**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 60166

**Manuscript Type:** MINIREVIEWS

**Invasive fungal infection before and after liver transplantation**

Ferrarese A *et al*. Fungal infection in liver transplant recipients

Alberto Ferrarese, Annamaria Cattelan, Umberto Cillo, Enrico Gringeri, Francesco Paolo Russo, Giacomo Germani, Martina Gambato, Patrizia Burra, Marco Senzolo

**Alberto Ferrarese, Francesco Paolo Russo, Giacomo Germani, Martina Gambato, Patrizia Burra, Marco Senzolo,** Multivisceral Transplant Unit, Padua University Hospital, Padua 35128, Italy

**Annamaria Cattelan,** Tropical and Infectious Disease Unit, Padua University Hospital, Padua 35128, Italy

**Umberto Cillo, Enrico Gringeri,** Padua University Hospital, Hepatobiliary Surgery and Liver Transplant Center, Padua 35128, Italy

**Author contributions:** Ferrarese A, Cattelan A and Senzolo M participated in research design, data analysis, and writing of the manuscript; Cillo U, Gringeri E, Russo FP, Germani G, Gambato M and Burra P participated in research design and preparation of the manuscript; all authors have contributed to, read, and approved the manuscript.

**Corresponding author: Alberto Ferrarese, MD, Academic Fellow,** Multivisceral Transplant Unit, Padua University Hospital, *via* Giustiniani 2, Padua 35128, Italy. alberto.ferrarese17@gmail.com

**Received:** October 18, 2020

**Revised:** November 15, 2020

**Accepted:** November 29, 2020

**Published online:** December 21, 2020

**Abstract**

Invasive infections are a major complication before liver transplantation (LT) and in the early phase after surgery. There has been an increasing prevalence of invasive fungal disease (IFD), especially among the sickest patients with decompensated cirrhosis and acute-on-chronic liver failure, who suffer from a profound state of immune dysfunction and receive intensive care management. In such patients, who are listed for LT, development of an IFD often worsens hepatic and extra-hepatic organ dysfunction, requiring a careful evaluation before surgery. In the post-transplant setting, the burden of IFD has been reduced after the clinical advent of antifungal prophylaxis, even if several major issues still remain, such as duration, target population and drug type(s). Nevertheless, the development of IFD in the early phase after surgery significantly impairs graft and patient survival. This review outlines presentation, prophylactic and therapeutic strategies, and outcomes of IFD in LT candidates and recipients, providing specific considerations for clinical practice.

**Key Words:** Acute-on-chronic liver failure; Sepsis; Cirrhosis; Candidemia; Acute liver failure; Invasive fungal infection

**Citation:** Ferrarese A, Cattelan A, Cillo U, Gringeri E, Russo FP, Germani G, Gambato M, Burra P, Senzolo M. Invasive fungal infection before and after liver transplantation. *World J Gastroenterol* 2020; 26(47): 7485-7496

**URL:** https://www.wjgnet.com/1007-9327/full/v26/i47/7485.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v26.i47.7485

**Core Tip:** Invasive fungal infection significantly influences the outcome of patients with acute liver failure or cirrhosis awaiting liver transplantation, as well as their post-operative course. This state-of-the-art review comprehensively describes the epidemiology and the therapeutic options on this field.

**INTRODUCTION**

Liver transplantation (LT) represents the best therapeutic option for end-stage liver diseases and hepatocellular carcinoma. The LT landscape has changed rapidly in the last decades, with a widespread diffusion of this practice, a significant expansion of indications, and an evolution in medical and surgical care. Therefore, although more patients than in the past are offered a graft and can survive after surgery, this changing scenario has determined a huge modification of characteristics of LT candidates and recipients, who are older, sicker and often display many extra-hepatic comorbidities[1].

In this setting, the burden of invasive infection, both before LT [especially in those with advanced cirrhosis or acute-on-chronic liver failure (ACLF)] and in the early post-operative course is still a major issue. Cirrhosis is a predisposing condition to such infections, because of a profound immune dysfunction, due to both an exhaustion of response to pathogens and persistent systemic inflammation[2]. Bacteria are responsible for the majority of invasive infections, determining a further impairment of hepatic and extra-hepatic organ disfunction in the pre-operative phase, and significantly affecting graft and patient’s survival in the early phase after surgery[3-5].

Nevertheless, considered rare in the past, invasive fungal infection occurs with an increasing prevalence in LT candidates, mostly due to the refinement of diagnostic criteria and the increasing burden of predisposing conditions. In the post-LT phase, the institution of antifungal prophylactic strategies has significantly improved patient outcome.

**INVASIVE FUNGAL DISEASE IN PATIENTS AWAITING LT**

***Epidemiology, risk factors, therapeutic options, outcomes***

By definition, an invasive fungal disease (IFD) is a disease process caused by invasive fungal infection. Current diagnostic criteria rely on three different levels of probability (*proven*, *probable* and *possible* IFD), mixing together host factors, clinical manifestations, and mycological evidence[6].

The epidemiology of IFD in cirrhotic patients has been heterogeneously reported, mainly in retrospective, single-center series, which included patients with different disease stages, prognosis (*i.e.*, waitlisted for a transplant) and hospital settings [*i.e.*, intensive care unit (ICU) *vs* regular ward]. Moreover, heterogeneous prevalence, diagnostic criteria and treatment protocols applied throughout the literature may have further influenced the actual epidemiology of such infections.

According to multicenter studies on hospitalized patients with cirrhosis, the prevalence of IFD is nearly 4%[7,8], although only *proven* IFD are usually considered. Most infections are caused by *Candida*; according to recent evidence, *albicans* and *non-albicans* strains have roughly similar prevalence[9].

The institution of surveillance protocols appears mandatory for an early diagnosis. These protocols should focus on patients at highest risk of IFD development, such as those with ACLF. Indeed, they encompass several risk factors, such as a profound immune-dysfunction, prolonged hospitalization, hepatic and extra-hepatic failure(s), indwelling (vascular) catheters, and long-term antibiotic therapies[3,10]. According to available studies on this specific population[11-16], the prevalence of IFD ranges between 1% and 47% (depending on diagnostic criteria and surveillance policies), significantly affecting short-term survival. Nevertheless, heterogeneous selection criteria across studies have not allowed a refinement of risk stratification to date (Table 1). Patients with severe alcoholic hepatitis are another high-risk group for IFD, especially for invasive aspergillosis (IA). Gustot *et al*[17] reported a high incidence of such infection in a prospective cohort of 94 patients with biopsy-proven severe alcoholic hepatitis, after a median time of 25 d from steroids introduction, and with a 100% transplant-free mortality. This report raised the question about the potential role of steroids for IA development in such a population; a meta-analysis in this field[18] partly confirmed this hypothesis, suggesting that opportunistic infections, especially fungal, seemed to be more frequent in this high-risk group, and may deserve special attention. IFD is a less frequent, but highly relevant complication also in patients with acute liver failure (ALF), carrying a high mortality risk, especially in case of a delayed diagnosis or institution of inappropriate treatment[19,20].

The occurrence of IFD often represents a detrimental event in patients with cirrhosis, leading to a significant increase in short-term mortality (35% to 50%), at a similar rate to that experienced after a multidrug-resistant organism bloodstream infection, especially when an appropriate antifungal treatment is not promptly initiated[7,9,21].

A detailed treatment algorithm for IFD in patients with cirrhosis is beyond the scope of this manuscript. The clinical keys of a successful treatment are early diagnosis, early administration of appropriate antifungal treatment, in close cooperation with Infectious Disease specialists. Considering *Candida* related IFD, ophthalmologic evaluation and removal of vascular/peritoneal catheters, as well as a shift towards *non-albicans* strains should be considered before starting antifungal therapy. Echinocandins are now considered the drugs of choice, to be continued for 2 wk after clearance of *Candida* from the bloodstream or symptoms resolution[22]. Considering IA, voriconazole represents the first therapeutic option, whereas echinocandins and liposomal amphotericin B (L-AmB) are other, albeit less effective, available drugs[23]. It is worth mentioning that voriconazole has been associated with hepatic and renal dysfunction, therefore therapeutic drug monitoring is recommended[24].

**Specific issues in the liver transplant setting**

IFD are a major issue in patients waiting for LT. As discussed above, occurrence of an IFD highlights the already impaired patient’s general condition, with an unpredictable evolution of hepatic and extra-hepatic organ(s) failure. This may potentially increase the need for a transplant, especially in a urgency-based system of organ allocation[25]. Nevertheless, according to the available data, several points should be considered; first, the effectiveness and treatment length of an appropriate antifungal therapy are very different from antibiotic therapies. Second, an IFD seems to develop in sicker patients than in the case of a bacterial infection, often as a superimposed infection[7,8]. Therefore, an active IFD should be viewed as a temporary contraindication for LT[26] (Figure 1). For the sickest patients who are waiting for a graft, surveillance protocols are mandatory, and antifungal prophylaxis has been advocated in selected cases. For instance, Gustot *et al*[27] suggested ICU admission and a baseline MELD score > 24 as factors for considering a prophylaxis against IA in patients with acute alcoholic hepatitis[16,27], but more data are needed before considering it as a standard practice. After diagnosis of IFD, consultation by expert Infectious Disease specialists should be always considered, in order to establish the best targeted antifungal treatment and its length. Moreover, antifungal stewardship aiming to avoid both adverse events and increasing resistance should always be pursued in the transplant setting.

The assessment of short-term outcome for each waitlisted patient should be individually discussed by the LT team, in order to consider the best timing for a waiting-list readmission (and a possible prioritization after infection recovery[4]). Conversely, other therapeutic options should be taken into account, to avoid futile transplantation[28,29].

**FUNGAL INFECTIONS EARLY AFTER LT**

**Epidemiology, risk factors, and outcome**

Although better outcomes have been reported after the introduction of novel antifungal agents and significant progress has been obtained after antifungal prophylaxis, IFD remains an important cause of early morbidity and mortality after solid organ transplantation (SOT). Recent large cohort studies on SOT recipients showed a 1-year post-transplant IFD rate of 4%-8%[30-32], with a changing epidemiology over time. Indeed, if *Candida* spp. and *Aspergillus* spp. are still the most common molds, there has been a rise of *non-albicans* Candidaspecies, carrying a higher mortality[33].

Broad-spectrum antibiotic therapy, parenteral nutrition, prolonged neutropenia, ICU stay, diabetes, pre-LT colonization, renal replacement therapy, cytomegalovirus (CMV) infection, re-interventions and choledochojejunostomy are established risk factors for post-LT IC[34,35], whereas pre-LT steroid administration, ALF, and renal replacement therapy seem to be more frequently associated with IA[36-38]. Recently, pre-LT *Aspergillus* colonization has been considered not a contraindication to LT in a single-center cohort of 27 patients; although they received appropriate post-operative prophylaxis (voriconazole +/- echinocandin), post-LT IA occurrence was 11%[39]. Most of the abovementioned risk factors are associated with patient’s severity at time of transplantation. This concept has been well demonstrated in ACLF patients, who experienced a significantly increasing post-LT IFD incidence, according to disease stage (ACLF grade 3 *vs* -2 *vs* -1: 15% *vs* 6.2% *vs* 3.4%)[40].

Although active IFD in the donor is a contraindication to donation, several cases of donor-derived IFD have been reported in the literature, mostly due to a latent infection at time of surgery[41]. Contamination of the organ during procurement appears to occur more commonly than transmission of infection. For instance, a large retrospective multicenter study from France showed a 1.33% *Candida* spp. prevalence in preservation fluid, being associated with a high rate of post-operative IFD and impaired survival[42].

Despite the adoption of preventive measures and antifungal stewardship, IFD still significantly affect the overall graft and patient survival. For instance, the TRANSNET study[43] reported 90 d cumulative mortality of 26% after IC occurrence, and 1-year survival of 59% after development of IA.

**Post-LT antifungal prophylaxis**

Antifungal prophylaxis is now being considered a milestone after LT, due to its safety and effectiveness[44,45]. A systematic review and metanalysis by Evans *et al*[46] showed a significant reduction in the odds for *proven* IFD and for IFD-related mortality among LT patients who received prophylaxis, even if overall mortality did not change significantly. Notably, this study provided robust data about fluconazole and L-AmB, whereas echinocandins were not investigated. That said, several issues in the field of antifungal prophylaxis, such as the type (universal *vs* targeted approach), length, and preferred molecule(s) to use, are currently debated.

The rationale of a targeted prophylaxis is to capture only high-risk patients (based on pre- and early post-LT characteristics), in order to avoid antifungal over-use, and to administer highly effective molecules. Indeed, several studies have clearly demonstrated the cost-ineffectiveness of antifungal prophylaxis in low-risk patients.

Considering the optimal prophylaxis duration, current guidelines suggest that targeted prophylaxis against IC and IA should be administered for 14-21 d[34,36], but heterogeneous lengths have been adopted in the post-transplant setting, also in view of the dynamic, poorly predictable post-operative course. Further, many attempts at regimen simplification or stratification according to patients’ risk factors have been proposed. Table 2 summarizes the current evidence on antifungal prophylaxis after LT[35,37,47-60]. Notably, heterogeneous inclusion criteria, treatment algorithms, and endpoints adopted, do not allow a robust comparison between studies, but it is worth mentioning that a large amount of data has been available in the last years.

A randomized, double-blind clinical trial including 200 high-risk LT recipients, compared prophylaxis with fluconazole 400 mg/d with anidulafungin 100 mg/d to be continued for 3 wk or until hospital discharge. The study showed a similar IFD occurrence between cohorts (5.1% *vs* 8%, *P* = 0.4), with no post-LT IFD related deaths in either. Furthermore, only one patient had to stop anidulafungin prophylaxis due to adverse drug-related events, strengthening the safety of this molecule in the post-LT setting. Another multicenter, randomized, controlled trial including 347 LT recipients recruited across 37 European Centers[51] demonstrated that micafungin prophylaxis (100 mg/d for 21 d or until hospital discharge) was equally effective and safe as standard of care (*i.e.*, fluconazole, caspofungin, or L-AmB), according to composite primary and secondary endpoints. The effectiveness of caspofungin (50 mg/d) has been also demonstrated in a large retrospective study from Spain, after comparison with standard fluconazole prophylaxis[56].

**Specific treatment issues in the liver transplant setting**

A detailed therapeutic algorithm for the treatment of each IFD is beyond the scope of this manuscript. Nevertheless, some treatment principles could be of help for clinical practice. As in the pre-LT setting, echinocandins and fluconazole are the most effective molecules for the treatment of IC, whereas L-AmB should be used as first-line therapy only in selected cases. A thorough knowledge of local epidemiology, as well as pre-operative colonization(s) represent crucial information before starting a therapeutic regimen. Source control, obtained by removal of indwelling vascular/abdominal catheters, is another important option to be considered. Regarding echinocandins, both micafungin and anidulafungin have been demonstrated to be safe and effective at therapeutic dose[51,61]. Notably, micafungin does influence through levels of m-TOR inhibitors, but not of tacrolimus and cyclosporine[62].

Current guidelines recommend voriconazole as the drug of choice for IA, whereas isavuconazole and L-AmB can be considered as alternatives[36]. Isavuconazole seems to have similar effectiveness to voriconazole, but with fewer side effects–also liver-related –, being a promising option especially in the early post-operative phase[63]. During the course of therapy (usually 12 wk regimen), a careful assessment of IS, liver and renal function are mandatory, as well as therapeutic drug monitoring. Moreover, daily dose of calcineurin inhibitors should be carefully reduced (about by 50%), whereas co-administration of voriconazole and mTORs should be avoided due to a high increase of serum concentration[64]. Other molecules could be of help for the treatment of rarer species, or as rescue therapies[65,66].

**CONCLUSION**

The occurrence of an invasive fungal disease significantly affects the natural history of LT candidates and recipients. In the peri-operative setting, it usually develops in the sickest patients, impairing hepatic and extra-hepatic organ function and being associated with high short-term mortality. An active IFD is still considered a contraindication to LT. Therefore, response to appropriate antifungal therapy and patient’s global outcome should be strictly evaluated by the LT team in accordance with Infectious Disease Specialists, in order to re-consider transplantation as a cost-effective therapeutic option. In the post-operative setting, IFD occurrence has been significantly reduced since the institution of prophylaxis, but it is still a serious complication, affecting graft and patient survival. Prophylactic regimens in patients deemed at high-risk may take into account the local epidemiology, risk of resistance, and potential adverse drug-related effects or interactions.

**REFERENCES**

1 **Toniutto P**, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. *Liver Int* 2017; **37**: 317-327 [PMID: 27634369 DOI: 10.1111/liv.13255]

2 **Albillos A**, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; **61**: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010]

3 **Ferrarese A**, Zanetto A, Becchetti C, Sciarrone SS, Shalaby S, Germani G, Gambato M, Russo FP, Burra P, Senzolo M. Management of bacterial infection in the liver transplant candidate. *World J Hepatol* 2018; **10**: 222-230 [PMID: 29527258 DOI: 10.4254/wjh.v10.i2.222]

4 **Ferrarese A**, Vitale A, Sgarabotto D, Russo FP, Germani G, Gambato M, Cattelan AM, Angeli P, Cillo U, Burra P, Senzolo M. Outcome of a First Episode of Bacterial Infection in Candidates for Liver Transplantation. *Liver Transpl* 2019; **25**: 1187-1197 [PMID: 31021050 DOI: 10.1002/lt.25479]

5 **Dionigi E**, Garcovich M, Borzio M, Leandro G, Majumdar A, Tsami A, Arvaniti V, Roccarina D, Pinzani M, Burroughs AK, O'Beirne J, Tsochatzis EA. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity. *Am J Gastroenterol* 2017; **112**: 588-596 [PMID: 28220780 DOI: 10.1038/ajg.2017.19]

6 **De Pauw B**, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813-1821 [PMID: 18462102 DOI: 10.1086/588660]

7 **Bajaj JS**, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, Garcia-Tsao G, Fallon M, Maliakkal B, Lai J, Vargas HE, Subramanian RM, Thuluvath P, Thacker LR, OʼLeary JG. Prediction of Fungal Infection Development and Their Impact on Survival Using the NACSELD Cohort. *Am J Gastroenterol* 2018; **113**: 556-563 [PMID: 29257141 DOI: 10.1038/ajg.2017.471]

8 **Piano S**, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, Soares EC, Kim DJ, Kim SE, Marino M, Vorobioff J, Barea RCR, Merli M, Elkrief L, Vargas V, Krag A, Singh SP, Lesmana LA, Toledo C, Marciano S, Verhelst X, Wong F, Intagliata N, Rabinowich L, Colombato L, Kim SG, Gerbes A, Durand F, Roblero JP, Bhamidimarri KR, Boyer TD, Maevskaya M, Fassio E, Kim HS, Hwang JS, Gines P, Gadano A, Sarin SK, Angeli P; International Club of Ascites Global Study Group. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. *Gastroenterology* 2019; **156**: 1368-1380.e10 [PMID: 30552895 DOI: 10.1053/j.gastro.2018.12.005]

9 **Bassetti M**, Peghin M, Carnelutti A, Righi E, Merelli M, Ansaldi F, Trucchi C, Alicino C, Sartor A, Toniutto P, Wauters J, Laleman W, Tascini C, Menichetti F, Luzzati R, Brugnaro P, Mesini A, Raviolo S, De Rosa FG, Lagunes L, Rello J, Dimopoulos G, Colombo AL, Nucci M, Vena A, Bouza E, Muñoz P, Tumbarello M, Losito R, Martin-Loeches I, Viscoli C. Clinical characteristics and predictors of mortality in cirrhotic patients with candidemia and intra-abdominal candidiasis: a multicenter study. *Intensive Care Med* 2017; **43**: 509-518 [PMID: 28271321 DOI: 10.1007/s00134-017-4717-0]

10 **Clària J**, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amorós À, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Nevens F, Trebicka J, Laleman W, Saliba F, Welzel TM, Albillos A, Gustot T, Benten D, Durand F, Ginès P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016; **64**: 1249-1264 [PMID: 27483394 DOI: 10.1002/hep.28740]

11 **Verma N**, Singh S, Taneja S, Duseja A, Singh V, Dhiman RK, Chakrabarti A, Chawla YK. Invasive fungal infections amongst patients with acute-on-chronic liver failure at high risk for fungal infections. *Liver Int* 2019; **39**: 503-513 [PMID: 30276951 DOI: 10.1111/liv.13981]

12 **Fernández J**, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, Reverter E, Martínez J, Saliba F, Jalan R, Welzel T, Pavesi M, Hernández-Tejero M, Ginès P, Arroyo V; European Foundation for the Study of Chronic Liver Failure. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. *Gut* 2018; **67**: 1870-1880 [PMID: 28847867 DOI: 10.1136/gutjnl-2017-314240]

13 **Theocharidou E**, Agarwal B, Jeffrey G, Jalan R, Harrison D, Burroughs AK, Kibbler CC. Early invasive fungal infections and colonization in patients with cirrhosis admitted to the intensive care unit. *Clin Microbiol Infect* 2016; **22**: 189.e1-189.e7 [PMID: 26551838 DOI: 10.1016/j.cmi.2015.10.020]

14 **Chen J,** Yang Q, Huang J, Li L. Risk Factors for Invasive Pulmonary Aspergillosis and Hospital Mortality in Acute-On-Chronic Liver Failure Patients: A Retrospective-Cohort Study. *Int J Med Sci* 2013; **10(12):** 1625-1631 [PMID: 24151434 DOI: 10.7150/ijms.6824]

15 **Lin LN**, Zhu Y, Che FB, Gu JL, Chen JH. Invasive fungal infections secondary to acute-on-chronic liver failure: a retrospective study. *Mycoses* 2013; **56**: 429-433 [PMID: 23368965 DOI: 10.1111/myc.12044]

16 **Levesque E**, Ait-Ammar N, Dudau D, Clavieras N, Feray C, Foulet F, Botterel F. Invasive pulmonary aspergillosis in cirrhotic patients: analysis of a 10-year clinical experience. *Ann Intensive Care* 2019; **9**: 31 [PMID: 30778699 DOI: 10.1186/s13613-019-0502-2]

17 **Gustot T**, Maillart E, Bocci M, Surin R, Trépo E, Degré D, Lucidi V, Taccone FS, Delforge ML, Vincent JL, Donckier V, Jacobs F, Moreno C. Invasive aspergillosis in patients with severe alcoholic hepatitis. *J Hepatol* 2014; **60**: 267-274 [PMID: 24055548 DOI: 10.1016/j.jhep.2013.09.011]

18 **Hmoud BS**, Patel K, Bataller R, Singal AK. Corticosteroids and occurrence of and mortality from infections in severe alcoholic hepatitis: a meta-analysis of randomized trials. *Liver Int* 2016; **36**: 721-728 [PMID: 26279269 DOI: 10.1111/liv.12939]

19 **Rolando N**, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. *Semin Liver Dis* 1996; **16**: 389-402 [PMID: 9027952 DOI: 10.1055/s-2007-1007252]

20 **Antoniades CG**, Berry PA, Wendon JA, Vergani D. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol* 2008; **49**: 845-861 [PMID: 18801592 DOI: 10.1016/j.jhep.2008.08.009]

21 **Bartoletti M**, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, Schramm C, Bruns T, Merli M, Cobos-Trigueros N, Seminari E, Retamar P, Muñoz P, Tumbarello M, Burra P, Torrani Cerenzia M, Barsic B, Calbo E, Maraolo AE, Petrosillo N, Galan-Ladero MA, D'Offizi G, Bar Sinai N, Rodríguez-Baño J, Verucchi G, Bernardi M, Viale P; ESGBIS/BICHROME Study Group. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. *Clin Microbiol Infect* 2018; **24**: 546.e1-546.e8 [PMID: 28818628 DOI: 10.1016/j.cmi.2017.08.001]

22 **Pappas PG**, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **62**: 409-417 [PMID: 26810419 DOI: 10.1093/cid/civ1194]

23 **Patterson TF**, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **63**: 433-442 [PMID: 27481947 DOI: 10.1093/cid/ciw444]

24 **Wang T**, Yan M, Tang D, Xue L, Zhang T, Dong Y, Zhu L, Wang X, Dong Y. Therapeutic drug monitoring and safety of voriconazole therapy in patients with Child-Pugh class B and C cirrhosis: A multicenter study. *Int J Infect Dis* 2018; **72**: 49-54 [PMID: 29793038 DOI: 10.1016/j.ijid.2018.05.009]

25 **Tschuor C**, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA; Liver Allocation Study Group. Allocation of liver grafts worldwide - Is there a best system? *J Hepatol* 2019; **71**: 707-718 [PMID: 31199941 DOI: 10.1016/j.jhep.2019.05.025]

26 **Trebicka J**, Sundaram V, Moreau R, Jalan R, Arroyo V. Liver Transplantation for Acute-on-Chronic Liver Failure: Science or Fiction? *Liver Transpl* 2020; **26**: 906-915 [PMID: 32365422 DOI: 10.1002/lt.25788]

27 **Gustot T**, Fernandez J, Szabo G, Albillos A, Louvet A, Jalan R, Moreau R, Moreno C. Sepsis in alcohol-related liver disease. *J Hepatol* 2017; **67**: 1031-1050 [PMID: 28647569 DOI: 10.1016/j.jhep.2017.06.013]

28 **Linecker M**, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, Clavien PA, Busuttil RW, Truog RD, Petrowsky H. Potentially inappropriate liver transplantation in the era of the "sickest first" policy - A search for the upper limits. *J Hepatol* 2018; **68**: 798-813 [PMID: 29133246 DOI: 10.1016/j.jhep.2017.11.008]

29 **Karvellas CJ**, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, Pavesi M, Gustot T, Ronco JJ, Arroyo V; Chronic Liver Failure Consortium and European Foundation for the Study of Chronic Liver Failure. Dynamic Prognostication in Critically Ill Cirrhotic Patients With Multiorgan Failure in ICUs in Europe and North America: A Multicenter Analysis. *Crit Care Med* 2018; **46**: 1783-1791 [PMID: 30106759 DOI: 10.1097/CCM.0000000000003369]

30 **Hosseini-Moghaddam SM**, Ouédraogo A, Naylor KL, Bota SE, Husain S, Nash DM, Paterson JM. Incidence and outcomes of invasive fungal infection among solid organ transplant recipients: A population-based cohort study. *Transpl Infect Dis* 2020; **22**: e13250 [PMID: 31981389 DOI: 10.1111/tid.13250]

31 **van Delden C**, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, Hirzel C, Khanna N, Weisser M, Garzoni C, Boggian K, Berger C, Nadal D, Koller M, Saccilotto R, Mueller NJ; Swiss Transplant Cohort Study . Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. *Clin Infect Dis* 2020; **71**: e159-e169 [PMID: 31915816 DOI: 10.1093/cid/ciz1113]

32 **Andes DR**, Safdar N, Baddley JW, Alexander B, Brumble L, Freifeld A, Hadley S, Herwaldt L, Kauffman C, Lyon GM, Morrison V, Patterson T, Perl T, Walker R, Hess T, Chiller T, Pappas PG; TRANSNET Investigators. The epidemiology and outcomes of invasive Candida infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis* 2016; **18**: 921-931 [PMID: 27643395 DOI: 10.1111/tid.12613]

33 **Fernández-Ruiz M**, Cardozo C, Salavert M, Aguilar-Guisado M, Escolà-Vergé L, Muñoz P, Gioia F, Montejo M, Merino P, Cuervo G, García-Vidal C, Aguado JM; CANDIPOP Project, the CANDI-Bundle Group; GEIRAS-GEMICOMED (SEIMC)REIPI. Candidemia in solid organ transplant recipients in Spain: Epidemiological trends and determinants of outcome. *Transpl Infect Dis* 2019; **21**: e13195 [PMID: 31610077 DOI: 10.1111/tid.13195]

34 **Aslam S**, Rotstein C; AST Infectious Disease Community of Practice. Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13623 [PMID: 31155770 DOI: 10.1111/ctr.13623]

35 **Giannella M**, Bartoletti M, Morelli M, Cristini F, Tedeschi S, Campoli C, Tumietto F, Bertuzzo V, Ercolani G, Faenza S, Pinna AD, Lewis RE, Viale P. Antifungal prophylaxis in liver transplant recipients: one size does not fit all. *Transpl Infect Dis* 2016; **18**: 538-544 [PMID: 27237076 DOI: 10.1111/tid.12560]

36 **Husain S**, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13544 [PMID: 30900296 DOI: 10.1111/ctr.13544]

37 **Saliba F**, Delvart V, Ichaï P, Kassis N, Botterel F, Mihaila L, Azoulay D, Adam R, Castaing D, Bretagne S, Samuel D. Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. *Clin Transplant* 2013; **27**: E454-E461 [PMID: 23656358 DOI: 10.1111/ctr.12129]

38 **Neofytos D**, Chatzis O, Nasioudis D, Boely Janke E, Doco Lecompte T, Garzoni C, Berger C, Cussini A, Boggian K, Khanna N, Manuel O, Mueller NJ, van Delden C; Swiss Transplant Cohort Study. Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study. *Transpl Infect Dis* 2018; **20**: e12898 [PMID: 29668068 DOI: 10.1111/tid.12898]

39 **Amin A**, Molina A, Quach L, Ito T, McMillan R, DiNorcia J, Agopian VG, Kaldas FM, Farmer DG, Busuttil RW, Winston DJ. Liver Transplantation in Patients with Pretransplant Aspergillus Colonization: Is It Safe To Proceed? *Transplantation* 2020 [PMID: 32301905 DOI: 10.1097/TP.0000000000003276]

40 **Artru F**, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, Lassailly G, Dharancy S, Boleslawski E, Lebuffe G, Kipnis E, Ichai P, Coilly A, De Martin E, Antonini TM, Vibert E, Jaber S, Herrerro A, Samuel D, Duhamel A, Pageaux GP, Mathurin P, Saliba F. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. *J Hepatol* 2017; **67**: 708-715 [PMID: 28645736 DOI: 10.1016/j.jhep.2017.06.009]

41 **Echenique IA**, Ison MG. Update on donor-derived infections in liver transplantation. *Liver Transpl* 2013; **19**: 575-585 [PMID: 23526639 DOI: 10.1002/lt.23640]

42 **Levesque E**, Paugam-Burtz C, Saliba F, Khoy-Ear L, Merle JC, Jung B, Stecken L, Ferrandiere M, Mihaila L, Botterel F. Fungal complications after Candida preservation fluid contamination in liver transplant recipients. *Transpl Int* 2015; **28**: 1308-1316 [PMID: 26147662 DOI: 10.1111/tri.12633]

43 **Pappas PG**, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; **50**: 1101-1111 [PMID: 20218876 DOI: 10.1086/651262]

44 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2016; **64**: 433-485 [PMID: 26597456 DOI: 10.1016/j.jhep.2015.10.006]

45 **Lucey MR**, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, Teperman LW. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl* 2013; **19**: 3-26 [PMID: 23281277 DOI: 10.1002/lt.23566]

46 **Evans JD**, Morris PJ, Knight SR. Antifungal prophylaxis in liver transplantation: a systematic review and network meta-analysis. *Am J Transplant* 2014; **14**: 2765-2776 [PMID: 25395336 DOI: 10.1111/ajt.12925]

47 **Sun HY**, Cacciarelli TV, Singh N. Micafungin versus amphotericin B lipid complex for the prevention of invasive fungal infections in high-risk liver transplant recipients. *Transplantation* 2013; **96**: 573-578 [PMID: 23842191 DOI: 10.1097/TP.0b013e31829d674f]

48 **Trudeau RE**, Bowman LJ, Wills AR, Crippin JS, Chapman WC, Anderson C. Once weekly fluconazole for antifungal prophylaxis post-liver transplantation. *HPB (Oxford)* 2013; **15**: 541-547 [PMID: 23458063 DOI: 10.1111/hpb.12006]

49 **Antunes AM**, Teixeira C, Corvo ML, Perdigoto R, Barroso E, Marcelino P. Prophylactic use of liposomal amphotericin B in preventing fungal infections early after liver transplantation: a retrospective, single-center study. *Transplant Proc* 2014; **46**: 3554-3559 [PMID: 25498088 DOI: 10.1016/j.transproceed.2014.06.065]

50 **Winston DJ**, Limaye AP, Pelletier S, Safdar N, Morris MI, Meneses K, Busuttil RW, Singh N. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *Am J Transplant* 2014; **14**: 2758-2764 [PMID: 25376267 DOI: 10.1111/ajt.12963]

51 **Saliba F**, Pascher A, Cointault O, Laterre PF, Cervera C, De Waele JJ, Cillo U, Langer RM, Lugano M, Göran-Ericzon B, Phillips S, Tweddle L, Karas A, Brown M, Fischer L; TENPIN (Liver Transplant European Study Into the Prevention of Fungal Infection) Investigators; TENPIN Liver Transplant European Study Into the Prevention of Fungal Infection Investigators. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clin Infect Dis* 2015; **60**: 997-1006 [PMID: 25520332 DOI: 10.1093/cid/ciu1128]

52 **Giannella M**, Ercolani G, Cristini F, Morelli M, Bartoletti M, Bertuzzo V, Tedeschi S, Faenza S, Puggioli C, Lewis RE, Pinna AD, Viale P. High-dose weekly liposomal amphotericin b antifungal prophylaxis in patients undergoing liver transplantation: a prospective phase II trial. *Transplantation* 2015; **99**: 848-854 [PMID: 25531982 DOI: 10.1097/TP.0000000000000393]

53 **Eschenauer GA**, Kwak EJ, Humar A, Potoski BA, Clarke LG, Shields RK, Abdel-Massih R, Silveira FP, Vergidis P, Clancy CJ, Nguyen MH. Targeted versus universal antifungal prophylaxis among liver transplant recipients. *Am J Transplant* 2015; **15**: 180-189 [PMID: 25359455 DOI: 10.1111/ajt.12993]

54 **Balogh J**, Gordon Burroughs S, Boktour M, Patel S, Saharia A, Ochoa RA, McFadden R, Victor DW, Ankoma-Sey V, Galati J, Monsour HP Jr, Fainstein V, Li XC, Grimes KA, Gaber AO, Aloia T, Ghobrial RM. Efficacy and cost-effectiveness of voriconazole prophylaxis for prevention of invasive aspergillosis in high-risk liver transplant recipients. *Liver Transpl* 2016; **22**: 163-170 [PMID: 26515643 DOI: 10.1002/lt.24365]

55 **Perrella A**, Esposito C, Amato G, Perrella O, Migliaccio C, Pisaniello D, Calise F, Cuomo O, Santaniello W. Antifungal prophylaxis with liposomal amphotericin B and caspofungin in high-risk patients after liver transplantation: impact on fungal infections and immune system. *Infect Dis (Lond)* 2016; **48**: 161-166 [PMID: 26513601 DOI: 10.3109/23744235.2015.1100322]

56 **Fortún J**, Muriel A, Martín-Dávila P, Montejo M, Len O, Torre-Cisneros J, Carratalá J, Muñoz P, Fariñas C, Moreno A, Fresco G, Goikoetxea J, Gavaldá J, Pozo JC, Bodro M, Vena A, Casafont F, Cervera C, Silva JT, Aguado JM; Grupo de Estudio de Infección en Pacientes Trasplantados-Grupo de Estudio de Micología Médica (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica), and Red Española de Investigación en Patología Infecciosa. Caspofungin versus fluconazole as prophylaxis of invasive fungal infection in high-risk liver transplantation recipients: A propensity score analysis. *Liver Transpl* 2016; **22**: 427-435 [PMID: 26709146 DOI: 10.1002/lt.24391]

57 **Chen YC**, Huang TS, Wang YC, Cheng CH, Lee CF, Wu TJ, Chou HS, Chan KM, Lee WC, Soong RS. Effect of Prophylactic Antifungal Protocols on the Prognosis of Liver Transplantation: A Propensity Score Matching and Multistate Model Approach. *Biomed Res Int* 2016; **2016**: 6212503 [PMID: 27747235 DOI: 10.1155/2016/6212503]

58 **Lavezzo B**, Patrono D, Tandoi F, Martini S, Fop F, Ballerini V, Stratta C, Skurzak S, Lupo F, Strignano P, Donadio PP, Salizzoni M, Romagnoli R, De Rosa FG. A simplified regimen of targeted antifungal prophylaxis in liver transplant recipients: A single-center experience. *Transpl Infect Dis* 2018; **20**: e12859 [PMID: 29427394 DOI: 10.1111/tid.12859]

59 **Jorgenson MR**, Descourouez JL, Marka NA, Leverson GE, Smith JA, Andes DR, Fernandez LA, Foley DP. A targeted fungal prophylaxis protocol with static dosed fluconazole significantly reduces invasive fungal infection after liver transplantation. *Transpl Infect Dis* 2019; **21**: e13156 [PMID: 31390109 DOI: 10.1111/tid.13156]

60 **Kang WH**, Song GW, Lee SG, Suh KS, Lee KW, Yi NJ, Joh JW, Kwon CHD, Kim JM, Choi DL, Kim JD, Kim MS. A Multicenter, Randomized, Open-Label Study to Compare Micafungin with Fluconazole in the Prophylaxis of Invasive Fungal Infections in Living-Donor Liver Transplant Recipients. *J Gastrointest Surg* 2020; **24**: 832-840 [PMID: 31066013 DOI: 10.1007/s11605-019-04241-w]

61 **Aguado JM**, Varo E, Usetti P, Pozo JC, Moreno A, Catalán M, Len O, Blanes M, Solé A, Muñoz P, Montejo M; TOSCANA Study Group. Safety of anidulafungin in solid organ transplant recipients. *Liver Transpl* 2012; **18**: 680-685 [PMID: 22328277 DOI: 10.1002/lt.23410]

62 **Muilwijk EW**, Lempers VJ, Burger DM, Warris A, Pickkers P, Aarnoutse RE, Brüggemann RJ. Impact of special patient populations on the pharmacokinetics of echinocandins. *Expert Rev Anti Infect Ther* 2015; **13**: 799-815 [PMID: 25947367 DOI: 10.1586/14787210.2015.1028366]

63 **Maertens JA**, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR 3rd, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann AJ. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016; **387**: 760-769 [PMID: 26684607 DOI: 10.1016/S0140-6736(15)01159-9]

64 **Groll AH**, Townsend R, Desai A, Azie N, Jones M, Engelhardt M, Schmitt-Hoffman AH, Brüggemann RJM. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. *Transpl Infect Dis* 2017; **19** [PMID: 28722255 DOI: 10.1111/tid.12751]

65 **Becchetti C**, Ferrarese A, Cattelan A, Barbieri S, Feltracco P, Saluzzo F, Cillo U, Senzolo M, Germani G, Burra P. Geotrichum capitatum Invasive Infection Early After Liver Transplant. *Exp Clin Transplant* 2020; **18**: 737-740 [PMID: 31801448 DOI: 10.6002/ect.2019.0170]

66 **Shoham S**, Dominguez EA; AST Infectious Diseases Community of Practice. Emerging fungal infections in solid organ transplant recipients: Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13525 [PMID: 30859651 DOI: 10.1111/ctr.13525]

**Footnotes**

**Conflict-of-interest statement:** The Authors have nothing to disclose regarding this manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** October 18, 2020

**First decision:** November 13, 2020

**Article in press:** November 29, 2020

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Kang KJ **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Liu JH

**Figure Legends**



**Figure 1 CT-scan.** A: Chest CT-scan of a young male patient with hepatitis B virus related cirrhosis and acute-on-chronic liver failure, waitlisted for liver transplantation, who developed invasive aspergillosis; B: He was temporarily withdrawn from the waiting list, and received antifungal treatment for a total of 13 d, with a clinical and radiological improvement. He subsequently died of bacterial super-infection before liver transplantation.

**Table 1 Studies assessing the prevalence of invasive fungal disease in patients with acute-on-chronic liver failure**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study design** | **Diagnostic criteria for IFD** | **Prevalence of IFD** | **Outcome** | **Risk factors for IFD** |
| Verma *et al*[11], 2019 | Single-center, retrospective study on ICU patients from India | EORTC/MSG diagnostic criteria | 39/264 (14.7%). 11 (28%) proven. 25 (64%) IC and 14 (36%) IA | In-hospital mortality 77% | Hemodialysis. Prior antibiotic use |
| Fernández *et al*[12], 2018 | Multi-center, prospective study on non-ICU ACLF patients across Europe | EORTC/MSG diagnostic criteria | 8/407 (1.9%). 7 (87%) IC. 1 (13%) IA | 28-d and 90-d mortality 57% and 71%, respectively | NR |
| Theocharidou *et al*[13]1, 2016 | Analysis from prospectively collected database on ICU patients across the United Kingdom | EORTC/MSG diagnostic criteria (only *proven* IFD considered for the analysis) | 8/782 (1%) | In-ICU and in-hospital mortality 0% | NR |
| Chen *et al*[14]2, 2013 | Retrospective single center study from China on IA | EORTC/MSG diagnostic criteria | 39/787 (4.9%) | Cumulative mortality 61% | Age. Hepatic encephalopathy. Steroid use |
| Lin *et al*[15]2, 2013 | Single center retrospective study from non-ICU hepatitis B cirrhotic patients from China | EORTC/MSG diagnostic criteria | 60/126 (47.6%). Proven IFD: 14 (23%). 9 (64%) C. Albicans 2 (14%) Criptococcus neoformans: 1 (7%) C. Tropicalis; 1 (7%) C. Glabrata; 1 (7%) IA | Cumulative mortality 40% | Hepatitis B viral load |
| Levesque *et al*[16], 2019 | Single center retrospective study on ICU patients with cirrhosis and IA in France | EORTC/MSG diagnostic criteria | 60/362 (16.6%). 43/60 (71.7%) fulfilled ACLF criteria. 17/60 (28%) had IA | IA associated cumulative in-hospital mortality 71% | NR |

1The manuscript did not extensively classify patients according to acute-on-chronic liver failure (ACLF) criteria; 2This study used the APASL criteria for ACLF diagnosis. Colonizations are not reported. ACLF: Acute-on-chronic liver failure; IA: Invasive aspergillosis; IC: Invasive candidiasis; IFD: Invasive fungal disease; NR: Not reported; ICU: Intensive care unit; EORTC: European Organization for Research and Treatment of Cancer; MSG: Mycoses Study Group.

**Table 2 Studies published in the last 10 years on fungal prophylaxis in the liver transplantation setting**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Study design** | **Prophylaxis regimen** | **Patient selection criteria** | **Outcomes** |
| Saliba *et al*[37], 2013 | Single-center study. LTs between 1999-2005. Effectiveness of targeted prophylaxis | Group 1: L-AmB (1 mg/kg/d for 1 wk, then 2.5 mg/kg/ twice a week for 3 wk) OR fluconazole (200-400 mg/d for 3 wk for those with pre-LT Candida colonization). Group 2: No prophylaxis | High risk group (≥ 1 RF): ALF; ICU prior to LT; re-LT; re-operation | Group 1: 198 LT recipients (n.146 L-Amb, n. 50 fluconazole, n. 2 amphotericinB). Group 2: 467 LT recipients. Lower 1 yr IFD occurrence in Group 1 (17.7% *vs* 32.4%; *P* < 0.001). IA occurrence not significantly different between groups. 1 yr graft and patient survival impaired after IFD occurrence |
| Sun *et al*[47], 2013 | Single-center study. LTs between 1997-2009. Comparative study for targeted prophylaxis in at-risk patients | Group 1: Amphotericin B lipid complex (5 mg/kg/d for 21 d). Group 2: Micafungin (100 mg/d for 21 d) | High risk group (≥ 1 RF): Post-LT RRT; re-LT; re-operation | Group 1 *vs* 2: 24 *vs* 18 LT recipients. Similar 90d IFD occurrence (11% *vs* 8.3%) and 90d mortality (29.2% and 22.2%) between groups |
| Trudeau *et al*[48], 2013 | Single-center study. LTs between 2005-2008. Effectiveness of universal prophylaxis | Fluconazole (200 mg i.v./p.o. once weekly for 3 mo) | High risk group (≥ 2 RF): Re-LT; sCr > 2 mg/dL or RRT within 48 h prior to LT; choledochojejunostomy; transfusion of > 40 BP; operation time > 11 h; peri-operative fungal colonization  | 221 LTs (18 fulfilled high risk criteria). 6 mo overall IFD occurrence equal to 4.9%. Higher IFD occurrence in high-risk patients (16.7% *vs*. 3.4%, *P* = 0.03) |
| Antunes *et al*[49], 2014 | Single-center study. LTs between 2008-2011. Effectiveness of targeted prophylaxis | Group 1 (high risk): L-AmB 100 mg/d for 2 wk OR nystatin alone. Group 2 (low-risk): Nystatin | High risk (≥ 1 RF): Urgent LT; sCr > 2 mg/Dl; AKI after LT; re-LT; re-operation; transfusion of > 40 BP | Group 1 *vs* Group 2: 104 *vs* 357 LT recipients. 66 (63%) patients belonging to group 1 received L-AmB prophylaxis. Cumulative 3-mo IFD occurrence 2.5%. Higher IFD occurrence in high-risk patients who didn’t receive L-AmB prophylaxis (4.5% *vs* 13%, *P* = 0.01) |
| Winston *et al*[50], 2014 | Randomized, double-blind trial. LTs between 2010-2011. Comparative trial for targeted prophylaxis | Group 1: Anidulafungin (200 mg/d loading those, then 100 mg/d) for 3 wk or until discharge. Group 2: fluconazole (400 mg/d, adjusted according renal function) for 3 wk or until discharge | High risk group (≥ 1 RF): Re-LT; ALF; Steroids for at least 2 wk before LT; ICU stay > 48 h. Colonization with Candida (> 2 sites) within 4 wk before LT; transfusion of ≥ 15 BP; operative time > 6 h; RRT at the time or within 7 d of LT; re-operation | 200 patients 1:1 randomized. Similar cumulative IFD occurrence between cohorts (5.1% *vs* 8%, *P* = 0.4). Equal 3 mo post-LT mortality (12% each arm). 0% IFD related deaths |
| Saliba *et al*[51], 2015 | Randomized, open-label study. LTs between 2009-2012. Comparative trial for targeted prophylaxis | Group 1: Micafungin (100 mg/d for 21 d or until discharge) in high risk patients. Group 2: Center-specific standard care (fluconazole 200–400 mg/d OR L-AmB 1–3 mg/kg/d OR caspofungin 70 mg loading dose followed by 50 mg/d) in high risk patients | High risk patients (≥ 1 RF): Re-LT; ALF; Pre- or post-operative sCr clearance ≤ 40 mL/min) or RRT; ICU 48 h prior to LT; re-operation within 5d of LT; choledochojejunostomy; peri-operative Candida colonization (≥ 2 positive cultures); prolonged mechanical ventilation > 48 h after LT; transfusion of ≥ 20 BP | Group 1 *vs* Group 2: 174 *vs* 173 LT recipients (140 and 137 LT completed the study in each arm). Micafungin was non inferior to standard of care (composite primary and secondary efficacy endpoints) |
| Giannella *et al*[52], 2015 | Prospective non-randomized trial. LTs between 2009-2013. Safety of high dose L-AmB for targeted prophylaxis | L-AmB 10 mg/Kg once a week until hospital discharge for a minimum of 2 wk | High risk for IC (≥ 2 RF): ICU in 90d prior LT; perioperative Candida colonization; Choledochojejunostomy; transfusion of > 40 BP; AKI; rejection within 2 wk after LT; CMV DNA > 100.000 copies/mL; prolonged or repeated operation. High risk for IA (≥ 1 RF): ALF; steroid treatment before LT; multivisceral transplant; RRT; rejection; re-LT; re-operation  | 76 patients enrolled (39 having ≥ 2 RF for IC; 37 having ≥ 1 RF for IA). 10 patients discontinued therapy (6 for L-AmB related adverse events; 4 for IFD). 2 episodes of proven IC occurred |
| Eschenauer *et al*[53], 2015 | Single-center study. LTs between 2008-2012. Effectiveness of targeted prophylaxis | Universal prophylaxis (LTs between 2008-2010): Voriconazole 200 mg BID. Targeted prophylaxis (LTs between 2010-2012): Group 1: Voriconazole 200 mg BID for 30 d. Group 2: Fluconazole 400 mg/d during post-LT ICU stay. Group 3: No prophylaxis | Inclusion criteria for Group 1 (≥ 1 RF): re-LT; ALF; RRT; re-operation within 30 d after LT. Inclusion criteria for Group 2 (≥ 1 RF): Choledochojejunostomy; transfusion of > 40 BP and operation time ≥ 11 h; candida colonization or infection within 3 mo before LT | Universal prophylaxis: 236 LTs. Targeted prophylaxis: 145 LTs (group 1 *vs* 2 *vs* 3: 78 *vs* 11 *vs* 55). Cumulative IFD occurrence 5.2% (targeted *vs* universal group: 6.9% *vs* 4.2%; *P* = 0.34). 40% breakthrough IFD. Similar 100-d mortality between targeted and universal prophylaxis group  |
| Balogh *et al*[54], 2016 | Single-center study. LTs between 2008-2014. Targeted prophylaxis against IA | Group 1: Voriconazole 200 mg BID for 90 d. Group 2: Oral nystatin OR fluconazole | High risk group: MELD score > 25. OR ≥ 2 RF: Pre-LT ICU stay > 24h; inotropic support; RRT; re-LT; Combined transplant; pre-LT mechanical ventilation; ALF | Group 1 *vs* Group 2: 174 *vs* 140 LT recipients; no episodes of IA occurred; no difference in graft and patient survival curves between cohorts |
| Perrella *et al*[55], 2016 | Single-center study. LTs between 2006-2012. Comparative observational study for targeted prophylaxis | Group 1: L-AmB (3 mg/kg/d). Group 2: Caspofungin (70 mg/d loading dose, then 50 mg/d) | High risk patients (≥ 3 RF): sCr clearance < 30 mL/min and/or sCr > 4 mg/mL. Pre-LT Candida colonization. Pre-LT antibiotic use > 10 d. Pre-LT hospitalization > 7 d. Operation time ≥ 9 h. Warm ischemia ≥ 45’. Re-LT. Transfusion of > 14 BP. Choledochojejunostomy | Group 1 *vs* Group 2: 28 *vs* 26 LTs. No episodes of IFD occurred in both groups |
| Fortún *et al*[56], 2016 | Multicenter study. LTs between 2005-2012. Comparative observational study for targeted prophylaxis | Group 1: Caspofugin (50 mg/d). Group 2: Fluconazole 100-400 mg/d (median 200 mg/d) | High risk group (≥ 1 RF): Re-LT; RRT within 30 d; LT for ALF. OR ≥ 2 of the following RF: Transfusion of ≥ 20 BP; Choledochojejunostomy; Peri-operative Candida colonization (≥ 2 sites); re-operation within 7 d | Group 1 *vs* Group 2: 97 *vs* 98 LT recipients. Median prophylaxis duration: 22 and 24 d, respectively. Similar 6-mo IFD occurrence (5.2% *vs* 12.2%). Reduced risk of IA in LT recipients receiving caspofungin. Similar overall mortality and IFD-related mortality between groups |
| Chen *et a*l[57], 2016 | Single-center study. LTs between 2005-2014. Effectiveness of targeted prophylaxis | Group 1: Anidulafungin (100 mg/d) OR micafungin (100 mg/d)1. Group 2: No prophylaxis | High risk patients: MELD ≥ 20 | Group 1 *vs* 2: 201 *vs* 201 LT recipients (propensity score matching). Similar IFD occurrence (11.2% *vs* 18.9%, *P* = 0.052). Lower cumulative mortality in Group 1 (23.4% *vs* 40.8%, *P* = 0.001) |
| Giannella *et al*[35], 2016 | Retrospective, single-center study. LTs between 2010-2014. Evaluation of risk factors for a targeted antifungal prophylaxis | Group 1 (no RF): No prophylaxis. Group 2 (1 RF IC): Fluconazole. Group 3 (high risk patients): Anti-mold agent | High-risk patients for IC (≥ 2 RF): Prolonged operation; choledochojejunostomy; Pre-LT Candida colonization; re-LT; AKI. High-risk patients for IA (≥ 1 RF): ALF; RRT after LT; re-operation; re-LT | 303 patients evaluated (Groups 1 *vs* 2 *vs* 3: 91 *vs* 61 *vs* 151). Antifungal prophylaxis administered to 45.9% patients (80 L-AmB; 18 caspofungin; 41 fluconazole). Cumulative IFD prevalence 6.3%. Fluconazole prophylaxis independently associated with IFD development.  |
| Lavezzo *et al*[58], 2018 | Single-center study. LTs between 2011-2015. Effectiveness of targeted prophylaxis | Group 1 (high risk): Amphotericin B lipid complex (3 mg/kg/d) OR L-AmB (2 mg/kg/d), for 5 to 10 d after LT. Group 2 (low risk): No prophylaxis  | High-risk group (≥ 1 RF): Hospitalization at LT or in the 30 d prior LT for infection; ALF; Primary-non-function; Steroid treatment at LT; sCr > 2 mg/dl before LT; RRT before or after LT; MELD > 30 at LT; re-LT, split liver, combined transplantation; Transfusion of ≥ 20 BP; choledochojejunostomy; re-operation; thymoglobulin therapy; positive fungal culture of donor preservation fluid  | Overall IFD prevalence 2.8% (all in the targeted prophylaxis group). 1 yr mortality higher in prophylaxis group (12.5% *vs* 1.8%, *P* = 0.001). 1-yr mortality higher in IFD patients (33.3% *vs* 6.4%; *P* < 0.001) |
| Jorgenson *et al*[59], 2019 | Single-center study. LTs between 2009-2016. Effectiveness of fixed dose prophylaxis | Group 1: Fluconazole fixed dose (400 mg/d for 14d) in at-risk patients. Group 2: Unsupervised antifungal protocols | High risk group (≥ 1 RF): Operation time > 10 h; re-operation within 30 d; re-LT; Pre LT dialysis; pre-LT Candida colonization; pre-LT hospitalization > 7 d; Choledochojejunostomy; MELD ≥ 35; transfusion ≥ 40 BP | High-risk patients: Group 1 *vs* Group 2: 50 *vs* 139. Reduction of 1-yr IFD among high-risk cohorts (12.5% *vs* 26.6%). Similar 1 yr patient and graft survival |
| Kang *et al*[60], 2020 | Multicenter, randomized, open-label trial. Living donor LTs 2012-2015. Comparative study for universal prophylaxis | Group 1: Micafungin (100 mg/d for 3 wk or until hospital discharge). Group 2: Fluconazole (100-200 mg/d for 3 wk or until hospital discharge) | Universal prophylaxis | Group 1 *vs* Group 2: 69 *vs* 75 LT recipients. IFD occurrence within 3 wk: 1/69 *vs* 0/75. Micafungin was non-inferior to fluconazole |

1Duration of prophylaxis not reported. BP: Blood products; IA: Invasive aspergillosis; IC: Invasive candidiasis; IFD: Invasive fungal disease; L-AmB: Liposomal amphotericin B; LT: Liver transplantation; RF: Risk factor; RRT: Renal replacement therapy; sCr: Serum creatinine; ICU: Intensive care unit.