Donor-Derived Fungal Infections in Organ Transplant Recipients: Guidelines of the American Society of Transplantation, Infectious Diseases Community of Practice


Background

Donor-derived fungal infections are a rare but significant complication in transplant recipients (1–3). The existence of a transmissible infection in the donor and the risk posed by such transmissions often remains unrecognized at the time of recovery of organs. The goals of the American Society of Transplantation, Infectious Diseases Community of Practice’s initiative on donor-derived fungal infections are to provide guidance on the evaluation and management of these infections, recognizing that definitive studies to adequately address all issues are lacking. Key objectives of this effort are to enhance our ability to identify donors with the potential to transmit these infections and facilitate timely recognition of transmission to the recipients. The recommendations are based on data and supportive evidence from the literature. However, the typical grading system (4) for ranking the quality of evidence was not used since level I or II studies (clinical trials) are lacking and most reports on donor-derived fungal infections exist as descriptive studies, case series or clinical experience (level III evidence). The proposed level of probability of these infections (proven, probable and possible) are presented in Supporting Tables S1–S4 and are based on published criteria (5). An infection that is potentially of donor origin must be reported to the Organ Procurement and Transplantation Network (OPTN) within 24 h of knowledge or concern (6).

Candidiasis

Kidney transplant recipients

The estimated frequency of donor-derived candidiasis is 1:1000 in kidney transplantation (2). Most infections are considered to result from contamination of the preservation fluid which can occur prior to or at the time of organ procurement (2,7–11). Isolates in donor-derived candidiasis were genotypically identical to those recovered from the preservation fluid in the respective cases (2). Rupture of an abdominal viscus as possible source of contamination was identified in 58% of the donors in one report (2). Candida species have been isolated from ~3.7% of the preservation fluids (7). When preservation fluid cultures did not yield Candida, infections appear to be unusual; however, the precise risk of infection when the preservation fluid...
cultures are positive is unknown (8,10,12–14) (Supporting Table S5). Transmissions from donors with candidemia have also been documented (1). Donor-derived candidiasis may manifest as candidemia, infected urinoma, perineal hematoma, abscess or a fungus ball (1,2,7,11). However, vascular complications such as mycotic aneurysm and anastomotic rupture are the most serious manifestations of these infections (2,9,15).

Management
Cultures from blood, urine and other clinically relevant sites should be obtained and antifungal therapy initiated in the recipient when Candida is visualized on stains or grown in preservation fluid or in cases of documented intestinal perforation in the donor. Doppler ultrasound should be performed at baseline and day 7 (8). CT or MR angiography should be considered if Doppler ultrasound is unremarkable but there is a strong clinical suspicion for pathology. Detection of aneurysm should prompt evaluation for the need for nephrectomy. If renal abscesses or perinephric collections are detected, drainage by surgical or interventional approaches should be considered.

Fluconazole is the preferred antifungal therapy. The urinary levels of fluconazole exceed the MIC for susceptible and most dose dependently susceptible species such as C. glabrata (16,17) (Table 1). The urinary excretion of the triazoles on the other hand is minimal (itraconazole 1%, voriconazole 5%, posaconazole 1%) (16). Although, the triazoles have been used to treat renal parenchymal infections, they are not recommended for urinary tract candidiasis (18). All azoles have the potential to increase calcineurin-inhibitor agent levels (Table 1) which should be monitored with dosage adjustments as necessary (19). The echinocandins are extensively metabolized with very little active drug recovered in the urine (20). Eradication of infection with these drugs in the renal parenchyma is more likely than in the collecting system (16). Thus, echinocandins should be considered as an alternative only if the Candida species is unknown or if there is a high likelihood of non-albicans Candida in the absence of lower urinary tract infection. Polyenes are active against most Candida (Supporting Table S6). Amphotericin B deoxycholate achieves high urinary levels (21). However, nephrotoxicity is a limiting factor with its use (22). The lipid formulations of amphotericin B do not achieve appreciable levels in either the renal parenchyma or urine (16,23,24).

In the absence of documented infection, empiric antifungal therapy may be discontinued after 2 weeks. In patients who develop clinical or microbiologic evidence of infection, imaging studies should be repeated and therapy should be extended to 4–6 weeks depending upon repeat imaging, cultures and clinical data. If vascular involvement is documented, a minimum of 6 weeks of antifungal therapy is recommended. Although existing data do not show a higher rate of invasive candidiasis with the use of deplet-ting antibody induction (25), its precise impact on the risk of donor-derived candidiasis remains unknown.

Donor candiduria does not contraindicate acceptance of the organ. Such recipients should be managed in a manner similar to those with positive preservation fluid. Use of organs from donors with untreated candidemia is not recommended. The risk of transmission from donors with appropriately treated candidemia and documented mycologic eradication is assumed to be low, but this is not known.

Key recommendations
• Definitive and larger studies are needed to identify the factors that predict the likelihood of transmission of Candida and the cost-effectiveness of routinely culturing the preservation fluid. Limited existing data are instructive but insufficient to mandate routine preservation fluid cultures in all cases.
• Prophylactic antifungal therapy should be initiated when yeast is visualized on stain or Candida species are isolated from the preservation fluid or in recovery of organs from donors with intestinal perforation.
• Fluconazole should be considered as the preferred drug for the treatment or prevention of donor-derived candidiasis.

Nonkidney Organ Transplant Recipients
Abdominal organ transplants
Candida has been isolated in ~4% of the preservation fluids from liver transplant recipients (22,26,27). Antifungal prophylaxis is commonly employed in liver transplant recipients at risk for invasive fungal infections (18). Preservation fluid cultures should be taken into consideration when determining the need for prophylaxis. Cultures of blood, urine and drainage fluids should be performed prior to initiating empiric therapy when Candida is identified in preservation fluid cultures or following organ procurement complicated by intestinal contamination. Microbiology of the donor duodenal contents in pancreas transplants suggests frequent contamination with Candida (28). Opening of the donor duodenum during the back bench procedure was associated with aggressive Candida arteritis following pancreatic transplantation (29). Therefore, some centers recommend instillation of amphotericin B through a nasogastric tube positioned into the donor duodenum during organ procurement (29). Additionally, most centers do not open or aspirate the donor duodenum contents during cold storage preservation.

Thoracic transplants
Candida species are frequent oropharyngeal colonizers and are commonly detected in donor respiratory tract cultures (30). Antifungal prophylaxis for ~3 months is commonly employed following lung transplantation (31). If routine prophylaxis is not employed and if the donor’s respiratory
sample yields *Candida*, empiric therapy should be considered and continued until bronchoscopy has confirmed the integrity of the bronchial anastomosis. A longer course may be considered in the recipients of bilateral or right lung transplants and in patients receiving depleting induction agents as these factors pose a risk for anastomotic infection (32). The choice of antifungal agent should be guided by the *Candida* species (Table 1).

Preservation fluid contamination and donor-derived *Candida* infections are unusual following cardiac transplantation. A review of over 100 donor left atrium and postreservation fluid cultures demonstrated positive cultures in 58% (including 2 with *Candida*) with no adverse clinical outcomes (33).

**Key recommendations**

- Liver transplant recipients in whom *Candida* species are identified in the preservation fluid cultures or in patients with surgeries complicated by intestinal contamination during organ recovery should receive empiric antifungal therapy for 2 weeks.
- Limited data are available regarding donor-derived fungal infections in pancreas transplantation. If the donor preservation fluid is positive for yeast and in the absence of routine employment of antifungal prophylaxis, treatment should be initiated as outlined for kidney transplant recipients.
- Antifungal therapy should be employed if donor bronchopulmonary secretions yield *Candida* until a repeat bronchoscopy is performed 1 week posttransplant to evaluate the anastomosis.

**Cryptococcosis**

Cryptococcosis occurs in 0.3–5% of transplant recipients (34). The vast majority of posttransplant cryptococcosis is considered to represent reactivation infection (35,36). However, transmission of infection from donor-derived, environmental and zoonotic sources (37–39) suggests that *de novo* acquisition occurs and that prior infection is not completely protective against disease. The terms cryptococcosis or cryptococcal disease are used herein for clinically overt infection (34).

Donors with cryptococcosis at any site may transmit infection (1,40–42). A cluster of transmissions from a donor to multiple recipients (with identical isolates by multilocus sequence typing) underscores the relevance of considering cryptococcosis in donors with an undiagnosed neurologic illness or meningoencephalitis (40). OPTN/UNOS Disease Transmission Advisory Committee also documented the occurrence of disseminated cryptococcosis from a donor with unrecognized meningoencephalitis (43). Although, many potential causes of meningoencephalitis exist, these data highlight the relevance of considering cryptococcosis in donors with an undiagnosed neurologic illness or meningoencephalitis. The potential for live donor transmission should also be recognized (44).

*C. gattii* was previously thought to be restricted to subtropical and tropical regions however, in the last decade it has emerged as a pathogen in British Columbia, Canada and the US Pacific Northwest (45–47). *C. gattii* can infect individuals with and without an identifiable immune defect (47) and is more likely to cause focal or mass lesions in the CNS and lung (47). The potential for *C. gattii* disease transmission from the donor while not known should be assumed to exist.

**Evaluation**

**Donor**

Cryptococcosis should be considered in donors with undiagnosed meningoencephalitis. *Cryptococcus* may also be the causative agent for pulmonary nodules of unknown etiology in potential donors. Specific risk factors for

### Table 1: Antifungal agents for *Candida* infections

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antifungal therapeutic drug monitoring</th>
<th>Therapeutic gaps</th>
<th>Nephrotoxic potential</th>
<th>Urinary penetration</th>
<th>Immunosuppressive drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>No</td>
<td><em>C. glabrata</em> C. <em>krusei</em></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Yes</td>
<td><em>C. glabrata</em> <em>C. krusei</em> (erratic)</td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Yes</td>
<td><em>C. glabrata</em> (erratic)</td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Yes</td>
<td><em>C. glabrata</em> (erratic)</td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>NA&lt;sup&gt;2&lt;/sup&gt;</td>
<td><em>C. parapsilosis</em></td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Micafungin</td>
<td>NA</td>
<td><em>C. parapsilosis</em></td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>NA</td>
<td><em>C. parapsilosis</em></td>
<td>No</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>NA</td>
<td><em>C. lusitaniae and C. guillermondii</em></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lipid formulations of amphotericin B</td>
<td>NA</td>
<td><em>C. lusitaniae and C. guillermondii</em></td>
<td>Yes</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>No</td>
</tr>
</tbody>
</table>

Data based on (18,20)

<sup>1</sup>Achieve low levels in urine and providers should consider using these medications only to treat pyelonephritis and infections involving the anastomosis rather than *Candida* cystitis; <sup>2</sup>NA = Not applicable; <sup>3</sup>Do not achieve appreciable levels either in the renal parenchyma or urine and should not be used for treating any type of renal candidiasis.
cryptococcosis include receipt of corticosteroids, iatrogenic immunosuppressants, sarcoidosis end-stage liver or renal disease, and rheumatologic disorders (48).

The utility of routine serum cryptococcal antigen testing in donors is unknown (1,40,49). However, serum cryptococcal antigen should be performed in donors with meningocencephalitis and in those with unexplained pulmonary lesions or fever of undetermined if they have underlying medical conditions predisposing to cryptococcosis. Donors with meningocencephalitis of undetermined etiology should undergo further evaluation that includes neuroimaging, cerebrospinal fluid (CSF) analysis and CSF cryptococcal antigen testing. A negative serum cryptococcal antigen in patients without HIV infection does not exclude cryptococcosis, and CSF antigen testing and fungal cultures should be performed in those with meningocencephalitis (50). Serum antigen has a lower diagnostic yield for isolated pulmonary cryptococcosis (51–53). In cases with focal disease such as cryptocoecoma or pulmonary lesions, histopathologic evaluation of all available biopsy material should be performed. Donors with pulmonary or extraneural cryptococcal disease should have CSF analysis including cryptococcal antigen testing to document CNS involvement.

The risk of transmission from a donor with untreated cryptococcal disease is assumed to be high (40,42,49). As such, use of organs from untreated donors with documented systemic or CNS cryptococcosis is not recommended and should only be a considered in candidates in whom the risk of death without transplant outweighs that of disease transmission. Likewise, organs from donors with cryptococcal disease receiving antifungal therapy should only be considered on an individualized basis and preferably procured only upon documentation of mycologic eradication. In the event that donor disease is discovered or confirmed after organ donation, OPTN/UNOS should be notified and all recipients should be treated preemptively with effective antifungal therapy.

**Recipient**

Donor-derived cryptococcosis should be considered in any of the following scenarios: (1) *Cryptococcus* is demonstrated microbiologically or histologically at the (nonlung) surgical or graft site; (2) cryptococcosis is documented at any site in the first 30 days after transplant, particularly atypical sites outside the lungs and CNS; or (3) cryptococcal disease is diagnosed in more than one recipient from a single donor. The recipient(s) should undergo diagnostic evaluation that includes CSF analysis, serum and CSF cryptococcal antigen testing, and cultures of the blood, urine and other clinically infected sites. If indicated, needle aspiration or biopsy samples should be submitted for microbiologic and histopathologic assessment. While *C. neoformans* may be incidentally recovered from respiratory specimens in an otherwise asymptomatic patient, it should always be considered pathogenic when recovered from a clinical sample in a transplant recipient and prompt an evaluation for evidence of disease and CNS involvement (54).

**Management**

Standard regimens for the treatment of cryptococcosis have been published (55, 56). Briefly, induction with a lipid formulation of amphotericin B and flucytosine followed by consolidation and maintenance therapy with fluconazole is recommended for moderate to severe, disseminated and CNS cryptococcosis (Table 2). Mild to moderate extra-CNS disease can be treated with fluconazole. Typical duration of treatment is 6–12 months. Longer treatment may be appropriate for patients whose disease has not resolved and for those requiring augmented immunosuppression for rejection. Voriconazole, itraconazole and posaconazole do not offer a benefit over fluconazole (56) and echinocandins lack activity against this yeast. Treatment recommendations are same for *C. gattii* and *C. neoformans* (56).

In recipients with cryptococcosis, reduction in immunosuppression should be considered, though rapid reductions should be avoided (57). This is particularly relevant in patients receiving tacrolimus as this agent has intrinsic antifungal activity (50) and synergistic interactions with the antifungal agents (58). Rapid dose reduction could potentially decrease overall antifungal efficacy while

<table>
<thead>
<tr>
<th>Table 2: Treatment of cryptococcal disease in organ transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient</strong></td>
</tr>
<tr>
<td><strong>Meningoencephalitis</strong></td>
</tr>
<tr>
<td>Induction</td>
</tr>
<tr>
<td>Preferred therapy</td>
</tr>
<tr>
<td>Liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day plus 5 flucytosine 100 mg/kg/day</td>
</tr>
<tr>
<td>Alternative therapy liposomal amphotericin B 3–4 mg/kg/day or amphotericin B lipid complex 5 mg/kg/day</td>
</tr>
<tr>
<td>Consolidation</td>
</tr>
<tr>
<td>Fluconazole 400–800 mg/day</td>
</tr>
<tr>
<td>Maintenance</td>
</tr>
<tr>
<td>Fluconazole 200 mg/day</td>
</tr>
<tr>
<td>Fluconazole 400 mg/day</td>
</tr>
</tbody>
</table>

Recommendations based on references (55) and (56).

¹ Dosages should be adjusted for renal dysfunction.
² Longer duration may be considered for those whose disease has not resolved.
³ Disseminated disease must be excluded in all patients. Those with disseminated disease, diffuse pulmonary infiltrates and acute respiratory failure should be treated with the same regimen as cryptococcal meningoencephalitis.
predisposing to immune reconstitution syndrome and allograft rejection (58). Consequently, a step-wise approach to lowering immunosuppression is suggested, starting with decreasing the corticosteroids. Treatment with T cell depleting agents should be avoided as their use was associated with a dose-dependent increase in the risk for cryptococcosis (59).

**Key recommendations**

- Donors with meningoencephalitis should undergo diagnostic evaluation for cryptococcosis including CSF analysis, cultures, and CSF cryptococcal antigen testing, neuroimaging and histopathologic examination of any clinically abnormal tissue.
- Donors with underlying medical conditions predisposing to cryptococcosis, including but not limited to those receiving immunosuppressant therapy, should undergo evaluation for signs and symptoms of meningoencephalitis. If none are noted, a serum cryptococcal antigen test should be performed. Potential donors with possible meningoencephalitis should undergo evaluation as recommended above, even if their underlying illness or immunosuppressive syndrome could explain the neurologic abnormalities.
- Recipients with suspected donor-derived cryptococcosis should have serum and CSF cryptococcal antigen testing and cultures of blood, urine and other specimens from clinically infected sites. Needle aspiration or biopsy samples from suspected sites of infection should be submitted for cytopathology and histopathologic assessment.
- Moderate to severe cryptococcosis, disseminated, and CNS disease should be treated with induction therapy with a lipid formulation of amphotericin B plus flucytosine followed by consolidation and maintenance therapy with fluconazole. Mild to moderate extra-CNS disease can be treated with fluconazole.

**Histoplasmosis**

*Histoplasma capsulatum* variety *capsulatum* is a dimorphic fungus that resides in the soil of certain regions of North, Central and South America, Africa and Asia. Up to 75% of the residents in certain areas of the Ohio and Mississippi River Valley of the United States may have been infected with *H. capsulatum* (60) (Supporting Figure S1). However, most infections are asymptomatic. Symptomatic infection is more common following high inoculum exposure and in immunosuppressed hosts.

Histoplasmosis occurs in 0.1–0.5% of the transplant recipients in endemic areas (61–67). In an ongoing study comprising 150 transplant recipients with histoplasmosis in the United States, 8 (5%) may have been donor-derived based upon the onset of illness within the first posttransplant month (3 patients) or demonstration of *Histoplasma* in the transplanted organ (5 patients; Personal communication, Assi M). Assuming that the incidence of posttransplant histoplasmosis in endemic areas is 0.2% (95% CI, 0.109–0.327%) (61–65) and that 5% may have been donor derived, the estimated incidence of donor-derived histoplasmosis would be approximately 1:10 000 transplants. The incidence rates, however, may vary in nonendemic or other regions of the world.

**Donor and Recipient Evaluation**

Since histoplasmosis occurs in only 0.5% of transplant recipients from endemic areas and 1–5% of healthy subjects have positive tests for *Histoplasma* antigen or antibodies, respectively routine testing of all donors from an endemic area is not warranted. If screening were performed, positive results are expected in 10:1000 by antigen detection and in 50:1000 by antibody testing.

The evaluation of a potential living donor should begin with prior history of histoplasmosis at any time or undiagnosed pneumonia in the last 2 years (Supporting Figure S2). If documented, further investigation should include pulmonary imaging studies and diagnostic tests. The presence of an H precipitin band by agar gel immunodiffusion (AGID), complement fixation (CF) titers of ≥1:32, antigenuria or antigenemia suggest active infection, while M precipitin bands and CF titers of 1:8–1:16 may represent active or inactive histoplasmosis in which the yeasts are not viable (68). Symptoms of pneumonia, fever, sweats, weight loss and/or findings of undiagnosed pneumonia, noncalcified nodules or lymphadenopathy may represent active disease and warrant additional studies, including bronchoscopic specimens which should be tested for *Histoplasma* antigen or a diagnostic biopsy and cultures of lesions. An individual with active disease would be an unsuitable donor and should be treated with itraconazole for 3–6 months prior to organ donation (69). In the absence of a prior history or clinical or radiographic findings suggestive of histoplasmosis in the donor, routine antigen or antibody testing is not recommended.

The explanted organ should be inspected for granulomas which should be examined microscopically by fungal stain and by fungal culture. If donor granulomas are noted, antigen and antibody testing should be performed. The live donor should also be evaluated for antifungal therapy if not previously treated. The recipient should be tested for antigenemia and antigenuria at 3-month intervals during the first year after transplantation (69). Positive tests for antigen would be an indication for treatment for histoplasmosis.

Deceased donors from endemic areas hospitalized for non-hemorrhagic neurological disease, fever of unknown origin, or pneumonia of unknown etiology may have undiagnosed histoplasmosis. These findings would support further
testing for histoplasmosis. Procurement of organs should not be delayed while awaiting test results which will facilitate the decision to use antifungal prophylaxis or therapy in the recipient. The liver and spleen should be inspected at the time of organ procurement from deceased donors. Findings suspicious for histoplasmosis include organomegaly or presence of focal lesions consistent with granulomas on the organ surfaces or cross sections. Some transplant programs do not use organs with unexplained organomegaly or lesions consistent with granulomas. However, if they are to be used, specimens should be obtained for fungal histopathology and culture. If lesions suspicious for _H. capsulatum_ are noted, serum antigen and antibody testing and cultures of appropriate tissues should be performed (Supporting Figure S3).

The approach to the evaluation of the recipient should include antigen testing or histopathology that are sensitive and rapid and provide the basis for initial diagnosis in most cases. Testing urine, serum (68, 70) and bronchoalveolar lavage fluid in patients undergoing bronchoscopy (71) offers the highest sensitivity for diagnosis by antigen detection. Serology in transplant recipients may not be reliably positive as antibodies have been positive in only 20% of the cases (72). Calcified and noncalcified lung nodules or mediastinal lymph nodes are common ‘incidental’ findings in individuals from endemic areas for histoplasmosis and usually do not indicate active infection or require further testing to exclude active histoplasmosis.

Management

**Prophylaxis**

The approach to the prevention of infection in the recipient is based upon the likelihood that the allograft contained viable organisms. If histoplasmosis was the cause of death in the deceased donor or if cultures or antigen tests were positive, the transplant recipient should be treated for 1 year for possible disseminated histoplasmosis. If fungal stains were positive but cultures of the allograft and antigen tests of the donor blood and urine were negative or if the donor CF titers were ≥1:32 or if H and/or M precipitins were present; a 3- to 6-month course of itraconazole is recommended (68) (Supporting Figure S3). Observation with monitoring for antigenemia and antigenuria at 3-month intervals is reasonable (69) if CF titers were 1:8 or 1:16 since transplant recipients with pretransplant CF titers in this range did not develop histoplasmosis (73).

**Treatment**

Treatment of histoplasmosis is summarized in Table 3 and is based on the published guidelines (69). Liposomal amphotericin B for 1–2 weeks is recommended in patients with more severe illness, followed by itraconazole. Treatment should be continued for at least 1 year, and until _Histoplasma_ antigen levels have become negative in the serum and have declined to <2 ng/mL in urine. Longer courses may be necessary depending upon the response. Antigen levels should be monitored at about 3-month intervals during therapy and for 1 year after discontinuation of therapy (69). Itraconazole is appropriate in patients with milder illness not requiring hospitalization. Consideration should be given to avoiding immunosuppression with T cell depleting antibodies.

Prolonged therapy with itraconazole may be required in some patients such as individuals in whom antigenemia and antigenuria fail to meet the criteria for discontinuation of therapy or who relapse upon discontinuation of therapy. Some physicians continue itraconazole indefinitely in patients who require augmented immunosuppression for rejection. Antigen levels should continue to be monitored at 3-month intervals during suppressive therapy. Voriconazole, posaconazole and fluconazole may be considered as alternatives to itraconazole (64,65,74) (Table 4). Fluconazole is the least active of the azoles for histoplasmosis but has been used successfully for the treatment and may be the best alternative in patients with itraconazole intolerance.

**Key recommendations**

- Living donors with active histoplasmosis should be treated for 3–6 months prior to organ donation.
- The liver and spleen from deceased donors should be inspected at the time of organ procurement. Visualization of granuloma in explanted organs does not absolutely contraindicate their use but serum should be obtained for fungal histopathology and culture. If lesions suspicious for _H. capsulatum_ are noted, serum antigen and antibody testing and cultures of appropriate tissues should be performed (Supporting Figure S3).

---

**Table 3: Treatment of a donor or prospective recipient with evidence for histoplasmosis prior to transplantation**

<table>
<thead>
<tr>
<th>Donor findings</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disseminated histoplasmosis</td>
<td>Itraconazole 200 mg once or twice daily for 12 months and until antigen clearance criteria met</td>
</tr>
<tr>
<td>Pulmonary histoplasmosis</td>
<td>Itraconazole 200 mg once or twice daily&lt;sup&gt;1&lt;/sup&gt; for 3–6 months and until antigen clearance criteria met&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fungal stain positive but culture negative, H and/or M precipitin band, CF ≥1:32</td>
<td>Itraconazole for 3–6 months and until antigen clearance criteria met</td>
</tr>
<tr>
<td>Granuloma, CF 1:8–1:16</td>
<td>Urine and serum antigen every 3 months for 1 year</td>
</tr>
</tbody>
</table>

<sup>1</sup>Antigenemia should be absent and antigenuria < 2 ng/mL. Antigen levels should continue to be measured at 3-month intervals for at least 1 year after stopping therapy and until they are negative. <sup>2</sup>Blood concentration of at least 1 µg/mL should be verified by HPLC, or 3 µg/mL by bioassay. <sup>3</sup>Alternatives to itraconazole are listed in Table 4.
Table 4: Treatment of histoplasmosis in organ transplant recipients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B¹</td>
<td>Moderately-severe or severe infection</td>
<td>3 mg/kg/day</td>
<td>Until the infection is controlled, then transition to an azole alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At least one year. Longer duration may be required if immunosuppression cannot be reduced, or if relapse occurs after treatment is stopped</td>
</tr>
<tr>
<td>Itraconazole²</td>
<td>Mild infection and stepdown after response to liposomal amphotericin B</td>
<td>200 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second line treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Mild infection and stepdown after response to liposomal amphotericin B</td>
<td>800 mg daily²</td>
<td>At least one year. Longer duration may be required if immunosuppression cannot be reduced, or if relapse occurs after treatment is stopped</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole²</td>
<td>Mild infection and stepdown after response to liposomal amphotericin B</td>
<td>400 mg BID orally</td>
<td>Indefinite duration; full treatment dose until completely resolved, then consider a lower dose as secondary lifelong prophylaxis.</td>
<td>Monitor serum levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole²</td>
<td>Mild infection and stepdown after response to liposomal amphotericin B</td>
<td>6 mg/kg BID × 2 doses, then 4 mg/kg BID, or 200–300 mg BID</td>
<td>Indefinite duration, full treatment dose until completely resolved, then consider the lower dose as secondary lifelong prophylaxis.</td>
<td>Monitor serum levels; levels may decrease with time.</td>
</tr>
</tbody>
</table>

Table modified from http://www.antimicrobek.org ESun Technologies, LLC with permission.

¹Amphotericin B lipid complex is an alternative, at a 5 mg/kg/day dosage. ²Blood concentration of at least 1 μg/mL should be verified by HPLC. ³Dosage should be adjusted for renal function.

be tested for antigen and antibodies to Histoplasma if suspicious lesions are noted and cultures sent.
- Antigenemia, antigenuria, H and/or M precipitin bands and CF titers of ≥1:32 provide strong evidence for active histoplasmosis.
- Liposomal amphotericin followed by itraconazole is recommended as therapy for moderately severe and severe histoplasmosis. Milder cases may be treated with itraconazole. Voriconazole, posaconazole and fluconazole are alternatives to itraconazole.

Coccidioidomycosis

*Coccidioides immitis* and *C. posadasii* are the etiologic agents of coccidioidomycosis. These dimorphic fungi are residents in selected desert soils of the lower Sonoran life zone. The areas of highest endemicity in the United States include the southwestern Arizona, the San Joaquin Valley of California and west Texas (75) and (Supporting Figure S4). *C. immitis* is the predominant species in California, whereas *C. posadasii* is found in the other endemic areas (76,77). An estimated 150 000 infections occur annually in the United States, primarily in residents or in individuals with travel to endemic areas. Outside of the United States, this fungus is found in northern Mexico with limited endemicity in Central and South America. Coccidioidomycosis is acquired by inhalation of arthroconidia that undergo transformation into spherules resulting in a primary pulmonary infection (78,79). Endospores from mature spherules can spread hematogenously to extrapulmonary sites. Once the host has developed cellular immunity, protection is complete and long-lasting despite ongoing exposure unless a profound change in host immunity occurs (80). Coccidioidomycosis occurs in 1.5–8.7% of the transplant recipients in endemic areas, typically in the first posttransplant year (81). Several cases of donor-derived coccidioidomycosis in transplant recipients have been reported (49,82–90).

Evaluation

Donor

Potential donors who reside or have resided in the endemic area with either symptomatic or occult infection can transmit the infection with the allograft. Approximately 60% of healthy persons with coccidioidomycosis are asymptomatic. Among healthy potential live donors within the endemic area, 2.1% were seropositive indicating recent
infection (91). Screening of live donors from the endemic area includes serology (enzyme immunoassay [EIA], complement fixation [CF] and immunodiffusion [ID]), chest imaging, fungal culture of respiratory secretions or tissue specimens (depending upon clinical and radiographic findings) and such screening should be performed prior to recovery of organs. The strengths and limitations of the available serologic assays are discussed in Supporting Table S7. A positive serological test or suggestive histopathology in the donor should prompt further evaluation to define the extent and activity of the infection in the donor. Chest imaging (chest radiograph or computed tomography, if radiograph is unremarkable) is recommended to assess the likely location of coccidioidal infection or granuloma. Elevated CF titers (1:16 or higher) may reflect disseminated infection (92). Further assessment to define the presence of extrapulmonary infection may be warranted in such instances, with particular attention to the CNS, cutaneous and osteoarticular infections. While negative serology does not exclude the possibility of previous coccidioidal infection, no further evaluation is warranted in the absence of history of coccidioidomycosis or active infection in the donor at the time of recovery of organs. Universal screening is not recommended for centers outside the endemic area.

A living donor whose evaluation has revealed the presence of coccidioidal infection should undergo an assessment to determine the extent and control of the existing infection (Supporting Figure S5). Coccidioidal serologies (EIA, CF, ID) should be performed. Additionally, chest imaging and respiratory cultures should be performed. Appropriate imaging studies, CSF analysis, and biopsy and culture of suspicious lesions based on specific manifestations should be considered. A donor with active infection would not be suitable for organ procurement. If evaluation reveals the presence of active pulmonary or extrapulmonary infection, it is prudent to delay organ donation until the infection is controlled. Control of infection is considered as resolution of symptoms, radiographic abnormalities and serology (at least a fourfold reduction of the CF titer). For a deceased donor whose coccidioidal infection was identified post mortem, further evaluation may be limited to testing of stored serum and tissue samples. These include serology, fungal culture of the blood or any stored body fluids or samples if available (Supporting Figure S6).

**Recipient**

The recipient of an organ from a donor with a history of residence in or travel to the endemic area should have baseline pretransplant serological screening performed at or just prior to transplantation. These serological tests will establish a benchmark for future comparison. When such a patient develops an unexplained febrile illness, serology should be repeated in addition to fungal cultures of blood, urine and other appropriate fluids and specimens based on the clinical presentation. Recipients of organs from a donor who is either seropositive or discovered to have active coccidioidal infection should have baseline (pretransplant or at the time of donor diagnosis posttransplant) serology as well as clinical evaluation as noted above, and antifungal prophylaxis initiated. An asymptomatic recipient receiving antifungal prophylaxis should be followed clinically. However, in instances where antifungal prophylaxis is withdrawn, serological monitoring should be performed every 2–3 months in the first 6–12 months, and every 6–12 months thereafter.

### Management

#### Prophylaxis

Fluconazole and itraconazole have proven to be efficacious for prophylaxis of coccidioidomycosis in transplant recipients (93–95) and both have been used for the prevention of donor-derived coccidioidomycosis (82,85) (Tables 5 and 6). Suggested regimens are fluconazole (400 mg daily) or itraconazole (200 mg twice daily) (82,85). For patients already receiving itraconazole, voriconazole, or posaconazole for *Aspergillus* prophylaxis, additional fluconazole is not required. Transplant recipients whose antifungal prophylaxis consists of an echinocandin or inhaled aerosolized amphotericin B and who are at risk for donor-derived

### Table 5: Suggested prophylaxis for transplant recipients of a donor with documented coccidioidomycosis

| 1. Donor with documented pulmonary coccidioidomycosis but no evidence of extrapulmonary coccidioidomycosis, seropositive, or culture positive: lung recipients: fluconazole 400 mg daily lifelong |
| Non lung recipients: fluconazole 400 mg daily for 12 months then consider decreased dose 200 mg daily thereafter |
| 2. Donor with documented pulmonary coccidioidomycosis but no evidence of extrapulmonary coccidioidomycosis, seronegative, culture negative: Lung recipients: fluconazole 400 mg daily lifelong |
| Non lung recipients: fluconazole 400 mg daily for 3–6 months then consider decreased dose 200 mg daily OR stop and observe without ongoing prophylaxis |
| 3. Documented extrapulmonary coccidioidomycosis: all recipients: fluconazole 400 mg daily lifelong |
| 4. Donor with positive serology, but no clear focus of infection: lung recipients: fluconazole 400 mg daily |
| Non lung recipients: fluconazole 400 mg daily for 12 months then consider decreased dose 200 mg daily thereafter |
| 5. Recipients already receiving posaconazole or voriconazole at full strength treatment doses for treatment or prophylaxis of other fungal organisms do not need additional fluconazole |
| 6. Recipients already receiving caspofungin, or inhaled formulations of amphotericin for prophylaxis of *Aspergillus* will still require fluconazole for coccidioidal prophylaxis |
| 7. All recipients should be monitored periodically for evidence of seroconversion |
| 8. If discontinuation of prophylaxis is contemplated, regular follow up clinically, radiographically and serologically is recommended |

*American Journal of Transplantation*  
doi: 10.1111/j.1600-6143.2012.04100.x
coccidioidomycosis should receive additional prophylaxis with an azole.

The optimal duration of prophylaxis for donor-derived coccidioidomycosis has not been determined. The lungs of an organ donor with active or previous coccidioidomycosis are likely to harbor organisms contained either in an area of inflammation or a granuloma (96). However, the precise risk of transmission from a previously infected donor via lung transplantation is not known. Since the organisms can remain viable within a granuloma, some centers employ lifelong prophylaxis in lung transplant recipients (96). Organs other than lungs may or may not harbor Coccidioides, and unless there is gross or histopathological evidence of such infection in the donor organ, the risk of donor-derived coccidioidomycosis is unknown. For recipients of nonlung organs from a donor with documented coccidioidomycosis, an option is to continue lifelong prophylaxis (perhaps with a fluconazole dose of 200 mg daily after the first posttransplant year). Alternatively, discontinuation of prophylaxis after 3–6 months with continued monitoring for clinical or serological evidence of coccidioidomycosis is also rational.

**Treatment**

The treatment of coccidioidomycosis has been summarized in published guidelines (97) and is outlined in Table 7. Fluconazole (400–800 mg daily) and itraconazole (200 mg twice or thrice daily) are the antifungal agents of choice for the treatment of coccidioidomycosis (97). For patients with rapidly progressive or severe infection, a lipid formulation of amphotericin B is recommended at a dose of 5 mg/kg/day (97). Both voriconazole and posaconazole are active in vitro for Coccidioides and have been used (86,98) as salvage therapy in transplant recipients. No standard recommendation for the duration of treatment exists as response to therapy may vary. Generally, the patient should be treated until the infection is quiescent based on clinical, serological and radiographic follow-up, and this may take months or years to achieve. Once control has been documented for at least 12 months, lifelong prophylaxis is recommended (93). Secondary prophylaxis most often employs a lower dose of the same azole used to treat the infection. Optimal regimens should include fluconazole dosed no less than 200 mg daily (for normal renal function) for pulmonary infections and no less than 400 mg daily for those with coccidioidal meningitis or extrapulmonary disease.

**Key recommendations**

- Donors with active coccidioidomycosis and those with old granulomas harboring viable organisms, regardless of the presence or absence of a positive serology have the potential to transmit infection to the recipients.
- Approach to diagnostic evaluation and management of donor-derived coccidioidomycosis is summarized in Supporting Figures S5 and S6, respectively.
- Lipid formulations of amphoterin B represent the agents of choice for the treatment of life-threatening or rapidly progressive coccidioidomycosis whereas fluconazole or itraconazole may be employed for most nonlife-threatening infections. Treatment should be followed by indefinite secondary prophylaxis, preferably using fluconazole.

**Aspergillus and Other Moulds**

Aspergillus species have been rarely cultured from the preservation fluid (22,99) and contaminated preservation fluid has been shown or suspected to be the mode of transmission of aspergillosis and mucormycosis associated with fungal arteritis, mycotic aneurysms, anastomotic infections and graft site abscesses/fungus ball in kidney and liver transplant recipients (22,100–104). Invasive filamentous fungal infections resulting from exposure to contaminated sources, infected donors or breaches in aseptic techniques during organ procurement, transport or implantation have been identified as a major complication of commercial or transplant tourism (105). Such infections frequently originate at the graft site and are associated with high rates of graft loss (105,106). Unrecognized infection in two donors (who were themselves transplant recipients) from whom multiple organs were recovered was associated with invasive aspergillosis (IA) in several recipients (107,108). Although not diagnosed at the time of death, both donors were critically ill transplant recipients with risk factors for IA (rejection, renal failure or depleting antibody receipt) and abnormal CNS and/or pulmonary manifestations/imaging results consistent with disseminated IA (107,108).

A recent review documented that graft-transmitted mucormycosis accounted for 14% of 169 cases of healthcare-associated mucormycosis reported in the literature (109).
Table 7: Treatment of coccidioidomycosis in transplant recipients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line treatments</td>
<td>Life-threatening or rapidly progressing infection</td>
<td>5 mg/kg/day</td>
<td>Until the rapid progression of infection is controlled, then transition to an azole alone</td>
<td></td>
</tr>
<tr>
<td>Lipid formulations of amphotericin B</td>
<td>Life-threatening or rapidly progressing infection</td>
<td>5 mg/kg/day</td>
<td>Until the rapid progression of infection is controlled, then transition to an azole alone</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Most non-life-threatening infections</td>
<td>400–800 mg daily</td>
<td>Full treatment dose until clinically resolved, then lifelong secondary prophylaxis 200–400 mg</td>
<td>Higher doses preferred by experts</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Most non-life-threatening infections</td>
<td>200 mg BID–TID</td>
<td>Indefinite duration; full treatment dose until completely resolved, then change to the lower dose or fluconazole as secondary lifelong prophylaxis</td>
<td>Monitor serum itraconazole levels</td>
</tr>
<tr>
<td>Meningitis (fluconazole preferred)</td>
<td>Meningitis (fluconazole preferred)</td>
<td>400–800 mg daily</td>
<td>Lifelong</td>
<td></td>
</tr>
<tr>
<td>Skeletal infections (itraconazole preferred)</td>
<td>Skeletal infections (itraconazole preferred)</td>
<td>200 mg BID–TID</td>
<td>Indefinite duration; full treatment dose until infection resolved, then continued secondary prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Second line (salvage) treatments</td>
<td>Most nonmeningeal, non-life-threatening infections, when first line therapies fail or not tolerated</td>
<td>400 mg BID orally</td>
<td>Indefinite duration; full treatment dose until completely resolved, then consider a lower dose as secondary lifelong prophylaxis</td>
<td>Monitor serum levels</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Most nonmeningeal, non-life-threatening infections, when first line therapies fail or not tolerated</td>
<td>400 mg BID orally</td>
<td>Indefinite duration; full treatment dose until completely resolved, then consider a lower dose as secondary lifelong prophylaxis</td>
<td>Monitor serum levels</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Most non-life-threatening infections, when first line therapies fail or are not tolerated</td>
<td>6 mg/kg BID × 2 doses, then 4 mg/kg BID, or 200–300 mg BID</td>
<td>Indefinite duration, full treatment dose until completely resolved, then consider the lower dose as secondary lifelong prophylaxis</td>
<td>Monitor serum levels; levels may decrease with time</td>
</tr>
</tbody>
</table>

Table modified from http://www.antimicrobe.org ESun Technologies, LLC with permission.

Primary hepatic mucormycosis occurred only in liver transplant recipients and renal mucormycosis manifested as acute rejection in four kidney transplant recipients (109). Donors who are near-drowning victims may acquire unusual moulds from contaminated water such as *Aphymysomyces elegans* (an agent of mucormycosis) and *Scedosporium apiospermum*, which may be transmitted with the organs (110,111). In both instances, the donors had a febrile illness with pulmonary infiltrates. Respiratory cultures after death ultimately grew *Scedosporium apiospermum* in one case (111). In the other report, none of the donor cultures, including endotracheal suction samples collected before death yielded a mould however, *A. elegans* from clinical samples in both kidney transplant recipients of the same donor had genotypically indistinguishable fingerprinting patterns (111). Another near-drowning victim in the same motor vehicle crash who also served as an organ donor did not transmit the infection to any of the recipients (111). The precise risk of transmissible infections in the setting of near drowning is unknown.

Donors with active invasive mould infections are not considered suitable for organ procurement. Slow growth of many filamentous fungi poses challenges to timely diagnosis. Nevertheless, awareness of situations where these infections are likely in the donor is important. Treatment of suspected or documented infection in the recipient due to aforementioned pathogens is summarized in Supporting Table S8.

Future Directions and Research

Donor-derived fungal infections have been reported largely as case reports and small series from individual centers and significant gaps in our knowledge base remain. With regards to candidiasis, a major unmet need is the assessment of precise sources of these infections, risk factors that lead to transmission and predictive value of preservation fluid cultures. A key issue with respect to diagnosis is the need to develop sensitive and reliable assays with a

*American Journal of Transplantation*
doi: 10.1111/j.1600-6143.2012.04100.x
rapid turn-around time that can be performed for screening of donors for active or prior infection. Optimal assays or biomarkers should be amenable to testing at the point of care and if necessary, directly on the available clinical specimens. Such research would have significant implications for timely recognition of these infections and for optimizing their management.

Contributors

Contributors and Donor-Derived Fungal Infections Working Group Members include the following:

Contributors (in alphabetic order) are as follows: Barbara D. Alexander, Duke University, Durham, NC; Maha Assi, University of Kansas, Wichita, KS; John W. Baddley, University of Alabama, Birmingham, AL; Janis E. Blair, Mayo Clinic, Scottsdale, AZ; Emily Blumberg, University of Pennsylvania, Philadelphia, PA; Steven D. Burdette, Wright State University, Dayton, OH; Cornelius J. Clancy, VA Pittsburgh Healthcare System University of Pittsburgh, Pittsburgh, PA; Graeme N. Forrest, Portland VA Medical Center, Portland, OR; Carlos A. Gomez, University of Pittsburgh, Pittsburgh, PA; Walter C. Hellingier, Mayo Clinic, Jacksonville, FL; Atul Humar, University of Alberta, Edmonton, Alberta, Canada; Shirish Huprikar, Mount Sinai School of Medicine, New York, NY; Michael G. Ison, Northwestern University Feinberg School of Medicine, Chicago, IL; Andre C. Kalil, University of Nebraska, Omaha; Camille N. Kotton, Massachusetts General Hospital, Boston, MA; Bernard M. Kubak, Ronald Reagan UCLA Medical Center & David Geffen School of Medicine at UCLA, Los Angeles, CA; Deepali Kumar, University of Alberta, Edmonton, Alberta, Canada; Marilyn E. Levi, University of Colorado, Denver, CO; Ajit P. Limaye, University of Washington, Seattle, WA; Olivier Lortholary, Institut Pasteur, Centre National de Référence Mycologie et Antifongiques and Université Paris Descartes, Hôpital Necker Enfants malades, APHP; Centre d’Infectiologie Necker Pasteur, Paris, France; Kieren A. Marr, Johns Hopkins University, Baltimore, MD; Steven D. Mawhorter, Cleveland Clinic, Cleveland, OH; Marian Michaels, University of Pittsburgh, Children’s Hospital Pittsburgh, Pittsburgh, PA; Michele I. Morris, University of Miami, Miami, FL; Kenneth J. Pursell, University of Chicago, Chicago, IL; Nasia Safdar, University of Wisconsin, Madison, WI; Nina Singh, University of Pittsburgh, Pittsburgh, PA; David van Duin, Cleveland Clinic, Cleveland, OH; and L. Joseph Wheat, MiraVista Diagnostics, Indianapolis, IN.

Acknowledgments

We thank Dr. Timothy L. Pruett (University of Minnesota, Minneapolis, MN); Dr. Robert J. Stratta (Wake Forest University, Winston Salem, NC) and Dr. Jose M. Aguado (University Hospital 12 de Octubre, Madrid, Spain) and Dr. Julian Torre-Cisneros (Reina Sofia University Hospital-MILIBIC, University of Córdoba, Spain) both from the Spanish Network for Research in Infectious Diseases (REIPI) for their thoughtful review of sections of the document. We are grateful to Courtney Wright and Christina Stamm (American Society of Transplantation) for logistical support under guidelines development.

References


Disclosure

Barbara D. Alexander, Grant/research support from Charles River Laboratories, Astellas and Pfizer, and consultant for bioMerieux, Bristol Myers Squibb and Becton Dickinson; John W. Baddley, Consultant for Pfizer, Merck and Abbott; Emily Blumberg, Data Safety Monitoring Board Pfizer; Cornelius J. Clancy, Investigator-initiated grant support from Pfizer, Merck and Astellas; David van Duin, Speaker for Astellas and consultant for Pfizer; Graeme N. Forrest, Research support from Astellas; Deepali Kumar, Honorary from Merck, Pfizer, Astellas and research support from Astellas and Merck; Kieren A. Marr, research grants from Astellas, Merck, Pfizer; advisory board and/or consultant for Astellas, Merck, Pfizer, Schering Plough; Michele l. Morris, Research funding from Astellas, Basilea and Pfizer, Speaker/Consultant/Advisory Group Participation—Merck, Pfizer, Astellas; Nina Singh, Investigator-initiated grant support from Pfizer, L. Joseph Wheat, President of MiraVista Diagnostics, a commercial laboratory that performs Histoplasma and coccidiodal antigen detection; There are no conflict of interest disclosures for other contributors.
Singh et al.


Singh et al.


Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Criteria for classification of donor-derived fungal infections

Table S2: Classification of donor-derived candidiasis in abdominal organ transplant recipients

Table S3: Classification of donor-derived cryptococcosis
**Table S4:** Classification of donor-derived endemic mycosis (histoplasmosis and coccidioiodomycosis)

**Table S5:** Summary of clinical studies with isolation of Candida species from preservation fluid and the association with graft-site candidiasis in kidney and kidney-pancreas transplant recipients

**Table S6:** Susceptibility patterns of Candida species

**Table S7:** Strengths and limitations of the diagnostic assays for coccidioiodomycosis

**Table S8:** Antifungal therapy for Aspergillus and other moulds (mucormycosis and scedosporiosis)

Figure S1: Map depicting endemic regions for histoplasmosis based on histoplasmin reactivity.

Figure S2: Evaluation and management of histoplasmosis in living donor based on clinical and radiographic findings during pretransplant workup.

Figure S3: Evaluation for histoplasmosis in deceased donor and recipient based on operative findings during transplantation.

Figure S4: Map depicting endemic regions for coccidioiodomycosis in the Americas.

Figure S5: Evaluation of living donor for coccidioidomycosis.

Figure S6: Evaluation of deceased donor for coccidioidomycosis.

*American Journal of Transplantation*
doi: 10.1111/j.1600-6143.2012.04100.x