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How I Treat Cryptococcosis in Organ Transplant Recipients

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Cryptococcosis is a significant opportunistic mycoses in organ transplant recipients. Topical developments in the field in the past few years have highlighted important issues and at the same time raised new questions regarding the management of this yeast. These include, for example, management of pretransplant cryptococcosis during transplant candidacy and timing of transplant in these instances; potential for donor transmission of cryptococcosis in light of recent fatal transmissions; and prevention and treatment of Cryptococcus-associated immune reconstitution syndrome. Discussed herein are challenges posed by these issues and evidence-based data to optimize the management of posttransplant cryptococcosis.

Keywords: Fungal infection, Cryptococcus, Transplant.

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Cryptococcosis is one of the most important opportunistic infections worldwide (*1*) and a significant posttransplant complication (*2*, *3*). Although the incidence of invasive candidiasis and aspergillosis in solid-organ transplant (SOT) recipients has decreased largely because of the advances in transplantation practices and wider use of antifungal prophylaxis, that of cryptococcosis has remained unchanged over the past two decades (*3*). Currently, cryptococcosis is the third most common mycoses in SOT recipients with an overall incidence of approximately 2.8% (range 0.3%–5%) (*3*). Between 53% and 72% of the cryptococcal disease in SOT recipients is disseminated or involves the central nervous system (CNS) (*4*). Overall mortality in SOT recipients with cryptococcosis in the current era is approximately 15% to 20% (*5*).

Our knowledge base of cryptococcosis has evolved, and topical developments in the field in the past few years have highlighted important issues and posed new challenges in the management of this mycosis. These include, for example, management of cryptococcosis during transplant candidacy and in the posttransplant period; potential for donor transmitted cryptococcosis; and Cryptococcus-associated immune reconstitution syndrome (IRS). The goals of this article are to discuss and present our perspective on these and other significant developments concerning cryptococcosis in transplant recipients based on evidence from the existing literature.

PRETRANSPLANT CRYPTOCOCCOSIS

Patients with end-stage liver disease are at risk for cryptococcosis as a result of cirrhosis-associated compromised host defenses including impaired cell-mediated immunity, phagocytic dysfunction, decreased antibody and immunoglobulins, and complement deficiency. Cirrhosis has come to be recognized as a major risk factor for cryptococcosis and for poor outcomes in those who develop disease (*6*, *7*). Indeed 21% to 36% of the cases of cryptococcosis in non-human immunodeficiency virus (HIV)-infected patients are now reported to occur in patients with liver cirrhosis (*7*, *8*). Unlike HIV-infected patients in whom cryptococcal disease presents primarily as meningoencephalitis, cirrhosis-associated cryptococcosis manifests most often as peritonitis (*6*). Cryptococcemia occurs in 50% to 71%, and mortality in cirrhotic patients with cryptococcosis ranges from 81% to 100% (*6*, *7*). Cirrhosis was a significant risk factor for 1-month mortality in patients with cryptococcal disease, and cryptococcosis accounted for 92% of these deaths (*7*, *9*). Thus, patients with end-stage liver disease are uniquely susceptible to cryptococcosis, and the disease usually carries grave prognosis in these patients.

Cryptococcosis can also occur in patients with end-stage renal disease and those requiring renal replacement therapy (*10*, *11*). Outcomes are influenced by concurrent medical conditions (*12*). In one report, 9 of 10 patients with cryptococcal peritonitis during continuous ambulatory peritoneal dialysis survived, whereas 7 of 8 of those with disseminated disease and comorbid conditions such as liver disease, HIV, or lupus died (*12*).

Anecdotal cases of transplants performed inadvertently in patients with unrecognized pretransplant cryptococcosis

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with favorable outcomes exist (*13*). A dilemma, however, is whether patients with cryptococcosis during transplant candidacy can safely undergo transplantation, the appropriate timing for transplantation, and management of posttransplant immunosuppression. Limited data and guidance are available in this context. Cryptococcosis developed in two kidney transplant recipients 3 months and 3 years posttransplant (*14*). Both patients underwent retransplantation 6 months and 3 years after completion of antifungal therapy, and no relapse was observed after follow-up for 12 and 18 months, respectively. Another kidney transplant patient with pretransplant pulmonary and meningeal cryptococcosis survived after amphotericin B deoxycholate (AmBd) and 5-fluorocytosine therapy (*15*). However, a case with pretransplant pulmonary cryptococcosis who underwent kidney transplantation 1 month after AmBd experienced a relapse, although the disease was successfully controlled by reinstitution of AmBd (*16*). It should be noted that these cases occurred over three decades ago before the availability of fluconazole when long-term suppression upon conclusion of AmBd was not a viable option.

More recently, two cases of cryptococcal meningitis in patients with liver cirrhosis were successfully transplanted 2 weeks and 39 months after the diagnosis (*17*). In both patients, the cultures for Cryptococcus had been rendered negative, titers of cryptococcal antigen had declined, and they were deemed to be clinically stable on a maintenance dose of fluconazole before liver transplantation (2 weeks in case 1 and 39 months in case 2). It is notable that in case 2, the yeast forms could still be visualized in a biopsy from pulmonary nodules after antifungal treatment for more than 24 months (*17*). However, the patient had negative lung biopsy cultures and had stable antigen titers in the previous 12 months. No relapse was observed during posttransplant follow-up despite a rejection episode that occurred 10 months after transplantation while he was on secondary prophylaxis with fluconazole.

Another potential scenario is detection of asymptomatic pulmonary nodules because of cryptococcosis in a living donor transplant candidate. In two such cirrhotic patients, the diagnosis was established by thoracoscopy, and one patient underwent wedge resection. Both patients received fluconazole for 2 weeks before and for a minimum of 6 months posttransplant with no recurrence or death at follow-up of 54 months (*18*).

Thus, transplantation may be cautiously undertaken in a candidate with cryptococcosis provided that disease control is achieved with adequate treatment before transplant, that is, resolution of related signs/symptoms, negative culture results for Cryptococcus, and stable or declining cryptococcal antigen titer. The precise timing of transplantation should also take into consideration the urgency of transplantation. At the minimum, the infection should be microbiologically eradicated (*18*). Fluconazole should be continued posttransplant along with close follow-up. The exact duration of secondary prophylaxis remains to be defined however, at least 12 months should be considered.

With regard to immunosuppression, it is preferable to use a calcineurin-inhibitor-based regimen given in vitro activity of these drugs against Cryptococcus (*19*). It is prudent to avoid T-cell depleting antibodies, particularly alemtuzumab, as its use has been associated with a dose-dependent risk of cryptococcosis (*2*). Another consideration is that rejection, which is a state of a heightened inflammatory response, may potentially lead to IRS (*17*).

RECOGNITION OF DONOR-DERIVED CRYPTOCOCCOSIS

Unrecognized cryptococcosis in the donor can be associated with devastating squeale in the recipients of these allografts. Several cases of donor-derived cryptococcosis have been reported (*13*, *20*). However, most incontrovertible transmission to date has been in a liver and two kidney transplant recipients from a donor with sarcoidosis and corticosteroid therapy who died with an undifferentiated neurologic illness. Autopsy findings later documented cryptococcal meningoencephalitis (*21*). Between 14 and 24 days posttransplant, the liver and one kidney recipient developed cryptococcemia and pneumonia and the other kidney recipient developed cryptococcemia and meningitis; two of three patients recovered with antifungal therapy, whereas the third died (*21*). The donor was at risk for cryptococcosis because of receipt of corticosteroids and presented with manifestations of cryptococcal meningitis which included headache, seizures, neurologic deficits, and hydrocephalus on imaging. However, cryptococcal meningitis was not suspected at the time of organ procurement. All recipient isolates were identical on multilocus sequence typing (*21*). Thus, cryptococcosis should be considered in potential donors with undiagnosed neurologic illness compatible with cryptococcosis or meningoencephalitis (*22*).

Detection of Cryptococcus in cultures from unusual sites in the early posttransplant period, such as the surgical sites/fossa (*13*) or instances after lung transplantation where transplanted organ is the sole site of involvement as documented by bronchoscopic isolation of this yeast (*23*), should also heighten the awareness that cryptococcosis may have been transmitted from the donor.

PULMONARY CRYPTOCOCCOSIS AND CRYPTOCOCCAL ANTIGEN POSITIVITY

Approximately 25% to 54% of transplant recipients with cryptococcosis have pulmonary disease, and in 6% to 33% the disease is limited to the lungs (*24*, *25*). Cryptococcal antigen has proven to be a valuable diagnostic assay for cryptococcosis. The sensitivity and specificity of serum antigen for the diagnosis of cryptococcal meningoencephalitis approach that of the cerebrospinal fluid (*26*). The test, however, is considered to be of limited value for the diagnosis of pulmonary cryptococcosis (*27*, *28*). Case series have documented a wide variability in serum antigen positivity, ranging from 33% to 100% in SOT recipients with pulmonary cryptococcosis (*4*, *8*, *29*). The determinants of serum cryptococcal antigen positivity and the reasons for antigen negativity in subsets of patients with pulmonary cryptococcosis, therefore, warrant discussion.

In a multicenter study comprising 48 SOT recipients with pulmonary cryptococcosis, serum cryptococcal antigen was positive in 83% with median titer 1:64 (*25*). Patients with concomitant extrapulmonary disease were more likely to have positive antigen, and antigen titers were higher in those with extrapulmonary disease or fungemia. Pulmonary disease may be detected in asymptomatic patients as an incidental finding. These patients typically present in the late posttrans-

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plant period at a time when they were on minimal immunosuppression (*25*). Nodular densities or mass lesions were more likely in patients with asymptomatic or incidentally detected pulmonary cryptococcosis than pleural effusions and infiltrates ($P=0.008$). Antigen titers were also higher in patients with symptomatic versus asymptomatic pulmonary cryptococcosis.

A major determinant of antigen positivity was also the type and characteristics of the pulmonary lesion. Well-circumscribed pulmonary nodules represent walled-off granulomas, whereas lesions with spread to the surrounding lung parenchyma or disseminated disease signify more advanced stages of disease reflecting the inability of the host to contain the yeast. Patients with single nodules are less likely to have a positive antigen than those with other radiographic presentations or more advanced lesions on imaging (*25*).

Thus, rates of cryptococcal antigen positivity and the titer in pulmonary cryptococcosis seem to be a function of the extent of disease at the time of diagnosis. Patients with disease limited to the lungs, particularly those with single nodules, may have negative antigen.

TREATMENT OF CRYPTOCOCCOSIS

Therapy should be dictated by the extent of disease, in particular whether there is CNS involvement. Guidelines of the Infectious Diseases Society of America and the American Society of Transplant recommend fungicidal therapy with a lipid formulation of amphotericin B and flucytosine in patients with neurologic and disseminated disease and severe respiratory disease (*30*, *31*). The basis of these recommendations is largely lower nephrotoxicity with the lipid polyenes compared with AmBd (*31*). In a study of SOT recipients, after controlling for factors that portend poor outcome, such as renal failure at baseline and fungemia, treatment with lipid polyenes versus AmBd was associated with improved survival (*5*). The precise reasons for these observations are not fully understood but may be related to the immunomodulatory potential of various polyenes.

Although AmBd has exceptional anticryptococcal activity, it is a potent proinflammatory stimulant (*32–35*). AmBd reduced the mortality in neutropenic mice with invasive pulmonary aspergillosis; however, it failed to improve the survival in corticosteroid-treated mice (*36*). It is plausible that, instead of attenuating, AmBd promotes the damage from excessive inflammation. Unlike AmBd, liposomal amphotericin B (L-AmB) either down-regulates or has no effects on inflammatory cytokine gene expression in macrophages (*37*, *38*). As a result, L-AmB may induce less inflammatory response during fungal infections which may be advantageous in corticosteroid-treated mice. In addition, the liposomes of L-AmB may also play a role in its antiinflammatory properties (*39–41*). Thus, our preference is to use lipid formulations of amphotericin B regardless of renal dysfunction.

Presently, antifungal susceptibility testing for cryptococcal isolates is not routinely performed given rarity of primary fluconazole resistance. In the absence of prior exposure to the azoles, the minimum inhibitory concentrations (MICs) of Cryptococcus to fluconazole typically range from 1 to 4 μg/mL. A peculiar observation, however, deserves mention. In a study to assess synergy between calcineurin inhibitors and antifungal agents in clinical isolates from SOT patients, susceptibility testing against fluconazole was performed (*42*). Despite the fact that only 1 of 74 patients had previously received fluconazole, the median MIC of the isolates to fluconazole was 16 μg/mL (*42*). Precise reasons for these observations are not known. It is possible that drug transporter expression modulation by immunosuppressive drugs as reported in other yeasts, for example, *Saccharomyces cerevisiae* or *Candida* or other as yet not fully understood factors account for these observations (*43*, *44*). Outcomes were not influenced by observed MICs, and these isolates demonstrated synergy with the calcineurin-inhibitor agents.

The use of triazoles such as voriconazole, itraconazole, and posaconazole does not offer a benefit over fluconazole, they are more expensive, and in HIV-infected patients, itraconazole was inferior to fluconazole (*45*, *46*). Newer azoles in development such as isavuconazole and albaconazole have good in vitro activity against cryptococci but are neither commercially available nor recommended at present (*47*, *48*).

MANAGEMENT OF IRS

Reduction of immunosuppression in transplant recipients with opportunistic infections is an intuitively logical clinical practice. However, rapid reduction of immunosuppression in conjunction with initiation of antifungal therapy may lead to IRS, the presentation of which mimics worsening cryptococcal disease (*49*, *50*). The cumulative effect of an immunosuppressive regimen in stable transplant recipients reflects induction of tolerance by suppression of Th1/Th17 and up-regulation of Th2, with or without Treg expansion (*51*). The basis of IRS is believed to be reversal of antiinflammatory responses (that restrain inflammation) toward proinflammatory responses (that promote inflammatory pathology) as a result of withdrawal of iatrogenic immunosuppression and reversal of pathogen-induced immunosuppression upon the use of antifungal therapy (*51*). Strategies for reduction in immunosuppression should be conducive to eradication of infection but minimize the risk of IRS and allograft rejection. Renal transplant recipients with IRS were more likely to experience allograft loss coincident with the occurrence of IRS, suggesting that the manner of reduction in immunosuppressive therapy can be critical.

Limited data are available that provide guidance on how best to manage immunosuppressives in transplant recipients with cryptococcosis. In clinical setting, calcineurin agents are often the first immunosuppressants to be reduced or withdrawn (*52*). Discontinuation, but not reduction, of calcineurin-inhibitor agents was associated with IRS (*53*). On the other hand, discontinuation or reduction of prednisone in patients receiving calcineurin-inhibitor agents did not influence the risk of IRS in one study (*53*). Thus, the goal should be reduction as opposed to abrupt cessation of calcineurin inhibitors with consideration given to tapering of corticosteroids first. In addition, calcineurin inhibitors have synergistic interactions with antifungals and are associated with better outcomes in posttransplant cryptococcosis (*42*).

Treatment of IRS remains challenging, and there is no proven therapy for it. Corticosteroids have been the most commonly used agents for treatment of IRS (*54*). In a ran-

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domized trial of tuberculosis-related IRS in HIV-infected patients, prednisone reduced the duration of hospitalization and led to more rapid improvement in symptoms and markers of inflammation (*55*). The receipt of corticosteroids during the management of the acute opportunistic infections, however, was not associated with a reduction in the overall risk of IRS in HIV-infected patients (*56*). Minor manifestations of IRS may resolve spontaneously within few weeks. Modifications in antifungal therapy are not warranted unless viable yeasts are documented in culture. Use of corticosteroids may be considered for life-threatening manifestations or severe disease particularly that involving the CNS. A tapering course of corticosteroids as used for adjunctive therapy for pneumocystosis has been proposed in this setting (*51*).

Given potential for adverse sequelae and nonspecific immunosuppressive effects of corticosteroids are less than ideal agents for IRS. There is mechanistic basis by which corticosteroids may in fact worsen inflammation than suppress it (*57*). In murine model studies, corticosteroids led to overexpression of inflammatory cytokines in response to lipopolysaccharide by altering signaling pathways regulating these responses (*57*). The permissive effects of corticosteroids in enhancing immune responsiveness are of potential concern, and there is an ongoing need for optimizing therapies for IRS.

Although known primarily for their cholesterol-lowering effects, statins have antiinflammatory attributes. They promote Th2/Tregs, inhibit Th1, and block Th17 development (*58*). A beneficial effect of these drugs has been shown for some inflammatory and autoimmune disorders. For example, in experimental autoimmune arthritis and myocarditis, statins inhibited proinflammatory cytokines and promoted a shift from Th1 to Th2 (*59*). In T-cell replete allogeneic hematopoeitic stem-cell transplantation recipients, a lower rate of grade II to IV graft versus host disease was observed in statin recipients than in those not receiving these (*60*). Paradoxically, the capacity to mount protective immune responses to pathogens is not diminished with statins (*60*). Thus, it is plausible that statins in patients at risk for IRS once the infection is microbiologically controlled may mitigate excessive inflammation. Future studies are warranted to investigate the effects of statins alone or in combination with other agents for IRS.

Because tumor necrosis factor-α plays a key role in recruitmenting inflammatory cells and granuloma formation, tumor necrosis factor-α inhibitors have been anecdotally used for IRS. Infliximab was successfully used for IRS refractory to high-dose corticosteroids and cyclophosphamide in CNS tuberculosis (*61*). Antiinflammatory effects of this agent ameliorated acute rejection after intestinal transplantation (*62*), and there is precedence for their use as antirejection agents in clinical setting (*63*).

FUTURE DIRECTIONS

Unlike several other opportunistic mycoses for which diagnostic tests or biomarkers are imperfect or unreliable (e.g., aspergillosis and mucormycosis) or effective antifungal drugs are lacking (e.g., scedosporiosis), diagnostic assays that offer timely diagnosis of cryptococcosis exist, and currently available antifungal drugs have exceptional in vitro activity against cryptococcosis. Yet, a subset of patients, in particular, those with CNS or disseminated disease have poor outcome. These data suggest that host response or immunologic sequelae of host-pathogen interaction may have a role in influencing Cryptococcus-related outcomes. SOT recipients with cryptococcal meningitis in whom mycologic eradication of the yeast in the cerebrospinal fluid was not achieved at 2 weeks had higher mortality than those with negative cultures (*64*). Use of immunomodulatory therapies such as interferon-γ to augment a suboptimal host response, as documented in HIV-infected patients, is of potential concern given risk for rejection (*65*). In an uncontrolled case series of refractory fungal infections, interferon-γ did not have adverse effects (*66*); however, further experience is needed in this area. Conversely, an excessive immune response manifesting as IRS may also pose daunting challenges in the management of cryptococcosis. Biomarkers that are diagnostically useful for IRS and in recognizing that a state of beneficial as opposed to exaggerated host immunity has been achieved during evolution of opportunistic infections are not known. Specific studies on diagnostic markers and therapies for IRS in transplant setting warrant investigations.

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