Invasive fungal infections in acute and chronic liver impairment: A systematic review

Tobias Lahmer¹ | Paula M. Peçanha-Pietrobom² | Roland M. Schmid¹ | Arnaldo Lopes Colombo²

¹Klinik und Poliklinik für Innere Medizin II, Klinikum rechts der Technischen, Universität München, Munich, Germany
²Division of Infectious Diseases, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil

Abstract
Patients with acute and chronic liver impairment are susceptible to invasive fungal infections such as candidemia and invasive pulmonary aspergillosis as a result of cirrhosis-associated immune dysfunction, humoral immunodeficiency, cell-mediated dysfunction and systemic inflammation. Besides classical risk factors for invasive fungal infection, acute-on-chronic liver failure, corticosteroid use, gastrointestinal bleeding, and prophylactic use of antibiotics are all additional conditions which are related to the potential development of fungal infections. Therefore, high-risk patients should be carefully followed by microbiological surveillance including cultures but also by imaging and fungal biomarkers for providing early diagnosis. Echinocandins are still the mainstay and first line antifungal therapy in cases of invasive candidiasis. Due to concerns of liver toxicity and in cases of renal impairment liposomal amphotericin B is a suitable alternative to voriconazole in patients with invasive pulmonary aspergillosis. Although, data of isavuconazole and posaconazole use in those patients are also promising more specific studies in the subgroup of patients with liver impairment are needed. Especially, due to the late diagnosis and multiple organ dysfunction usually present in patients with liver impairment morbidity and mortality rates remain high. Based on the broad spectrum of diverse reports with varying content and quality and in some cases lack of evidence we performed a systematic review on this topic.

Keywords
candidemia, end-stage liver disease, invasive fungal infection, invasive pulmonary aspergillosis, liver impairment, severe alcoholic steatohepatitis

1 | INTRODUCTION
Invasive fungal infections (IFI) are more and more recognised as an emerging problem associated with increased morbidity and mortality rates, beyond the typical at-risk patients.¹⁻³ One of these groups are patients with liver impairment. This includes not only patients with acute liver failure (ALF) but also patients with chronic end-stage liver disease (ESLD) and the subgroup of patients with severe alcoholic hepatitis (SAH), which are associated with a variety of host immune dysfunctions.⁴⁻⁵

Although, best investigated in ESLD, the so-called cirrhosis-associated immune dysfunction (CAID) can serve as a model for liver impairment...
impairment also in ALF. In these patients, not only the innate but also the adaptive immune functions with an increased susceptibility to infections is disturbed.\textsuperscript{6,7} CAID involves a state of immunodeficiency, and in parallel a state of persistent activation of the immune system cells, with increased production of pro-inflammatory cytokines and systemic inflammatory response syndrome (SIRS).

CAID is a multifactorial process, resulting from bacterial overgrowth, dysbiosis and increased translocation, which is responsible for a continuous (over) stimulation of immune system cells.

As recently reviewed by Albillos et al. this interaction of gut bacteria with the immune system lead to a so-called 'immune paralysis' followed by an immune dysfunction at multiple cell levels (neutrophils, monocytes, T and B lymphocytes and natural killers).\textsuperscript{6}

The incidence of infections in patients with liver impairment has been evaluated in previous therapeutic trials as part of the secondary outcomes or adverse events of the studied intervention. However, these studies are typically not designed to address the issue of infection complications, in detail IFI, in liver impairment patients.

Following these implications, IFI are underrepresented in studies but much more in clinical practice. This is why IFI are associated with an increased risk of morbidity and elevated mortality rates that may rise up between 73% and 100% in patients infected by \textit{Candida} \textit{spp.} or \textit{Aspergillus} \textit{spp.}\textsuperscript{4,6,9,30} Referring to the morbidity, the burden of IFI in patients with acute and chronic liver failure has been recently addressed in more focused cohort studies showing prevalence rates ranging between 2.5% and 10\%.\textsuperscript{11-13}

In this scenario, aim of this review is to address epidemiological, clinical aspects and challenges in the early diagnosis and treatment of IFI in patients with acute and chronic liver impairment.

2 | METHODS

2.1 | Literature search

In this systematic review, we searched PubMed from January 1960 up to December 2020, for articles published in the context of fungal infections and liver disease. Focus was for both, \textit{Aspergillus} \textit{spp.} and \textit{Candida} \textit{spp.} infections: ALF; alcoholic steato hepatitis and ESLD.

The search strategy was: ('ALF and aspergillosis/candidiasis' OR 'ALF and invasive pulmonary aspergillosis' OR 'ALF and mould infection' OR 'ALF and invasive fungal disease') AND ('alcoholic hepatitis and aspergillosis/candidiasis OR SAH and fungal infection' OR 'alcoholic steato hepatitis and aspergillosis' OR 'alcoholic steato hepatitis and fungal infection') AND ('liver cirrhosis and aspergillosis' OR 'liver cirrhosis and pulmonary aspergillosis' OR 'liver cirrhosis and invasive fungal disease' OR 'acute-on-chronic liver failure and Aspergillosis' OR 'acute-on-chronic liver failure' OR 'pulmonary aspergillosis' OR 'acute on chronic liver failure and invasive fungal disease'). The same approach was used for \textit{Candida} \textit{spp.} and rare fungal infections.

The search was limited to English. We additionally searched reference list of included studies and relevant publications.

2.2 | Study selection criteria

For a study to be eligible for inclusion in this review, patients were required to have been diagnosed with underlying liver disease covered in this review based on underlying risk factors and clinical, laboratory, tissue histopathology and radiological findings.

Patients after liver transplantation were excluded from this review. On the one hand, these Patients are still represented in the current guidelines (solid organ transplantation), and on the other hand, the focus of this review is on patients with liver disease and not obvious immunosuppression and the risk for fungal infections.

Following our search criteria, a total of 665 articles could be identified on PubMed. Using our selection criteria and exclude doubled papers in each search category a total of 57 papers left which were included in this review.

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article related to micro-organisms.

3 | INVASIVE CANDIDIASIS (IC) IN ACUTE AND CHRONIC LIVER FAILURE

Patients with acute-or-chronic liver impairment are risk populations for developing fungemia and spontaneous \textit{Candida} \textit{spp.} peritonitis. Fungemia due to \textit{Candida} \textit{spp.} is the most common presentation of IFI in this population, accounting for >70% of all cases of invasive candidiasis (IC).\textsuperscript{9}

3.1 | Invasive candidiasis in ALF

Patients with ALF may present a high susceptibility to \textit{Candida} \textit{spp.} infections especially based on the impaired phagocytic function, the need for invasive procedures and exposition to antibiotic treatment.\textsuperscript{6} Data are scarce revealing on the epidemiology of invasive candidiasis in ALF patients excluding the scenario of liver transplantation and acute-on-chronic liver failure (ACLF). A prospective study published in the 90's described 32% of \textit{Candida} \textit{spp.} infections in 50 patients with ALF.\textsuperscript{14} Of note, this study has some limitations concerning diagnostic criteria of invasive candidiasis once cultures obtained from respiratory and mucosal samples were also considered as evidence of infection in some cases. Otherwise, if only cases with microbiologic documented invasive \textit{Candida} infections were considered, the prevalence remains 8% (4/50 patients).\textsuperscript{14} No further data has been published since then with this constellation.

3.2 | Invasive candidiasis in SAH

Severe alcoholic hepatitis is an acute hepatic manifestation typically following a heavy alcohol ingestion. SAH presents a clinical
setting of liver inflammation, hepatocyte injury, and fibrosis with a varying spectrum, from mild abnormalities of liver parameters to life-threatening (acute) liver failure. Beyond the typical liver injury often combined with hepatic encephalopathy, patients with SAH frequently develop renal impairment and multi-organ failure. The treatment for SAH is until now a matter of debate, however, corticosteroids (prednisolone 40 mg/day for up to 28 days), are still the most widely used treatment option. In addition to the high mortality rates caused by SAH itself, infections are one of the main complications, as well as one of the major causes of mortality in this setting. Patients with SAH are prone to infections, especially of bacterial origin, which are present in 30%–80% of SAH cases.

Only small series are published addressing IC specifically in SAH patients. The few available data assume a rate of IC in SAH varying between 2% and 9% which is associated with high mortality rates. Considering that five out eight cases of IC were documented in ICUs, it is difficult to determine whether episodes of candidemia were strongly related to the scenario of SAH or were mainly secondary to all other risk conditions usually seen in critically ill patients demanding life support for long periods. The main epidemiological studies in this scenario were summarised in Table 1.

### 3.3 Invasive candidiasis in ESLD

Most series of IC in ESLD point to ALF secondary to viral infections and alcoholic hepatitis treated with high dose corticosteroids as the main underlying conditions associated to this fungal infection. The condition that most substantially increases the risk of IC is ACLF that is a syndrome characterised by acute decompensation of patients with chronic cirrhosis, multiple organ failure(s) and high short-term mortality. Fernández et al evaluated a cohort of 642 patients with ACLF or only acute decompensation without other organs failures and found that invasive fungal isolation, invasive candidiasis and invasive aspergillosis were much more likely to be documented in the first group of patients (3.9% vs 0.4%, \( p = .005 \)).

It is consensus that most cases of IC in ESLD can be characterised as health care associated infections (65%–100%). Moreover, at the time of diagnosis, most patients are usually hospitalised in ICU and exposed to several classical risk conditions for IC as invasive medical procedures, antibiotics, steroids, parenteral nutrition, and haemodialysis.

Indeed, in the large series published by Bassetti et al, a multicentre study enrolling 241 patients with IC documented in 14 medical centres, 50.2% of them were admitted at ICU at the time of the diagnosis.

Besides the exposition to classical risk factors for candidemia, ESLD patients are more prone to develop gastrointestinal bleeding which is a risk condition for translocation and severe infections. Of note, this condition preceded 18% of all 241 episodes of IC reported by Bassetti et al. In a recent case-control study conducted by Bartoletti et al., the authors investigated 90 cases of IC in ESLD and 180 controls, where they identified the following independent risk factors for this conditions: previous (<30 days) gastrointestinal endoscopy (what may suggest previous gastrointestinal bleeding), previous (<30 days) antibiotic treatment for at least 7 days, presence of central venous line, total parenteral nutrition at infection onset and length of hospital stay.

Finally, severity of liver disease confirmed by a higher MELD- (model for ESLD) and Child Pugh score are both associated with higher risk of *Candida* spp. infections. The largest casuistic discussing IC in liver disease did not individualise the aetiology and risk conditions associated with candidemia and intra-abdominal candidiasis. The main comorbidities found were previous abdominal surgery and renal failure.

### Table 1 Candidemia and invasive pulmonary aspergillosis in patients with SAH

| Author/year | Study population (N), Study design | Clinical presentation of IFI (number of diagnosed patients) | Proportion of patients that received antifungal treatment | Mortality rate (%) / follow-up period |
|-------------|-----------------------------------|-------------------------------------------------------------|----------------------------------------------------------|---------------------------------------|
| Gustot T et al. 2014<sup>16</sup> | All adult patients admitted with a biopsy-proven diagnosis of SAH and recent onset of jaundice (94), prospective | Invasive aspergillosis, (15) Candidemia, (2) | 73% | NA 93%, 3 months |
| Lahmer T et al. 2014<sup>5</sup> | Critically ill patients with histological proven AH (12), retrospective | Invasive aspergillosis, (5) Candidemia, (3) | 100% | 100%, in-hospital 100%, in-hospital |
| Wernlund PG et al. 2014<sup>19</sup> | All patients admitted with AH for whom a blood culture was taken (32), retrospective | Candidemia, (1) Peritonitis + candidemia, (1) | NA | 33% in-hospital |

Abbreviations: IFI, invasive fungal infection; NA, not available.
In contrast, spontaneous peritonitis is a severe complication of advanced liver cirrhosis that can be found in up to 12% of patients with ESLD. Fungi are implicated as the aetiologic agent of spontaneous peritonitis in 3%-10% of cases, exhibiting higher mortality rates when compared to bacterial peritonitis (35%-100% vs 10%-50%).

The most comprehensive review on spontaneous fungal peritonitis (SFP) was published by Tariq in 2019 and reported a total of 82 cases described in the literature so far. Candida species, predominantly Candida albicans was the main fungal pathogen described (48%-81.8%) followed by Candida glabrata (6.66%-20%). Cryptococcus neoformans was the second most common genera of yeasts causing SFP.

The exposition of patients to broad spectrum antibiotics is a major inducer of gastrointestinal dysbiosis and increases substantially their risk of developing IC.

Antibiotic prophylaxis is frequently prescribed for ESLD patients with gastrointestinal bleeding, with previous SBP and patients with ascites exhibiting fluid protein <1.5 g/dl associated to either impaired renal functional or liver failure. In this context, the reduction in the intestinal bacterial microbiota results in significant fungal colonisation that may lead to translocation across the damaged gastrointestinal tract mucosa into the peritoneal cavity. The immunosuppression and malnutrition that are characteristically found in cirrhotic patients are both conditions that may promote fungal translocation and SFP.

In Table 2 epidemiological and clinical aspects related to candidemia and episodes of SFP in patient with ESLD as reported by studies describing at least 10 cases are described.

### 4 INVASIVE PULMONARY ASPERGILLOSIS IN ACUTE AND CHRONIC LIVER FAILURE

Approximately 43%-80% of invasive pulmonary aspergillosis (IPA) cases appear in nonhaematological malignancy patients. Typically, these patients do not fulfil the EORTC/MSG criteria for invasive aspergillosis, radiological findings are unspecific, and the performance of fungal biomarkers may be suboptimal when only serum samples are tested.

Lack of awareness, delayed diagnosis and treatment resulting in dramatically high mortality rates of up to 90%-100%. Even more, prophylactic strategies are until now neither established nor systematically investigated. In the following, the role of IPA in acute and chronic liver failure will be reviewed.

#### 4.1 Invasive pulmonary aspergillosis in ALF

The incidence and clinical relevance of IFI, especially of IPA in ALF is unknown and might be underdiagnosed. There are only small reports focusing on IPA in ALF, as described in Table 3. Even in the largest cohort study of Zhang et al. from 2017 most patients with IPA are not suffering from ALF but from ACLF which will be discussed in the following.

Based on these data a general recommendation for screening of these patients could not be given, it should be recognised as a potential complication especially in cases of pulmonary worsening under antibiotic treatment.

#### 4.2 Invasive pulmonary aspergillosis in SAH

Although, associated with tremendously high fatality rates, little is known about the incidence of IPA in SAH. Based on selected reports, incidences vary between 16% and 42% (see Table 1).

Controlled postmortem or autopsy studies were not reported in patients with SAH and IPA.

Two important case series addressed IPA in SAH. A prospective study that followed 94 biopsy-proven severe AH episodes along 3 months reported fifteen cases of invasive aspergillosis (six proven, eight probable, and one possible) in this setting. The severity of this condition resulted in 100% of mortality in patients not eligible for liver transplantation, despite antifungal treatment. Another retrospective study of biopsy-proven SAH in ICU, found an even higher incidence of 40% of IA, with 100% mortality.

The high-reported mortality rates, above all in the ICU cohort, may also be explained by relevant comorbidities such as respiratory failure, acute decompensation of the liver or other coinfections beyond the SAH.

Beyond CAID caused immunodeficiency, superimposed SAH seems to worsen the immune status by a more markedly immunosuppressive profile of T lymphocytes (higher interleukin-10 expression and lower interferon-γ production) due to overexpression of inhibitory receptors (PD1, PDL1, TIM3 and galectin-9) and reduced neutrophil antimicrobial activities. Thus, it is reasonable to expect a higher incidence of infection in SAH than in ESLD.

On the other hand, a reasonable consideration is that corticosteroid treatment further increases the risk of infection; this is supported by some trials that evaluated corticosteroid treatment in SAH. However, these data are overall based on bacterial infections and furthermore a network meta-analysis did not show a significant association between infection and either treatment (corticosteroids or steroid free) compared to placebo.

Nonetheless, a high level of suspicion should be maintained with regard to all admitted patients with a diagnosis of SAH, as SIRS criteria and acute phase proteins are not accurate diagnostic markers for infection in these patients. Especially in patients with need for ICU and a MELD score >24, as described by Karakike et al.

#### 4.3 Invasive pulmonary aspergillosis in ESLD

As reported above, patients with ESLD have a poor short-term prognosis, especially in cases of ACLF and need for ICU.
**TABLE 2** Studies on invasive candidiasis in ESLD including 10 or more patients

| Author/year       | Study population (N), Study design                                                                 | Clinical presentation of IFI, (number of patients evaluated) | Proportion of fungal healthcare-associated infection | Proportion of patients that received antifungal treatment | Mortality rate (%)/follow-up period |
|-------------------|----------------------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------|-----------------------------------|
| Choi et al., 2004  | Patients with ascites samples positive for *Candida* species (21), retrospective                  | SFP, (10)                                                   | NA                                                | –                                                       | 50%/in-hospital                   |
| Hwang et al., 2014 | Patients with spontaneous Peritonitis (416), retrospective                                          | SFP, (10)                                                   | 80%                                               | 33.3%                                                   | 73.3%/30-day                      |
| Karvellas et al., 2015 | Cirrhotic patients with spontaneous peritonitis (126), retrospective multicentre cohort database | SFP, (11)                                                   | NA                                                | 81.8%                                                   | 100%/30-day                       |
| Bremmer et al., 2015 | Patients with SFP (25), retrospective                                                               | SFP, (25)                                                   | NA                                                | 60%                                                     | 60%/30-day                        |
| Alexopoulou et al., 2015 | Cirrhotic patients with culture-positive infection (185), retrospective                            | SFP, (11) candidemia, (8)                                   | 63.2%                                             | 47.4%                                                   | 57.9%/30-day                      |
| Friedrich et al., 2016 | Patients with their first episode of spontaneous peritonitis (311), retrospective                | SFP, (10)                                                   | 80%                                               | NA                                                      | NA                                |
| Lahmer et al., 2016  | Critically ill patients with liver cirrhosis (205), retrospective                                 | SFP, (20)                                                   | 65%                                               | 30%                                                     | 90%/in-hospital                   |
| Bassetti et al., 2017  | Cirrhotic adult patients with IAC and candidemia (241), retrospective multicentre cohort           | IAC, (72) candidemia, (169)                                 | 86.3%                                             | 88.4%                                                   | 35.3%/30-day                      |
| Bajaj, 2018         | Inpatients with cirrhosis (2.743), prospective, multicentre                                       | SFP, (8) Candidemia, (16)                                   | 100%                                              | 100%                                                    | SFP 57% Candidemia 64%/30-day     |
| Verma et al., 2019  | Critically ill patients with acute-on-chronic liver failure (264), retrospective                  | Invasive candidiasis, (25) invasive aspergillosis, (24)     | NA                                                | 76%                                                     | 77%/in-hospital                   |
| Bartoletti et al., 2020 | Hospitalised adult patients with liver cirrhosis for whom a blood culture was taken (270), prospective, multicentre case-control-control (1:2:2) | Candidemia, (90)                                            | 100%                                              | 84.5%                                                   | 41%/30-day                        |
TABLE 3  Invasive pulmonary aspergillosis in patients with acute liver failure

| Author/year | Study population (N), Study design | Clinical presentation of IFI, (number of patients evaluated) | Patients that received antifungal treatment (%) | Mortality rate (%)/follow-up period |
|-------------|-----------------------------------|---------------------------------------------------------------|-------------------------------------------------|-----------------------------------|
| Park GR et al., 198251 | Critically ill patients with acute liver failures (5), retrospective (case series of autopsies) | IPA (3) Brain abscess (2) Dissemination to heart, kidney and bowel was also documented | 0 | 100%/in-hospital |
| Walsh TJ et al. 198352 | A 9-year-old boy, 50- and 66-year-old women, retrospective (case series of autopsies) | IPA (3) Dissemination to brain was present in 2 of cases, and to liver, heart, spleen, pancreas, kidneys and thyroid in the other one | 0 | 100%/in-hospital |
| Watanabe A et al. 198730 | Patients with acute hepatic failure (36), retrospective | IPA (four pneumonia and two fungus balls) | 0 | 80%/66% in-hospital |
| Rolando et al., 199114 | Patients admitted at the hospital for acute hepatic failure (50), retrospective | IPA (1) | 0 | 100%/in-hospital |
| Zhang et al., 201829 | Patients with liver failure (1077), of whom 665 had acute hepatic disease, retrospective | IPA (53) | 83 | 83%/in-hospital |

Abbreviations: IFI, invasive fungal infection; IPA, invasive pulmonary aspergillosis.

In a French cohort, 80% of deaths in cirrhotic patients hospitalised in the ICU were related to infection and, in a meta-analysis, infection quadrupled the mortality of cirrhotic patients.31,32 Nearly 30% of ICU patients with ESLD have acquired or will acquire infections. The high incidence can mainly be explained by the CAID.6 Most cases of IFI are caused, as described above, by Candida spp. However, Aspergillus spp., especially in respiratory samples, have emerged as an important cause of life-threatening IFI in patients with ESLD (see Table 4).

Reported incidences vary between 0.3% and 14%, whereas the most studies report IPA rates of 5%–6% of observed patients.33,34 Studies with higher incidences typically report about critically ill patients.35 Risk factors for IPA in this population are a higher CHILD Pugh score (most patients CHILD C), elevated MELD and a higher ACLF grade. IPA in ESLD is typically associated with critical illness including mechanical ventilation with a higher proportion of patients with need of renal replacement therapy. COPD is in nearly 30% of these patients a typical comorbidity. This is in the line with the findings of Pratess et al.34 In this study, only 1.3% of the included patients had probable IPA. However, none of these patients were critically ill or fulfilled the criteria mentioned above.

High mortality rates of up to 100% in ESLD patients with IPA may be explained by CAID but furthermore, by the delayed diagnosis due to a low index of suspicion and often the misinterpretation of fungal samples as colonisation.

5 | OTHER FUNGAL INFECTIONS IN PATIENTS WITH LIVER IMPAIRMENT

Besides IC and Aspergillosis, considering the impaired phagocytic function usually associated to patients with advanced liver disease, cases of cryptococcosis and endemic mycosis have also been reported in this population.

Infections caused by Cryptococcus spp. have been described mostly in patients with ESLD.

The recent systematic review regarding SFP described Cryptococcus neoformans as the second main fungal pathogen, after Candida spp.24 One of the main manifestations of cryptococcal disease in this scenario are spontaneous peritonitis, representing at least 30% of cases, followed by meningitis and pulmonary disease.36,37 Fifty per cent of patients with spontaneous peritonitis had simultaneously positive blood cultures for Cryptococcus spp.36,38 Moreover, decompensated liver cirrhosis is described as a risk factor for developing cryptococcal invasive disease, with an adjusted odds ratio of 23.8 and 5.3 in the Taiwanese and United States casuistics, respectively.37,39 The authors mentioned that cryptococcosis in patients with cirrhosis was associated with high mortality rates (80%) and rapid progression to death, with median survival of 6 days in an American retrospective cohort.36,40,41 It is important to mention that a significant proportion of cirrhotic patients included in the case series with cryptococcosis (at least 9%–32%) had additional comorbidities such as malignancy, HIV infection, and solid organ transplantation.36,38,40

The diagnosis of peritonitis and invasive cryptococcal disease poses a challenge in this population due to low clinical suspicion and long time to yield Cryptococcus spp. in cultures, especially in the context of spontaneous peritonitis. On the other hand, when invasive disease is present, positivity of blood cultures may be as high as 56%.40 Regarding peritonitis, the ascitic fluid presents modest pleocytosis, with possible counts of less than 250 per mm3 in 40 to 80% of cases. Lymphocyte-dominant features may be found.36,38 A suggested strategy in patients with ESLD and spontaneous peritonitis with ascitic negative bacterial culture and, low polymorphonuclear
cells or lymphocyte dominancy is to proceed India ink stain and cryptococcal antigen of the material to improve sensitivity of the exam.38

Few reports on endemic mycoses including coccidioidomycosis and histoplasmosis have been published in this particular setting.42-45 Even in endemic areas for coccidioidomycosis, the prevalence of this fungal disease within ESLD patients was less than 5%, exhibiting mainly pulmonary manifestations. Indeed, liver disease is not an established risk factor for the acquisition of endemic mycoses or for its dissemination. No specific recommendations are possible to be made considering the lack of scientific evidences on this subject. In Table 5 the limited data available about cryptococcus and endemic mycosis in patients with chronic liver failure are summarised.

Sporadic reports have associated SAH and concomitant corticosteroid use with *Pneumocystis jirovecii* pneumonia (PCP), with a 100% case-fatality rate.46,47 Few additional reports mentioned cases of mucormycosis, and fusariosis in patients with SAH.48,49

| Author/year | Study population (N), Study design | Clinical presentation of IFI (number of patients evaluated) | Patients that received antifungal treatment (%) | Mortality rate (%)/ follow-up period |
|-------------|----------------------------------|----------------------------------------------------------|-----------------------------------------------|-------------------------------------|
| Meersseman W et al., 20043 | Adult patients with microbiological or histopathologic evidence of infection with *Aspergillus* (127), retrospective cohort | IPA (6) | 32% | 100%/in-hospital |
| Wu Z et al., 201291 | Adult patients with ACLIF (470), retrospective cohort | IPA (29) | 100% | 86%/in-hospital |
| Hassan et al., 20148 | Critically ill patients with ESLD (46), prospective study | Invasive aspergillosis (5) Candidemia (4) | NA | 28%/in-hospital |
| Chen J et al. 201432 | patients with liver cirrhosis (6600), retrospective cohort | IPA (19) | 63% | 89%/in-hospital |
| Prattes J et al. 201724 | Patients with liver cirrhosis presenting with fever and/ or respiratory symptoms (150), prospective cohort | Invasive aspergillosis (2) | 100% | 0%/in-hospital |
| Gao J et al. 201835 | Patients with ACLIF (565), retrospective cohort | Invasive pulmonary aspergillosis (20) | 100% | 55%/90-days |
| Levesque et al. 201931 | Adult patients critically ill with cirrhosis (986), retrospective | putative IPA(15) proven ipa (2) 15 pulmonary 2 brain and lung 43% colonisation | 76% | 71%/in-hospital |
| Verma et al. 201933 | Critically ill patients with acute-on-chronic liver failure (264), retrospective | Invasive candidiasis, (25) invasive aspergillosis, (24) | 76% | 77%/in-hospital |
| Lahmer et al. 201932 | Critically ill patients with underlying liver cirrhosis (84), retrospective | IPA (12) | 85% | 100%/in-hospital |

Abbreviations: IPA, invasive pulmonary aspergillosis.
6 | DIAGNOSTIC APPROACH FOR IFI

The low clinical response to antifungal therapy documented in most case series is probably related to a combination of factors including the severity of underlying conditions, low suspicion of fungal infections by clinicians, limited sensitivity of available diagnostic methods and late diagnosis and initiation of antifungal treatment (see Tables 1–5). Indeed, checking 16 papers where details about the chronology of the diagnosis were provided by the authors, 25% of 306 episodes of fungal infections had their microbiological documentation available for the clinicians only post-mortem. This finding emphasises the unattended need for validation of better diagnostic algorithms for IFIs in patients with liver disease.

A reasonable first step in building better strategies for the early recognition of IFIs could be to routinely check for risk conditions of IFI in this population. In this context, the presence of gastrointestinal bleeding, exposition to broad spectrum antibiotics, corticosteroids, invasive medical procedures, haemodialysis, parenteral nutrition and ACLF should be considered as red flags for the possibility of IFIs. In addition, advanced liver disease scores estimated by MELD > 25 and CHILD C as well as global clinical severity with high APACHE II, SOFA and Charlson scores are all factors associated to high risk of morbidity and mortality by IFI. 

Consequently, patients categorised as high-risk populations should be closely monitored for the possibility of IFI, including candidemia, SFP or IPA, what means to collect high volume blood and ascitic liquid fluid cultures or bronchoalveolar lavage (BAL) fluid using standard microbiological procedures for investigating the correct aetiology of any putative fungal infection in progress. 

Due to the low sensitivity and diagnostic delay of conventional cultures, new strategies have been developed for providing early recognition of patients with fungal infections, including PCR-based assays and fungal antigen tests. Unfortunately, there is a lack of data on the performance of non-culture methods used for the diagnosis of IFI in patients with acute-or-chronic liver impairment. An additional problem to mitigate the specificity of test results might be that the rate of fungal colonisation reaches up to 25% in critically ill patients with liver impairment. 

This is in the line with some evidence suggesting that this population is more likely to generate false-positive results, for example of 1.3 Beta D Glucan (BDG) assays, a pan-fungal antigen test that has been widely used to early detect patients with invasive candidiasis and is also used in cases of IPA. Otherwise, these antigen tests may be useful to exclude the possible fungal infections considering its high negative predictive value, including patients with suggested IPA. A single-centre study conducted by Verma et al., evaluating 39 episodes of invasive fungal infection in patients with ACLF, found sensitivity and specificity rates using BDG (80 pg/ml) for diagnosing IFI of 97.4% and 60%, respectively. A retrospective study delineated to assess the usefulness of detecting B-D-glucan level in peritoneal fluid for diagnosis of IAC in 33 critically ill adult patients presenting intra-abdominal infections found that a cut off value ≤310 pg/ml could eliminate fungal peritonitis with a negative predictive value of 100%. Nevertheless, no cirrhotic patient was included in this casuistic.

Beyond biomarkers, major diagnostic criteria for spontaneous peritonitis is a polymorphonuclear leukocyte count >250 cells/mm³ in ascitic fluid. It is important to mention that differences in cytology and biochemical analysis of peritoneal fluid fail to predict fungal infections
from any other pathogens, and coinfections with bacteria can be present in up to 75% of cases. Aiming to improve fungal infection diagnosis, inoculation of ascitic fluid into aerobic and anaerobic blood culture bottles and standard microbiological testing should be performed.

Even more challenging, as reported in Verma’s study and other series, is to achieve laboratorial criteria required for the categorisation of proven diagnosis of IPA in non-neutropenic patients. Clinical manifestations such as fever or cough are nonspecific of any infection, and the characteristic radiologic features of invasive aspergillosis represented by nodules, halo signs and crescent-air are present in only a minority of non-neutropenic patients. Screening diagnostic algorithms such as the modified AspICU score may be helpful but have not been validated in patients with liver impairment so far.

Non-culture based assays usually play a crucial role in the early diagnosis of invasive aspergillosis, including the detection of Galactomannan (GM) as well as specific PCRs.

The angio-invasive pattern of Aspergillus spp. infection typically documented in neutropenic haematologic patients that is responsible for the high sensitivity of the GM detection in serum samples may be absent in non-neutropenic ICU patients. As a consequence, the ESCMID–ECMM–ERS guideline of 2017 for the clinical management of aspergillosis downgraded the use of GM in blood samples in ICU patients, suggesting the implementation of GM detection in BAL fluids as the best strategy for diagnosing IPA in this population. By using a cutoff value of >1 ODI (optical density index), the test may yielded sensitivity results up to 90%-100% and specificity ranging from 75% to 92%.

PCR-based methods may be performed in any biological material and they are able to detect even minimal quantity of fungal DNA in all samples tested, but the vast majority of Candida PCR data are for whole blood or blood fractions. In addition, there are some concerns with the standardisation of these PCR assays that are usually ‘in house tests’ with substantial differences in methodologies used by different laboratories. A study comparing PCR with conventional microbiological tests for identification of Candida spp in blood and duodenal fluid in patients with liver cirrhosis found that PCR-based techniques were able to detect fungal pathogens in 96% of all episodes documented by positive cultures and provided additional fungal DNA detection in 44% of culture-negative episodes. No identification in ascites neither by culture or PCR was made.

Therefore, further studies are needed to demonstrate the cost effectiveness of universal screening of high-risk populations, as ESLD patients with multiple organ failures or sepsis after gastrointestinal bleeding, using BDG, GM and PCR methods for early detection of IFI in patients with liver impairment.

However, a trend towards an increase in frequency of C. glabrata candidemia is observed worldwide, with concerns about fluconazole resistance. An increasing number of C. glabrata infection was also documented in patients with liver disease (14.5% prevalence in a casuistic of 241 cases). Although, most isolates remain susceptible to echinocandins, some centres have already documented resistance, with prevalence rates usually less than 3%-5%.

All randomised clinical trials with echinocandins enrolled basically patients with fungemia (instead of deep-seated Candida infections), with the consequence that international guidelines recommend echinocandin usage as first line treatment in the management of different clinical presentations of invasive candidiasis.

Of note, preexisting liver disease was an exclusion criteria in the main RCT that compared echinocandins with azoles in the treatment of IC. Despite limitations of the actual scientific evidences available in this particular setting, echinocandins presents the advantage of limited drug-drug interaction when compared to fluconazole and there is no recommendation for adjusting dose in renal failure. Finally, in a recent randomised clinical trial isavuconazole failed to demonstrate non-inferiority when compared to caspofungin in the treatment of patients with IC. This result corroborates the better results of anidulafungin in comparison to fluconazole in another randomised clinical study conducted in patients with IC. It is not clearly demonstrated if there is any preferable echinocandin to be used in patients with advanced liver failure. Anidulafungin is probably the safer choice in patients with hepatic failure once its metabolic pathway does not involve the liver.

Although, caspofungin and micafungin undergo substantial hepatic metabolism, apparently, in two smaller clinical experiences only minimal changes in pharmacokinetics of caspofungin has been reported in patients with liver failure, apparently with no clinical impact, even in patients with Child–Pugh B or C liver disease. On the other hand, an increase of the AUC during caspofungin treatment, resulted in a manufacturer’s dose reduction recommendation for patients with Child–Pugh B or C liver disease. Nevertheless, Gustot et al. recently showed that dose reduction of caspofungin to 35 mg in cirrhotic patients resulted in lower drug exposure than that obtained by non-cirrhotic patients using the conventional approved dose.

Consequently, the correct dose of caspofungin in patients with liver impairment is still under debate and further prospective studies are necessary to establish a stable recommendation.

De-escalation therapy to azoles (especially fluconazole) should be encouraged whenever possible after clinical stabilisation of the patients. As recommended in recent guidelines fluconazole treatment is indicated in non-critically ill patients infected by Candida isolates if these are susceptible to azoles.

Referring to the IAC treatment, several studies have reported a low penetration rate and altered pharmacodynamics of echinocandins into the abdominal cavities what might be a reason for echinocandin resistance, for example for Candida glabrata in deep seated IC.
In patients with suspected azole- and/or echinocandin-resistant *Candida* spp. infections, lipid formulation Amphotericin B (3–5 mg/kg daily) is recommended. The duration of therapy for candidemia without obvious metastatic complications is 14 days after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia which can be also used in cases of IAC.67,68

To date, the antifungal agents licenced for the first line treatment of IPA include voriconazole, isavuconazole and liposomal amphotericin B. However, as also stated in the latest ESCMID-ECMM-ERS guidelines, liposomal amphotericin B is usually the first therapeutic option in patients with liver insufficiency.60 This recommendation is based on the experiences of drug-drug interactions and toxicities in patients with liver impairment and voriconazole treatment. In contrast, in two small studies, the treatment with liposomal amphotericin B in patients with liver impairment presented good tolerability.58,86

Overall, Isavuconazole opens a new possibility for treatment of IA, with fewer toxicities than polienics and voriconazole, presenting predictable pharmacokinetics.87

Moreover, as recently published by Maertens et al.88 posaconazole was non-inferior to standard treatment with voriconazole.

Although, promising data in patients with neutropenia or allo-HSCT are available, we certainly need further investigations about the efficacy and tolerance of isavuconazole and posaconazole in critically ill patients and ESLD.

The role of antifungal prophylaxis has not been correctly investigated. Nevertheless, based on specificities of different clinical scenarios it could be considered as an individual approach.

8 | CONCLUSION

Patients with acute-or-chronic liver impairment are prone to infections, mainly of bacterial origin, however, IFI are emerging, are underdiagnosed and are associated with high morbidity and mortality rates.

Based on pathophysiological implications rooted in complex interactions between liver impairment and the immune system, a high suspicion to IFI is warranted. A prompt and aggressive diagnostic strategy, including traditional cultures of specimens, biomarkers and imaging is needed to reveal these opportunistic infections. This strategy includes also an adequate antifungal treatment which was associated with a decreased risk of 30-day mortality. The role of antifungal prophylaxis is currently unknown and should be investigated in clinical trials.

AUTHOR CONTRIBUTION

Tobias Lahmer: Conceptualization (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). Paula Massaroni Pecanha-Pietrobom: Conceptualization (equal); Data curation (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). Roland Schmid: Conceptualization (equal); Data curation (equal); Writing – review & editing (equal). Arnaldo Lopes Colombo: Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

ORCID

Tobias Lahmer https://orcid.org/0000-0003-1008-5311
Paula M. Pecanha-Pietrobom https://orcid.org/0000-0003-0360-9922

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