

# Liver fungal infections: an overview of the etiology and epidemiology in patients affected or not affected by oncohematologic malignancies

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**Abstract:** Fungal infections of the liver, most commonly caused by *Candida* spp., often occur in patients with hematologic malignancies treated with chemotherapy. Colonization of the gastrointestinal tract is thought to be the main origin of dissemination of *Candida*; mucositis and neutropenia facilitate the spread of *Candida* from the gastrointestinal tract to the liver. Hepatic involvement due to other fungi is a less common infectious complication in this setting. Fungal infections represent a less common cause of hepatic abscesses in non-oncohematologic population and the trend appears to be decreasing in recent years. Understanding of the etiology and epidemiology of fungal infections of the liver is indicated for an appropriate antimicrobial therapy and an overall optimal management of fungal liver infections.

**Keywords:** fungal liver infections, antifungal agents, hepatosplenic candidiasis, acute disseminated candidiasis, life-threatening infections

## Background

Invasive fungal infections (IFIs) have become a leading cause of morbidity and mortality in oncohematologic patients and hematopoietic stem cell transplantation (HSCT) recipients.<sup>1</sup> Overall, *Candida* spp. are a leading cause of fungal liver infections in oncohematologic patients. Hepatic involvement due to yeasts other than *Candida* spp., molds, and dimorphic fungi is a less common, but severe, infectious complication in this setting. Fungal infections represent <2% of the total isolates in pus from hepatic abscesses in patients without oncohematologic malignancies.<sup>2,3</sup> This review will briefly touch upon the etiology and epidemiology of fungal infections among patients with or without oncohematologic malignancies in order to suggest the adequate management of these entities.

## Materials and methods

A literature search using the MEDLINE database up to February 2017 was performed in order to identify all papers on liver fungal infections. A full-text search by using the MeSH terms "liver fungal infections" OR "fungal liver abscess" OR "fungal hepatic abscess" was conducted. A review of the bibliographies of relevant articles was also performed. Results were categorized and summarized according to the host characteristics (patients with or without oncohematologic malignancies, neonates and children, liver transplantation, and human immunodeficiency virus [HIV]) and the etiology (*Candida*, *Aspergillus*, other fungi). Finally, we synthesized the various liver fungal infections in the different clinical settings (Table 1), the findings from studies

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on hepatosplenic candidiasis (HSC) in patients with oncohematologic malignancies (Table 2), the findings from studies on liver fungal infections in patients who had undergone liver transplantation (Table 3), and the uncommon causes of liver fungal infections in patients with (Table 4) or without (Table 5) oncohematologic malignancies.

## Patients with oncohematologic malignancies

### *Candida*

HSC is a serious infective complication in oncohematologic patients.<sup>4–6</sup> Before the widespread use of antifungal prophylaxis, HSC occurred in <10% of patients with hematologic malignancies, mainly acute leukemia, or after HSCT, mainly allogeneic HSCT.<sup>7</sup> Today, thanks to the primary

systemic antifungal prophylaxis, the incidence of HSC has significantly reduced.<sup>8,9</sup> Anttila et al, in a retrospective Finnish study conducted from 1980 to 1993, observed 38 (6.8%) cases of HSC among 562 adult patients with acute leukemia. The incidence was higher among patients with acute lymphatic leukemia (ALL) than among those with acute myeloid leukemia (AML; 11.3% versus 5.1%, respectively;  $P=0.01$ ). The median duration of severe neutropenia (absolute neutrophil count [ANC]: <500 cells/ $\mu$ L) before the diagnosis of HSC was 19 days (range, 8–45 days). Seventy-eight percent of patients (28/38) died, whereas the median survival from HSC diagnosis was 9.5 months. Patients in remission had a longer survival than those with newly diagnosed or refractory or relapsed leukemia ( $P=0.0065$ ).<sup>10</sup> Similarly, Sallah et al, in a retrospective US

**Table 1** Overview of liver fungal infections in different types of patients

Host	<i>Candida</i>	<i>Aspergillus</i>	Other fungi
Oncohematologic patients	Incidence reduced after introduction of primary systemic antifungal prophylaxis. The main risk factor is severe and prolonged neutropenia	Mainly due to disseminated disease. Primary hepatic infection is not very frequent. The strongest risk factor is prolonged neutropenia	Unusual complication among oncohematologic patients. Liver fungal infections due to endemic fungi should be suspected in patients from certain geographic areas Anecdotal cases
Non-oncohematologic patients	Unusual complication among immunocompetent patients. Biliary tract infections were described mainly in patients with PSC	Unusual complication among immunocompetent patients. Biliary tract infections were described mainly in patients with PSC	
Neonates and children	Unusual complication among neonates and children. Mainly in disseminated candidiasis	Anecdotal cases	Anecdotal cases
Liver transplantation	Thrombosis of hepatic artery is the main risk factor. Increased risk in selected patients (high-risk patients)	Thrombosis of hepatic artery is the main risk factor. Increased risk in selected patients (high-risk patients)	Liver fungal infections due to endemic fungi should be suspected in patients from certain geographic areas
HIV patients	Unusual complication among HIV patients	Unusual complication among HIV patients	Endemic mycoses are possible

**Abbreviations:** HIV, human immunodeficiency virus; PSC, primary sclerosing cholangitis.

**Table 2** Summary of findings from studies on HSC in patients with oncohematologic malignancies

Reference	Type of study	Country	Time span	HSC cases	Comments
Anttila et al <sup>10</sup>	Retrospective cohort	Finland	1980–1993	38	6.8% cases among 562 adult patients suffering from acute leukemia; death rate equal to 78%
Sallah et al <sup>11</sup>	Retrospective cohort	USA	1990–1998	23	Review of HSC cases in patients with acute leukemia; mortality rate equal to 17.4%
Pagano et al <sup>12</sup>	Retrospective cohort	Italy	1990–2000	28	Review of HSC cases in patients with different oncohematologic malignancies; fatality rate equal to 15%
Chen et al <sup>14</sup>	Retrospective cohort	Taiwan	1995–2002	37	7.4% cases among 500 adult patients suffering from acute leukemia; death rate equal to 18.9%
De Castro et al <sup>7</sup>	Retrospective cohort	France	2000–2007	24	Review of HSC cases in patients with different oncohematologic malignancies; fatality rate equal to 46%
Sallah et al <sup>16</sup>	Retrospective cohort	USA	1990–1998	23	5.4% cases among 423 patients suffering from acute leukemia

**Abbreviation:** HSC, hepatosplenic candidiasis.

**Table 3** Summary of findings on liver fungal infections in patients who had undergone liver transplantation

Reference	Type of study	Country	Comments
Annunziata et al <sup>51</sup>	Case report	USA	Hepatic abscess by <i>Candida glabrata</i> in a 48-year-old man 8 years after OLT
Fortún et al <sup>52</sup>	Case series	Spain	Description of four cases with <i>C. glabrata</i> , one with a frank hepatic abscess, the others with fungal isolation from the bile
Alexander et al <sup>53</sup>	Retrospective cohort	Germany	One case of liver fungal infection by <i>C. glabrata</i> among 28 cases of IFIs post-OLT
Musso et al <sup>55</sup>	Case report	Italy	Bilioma related to <i>Candida norvegensis</i> in a 47-year-old man
Mazza et al <sup>56</sup>	Case report	France	Liver abscess caused by <i>Aspergillus fumigatus</i> in a woman 3 years after OLT
Vucicevic et al <sup>57</sup>	Retrospective cohort	USA	One case of hepatic coccidioidomycosis out of 391 patients post-OLT
Abboud et al <sup>59</sup>	Case report	Brazil	Liver abscess related to mucormycosis in a 23-year-old woman
Davari et al <sup>60</sup>	Case series	Iran	Hepatic involvement in two patients out of four with diagnosis of mucormycosis after OLT among 51 liver transplant recipients

**Abbreviations:** IFI, invasive fungal infection; OLT, orthotopic liver transplantation.

**Table 4** Uncommon causative pathogens of liver fungal infections in patients with oncohematologic malignancies

Causative agent	Reference Type of study	Country	Comments
<i>Rhodotorula</i> spp.	Rusthoven et al <sup>23</sup> Case report	USA	Patient with acute myelogenous leukemia
<i>Trichosporon loubieri</i>	Bhaskaran et al <sup>24</sup> Case report	USA	Patient with relapsed B-cell acute lymphoblastic leukemia after an allogeneic HSCT
<i>Geotrichum capitatum</i>	Amft et al <sup>25</sup> Case report	Italy	Patient with non-Hodgkin's lymphoma
<i>Cryptococcus neoformans</i>	Liu et al <sup>26</sup> Case report	Taiwan	Patient with myelodysplastic syndrome and cryptococcal meningoencephalitis
	Suzuki et al <sup>27</sup> Case report	Japan	Old patient with HTLV-I
Mucormycosis	Khan et al <sup>28</sup> Case report	India	Young patient with acute lymphoblastic leukemia on chemotherapy
	Oliver et al <sup>29</sup> Case report	USA	Bone marrow transplant recipient in whom hepatic fungal infection developed after ingestion of multiple naturopathic medicines
<i>Pneumocystis jirovecii</i>	Cordonnier et al <sup>31</sup> Fifth European Conference on Infections in Leukemia (ECIL-5)	Different nations	Pneumonia is rare in HSCT recipients unless patients do not comply with antifungal prophylaxis

**Abbreviations:** HSCT, hematopoietic stem cell transplantation; HTLV, human T-lymphotropic virus.

study conducted from 1990 to 1998, analyzed 23 cases of HSC in patients with acute leukemia (AML 15 and ALL 8). All patients but 3 had a remission of leukemia. The median duration of neutropenia before the diagnosis of HSC was 17 days (range, 12–38 days); 4 patients died within 1–6 months from the time of diagnosis.<sup>11</sup> In a retrospective Italian study conducted in 1990s, Pagano et al evaluated 28 cases of HSC in hospitalized patients with hematologic malignancies. According to the 2002 European Organization for Research and Treatment of Cancer/Mycoses Study Group definition, the cases were classified as proven (18 cases; 64%), probable (8 cases; 29%), and possible (2 cases; 7%) infection. AML (20 cases; 71%), ALL (5 cases; 18%), and non-Hodgkin's lymphoma (3 cases; 11%) were the under-

lying hematologic diseases of the observed patients. HSC was diagnosed after the remission of neutropenia in 54% of patients (15/28 cases), whereas in the remaining 46% (13/28 cases) it was observed before the chemotherapy. About 80% of cases had a severe (ANC: <500 cells/ $\mu$ L) and prolonged (median of 20 days) neutropenia before the onset of HSC; on the contrary, at the time of diagnosis, almost all of the patients (25/28 cases) had a high ANC. Systemic antifungal prophylaxis had been administered only in 14% of the cases (3/22 patients), whereas the remaining ones (19/22 patients; 86%) had received topical antifungal prophylaxis. Only nine patients had a positive blood culture: *C. albicans* (5 cases), *C. parapsilosis* (1 case), *C. krusei* (1 case), *C. tropicalis* plus *C. lipolytica* (1 case), and *C. albicans* plus *C. tropicalis*

**Table 5** Uncommon causative pathogens of liver fungal infections in patients without oncohematologic malignancies

Causative agent	Reference Type of study	Country	Patient's underlying condition
<i>Phaeoacremonium parasiticum</i>	Marciano et al <sup>13</sup> Retrospective cohort	USA	Chronic granulomatous disease
Basidiobolomycosis	Hassan et al <sup>42</sup> Retrospective cohort	Iraq	Biliary tract diseases
	van den Berk et al <sup>43</sup> Case report	The Netherlands	
	Geramizadeh et al <sup>50</sup> Case report	Iran	
	Vucicevic et al <sup>57</sup> Retrospective cohort	USA	
<i>Coccidioides</i> spp.	Abboud et al <sup>59</sup> Case report	Brazil	Orthotopic liver transplantation
Mucormycosis	Davari et al <sup>60</sup> Case report	Iran	Human immunodeficiency virus
	Cazorla et al <sup>63</sup> Case report	France	

(1 case). *Candida* spp. were found only in 6 out of 15 patients who had biopsies. The overall mortality rate was about 15% (4/28 patients); however, all patients delayed the treatment for the underlying hematologic disease.<sup>12,13</sup> From 1995 to 2002, Chen et al found 37 (7.4%) cases of HSC out of 500 adult patients with acute leukemia receiving chemotherapy. Fifteen patients had proven infection; instead, 22 were considered to have probable infection. No rate difference was observed between the patients with AML and those with ALL (29/378 patients [7.7%] versus 8/122 patients [6.6%], respectively). Overall, only seven patients died due to HSC.<sup>14</sup> In a retrospective French study, De Castro et al analyzed 24 cases of HSC in oncohematologic patients (during the period 2000 to 2007) occurred in two major Paris centers for the management of hematologic malignancies. Acute leukemia (ALL or AML, 18 cases; 75%), lymphoma (4 cases; 17%), autologous HSCT (1 case; 4%), and chronic neutropenia (1 case; 4%) were the underlying hematologic conditions of the patients. All cases were classified according to the revisited European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for IFIs: proven (6 cases; 25%), probable (3 cases; 12.5%), and possible (15 cases; 62.5%) infection. All cases occurred in patients who did not receive antifungal prophylaxis and almost all patients were colonized by *Candida* spp. Four patients died within 3 months after the HSC diagnosis; the overall mortality during the scheduled follow-up period was 46% (11/24 subjects). In the multivariate analysis, failure of hematologic remission at the HSC diagnosis (hazard ratio 5.60, 95% CI: 1.39–22.5;  $P=0.015$ ) and long duration (>1 month) of neutropenia (hazard ratio 4.33, 95% CI:

1.24–15.2;  $P=0.022$ ) were the only independent predictors of death.<sup>7,15</sup> Finally, in another retrospective study, Sallah et al found that younger age (odds ratio [OR] 1.96, 95% CI: 1.72–2.99;  $P=0.009$ ), duration of neutropenia  $\geq 15$  days (OR 11.7, 95% CI: 3.04–45.1;  $P=0.0003$ ), and use of prophylactic quinolones (OR 3.85, 95% CI: 1.11–13.4;  $P=0.039$ ) were the only independent predictors of the development of HSC in patients with acute leukemia.<sup>16</sup> In Table 2, data from the above-mentioned studies are summarized.

### Aspergillus

Aspergillosis is the most common mold infection in oncohematologic setting.<sup>17</sup> *A. fumigatus* is the most commonly isolated species to cause invasive aspergillosis (IA); however, an increased incidence of non-*fumigatus* *Aspergillus* spp. is a major concern in oncohematologic patients.<sup>18</sup> Pulmonary infection is the most frequent form of IA in immunocompromised patients, including patients with hematologic malignancies and HSCT recipients; at any rate, extrapulmonary IA can develop within any anatomic site and disseminated disease is particularly common among patients with prolonged neutropenia.<sup>19</sup> Furthermore, isolated primary extrapulmonary infection, such as gastrointestinal and hepatic involvement, has been described.<sup>20–22</sup>

### Other fungi

Hepatic involvement due to invasive yeast infections other than *Candida* spp. is an unusual complication in oncohematologic patients. Based on our knowledge, hepatic fungal infections due to *Rhodotorula* spp., *Trichosporon* spp., *Geotrichum* spp., and *Cryptococcus* spp. have been

described in this context.<sup>23–27</sup> Although invasive mold infections by pathogens other than *Aspergillus* spp. are an emerging cause of opportunistic mycoses in patients with hematologic malignancies, only rarely has hepatic involvement been reported.<sup>28,29</sup> Eventually, involvement of the liver is possible in the endemic fungal infections, such as blastomycosis, coccidioidomycosis, and histoplasmosis, whereas hepatic pneumocystosis has been reported exclusively in HIV-infected individuals.<sup>30,31</sup> Uncommon causative pathogens of liver fungal infections in patients with oncohematologic malignancies are summarized in Table 4.

## Patients without oncohematologic malignancies

### Chronic granulomatous disease (CGD)

#### *Candida*

Lublin et al analyzed the clinical presentation, diagnostic procedures, and surgical management of hepatic abscesses in patients with CGD between 1980 and 2000. Of 61 cases of hepatic abscess, 22 patients with CGD were treated at the local National Institutes of Health; the median age at the time of initial hepatic abscess presentation was 14 years. Subjective fever was the most frequent presenting symptom, and the erythrocyte sedimentation rate was elevated in 98% of cases. Fifty-two cases were managed surgically and eight cases were managed with percutaneous drainage. One patient refused surgery. The surgical complication rate was 56%; however, there were no deaths directly related to the hepatic abscesses. *Staphylococcus aureus* was the most frequent organism identified in culture (23 cases [88% of all positive cultures]), followed by one case each of *Nocardia* and *Lactobacillus* and one case consisting of multiple organisms (*C. glabrata*, *Streptococcus mitis*, and *S. aureus*). No organism was cultured in 15 (37%) cases.<sup>32</sup>

#### *Aspergillus*

Marciano et al assessed the impact of common severe infections in CGD by examining the records of 268 patients followed at a single center over four decades. Fungal infection accounted for 21 deaths (21/38 [55%]). Overall *Aspergillus*-specific mortality was 9%. *A. fumigatus* was isolated from 10 patients, *A. tanneri* from 2 patients, and *A. nidulans* was identified from 1 fatal fungal infection. In three cases, *Candida* spp. were isolated as a possible cause of death.<sup>33</sup> Mamishi et al described an *Aspergillus* osteomyelitis of the

ribs and hepatic abscess in a 5-year-old boy. The patient was successfully treated with amphotericin B.<sup>34</sup>

### Other fungi

Other fungi, such as *Phaeoacremonium parasiticum*, have been described in patients with CGD.<sup>33</sup>

### Biliary tract diseases

#### *Candida*

Kulaksiz et al analyzed 148 bile samples taken at endoscopic examination of 67 consecutive patients with primary sclerosing cholangitis (PSC). *Candida* spp. were found in >8% of patients. This study suggests that candidal infection of the bile ducts should be considered in the empirical treatment of patients with PSC.<sup>35</sup> Lima et al reported a rare case of *C. glabrata* liver abscess and fungemia complicating acute calculus cholecystitis in a 64-year-old female patient who had no history of immunosuppression or diabetes mellitus. The patient underwent cholecystectomy, resection of liver abscess, and systemic antifungal therapy.<sup>36</sup> Lai et al reported a case of candidal liver abscesses and concomitant candidal cholecystitis in a diabetic patient. Bile and aspirated pus culture repeatedly tested positive, and blood negative, for *C. albicans* and *C. glabrata*. Cholecystitis was cured by percutaneous gallbladder drainage and amphotericin B therapy.<sup>37</sup> Friedman et al described a case of a 39-year-old man with severe diabetes mellitus, chronic pancreatic insufficiency, intrapancreatic choledochal stricture, and secondary biliary cirrhosis, who developed postsurgical fungemia and large hepatic abscesses due to *C. glabrata*.<sup>38</sup> Melero et al described a case of PSC and Crohn's disease with multiple fungal liver abscesses caused by *C. albicans*. The patient had developed a duodenal-biliary fistula. Antibiotic therapy produced clinical response, and surgery was performed to repair the fistula.<sup>39</sup>

#### *Aspergillus*

Kulaksiz et al analyzed 148 bile samples taken at endoscopic examination of 67 consecutive patients with PSC. *Aspergillus* spp. were not found. This study suggests that infection of the bile ducts by this mold should not be considered in the empirical treatment of patients with PSC.<sup>35</sup> Erdman et al reported a case of a 19-year-old girl with a history of recurrent late-onset, febrile cholangitis after a portoenterostomy.<sup>40</sup> *A. terreus* was isolated from her biliary fluid obtained at percutaneous transhepatic cholangiography. Moreover, *A. fumigatus* was described as a superinfection of a bilioma.<sup>41</sup>



### Other fungi

Recently, biliary tract disease related to fascioliasis was seen to be complicated by basidiobolomycosis.<sup>42</sup> Usually, basidiobolomycosis is a subcutaneous infection, but rarely, if undiagnosed, can provoke a fatal hepatic infection, even in adult immunocompetent patients.<sup>43</sup>

### Neonates and children

#### *Candida*

In newborns, *Candida* spp. infections are the leading cause of IFIs, which are potentially life-threatening.<sup>44</sup> Sharma et al reported a case of *C. albicans* liver abscess in a preterm neonate, secondary to malposition of umbilical lines that presented with respiratory difficulty and other clinical features of sepsis, which were managed medically and the infant was discharged successfully.<sup>45</sup> Picone et al reported the case of a 31-week gestational age neonate with *C. albicans* sepsis and a hepatic abscess. Diagnosis relied on clinical and radiologic signs of sepsis, liver function impairment, and culture isolation of *Candida* spp. from the sterile sites. Liver ultrasound documented the presence of a multiloculated abscess. Treatment with micafungin resulted in normalization of liver function, inflammatory laboratory values, and improvement of clinical condition. After 30 days of treatment, the liver abscess resolved, and at the 8-month follow-up, the infant is doing well. Prompt diagnosis and antifungal treatment avoided surgical drainage and liver surgery in this high-risk neonate.<sup>46</sup> Of note, *C. parapsilosis* is increasingly being recognized as an important cause of invasive candidiasis in neonates.<sup>47,48</sup>

#### *Aspergillus*

*A. terreus* is reported in an immunocompromised child; he was affected by common variable immunodeficiency and the hepatic infection occurred while the patient was receiving secondary prophylaxis with fluconazole after an episode of pulmonary candidiasis.<sup>49</sup>

### Other fungi

Geramizadeh et al described for the first time a case of an isolated liver involvement of basidiobolomycosis in a 2-year-old girl, who presented with a liver mass resembling a hepatic abscess.<sup>50</sup>

### Liver transplantation

#### *Candida*

When *Candida* spp. have been determined as a causative agent of hepatic abscesses following orthotopic liver

transplantation (OLT), non-*albicans* species have played an important role. In 1997, Annunziata et al illustrated the case of a 48-year-old man who had developed a hepatic abscess by *C. glabrata* 8 years after OLT. The authors attributed the phenomenon to the stenosis of hepatic artery, resulting in bile infarcts presumably contaminated through the biliary tract with yeast from the biliary–enteric anastomosis. The combination of percutaneous drainage and medical therapy with amphotericin B for 10 weeks allowed a safe and decisive retransplantation.<sup>51</sup> In 1997, Fortún et al described four cases of IFI post-OLT due to *C. glabrata* of which in three cases the yeast was isolated from the biliary material; of these last three cases an abscess was reported only in one case. The abscess treatment included amphotericin B plus drainage, and the patient recovered uneventfully.<sup>52</sup> *C. glabrata* was also found as responsible in the only case of IFIs related to fungal liver infection in a German retrospective study including 28 cases of IFIs following OLT. The study was aimed at establishing the role of hepatic iron overload (measured in the liver explants by Perl's Prussian blue stain) as a risk factor of IFIs.<sup>53</sup> Although this association is not elucidated in detail, this information represents another tile in the mosaic of the factors predisposing to IFIs after OLT.<sup>54</sup> Another non-*albicans* form was described in a more recent case report from Italy involving a 47-year-old man suffering from a deep-seated candidiasis following OLT. Cultural examination of material from bilioma revealed *C. norvegensis*, a rare species characterized by an inherent resistance to fluconazole. The clinical outcome of the patient was positive owing to the endoscopic procedure plus treatment with anidulafungin.<sup>55</sup>

#### *Aspergillus*

Mazza et al described, in 1996, the case of a woman who had undergone an OLT in 1992 and, 3 years later, presented with a clinical picture of persistent fever, asthenia, and alteration of liver enzymes; imaging examination showed fluid collection in the left liver lobe. *A. fumigatus* was isolated from the material obtained via aspiration, and therapy with itraconazole was successfully started. No entry site was identified; of note, the patient had been diagnosed with a Burkitt's lymphoma just 18 months earlier and consequently treated with chemotherapy which was another risk factor.<sup>56</sup>

### Other fungi

Vucicevic et al, in a comprehensive retrospective review of medical records of 391 liver transplant recipients from June 1999 to December 2007, found 1 case of hepatic

coccidioidomycosis (out of 12 post-OLT infections by *Coccidioides* spp.).<sup>57</sup> Coccidioidomycosis is to be suspected in endemic areas (such as southwestern USA and some parts of Central America and South America) and in immunosuppressed patients; pulmonary manifestations are the most frequent ones, but a disseminated disease with the involvement of different organs is possible.<sup>58</sup> Abboud et al reported the case of a 23-year-old woman with a history of OLT due to PSC. Forty-seven days later, she presented with fever and pain at the right hypochondrium; abdominal ultrasound scanning demonstrated a hepatic abscess in the right lobe. Histopathologic examination following liver biopsy revealed diagnosis of mucormycosis; she was successfully treated with the sequential use of amphotericin B and posaconazole without surgery. Of note, the donor himself was under immunosuppressive therapy, being a kidney transplant recipient; so, the fungal infection might have been transmitted by the allograft.<sup>59</sup> Two cases of liver mucormycosis after OLT, among a small series of four, had been previously described by Iranian authors, which were unfortunately characterized by unfavorable outcome, although both underwent therapy with amphotericin B and one case had aggressive surgical debridement.<sup>60</sup> As a matter of fact, mucormycosis, a life-threatening infection due to fungi of the order Mucorales, is burdened with a very high fatality rate.<sup>61</sup> In Table 3, data regarding liver fungal infections after OLT are summarized.

## HIV

### *Candida*

Alvarez et al illustrated in 2000 a case of a young woman with advanced HIV disease who presented with two hypoechoic lesions in the left liver lobe. These lesions were of polymicrobial origin, and *C. albicans* turned out to be one of the culprits. After adequate antifungal treatment, the patient was discharged and then was lost to follow-up.<sup>62</sup>

### Other fungi

Cazorla et al, describing a small case series of extracerebral cryptococcosis, reported the case of a 39-year-old man infected with HIV and with a liver abscess related to *C. neoformans*.<sup>63</sup>

## Conclusion

IFIs have become a leading cause of morbidity and mortality in oncohematologic patients and HSCT hosts.<sup>18</sup>

Of course, these subjects are generally prone to develop other kinds of infections also. For example, without a proper prophylaxis, the risk of hepatitis B reactivation ranges from

18% to 73%, and is about 61% in HBsAg positive patients with lymphoma and acute leukemia, respectively; the risk is 34%–68% and 2.8%–12.5%, respectively, in individuals with the same pathologies but are HBsAg negative and anti-HBc positive.<sup>64</sup> B-cell-depleting agents, anthracycline, and high doses of steroids pose the highest risk of hepatitis B reactivation in the oncohematologic setting.<sup>65</sup>

Another relevant issue is represented by bacterial infections, a dramatic problem in the era of antimicrobial resistance.<sup>66</sup> In a large Spanish cohort reviewing 991 cases of HSCT, 44 episodes of bloodstream bacterial infections per 10,000 transplant days in allogeneic HSCT recipients were described.<sup>67</sup> Febrile neutropenia occurs in up to 80% of patients with hematologic malignancies, and major bacterial infections such as the ones of the bloodstream are held accountable in 10%–25% of cases.<sup>68</sup>

Focusing on IFIs, there are several studies investigating their incidence and the main risk factors linked with their development, although it is not simple to account for the large variety of malignant diseases and for the different treatment strategies, each of them carrying distinct risk profiles. For sure, infections by *Aspergillus* spp. have overcome the ones by *Candida* spp., a shift probably driven by the role of antifungal prophylaxis.<sup>69</sup> Overall, AML is the disease having the major risk of IFIs, which varies from 10% to 25%; in chronic lymphoproliferative disorders, the incidence of IFIs ranges from 0.5% to 10.8%. The incidence of IFIs is from 3% to 8% among autologous HSCT recipients and from 7% to 15% among allogeneic HSCT recipients; in other categories (e.g., myeloproliferative neoplasms), data are scarce and related to old cohorts.<sup>70</sup>

A liver abscess can mainly develop after translocation of fungi from the gut to the liver via the portal circulation, but it is an unusual occurrence.<sup>71,72</sup> Overall, the major risk factors for IFIs in these patients are the underlying malignancy, neutropenia, and the degree of immunosuppression.<sup>73–77</sup> Fungal infections represent a less common cause of hepatic abscesses among patients without oncohematologic malignancies.<sup>78,79</sup> Hepatic abscesses are common in tropical countries and are most commonly caused by *Candida* spp.<sup>79</sup> Although hepatic involvement due to *Candida* spp. may affect immunocompetent patients without any comorbidity, in the non-oncohematologic setting, individuals more prone to fungal infections of the liver, not exclusively by *Candida* spp., usually suffer from distinct clinical conditions.<sup>80</sup> Fungal hepatic involvement after OLT is a relatively rare, but potentially severe complication. Thrombosis of hepatic artery seems to be the most important predisposing factor. Although bacteria

represent the most common causative agents, fungi cannot be neglected in the differential diagnosis, considering their impact, in terms of morbidity and mortality, in the setting of posttransplantation infections.<sup>81</sup> Indeed, in the light of the recommendations from the most authoritative international societies, antifungal prophylaxis following OLT, to prevent IFIs, is not mandatory for low-risk patients, but it is necessary under several circumstances: 1) only against *Candida* spp. for patients with perioperative *Candida* colonization complicated operations or choledochojejunostomy anastomosis and 2) against both *Candida* and *Aspergillus* for patients at high risk, undergoing renal replacement therapy posttransplant and with the high probability of reoperation.<sup>82</sup> Finally, the management of patients suffering from HIV and diagnosed with fungal hepatic abscesses should follow the same rules as non-HIV patients; however, data from literature are poor, particularly when it comes with fungal hepatic abscesses.<sup>83,84</sup>

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## Author contributions

This review was mainly written by MF and MC. AEM and MF collected the data. IG, SB, VS, and MCP supervised the writing of the paper. All authors contributed toward data analysis, drafting, and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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