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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Cryptococcosis in Liver Transplant Candidates and Recipients

Sara Gore [1] · Graeme N. Forrest [1,2]

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Abstract

Purpose of Review Evaluate the epidemiology, risk factors, pathophysiology, and clinical outcomes of cryptococcal infections in patients with advanced liver disease or liver transplantation.

Recent Findings Cryptococcal infections in patients with advanced liver disease (ALD) are uncommon but associated with high mortality. Less than 10% of patients in a prospective study of non-HIV-infected cryptococcal meningitis patients had ALD. Significantly, fever was uncommon, resulting in delays in diagnosis. Modalities for diagnosing cryptococcal infections include the rapid lateral flow cryptococcal antigen (CrAg) assay from serum and cerebrospinal fluid (CSF) specimens and multiplex polymerase chain reactions from CSF. Screening all ALD patients with CrAg has not been beneficial.

Summary Cryptococcal infections in patients with ALD and liver transplantation result in poor outcomes due to diagnostic delays and concomitant impaired liver function with hepatotoxic therapies. A high index of suspicion is necessary as routine screening has very low yield for early detection.

Keywords Cryptococcus · Meningitis · Antifungal therapy · Cirrhosis · Liver transplantation

Introduction

Cryptococcus is an encapsulated yeast within the genus of basidiomycetous fungi. There are two main species that are commonly associated with human disease: *Cryptococcus neoformans* and *Cryptococcus gattii*. These species are distinguished by their antigenic diversity; *C. neoformans* strains are of serotypes A and D, while *C. gattii* strains are of serotypes B and C [1]. There are 2 subspecies of *C. neoformans* and 5 subspecies of *C. gattii*, and all are assigned taxonomic names to reflect their antifungal activity [2, 3]. *Cryptococcus neoformans* is found worldwide in association with the excrement of certain bird species (e.g., pigeons) and environmental scavengers [4]. *Cryptococcus neoformans* causes disease in both immunocompromised and immunocompetent hosts while *C. gattii* has emerged as an important pathogen in outbreaks within British Columbia and the Pacific Northwestern USA [5]. Patients living with HIV still remain at the greatest risk for cryptococcal infections; however, in some areas, rates in non-HIV-infected patients are now higher, most likely due to widespread immune reconstitution with antiretroviral therapy [6•].

Liver transplantation (LT) is a well-established important risk factor for severe cryptococcal infections due to immunosuppressive medical therapy, but advanced liver disease (ALD) is increasingly being recognized as an important risk factor and is associated with high mortality [7]. It was due to the improvements in survival of HIV-infected patients that an association with ALD and cryptococcal disease was detected [8, 9]. There are immunologic differences between a liver transplant recipient (LTR) and ALD patients, and as such their epidemiology and clinical presentations are different and will be discussed separately [7, 10, 11]. Diagnosis and management are similar for both hosts, thus will not differentiate.

Advanced Liver Disease Patients

For the purpose of this review, patients with ALD include patients with cirrhosis, autoimmune hepatitis, and untreated chronically active viral hepatitis B and C (HBV and HCV) [10–13].

Topical Collection on *Fungal Infections in Transplantation*

✉ Sara Gore
goresa@ohsu.edu

[1] Division of Infectious Diseases, Oregon Health and Science University, L-457, 3181 SW Sam Jackson Rd, Portland, OR 97239, USA

[2] VA Portland Healthcare System, Portland, OR, USA

Epidemiology

Cryptococcal infections in ALD patients were observed in the 1990s and 2000s, mostly due to the large cohort of chronic HCV patients that were pending or too ill for LT [14]. Unfortunately, epidemiologic studies on the rates of cryptococcal infection in ALD and pre-LT recipients are lacking, with single-center studies and case reports suggesting an incidence of < 0.5% [7, 10]. The rates of cryptococcal infections in ALD populations are unknown due to underdiagnosis, underreporting, and lack of a denominator. The best data available is a retrospective 13-year study evaluating all cryptococcal meningitis (CM) admissions in the USA based on ICD-9 codes [15•]. Of the 30,000 hospital admissions with CM, 6689 (21%) were not HIV-related, and 67% of these patients were male. The authors calculated the relative prevalence (RP) of co-morbidities with liver disease and found that liver failure (RP 6.1), autoimmune hepatitis (RP 10), liver cirrhosis (RP 2.8), and co-infections causing viral hepatitis (RP 2.6) were significantly associated with CM. This compares to organ transplantation, which had an RP of 36 [15•]. The study was limited by the under detection of cryptococcosis in non-HIV individuals, thus may underestimate the risk with ALD. Marr et al. performed a large, multicenter, longitudinal study of 145 HIV-negative patients with proven cryptococcal infection, of which 14 (9%) had ALD and followed them for 2 years. The mortality and morbidity were over 80% with this ALD group [11••]. Unfortunately, this study was from selected sites in the USA, thus does not give a global perspective of the problem and assumes that a pre-mortem diagnosis was made. A study of 232 consecutive cases of *Cryptococcus* over 12 years by Spec et al. identified 25 (10.3%) with concurrent ALD, with a mortality rate of 80% [10•]. These data reflect the poor prognosis of this infection in patients with ALD.

The largest prospective study specifically screening all ALD patients for cryptococcosis with the latex agglutination CrAg assay was performed at a single center in Korea [16••]. None of the 294 persons tested had a cryptococcal infection, making it unlikely that routine screening in this population would be cost-effective compared with HIV-infected individuals [16••]. This result is disappointing as it demonstrates both the rarity of the event in ALD patients and the randomness of the infection, along with the role of immune dysfunction in diagnosis and clinical presentation.

Pathophysiology

The pathogenesis of cryptococcal infections and the host immunologic response to these infections is a complex interaction and is too long for this review [17, 18]. Although ALD and organ transplantation have different immunologic responses to cryptococcal infections, the organism has factors that make it opportunistic based on the holes created in the immune system, also known as the damage-response framework (DRF) [19•].

Cryptococcus has a thick lipopolysaccharide capsule composed of glucuronoxylomannan (GXM; the target of the antigen detection assays). The capsule is antiphagocytic and is considered an essential virulence factor [17]. This inhibition of macrophage and phagocytic activity impacts the host response, and combined with its ability to replicate intracellularly, allows for *Cryptococcus* to escape the host defense system and spread through the body [17]. This may explain why inhalation is the suspected route of infection and how it can spread to the central nervous system (CNS) [18]. The capsular GXM contributes to the inflammation caused by the yeast in the CSF, which in turn necessitates yeast clearance from the CSF in order to manage infection [18]. A thorough review on the impact of *Cryptococcus* on host cytokines, phagocytosis, other white cells, and adaptive immunity, including T cells, was performed by Rohatgi and Pirofski and explains how the organism manipulates these factors to evade being killed [17]. They also describe how absence of these factors which are seen with ALD can lead to serious infection.

The host response to cryptococcal infection primarily involves a helper T cell response (CD4), along with important cytokines such as tumor necrosis factor (TNF), interferon-γ (IFN-γ), and interleukin-2 (IL-2), resulting in granulomatous inflammation [18]. The GXM itself is immunomodulatory and preferentially stimulates the Th2 over Th1 response [20].

Immunocompetent individuals exposed frequently to *Cryptococcus* have been shown to be resistant to cryptococcal disease; however, immune defects such as anti-granulocyte macrophage colony-stimulating factor antibodies have led to the development of cryptococcosis in this group [21]. The greatest risk factor for the development of cryptococcosis is the weakened CD4 response seen in HIV-infected patients with CD4 counts < 100, and those immunosuppressed with corticosteroids and anti-rejection medications [22]. Maziarz and Perfect identified that cryptococcosis has a "Goldilocks paradigm of immunity - It produces disease when immunity is too little or too much, but when the human host immunity is just right, disease does not appear" [18].

The mechanisms of immune dysfunction that allow for cryptococcosis to occur in patients with ALD appear to be multiple defects in the immune system [23, 24]. The liver mitigates infections through its reticuloendothelial cells (Kupffer cells), which clear cytokines, bacteria, and endotoxin from the circulation [7, 24]. In addition, hypogamma globulinemia caused by deficiencies in protein manufacturing leads to impairment of monocyte, neutrophil, macrophage, and lymphocyte chemotaxis [10, 17, 24]. An underappreciated impact of the known dysfunction in ALD is that there is also associated T cell dysfunction [25]. As a result of these

cellular and immunologic defects, patients with ALD have similar risk profiles for the development of cryptococcal infections as organ transplant recipients. Similarly, active and untreated HBV or HCV infections alter the immune system to increase the risk of cryptococcal infections [12, 26]. It appears that chronic HBV or HCV can reduce IL-2 and interferon-γ (IFN- γ) levels, leaving sufficient gaps in the immune system for cryptococcal infections to occur [12, 17].

Iron overload is another proposed risk factor for the development of cryptococcosis in ALD and LTR. ALD often results in iron overload attributed to decreased hepcidin levels and increased intestinal iron absorption [27]. *Cryptococcus* capitalizes on host iron stores and utilizes iron as a cofactor in key mechanisms of pathogenesis and virulence [27]. Iron is essential to the formation and size of the *Cryptococcus* polysaccharide capsule along with the yeast's temperature tolerance. The CIR1 (*Cryptococcus* iron regulator) gene has been shown to play a key role in these and other virulence factors, and CIR1 knockout animal models lack virulence [28]. The iron-overloaded state may persist and lead to infectious complications in the post-transplant period [27]. In one study, patients with pre-transplant hepatic iron overload without a diagnosis of hereditary hemochromatosis had decreased post-transplant survival as compared with those without evidence of iron overload, with infections as the primary identifiable cause of death in those with iron overload [29]. A subsequent study found a significant association between hepatic iron overload in the native liver and invasive fungal infections [30].

This complexity of immune dysregulation in ALD makes the host very susceptible to cryptococcal infections. The downregulation of cytokines and immunomodulation can suppress a florid immune response to cryptococcal infection, resulting in minimal signs and symptoms, which can delay diagnosis and lead to high mortality.

Clinical Presentation

The clinical presentation of cryptococcal infections in patients with ALD is very subtle and often missed as explained by the immune dysregulation. The most important finding by Marr et al. was that fever was uncommon on presentation, occurring in less than 30% of subjects, and its absence was associated with a significant diagnostic delay (mean 48.2 vs. 16.5 days; $P = .007$) [11••].

Patients with ALD frequently have concurrent metabolic encephalopathy, making it almost impossible to determine if mental status changes are due to metabolic derangements, gastrointestinal bleed, or infection [16, 26, 31]. Cryptococcal peritonitis and meningitis appear to be the most common presentations, followed by fungemia, myositis, and cellulitis; however, this is based off of limited reporting [9, 10, 32–37]. The peritonitis is usually lymphocytic predominant, exudative, and often initially sterile, though rarely yeast can be seen on the initial ascitic tap and 50% will have cryptococcemia [37••]. Positive CrAg from the peritoneal fluid has been reported, but the sensitivity and specificity from this site are unknown [37••]. The presence of cryptococcal peritonitis in ALD patients does not necessarily mean there is associated meningitis, like with OLT recipients. However, the presence of cryptococcal pneumonia in ALD patients does denote meningitis as well [9, 14, 31, 33, 35, 36, 38–41] (Table 1). Given that most ALD are severely ill, having a cryptococcal infection often means they are ineligible for liver transplant. There are scenarios where patients who complete induction antifungal therapy and remain stable on fluconazole can proceed to liver transplant, but this is uncommon [59].

In summary, cryptococcal infections in patients with ALD are infrequent, but when present, are often subtle or missed due to the severity of illness. As a result, cryptococcal infection in ALD carries a high mortality rate.

Liver Transplant Recipients

There are important differences in the clinical presentation, pathology, and outcomes of cryptococcal infections in LTR as compared with ALD patients.

Epidemiology

Cryptococcal infections are the third most commonly occurring invasive fungal infection in LTR at about 8% of all invasive fungal infections [60]. However, LTR appears to have a lower mortality from cryptococcal infections with proposed reasons including a protective effect from the antifungal properties of calcineurin inhibitors, earlier diagnosis due to provider awareness, and the ability to modulate immunosuppressive medications [7, 11, 61, 62]. In a study of 111 total cryptococcal infections in organ transplant recipients, the time to onset of cryptococcal infections was earlier with LTR (< 12 months) compared with other organ transplants (12–18 months), which may be due to a higher intensity of immunosuppression [14, 63, 64].

Pathophysiology

In LTR, medically induced immunosuppression has the greatest impact on the pathophysiology of cryptococcal infections due to alteration of the host response.

LT considerably impacts the immune system with induction therapies such as thymoglobulin or alemtuzumab, maintenance immunosuppression with agents such as corticosteroids and calcineurin inhibitors, or combinations of these factors [7, 65]. These drugs impact the T-helper cells with

Table 1 Summary of cryptococcal infections in patients with ESLD without HIV

Reference year	Liver disease and other factors	Number of patients	Sites of infection	Treatment	Mortality
1963 [42]	Lymphoma	2	Liver	c-AmB	100%
1967 [43]	Cirrhosis	1	CNS	c-AmB	100%
1982 [44]	Cirrhosis (alcohol)	1	Peritonitis	c-AmB + 5FC	100%
1990 [45]	Cirrhosis, prednisone	1	Peritonitis, colitis, and skin	None	100%
1995 [9]	Cirrhosis	2	Peritonitis	c-AmB + 5FC	50%
2000 [46]	Cirrhosis, HBsAg, and eAg	1	Peritonitis	c-Amb + fluconazole	100%
2001 [32]	Cirrhosis, alcohol, HCV	1	Myositis	L-amB 20 days, fluconazole 1 year	0%
2002 [47]	Lymphoma, cirrhosis, breast ca	3	Peritonitis, fungemia 2 of 3	c-AmB × 1	100%
2004 [22]	4 HCV cirrhosis, 1 HBV cirrhosis	5	4 fungemia, 1 peritonitis, 1 meningitis	4 L-amB, 1 + 5FC	100%
2005 [48]	Alcohol cirrhosis	1	Peritonitis	L-amB	100%
2005 [49]	Cirrhosis	1	Peritonitis	L-amB	100%
2005 [50]	Cirrhosis	3	Meningitis, blood, peritonitis, pleural cutaneous	Fluconazole	100%
2005 [38]	Cirrhosis	2	Peritonitis and fungemia, peritonitis, meningitis, and fungemia	L-amB	100%
2006 [39]	Cirrhosis, HCV	1	Peritonitis, meningitis fungemia	Fluconazole, then AmB	0%
2008 [51]	ESLD	12	Various	Various	100%
2009 [52]	HBV ESLD	1	Prostatitis	Fluconazole	0%
2009 [53]	Alcohol cirrhosis	1	Meningitis, peritonitis, fungemia	L-amB + 5FC	100%
2011 [54]	HCV cirrhosis	1	Cutaneous (labia)	Fluconazole, then L-amB, then fluconazole	0%
2013 [55]	HBV and HCV cirrhosis	1	Peritonitis, meningitis	Amb + 5FC, fluconazole	100%
2014 [40]	HBV, HCV cirrhosis	2	Peritonitis, fungemia	AmB, fluconazole	50%
2014 [56]	HBV cirrhosis	1	Meningitis, fungemia	AmB	100%
2014 [35]	ESLD undifferentiated	5	Peritonitis	AmB	100%
2015 [7]	ESLD undifferentiated	112	77% disseminated	Various	55% mortality
2015 [12]	HCV/HBV	34	75% disseminated	Various	41%
2016 [57]	HCV alcohol cirrhosis	1	Fungemia	L-amB	100%
2016 [10]	Various	25	Meningitis 44%, fungemia 56%, pulmonary 28%, peritonitis 20%,	Various	80% at 6 days
2017 [13]	Autoimmune cirrhosis, corticosteroids	1	Peritonitis	AmB	100%
2018 [58]	HBV cirrhosis	1	Pleuritis, peritonitis	None	100%
2018 [31]	Autoimmune cirrhosis	1	Fungemia and peritonitis	None	100%
2019 [26]	HCV cirrhosis	1	Fungemia	None	100%
2019 [41]	HBV cirrhosis	1	Pleural effusion	AmB, fluconazole	0%

AmB amphotericin B unspecified, *c-AmB* conventional amphotericin B, *ESLD* end-stage liver disease, *5FC* 5-flucytosine, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *L-amB* lipid formulation amphotericin B

varying degrees of depth and duration of suppression, often in patients with immune systems co-infected with other viruses such as HBV and HCV leading to further immune depletion [7]. Due to their broad immunosuppressive activity, corticosteroids have been associated with an increased risk of cryptococcosis; however, the precise daily dose that confers a higher risk in LTR remains unknown [65].

Although calcineurin-inhibitor-based regimens that include tacrolimus and cyclosporine can reduce T-helper cell activity, these agents are also known to enact

in vitro cryptococcal inhibition [66]. It is speculated that the fungal homologs of calcineurin inhibitors lead to this anticryptococcal activity. In a retrospective study evaluating *Cryptococcus* in solid organ transplant recipients, patients receiving tacrolimus or cyclosporine were more likely to have limited pulmonary disease and less likely to have disease disseminated to the CNS [64]. Mortality was significantly lower in those who received tacrolimus or cyclosporine-based regimens; however, patients on these agents were more likely to develop cryptococcal infection over a year after transplant [64]. T cell-depleting antibodies such as alemtuzumab and antithymocyte globulin (ATG) cause profound lymphocyte depletion of CD4+ T cells which may last for several months and have been associated with an increased risk for cryptococcosis [67]. When used for induction, these agents allow for reduction of long-term immunosuppression, which may actually limit infectious complications [68]. In contrast, the allograft dysfunction and the additional immunosuppressive agents used in the setting of organ rejection lead to an increased risk of cryptococcal infection. The anti-CD52 monoclonal antibody alemtuzumab carries a higher risk of opportunistic infections when administered to manage rejection as compared with induction alone, with 21% of patients who received one or more doses of alemtuzumab for rejection developing an opportunistic infection compared with 4.5% of patients who received basiliximab for induction alone [69]. Out of the 56 opportunistic infections, 32% were fungal infections: Two patients developed cryptococcal infections and the majority developed esophageal candidiasis [69]. Another study showed a dose-response increase in cryptococcal infections with alemtuzumab and ATG exposure. The cumulative incidence of *Cryptococcus* increased from 1.2% with a single dose of alemtuzumab or ATG to 3.5% in those who received 2 or more doses [67].

Thrombocytopenia is another proposed factor increasing the risk of fungal infections in LTR. In a study assessing characteristics of patients with post-liver transplant thrombocytopenia, patients with a post-transplant platelet nadir < 30 had higher rates of early post-transplant fungal infections (3/21) as compared with those with a nadir > 30 (1/29; $P = 0.6$) [70]. Profound thrombocytopenia proceeded the fungal infection in all patients. Causation is not clearly demonstrated, and these findings were not statistically significant. However, *Cryptococcus* has been shown to inhibit platelet activation [71], and platelets may also play an important role in host response to fungal infections.

Therefore, in LTR, there is a delicate balance between sufficient immunosuppression to prevent rejection and excess immunosuppression resulting in increased risk of cryptococcal. However, the calcineurin inhibitors may offer some protection and minimizing corticosteroids and T cell-depleting agents also appear to reduce the risk.

Clinical Presentation

The clinical presentation of cryptococcal infections in LTR is often insidious and disease is frequently disseminated at the time of diagnosis [65]. The neurologic presentation of CM is similar to that in non-transplant recipients; prolonged headache, altered mental status, fevers, and sometimes weakness are usually prominent symptoms compared with photophobia and nuchal rigidity [22]. Patients can have pneumonia with either solitary or multiple pulmonary nodules [63]. Likewise, neuroimaging can show meningitis or mass lesions, and should be performed before lumbar puncture [22, 72]. Cryptococcal infections can present with both pulmonary and neurologic findings; about 50–75% of LTRs have extrapulmonary disease [64, 73]. Other sites where cryptococcal lesions can occur include the skin and soft tissues, the prostate gland, liver, kidney, bones, and joints [52, 74–76]. LTR had a 6-fold higher risk of developing disseminated disease compared with other organ transplants, so blood cultures should also be drawn [64, 77].

Diagnosing a cryptococcal infection within 30 days after LTR should raise concern for a donor-derived infection [75, 78]. However, a cluster of donor-derived cryptococcal infections from a single donor occurred up to 3 months after transplant, much longer than typically has been described [79••].

Diagnosis

The diagnosis of cryptococcosis in both ALD and LTR is the same and the diagnosis of disseminated cryptococcal infection requires high clinical suspicion. Where possible, blood cultures, serum CrAg, neuroimaging, and biopsy of suspected lesions should be performed. However, meningitis is life-threatening in this population and should be excluded promptly, so lumbar puncture should be performed for diagnosis of CM prior to starting antifungal therapy. It is both a diagnostic and therapeutic procedure [22]. The opening pressure should be recorded prior to removal of a large volume (> 10 ml) of CSF with Gram stain, culture, cell count, protein, glucose, and CrAg sent from the CSF [22]. We still recommend performing a lumbar puncture in ALD patients with cryptococcal disease, especially if they have pneumonia as about 50% will have meningitis and challenges associated with the neurologic exam in the setting of encephalopathy. We recognize that there are tremendous risks given that these patients frequently have thrombocytopenia and coagulopathy; thus, the risk of an epidural bleed in this scenario has to be considered.

CrAg is the preferred diagnostic method from CSF and serum [80]. There are currently two CrAg tests commercially available: the latex agglutination test and the lateral flow assay (LFA) [22, 80]. The LFA is preferred over the latex agglutination test as it is a point-of-care test that is inexpensive with a rapid turnaround time and identifies all cryptococcal serotypes, unlike the latex assay which can miss *C. gattii* [80, 81]. The LFA from serum has a median sensitivity of 100% (95.6%, 100%) and median specificity of 99.5% (95.7%, 100%). In CSF specimens, the median sensitivity was 100% (96.2%, 100%) and the median specificity was 97.7% (70.4%, 100%) [82]. The limitations of the LFA include the prozone phenomenon and the low-level titers seen in negative patients [83, 84]. Also, with lower titers, false positive CrAg has been reported [83]. The India ink test is no longer recommended as it is not sensitive compared with the CrAg [22]. Other tests that can be performed from the CSF include multiplex polymerase chain reaction (PCR) technology, which offers the ability to identify a broad panel of bacteria, viruses, and fungi from the CSF in under 3 h. The Filmarray ME panel (Biomerieux, North Carolina) was approved for the rapid diagnosis of *C. neoformans* and *C. gattii* from CSF along with 18 other organisms [85]. However, there have been concerns with the sensitivity of this test, with a study showing only 83% sensitivity compared with CrAg, although this was in a primarily HIV-positive population [86]. Future testing may include (1,3)-beta-D-glucan from CSF. A study in 117 HIV-infected patients in Uganda showed a sensitivity of 89% and specificity of 85%, and titers > 500 pg/ml were associated with three times the risk of mortality [87].

Again, having a high index of suspicion in these patients is usually the only way to make an early diagnosis. Given serum CrAg's low cost and rapid turnaround, it could be utilized for screening of early cryptococcal infection in LTR or ALD patients.

Management

Recommendations for the treatment of *Cryptococcus* in solid organ transplant recipients are outlined in detail in the Infectious Disease Society of America's Clinical Practice Guidelines for the Management of Cryptococcal Disease [22] and the guidelines on cryptococcosis in solid organ transplantation from the American Society of Transplantation Infectious Diseases Community of Practice [65]; therefore, we will not outline this topic in detail. It is important to note that the mainstays of treatment include antifungals, reduction in immunosuppression when possible, and management of intracranial pressure in the setting of meningitis. For LTR who are on corticosteroids and calcineurin inhibitors, it may be beneficial to decrease the corticosteroid dose prior to the calcineurin inhibitor due to the antifungal activity of the latter [61]. When accessible, we prefer lipid formulations of amphotericin B over conventional amphotericin B (amphotericin deoxycholate) to limit nephrotoxicity and subsequent fluctuations in immunosuppressive agent levels.

Dose adjustments and monitoring in the setting of end-stage liver disease are outlined in Table 2 and interactions between antifungals and immunosuppressants are outlined in Table 3. The use of 5-flucytosine (5FC) is important for clearance of cryptococcal organisms from the CSF [18, 90]. However, the limitation of 5FC in ALD is that it is cleared renally, and requires therapeutic drug monitoring, which is usually sent to a specialty laboratory. 5FC toxicity can worsen underlying liver disease and needs to be monitored closely. Fluconazole is metabolized in the liver and can produce toxic levels if not closely observed, plus it directly interacts with calcineurin inhibitors, increasing their levels [61, 91]. Lastly, adjunctive corticosteroids in the acute treatment of CM have shown to decrease clearance of cryptococcal organisms from the CSF and increased mortality in HIV-infected patients, and as such is not recommended [65, 92].

Table 2 *Cryptococcus* treatment in advanced liver disease

Antifungal	Toxicities	Hepatic dysfunction	Renal dysfunction	Therapeutic drug monitoring
Fluconazole	Hepatotoxicity, QT prolongation, alopecia, xerosis.	No dose adjustments necessary but should be approached with caution. Hepatotoxicity can occur with azoles [88].	Reduce dose by 50% in creatinine clearance < 50 ml/min and by 75% in creatinine clearance < 20 ml/min.	Not generally recommended, but can consider in the setting of renal dysfunction [88].
Lipid formulation amphotericin	Nephrotoxicity, hypokalemia, hypomagnesemia, infusion reactions.	No dose adjustments.	No dose adjustments. Requires close monitoring of renal function and electrolytes.	None.
5-Flucytosine	Myelosuppression, hepatotoxicity, nausea, and diarrhea.	No dose adjustments necessary but should be approached with caution. Hepatotoxicity can occur in 7–41% [88].	Dose reduction for creatinine clearance < 40 ml/min.	Recommend trough 20–40 mg/l and peak 50–100 mg/l [88].

Table 3 *Cryptococcus* treatment and immunosuppressive medications

Antifungal	Calcineurin inhibitors (tacrolimus and cyclosporine)	mTOR inhibitors (sirolimus and everolimus)	Anti-metabolites (mycophenolate and azathioprine)	Notes
Fluconazole	May increase serum tacrolimus and cyclosporine levels via CYP3A4 inhibition. Requires close monitoring of tacrolimus and cyclosporine levels.	May increase serum sirolimus and everolimus levels via CYP3A4 inhibition. Requires close serum monitoring.	No interactions	Usually well-tolerated at higher doses. Primary concern is for CYP3A4 inhibition-mediated drug interactions.
Lipid formulation amphotericin	Nephrotoxicity may require dose adjustments.	Nephrotoxicity may require dose adjustments.	Nephrotoxicity may require dose adjustments.	Lipid preferred over conventional due to lower risk of nephrotoxicity and lower mortality in SOT [89].
5 Flucytosine	No interactions.	No interactions.	No interactions.	Renally cleared, and increased drug levels in the setting of renal dysfunction can worsen myelosuppression.

This complexity of toxic medications with serious underlying diseases probably explains why mortality is so high with this population. Unfortunately, even alternative antifungals and other therapies have failed to show any benefit.

Adjunctive and Experimental Therapies

Corticosteroids are not recommended for the routine treatment of cryptococcal infections in ALD or LTS. However, they may be helpful for management of immune reconstitution inflammatory syndrome (IRIS) or cerebral cryptococcomas [22] and research is underway to assess the utility of steroids for cryptococcal meningitis following microbiologic clearance in the non-HIV-infected population [93]. Sertraline has in vitro activity against *Cryptococcus*, but a recent randomized controlled trial showed no improvement in mortality with adjunctive sertraline therapy for cryptococcal meningitis in people living with HIV [94]. Given this data, it is unlikely that sertraline will be studied as adjunctive therapy in non-HIV patients. Neurapheresis, which involves external filtration of yeast from the CSF, has been demonstrated to effectively decrease yeast concentration in vitro and in rabbit models, but human studies are pending at this time [95].

Conclusion

Cryptococcal infections in patient with ALD or LTR are difficult to diagnose and are associated with high mortality. Even though infections are uncommon, the mortality is so high that providers should have a high index of suspicion for these infections and could screen with the serum CrAg assay despite the limitations. Unfortunately, even with an early diagnosis, the toxicity of antifungal treatments, which are metabolized in a failing liver, can also increase the mortality. The hope is that therapeutics with minimal toxicities are developed for this population in the future.

Compliance with Ethical Standards

Conflict of Interest Sara Gore and Graeme Forrest declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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