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Cryptococcus transmission through solid organ transplantation in the United States: A Report from the Ad Hoc Disease Transmission Advisory Committee

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Data are not shared as data are collected under Medical Peer review.

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Abstract

Cryptococcus species can cause serious life-threatening infection in solid organ transplant recipients by reactivation of prior infection, post-transplant *de novo* infection, or donor transmission from the transplanted organ. Although previously reported in the literature, the extent of donor-derived cryptococcosis in the United States has not been documented. We analyzed potential donor-derived *Cryptococcus* transmission events reported to the Organ Procurement and Transplantation Network (OPTN) for investigation by the ad hoc Disease Transmission Advisory Committee (DTAC). All reports between 2009–2019 in which transmission to recipients was designated proven or probable, or determined to be averted due to implementation of prophylaxis (intervention without disease transmission – "IWDT") were included. During 2009–2019, 58 reports of potential donor-derived cryptococcosis were submitted to DTAC. Among these reports, 12 donors were determined to have resulted in proven or probable transmission to 23/34 (67.6%) recipients. Most of these donors (10/12 (83%)) exhibited central nervous system-related symptoms prior to death and 5/23 (22%) infected recipients died. For 11 different donors, prophylaxis, most often with fluconazole, was administered to 23/35 (65.7%) recipients. Clinicians should maintain awareness of donor-derived cryptococcosis and consider prompt prophylaxis or treatment followed by reporting to OPTN for further investigation.

Introduction

Cryptococcus species are fungi that can cause serious infection in immunocompromised patients, including solid organ transplant recipients (SOT) [1,2]. A multicenter prospective study from 2001 to 2006 identified cryptococcosis as the third most common invasive fungal infection in SOT recipients but generally occurred late after transplant with a median time to presentation of ~1.5 years post-transplantation [3]. The majority of cases of cryptococcosis after organ transplantation are due to reactivation of latent infection or *de novo* environmental acquisition [1]. On rarer occasions, donor-derived cryptococcosis has been described with a risk for significant morbidity among recipients [4, 5, 6].

Information on the clinical course, treatment, and outcomes of donor-derived cryptococcosis is limited to a few published case reports and series. In the United States, all suspected, unexpected donor-derived disease transmission events are supposed to be reported by transplant centers and organ procurement organizations to the Organ Procurement and Transplantation Network (OPTN) for investigation by the ad hoc Disease Transmission Advisory Committee (DTAC) [7]. Therefore, we analyzed all DTAC-investigated cases of potential donor-derived cryptococcosis in the United States to ascertain further the epidemiology, prevention, and treatment strategies.

Methods

All potential donor-derived cryptococcosis cases reported to the OPTN/DTAC during 2009–2019 were reviewed. The adjudication schema has evolved over time as previously described [8]. Cases with DTAC-adjudicated proven or probable (combined as P/P) transmission from an organ donor to ≥1 recipient were included in this analysis. In addition, cases with DTAC adjudication of intervention without disease transmission (IWDT), in which donor transmission may have been prevented by the administration of effective antifungal agents, were included in the analysis. The adjudication schema has varied over time and nuances of being called proven, probable, or IWDT have similarly evolved but the tables presented here reflect the adjudication of the DTAC members at the time of evaluation with the exception of reports received before 2012 when events were classified only by donor without recording events for each organ recipient [8]. In these early cases, the authors used the current adjudication schema for individual recipients.

The following donor-specific variables were collected when available: mechanism of death, cryptococcosis testing including culture of blood and bronchoalveolar lavage (BAL) and antigen testing of blood, autopsy findings, and central nervous system symptoms. Recipient-specific variables analyzed included organ received by recipient, cryptococcosis testing, antifungal prophylaxis or treatment, clinical outcomes, and DTAC adjudication regarding disease transmission (proven, probable, or IWDT). When available, the number of days between organ transplantation and onset of symptoms leading to a cryptococcosis diagnosis were collected.

This study used data from the OPTN. The OPTN data system includes reported data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the OPTN. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor.

Results

During 2009–2019, 58 reports of potential donor-derived cryptococcosis were submitted to the OPTN/DTAC either from the OPO or a recipient center. These reports involved 58 donors and 180 recipients. Of these, 23/58 (40%) reports, involving 23 donors and 69 corresponding recipients, were deemed proven, probable or IWDT. Among submitted reports, 35/58 (60%) reports, involving 35 donors and 111 recipients, were adjudicated as possible, unlikely, or excluded by DTAC, and are not included in these analyses with exception of possible cases that were part of IWDT donor adjudications (Figure 1).

Among the 23 reports included in these analyses, 12 (12 donors with 34 recipients) had at least one recipient adjudicated as having proven or probable (P/P) transmission (Table 1). Among these 23 reports, 23/34 (68%) recipients developed infection (13/19 kidney, 5/5 lung, 4/8 liver, and 1/2 heart transplant recipients). More than one recipient from a common donor developed P/P transmission in eight of 12 reports. The median duration from transplantation to symptom onset was 45 days (range 8–359). Of note, only 3 cases were diagnosed after 100 days (Figure 2). Five recipients (22%) died. Of these reports, 3/34 (8%) recipients

received antifungal prophylaxis and were classified as IWDT. Eight recipients (25.8%) had no evidence of infection despite absence of intervention and were classified as excluded (Figure 1).

In the other 11 reports (11 donors with 35 recipients), no recipient met classification criteria for P/P transmission. However, these reports had at least one recipient each adjudicated as IWDT (Table 2) based on antifungal prophylaxis received. Among these 11 reports, 20/35 (57%) recipients from cases associated with IWDT plus three of the 34 recipients from cases associated with at least one recipient with P/P transmission were adjudicated as IWDT (10/16 kidney, 7/8 lung, 4/7 liver, and 2/4 heart transplant recipients). When the prophylactic agent was reported, fluconazole was the most commonly used drug (12/23 (52%)).

Cryptococcosis was identified after organ procurement and implantation in 9/12 (75%) donors with P/P transmission. Among these nine donors, four had a positive serum cryptococcal antigen (CrAg), two had positive blood cultures, one had a positive bronchoalveolar lavage (BAL) culture, and one had both positive serum CrAg and positive blood culture. *Cryptococcus* spp. was isolated from one donor bronchus culture obtained around the time of implantation. For two of the nine donors, *Cryptococcus* spp. was identified by examination of autopsy tissues (Table 1).

Among donors associated with only IWDT, 7/11 (64%) donors showed evidence of *Cryptococcus* spp. and all had BAL performed. *Cryptococcus* spp. was isolated in three (27.3%). Blood cultures were performed on 10/11 (91%) donors associated with only IWDT, and the cultures from 2/11 (18.2%) donors yielded *Cryptococcus* spp. Recipient testing modalities are described in Table 2.

The median age of the 23 donors was 52 years (range 19–70 years), 14 died of CNS-related causes, including hemorrhagic or ischemic stroke (nine donors) or seizure (one donor); three had an underlying immune compromising condition. Of the 12 P/P donors, CNS-specific signs or symptoms were identified among 11/12 (92%) donors and included headache, seizure, altered mental status, or other neurological symptoms. Hydrocephalus was identified through computed tomography (CT) in two donors. Among 11 donors associated with only IWDT, 3/11 (27%) donors had CNS-specific findings, including headache, altered mental status, or radiographic evidence of hydrocephalus. Overall, 14/23 (61%) P/P or only IWDT donors exhibited CNS-specific signs or symptoms.

Discussion

Donor-derived cryptococcosis is an uncommon but important complication of solid organ transplantation in the United States. DTAC determined that during 2009–2019, transmission occurred to 23 recipients and an additional 23 recipients had infections potentially averted with antifungal prophylaxis. During this time, 101,006 deceased donors had organs recovered for transplantation in the United States, suggesting that transmission occurred or was averted through directed prophylaxis in recipients from one in ~4,400 (23/101,006) donors. However, this number may be an underestimate. Given the relatively long latency period of *Cryptococcus* reactivation, up to one year after transplant, it is possible that some

cases may not have been considered donor-derived infections and were not reported to DTAC. Likewise, it is possible that some of the late presenting cases were not truly donor associated but were adjudicated as such given that more than one recipient was infected (Table 1, Donors 12 and 8). While most donor-derived cryptococcus has been noted in the first month after transplant, others have noted delayed presentations [5,9]

Cryptococcus infections, although uncommon, can be severe and result in death; as shown in this study, 22% of ill recipients died between 11 and 368 days after transplant.

Prompt recognition and reporting of cryptococcosis in donors and recipients is essential as identification of cryptococcal infection in a donor or a recipient can allow for implementation of prophylaxis which may avert disease in other recipients. In the present study, when P/P donor-derived infection was identified in one recipient from 12 donors, infection was subsequently identified in another 11 recipients from these donors. This underscores the need for a high index of suspicion for donor-derived infection and prompt reporting to allow for early intervention. The institution of prophylaxis in at least three recipients may have averted serious harm. Though this sample size is small, lung recipients appeared to be at highest risk, with 100% of exposed lung recipients acquiring *Cryptococcus*. A lower proportion of recipients of other organs developed disease: 13 out of 19 kidney recipients, four out of eight liver recipients, and one out of two heart recipients.

Recognition of cryptococcosis in donors can be challenging. Only five of the 12 donors involved in P/P transmission had evidence of cryptococcosis on culture or autopsy and underlying risk factors were not usually described. While underlying risk factors were not usually described it is notable that three donors had immunosuppressed states. A clue to potential donor cryptococcosis is the presence of CNS signs and symptoms, particularly in those for whom an intracranial hemorrhage or cerebral vascular event would be epidemiologically unlikely [9, 10, 11]. Most donors implicated in P/P transmission died from a CNS etiology or experienced CNS-related signs or symptoms prior to death. Clinicians caring for SOT recipients should maintain awareness of donor-derived cryptococcosis, particularly when donors have underlying immunocompromising conditions or evidence of CNS signs or symptoms. In addition, five donors, including four without other laboratory evidence of cryptococcosis, had positive serum CrAg on retrospective testing. DTAC previously reported on donors with CNS infection, which may have included some of the cases in the present study [10]. Likewise, the CDC, through its role on DTAC, previously reported 16 other infections of central nervous system infections transmitted through solid organ transplantation including West Nile virus, rabies, lymphocytic choriomeningitis virus, *Balamuthia mandrillaris*, microsporidiosis, and Eastern Equine Encephalitis virus [12,13]. Two other reports implicated cryptococcal infection in ischemic stroke [14,15], again highlighting the need for organ procurement organizations and transplant centers to maintain a high index of suspicion [10].

Donors with unexpected CNS findings, such as aseptic meningitis, stroke at a young age or increased intracranial pressure or underlying risks for cryptococcus may warrant testing with serum CrAg or if suspicion is high, an evaluation of cerebrospinal fluid with a CrAg assay prior to donation. Even if the results are available after implantation, appropriate

communication through OPTN would allow transplant centers to evaluate recipients and intervene with antifungal prophylaxis. Likewise, if cryptococcosis occurs after transplantation, even if months after transplantation, communication by reporting to the OPTN as a potential donor transmission is critical so that other transplant centers can be notified and evaluate recipients of organs from the same donor. Failure to communicate was hypothesized to contribute to at least one fatal outcome in a previous report [5].

The current study is subject to several limitations. While OPTN policy15.5 mandates reporting of potential donor-derived infections by transplant centers to OPTN for DTAC adjudication, reporting relies on clinician recognition of cryptococcosis being potentially of donor etiology. The cases described here may therefore not represent all donor-derived cryptococcosis during the study period, particularly since donor-derived infections were reported up to a year after transplantation. The impact on these findings are difficult to quantify. As a comparison, 0.37% of SOT recipients in California and Florida developed cryptococcosis according to a report analyzing billing data. Crudely applying this proportion to the 347,841 organ transplants during 2009–2019 would suggest 1,287 cryptococcal infections in SOT recipients could have occurred [16]. Even a small proportion of undetected donor-derived infections among overall cases could substantially increase the numbers reported here. It is possible that some recipients classified as IWDT would not have developed disease even if they did not receive prophylaxis and therefore the role of prophylaxis may be overestimated. As previously mentioned, IWDT designation has evolved over time and therefore, some of the classifications presented here may have been differently adjudicated when applying subsequent criteria. Finally, data available on each case reviewed by DTAC are limited to 45 days after the initial report and by the information released by the donor and transplant centers which may not include all medical records or treatment specifics such as type, dosing, and duration. Accordingly, these limitations may have reduced DTAC's ability to correctly adjudicate donor-derived cryptococcosis or identify all donor risks or recipient use of prophylaxis.

In summary, although uncommon, donor-derived cryptococcosis confers a high risk of mortality to solid organ transplant recipients. Organ procurement organizations could consider implementing cryptococcal antigen testing of donors with CNS disease or symptoms to guide antifungal prophylaxis decisions for recipients and prevent adverse outcomes. Clinicians caring for transplant recipients should maintain awareness and consider close monitoring of recipients of donors who died of CNS-related conditions. All suspected donor-derived cryptococcosis should be reported to the OPTN for DTAC investigation.

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Abbreviations:

DTAC	ad hoc Disease Transmission Advisory Committee
BAL	Bronchoalveolar lavage
CDC	Center for Disease Control and Prevention
CrAg	Cryptococcal antigen
HRSA	Health Resources and Services Administration
IWDT	Intervention without disease transmission
OPTN	Organ Procurement and Transplantation Network
SOT	Solid organ transplant recipients

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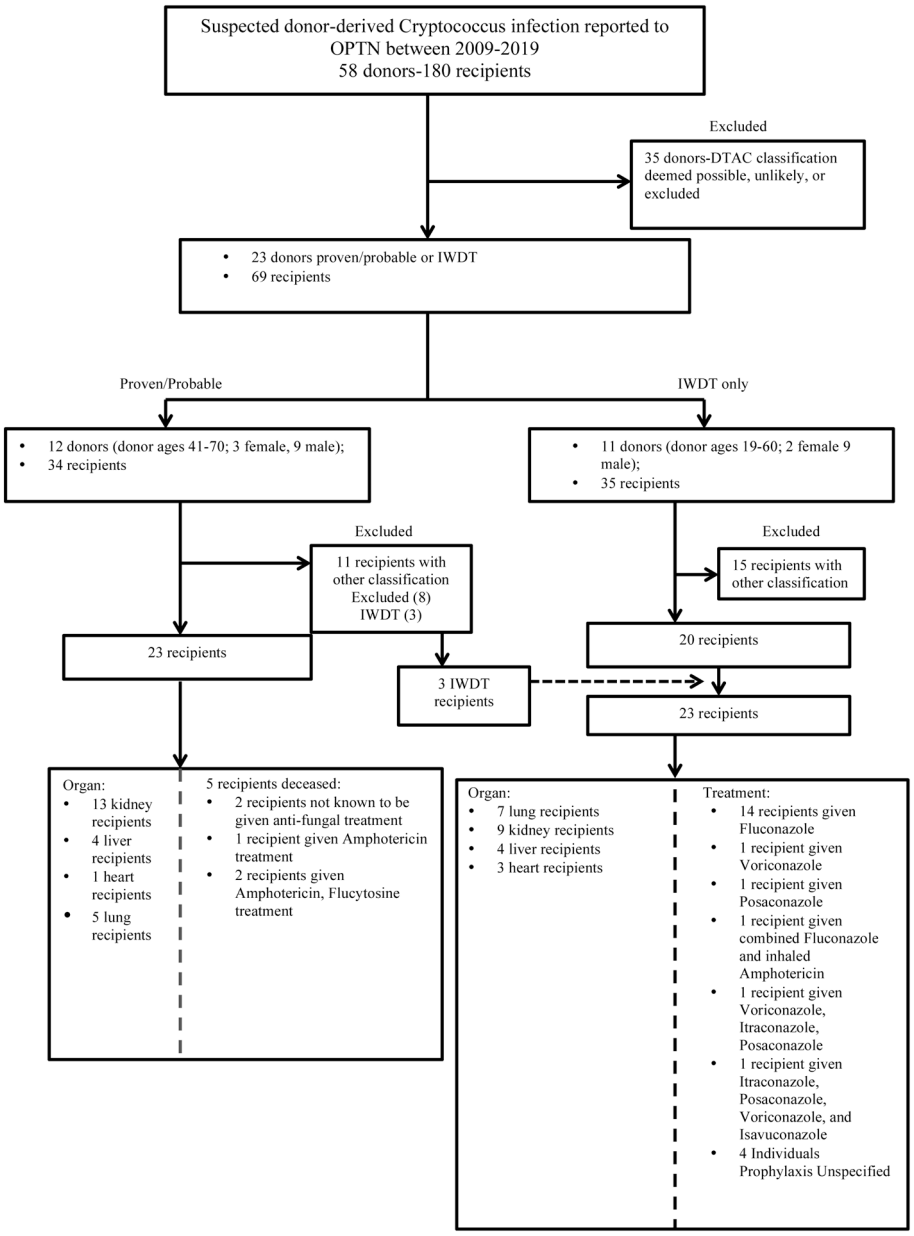

Figure 1.
Suspected donor-derived Cryptococcus infection reported to OPTN between 2009 and 2019

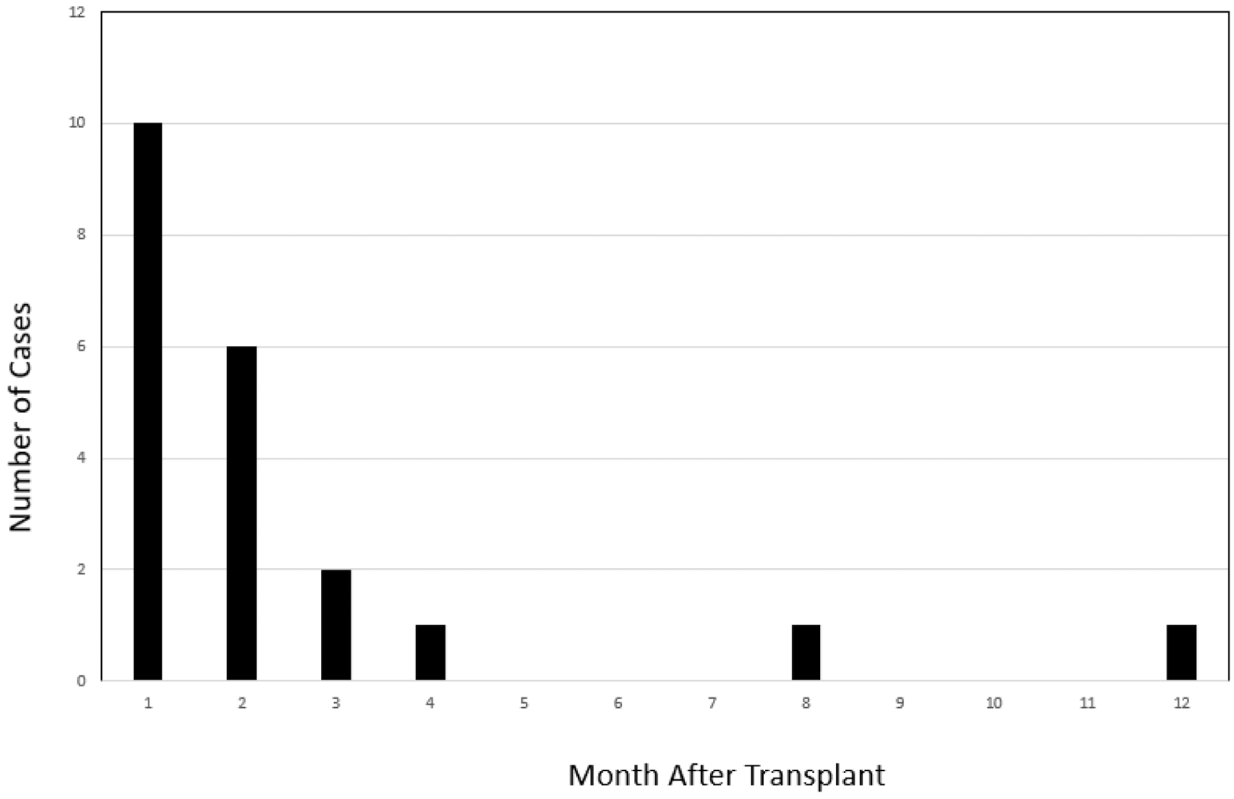

Figure 2.
Number of recipients with proven or probable donor derived Cryptococcus based on time from transplant (N=21).

Table 1:

Donor-derived Cryptococcal Infections Designated as Proven or Probable by the OPTN Disease Transmission Advisory Committee, 2009–2019

Year; DON Age/Sex	Overall Adjud.	DON Cause of Death / Risk for Crypto	DON Blood Culture	DON Serum CrAg	BAL DON	DON Autopsy/ pathology	CNS Signs and Sx	REC #	REC Organ	REC Test (CrAg| culture)	REC Sx	Fungal Proph	Fungal Treat	REC 45 day Follow-up	# Days until Diag
1; 2010; 51/F	P/P	Seizure/ Immunosuppressed host	Neg	Pos Retrosp 1:64	DON BAL without Crypto	CNS Crypto	HA, seizures, Hydro	1	Left Kidney	+CSF| +Blood	HA, malaise, fever	Ampho	Flu	Alive, No Sx	23
	P/P							2	Liver	+ pathology +Serum CrAg| +Blood	Refractory ITP	NA	Ampho	Alive, No Sx	13
	P/P							3	Right Kidney	+CSF	HA, fever	Ampho	Ampho; 5FC	Alive, with Sx	30
2; 2010; 51/M	P/P	Stroke	Neg	Neg Retrosp	DON BAL without Crypto (DON bronch cultures at the time of implant Pos Crypto)	No Autop	HA, ICH	1	Bilateral Lung	+Resp	No Sx	Vori	Vori	Alive, No Sx	0
	IWDT							2	Liver	NA	No Sx	Flu	NA	Alive, No Sx	NA
3; 2011; 62/M	P/P	Stroke	Neg	Pos Retrosp	DON BAL Neg for Crypto	Confirmed CNS Crypto	HA, AMS, Hyrdo	1	Left Kidney	+Blood	Seizure, shortness of breath	NA	Ampho	UK	29
	Excluded							2	Liver	−Serum CrAg	No Sx	NA	NA	Alive, No Sx	NA
	Excluded							3	Right Kidney	−Serum CrAg	No Sx	NA	NA	Alive, No Sx	NA
4; 2012; 41/M	P/P	ICH	Pos	No Done	DON BAL without Crypto	No Autop	Lethargy, AMS	1	Heart	+Blood	UK	NA	Ampho	Alive, No Sx	9

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Year; DON Age/Sex	Overall Adjud.	DON Cause of Death / Risk for Crypto	DON Blood Culture	DON Serum CrAg	BAL DON	DON Autopsy/ pathology	CNS Signs and Sx	REC #	REC Organ	REC Test (CrAg| culture)	REC Sx	Fungal Proph	Fungal Treat	REC 45 day Follow-up	# Days until Diag
5; 2016; 49/M	P/P	Stroke	Neg	Not Done	DON BAL Pos for Crypto	No Autop	ICH	1	Bilateral Lung	−Serum CrAg| +Resp	NA	Vori	Flu	Alive, No Sx	9
	Excluded							2	Left Kidney	NA	NA	NA	NA	Alive, No Sx	NA
	Excluded							3	Liver	NA	NA	NA	NA	Alive, No Sx	NA
	Excluded							4	Right Kidney	NA	NA	NA	NA	Alive, No Sx	NA
6; 2016; 41/M	IWDT	Stroke	Pos	Pos Retrosp 1:320	Sputum Neg	No Autop	HA, AMS	1	Heart	NA	HA decreased hearing	Flu	No	Alive, No Sx	NA
	P/P							2	Left Kidney	+Serum CrAg	UK	No	Ambisome; 5FC	Alive, No Sx	18
	P/P							3	Liver	+Serum CrAg	No Sx	None	Ambisome; 5FC	Alive, No Sx	8
	IWDT							4	Right Kidney	NA	No Sx	Flu	None	Alive, No Sx	NA
7; 2016; 53/F	P/P	Anoxia	Neg	No Done	No Done	No Autop	AMS	1	Left Kidney	+Blood	AMS; lethargy	NA	NA	Died	45
	P/P							2	Liver	−Serum CrAg +CSF CrAg	HA	NA	Ampho	Alive, with Sx	53
	P/P							3	Right Kidney	+Serum CrAg	Malaise, HA	NA	Ampho	Alive, No Sx	51
8; 2016; 55/M	P/P	ICH	Pos	No Done	Sputum Neg	No Autop	Vertigo, HA	1	Liver	+CSF culture +Blood culture	Dizziness, AMS herniaton, death	NA	Ampho, 5FC	Died	106
	P/P							2	Left Kidney	+ CSF CrAg	AMS, decreased appetite weakness	NA	Ampho, 5FC	Alive, No Sx	67
	P/P							3	Lung	+Serum CrAg	NA	NA	Ampho, Posi	Alive, No Sx	89

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Year; DON Age/Sex	Overall Adjud.	DON Cause of Death / Risk for Crypto	DON Blood Culture	DON Serum CrAg	BAL DON	DON Autopsy/ pathology	CNS Signs and Sx	REC #	REC Organ	REC Test (CrAg| culture)	REC Sx	Fungal Proph	Fungal Treat	REC 45 day Follow-up	# Days until Diag
9; 2017; 70/M	P/P	ICH	Neg	Pos Retrosp	Sputum Neg	No Autop	Tremors, Difficult walking Possible Parkinson's disease	1	Left Kidney	+CSF CrAg Skin biopsy	Skin lesion	NA	Flu	Alive, No Sx	54
	P/P							2	Right Kidney	+Serum CrAg	ASx	NA	Flu	Alive, No Sx	NA
10; 2018; 59/M	P/P	Aseptic menigitis, stroke	Neg	No Done	Sputum Neg	No Autop	HA and prior stroke	1	Left Kidney	+CSF CrAg	Renal dysfunction, Resp failure	NA	Flu; Ampho	Alive, with Sx	16
	P/P							2	Right Kidney	Kidney biopsy; +Blood culture; +Serum CrAg 1:32	NA	NA	Ampho; 5FC	Died	11
11; 2018; 46/F	P/P	Drug Overdose	Neg	Pos Retrosp	Sputum Neg	No Autop	HA	1	Left Kidney	+Serum CrAg	Fever	NA	Vori	Alive, No Sx	46
	P/P							2	Right Kidney	+Blood culture; Autopsy lung	UK	NA	UK	Died	48
12; 2019; 62/M	P/P	Motor vehicle crash	Neg	Neg	Sputum Neg	No Autop	None	1	Right Lung	+Blood culture	Crypto Meningitis, HA	NA	Ampho ; 5FC; Flu	UK	225
	P/P							2	Left Lung	+Blood culture	Failure to thrive, malaise, AMS	NA	Ampho	Died	359
	Excluded							3	Right Kidney	NA	NA	NA	NA	Alive, No Sx	NA
	Excluded							4	Left Kidney	NA	NA	NA	NA	Alive, No Sx	NA
	Excluded							5	Liver	NA	NA	NA	NA	NA	NA

Abbreviations alphabetically

5FC= Flucytosine

Adjud.= Adjudication

Ampho = Amphotericin B/liposomal amphotericin

AMS = Altered mental status

Autop = Autopsy

Bronch = Bronchus

CrAg = Cryptococcal Antigen

Crypto = Cryptococcus

DON = Donor

Flu = Fluconazole

HA = Headache

Hydro = Hydrocephalus

ICH= Intracranial hemorrhage

NA = Not Applicable

Neg = Negative

P/P = Proven/Probable

Pos = Positive

Posi = Posaconazole

Proph =Prophylaxis

REC = Recipient

Resp = Resp

Retrosp = Retrospective

Sx = Symptoms

Treat = Treatment

UK = Unknown

Vori = Voriconazole

Table 2:

Designated as IWDT by the OPTN Disease Transmission Advisory Committee Based on Suspected Exposure to Donor Cryptococcus, 2009–2019

Overall Recipient Adjudication	Donor Mechanism of Death / Risk for Cryptococcus	Donor Blood Cultures	Donor Serum Cryptococcus Antigen (CrAg)	BAL Donor Cultures	Donor Autopsy /or Pathology	Donor Symptoms Compatible with CNS Cryptococcus	Recipient #	Recipient Organ	Recipient Test (CrAg|culture)	Recipient Symptoms	Antifungal Prophylaxis	Antifungal Treatment	Recipient Outcome
IWDT	Gunshot injury	Negative	Negative	Cryptococcus in fungal culture	Not performed	No	1	Bilateral Lung	NA	NA	voriconazole →itraconazole →posaconazole	NA	Alive, asymptomatic
Excluded							2	Left Kidney	NA	NA	NA	NA	Alive, asymptomatic
IWDT							3	Right Kidney	NA	NA	Fluconazole	NA	Alive, asymptomatic
IWDT	Intracranial hemorrhage	Negative	Not performed	Cryptococcus in fungal culture	Not performed	No	1	Liver	NA	Asymptomatic	Fluconazole	NA	Alive, asymptomatic
Excluded							2	Right Kidney	NA	Asymptomatic	NA	NA	Alive, asymptomatic
IWDT	Cardiovascular disease	Negative	Not performed	Negative	Autopsy Not performed Path lung ca++ node with yeast c/w C. neoformans	No	1	Bilateral Lung	Negative Serum CrAg	Asymptomatic	Voriconazole	NA	Alive, asymptomatic
IWDT	Intracranial hemorrhage	Negative	Negative	Cryptococcus in fungal culture	Not performed	No	1	Heart	NA	None	Fluconazole	NA	Alive, asymptomatic
Excluded							2	Left Kidney	NA	None	NA	NA	Alive, asymptomatic
IWDT							3	Left Lung	NA	None	Unspecified antifungal	NA	Alive, asymptomatic
Excluded							4	Liver	NA	NA	NA	NA	Alive, asymptomatic
Excluded							5	Right Kidney	NA	None	NA	NA	Alive, asymptomatic
IWDT							6	Right Lung	NA	None	Fluconazole; inhaled amphotericin	NA	Alive, asymptomatic

Overall Recipient Adjudication	Donor Mechanism of Death / Risk for Cryptococcus	Donor Blood Cultures	Donor Serum Cryptococcus Antigen (CrAg)	BAL Donor Cultures	Donor Autopsy /or Pathology	Donor Symptoms Compatible with CNS Cryptococcus	Recipient #	Recipient Organ	Recipient Test (CrAg|culture)	Recipient Symptoms	Antifungal Prophylaxis	Antifungal Treatment	Recipient Outcome
IWDT	Cerebral ischemic encephalopathy Immunosuppressed host	Positive	Not performed	Negative	Not performed	Altered Mental Status	1	Liver	Negative Serum CrAg; Negative CSF CrAg	Altered mental status due to IS	Fluconazole	NA	Alive, asymptomatic
Possible	Motor vehicle accident	Negative	Negative	Negative	Not performed	No	1	Heart	Positive Blood Culture	Sepsis	NA	Amphotericin; flucytosine	Died - unrelated
IWDT							2	Left Kidney	NA	None	Unspecified antifungal	NA	Alive, asymptomatic
Excluded							3	Liver	NA	None	NA	NA	Alive, asymptomatic
IWDT							4	Right Kidney	NA	None	Unspecified antifungal	NA	Alive, asymptomatic
IWDT	Intracranial hemorrhage	Negative	Negative	Negative	Autopsy not performed/ Lymph node + culture	Headache and hydrocephalus	1	Heart	Negative Serum CrAg	Necrotizing pneumonia presumed bacterial	Itraconazole →posaconazole →voriconazole	Isavuconazole	Died - unrelated
IWDT							2	Left Kidney	Negative Serum CrAg	None	Fluconazole	NA	Alive, asymptomatic
IWDT							3	Right Kidney	Negative Serum CrAg	None	Fluconazole	NA	Alive, asymptomatic
IWDT	Intracranial hemorrhage	Negative	Negative	Negative	Not performed	No	1	Bilateral Lung	Negative Serum CrAg; Positive Respiratory	No symptoms; positive BAL Culture on day +1 post-transplant	Posaconazole	NA	Alive, asymptomatic
IWDT							2	Liver	Negative Serum CrAg	None	Fluconazole	NA	Alive, asymptomatic
Non-evaluable							3	Right Kidney	NA	None	NA	NA	Unknown
IWDT	Blunt Injury	Negative	Not performed	Negative	Not performed	Yes	1	Bilateral Lung	NA	NA	Unspecified antifungal	NA	Alive, asymptomatic
Possible							2	Left Kidney	Positive Serum CrAg; Positive Blood Culture; Positive CSF Culture	Altered Mental Status	NA	NA	Alive, asymptomatic

Overall Recipient Adjudication	Donor Mechanism of Death / Risk for Cryptococcus	Donor Blood Cultures	Donor Serum Cryptococcus Antigen (CrAg)	BAL Donor Cultures	Donor Autopsy /or Pathology	Donor Symptoms Compatible with CNS Cryptococcus	Recipient #	Recipient Organ	Recipient Test (CrAg|culture)	Recipient Symptoms	Antifungal Prophylaxis	Antifungal Treatment	Recipient Outcome
Excluded							3	Liver	Negative Serum CrAg	NA	NA	NA	Died - unrelated
IWDT							4	Right Kidney	Negative Serum CrAg	NA	Fluconazole	NA	Alive, asymptomatic
Possible	Blunt injury	Not performed	Not performed	Negative	Not performed	No	1	Left Lung	Positive Respiratory Culture	NA	NA	Fluconazole →voriconazole	Alive, asymptomatic
IWDT							2	Right Lung	Negative Bronchoalveolar Lavage Culture	NA	Fluconazole	NA	Alive, asymptomatic
Excluded							3	Left Kidney/ Pancreas	Negative Serum CrAg	NA	None	NA	Alive, asymptomatic
Excluded							4	Heart	NA	NA	None	NA	Alive, asymptomatic
Excluded							5	Right Kidney	NA	NA	None	NA	Alive, asymptomatic
Excluded							6	Liver	NA	NA	None	NA	Alive, asymptomatic
IWDT	Cerebral edema/ Immunosuppressed host	Positive	Not performed	Negative	Not performed	Headache and altered mental status	1	Left Kidney	NA	NA	Fluconazole	NA	Alive, asymptomatic
IWDT							2	Right Kidney	NA	NA	Fluconazole	NA	Alive, asymptomatic

ations : CrAg = Cryptococcal Antigen; IWDT = Intervention without Disease Transmission; NA = Not Available; F = Female; M = Male; IS = Immunosuppressive Medication