate prophylaxis.

Model of End-Stage Liver Disease (MELD) score was first developed in 2000 to predict mortality of patients undergoing transjugular intrahepatic portosystemic shunts and is now widely used to prioritize patients who require liver transplantation. Prognostic value of the MELD score has been assessed both for bacterial infections and post-transplant survival. In a recent paper from a single center, retrospective analysis of 667 liver transplants identified that MELD scores of 20–30 or ≥30 were associated with a 2.0-fold or 4.3-fold increase in relative risk of fungal infections.[54] It is postulated from this observation that the routinely calculated MELD score may serve as a simple and practical tool to predict the risk for infections and at the same time identify candidates for antifungal prophylaxis.

The American Society of Transplantation and the American Society of Transplant Surgeons recommend fluconazole as the antifungal prophylaxis of choice against candidiasis followed by lipid formulations of amphotericin B in centers with high rates of non-albicans *Candida* spp. Caspofungin is being used for antifungal prophylaxis in liver transplant recipients.[7] Echinocandins may become the antifungal prophylaxis of choice for liver transplant recipients, given the efficacy and safety demonstrated in high-risk liver transplant patients combined with the increasing incidence of infections due to non-albicans *Candida* spp.[55]

There is no consensus with regards to the duration of antifungal prophylaxis. Given the paucity of studies in defining the duration of antifungal prophylaxis, Pappas and

Silveira recommend ≥4 weeks or as long as the risk period warrants prophylaxis.[55]

Antimicrobial stewardship programs

The scope of antimicrobial stewardship programs in the management of infections is expanding.[56,57] This is timely given the surveillance studies showing an increase in IC in both intensive care units and nonintensive care settings. With broad-spectrum antibiotic use a recognized risk factor for candidiasis, antimicrobial stewardship programs may help to prevent IFIs. More recently, antimicrobial stewardship programs are monitoring the use of antifungal drugs which may improve the management of IFIs and also prevent the emergence of resistant *Candida* spp.[58,59]

Infection control

Nosocomial fungal infections caused by *Candida* spp. and *Aspergillus* spp. are increasingly being recognised.[60] The National Healthcare Safety Network data collected during 2009–2010 from US hospitals reports *Candida* spp. features among the top eight pathogens (*Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, coagulase-negative staphylococci, *Klebsiella pneumonia*, *Klebsiella oxytoca*, and *Klebsiella pseudomonas*, and *Enterobacter* spp.) that are major contributors to health care-associated infections.[61] *Candida* spp. rank as the third most common cause of central line-associated bloodstream infections in US intensive care units.[62] Among solid organ transplant recipients, candidemia compared to the Gram-positive and Gram-negative bloodstream infections was associated with a higher crude mortality.[4] Nosocomial transmission of *Candida* spp. from health care workers to patients has been documented and also implicated in outbreaks.[60] Infection control programs with the goal of reducing health care-associated infections and thereby improving patient safety have grown since the results of the Study on the Efficacy of Nosocomial Infections and Infection Control Practices (SCENIC).[63] Strategies to prevent central line-associated bloodstream infections, which include educating health care personnel about central line care, ensuring adherence to infection prevention practices at time of insertion (attention to hand hygiene, avoiding femoral veins, maximal sterile barrier precautions, chlorhexidine-based antiseptic for skin preparation), disinfecting catheter hubs prior to each use, and removing nonessential catheters, are some of the current recommendations from the Society of Healthcare Epidemiology of America and Infectious Diseases Society of America.[64] There is currently no evidence to support the isolation of patients with *Candida* colonization or infection.[65] Hand washing is recognized as an important and effective procedure for preventing health care-associated infections, recognizing the fact that *Candida* spp. are carried on the hands of health care workers.[66]

Treatment of *Candida* infections

Empiric treatment with an anti-*Candida* agent for suspected IC followed by definitive therapy by selecting the appropriate agent based on the species of *Candida* isolated and susceptibility profile, if available, is recommended.[27] A delay in starting antifungal treatment has been associated with increased mortality.[67] Four categories of antifungal agents are available and all are effective for treating *Candida* infections: the polyenes (amphotericin B, deoxycholate amphotericin, liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion), the triazoles (fluconazole, itraconazole, voriconazole, and posaconazole), the echinocandins (caspofungin, anidulafungin, and micafungin), and flucytosine. The treatment guidelines from the Infectious Diseases Society of America for managing candidiasis are also recommended for liver transplant recipients.[15,68]

Improved survival associated with echinocandin use from reviewing seven randomized antifungal treatment trials for IC has led to a more definite consensus and reiterates the Infectious Diseases Society of America recommendations of using echinocandins for most patients with IC.[69] Caspofungin, micafungin, and anidulafungin are the three licensed echinocandins which have turned out to be valuable options in the treatment of fungal infections in the 21st century.[70] Their popularity seems to be well justified: they have broad candidacidal activity compared to the triazoles (they are effective against fluconazole-resistant *Candida* spp.), they have an excellent side effect profile (with low potential for nephrotoxicity and hepatotoxicity), and they did very well in the early trials (achieving superiority over comparators in some of the studies).[71,72]

With the availability of more antifungal drugs, several important points should be borne in mind when treating patients with candidemia/IC. Emergence of resistant fungi and breakthrough IFIs in patients already on antifungals has been reported in liver transplant recipients. These include resistant *C. glabrata* strains while on azoles, breakthrough *C. glabrata* and *C. parapsilosis* while on micafungin, and trichosporonosis while on caspofungin.[73–75] Pharmacokinetics and pharmacodynamics of antifungal drugs vary and should be considered while treating certain IFIs, especially those involving the heart, central nervous system, and eyes; the use of intravenous or oral formulations depending on the

patients clinical status and drug–drug interactions while on immunosuppressants and concomitant medications should also be considered.

Conclusion

Candida remains the most common fungal infection in liver transplant recipients. Antifungal prophylaxis with fluconazole or an echinocandin for selected patients at higher risk for candidemia will likely help to reduce the risk of IC. Diagnosis is difficult. Blood cultures, although of modest sensitivity, are a must. The role of nonculture diagnostics such as BDG needs to be formally studied in liver transplant recipients. Early treatment with an echinocandin is recommended, although the risk of breakthrough infections should be recognized.

Disclosure

The authors report no conflicts of interest in this work.

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