Invasive Fungal Infections in Solid Organ Transplant Recipients

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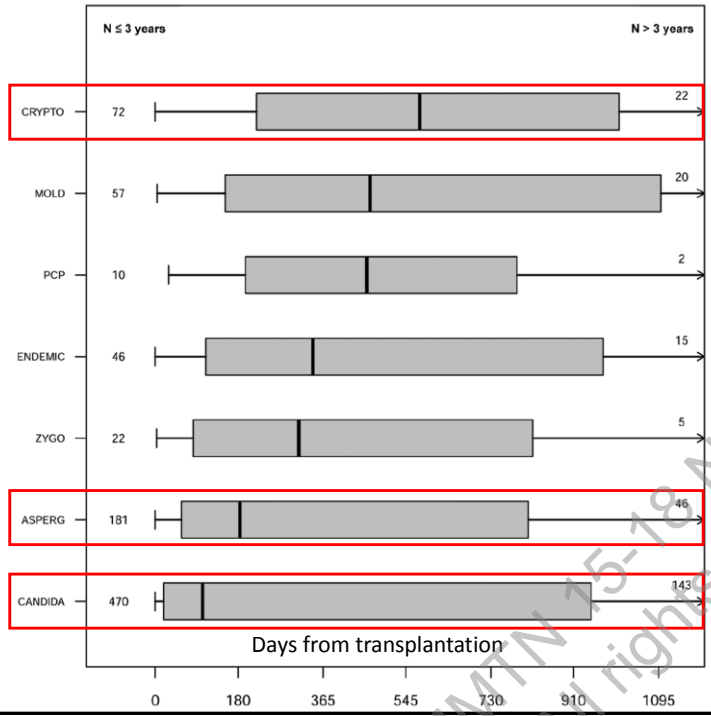
Outlines

- Epidemiology
- Candidiasis
- Aspergillosis
- Cryptococcosis



TRANSNET
23 centers
Surveillance cohort
N=1,063 SOT recipients
IFI, n=1,208
Mar 2001 to Mar 2006

Pappas et al. Clin Infect Dis 2010

No. (%) of Invasive Fungal Infection (IFI) Cases in the Surveillance Cohort, by Transplant Type

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

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

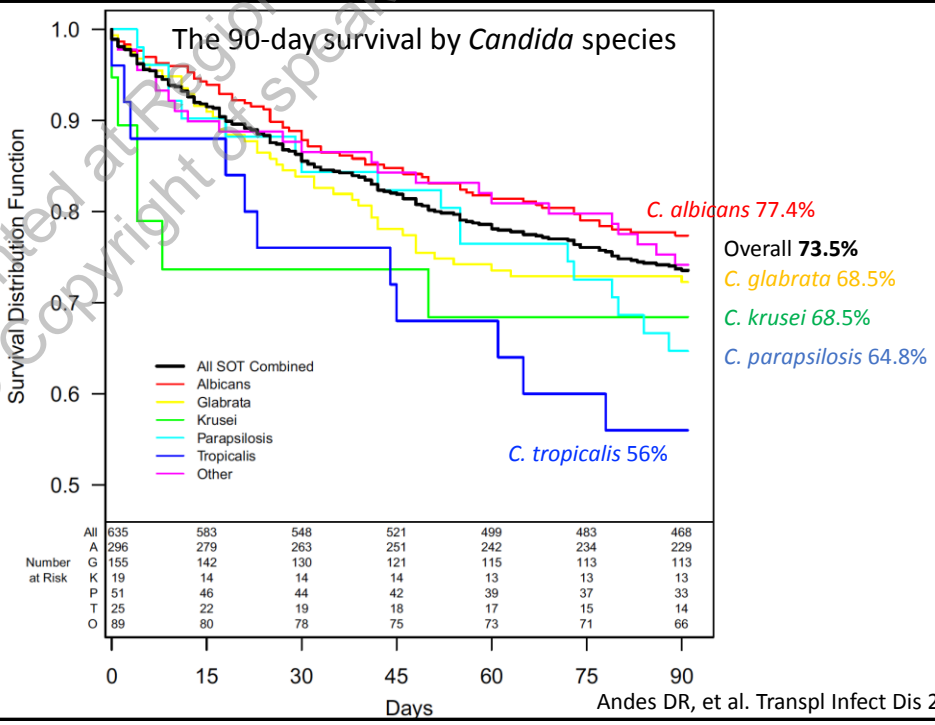
- Invasive candidiasis: 1.9%
- Invasive aspergillosis: 0.7%
- Cryptococcosis, mold infections other than aspergillosis or mucormycosis, and endemic fungal infections: ~0.2%
- All other IFI types: <0.1%

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%

Andes DR, et al. Transpl Infect Dis 2016



Andes DR, et al. Transpl Infect Dis 2016

Risk factors for Candida infection and recommended prophylactic strategies

Organ	Risk factors	Antifungal prophylaxis	Duration
Liver	Prolonged or repeat operation Retransplantation Renal failure Choledocho-jejunostomy *Candida* colonization High transfusion requirement	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	Up to 4 weeks or Until resolution of risk factors
Small bowel	Graft rejection/dysfunction Enhanced immunosuppression Anastomotic dysruption Abdominal reoperation Multivisceral transplantation	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks Until healing of anastomosis and absence of rejection
Pancreas	Enteric drainage Vascular thrombosis Postperfusion pancreatitis	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks

[1]If high rates of non-*albicans* spp or risk factors for *Aspergillus*.

Silveira FP, et al. Am J Transplantation 2013

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)

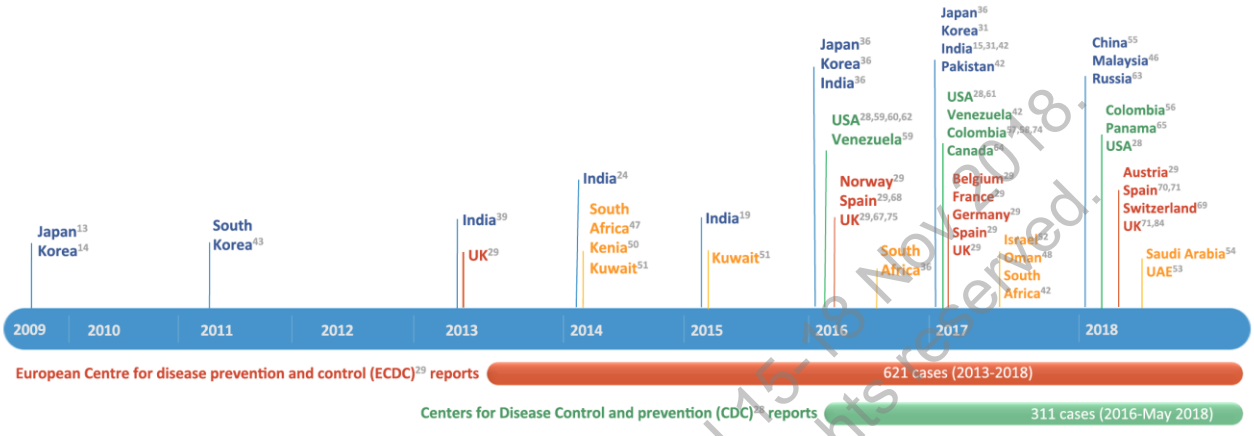
Andes DR, et al. Transpl Infect Dis 2016

Summary of echinocandin prophylaxis in high-risk liver transplant recipients

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

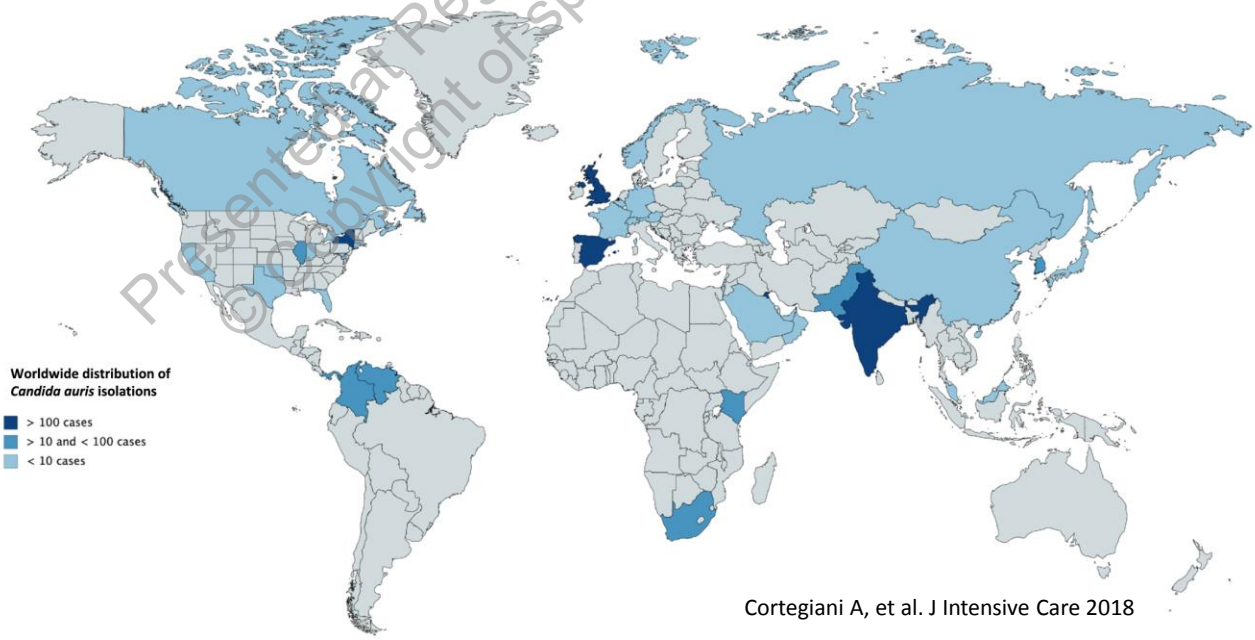
Pappas PG, et al. Am J Transplant 2006
Fortun J, et al. Transplantation 2009
Sun HY, et al. Transplantation 2013
Saliba F, et al. Clin Infect Dis 2015
Winston Am J Transplant 2014

Timeline chart of *C. auris* reported cases



Cortegiani A, et al. J Intensive Care 2018

Worldwide distribution of *C. auris* reported cases



Cortegiani A, et al. J Intensive Care 2018

Clinical Infectious Diseases

BRIEF REPORT

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

Marwan M. Azar,[1,2] Sarah E. Turbett,[3,4] Jay A. Fishman,[3,4] and Virginia M. Pierce[1,2,5]

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

The donor: bronchiectasis
The recipient: idiopathic pulmonary fibrosis
BAL specimens: *Candida haemulonii* → *C. auris*

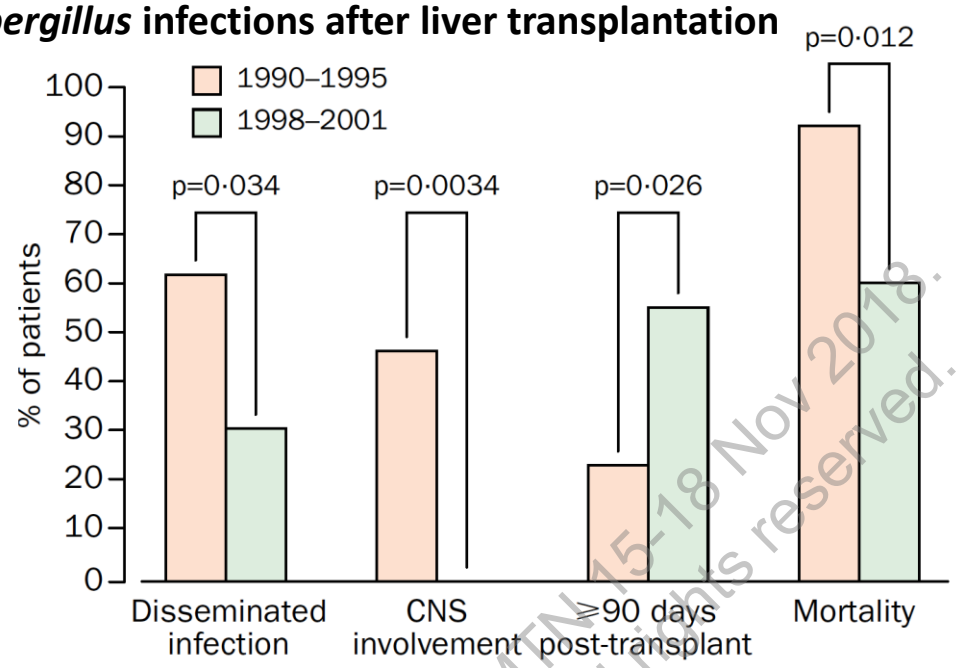
Azar MM, et al. Clin Infect Dis 2017

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%

Singh N, et al. Am J Transplant 2013

Aspergillus infections after liver transplantation



Singh N, et al. Lancet Infect Dis 2003

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)

Singh N, et al. Am J Transplant 2013

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

Singh N, et al. Am J Transplant 2013

Recommendations for prophylaxis for invasive aspergillosis in solid organ transplant recipients

Organ	Risk factors	Antifungal prophylaxis	Duration
Lung	**Presence of one of these risk factors (II-2)**	Inhaled amphotericin B 6 mg/q8 or 25 mg/day	Preferably guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors.
	Pretransplant *Aspergillus* colonization	OR	
	Posttransplant *Aspergillus* colonization within a year of transplant		
	Presence of more than one of these risk factors (II-3,III)		
	Induction with alemtuzumab or Thymoglobulin	Inhaled Abelcet 50 mg	Once every 2 days for 2 weeks and then once per week for at least 13 weeks
	Single lung transplant	OR	
	Aspergillus colonization following cytomegalovirus infection	Inhaled Ambisome 25mg	Three times/week for 2 months, followed by weekly administration for 6 months and twice per month afterwards
	Rejection and augmented Immunosuppression (particularly use of monoclonal antibody posttransplant with *Aspergillus* colonization)	OR	
		Voriconazole 200 mg bid	
		OR	
	Acquired hypogammaglobulinemia (IgG < 400 mg/dL)	Itraconazole 200 mg bid	4 months or longer

Singh N, et al. Am J Transplant 2013

Recommendations for prophylaxis for invasive aspergillosis in solid organ transplant recipients

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

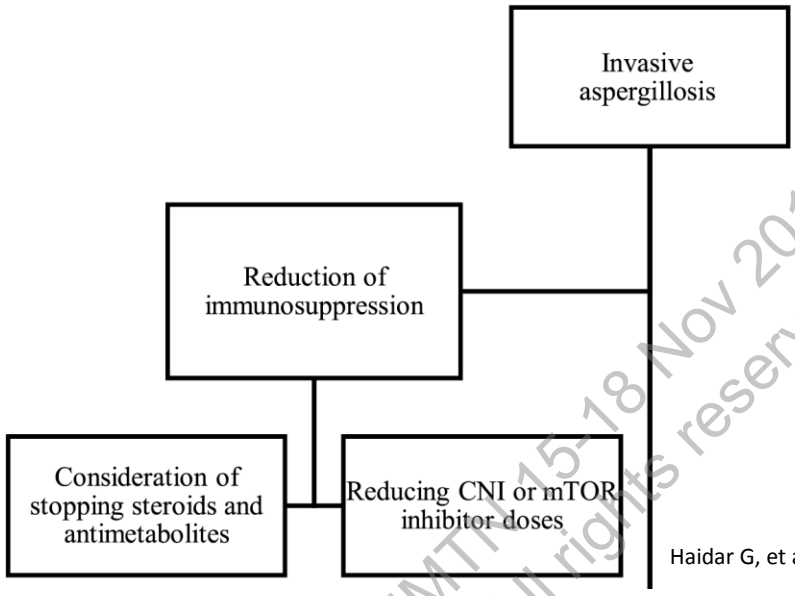
Singh N, et al. Am J Transplant 2013

Treatment of invasive aspergillosis

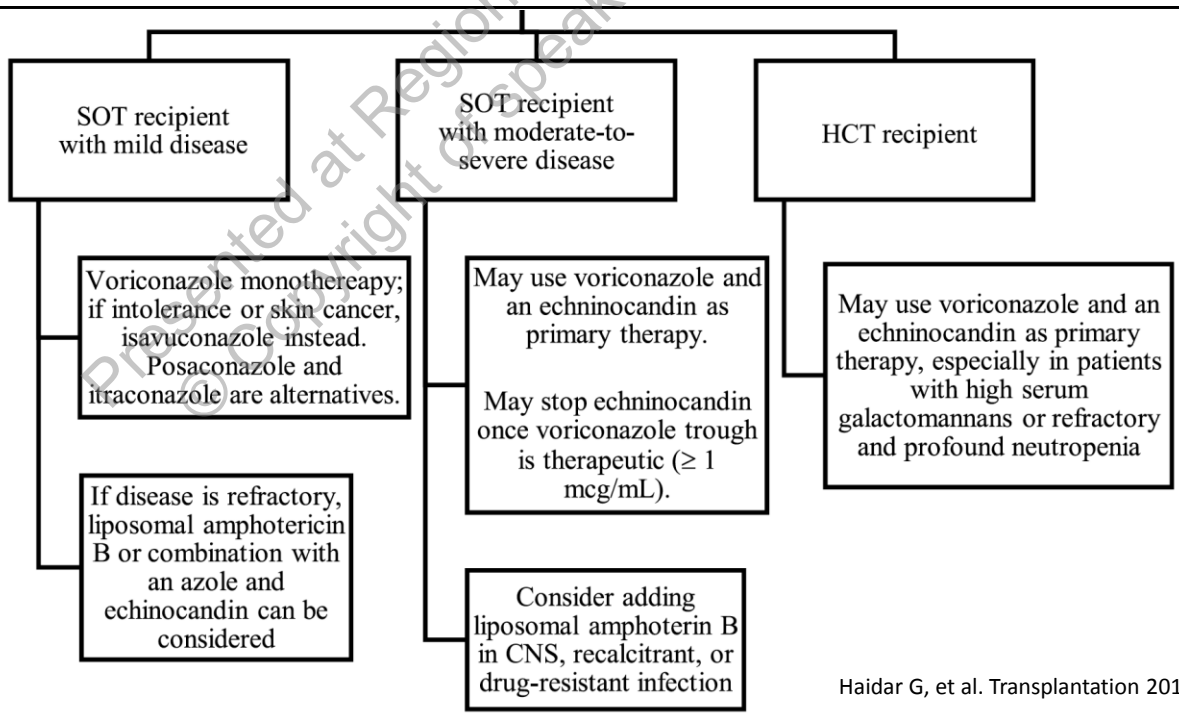
- Primary therapy
  - Voriconazole
- Alternative therapy
  - AmBisome 3-5 mg/kg/day
  - Abelcet 5 mg/kg/day
  - Caspofungin 70 mg/day day 1 and 50 mg/day thereafter
  - Micafungin 100-150 mg/day
  - Posaconazole 200 mg qid initially and then 400 mg bid PO
  - Itraconazole 200-400 mg/kg/day orally

Singh N, et al. Am J Transplant 2013
Patterson TF, et al. Clin Infect Dis 2016

Proposed approach to combination antifungal therapy in the management of IA



Haidar G, et al. Transplantation 2018



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 (encochleated) 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

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

Baddley JW, et al. Am J Transplantation 2013

Original Clinical Science

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

Singh N, et al. Transplantation 2015

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

Sun HY, et al. Clin Infect Dis 2011

CASE REPORT

WILEY

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

Jose F. Camargo[1] | Jacques Simkins[1] | Denise C. Schain[2] | A. Adrian Gonzalez[2] | Maria L. Alcaide[1] | Shweta Anjan[1] | Giselle Guerra[3] | David Roth[3] | Warren L. Kupin[3] | Adela Mattiazzi[3] | Yaohong Tan[4] | Clara Milikowski[4] | Michele I. Morris[1] | Lilian M. Abbo[1]

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*.

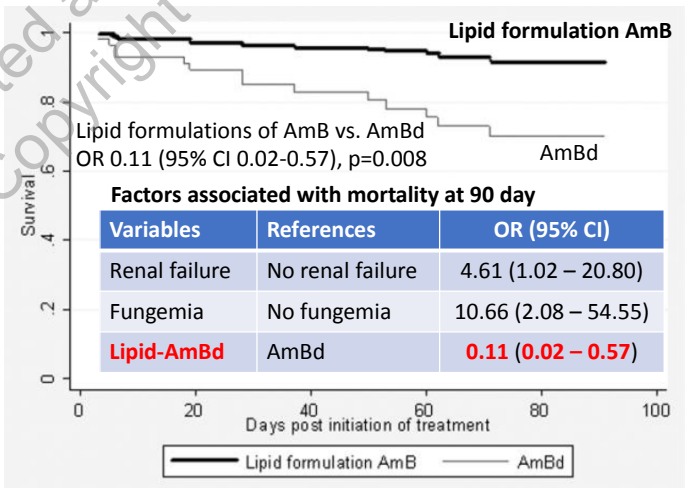
Camargo JF, et al. Transpl Infect Dis 2018

Antifungal therapy for cryptococcal disease in solid organ transplant recipients

Meningoencephalitis or disseminated disease	
Induction	Duration
Preferred therapy	
Liposomal amphotericin B 3–4 mg/kg/day or Amphotericin B lipid complex 5 mg/kg/day plus flucytosine 100 mg/kg/day[1]	Minimum of 2 weeks
Alternative therapy	
Liposomal amphotericin B 3–4 mg/kg/day or Amphotericin B lipid complex 5 mg/kg/day	Minimum of 4–6 weeks
Consolidation	
Fluconazole 400–800 mg/day	8 weeks
Maintenance	
Fluconazole 200–400 mg/day	6–12 months
Pulmonary Disease	
Asymptomatic or mild-to-moderate disease	
Fluconazole 400 mg/day	6–12 months
Severe pulmonary disease, or azole use not an option	
Same as for CNS disease	

Baddley JW, et al. Am J Transplantation 2013

Lipid Formulations of Amphotericin B Significantly Improve Outcome in Solid-Organ Transplant Recipients with Central Nervous System Cryptococcosis

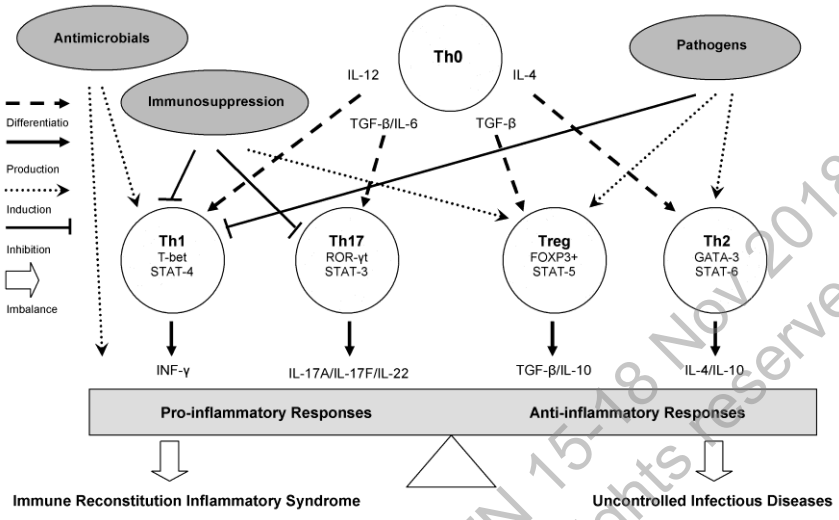


Factors associated with mortality at 90 day

Variables	References	OR (95% CI)
Renal failure	No renal failure	4.61 (1.02 – 20.80)
Fungemia	No fungemia	10.66 (2.08 – 54.55)
Lipid-AmBd	AmBd	**0.11 (0.02 – 0.57)**

Sun HY, et al. Clin Infect Dis 2009

Proposed pathogenesis of Immune Reconstitution Inflammatory Syndrome (IRIS)



Sun HY, Singh N. Curr Opin Infect Dis 2009

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).

Baddley JW, et al. Am J Transplantation 2013

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)

Sun HY, et al. Clin Infect Dis 2015

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!