Invasive Fungal Infections in Solid Organ Transplant Recipients

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Outlines

• Epidemiology
• Candidiasis
• Aspergillosis
• Cryptococcosis
No. (%) of Invasive Fungal Infection (IFI) Cases in the Surveillance Cohort, by Transplant Type

<table>
<thead>
<tr>
<th>IFI type</th>
<th>Kidney (n = 332)</th>
<th>Liver (n = 378)</th>
<th>Pancreas (n = 128)</th>
<th>Lung (n = 248)</th>
<th>Heart (n = 99)</th>
<th>Small bowel (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>164 (49)</td>
<td>255 (68)</td>
<td>97 (76)</td>
<td>56 (23)</td>
<td>48 (49)</td>
<td>19 (85)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>47 (14)</td>
<td>42 (11)</td>
<td>6 (5)</td>
<td>109 (44)</td>
<td>23 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zygomyces</td>
<td>8 (2)</td>
<td>9 (2)</td>
<td>0 (0)</td>
<td>8 (3)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other mold</td>
<td>10 (3.0)</td>
<td>9 (2.4)</td>
<td>4 (3.1)</td>
<td>49 (19.8)</td>
<td>7 (7.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unspecified mold</td>
<td>7 (2.1)</td>
<td>8 (2.1)</td>
<td>0 (0.0)</td>
<td>7 (2.8)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>49 (15)</td>
<td>24 (6)</td>
<td>6 (5)</td>
<td>6 (2)</td>
<td>10 (10)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Endemic mycoses</td>
<td>33 (10)</td>
<td>17 (5)</td>
<td>8 (6)</td>
<td>3 (1)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumocystosis</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>4 (2)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other yeast</td>
<td>6 (1.8)</td>
<td>9 (2.4)</td>
<td>5 (3.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unspecified yeast</td>
<td>3 (0.9)</td>
<td>5 (1.3)</td>
<td>1 (0.8)</td>
<td>6 (2.4)</td>
<td>0 (0.0)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Pappas et al. Clin Infect Dis 2010
Twelve-month cumulative incidence (CI) estimates of IFI in incidence cohort of TRANSNET

- May 2002 to May 2005: 501 episodes of the first IFI developed in 16,459 SOT recipients
- Overall: 3.1% in 15 sites
- Small bowel: 11.6% in 1 site
- Lung and heart-lung: 8.6% in 11 sites
- Liver: 4.7% in 15 sites
- Pancreas and kidney-pancreas: 4.0% in 15 sites
- Heart transplant recipients: 3.4% in 13 sites
- Kidney: 1.3% in 15 sites

Pappas et al. Clin Infect Dis 2010

The 12-month CI estimates of the first IFI of each specific IFI type

- Invasive candidiasis: 1.9%
- Invasive aspergillosis: 0.7%
- Cryptococcocosis, mold infections other than aspergillosis or mucormycosis, and endemic fungal infections: ~0.2%
- All other IFI types: <0.1%

Pappas et al. Clin Infect Dis 2010
Invasive Candidiasis (IC) in TRANSNET

- 639 cases with IC
  - *Candida albicans*: 46.3%
  - *Candida glabrata*: 24.4%
  - *Candida parapsilosis*: 8.1%
  - 68 cases >1 *Candida* species
- The most common IC sites
  - Bloodstream: 44%
  - Intra-abdominal infection: 14%
- The median time to onset: 80 days
  - Early (<30 days): 33.3%
  - Late (>30 days): 66.7%

- Transplant organ type
  - Liver: 41.1%
  - Kidney: 35.3%
  - Kidney-pancreas: 9.1%
  - Lung: 8.7%
- Allograft rejection: 38%
- Receiving antifungal prophylaxis at the time of IC: nearly 40%
  - Triazole 29.9%
  - Amphotericin B 6.1%
  - Echinocandins 3.9%

The 90-day survival by *Candida* species

- *C. albicans*: 77.4%
- *C. glabrata*: 68.5%
- *C. krusei*: 68.5%
- *C. parapsilosis*: 64.8%

Overall 73.5%
Risk factors for Candida infection and recommended prophylactic strategies

<table>
<thead>
<tr>
<th>Organ</th>
<th>Risk factors</th>
<th>Antifungal prophylaxis</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Prolonged or repeat operation</td>
<td>Fluconazole 400 mg/day</td>
<td>Up to 4 weeks or until resolution of risk factors</td>
</tr>
<tr>
<td></td>
<td>Retransplantation</td>
<td>LFAmB 3–5 mg/kg/day(^1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Choledocho-jejunostomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Candida</em> colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High transfusion requirement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>Graft rejection/dysfunction</td>
<td>Fluconazole 400 mg/day</td>
<td>At least 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Enhanced immunosuppression</td>
<td>LFAmB 3–5 mg/kg/day(^1)</td>
<td>Until healing of anastomosis and absence of rejection</td>
</tr>
<tr>
<td></td>
<td>Anastomotic disruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal reoperation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Multivisceral transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Enteric drainage</td>
<td>Fluconazole 400 mg/day</td>
<td>At least 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Vascular thrombosis</td>
<td>LFAmB 3–5 mg/kg/day(^1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postperfusion pancreatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)If high rates of *non-albicans* spp or risk factors for *Aspergillus*.


Recommendations for the prevention of IFI in LTx – A European perspective

- If one major or two minor criteria:
  - Micafungin (A–II)
  - Caspofungin (A–II)
  - Lip-AB IV (A–II)
  - AB lipid complex IV (A–II)
  - Anidulafungin (B–III)

- 2–4 weeks or until resolution of risk factors

Clin Microbiol Infect 2014; 20 (Suppl. 7): 27–48
Invasive Candidiasis

• Breakthrough IC cases in TRASNET
  • Triazole prophylaxis: *C. glabrata*
  • Echinocandin prophylaxis: *C. parapsilosis* (11.5%, 6/52)

Summary of echinocandin prophylaxis in high-risk liver transplant recipients

<table>
<thead>
<tr>
<th>Author</th>
<th>SOT (case No.)</th>
<th>Agent (case No.; IFI %)</th>
<th>High-risk</th>
<th>Comparator (case No.; IFI %)</th>
<th>Breakthrough (case No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguado</td>
<td>SOT (62)</td>
<td>Anidulafungin (62, NA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fortun</td>
<td>Liver (71)</td>
<td>Caspofungin (71, <strong>2.8%</strong>)</td>
<td>Yes</td>
<td>NA</td>
<td><em>Mucor</em> spp (1); <em>C. albicans</em> (1)</td>
</tr>
<tr>
<td>Sun</td>
<td>Liver (42)</td>
<td>Micafungin (18, <strong>8.3%</strong>)</td>
<td>Yes</td>
<td>L-AmB (24, <strong>11.1%</strong>)</td>
<td>Invasive candidiasis (2)</td>
</tr>
<tr>
<td>Saliba</td>
<td>Liver (344)</td>
<td>Micafungin (172, <strong>2.4%</strong>)</td>
<td>Yes</td>
<td>Flu/L-AmB/Caspo (172, <strong>4.7%</strong>)</td>
<td>Aspergillosis (2); Candidiasis (2)</td>
</tr>
<tr>
<td>Winston</td>
<td>Liver (200)</td>
<td>Anidulafungin (100, <strong>5.1%</strong>)</td>
<td>Yes</td>
<td>Fluconazole (100, <strong>8.0%</strong>)</td>
<td>Candidiasis (5)</td>
</tr>
</tbody>
</table>

Fortun J, et al. Transplantation 2009
Sun HY, et al. Transplantation 2013
Winston Am J Transplant 2014
Timeline chart of *C. auris* reported cases


Worldwide distribution of *C. auris* reported cases

Donor-Derived Transmission of *Candida auris* During Lung Transplantation

Marwan M. Azar,1,2 Sarah E. Turbitt,3,4 Jay A. Fishman,3,4 and Virginia M. Pierce1,2,5

1Department of Pathology, Massachusetts General Hospital, 2Department of Pathology, Harvard Medical School, 3Department of Medicine, Massachusetts General Hospital, 4Department of Medicine, Harvard Medical School, and 5Department of Pediatrics, Massachusetts General Hospital, Boston

The donor: bronchiectasis

The recipient: idiopathic pulmonary fibrosis

BAL specimens: *Candida haemulonii* → *C. auris*


Invasive Aspergillosis

- 1–15% of the SOT recipients
- Mortality rate in transplant recipients with IA historically has ranged from 65% to 92%
  - currently reported mortality rate in IA among SOT recipients is 22%

Risk factors for invasive aspergillosis in organ transplant recipients

- **Liver transplant recipients**
  - Re-transplantation
  - Renal failure, particularly requiring renal replacement therapy
  - Transplantation for fulminant hepatic failure
  - Reoperation

- **Lung transplant recipients**
  - Single lung transplant
  - Early airway ischemia
  - Cytomegalovirus infection
  - Rejection and augmented immunosuppression
  - Pre-transplant *Aspergillus* colonization
  - Post-transplant *Aspergillus* colonization within a year of transplant
  - Acquired hypogammaglobulinemia (IgG < 400 mg/dL)

Risk factors for invasive aspergillosis in organ transplant recipients

• Heart transplant recipients
  • Isolation of *Aspergillus* species in respiratory tract cultures
  • Reoperation
  • CMV disease
  • Post-transplant hemodialysis
  • Existence of an episode of invasive aspergillosis in the program 2 months before or after heart transplant

• Kidney transplant recipients
  • Graft failure requiring hemodialysis
  • High and prolonged duration of corticosteroids


Recommendations for prophylaxis for invasive aspergillosis in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Organ</th>
<th>Risk factors</th>
<th>Antifungal prophylaxis</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Presence of some of these risk factors (II-IV)</td>
<td>Inhaled amphotericin B 8 mg/q2 or 25 mg/day OR</td>
<td>Preferably guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors.</td>
</tr>
<tr>
<td></td>
<td>Pretransplant <em>Aspergillus</em> colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posttransplant <em>Aspergillus</em> colonization within a year of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of more than one of these risk factors (II-III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Induction with alemtuzumab or thymoglobulin</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Single lung transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Aspergillus</em> colonization following cytomegalovirus infection</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Rejection and augmented immunity and anti-platelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunosuppression (particularly use of monoclonal antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>posttransplant with <em>Aspergillus</em> colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acquired hypogammaglobulinemia (IgG &lt; 400 mg/dL)</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Inhaled Abelcet 50 mg QD OR</td>
<td>Once every 2 days for 2 weeks and then once per week for at least 13 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhaled Ambisome 25mg QD OR</td>
<td>Three times/week for 2 months, followed by weekly administration for 8 months and twice per month afterwards</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole 200 mg bid QD OR</td>
<td>4 months or longer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itraconazole 200 mg bid QD</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations for prophylaxis for invasive aspergillosis in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Organ</th>
<th>Risk factors</th>
<th>Antifungal prophylaxis</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver II-2</td>
<td>Re-transplantation</td>
<td>Lipid formulation of amphotericin B (3-5 mg/kg/day) or an echinocandin</td>
<td>Initial hospital stay or for 4 weeks posttransplant</td>
</tr>
<tr>
<td></td>
<td>Renal failure, particularly requiring renal replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reoperation involving thoracic or abdominal cavity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart II-3</td>
<td>Isolation of Aspergillus species in respiratory tract cultures</td>
<td>Itraconazole 200 mg bid</td>
<td>50-150 days</td>
</tr>
<tr>
<td></td>
<td>Reoperation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV disease</td>
<td>OR voriconazole 200 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posttransplant hemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Existence of an episode of IA in program 2 months before or after heart transplant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Treatment of invasive aspergillosis

- **Primary therapy**
  - Voriconazole

- **Alternative therapy**
  - AmBisome 3-5 mg/kg/day
  - Abelcet 5 mg/kg/day
  - Caspofungin 70 mg/day day 1 and 50 mg/day thereafter
  - Micafungin 100-150 mg/day
  - Posaconazole 200 mg qid initially and then 400 mg bid PO
  - Itraconazole 200-400 mg/kg/day orally

Proposed approach to combination antifungal therapy in the management of IA

Invasive aspergillosis

Reduction of immunosuppression

Consideration of stopping steroids and antimetabolites

Reducing CNI or mTOR inhibitor doses

SOT recipient with mild disease

Voriconazole monotherapy; if intolerance or skin cancer, isavuconazole instead. Posaconazole and itraconazole are alternatives.

If disease is refractory, liposomal amphotericin B or combination with anazole and echinocandin can be considered

SOT recipient with moderate-to-severe disease

May use voriconazole and an echinocandin as primary therapy.

May stop echinocandin once voriconazole trough is therapeutic (≥ 1 mcg/mL).

Consider adding liposomal amphoterin B in CNS, recalcitrant, or drug-resistant infection

HCT recipient

May use voriconazole and an echinocandin as primary therapy, especially in patients with high serum galactomannans or refractory and profound neutropenia

Haidar G, et al. Transplantation 2018
Drug Resistant *Aspergillus fumigatus*: Shaded areas show countries reporting *A. fumigatus* strains with TR34/L98H and TR46/Y121F/T289A resistance mechanism in clinical or environmental isolates

Verweij et al. CID 2015

Other strategies

- New agents
  - Isavuconazole
  - Oral (encocheated) formulation of amphotericin B
  - A highly bioavailable formulation of itraconazole (SUBA-itraconazole)

Haidar G, et al. Transplantation 2018
https://clinicaltrials.gov/ct2/show/NCT03167957
Lindsay J, et al. J Antimicrobial Ther 2017

Presented at Regional MMTN 15-18 Nov 2018. © Copyright of speaker. All rights reserved.
Cryptococcosis

• The third most commonly occurring invasive fungal infection in SOT recipients
• The overall incidence of cryptococcosis in SOT recipients ranges from 0.2% to 5%
• Typically a late-occurring infection; the median time to onset usually ranges from 16 to 21 months post-transplantation
• Mortality in SOT recipients with cryptococcosis has ranged from 33% to 42%, may be as high as 49%
  • 14% in the current era


Cryptococcosis in Patients With Cirrhosis of the Liver and Posttransplant Outcomes

• Cirrhosis-associated compromised host defenses
  • impaired cell-mediated immunity, phagocytic dysfunction, decreased antibody and immunoglobulins, and complement deficiency
• A total of 112 patients with liver cirrhosis and cryptococcosis
  • 90-day mortality: 57.1% (64/112)
• Liver transplantation was performed in 8 (20.5%) patients among 39 patients listed for transplantation
  • Two with active but unrecognized disease before transplantation
  • The median duration of antifungal use before liver transplantation: 42.5 days (IQR, 8-130 days)
  • One (12.5%, 1/8) died on Day 249 unrelated to fungal infection.
• Transplantation after recent cryptococcal disease
  • may not be a categorical exclusion and
  • may be cautiously undertaken in patients who are otherwise deemed clinically stable

Unrecognized Pre-transplant and Donor-Derived Cryptococcal Disease in Organ Transplant Recipients

- **Very early-onset** disease (< 30 days) developed in 9 (5%) of the 175 patients at a mean of 5.7 days after transplantation
  - Very early cases were more likely to present with disease at unusual locations
    - transplanted allograft and surgical fossa/site infections (55.6% [5/9] vs. 7.2% [12/166]; P <.001).
  - Two cases with onset on day 1 after OP
    - the result of undetected pre-transplant disease
  - Five cases involving the allograft or surgical sites (lung [1]; CNS, lung, abdominal cavity, blood [1]; heart & lung [1]; biliary tract [1]; biliary tract, GU, blood [1])
    - the result of donor-acquired infection

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**CASE REPORT**

A cluster of donor-derived *Cryptococcus neoformans* infection affecting lung, liver, and kidney transplant recipients: Case report and review of literature

Jose F. Camargo¹ | Jacques Simkins¹ | Denise C. Schain² | A. Adrian Gonzalez² | Maria L. Alcaide¹ | Shweta Anjan¹ | Giselle Guerra³ | David Roth³ | Warren L. Kupin¹ | Adela Mattiazi³ | Yaohong Tan⁴ | Clara Milikowski⁴ | Michele I. Morris¹ | Lilian M. Abbo¹

1. The **onset** of illness in the **kidney** (Day 60) and **liver** (Day 102) recipients occurred more than 8-12 weeks after transplantation. For lung recipients, the onset was Day 5.
2. The **donor** was a case of diabetes and alcohol abuse. He presented with nausea and vomit. Brain CT showed several bilateral subacute infarcts and chest CT RLL pneumonia. His **blood** and **BAL** cultures later grew *C. neoformans*.

Camargo JF, et al. Transpl Infect Dis 2018
Antifungal therapy for cryptococcal disease in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Meningoencephalitis or disseminated disease</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td></td>
</tr>
<tr>
<td>Preferred therapy</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B 3–4 mg/kg/day or</td>
<td>Minimum of</td>
</tr>
<tr>
<td>Amphotericin B lipid complex 5 mg/kg/day</td>
<td>2 weeks</td>
</tr>
<tr>
<td>plus flucytosine 100 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Alternative therapy</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B 3–4 mg/kg/day or</td>
<td>Minimum of</td>
</tr>
<tr>
<td>Amphotericin B lipid complex 5 mg/kg/day</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td>Consolidation</td>
<td></td>
</tr>
<tr>
<td>Fluconazole 400–800 mg/day</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
</tr>
<tr>
<td>Fluconazole 200–400 mg/day</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic or mild-to-moderate disease</td>
<td></td>
</tr>
<tr>
<td>Fluconazole 400 mg/day</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Severe pulmonary disease, or azole use not</td>
<td></td>
</tr>
<tr>
<td>an option</td>
<td></td>
</tr>
<tr>
<td>Same as for CNS disease</td>
<td></td>
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</tbody>
</table>

Lipid formulations of Amphotericin B significantly improve outcome in solid-organ transplant recipients with central nervous system cryptococcosis

Lipid formulation AmB

Factors associated with mortality at 90 day

<table>
<thead>
<tr>
<th>Variables</th>
<th>References</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>No renal failure</td>
<td>4.61 (1.02 – 20.80)</td>
</tr>
<tr>
<td>Fungemia</td>
<td>No fungemia</td>
<td>10.66 (2.08 – 54.55)</td>
</tr>
<tr>
<td>Lipid-AmBd</td>
<td>AmBd</td>
<td>0.11 (0.02 – 0.57)</td>
</tr>
</tbody>
</table>

Proposed pathogenesis of Immune Reconstitution Inflammatory Syndrome (IRIS)

Features of IRIS in patients with cryptococcosis (III)

1. New or worsening appearance of any of the following manifestations:
   (a) CNS: Clinical or radiographic manifestations consistent with inflammatory process, such as contrast enhancing lesions on neuroimaging studies (CT or MRI); CSF pleocytosis, defined as >5 white blood cells; or increased intracranial pressure, that is, opening pressure >20 mm of water (with or without hydrocephalus).
   (b) Lymph nodes, skin or soft tissue lesions, for example, cellulitis or abscesses.
   (c) Pulmonary, for example, nodular, cavitary, mass lesions, pleural effusions (detected by chest radiography or CT).
   (d) Other focal tissue involvement with histopathology showing granulomatous lesions and
2. Symptoms occurred during receipt of appropriate antifungal therapy and could not be explained by a newly acquired infection and
3. Negative results of cultures for C. neoformans during the diagnostic workup for the inflammatory process.

Note: Table constructed from references (75, 78, 79).
Predictors of Immune Reconstitution Inflammatory Syndrome (IRIS) in Organ Transplant Recipients With Cryptococcosis

- Of 89 SOT recipients, 13 (14%) developed IRIS
- Factors independently associated with IRIS
  - Central nervous system (CNS) disease (adjusted odds ratio [AOR], 6.23; P = .03)
  - Discontinuation of calcineurin inhibitor (AOR, 5.11; P = .02)
- Percentage of patients developing IRS ($X^2$ for trend, p=0.0001)
  - 0 factor: 2.6% (1/13)
  - 1 factor: 18.8% (6/32)
  - 2 factors: 50% (6/12)

Summary

- Despite highly effective antifungal prophylaxis for candidiasis in SOT recipients, breakthrough IFI occurs.

- Emergence of drug-resistance Candida and Aspergillus species poses significant challenges in patient care.

- Immune Reconstitution Inflammatory Syndrome (IRIS) also occurs in SOT recipients with cryptococcosis.
Thank you!