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Outcomes of cryptococcosis in renal transplant recipients in a less-resourced health care system

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Abstract

Background: Cryptococcosis is the second most common cause of invasive fungal infections in renal transplant recipients in many countries, and data on graft outcome after treatment for this infection is lacking in less-resourced health care settings.

Methods: Data from 47 renal transplant recipients were retrospectively collected at a single institution during a period of 13 years. Graft dysfunction, graft loss, and mortality rates were evaluated. Predictors of mortality and graft loss were estimated.

Results: A total of 38 (97.4%) patients treated with amphotericin B deoxycholate (AMBd) showed graft dysfunction after antifungal initiation and 8 (18.2%) had kidney graft loss. Graft loss within 30 days after cryptococcosis onset was significantly associated with disseminated infection, greater baseline creatinine levels, and graft dysfunction concomitant to AMBd therapy and an additional nephrotoxic condition. The 30-day mortality rate was 19.2% and it was significantly associated with disseminated and pulmonary infections, somnolence at admission, high CSF opening pressure, positive CSF India ink, creatinine levels greater than 2.0 mg/dL at admission, graft dysfunction in patients treated with AMBd and an additional nephrotoxic condition and graft loss within 30 days.

Conclusion: Graft dysfunction was common in renal transplant recipients with cryptococcosis treated with AMBd. The rate of graft loss rate was high, most frequently in patients with

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AUTHORS CONTRIBUTIONS

Ponzio V., Camargo L. F., and Colombo A. L. involved in design, data analysis, and drafting article; Medina-Pestana J involved in critical revision and approval of article; Perfect J. R. involved in Critical revision of article.

CONFLICTS OF INTEREST

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concomitant nephrotoxic conditions. Therefore, the clinical focus should be on the use of less nephrotoxic lipid formulations of amphotericin B in this specific population requiring a polyene induction regimen for treatment of severe cryptococcosis in all health care systems caring for transplantation recipients.

Keywords

amphotericin B; cryptococcosis; less-resourced health care system; renal dysfunction; renal transplantation

1 | INTRODUCTION

Cryptococcosis is a life-threatening invasive fungal disease caused by an encapsulated yeast, *Cryptococcus* spp. complex, predominantly represented by *Cryptococcus neoformans* and *C. gattii*.¹ Although the majority of infections occur by inhalation of infectious propagules from the environment,² the disease can be directly acquired from an infected transplanted organ.³⁻⁵ *C. neoformans* has a worldwide distribution with sporadic occurrences of infection, particularly among patients with impaired cell-mediated immunity, including transplant recipients.^{2,6,7}

During the 1980s and 1990s, cryptococcosis was considered a major fungal infection among patients with acquired immune deficiency syndrome (AIDS).^{2,8} After the advent of highly active antiretroviral therapy, the burden of all opportunistic infections related to AIDS patients, including cryptococcosis, decreased substantially.⁹⁻¹³ On the other hand, solid organ transplant recipients persistently continue to be a major “at risk” population for cryptococcosis. For example, current experience indicates that 18%-65% of all cryptococcal diseases reported among HIV-negative patients occur in organ transplant recipients^{7, 14,15} and with an increasing worldwide transplant population, it is likely that cryptococcosis will continue to increase.

Cryptococcosis is specifically recognized as the second most common invasive fungal infection in renal transplant recipients in many countries, including Brazil,^{16, 17} with incidence rates ranging from 0.3% to 5.5% and overall mortality rates as high as 20%-50% have been reported.¹⁸⁻²³ Amphotericin B formulations are considered the best option for primary therapy and the 2010 IDSA Guidelines recommend lipid formulations of amphotericin B.²⁴⁻²⁷ However, amphotericin B deoxycholate (AMBd) has been extensively used to treat cryptococcosis after renal transplantation in some cases related to acquisition costs^{21,24, 27-29} despite the fact that these patients face a high risk of nephrotoxicity and are frequently exposed to other nephrotoxic drugs such as calcineurin inhibitors.

Although AMBd-related nephrotoxicity in renal transplant recipients is expected, data regarding the impact of this therapeutic strategy are scarce in the medical literature in resource-limited medical communities.²⁹⁻³² The North-American Guidelines for cryptococcosis suggest the use of lipid formulations of amphotericin B associated with flucytosine for induction therapy of central nervous system (CNS) and disseminated disease in solid organ transplant (SOT).²⁵ However, in most resource-limited countries, these 2 treatment options are either not available or too expensive. The purpose of this study was

therefore to assess renal allograft dysfunction and its impact on renal transplant recipients with cryptococcosis receiving antifungal therapy in a single institution with standardized medical care system and without use of flucytosine and lipid formulations of amphotericin B.

2. | PATIENTS AND METHODS

2.1 | Patients

The study consisted of a retrospective medical record review of all patients who developed cryptococcosis after renal transplantation at the Federal University of São Paulo, Brazil, during a period of 13 years. Cases were identified by checking multiple sources: clinical forms completed by Infectious Diseases consults, the International Classification of Disease—Tenth Revision codes from charts, mycological laboratory and histopathology records, and cryptococcal antigen test results.

2.2 | Definitions

An incident case was defined as a patient who developed cryptococcosis after renal transplantation based on the following diagnostic criteria^{33,34}: (i) *Cryptococcus neoformans* or *C. gattii*-positive culture obtained from any site; or (ii) a significant cryptococcal antigen titer (1:8) in cerebrospinal fluid (CSF) or serum specimens with a compatible clinical and/or radiographic presentation; or (iii) biopsy specimens exhibiting encapsulated “yeast-like” forms consistent with *Cryptococcus* spp. The involved sites were classified as: (i) CNS; (ii) pulmonary; and (iii) skin, soft-tissue and/or osteoarticular.²² Disseminated cryptococcosis was defined as the involvement of at least 1 non-contiguous organ systems or the presence of fungemia.²⁰ Primary therapy was defined as the first systemic antifungal regimen administered for at least 2 consecutive days.¹⁴ “Additional nephrotoxic conditions” were defined as any other reason for nephrotoxicity such as pyelonephritis, other administered nephrotoxic drug, rejection of transplanted organ, or acute tubular necrosis secondary to sepsis. However, usage of calcineurin inhibitors was not included as one of the nephrotoxic conditions for this analysis.

2.3 | Graft dysfunction

Renal allograft baseline outcomes were examined by analyzing the serum creatinine level at the time of the diagnosis of the cryptococcosis, first day of antifungal therapy, peak value during antifungal therapy and 15 days, 1, 2, 3, 6, 12, 18, 24, 36, and 48 months after the diagnosis of cryptococcal infection. Graft dysfunction was evaluated by comparing the serum creatinine level at the time of the cryptococcosis diagnosis (baseline creatinine) with the peak creatinine value observed during antifungal therapy and follow-up. Peak creatinine levels were defined as the maximum creatinine value during the study evaluation period. The intensity of dysfunction was also classified using 3 categories: (i) mild—the serum creatinine value increased up to 25% from baseline to peak; (ii) moderate—the increase was 26-50% from baseline to peak; and (iii) severe—the increase was greater than 50%. Graft loss was defined as the need for dialysis with or without graft removal.

2.4 | Mortality

The mortality rate was assessed at 30 and 90 days after the diagnosis of cryptococcosis and risk factors associated with this acute mortality were analyzed.

2.5 | Data collection

Epidemiological and clinical data in all cases of cryptococcal infection were collected from the medical records using a standard clinical report form. Variables assessed included demographic data, prior and concomitant infections, episodes of graft rejection, detailed transplant descriptions, immunosuppressive regimens and relevant laboratory data. In addition, we collected all data related to the antifungal therapeutic regimens employed, including the duration of therapy, total doses of AMBd, and concomitant use of other nephrotoxic agents.

2.6 | Statistical analysis

Continuous data were presented as either the mean $\pm$ SD or the median and range, and categorical data were presented as proportions. Univariate analyses were performed to compare categorical variables between the patients with and without graft loss using either the Chi-square or Fisher's exact test, as appropriate. The one-way ANOVA method was used to test differences between means. The same analyses were used to evaluate factors associated with mortality. Graft survival rates were estimated using Kaplan-Meier methods, and comparisons between groups were performed using log-rank tests. All analyses were performed using SPSS software for Windows, version 11.5 (SPSS, Chicago, IL). A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline and clinical characteristics

During the 13-year study period, a total of 47 cases of cryptococcosis were identified among 5623 renal transplant recipients, representing an incidence rate of 8.4 per 1000 renal transplants in this health care system. The median follow-up period after cryptococcal diagnosis was a robust 18.8 months, ranging from 0 days to 11 years. Of note, 36% of the patients died within 6 months after diagnosis of cryptococcosis and the follow-up was not available for 5 patients. As indicated in Table 1, 32 of 47 (68.1%) patients were male, and the mean ($\pm$ SD) age was 41 ± 11.28 years (range 20-67). Among these 47 patients, 31(66%) were living-related donor recipients. This finding is consistent with the profile of donor types observed in our institution during the study period. Acute rejection episodes preceding fungal disease were documented in 18 (38.3%) patients, ranging from 37 days to 199 months before the onset of cryptococcal infection (average of 35 months). Patients with organ rejections were treated with high-dose steroid therapy (17 patients) and/or an antibody preparation (2 patients muromonab-CD3 and 2 thymoglobulin). Other baseline characteristics are outlined in Table 1.

Cryptococcosis occurred >1 year after transplant in 76.6% of patients (median time of 42 months). Regarding the site of infection, CNS involvement occurred in 74.5% (35/47) of cases, pulmonary or cutaneous involvement occurred in 34% (16/47) each, and a

disseminated infection was observed in 42.6% (20/47) (Table 1). Regarding pulmonary involvement, 7 of 16 (43.7%) had evidence of respiratory insufficiency and in 8 cases, the pulmonary radiographs were multifocal in character, with 2 cases presenting as pleural effusions. Forty-five recipients received antifungal treatment, and the other 2 patients died before diagnosis. Primary therapy included AMBd in 41 of 47 (87.2%) patients and fluconazole alone in 4 (8.5%) patients as induction therapy, with a duration of therapy ranging from 2 to 219 days and a median of 16 days. No patient received concomitant flucytosine treatment. The mean dose of AMBd therapy was 0.7 mg/kg/day (SD $\pm$ 0.15). The patients initially treated with AMBd had their therapy switched to fluconazole as soon as they were clinically stable as judged individually by caregivers. The mean total duration of therapy was 124.03 days (SD $\pm$ 105.11), ranging from 1 to 415 days.

3.2 | Allograft dysfunction

Creatinine values were available for 44 of 47 patients because 2 patients died before diagnosis and creatinine levels were missing for 1 patient who received fluconazole. The mean baseline serum creatinine value was 2.6 ± 1.66 mg/dL (range 0.6-7.6 mg/dL), and the mean peak creatinine level was 3.9 ± 2.17 mg/dL (range, 1.0-10.8 mg/dL). Of these 44 patients, 42 (95.5%) showed an increase in serum creatinine levels after starting antifungal therapy. All but 3 of the patients who had allograft dysfunction were treated with AMBd; the remaining patients were treated with fluconazole. With regard to dysfunction intensity in patients treated with AMBd, 46.2% (18/39) of cases met the criteria for severe dysfunction, 28.2% (11/39) had moderate graft dysfunction, and 25.6% (10/39) had mild graft dysfunction. Indeed, in 31 of the 39 (79.5%) patients who developed graft dysfunction, AMBd was the only nephrotoxic condition detected, except the use of calcineurin inhibitors in 20 patients. The 8 remaining patients who were treated with AMBd and developed graft dysfunction had simultaneous nephrotoxic conditions before antifungal therapy and are described as follows: 3 cases of acute episodes of renal rejection, 2 cases of pyelonephritis, 2 cases of sepsis and 1 case of acute tubular necrosis. The creatinine value pattern between the patients for whom AMBd was the sole nephrotoxic condition and the patients who had another condition associated with AMBd is outlined in Figure 1.

The allograft was lost during the course of antifungal therapy in 8 of 44 (18.2%) renal transplant recipients, and all but one of these 8 patients had received AMBd. Furthermore, 25% of the deceased-related donor recipients had allograft loss compared to 11.1% of the living-related donor recipients. Renal graft loss occurred between 1 and 39 days after starting antifungal therapy. Among the 7 patients who were treated with AMBd and lost their grafts, 4 patients had another nephrotoxic condition associated with AMBd therapy.

Univariate analysis consistently demonstrated that graft loss within 30 days after cryptococcosis was significantly associated with disseminated infections, greater baseline serum creatinine levels and graft dysfunction after AMBd treatment in the presence of additional nephrotoxic conditions (Table 2). Graft survival analysis shows that the probability of graft survival after the diagnosis of cryptococcosis was significantly lower in patients treated with AMBd who had graft dysfunction in the presence of an additional nephrotoxic condition than in those without such a condition ($P = .02$, log rank test) (Figure

2). Of note, the amphotericin B duration and the modification of the immunosuppressive regimen, including suspension of a calcineurin inhibitor, were similar in both groups (Table 2). A multivariable analysis was not able to identify any independent risk factors associated with graft loss, and this finding was probably because of the limited number of patients.

We were not able to identify any correlation between a specific immunosuppressive regimen used in combination with amphotericin B and graft dysfunction. Indeed, graft dysfunction was even reported with patients receiving amphotericin B and rapamycin (a non-nephrotoxic immunosuppressive) at the time cryptococcosis was diagnosed. Finally, during the period of this study, only 3 patients (6.4%) met our criteria for immune reconstitution inflammatory syndrome (IRIS). The IRIS occurred after the graft dysfunction, and by timing did not appear to be associated with the allograft loss.

3.3 | Predictors of death

In our study, 9 of the 47 (19.2%) patients died within 30 days of being diagnosed with cryptococcosis, and 13 of 45 (28.9%) patients died within 90 days of diagnosis. The overall mortality rate in the study group was 48.9% (23/47). Based on the univariate analysis, the following factors were significantly ($P < .05$) associated with high mortality at 30 days: disseminated and pulmonary infection, creatinine levels greater than 2.0 mg/dL at admission, somnolence at admission, high CSF opening pressure, positive CSF India ink, graft dysfunction in patients treated with AMBd with additional nephrotoxic conditions and graft loss within 30 days (Table 3).

4 | DISCUSSION

This study demonstrates important aspects of cryptococcosis in renal transplant recipients, treated with AMBd in a single public kidney transplant center in Brazil. Over the course of 13 years, 0.8% of renal transplant recipients developed cryptococcosis, and most occurred a long time after transplantation. The incidence of cryptococcosis in renal transplant recipients observed in this study was similar to the low incidence rates reported by other groups (0.3%-5.5%),^{16,18,20-23,32,35-39} but with high mortality.²³ Among these 47 patients, the majority had received AMBd (87.2%) as first-line therapy. Unfortunately, flucytosine or lipid formulation of amphotericin B were not available or used during the study period, respectively.

Data on the antifungal treatment of cryptococcosis in SOT recipients are still scarce, particularly in Latin American countries but the transplant recipient populations are enlarging in these less-resourced areas. Considering that SOT represents only 5%-10% of all patients enrolled in clinical trials of cryptococcosis, recommendations for antifungal therapy in this particular population are extrapolated from data generated from studies of other high-risk populations, retrospective cohorts from many different medical centers in resource-available health care systems and expert opinions.^{25,40,41} In our study, almost all of the patients received AMBd as a primary therapy, which is in accordance with a multicenter study published by Singh et al, in which 67.5% of the cases were initially treated with a AmBd.²⁴ Despite the notable AMBd-related nephrotoxicity and its consequences in terms of the length of hospital stay, total cost of health care and mortality rates, AMBd remains a

cornerstone in the treatment of cryptococcosis worldwide primarily because of the high acquisition costs for lipid formulations of amphotericin B.⁴²⁻⁴⁴ The clinical impact of AMBd-nephrotoxicity appears to be amplified in patients exposed to other nephrotoxic conditions and in patients with preexisting renal dysfunctions before the initiation of AMBd treatment.⁴⁵⁻⁴⁷ In this study, 95.5% of the cases developed renal graft dysfunction after beginning antifungal therapy for cryptococcosis. Furthermore, severe dysfunction was observed in 46.2% of these patients, and a substantial percentage (18.2%) of the patients in this study progressed to graft loss after the infection. For context, data recently provided by our institution describing a cohort of 10 400 kidney transplants reported 12.7% graft loss in deceased- related donor recipients after 1 year of transplant and 6.5% in living- related donor recipients within 1 year of transplant⁴⁸

Although AMBd-related nephrotoxicity in renal transplant recipients is a crucial issue, it has been critically addressed in the medical literature.^{31,32} Conti et al showed that almost all renal transplant recipients (10 of 11) had graft loss after treatment with AMBd.³¹ Also, in a retrospective study conducted by Wingard et al,⁴³ 15 of 42 (36%) solid organ transplant recipients with aspergillosis presented with serum creatinine levels higher than 2.5 mg/dL after starting AMBd, and 18% of these patients required hemodialysis but solid organ transplant recipients were less likely to die compared with bone marrow transplant patients. To limit graft damage by AMBd, some authors have suggested treating cryptococcosis with low doses of AMBd or repeated withdrawal of the antifungal drug when facing renal dysfunction.^{29,30} Of note, both strategies may negatively influence the patient outcome and the length of hospital stay.⁴⁹ Switching from AMBd to a less nephrotoxic antifungal agent after facing renal dysfunction may be a delayed strategy in the light of findings reported by Klibanov et al They found that only 5 of 25 patients who received AMBd and developed nephrotoxicity showed any improvement of their ongoing renal impairment after switching to an antifungal agent with less renal toxicity.⁵⁰

Our data consistently showed that AMBd-treated cryptococcosis is associated with a high frequency of renal dysfunction and graft loss. In fact, graft loss was higher in patients exposed to AMBd with other nephrotoxic conditions. A recent study reviewed the literature of all cases of cryptococcosis in SOT recipients available in the PubMed database and found a significantly lower mortality rate among patients receiving lipid formulations of amphotericin B compared with those receiving AMBd and a higher mortality rate among patients with renal failure at baseline.⁵¹ In another study of SOT recipients, patients treated with lipid formulations of amphotericin B had improved survival when compared with AMBd, even after controlling for factors such as renal failure at baseline and fungemia. In this study the lipid formulation of amphotericin B-treated group mortality was 10.9% compare to 40% in the AMBd-treated group.²⁶ As noted in our study 90 day mortality reached almost 30%, it is likely that reduced nephrotoxicity in our patients could translate into a substantial mortality benefit. For mild-to-moderate non-CNS disease, fluconazole is recommended as primary therapy, avoiding AMBd nephrotoxicity.^{24,25} Consequently, it is reasonable to advocate that AMBd should be avoided in this particular setting when the patients have higher baseline creatinine levels and concomitant exposure to other nephrotoxic conditions. These data lend support to recent recommendations from experts suggesting the use of lipid formulations of amphotericin B as the primary therapy in patients

with cryptococcal meningoencephalitis, owing to the fact that many transplant recipients receive calcineurin inhibitors that also possess renal dysfunction capabilities.^{52,53} However, it is difficult to attribute allograft dysfunction exclusively to AMBd use because it is important to note that our population also had many other putative nephrotoxic conditions, such as acute episodes of renal rejection, pyelonephritis, sepsis, acute tubular necrosis and the use of calcineurin inhibitors.

Dissemination of infection was correlated to graft loss in our study but just 3 patients had renal cryptococcosis as demonstrated by graft biopsy and yeast invasion of the kidney is not likely to explain this correlation. On the other hand, the baseline creatinine value of patients with dissemination of the infection was much higher than patients without dissemination, and this finding might explain the result. Previous studies have described allograft loss and IRIS related to the discontinuation of calcineurin inhibitor.^{54,55} However, IRIS and its management did not correlate with graft loss in this study.

Infection is still the main cause of death in our institution and cryptococcosis is a prevalent, life-threatening mycoses in renal transplant recipients, and mortality rates have ranged from 31% to 76%.^{20-22,30,32,36,39,48} The significant predictors for death in SOT recipients are based on organ dysfunction and the severity of the disease, such as a high serum creatinine value at admission, disseminated infection and liver failure.^{21,22,56,57} These findings are supported by this study, in which disseminated infection and creatinine levels upon admission higher than 2 mg/dl were direct predictors of mortality. Finally, somnolence at admission, baseline positive CSF India ink, graft loss within 30 days and the presence of another nephrotoxic condition in patients treated with AMBd and with graft dysfunction were also found as predictors of mortality in our study. Probably, pulmonary involvement was a predictor of death because of the severe lung disease described secondary to late diagnosis (median of 102 days of pulmonary symptoms before diagnosis).

This study has certain limitations, including the fact that it is a retrospective study dealing with small numbers of patients. Another relevant limitation is the use of serum creatinine values to estimate renal function in transplantation, because a variety of conditions and drugs can also affect creatinine levels. Nevertheless, this study represents the largest series ever published by a single medical center of renal transplant recipients in which patients could be evaluated by the same team in accordance with the same management criteria.

In summary, this study details allograft renal dysfunction after cryptococcosis in kidney transplant recipients. We found that graft dysfunction is common in patients treated for cryptococcosis and can drastically influence graft survival in this setting, especially in patients with conditions that clearly increase the risk of nephrotoxicity. It is extremely important in resource-limited health care systems that for this infection (meningitis/disseminated disease) every effort is made to use lipid formulations of amphotericin B for induction therapy or even consider the combination of flucytosine or fluconazole and make an effort to avoid AMBd. Finally, flucytosine should also be available for optimal combination induction therapy in health care systems that care for renal transplant recipients. In less-resourced health care systems the exceptions for successful management

of cryptococcosis can be similar to resource-available systems and outcomes could be significantly improved by protecting renal functions.

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Abbreviations:

AIDS	Acquired Immune Deficiency Syndrome
AMBd	Amphotericin B deoxycholate
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
IRIS	Immune Reconstitution Inflammatory Syndrome
SD	Standard Deviation
SOT	Solid Organ Transplant

REFERENCES

1. Kwon-Chung KJ, Bennett JE, Wickes BL, et al. The case for adopting the “Species Complex” nomenclature for the etiologic agents of cryptococcosis. *mSphere*. 2017;2:e00357–16.
2. Maziarz EK, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am*. 2016;30:179–206. [PubMed: 26897067]
3. Ooi BS, Chen BT, Lim CH, Khoo OT, Chan DT. Survival of a patient transplanted with a kidney infected with *Cryptococcus neoformans*. *Transplantation*. 1971;11:428–429. [PubMed: 4934356]
4. Beyt BE Jr. Diagnosis of cryptococcal endophthalmitis. *Am J Clin Pathol*. 1984;81:272.
5. Kanj SS, Welty-Wolf K, Madden J, et al. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. *Medicine (Baltimore)*. 1996;75:142–156. [PubMed: 8965683]
6. Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. *J Infect Dis*. 1999;179:449–454. [PubMed: 9878030]
7. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis*. 2001;33:690–699. [PubMed: 11477526]
8. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS—100 years after the discovery of *Cryptococcus neoformans*. *Clin Microbiol Rev*. 1995;8:515–548. [PubMed: 8665468]
9. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860. [PubMed: 9516219]

10. Hung CC, Chang SC. Impact of highly active antiretroviral therapy on incidence and management of human immunodeficiency virus-related opportunistic infections. *J Antimicrob Chemother.* 2004;54:849–853. [PubMed: 15456733]
11. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. *Clin Infect Dis.* 2003;36:789–794. [PubMed: 12627365]
12. Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O. Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras. *AIDS.* 2004;18:555–562. [PubMed: 15090810]
13. Friedman GD, Jeffrey Fessel W, Udaltsova NV, Hurley LB. Cryptococcosis: the 1981–2000 epidemic. *Mycoses.* 2005;48:122–125. [PubMed: 15743430]
14. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med.* 2007;4:e21. [PubMed: 17284154]
15. Bratton EW, El Husseini N, Chastain CA, et al. Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. *PLoS ONE.* 2012;7:e43582. [PubMed: 22937064]
16. Moysés Neto M, Muglia V, Batista MEPN, et al. Infecção por fungos e transplante renal: análise nos primeiros 500 pacientes transplantados no Hospital das Clinicas da Faculdade de Medicina de Ribeirão Preto - USP. *J Bras Nefrol.* 1995;17:162–170.
17. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis.* 2010;50:1101–1111. [PubMed: 20218876]
18. Gallis HA, Berman RA, Cate TR, Hamilton JD, Gunnells JC, Stickel DL. Fungal infection following renal transplantation. *Arch Intern Med.* 1975;135:1163–1172. [PubMed: 1100007]
19. Vilchez RA, Irish W, Lacomis J, Costello P, Fung J, Kusne S. The clinical epidemiology of pulmonary cryptococcosis in non-AIDS patients at a tertiary care medical center. *Medicine (Baltimore).* 2001;80:308–312. [PubMed: 11552084]
20. Vilchez R, Shapiro R, McCurry K, et al. Longitudinal study of cryptococcosis in adult solid-organ transplant recipients. *Transpl Int.* 2003;16:336–340. [PubMed: 12759725]
21. Wu G, Vilchez RA, Eidelman B, Fung J, Kormos R, Kusne S. Cryptococcal meningitis: an analysis among 5,521 consecutive organ transplant recipients. *Transpl Infect Dis.* 2002;4:183–188. [PubMed: 12535260]
22. Husain S, Wagener MM, Singh N. *Cryptococcus neoformans* infection in organ transplant recipients: variables influencing clinical characteristics and outcome. *Emerg Infect Dis.* 2001;7:375–381. [PubMed: 11384512]
23. George IA, Santos CAQ, Olsen MA, Powderly WG. Epidemiology of cryptococcosis and cryptococcal meningitis in a large retrospective cohort of patients after solid organ transplantation. *Open Forum Infect Dis.* 2017;4:ofx004. [PubMed: 28480277]
24. Singh N, Lortholary O, Alexander BD, et al. Antifungal management practices and evolution of infection in organ transplant recipients with *Cryptococcus neoformans* infection. *Transplantation.* 2005;80:1033–1039. [PubMed: 16278582]
25. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2010;50: 291–322. [PubMed: 20047480]
26. Sun HY, Alexander BD, Lortholary O, et al. Lipid formulations of amphotericin B significantly improve outcome in solid organ transplant recipients with central nervous system cryptococcosis. *Clin Infect Dis.* 2009;49:1721–1728. [PubMed: 19886800]
27. Moretti ML, Resende MR, Lazera MS, Colombo AL, Shikanai-Yasuda MA. [Guidelines in cryptococcosis-2008]. *Rev Soc Bras Med Trop.* 2008; 41: 524–544. [PubMed: 19009203]
28. Singh N, Husain S. Infections of the central nervous system in transplant recipients. *Transpl Infect Dis.* 2000;2:101–111. [PubMed: 11429020]
29. Stamm AM, Diasio RB, Dismukes WE, et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med.* 1987;83:236–242. [PubMed: 3303926]

30. Nobrega JP. Amphotericin B in the treatment of neurocryptococcosis in patients subjected to renal transplantation. *Arq Neuropsiquiatr.* 1988;46:117–126. [PubMed: 3060061]
31. Conti DJ, Tolkoff-Rubin NE, Baker GP Jr, et al. Successful treatment of invasive fungal infection with fluconazole in organ transplant recipients. *Transplantation.* 1989;48:692–695. [PubMed: 2552628]
32. Shaariah W, Morad Z, Suleiman AB. Cryptococcosis in renal transplant recipients. *Transplant Proc.* 1992;24:1898–1899. [PubMed: 1412904]
33. Chen SC. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother.* 2002;49(Suppl 1):57–61. [PubMed: 11801583]
34. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from 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. *Clin Infect Dis.* 2008;46:1813–1821. [PubMed: 18462102]
35. Watson AJ, Russell RP, Cabreja RF, Braverman R, Whelton A. Cure of cryptococcal infection during continued immunosuppressive therapy. *Q J Med.* 1985;55:169–172. [PubMed: 3889977]
36. Sampaio M, Ianhez LE, Sabbaga E. Protective effect of cyclosporine in human renal posttransplant cryptococcosis. *Transplant Proc.* 1992;24:3091. [PubMed: 1466069]
37. Tharayil John G, Shankar V, Talaulikar G, et al. Epidemiology of systemic mycoses among renal-transplant recipients in India. *Transplantation.* 2003;75:1544–1551. [PubMed: 12792512]
38. Kong NC, Shaariah W, Morad Z, Suleiman AB, Wong YH. Cryptococcosis in a renal unit. *Aust N Z J Med.* 1990;20:645–649. [PubMed: 2285381]
39. John GT, Mathew M, Snehalatha E, et al. Cryptococcosis in renal allograft recipients. *Transplantation.* 1994;58:855–856. [PubMed: 7940723]
40. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis.* 2010;51:225–232. [PubMed: 20536366]
41. Dismukes WE, Cloud G, Gallis HA, et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. *N Engl J Med.* 1987;317:334–341. [PubMed: 3299095]
42. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis.* 2001;32:686–693. [PubMed: 11229835]
43. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis.* 1999;29:1402–1407. [PubMed: 10585786]
44. Ullmann AJ, Sanz MA, Tramarin A, et al. Prospective study of amphotericin B formulations in immunocompromised patients in 4 European countries. *Clin Infect Dis.* 2006;43:e29–e38. [PubMed: 16838223]
45. Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL. Risk factors for Amphotericin B-associated nephrotoxicity. *Am J Med.* 1989;87:547–552. [PubMed: 2816970]
46. Bates DW, Su L, Yu DT, et al. Correlates of acute renal failure in patients receiving parenteral amphotericin B. *Kidney Int.* 2001;60:1452–1459. [PubMed: 11576359]
47. Berdichevski RH, Luis LB, Crestana L, Manfro RC. Amphotericin B-related nephrotoxicity in low-risk patients. *Braz J Infect Dis.* 2006;10:94–99. [PubMed: 16878259]
48. de Castro Rodrigues Ferreira F, Cristelli MP, Paula MI, et al. Infectious complications as the leading cause of death after kidney transplantation: analysis of more than 10,000 transplants from a single center. *J Nephrol.* 2017;30:601–606. [PubMed: 28211034]
49. Bratton EW, El Husseini N, Chastain CA, et al. Approaches to antifungal therapies and their effectiveness among patients with cryptococcosis. *Antimicrob Agents Chemother.* 2013;57:2485–2495. [PubMed: 23478968]
50. Klivanov OM, Raasch RH, Rublein JC. Changes in renal function after changes in antifungal drug therapy. *Am J Health Syst Pharm.* 2004;61:50–53. [PubMed: 14725121]

51. Sun HY, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. *Clin Infect Dis*. 2009;48:1566–1576. [PubMed: 19402789]
52. Singh N, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. *Clin Infect Dis*. 2008;47:1321–1327. [PubMed: 18840080]
53. Singh N How I treat cryptococcosis in organ transplant recipients. *Transplantation*. 2012;93:17–21. [PubMed: 22015465]
54. Singh N, Lortholary O, Alexander BD, et al. Allograft loss in renal transplant recipients with cryptococcus neoformans associated immune reconstitution syndrome. *Transplantation*. 2005;80:1131–1133. [PubMed: 16278598]
55. Sun HY, Alexander BD, Huprikar S, et al. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. *Clin Infect Dis*. 2015;60:36–44. [PubMed: 25210020]
56. Singh N, Alexander BD, Lortholary O, et al. Cryptococcus neoformans in Organ Transplant Recipients: impact of Calcineurin-Inhibitor Agents on Mortality. *J Infect Dis*. 2007;195:756–764. [PubMed: 17262720]
57. Vilchez RA, Linden P, Lacomis J, Costello P, Fung J, Kusne S. Acute respiratory failure associated with pulmonary cryptococcosis in non-aids patients. *Chest*. 2001;119:1865–1869. [PubMed: 11399716]

FIGURE 1.

Temporal trend of serum creatinine levels in patients treated with amphotericin B according to the presence ($n = 8$) or absence of additional nephrotoxic conditions ($n = 31$)

FIGURE 2. Kaplan-Meier graft survival analysis in patients treated with AMBd and who had allograft dysfunction according to the presence (n = 8) or absence of additional nephrotoxic conditions (n = 31)

TABLE 1

Demographic and clinical characteristics of the 47 study patients

Characteristics	Value, % (No. of patients) (n = 47)
Mean age $\pm$ SD (range), years	41 $\pm$ 11.28 (20-67)
Male	68.1 (32)
Retransplant ^a	6.4 (3)
Donor type	
Deceased	34 (16)
Living	66 (31)
Immunosuppressive agent received ^b	
Prednisone	100 (47)
Mycophenolic acid ^c	44.7 (21)
Cyclosporine A	38.3 (18)
Azathioprine	34 (16)
Tacrolimus	31.9 (15)
Rapamycin	6.4 (3)
Prior rejection	38.3 (18)
Diabetes mellitus	23.4 (11)
Cytomegalovirus infection	23.4 (11)
Time to onset of infection after transplant, average months (range)	42 (20 d-17 y)
Sites of involvement	
CNS	74.5 (35)
Pulmonary	34 (16)
Skin, soft-tissue, or osteoarticular	34 (16)
Disseminated infection ^d	42.6 (20)
Antifungal therapy	
Amphotericin B	87.2 (41)
Fluconazole	8.5 (4)
None	4.3 (2)

CNS, central nervous system; SD, standard deviation.

^aIndicates prior receipt of a renal transplant.^bImmunosuppressive agent that remained unchanged within 3 mo of the onset of cryptococcosis.^cIncludes mycophenolate mofetil or mycophenolate sodium.^dDefined as the involvement of at least two noncontiguous organ systems or the presence of fungemia.

TABLE 2

Analysis of the variables associated with kidney graft loss within 30 d after cryptococcosis

Variables (n°. patients) n = 39	No Graft Loss, % n = 33	Graft Loss, % n = 6	P value
Age > 50 y, years ¹³	27.3	66.7	.082
Male (25)	63.6	66.7	.635
Retransplant ^{a3}	6.1	16.7	.403
Donor type			
Deceased ¹²	27.3	50	.257
Living ²⁷	72.7	50	
Cytomegalovirus infection ^{b4}	6.1	33.3	.104
Prior rejection ¹⁵	39.4	33.3	.579
Diabetes mellitus ⁸	21.2	16.7	.642
Baseline creatinine, mean, $\pm$ SD, mg/dL ³⁶	2.3 $\pm$ 1.31	5.1 $\pm$ 1.89	.0001
Sites of involvement			
CNS ²⁷	69.7	66.7	.612
Pulmonary ¹²	24.2	66.7	.06
Skin, soft-tissue, or osteoarticular ¹⁴	33.3	50	.365
Disseminated infection ¹⁵	30.3	83.3	.024
AMBd as primary therapy ³⁵	90.9	83.8	.502
Duration of AMBd therapy, mean $\pm$ SD, days ³⁵	25.1 $\pm$ 23.16	21.6 $\pm$ 34.4	.858
Dose of AMBd, mean, $\pm$ SD, mg/Kg ³²	0.7 $\pm$ 0.15	0.7 $\pm$ 0.12	.281
Change in immunosuppressive regimen after infection ^{28d}	78.1	60	.352
Presence of additional nephrotoxic condition ^{6ce}	7.1	80	.0001

AMBd, amphotericin B deoxycholate; CNS, central nervous system; SD, standard deviation.

^aIndicates prior receipt of a renal transplant.^bInfection occurring within 6 mo of the onset of cryptococcosis.^cPatients treated with AMBd who developed graft dysfunction and had an additional nephrotoxic condition.^dData were available for 37 patients.^eData were available for 33 patients.

TABLE 3

Analysis of variables associated with mortality 30 d after cryptococcosis in study patients

Variables (n° patients) n = 47	Survival, % n = 38	Death, % n = 9	P value
Age, mean, $\pm$ SD, years ⁴⁷	451 $\pm$ 1107	497 $\pm$ 10.50	.271
Male ³²	68.4	66.7	.604
Retransplant ^{a3}	7.9	0	.520
Prior rejection ¹⁸	36.8	44.4	.476
Cytomegalovirus infection ^{b4}	7.9	11.1	.586
Receipt of a calcineurin-inhibitor agent ^{c32}	68.4	66.7	.604
Duration of symptoms before diagnosis, mean, $\pm$ SD ⁴²	44.4 $\pm$ 48.83	58.8 $\pm$ 125.09	.598
Time to diagnose after admission, mean, $\pm$ SD ⁴²	5.8 $\pm$ 9.18	8.4 $\pm$ 12.11	.514
Sites of involvement ⁴⁷			
CNS ³⁵	68.4	100	.052
Pulmonary ¹⁶	26.3	66.7	.031
Skin, soft-tissue, or osteoarticular ¹⁶	34.3	33.3	.641
Disseminated infection ²¹	31.6	88.9	.003
Creatinine at admission >2 mg/dL ^{d27}	52.8	88.9	.05
Somnolence at admission ^{e17}	38.5	77.8	.049
Headache at admission ^{e23}	69.2	55.6	.361
CSF opening pressure ^f , cmH ₂ O ²³	24.8 $\pm$ 285.19	55.5 $\pm$ 32.71	.002
CSF cell count ^f , mean, $\pm$ SD, mm ³³²	168.7 $\pm$ 285.19	87.3 $\pm$ 87.10	.467
CSF glucose ratio ^f , mean, $\pm$ SD, mg/dL ³²	47.2 $\pm$ 23.53	45.3 $\pm$ 21.98	.848
Positive CSF India ink ^{g11}	24	71.4	.032
CSF antigen titer $>1:1024$ ^{h11}	38.1	60	.346
AMBd as primary therapy ⁴¹	89.5	100	.495
Unfavorable response with 2 wk ⁱ²¹	52	88.9	.056
Change in immunosuppressive regime after infection ⁱ³¹	87.1	12.9	.296
Presence of additional nephrotoxic condition ^{j8}	11.8	57.1	.018
Graft loss within 30 d ^{k6}	8.3	100	.002

AMBd, amphotericin B deoxycholate; CNS, central nervous system; CSF, cerebrospinal fluid; SD, standard deviation.

^aIndicates prior receipt of a renal transplant.^bInfection occurring within 6 mo of the onset of cryptococcosis.^cAt cryptococcosis diagnosis.^dData were available for 45 patients.

^eData were available for 35 patients.

^fIn the first CSF.

^gData were available for 32 patients.

^hData were available for 27 patients.

ⁱData were available for 34 patients.

^jData were available for 41 patients. Patients treated with AMBd who developed graft dysfunction and had an additional nephrotoxic condition.

^kData were available for 39 patients.