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Authors

Iqbal, Humzah
Mehmood, Bilal Fazal
Jones, Katherine
et al.

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Review Article

Fungal infections in liver cirrhosis

Humzah Iqbal[1]^, Bilal Fazal Mehmood[1], Katherine Jones[1], Aalam Sohal[2]^, Marina Roytman[3]

[1]Department of Internal Medicine, University of California San Francisco, Fresno, CA, USA; [2]Department of Hepatology, Liver Institute Northwest, Seattle, WA, USA; [3]Division of Gastroenterology and Hepatology, University of California San Francisco, Fresno, CA, USA

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Correspondence to: Aalam Sohal, MD. Department of Hepatology, Liver Institute Northwest, 3216 NE 45th Place Suite 212, Seattle, WA 98105, USA. Email: aalamsohal@gmail.com.

Abstract: Liver cirrhosis is a chronic condition that is associated with a variety of complications across organ systems. Patients with cirrhosis also suffer from immune dysfunction, which may predispose them to catastrophic bacterial and fungal infections. Bacterial infections in liver cirrhosis have been well-documented, however, data remains scarce regarding fungal infections. *Candida* and *Aspergillus* have been reported as the most common pathogens among patients with cirrhosis, causing both invasive and non-invasive infections. However, other pathogens such as *Coccidioides*, *Pneumocystis*, *Cryptococcus*, and *Rhizopus* have been increasing in incidence. Diagnosis of fungal infection is often difficult, particularly in regards to distinguishing colonization from invasive infection. Serum markers such as beta-D-glucan (BDG) and galactomannan are beneficial diagnostic tools in conjunction with fungal cultures and imaging modalities. Bronchoscopy with bronchoalveolar lavage (BAL) or lung biopsy can be useful adjuncts as well. Liver transplantation is another important consideration as invasive fungal infection (IFI) is a contraindication to transplant surgery. Additionally, patients are at increased risk for infection due to immunosuppression in the post-transplant period. We aim to discuss the mechanisms responsible for immune dysfunction in advanced liver disease, the epidemiology of fungal infections in this population, as well as presentations and management considerations pertaining to specific pathogens and antifungal regimens.

Keywords: Cirrhosis; fungal infection; immune dysfunction; opportunistic infection

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Introduction

Liver cirrhosis is a leading cause of morbidity and mortality, and accounts for over $1.4 billion per year in healthcare costs in the United States (US) annually (1). Cirrhosis is associated with a host of complications involving multiple organ systems. Immune dysfunction is a prevalent but often neglected complication of cirrhosis that accounts for approximately 30% of mortality (2). The risk of developing infections and/or sepsis is increased almost two-fold in hospitalized patients with cirrhosis compared to patients without cirrhosis (3). Immunodeficiency in cirrhosis is a result of derangement in both innate and acquired immunity, as well as an increase in systemic inflammation due to overstimulation of immune cells and overproduction of proinflammatory cytokines (4,5). Fungal infections in cirrhosis are less common than bacterial, however, they are associated with significant mortality and poor outcomes (6). The most common fungal pathogens seen in cirrhosis are *Candida* spp. and *Aspergillus* spp. However, other fungal species have been increasing in incidence in cirrhotic patients, though studies are limited (7). In this review

^ ORCID: Humzah Iqbal, 0000-0003-0873-2524; Aalam Sohal, 0000-0001-8365-7240.

article, we will discuss the epidemiology, pathogenesis, and treatment of invasive and non-invasive fungal infections (IFIs) in patients with cirrhosis.

Epidemiology

A systematic review conducted by Arvaniti *et al.* examined the prognostic importance of infection in predicting mortality rates in patients with cirrhosis, concluding that documented infection of any kind, including fungal infections, have a 4-fold increase in mortality compared to those without infection (8). A large multicenter epidemiologic study revealed patients with cirrhosis admitted to the intensive care unit (ICU) had a higher frequency of fungal infections compared to patients without cirrhosis (25% *vs.* 19%), with a trend towards statistical significance (P=0.05). Furthermore, the overall mortality rate of patients with cirrhosis requiring ICU level care was 42% compared to 24% in those without cirrhosis, a difference that was noted to be statistically significant (9). Additionally, Bartoletti *et al.* found that patients with acute-on-chronic liver failure (ACLF) who developed opportunistic bacterial or fungal infection had higher mortality than those without infection (75% *vs.* 54%, P=0.011) (10). Supportive modalities during hospitalization, such as the use of corticosteroids, placement of invasive vascular access, and external measures such as hemodialysis all place ACLF patients at increased risk for nosocomial infections (6). Furthermore, severity of the host's ACLF plays an important role in the development of a fungal infection (11). Bajaj *et al.* demonstrate this point in a large multicenter study on patients with cirrhosis admitted non-electively, revealing a Model for End-Stage Liver Disease (MELD) score >20 at the time of admission was a significant predictor of developing a nosocomial infection (P<0.0001) (12).

The prevalence of fungal infections in cirrhosis is 3–7%, varying by type (invasive *vs.* non-invasive), severity of existing liver disease (compensated *vs.* decompensated states), and the level of care required during hospitalization ICU *vs.* general medical unit) (6). The majority of the infections observed are nosocomial in origin, further complicating the course of the hospitalized patients (6). A large systematic review pooled data from 17 studies that examined multiple fungal infections in hospitalized patients with cirrhosis, with an overall prevalence reported as 10.2% (7). However, when narrowing this data to examine IFIs, the pooled prevalence was 9.5%, suggesting that the majority of fungal infections in cirrhosis were invasive (7). Moreover, there was an observed correlation between the severity of liver disease and the risk for developing fungal infection, with rates of IFI ranging from 10–14% in patients with evidence of decompensation or critical illness (13).

Distinguishing between IFI and fungal colonization has also been a topic of interest. Theocharidou *et al.* compared patients with cirrhosis and those with severe cardiovascular disease in the ICU and found higher rates of both IFI (1% *vs.* 0.4%, P=0.025) and fungal colonization (23.8% *vs.* 13.9%, P=0.001). Interestingly, there was no difference in mortality between colonized patients who received antifungal therapy and patients who did not receive antifungals (14). These findings emphasize the importance of obtaining a thorough infectious workup in order to identify patients with cirrhosis who have IFI rather than fungal colonization. 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 have provided definitions and diagnostic criteria for the diagnosis of IFI. The diagnosis requires a compatible clinical syndrome along with recovery of a pathogen from a sterile site (i.e., blood, cerebrospinal fluid). Fungal cultures, polymerase chain reaction (PCR), and in some cases antibodies may be used. Imaging evidence of fungal invasion and direct histological visualization of pathogens may also aid in the diagnosis (15).

In a large meta-analysis of 31,984 patients with cirrhosis, invasive candidiasis was determined to be the most common IFI, with a reported pooled prevalence of 4.0%. The second most common IFI observed was invasive aspergillosis (IA), with a pooled prevalence of 2.8%. A higher prevalence of both candida and aspergillosis was observed in patients admitted to the ICU. *Cryptococcus* is observed as the third most common IFI in patients with evidence of decompensated cirrhosis (7). However, *Cryptococcus* often has a delayed diagnosis and as such often carries a poor prognosis when identified in patients with decompensated disease (13).

When considering infections observed in a decompensated state, spontaneous bacterial peritonitis (SBP) is a well-documented occurrence with observed estimates of 10–30% of patients with ascites. Spontaneous fungal peritonitis (SFP) is rare by comparison. A retrospective case-control study reviewed 231 patient cases with cirrhosis admitted for peritonitis, of these only 3.5% were attributed to

Table 1 Fungal pathogens in patients with cirrhosis

Pathogen	Endemic areas	Infection rate in cirrhosis	Primarily affected organs	Associated signs and symptoms	Treatment
Candida albicans	Worldwide	9–16%	Skin, mucous membranes, gastrointestinal tract, blood	Oral thrush, rash, dysuria	Azoles, amphotericin B
Pneumocystis	Worldwide, prevalent in immunocompromised	Indeterminate	Lungs	Fever, cough, dyspnea	Trimethoprim-sulfamethoxazole, pentamidine, atovaquone
Cryptococcus	Worldwide, prevalent in immunocompromised	6–21%	Lungs, CNS	Headache, fever, confusion, cough, meningitis	Fluconazole, amphotericin B, flucytosine
Aspergillus	Worldwide, found in soil and decaying organic matter	5–14%	Lungs, sinuses, skin, eyes	Fever, cough, chest pain, dyspnea, sinus congestion	Voriconazole, amphotericin B, caspofungin
Coccidioides	Southwestern United States, Central and South America	~4%	Lungs, skin, bones	Fever, cough, chest pain, rash, joint pain, meningitis	Fluconazole, itraconazole, amphotericin B
Rhizopus	Worldwide	Indeterminate	Sinuses, lungs, skin, CNS	Nasal congestion, facial pain, black eschar	Surgical debridement, amphotericin B, posaconazole, isavuconazole

CNS, central nervous system.

SFP, with *Candida* spp. accounting for 87.5% of the observed cases (16). Although rare, the diagnosis of SFP was associated with poor outcomes with an estimated in-hospital mortality of 62.5%. The only way to definitively differentiate between SBP and SFP is an ascitic fluid culture and may not always yield a definitive result (16). Culture bottles should ideally be inoculated at bedside, as this has been shown to improve ascitic culture yield (17,18). Further studies are needed to explore additional methods to improve culture yield. Cases, where adequate SBP treatment does not result in clinical improvement, should raise suspicion for possible underlying fungal involvement. Other sites of IFI can be seen in patients with cirrhosis as well. A systematic review by Tariq *et al.* specifically investigated *Cryptococcus* among patients with cirrhosis and found peritonitis to be the most common manifestation of the infection, followed by meningitis and pulmonary disease (19). Aside from cryptococcal meningitis, central nervous system (CNS) fungal infections in cirrhosis are primarily limited to case reports (20,21).

Despite treatment availability, the overall prognosis for invasive fungal disease remains poor, with mortality rates of 45–60% in candidemia, and even higher for those diagnosed with IA (6). A summary of fungal pathogens in patients with cirrhosis is presented in *Table 1*.

Pathogenesis

The immune dysfunction in patients with cirrhosis leading to fungal infections is multifactorial.

Malnutrition causes notable alterations in metabolism, including increased protein catabolism and insulin resistance, resulting in a weakened state of starvation. Impaired intestinal tight junctions allow for translocation of endotoxins, disrupting the gut microbiome and resulting in dysbiosis. Iatrogenic factors such as corticosteroid use, and prolonged antibiotic therapy predispose patients to the development of multi-drug-resistant organisms. The culmination of these factors creates a state of immune dysfunction, the degree of which influences both the severity and progression of liver disease (13).

Impaired hepatic synthetic function results in a reduction of immunoglobulins and complement factors, decreasing opsonization and phagocytosis by antigen-presenting cells (APCs), such as macrophages. This ultimately allows fungal pathogens to go undetected by the host's immune system. At the level of the gut, lack of immune surveillance compromises the intestinal barrier resulting in alterations in

the gut microbiome, along with translocation of endotoxins such as lipopolysaccharide (LPS). The release of endotoxins is further exacerbated by portosystemic shunting that is observed with progression of liver disease (13). Collectively, this process can be defined as cirrhosis-associated immune dysfunction (CAID) (5).

When liver disease has progressed to the point of cirrhosis, the immune system has reached a state of exhaustion. Chronic activation of innate immune cells, such as neutrophils, results from continued circulation of pro-inflammatory molecules like LPS, along with other pathogen-associated molecular patterns (PAMPs). These pro-inflammatory molecules interact with the toll-like receptors located on the surface of neutrophils, resulting in increased production of reactive oxygen species (ROS) (13). Interestingly, Taylor *et al.* studied neutrophil function in patients with cirrhosis by examining phagocytic activity and production of ROS. The group observed that neutrophil capacity was a significant predictor of survival in stable cirrhosis, with oxidative burst ≥12% predicting 90-day mortality with 80% sensitivity and 71% specificity (22). The increase in oxidative damage along with the production of metalloproteases by chronic neutrophil activation is thought to contribute to the development of multiorgan dysfunction syndrome observed in the late stages of liver disease (23,24).

The process by which CAID occurs is not linear. While an unregulated inflammatory state leads to increased tissue damage, the increased circulation of PAMPs may also result in a state of endotoxin tolerance (5). For example, Knooihuizen *et al.* tested the fungicidal capacity of neutrophils isolated from hospitalized patients with cirrhosis (24). The group examined the ability of neutrophils to coordinate swarming to control the hyphal growth of *Candida albicans*, a commonly observed fungal pathogen in cirrhosis. The study revealed a significant reduction in swarming in neutrophils isolated from patients with cirrhosis compared to those from healthy controls. The group postulated the observed decrease in swarming may be related to neutrophil exhaustion in the setting of elevated inflammatory cytokines, ultimately leading to maladaptive immune function (24). An inverse relationship between neutrophil function and the risk of IFIs has been well documented and is associated with higher rates of infection with *Candida* and *Aspergillus* spp. (25).

In addition to the observed dysfunction in the innate response, CAID also impacts the adaptive immune response. In healthy, immunocompetent individuals, fungal antigens are detected by APCs and subsequently presented to $CD8^+$ T-cells. This cytotoxic T-cell population responds by producing inflammatory cytokines including interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF), further activating phagocytes for the isolation and control of invading fungal pathogens. In addition, cytotoxic T-cells can act directly on infected APCs through the secretion of perforin and granzyme, as a direct killing mechanism (26). Lebossé *et al.* isolated $CD8^+$ T-cell populations from patients with cirrhosis and examined this subset for phenotypic and functional differences compared to $CD8^+$ T-cells isolated from healthy volunteers. The study revealed an increase in a subset of human leukocyte antigen (HLA)-DR^+CD8^+ T-cells that notably demonstrated an increased surface expression of immune checkpoint inhibitors, including programmed cell death protein (PD)-1, cytotoxic T lymphocyte (CTL)A-4, and T-cell immunoglobulin and mucin domain (TIM)-3. Initially this observation was attributed to an exhausted T-cell profile, with an increase in inhibitory signaling thought to be secondary to a lack of functional response. However, this decreased response was reversed with the addition of CTLA-4 blockade, resulting in restored TNF-α production. In addition to the decreased functional signaling response that is typically observed in an exhausted T-cell profile, this subset should also demonstrate an increased level of apoptosis, which was not observed in the HLA-DR^+CD8^+ T-cells isolated from patients with cirrhosis (26). The result of this study suggested these cytotoxic T-cells were immune tolerant, rather than terminally exhausted. More recent theories have supported this theory, characterizing the upregulation of inhibitory receptors as an adaptive response to chronic inflammation (27).

Whether an exhaustive or tolerant state, the progression of cirrhosis to immune paresis results in an ineffective response to invading fungal pathogens, placing patients at an overall increased risk of infection and subsequent deterioration. The development of CAID is shown in *Figure 1*. Other risk factors for IFI among patients with cirrhosis include previous abdominal surgery, renal failure, and parenteral nutrition. Additionally, severity of liver disease represented by a higher MELD or Child-Pugh score is associated with increased risk of IFI as well (28).

Candida albicans

Candida albicans is a prevalent opportunistic fungal pathogen widely distributed in the environment. It is a commensal organism found in the human microbiota,

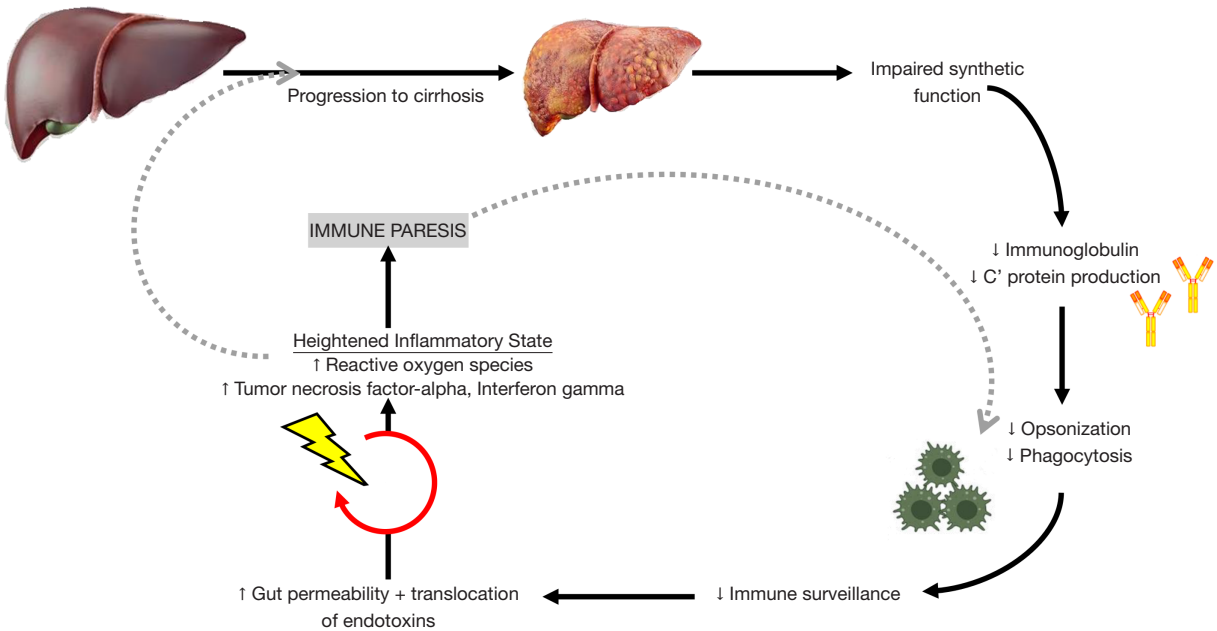

Figure 1 The development of CAID. The progression of liver disease to cirrhosis triggers a cascade of events that lead to immune paresis, that may collectively be referred to as CAID. Impaired hepatic synthetic function results in decreased immunoglobulin and complement protein production. This decreases the rate of opsonization and subsequent phagocytosis by neutrophils and macrophages. Overall, this leads to a decrease in immune surveillance. At the level of the gut, persistent inflammation and impaired tight junctions allow for the translocation of bacteria and endotoxin, increasing the rate of peritoneal and blood stream infection. Inflammation caused by persistently elevated cytokine production triggers immune tolerance in persistently activated neutrophils and cytotoxic T-cells that allow for unregulated pathogen proliferation. CAID, cirrhosis associated immune dysfunction.

predominantly in the gastrointestinal and genitourinary tracts (29). *Candida* colonization is detectable in up to 60% of healthy individuals and is a risk factor for the development of invasive infection. Invasion generally occurs when a colonized individual suffers an insult to the mucosa or becomes immunocompromised (30). The prevalence of *Candida* infections has risen significantly in recent decades due to increased use of broad-spectrum antibiotics, immunosuppressive therapies, and invasive medical procedures. *Candida* infections can manifest as mucocutaneous infections or as invasive diseases, affecting individuals with compromised immune status or underlying health conditions (31).

Candida infections represent a significant health burden among patients with liver cirrhosis. The compromised immune response in patients with cirrhosis, particularly impaired neutrophil function and reduced phagocytic activity, creates an environment conducive to *Candida* proliferation. Fernández *et al.* found that *Candida* accounted for 70–90% of fungal infections among this patient population (6).

The disruption of the gut mucosal barrier in patients with cirrhosis contributes to the translocation of *Candida* from the gastrointestinal tract into the bloodstream. *Candida* accounts for 7–9% of all bloodstream infections in patients with cirrhosis, and up to 30% of these cases result in septic shock (32). A multicenter study conducted by Bassetti *et al.* demonstrated a 35% 30-day mortality rate in patients with cirrhosis with candidemia and/or intra-abdominal candidiasis [odds ratio (OR) 2.2, 95% confidence interval (CI): 1.2–4.5]. Candidemia and septic shock (OR 3.2, 95% CI: 1.7–6) were identified as independent factors associated with 30-day mortality (32). Non-bloodstream infections are also associated with poor outcomes, with the study by Verma *et al.* demonstrating that patients with esophageal candidiasis were more likely to have decompensated cirrhosis (63% *vs.* 49%; P=0.046), higher MELD score (12.4 *vs.* 11.2; P=0.007), and presentation as ACLF (26% *vs.* 10%; P=0.003) (33).

In conclusion, the relationship between *Candida*

infections and liver cirrhosis is profound, with patients with advanced liver disease exhibiting a significantly higher prevalence of *Candida*-related complications compared to the general population. Understanding the mechanisms underlying this relationship, particularly the immune dysregulation and gut dysbiosis in individuals with cirrhosis, is crucial in developing targeted preventive and therapeutic strategies to mitigate the impact of *Candida* infections in this vulnerable patient population.

Pneumocystis

Pneumocystis, specifically *Pneumocystis jirovecii*, is an opportunistic fungal pathogen causing pneumonia in immunocompromised individuals. It is commonly found in the environment and is transmitted via airborne routes. Pneumocystis pneumonia (PCP) was historically associated with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients but has increasingly been recognized in non-HIV immunocompromised populations, such as those receiving immunosuppressive therapies or individuals with underlying conditions compromising their immune systems. The prognosis of PCP in non-HIV patients is poor, with mortality rates ranging anywhere from 30–60% (34).

While data specifically addressing PCP in patients with cirrhosis remains limited, studies have demonstrated an increased risk of PCP in individuals with advanced liver disease. The compromised cellular immunity in individuals with advanced liver disease, characterized by reduced $CD4^+$ T-cell counts and impaired alveolar macrophage function, predisposes them to *Pneumocystis* infection (35). Notably, a retrospective analysis by Franceschini *et al.* reported that decompensated liver cirrhosis, especially alcohol-related cirrhosis, is an independent risk factor for PCP infection (36). Additionally, the use of corticosteroids or immunosuppressive agents in alcohol-related hepatitis (ARH) or end-stage liver disease further exacerbates susceptibility to PCP, leading to severe respiratory compromise and increased mortality rates in this population. A retrospective study by Faria *et al.* further highlights the dangers of corticosteroid use in patients with Maddrey's discriminant function (MDF) scores >32, describing 7 patients who were treated for ARH with corticosteroids and subsequently developed PCP, with 100% mortality (37). Diagnosis can be delayed in these patients as a high degree of suspicion is needed in order to obtain the relevant sputum or bronchoalveolar lavage (BAL) samples. A low threshold to obtain these samples and studies should be maintained in patients with cirrhosis, especially those on corticosteroid therapy.

Cryptococcus

Cryptococcus neoformans is an encapsulated yeast that is commonly found in the respiratory tract and can lead to disseminated infection in immunocompromised individuals (38). Cryptococcal infection is responsible for a significant global burden, accounting for approximately 700,000 deaths per year (39). Approximately 80–90% of cases occur in patients with HIV with lungs and CNS being the most commonly affected sites (40). Data are limited regarding cryptococcal infections in advanced liver disease, however, cirrhosis has been identified as an independent risk factor for developing cryptococcal infection (41). As many as 21–36% of cryptococcal infections in non-HIV patients are in patients with cirrhosis (42). A case-control study by Lin *et al.* found that decompensated liver cirrhosis is a risk factor for invasive cryptococcal infection (43). Additionally, a retrospective study by Cheng *et al.* demonstrated that severity of cirrhosis was associated with dissemination of cryptococcal infection as well as mortality from cryptococcal meningitis (44). Cryptococcemia occurs in 50–70% of patients with cirrhosis-associated cryptococcosis (45).

Increased susceptibility of patients with cirrhosis to cryptococcal infection is thought to be due to impaired complement function, leukocyte dysfunction, and reduced opsonization (40). A retrospective study by Zhou *et al.* sought to assess outcomes and predictors of end-stage liver disease with cryptococcosis and found that cryptogenic liver disease, activated partial thromboplastin time, and Child-Pugh score were associated with mortality. Additionally, the Model for End-Stage Liver Disease-sodium (MELD-Na) score was a significant predictor of 30-day mortality and Child-Pugh score was a significant predictor of 90-day mortality in patients with cirrhosis and cryptococcal infection (46).

Immunocompetent patients with cryptococcal meningitis without HIV and without history of organ transplantation are managed with Amphotericin B plus flucytosine for 6–10 weeks followed by fluconazole 400 mg daily for an additional 8 weeks. For mild to moderate pulmonary infection or dissemination without meningeal involvement, fluconazole 400 mg daily for 6–12 months is recommended. Severe pulmonary disease is managed similarly to CNS infection (47). Patients with pre-existing liver disease are at

increased risk for azole hepatotoxicity, and therefore should be monitored closely (48). There is a need to develop treatment guidelines for patients with advanced liver disease and cryptococcal infection.

Aspergillus

Aspergillus spp. is an opportunistic fungal pathogen that has low virulence in immunocompetent individuals and frequently causes asymptomatic colonization of the respiratory tract. However, invasive infection may occur in those in an immunocompromised state (49). *Aspergillus fumigatus* is most commonly associated with invasive disease. Diagnosis of IA is made via BAL or lung biopsy (50). The prevalence of IA has been increasing among patients with liver disease in recent years. A prospective cohort study by Prattes *et al.* found a prevalence of 1.3% among patients with cirrhosis (51). However, critical illness may increase this number as Lahmer *et al.* found a prevalence of 14% among patients with cirrhosis in the ICU (52). Multiple studies have found IA to be a significant predictor of mortality among patients with cirrhosis, particularly those with decompensated liver disease. A meta-analysis by Verma *et al.* found an overall mortality rate of 81.8% among patients with cirrhosis and IA. The authors also found that IA was associated with 8.9 times higher odds of death compared to patients with cirrhosis who did not have IA (53). Levesque *et al.* performed a retrospective study of 986 patients with cirrhosis over a 10-year period and identified patients with a positive *Aspergillus* culture. Among these, patients with chronic obstructive pulmonary disease (COPD) had higher odds of IA (OR 6.44; 95% CI: 1.43–28.92; P=0.015). Additionally, in-hospital mortality was 71% in those with IA compared to 19% in the colonized group (P<0.001) (54). A prospective study of 94 patients admitted with ARH by Gustot *et al.* found that baseline MELD ≥ 24 was an independent risk factor for IA. They also found that transplant-free survival rate among those with IA was 0% at 3 months, compared to 53% in those without IA (55). Patients with underlying liver disease should be evaluated diligently for IA and prophylactic antifungals should be considered, particularly in patients with COPD, ARH, or those admitted to the ICU.

Coccidioides

Coccidioides is a fungal pathogen that is primarily found in the southwestern US and parts of Central America (56). Infection in endemic regions occurs through inhalation of spores which are found in the soil, and the majority of cases are asymptomatic (57). Respiratory symptoms are the most common manifestation of coccidioidal infection, however, dissemination to other sites can occur in predisposed individuals (58). Previous literature has identified risk factors for disseminated coccidioidomycosis (DCM) to include HIV, solid organ transplantation, and hematologic malignancy (59). Data regarding coccidioidomycosis in patients with cirrhosis is lacking. A prospective study by Blair *et al.* found a 1-year coccidioidomycosis incidence of 4.2% in patients with cirrhosis, compared to 0.04% within the general county population during the same period (60). Cirrhosis may cause increased susceptibility to coccidioidal infection through a similar mechanism as seen in cryptococcosis and aspergillosis. Cirrhosis may also cause increased susceptibility to severe infection and DCM. A recent case series by Ho *et al.* describes four patients aged 35–56 years who developed DCM with a pre-existing history of cirrhosis. All four patients had uniquely severe presentations with rapid decline, and ultimately died from DCM which is an uncommon outcome (61). Another case series of three patients with cirrhosis by Blohm *et al.* describes a similar phenomenon, as well as miliary pattern on chest imaging seen in all three cases (62). We previously performed a retrospective analysis of 32 patients with DCM and chronic liver disease, and found that the majority had hepatitis C infection with an active viral load, suggesting that active viral hepatitis may also play a role in immune dysfunction predisposing patients to coccidioidal dissemination (63). More studies are needed to examine this relationship further. Patients with liver cirrhosis and symptoms of or known coccidioidomycosis should be evaluated diligently in order to prevent morbidity and mortality. Further studies regarding the association between liver disease and coccidioidomycosis are needed.

Initial treatment of coccidioidomycosis is most commonly fluconazole 400–1,200 mg daily based on the location and severity of disease with CNS infection requiring higher doses. Amphotericin B can be given in cases of severe osseous disease, or failure to respond to oral azole therapy (64). Patients with liver cirrhosis should be closely monitored for azole hepatotoxicity.

Rhizopus

Rhizopus spp. are filamentous fungal pathogens that are commonly responsible for mucormycosis infections,

which are generally sinopulmonary or rhinocerebral in nature. *Rhizopus* infections are rare, and are usually seen in immunocompromised patients who have hematological malignancy, solid organ transplant, or uncontrolled diabetes (65). However, some case reports describe *Rhizopus* infections in patients with liver disease. Lewitt *et al.* report a case of a 36-year-old female patient with chronic hepatitis C who developed an intracranial abscess due to *Rhizopus* despite not having any other immunocompromising factors (66). Makino *et al.* reported a 66-year-old female patient with autoimmune hepatitis who developed skin abscesses due to *Rhizopus* and ultimately died from her infection despite antifungal therapy (67). McBride *et al.* had also previously reported a young immunocompetent male patient with hepatic dysfunction of likely toxic etiology who developed disseminated *Rhizopus* infection of the respiratory and gastrointestinal tracts (68). Arantes *et al.* describe a case of a female patient with alcohol-related cirrhosis who developed a necrotic ulcer at her intravenous (IV) site on the arm due to *Rhizopus* which ultimately led to her death (69). Current data regarding *Rhizopus* infections in advanced liver disease are limited to case reports, and larger studies are still needed.

Liver transplantation and fungal infections

Although the use of corticosteroids in the liver transplant population has been reduced, it is still widely used in the treatment of ARH. This can be problematic, as steroids suppress the type 1 helper T cell (Th1) mediated cellular response, which normally functions to clear fungal pathogens via macrophage phagocytosis. The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial provides additional insight on the use of prednisolone in ARH, revealing a reduction in short term (28-day) mortality, without significant improvement in long-term outcomes at 90 days or 1 year (70). Corticosteroids should be used with caution in patients with progressive liver disease and should be monitored closely for evidence of infection.

The patient population also plays a critical role in assessing susceptibility to IFIs. Liver transplant recipients are of particular concern, with an estimated incidence of IFI ranging from 4% up to 40% (13). According to Barros *et al.* there is a temporal association with IFIs in the post-transplant period, with *Candida* species representing approximately 85% of all cases during the first 6 months post-operatively. In contrast, IA represents 2% of all IFIs in liver transplant patients, with an estimated time to infection after transplantation of 18 days (13). Cryptococcus is the third most common IFI among transplant recipients with an estimated time to infection of less than one year post-operatively. By comparison, infection rates with PCP have declined in the setting of widespread post-transplant prophylaxis. A cohort study conducted in Copenhagen examined the efficacy of PCP prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) in liver transplant recipients during 2011–2019. Among the 343 liver transplant patients included in the study, 269 received PCP prophylaxis, and of those on prophylactic therapy, zero cases of PCP were reported during the first 6 months post-operatively (71).

Diagnostic testing

Beta-D-Glucan (BDG)

Utilization of the appropriate diagnostic modalities is imperative for early identification and treatment of IFIs. Broadly, fungal cell wall markers, such as serum 1,3-BDG, may help clinicians identify evidence of IFI prior to culture results. Although this marker carries a lower sensitivity (75–83%) and specificity (63–87%) it serves as a valuable negative predictive tool, with an estimated negative predictive value of 92–97% (72,73). It should also be noted that the sensitivity and specificity of BDG varies based on fungal pathogen. For example, this marker has a higher sensitivity and specificity in the detection of PCP (96% and 84% respectively), compared to IA (77% and 83% respectively). In the appropriate clinical context, BDG may be used to help rule out the presence of fungal pathogens but should be used with caution given its wide variability (72). BDG testing can be affected by treatment with immunoglobulins, antifungals, and albumin, and this should be taken into consideration when reviewing test results (74).

Galactomannan

Similar to BDG, serum galactomannan is a cell wall marker that may be used in the identification of IFI. More specifically, this marker serves as a polysaccharide component in the cell wall of *Aspergillus* species, which is released during angioinvasion. Galactomannan can be detected up to 5–8 days prior to clinical or radiographic evidence of the disease (72). Although galactomannan is considered specific to IA, cross-reactivity has been reported with yeast, such as *Candida* and *Cryptococcus* species. It should

also be noted that concurrent treatment with piperacillin-tazobactam was previously reported to yield false positive results, however, current formulations of the antibiotic have mitigated this testing error in the United States. Overall galactomannan carries a sensitivity of 33–38% and specificity of 87–97% (6). When combined with a positive serum BDG, galactomannan is highly specific for IA, with an estimated specificity of 98% (72). When clinically indicated, BAL sampling can improve the test's overall sensitivity (56–73%) and specificity (89–94%), and in non-mechanically ventilated patients may serve as a beneficial adjunct (6). It has lower diagnostic yield compared to lung biopsy, but in the absence of discrete nodules or lesions that are amenable to biopsy, BAL should be considered (75). When BAL is contraindicated, induced sputum may be useful in the assessment of galactomannan. In fact, a study conducted by Kimura *et al.* found sputum testing to be comparable to BAL in galactomannan detection (76). In the presence of associated respiratory symptoms, imaging modalities are often employed, but frequently yield non-specific findings and further testing is often required.

Fungal blood cultures

Regarding fungemia, blood cultures are the gold standard for diagnosis. However, this diagnostic tool carries a low sensitivity of approximately 50% and requires extended incubation times which may result in delayed treatment (31). To help mitigate this, two additional diagnostic modalities, Matrix Associated Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) and peptide nucleic acid fluorescence in situ hybridization (FISH), have been generated in hopes of decreasing the time to identification of *Candida* species. In addition, these techniques allow clinicians to distinguish *Candida albicans* from glabrata (6).

Pathogen-specific testing

For PCP, If concomitant HIV is present, an elevated lactate dehydrogenase (LDH) can serve as a useful indicator of infection; in the absence of HIV, its use is debated (77). It should be noted that LDH may also be elevated in the setting of acute lung injury without PCP infection. Radiographic findings typically reveal diffuse patchy ground glass opacities and may occasionally appear with cavitary lesions (77). The preferred method of diagnosis is microbiologic identification via induced sputum culture, BAL, or lung tissue biopsy when clinically indicated and can be safely performed. Definitive diagnosis is based on either direct immunofluorescent antibody testing or polychrome stains, such as methenamine silver. Direct immunofluorescence yields a nearly 90% sensitivity when compared to staining, but a lower specificity of 94% versus 99% respectively. When infection burden is low, PCR assays may provide greater ability to detect PCP, however, this method cannot distinguish between colonization and active infection. Histopathology from lung biopsy will reveal alveoli with eosinophilic exudates and may occasionally show granulomatous inflammatory changes (77).

Culture is considered the gold standard for diagnosis of coccidioidomycosis. Serum antibody testing is also widely available and frequently used but may yield false negatives in the early stages of infection. Therefore, in cases of high clinical suspicion serial testing should be pursued (78). Other tools such as antigen-based assays provide a variety of options for testing, including serum, urine, and cerebrospinal fluid. When available, enzyme immunoassays can provide results within hours, but have varying sensitivity and specificity, with estimates ranging from 59–88% and 68–90% respectively. In this case, clinicians should consider confirmatory testing with immunodiffusion and complement fixation, as it provides improved specificity and may support the continuation of antifungal therapy (78).

Similar to IA, mucormycosis is angio-invasive and requires a high index of clinical suspicion for identification and timely initiation of therapy. In rhino-orbital disease, patients often present with reports of headache, facial pain, and may have evidence of black or blood-tinged nasal secretions. Similarly, pulmonary involvement may result in evidence of hemoptysis, along with reports of fever, cough, or chest pain. When clinical suspicion is high for rhino-orbital involvement endoscopic examination of the nasal cavity can be employed. Non-contrast computed tomography (CT) and magnetic resonance imaging (MRI) of the paranasal sinuses and orbits can provide supportive evidence of fungal invasion, including bone erosion and sinusitis (79). In the case of pulmonary involvement, radiographic imaging may reveal an atoll sign or evidence of multiple nodules. Confirmatory testing includes microbiological examination of nasal mucosal secretions, BAL, or tissue biopsy on a potassium hydroxide wet mount. This will reveal ribbon-like structures with aseptate hyphae branching at characteristic right angles (79). Culture is another important tool in the diagnosis of mucormycosis. Sabouraud dextrose agar is used, and when present mucor

will grow within 72 hours of plating. However, this culture has a low sensitivity of 50%, and in cases where clinical suspicion is high, treatment should not be withheld (79).

Diagnosis of cryptococcus relies on direct examination of body fluids with India ink, or histopathologic examination of tissue samples with mucicarmine and alcian blue. In addition, diagnostic tools such as enzyme-linked immunosorbent assay (ELISA) and latex agglutination, provide highly sensitive and specific options in the identification of the polysaccharide capsule from serum or cerebrospinal fluid (80).

Treatment

Candida

When diagnostic evidence is suggestive of invasive candidiasis, an echinocandin should be initiated in a timely manner. Fluconazole is no longer considered a first line agent given growing resistance of *C. glabrata* and *C. krusei* species (6). Caspofungin also presents issues, as dose adjustment is required in the setting of advanced cirrhosis. Instead, micafungin is a reasonable alternative that is not impacted by the presence of impaired hepatic function. The timing of treatment should be guided by blood cultures and continued for at least two weeks after the first set of negative cultures. Ultimately the duration of therapy is defined by source control and each patient should undergo an echocardiogram and fundoscopic exam to rule out cardiac or retinal invasion (6).

Aspergillus

When considering treatment of IA, voriconazole is considered a first line agent, but should be used cautiously as it carries the potential for hepatotoxicity. In addition, the drug requires cytochrome P-450 isoenzymes in its metabolism, increasing the risk of potential drug-drug interactions (81). The mechanism of hepatic injury with voriconazole is not fully understood but has been reported to cause transient elevations in serum aminotransferases in 11–19% of cases (82). In patients with Child-Pugh class A and B, a 50% reduction in the maintenance dose following the loading dose is recommended. Duration of therapy ranges from 6–12 weeks and may be prolonged in the setting of immunosuppression. As an alternative, the Infectious Disease Society of America (IDSA) recommends the initiation of isavuconazole in the setting of IA due to its improved side effect profile. Lipid-formulations of amphotericin B may also be considered in refractory cases (6).

Pneumocystis

TMP-SMX is considered the first-line therapy for PCP. Although data on duration of therapy in the non-HIV population is sparse, current recommendations suggest a 21-day total course in the setting of severe infection. Present recommendations for liver transplantation include routine implementation of PCP prophylaxis with TMP-SMX for at least 6–12 months post-operatively (83).

Coccidioides

The treatment of coccidioidomycosis varies based on severity of disease or presence of systemic involvement. Both fluconazole and itraconazole are commonly used agents in the treatment of coccidioidomycosis and have been deemed effective for multiple forms of the disease, including meningitis (84). Fluconazole is widely available and has a preferable side effect profile but is associated with a lower treatment response rate (37%) when compared to itraconazole (70%). Itraconazole is also associated with lower relapse rates by comparison (78). If a lack of treatment response is noted with these therapies, voriconazole may be trialed. Although the liposomal formulations of amphotericin B have an improved side effect profile, treatment with this agent is reserved for cases refractory to triazole therapy. It should also be noted that intravenous amphotericin is ineffective in treating CNS involvement. Duration of therapy depends on severity of disease and presence of dissemination. For isolated pulmonary disease, treatment is recommended for 3–6 months, with consideration for prolonged treatment in severe or chronic cases. In transplant recipients with a positive serologic test, life-long suppressive therapy with fluconazole is recommended (84,85).

Rhizopus

As with other IFIs, risk of disseminated disease is higher in immunocompromised populations. With this in mind, the rapid initiation of treatment is imperative, as patients with evidence of disseminated disease have an estimated 96% mortality rate (86). Corticosteroids and uncontrolled diabetes are two prominent risk factors for mucormycosis, contributing to impairment of phagocytic clearance of

the fungal pathogen. Thus, glycemic control is of utmost importance in the treatment of mucormycosis, and in patients with comorbid diabetes, blood glucose should be monitored closely. When possible, surgical resection is recommended, as debulking surgery has been reported to confer an overall improved chance of survival (87). Amphotericin B is considered the first line agent in the treatment of mucormycosis, and the liposomal formulation is preferred to mitigate the drug's nephrotoxic effects. Other antifungal agents should be avoided as mucormycosis has well documented resistance to azole therapies. Alternatives such as posaconazole and isavuconazole can be used for adjunctive or salvage therapy. In addition, posaconazole and isavuconazole may also be used as step-down therapies in patients who have undergone treatment with amphotericin (79).

Cryptococcus

Most data regarding cryptococcus is in relation to HIV, however this opportunistic infection can present issues in any immunocompromised host, including those with a history of organ transplantation and cirrhosis, and carries an associated mortality rate of 20% (88). The mainstay of treatment is a combination of amphotericin B and 5-fluorocytosine. Fluconazole may be coupled with amphotericin B when flucytosine is not available or poorly tolerated. In cases of CNS involvement, elevated opening pressures often require serial therapeutic lumbar punctures to achieve a 50% reduction in opening pressure, or goal opening pressure of 20 centimeters (cm) H_2O (88). Induction therapy in patients without HIV or a history of transplant is 4 weeks. The duration of induction varies based on the presence of neurologic impairment, degree of immunosuppression at the time of initiation, and response to therapy (88).

In a discussion on the management of bacterial and fungal infections in cirrhosis, Fernández *et al.* state the decision to empirically treat should be guided by infection severity (more specifically the presence of shock states), risk for multidrug resistant organisms, and local epidemiologic trends. In addition, the group advocates for the re-evaluation of therapy after 48–72 hours to not only determine efficacy, but also de-escalation of therapy when appropriate. The decision to initiate therapy in this case is supported by the associated high mortality rates observed in patients with decompensated cirrhosis and concurrent IFIs, such as candidemia, with a documented 28-day mortality rate of up to 60% (6). Current guidelines and literature do not recommend prophylactic antifungal therapy in patients with cirrhosis, as there has not been any survival benefit demonstrated with this approach (14). In patients who are awaiting liver transplantation, IFI may exacerbate hepatic dysfunction thus increasing the need for transplantation. However, active IFI is considered a temporary contraindication for transplant surgery. Therefore, patients with IFI who are awaiting liver transplantation warrant a multidisciplinary discussion to determine the most appropriate therapy, length of treatment, and timing to re-enter the waitlist for transplant (89). Details regarding the management of liver transplant patients is beyond the scope of this manuscript and have been presented elsewhere (89).

Conclusions

Cirrhosis of the liver is associated with a host of complications, including immune dysfunction. Patients with cirrhosis are at increased risk for a variety of infections, most commonly by bacterial pathogens. However, the incidence of fungal infections in advanced liver disease is increasing and is associated with significant short-term mortality and poor outcomes. Candidiasis and aspergillosis are the most common fungal infections in cirrhosis, while data regarding pneumocystis, cryptococcus, coccidioidomycosis, and mucormycosis are more limited. Based on previous studies, impaired immunity in cirrhosis-related liver dysfunction not only increases the risk of fungal infection, but also the susceptibility to developing invasive or disseminated infection. Fungal infections in cirrhosis are usually treated with oral azole therapy, and Amphotericin B or other agents based on the site and severity of infection. Patients with cirrhosis showing signs or symptoms of fungal infection should be evaluated with caution and diligence in order to expedite appropriate management, and to prevent morbidity and mortality. Future epidemiological studies and randomized control trials are needed in order to further elucidate the mechanisms, risks, complications, and most appropriate management of advanced liver disease with fungal infections. Additionally, treatment guidelines for fungal infections in patients with advanced liver disease are needed.

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Footnote

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