Prevention of Fungal Infections: What is the Evidence for Antifungals?

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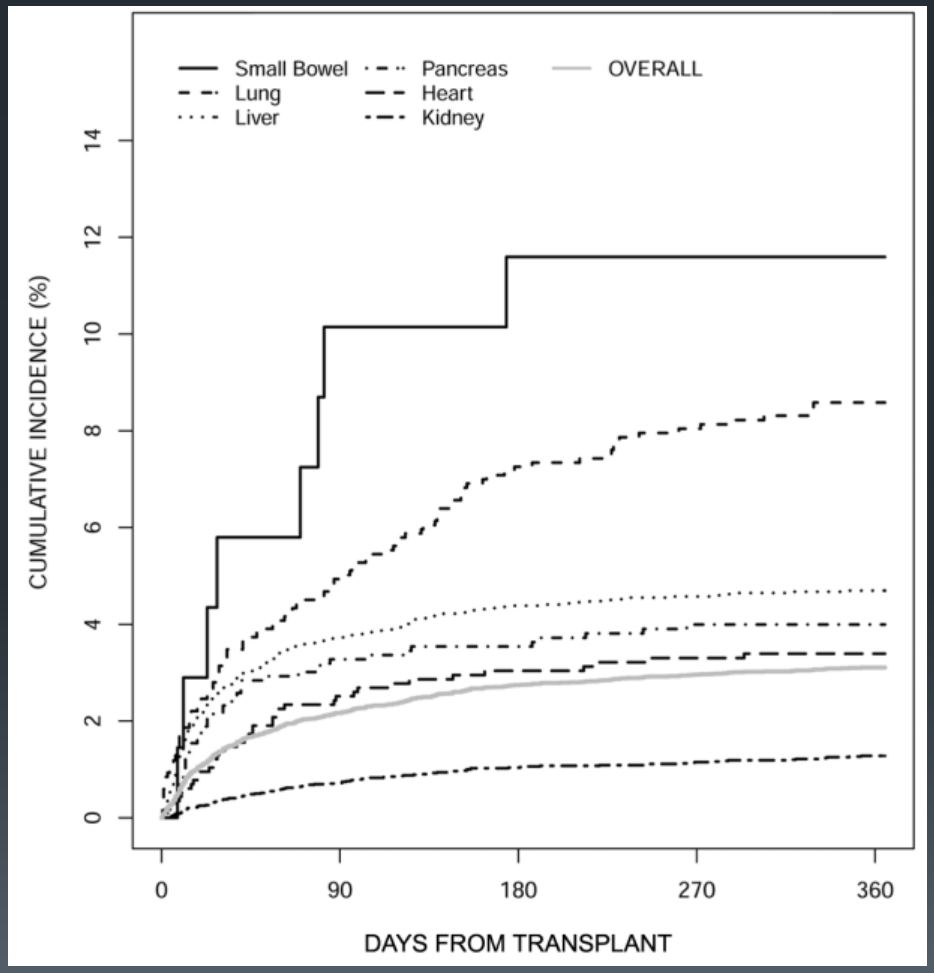
General Principles for Prophylaxis

- Risk of infection
- Potential severity of the consequences of disease
- Effectiveness of prophylaxis
- Consequences of prophylaxis for that individual patient

EPIDEMIOLOGY

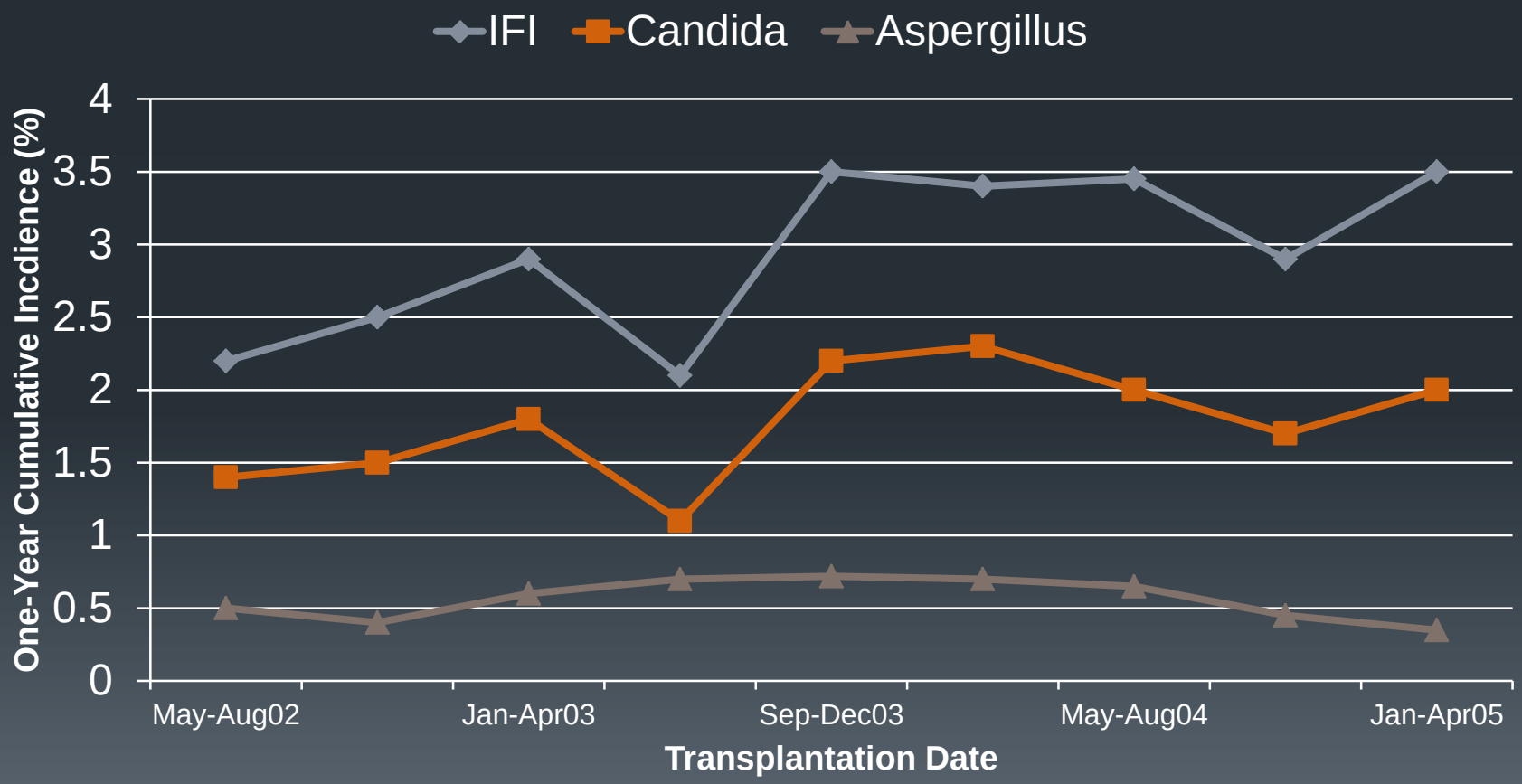
Risk of Fungal Infection

Cumulative Incidence of IFI in SOT



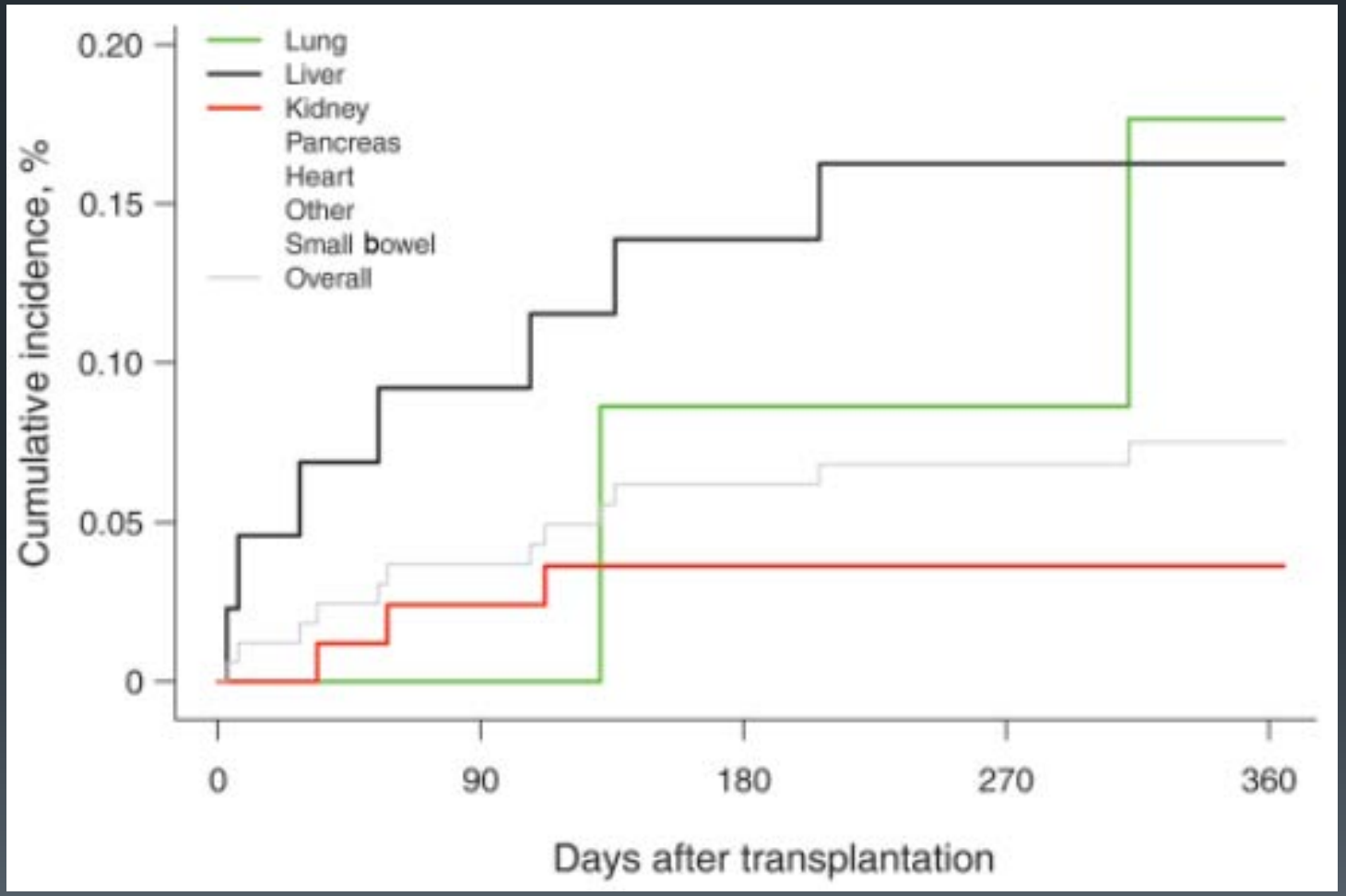
Pappas P Clin Infect Dis. 2010 Apr 15;50(8):1101-11

1-Year Cumulative Incidence of IFI, *Candida* and *Aspergillus* Infection



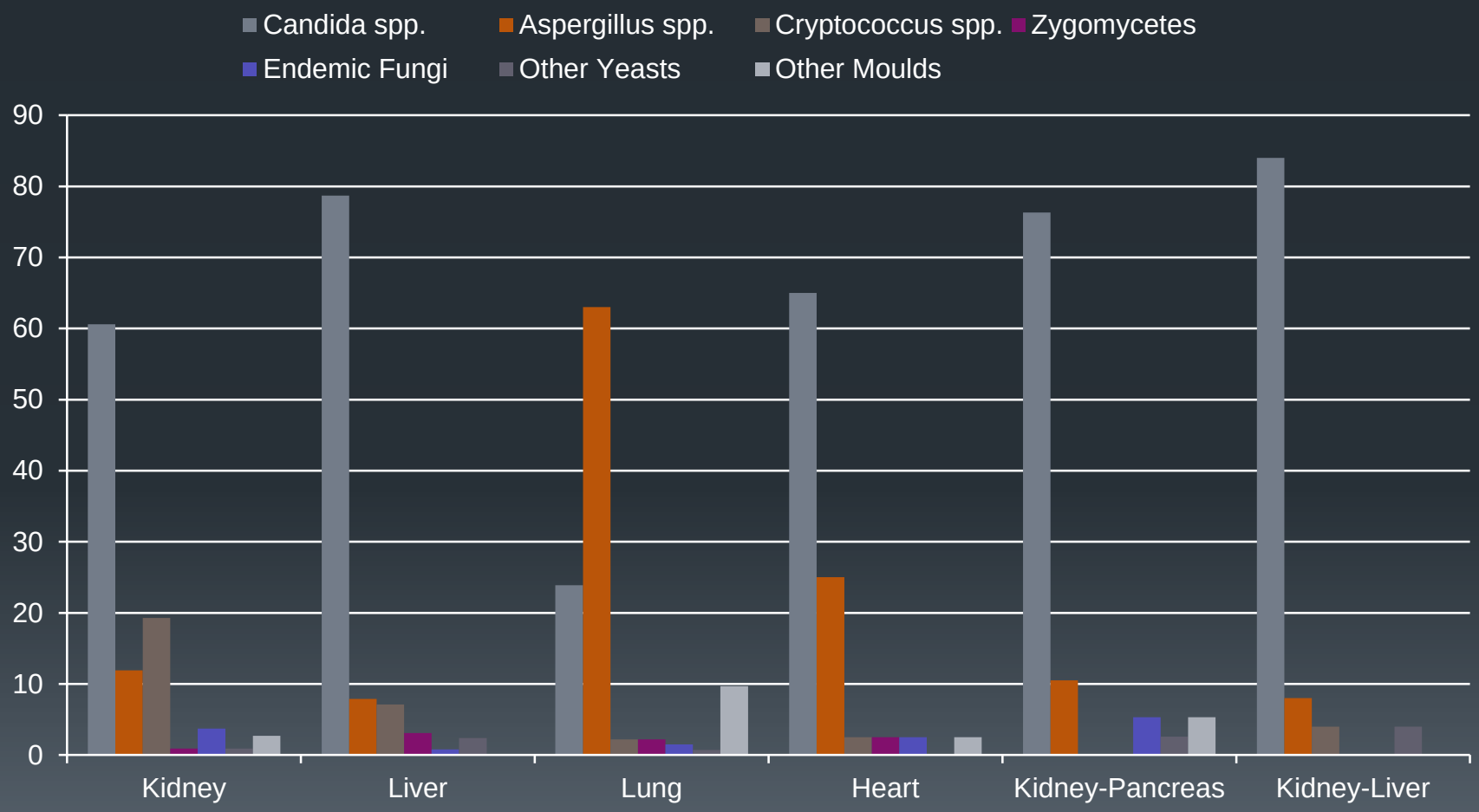
Pappas et al. CID 2010;50

Invasive Mucoralis in SOT



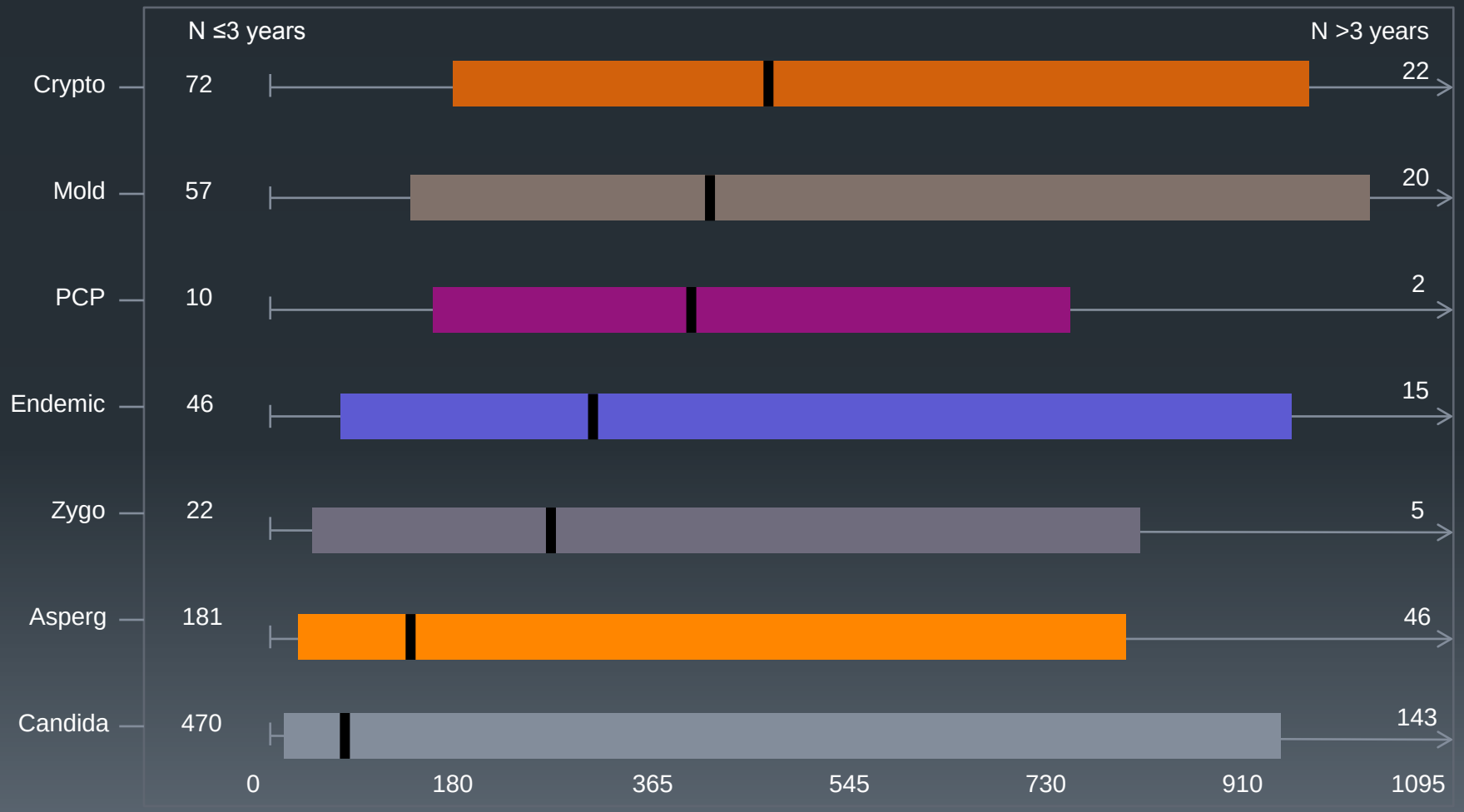
Park BJ EID 2011;17(10):1855-64

Recent Data on Distribution of IFI in Solid Organ Transplantation



Neofytos D Transplant Infect Dis 2010;12(3):220-229

Timing of IFI



Pappas P Clin Infect Dis 2010;50

Endemic Mycoses in SOT

Fungus	Reported Rate	Time to Onset
Coccidioidomycosis	1.4-6.9%	3-12 mths
Histoplasmosis	0.23-0.5%	12-18 mths

1. Vucicevic D Am J Transplant 2011 Jan;11(1); 2. Freifeld AG Curr Opin Organ Transplant 2009 Dec;14(6):601-5

RISK FACTORS

Risk of Fungal Infection

Risk Factors for IFI Common to All SOT

- Technical/Anatomical Abnormalities
  - Skill in operative/perioperative management
  - Vascular access devices
  - Drainage catheters/endotracheal tubes
- Intensity of Environmental Exposures
  - Community
  - Nosocomial
- Net State of Immunosuppression
  - CMV and other herpes viruses
  - Treatment of rejection with steroid or monoclonal antibodies
  - Renal failure

Fernanda P. Med Mycol 45;4:305-320

Lower Risk (<4%) with 1 Risk Factor

- Choledochojejunostomy anastomosis
- Retransplantation
- Intra-operative administration of ≥40 units of cellular blood products
- Preoperative serum creatinine ≥2.0 mg/dL or need for any form of dialysis within 48 h prior to OLT
- *Candida* spp. isolated from surveillance culture between 48 h before until 48 h after OLT
- Return to the operating room within 5 d of OLT for laparotomy
- Primary graft nonfunction

Pappas PG, et al. Am J Transplant 2006;6:386-91

Unique Factors Contributing to the Risk of Infection in Lung Transplantation

Continuous contact with pathogens

Higher state of immunosuppression

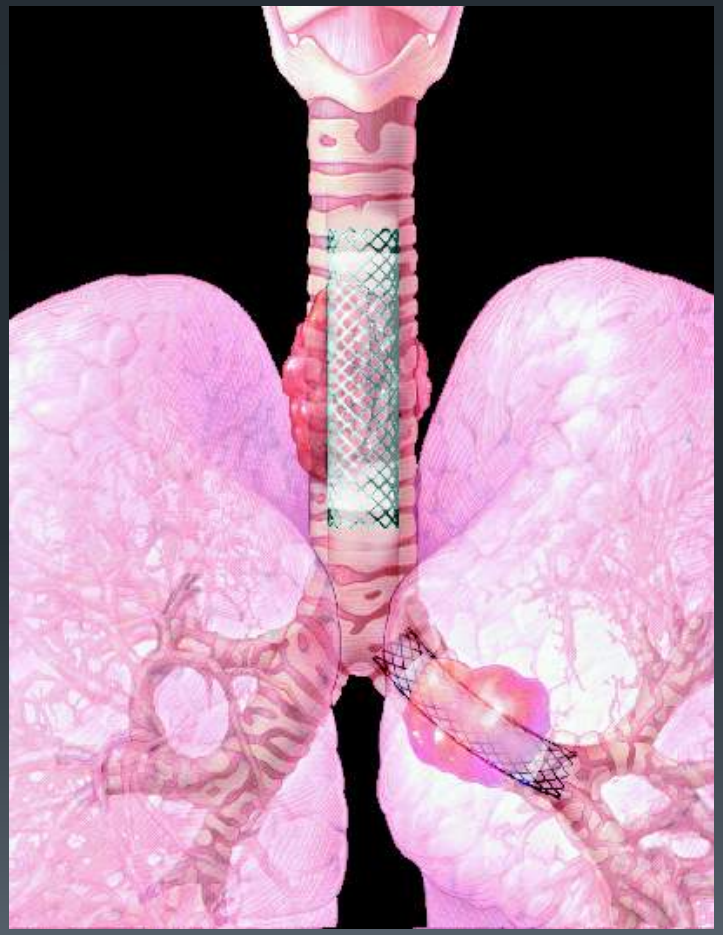
Airways colonization

Pulmonary stent

The native lung

Hypogammaglobulinemia

CARV Infection



Denervation

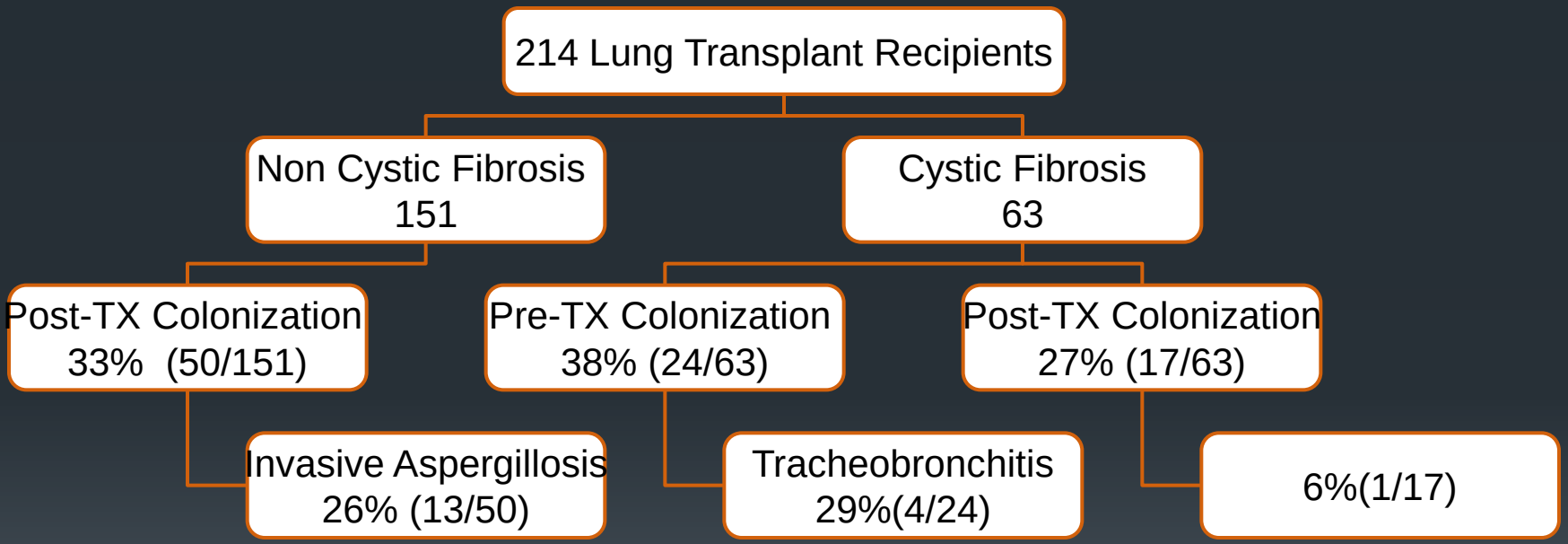
Impaired cough reflex

Ischemic reperfusion injury

Decrease mucociliary clearance

Husain S. Clin Chest Med 2009;30(2):307-13

Colonization



1. Helmi M. Chest 2003;123(3):800-8; 2. Nunley 2001 Chest 1998;114(5):1321-9

Unique Risk Factors: Kidney Pancreas

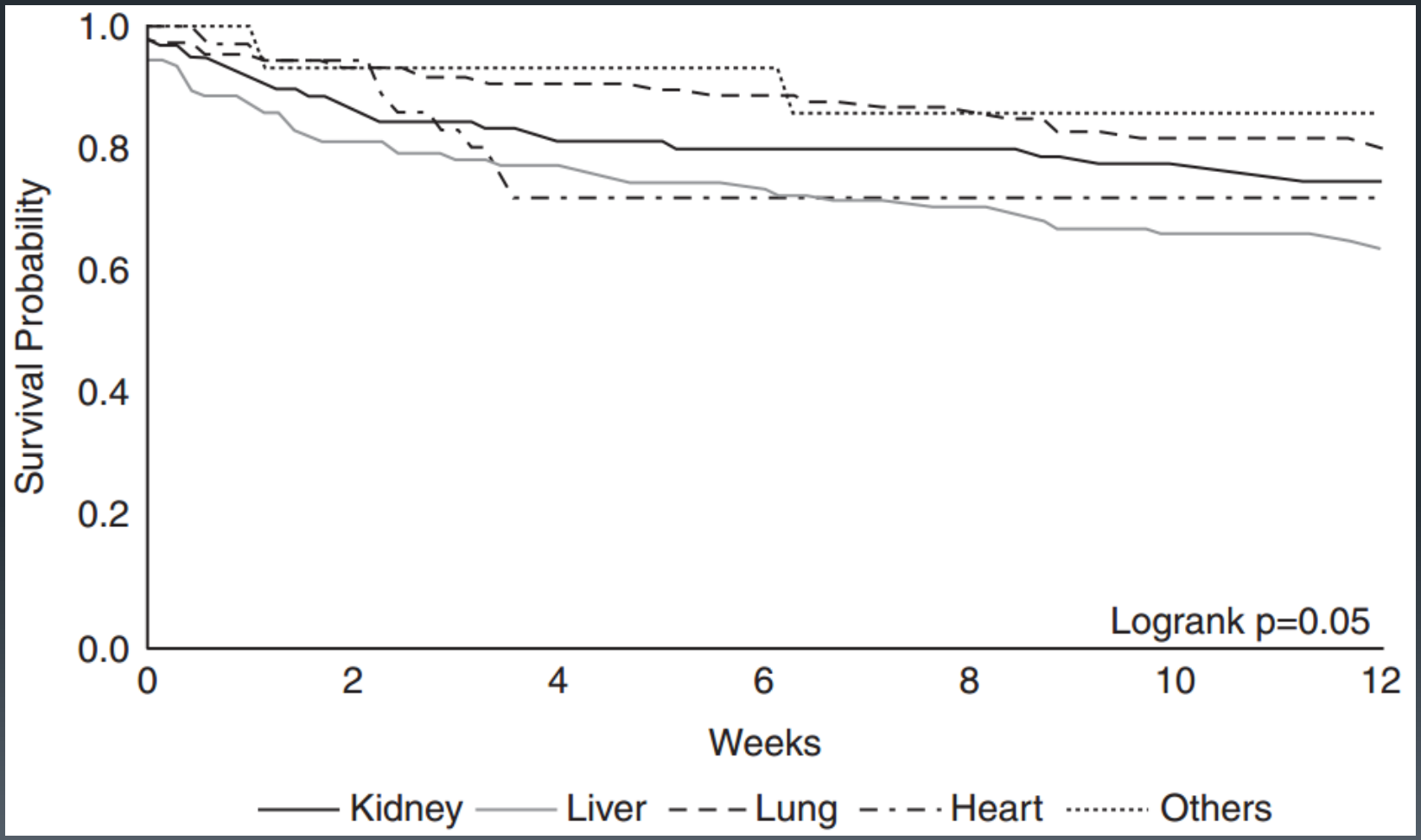
- 445 consecutive pancreas transplantation
  - SPK 200, pancreas 138, PAK 107
- Risk factors
  - Enteric drained
  - SPK & PAK
  - Donors age >50 years
- Other
- Reperfusion pancreatitis
- Graft thrombosis

Benedetti E. J Am Coll Surg 1996;183(4):307-16; 2. Kubak BM. Transpl Infect Dis 2002;4(S3):24-31

MORTALITY

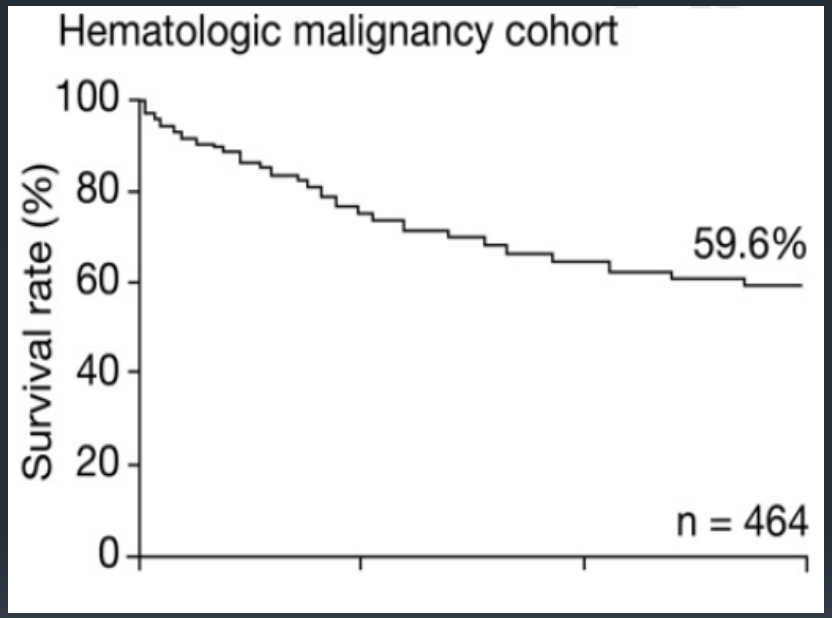
Severity of Fungal Disease

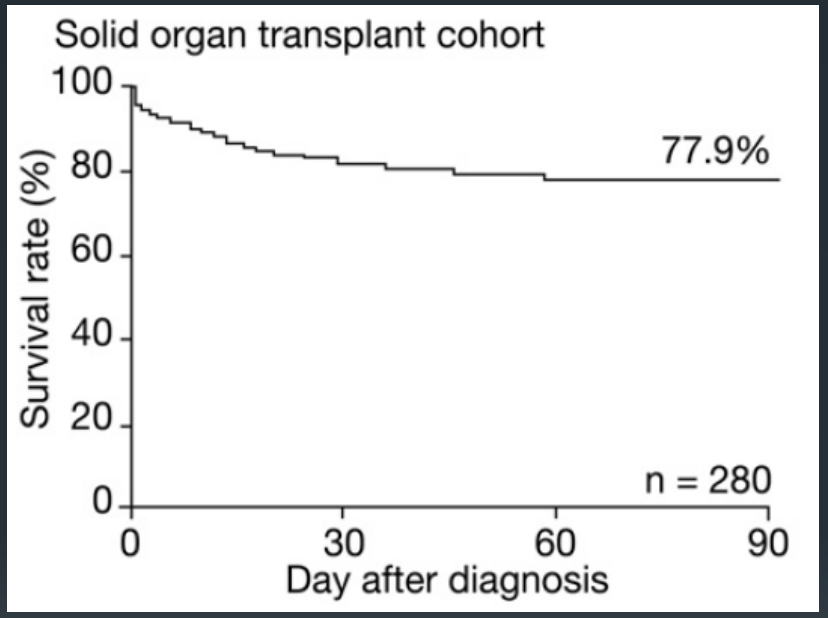
Mortality Associated with IFI in SOT



Neofytos D. Transplant Infect Dis 2010;12(3):220-229

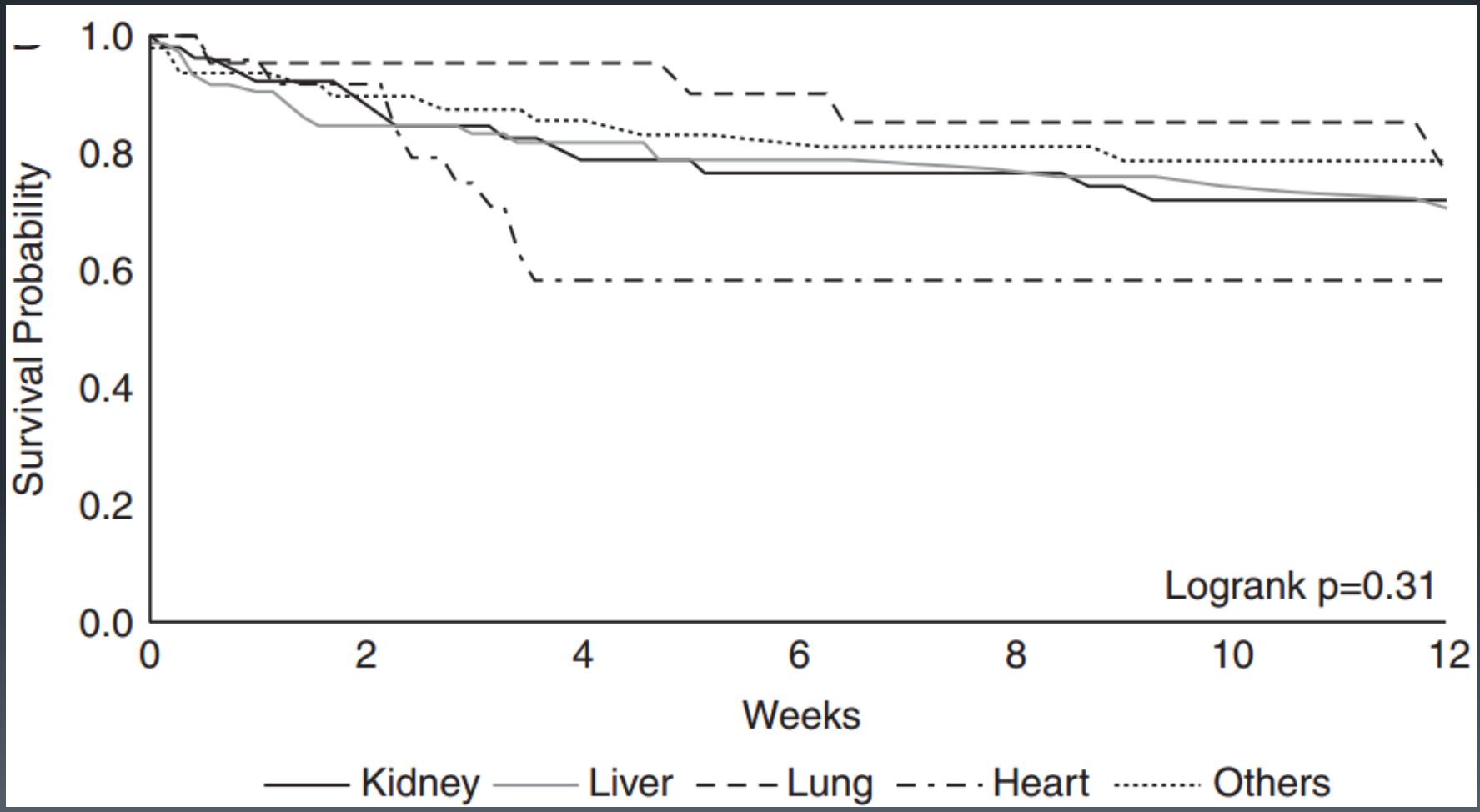
Mortality with Invasive Aspergillosis





Steinbach WJ et al. J Infect 2012 Article in press

Mortality Associated with Candidiasis in Solid Organ Transplantation



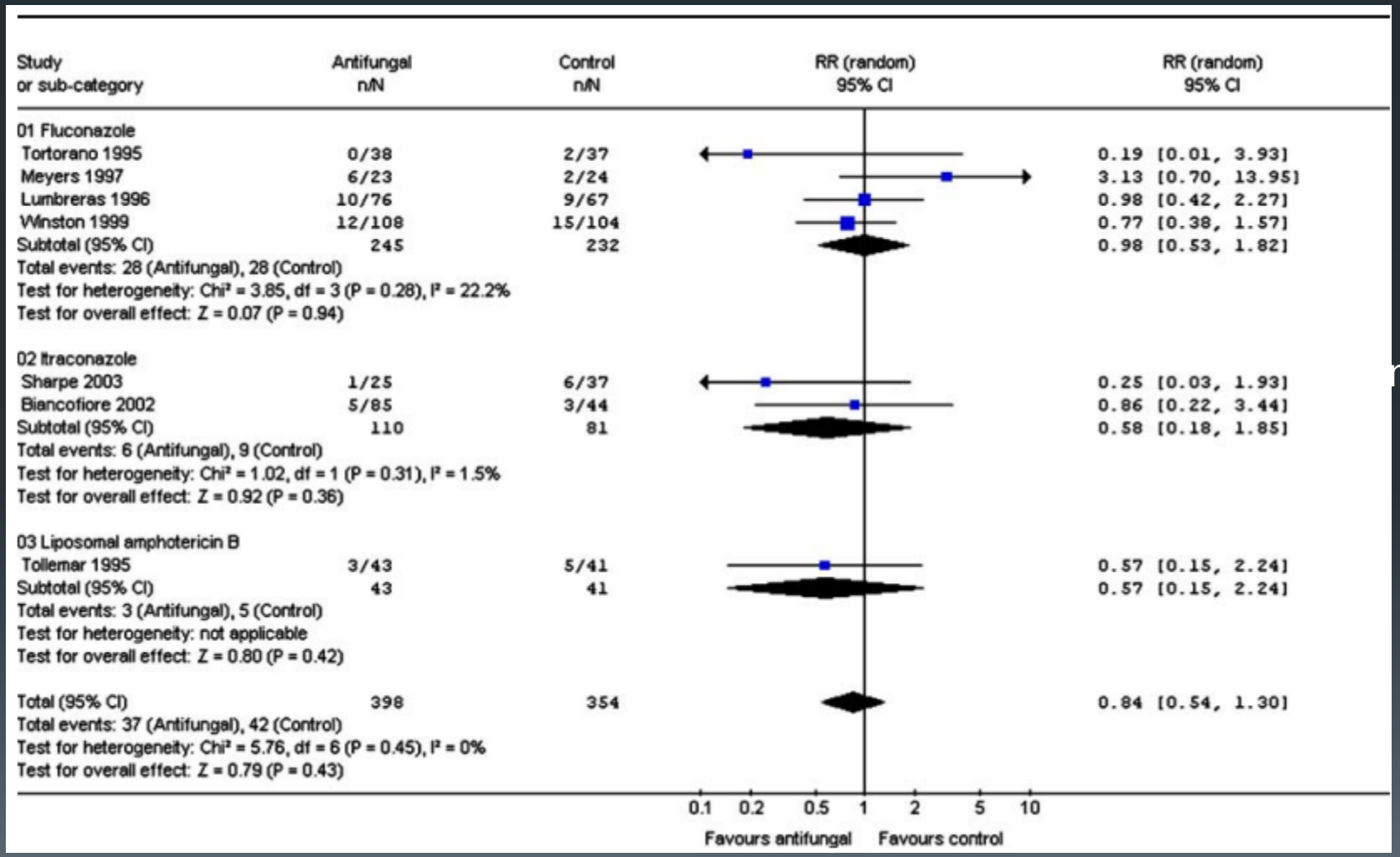
Neofytos D. Transplant Infect Dis 2010;12(3):220-229

Effectiveness of Antifungal Prophylaxis

Meta-Analyses of Antifungal Prophylaxis in LTR

Outcomes	Cruciani RR (95%CI) N=698	Playford EJ RR (95%CI) N=1052
Total Fungal Infection	0.31 (0.21-0.46)	0.44 (0.28-0.69)
Invasive Infection	0.33 (0.18-0.59)	0.39 (0.18-0.85)
Superficial Infection	0.27 (0.16-0.45)	0.25 (0.13-0.51)
Empiric Treatment	0.80 (0.39-1.67)	0.95 (0.49-1.83)
Adverse events	1.38 (1.04-1.83)	1.2 (0.68-2.12)
Fungal colonization	**-**	**0.51 (0.41-0.62)**
Resistant Fungal col.	**-**	**1.57 (0.76-3.24)**
Mortality	**1.06 (0.69-1.64)**	**0.84 (0.54-1.30)**

1. Cruciani M, et al. Liver Transpl 2006;12:850-8; 2. Playford EG, et al. Eur J Clin Microbiol Infect Dis 2006;25:549-61



Playford EG, et al. Eur J Clin Microbiol Infect Dis. 2006;25(9):549-61

ABLC Prophylaxis in HR LTR

- In total, 251/615 patients (40.8%) experienced ≥1 episodes of any fungal infection during follow-up including 91 (14.8%) cases which were considered to be proven IFI
- Low-dose ABLC (Abelcet®, Cephalon, Maisons-Alfort, France) was administered prophylactically in patients meeting ≥1 of the following criteria:
  - Acute liver failure
  - End-stage cirrhosis treated in the ICU
  - Re-transplantation and early re-interventions
- ABLC was administered at a dose of 1 mg/kg/day for 1 week after which the dose was reduced to 2.5 mg/kg twice a week for the subsequent 2 weeks

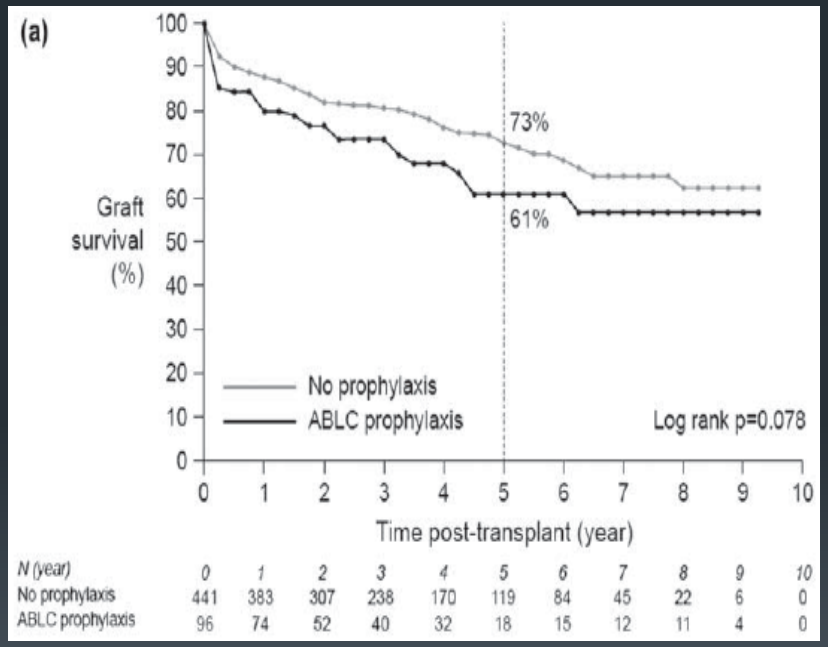
Saliba F. Med Mycol 2013;51:155–163

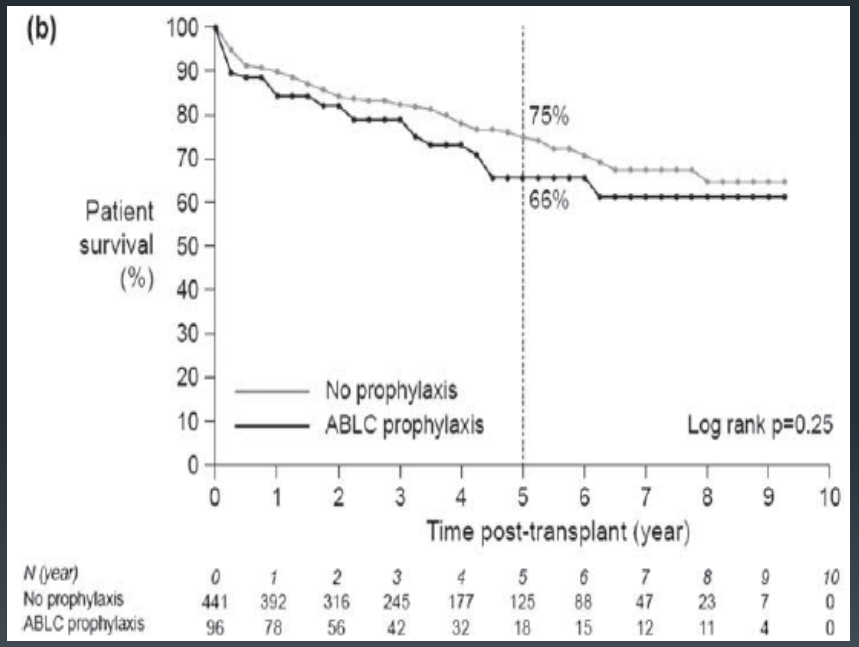
ABLC Prophylaxis in HR LTR

	ABLC prophylaxis (n=146)	No ABLC prophylaxis (n=469)	*P* value
Any *Candida* infection	**43 (29.5%)**	**193 (41.2%)**	**0.011**
Candida colonization (lung, urine, gastro-intestinal, excluding skin)	37 (25.3%)	161 (34.3%)	0.04
Probable invasive *Candida* infection (> 2 sites)	15 (10.3%)	110 (23.5%)	0.0005
Proven invasive *Candida* infection	10 (6.8%)	47 (10%)	0.25
Candidemia	5 (3.4%)	12 (2.6%)	0.57
Candiduria	8 (5.5%)	51 (10.9%)	0.053
Abdominal *Candida* infection			
At any time point	10 (6.8%)	54 (11.5%)	0.11
Probable or proven invasive *Candida* infection treated with systemic antifungals			
At any time point	27 (18.5%)	152 (32.4%)	0.001
Any *Aspergillus* infection			
Probable aspergillosis	**6 (4.1%)**	**15 (3.2%)**	**0.60**
Proven aspergillosis	**2 (1.4%)**	**13 (2.8%)**	**0.54**

Saliba et al Med Mycol 2013;51:155-163

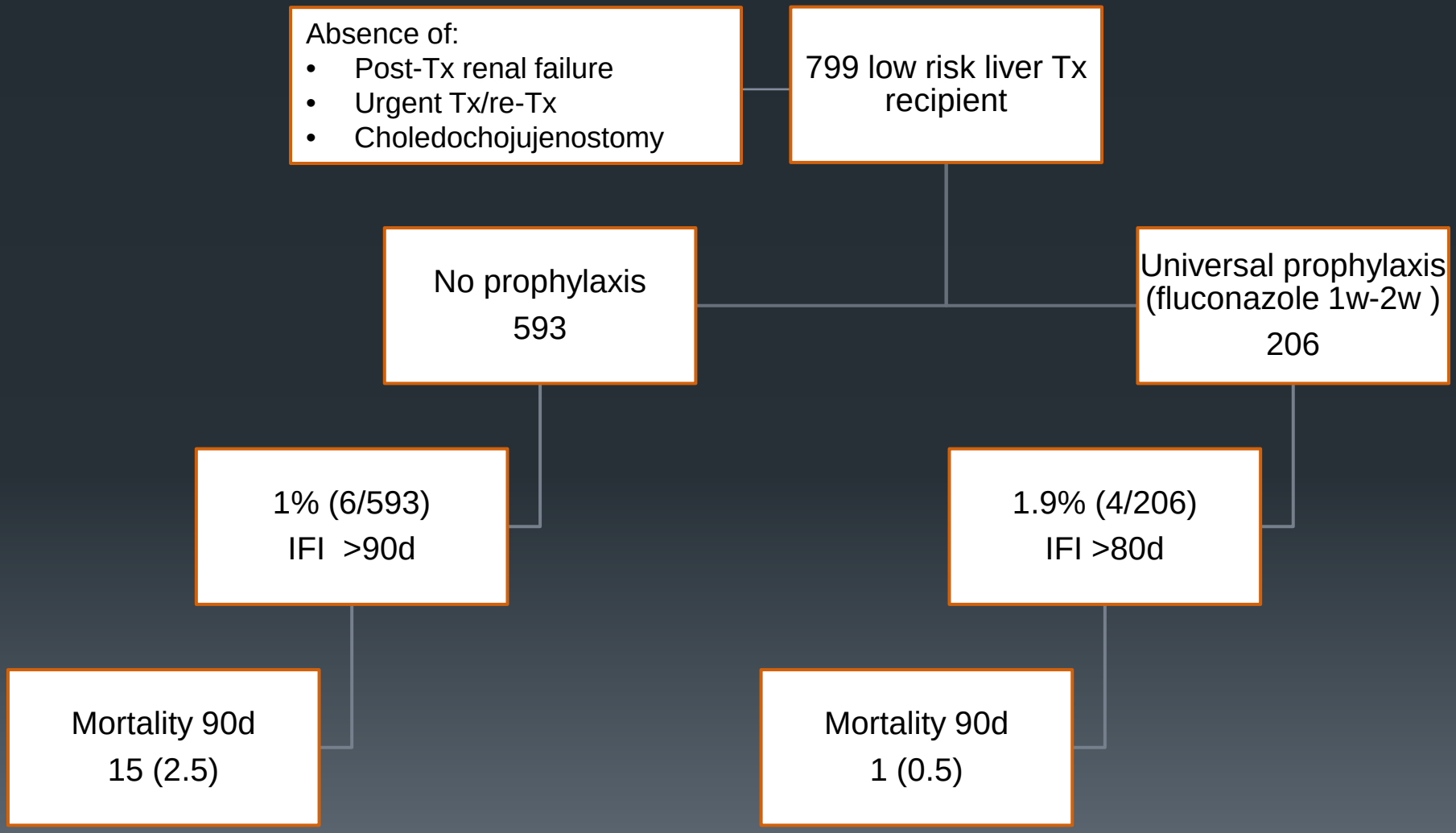
Patient Outcomes in ABLC Prophylaxis





Saliba et al. Med Mycol 2013;51:155-163

Azole Prophylaxis in Low-Risk LTR



San Juan R. Transplantation 2011;92(3):346-50

Characteristics of Low-Risk LTR According to Inclusion or Not in UPF

	UPF (N=206)	No UPF (N=593)	*P*
Induction immunosuppression including: n (%)			
Cyclosporine	35 (17)	211 (35.6)	<0.0001
Tacrolimus	165 (80.1)	294 (49.6)	<0.0001
Early surgical graft complications (stenosis or dehiscence): n (%)	9 (4.4)	40 (6.7)	
At least one episode of early acute rejection: n (%)	36 (17.5)	115 (19.4)	
At least one episode of early bacterial infection: n (%)	47 (22.8)	125 (21.1)	
At least one episode of CMV disease in the first 6 mo: n (%)	18 (8.7)	61 (10.3)	
At least one episode of IFI in the first 30 d of transplant: n (%)	**4 (1.9)**	**6 (1)**	
IFI due to fluconazole-resistant *Candida*	**2 (0.9)**	**0**	
Global early mortality: n (%)	**1 (0.5)**	**15 (2.5)**	

San Juan R. Transplantation 2011;92(3):346-50

Echinocandins: Caspofungin

- Prospective open label trial in 78 HR LT patients with follow-up for 100 days

Outcome	Frequency
IFI Incidence	2.8% (2/71)
Dose Reduction	15.5% (11/71)
Discontinuation	8.4% (6/71)

Fortun Transplantation 2009 Feb 15;87(3):424-35

Micafungin vs. ABLC for the Prevention of IFIs in High-Risk LTRs

- The efficacy and safety of targeted prophylaxis with micafungin or ABLC was assessed in a sequential cohort of high-risk patients and compared with those without high risk who did not receive prophylaxis. Outcomes were assessed at 90 days
- IFIs developed in **11.1% (2/18)** of micafungin recipients, **8.3% (2/24)** of ABLC recipients, and **3% (7/234)** of patients without high risks (P=0.12)
- In nondialyzed patients, ABLC vs. micafungin recipients had significantly higher serum creatnine on day 14 (P=0.04)

Targeted Antifungal Prophylaxis in Heart Transplant Recipients

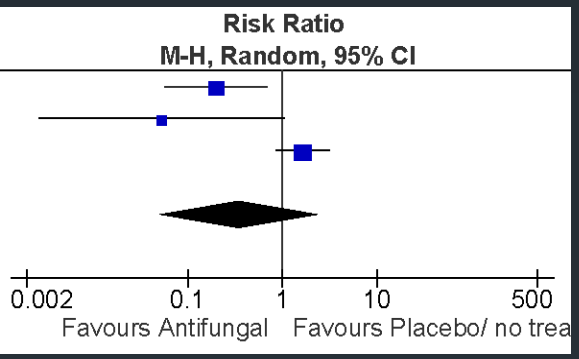
- In a prospective cohort (2003-10), prophylaxis with an echinocandin was only administered to patients with risk factors (13/133) and duration was personalized, starting with the risk factor (reoperation CMV, MCD infection) and continued a median of 20 days after resolution
- Antifungal prophylaxis was prescribed only in 9.8% of recipients and was effective in all but one patient .
- Despite suffering an outbreak of IA in the ICU due to extremely high concentration of spores in the air (3 cases with no personal risk factors), there was a reduction in the incidence of IA (8.6% vs. 2.2%; P=0.01) and *Aspergillus*-related mortality (5.75% vs. 1.5%; P=0.06)

Munoz P. Transplantation 2013

Overall Estimate of IA in Comparative Studies (Antifungals with No Prophylaxis)

Study or Subgroup	Antifungal Events	Antifungal Total	Placebo/ No treatment Events	Placebo/ No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Reichenspurner 1997	3	126	12	101	36.9%	0.20 [0.06, 0.69]	1997
Calvo 1999	0	52	2	13	21.9%	0.05 [0.00, 1.04]	1999
Tofte 2012	16	57	14	82	41.2%	1.64 [0.87, 3.10]	2012
Total (95% CI)		**235**		**196**	**100.0%**	**0.36 [0.05, 2.62]**	
Total events	19		28				

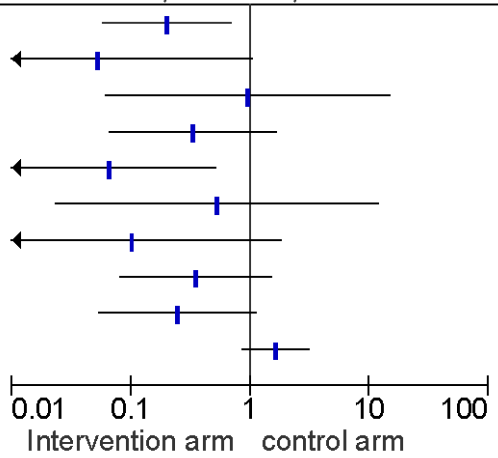
Heterogeneity: Tau² = 2.41; Chi² = 13.28, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 1.02 (P = 0.31)



Bhaskaran A :In print Current Infectious Disease Reports

Effect Sizes of Comparative Studies Using Various Antifungals for IA

Study or Subgroup	intervention arm Events	Total	control arm Events	Total	Risk Ratio M-H, Random, 95% CI	Year
Reichenspurner 1997	3	126	12	101	0.20 [0.06, 0.69]	1997
Calvo 1999	0	52	2	13	0.05 [0.00, 1.04]	1999
Drew 2004	1	51	1	49	0.96 [0.06, 14.94]	2004
Mattner 2005	2	65	5	54	0.33 [0.07, 1.65]	2005
Husain 2006	1	65	7	30	0.07 [0.01, 0.51]	2006
Lowry 2007	0	11	1	18	0.53 [0.02, 11.93]	2007
Cadena 2009	0	35	4	32	0.10 [0.01, 1.82]	2009
Monforte 2010	3	104	4	49	0.35 [0.08, 1.52]	2012
Koo 2012	2	83	8	82	0.25 [0.05, 1.13]	2012
Tofte 2012	16	57	14	82	1.64 [0.87, 3.10]	2012



Bhaskaran A :In print Current Infectious Disease Reports

Effect of Antifungal Prophylaxis on Colonization

- A single study by Tofte el al compared the incidence of *Aspergillus* colonization with universal voriconazole and no prophylaxis. They reported an incidence rate of 21% (12/57) in the voriconazole arm and 28% (23/82) in the control arm, p-value= 0.48.

- The indirect comparison involving more than 637 patients, the incidence *Aspergillus* colonization employing universal prophylaxis with various anti-fungals and no prophylaxis did not yield significant results.

Bhaskaran A :submitted

Consequences of Antifungal Prophylaxis

AMPHO

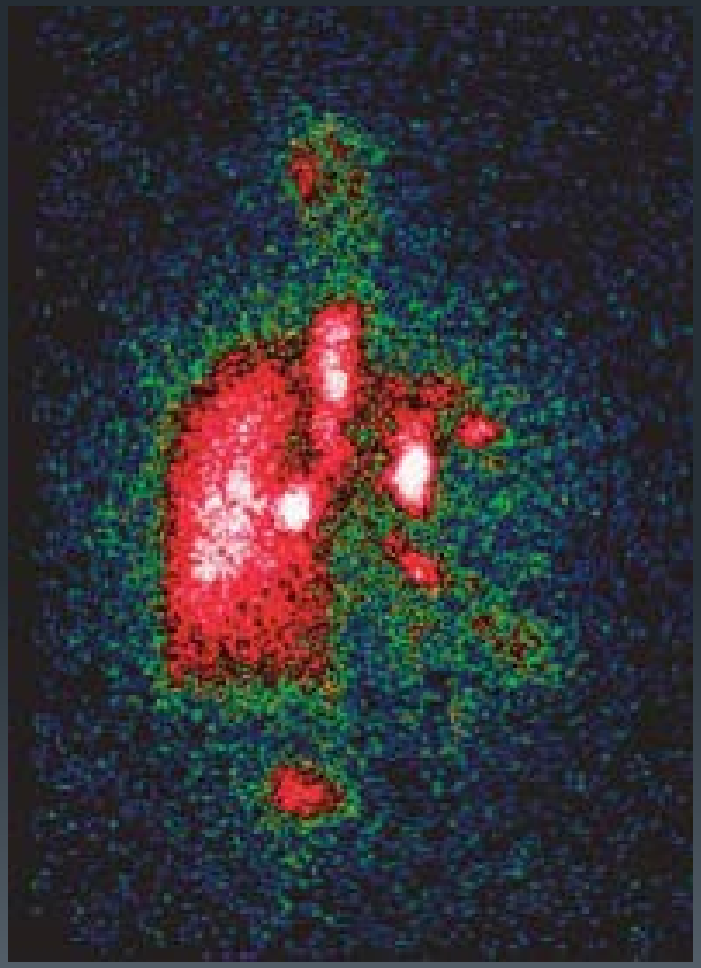
the Terrible

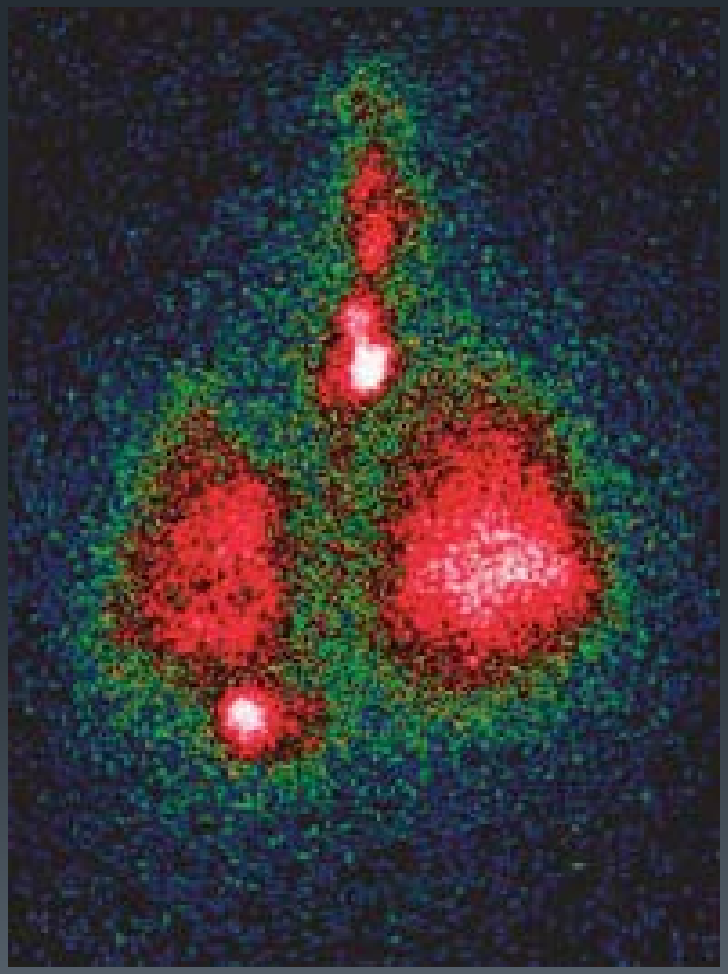
Adverse Events with Inh AMB Preparations

	L-AMB (n=118)	ABLC (n=51)	AMB-D (n=49)
Wheezing	4%	4.2%	6.4%
Cough	10%	2.1%	10.6%
SOB	NR	2.1%	20%
Nausea	7%	2.1%	8.5%
Decline in FEV1	None	11.1%	10.6%
>1 AE	NR	27.5%	42.9%
Discontinuation	2.5%	5.9%	12.2%

1. Roman A 2005; 2. Drew RH 2004

Where in the Lung Did the Drugs Go?





Corcoran et al. Am J Transplant 2006;6:2765–2773

Amphotericin Concentration in ELF & Serum

Sample collection time after last dose (hrs)	Number of subjects	ELF conce120ntration median mcg/mL	25-75 IQR	Plasma concentration median mcg/mL	25-75 IQR	ELF/plasma ratio
4	5	7.20	1.3-17.6	0.08	0.06-0.11	90
24	6	8.26	3.9-82.7	0.05	0.03-0.06	165.2
48	5	2.15	1.4-5.5	0.05	0.03-0.06	43
72	4	1.25	0.75-5.5	0.02	0.009-0.06	62.5
96	6	0.80	0.55-1.4	0.01	0.009-0.02	80
120	4	1.04	0.44-1.6	0.005	0.004-0.01	208
144	1	4.25	-	0.01	-	425
168	3	1.14	0.01-1.9	0.005	0.002-0.02	228
192	1	0.25	-	0.0019	-	131.5

Husain S. Transplantation 2010;90(11):1215-9

Implication

- Invasive candidiasis
  - 11% (11/100) in inh ABLC study
  - 4% (6/153) in inh Ambisome Study

1. Drew RH. Transplantation 2004;77(2):232-7; 2. Monforte V J Heart Lung Transplant 2010;29(5):523-30

Voriconazole and Skin Cancer in LTR

Study	Patients with skin cancer	Risk factors	Hazard ratio
Vadnerkar et al, 2010	17	Duration of voriconazole therapy Residence in high sun exposure area	2.1 3.8
Singer et al, 2012	50	Exposure to voriconazole therapy	2.6
Zwald et al, 2012	28	Duration of voriconazole therapy Time since Tx Pre-Tx skin cancer	NR
Feist et al, 2012	17	Duration of voriconazole therapy Age Pre-Tx skin cancer	1.8 2.8 11.0

Bhaskaran A. Semin Respir Crit Care Med 2013;34(3)

Hepatic Enzymopathy

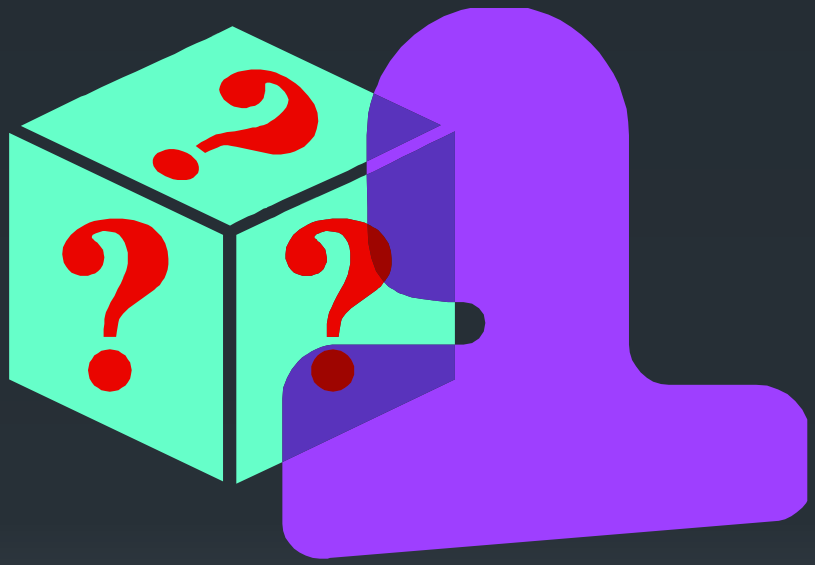
Author	Definition	Elevated LFTs (%)	Discontinuation (%)
Husain et al, 2006	>3x increase AST, ALT, ALK and Bili on voriconazole	37	14
Cadena et al, 2009	>3x increase AST, ALK >1.5x increase Bili in the absence of other etiologies and improvement with d/c of voriconazole	34	34
Luong et al, 2012	>3x increase AST, ALT, ALK and Bili or voriconazole	51	34

Bhaskaran A. Semin Respir Crit Care Med 2013;34(3)

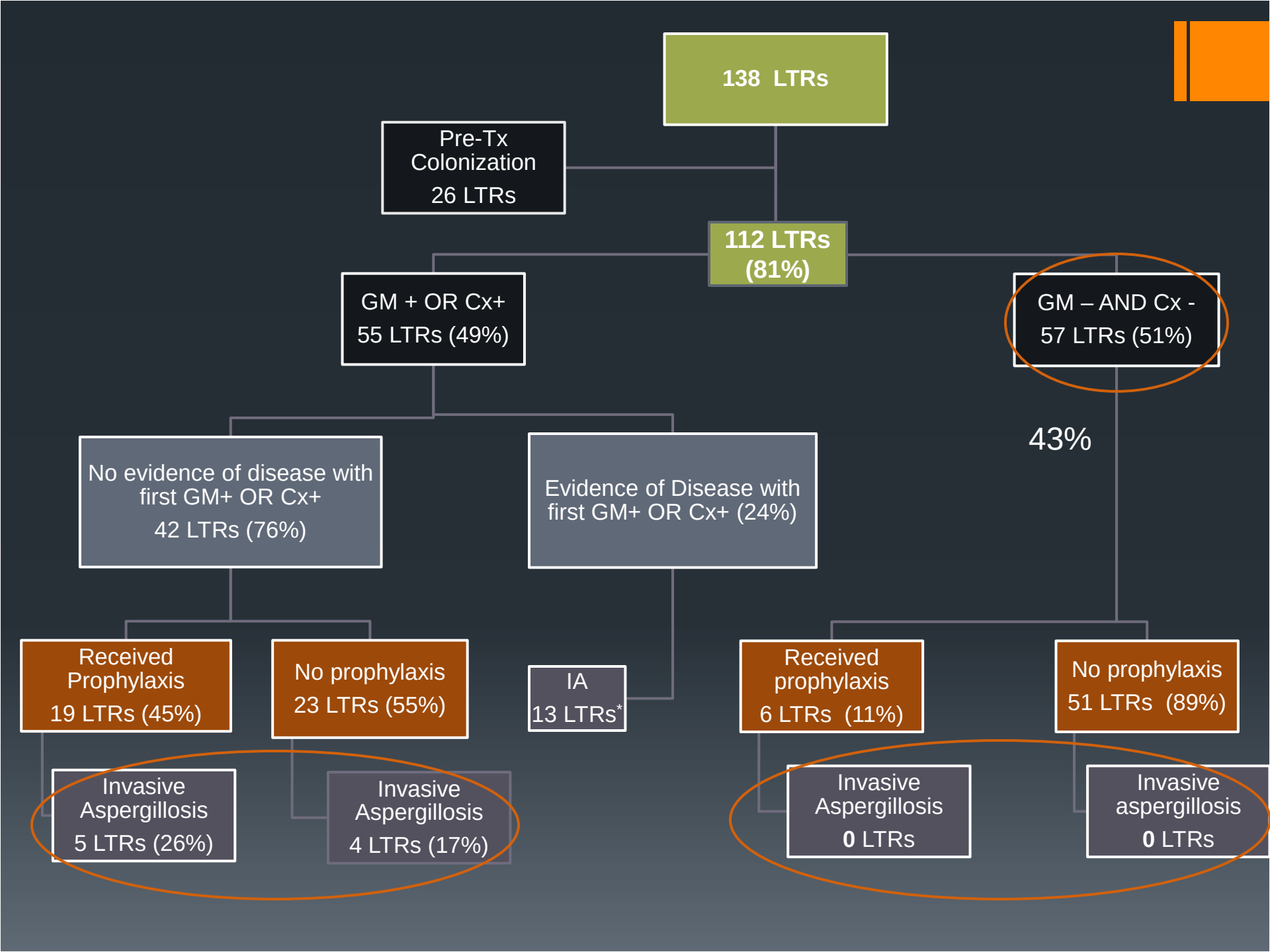
Should We Continue Universal Voriconazole Prophylaxis & Extend Beyond 1 Year?

- Increased risk of side effects
  - Hepatic enzymopathy
  - Periostitis
- Development of resistant *Aspergillus* strains
- Selection of non-*Aspergillus* spp. (eg. *zygomycetes*)
- **Association with SCC?**

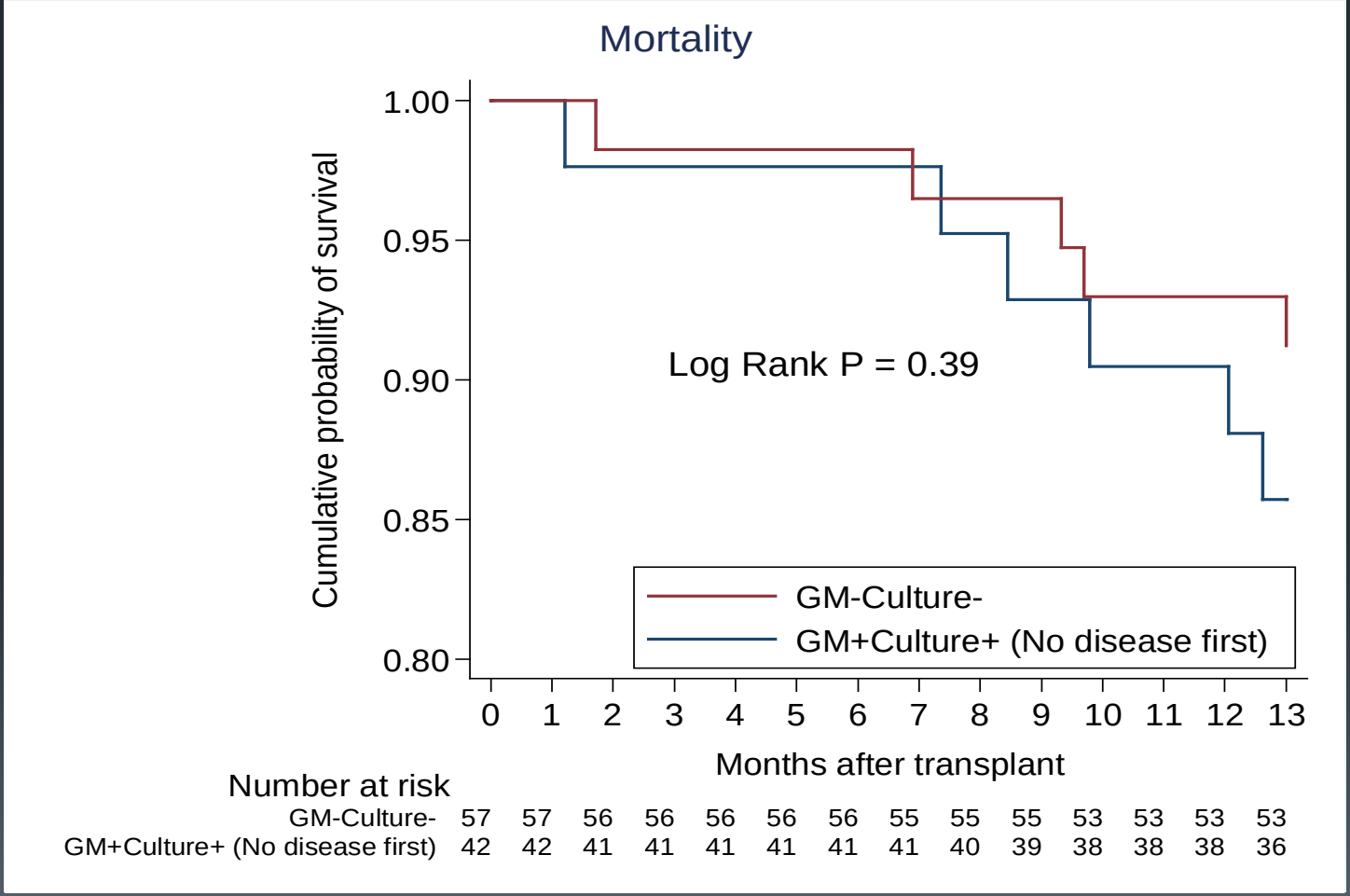
How to Better Risk Stratify LTRs for IA?



- Clinical risk stratification through cohort studies
- Measurement of immunity against *Aspergillus*
- Use of galactomannan assay or *Aspergillus* PCR to identify the patient at higher risk of IA


138 LTRs
Pre-Tx Colonization
26 LTRs
112 LTRs (81%)
GM + OR Cx+
55 LTRs (49%)
GM – AND Cx -
57 LTRs (51%)
43%
No evidence of disease with first GM+ OR Cx+
42 LTRs (76%)
Evidence of Disease with first GM+ OR Cx+ (24%)
Received Prophylaxis
19 LTRs (45%)
No prophylaxis
23 LTRs (55%)
IA
13 LTRs*
Received prophylaxis
6 LTRs (11%)
No prophylaxis
51 LTRs (89%)
Invasive Aspergillosis
5 LTRs (26%)
Invasive Aspergillosis
4 LTRs (17%)
Invasive Aspergillosis
0 LTRs
Invasive aspergillosis
0 LTRs

Kaplan Meier Curve - Mortality



What Are We Doing?

Antifungal Prophylaxis in Liver Transplant

- Survey of all liver transplants in North America
- Response rate of 63% (67 centers)
- Targeted prophylaxis 72% (43 centers)
- Universal prophylaxis 28% (16 centers)

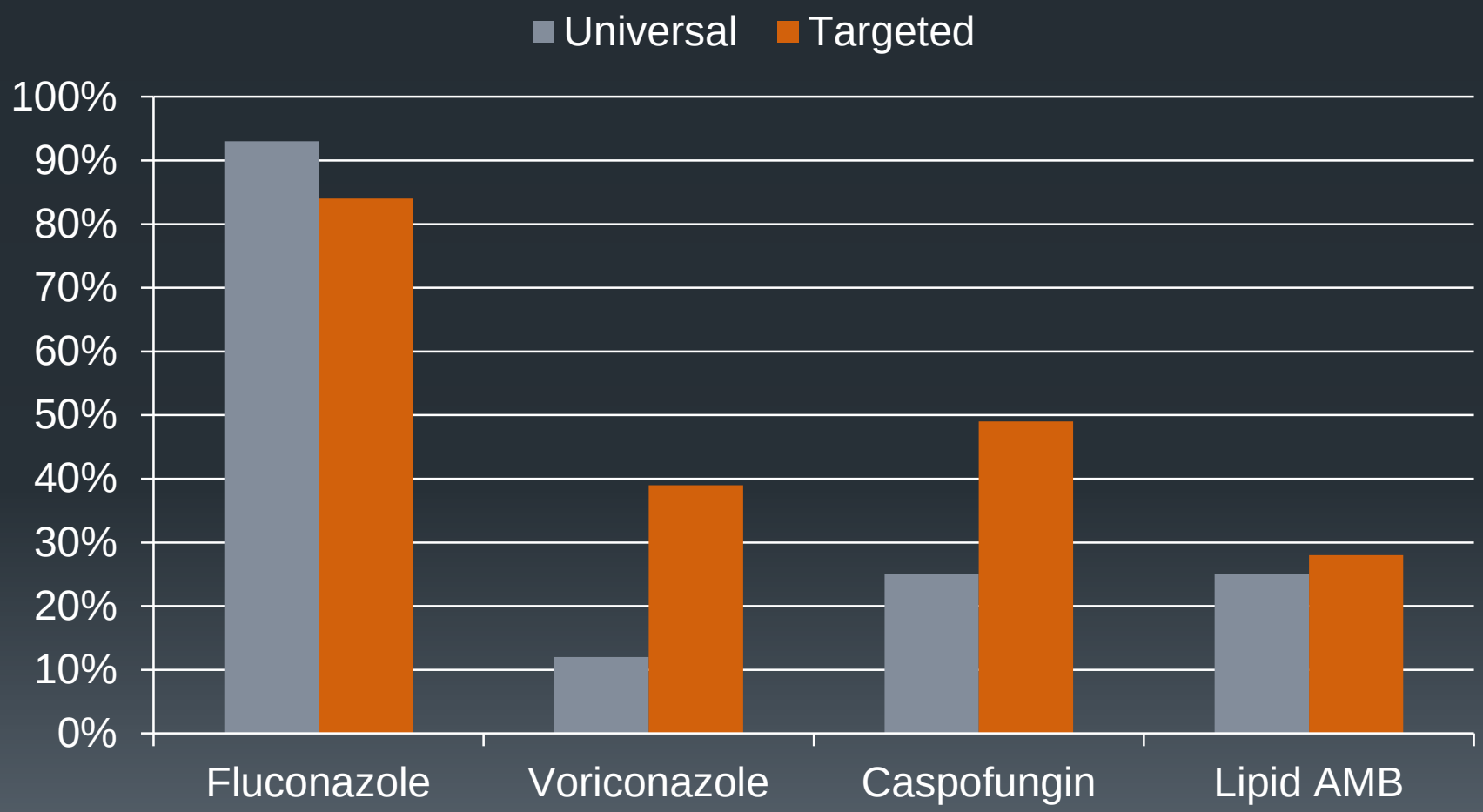
Singh N. Am J Transplant 2008;8(2):426-31

Indication for Targeted Prophylaxis

Clinical condition	Percentage
Retransplantation	78%
Dialysis requirement	72%
Re-exploration	61%
Fulminant hepatic failure	57%
Colonization with *Candida* spp.	57%
Prolonged ICU stay or ventilatory requirement	48%
High transfusion requirements	39%
Receipt of T-cell depleting antibodies	4%

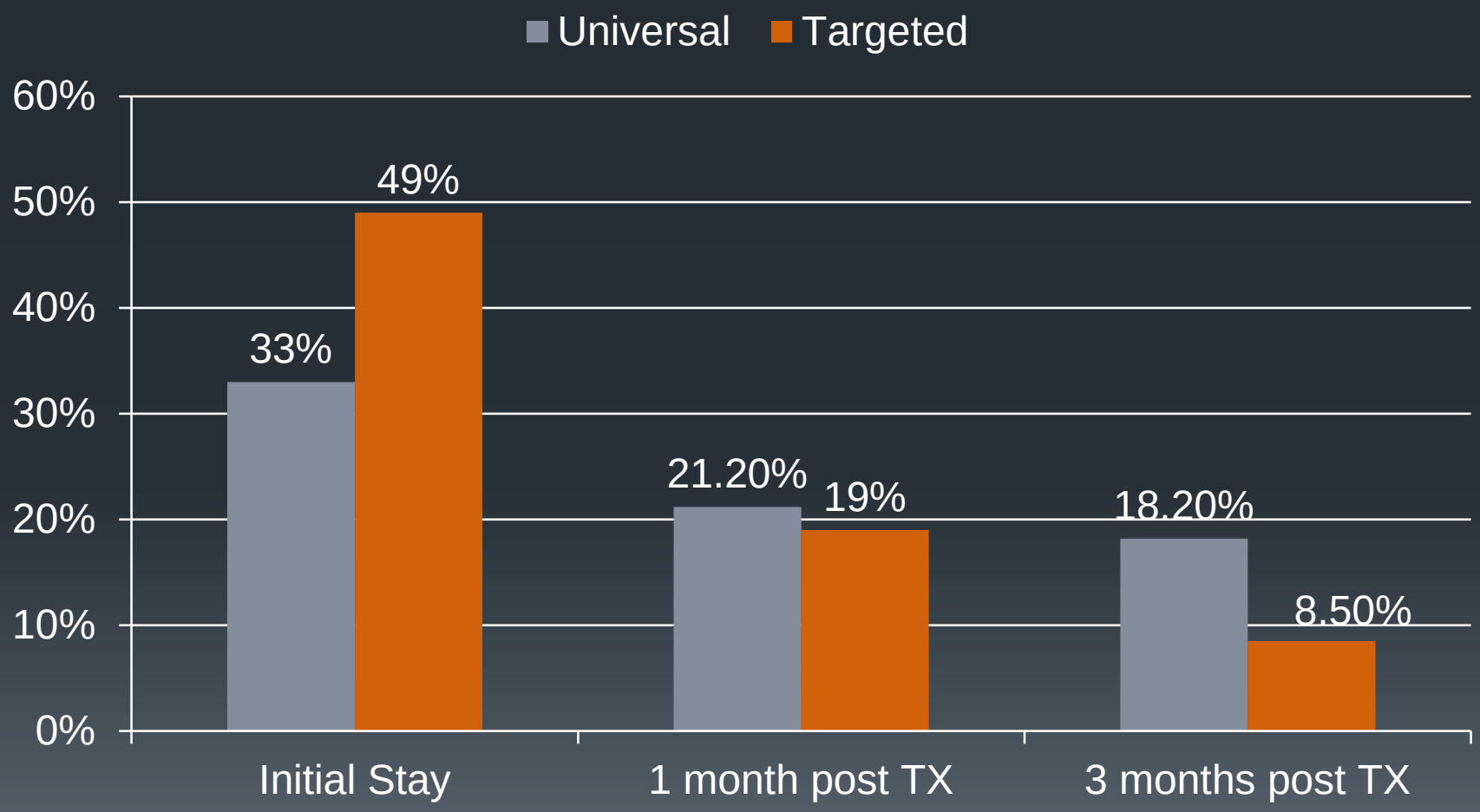
Singh N. Am J Transplant 2008;8(2):426-31

Choices of Antifungal Agents: Liver



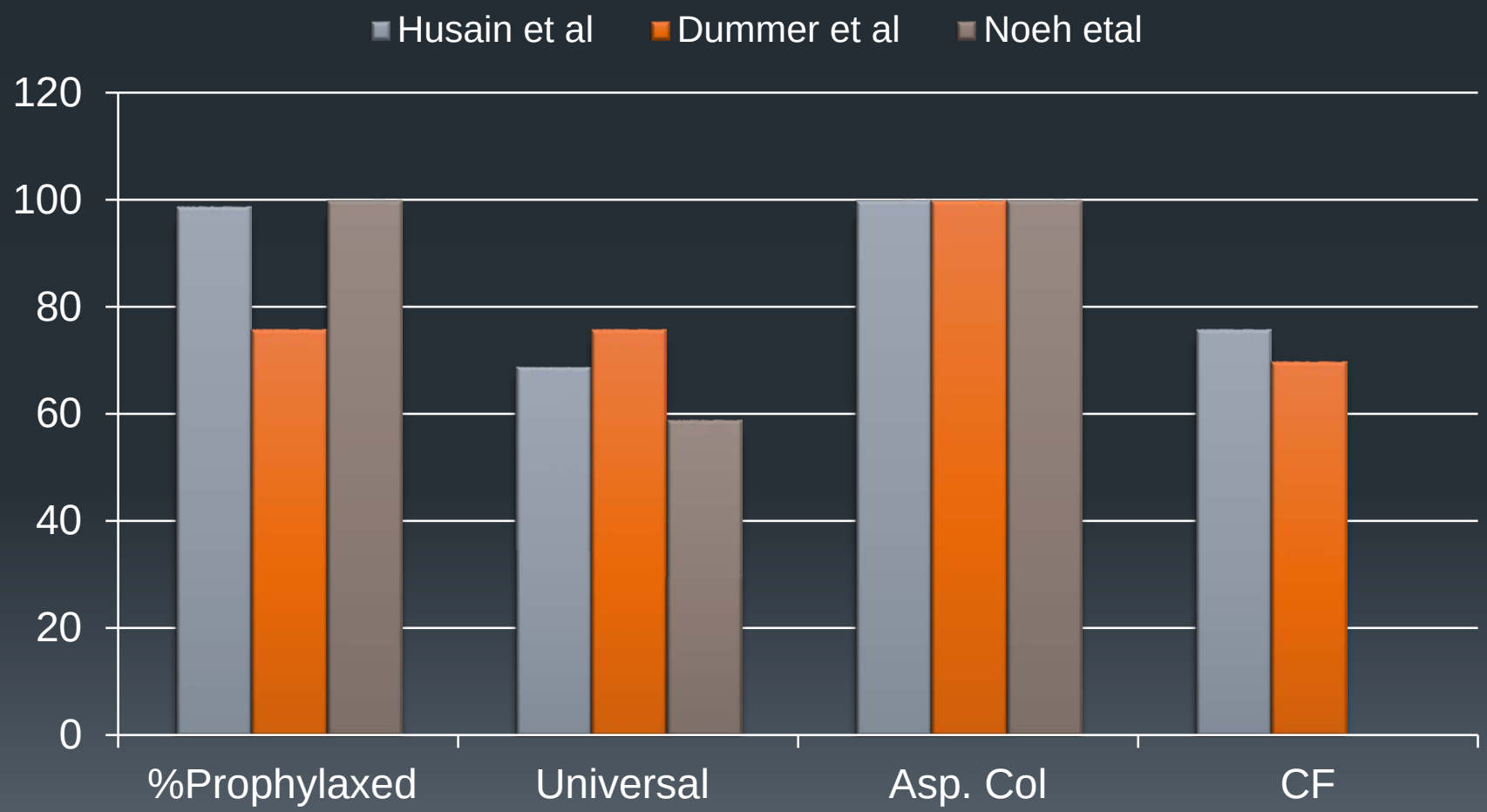
Singh N. Am J Transplant 2008;8(2):426-31

Duration of Antifungal Prophylaxis in Liver Transplant Recipients

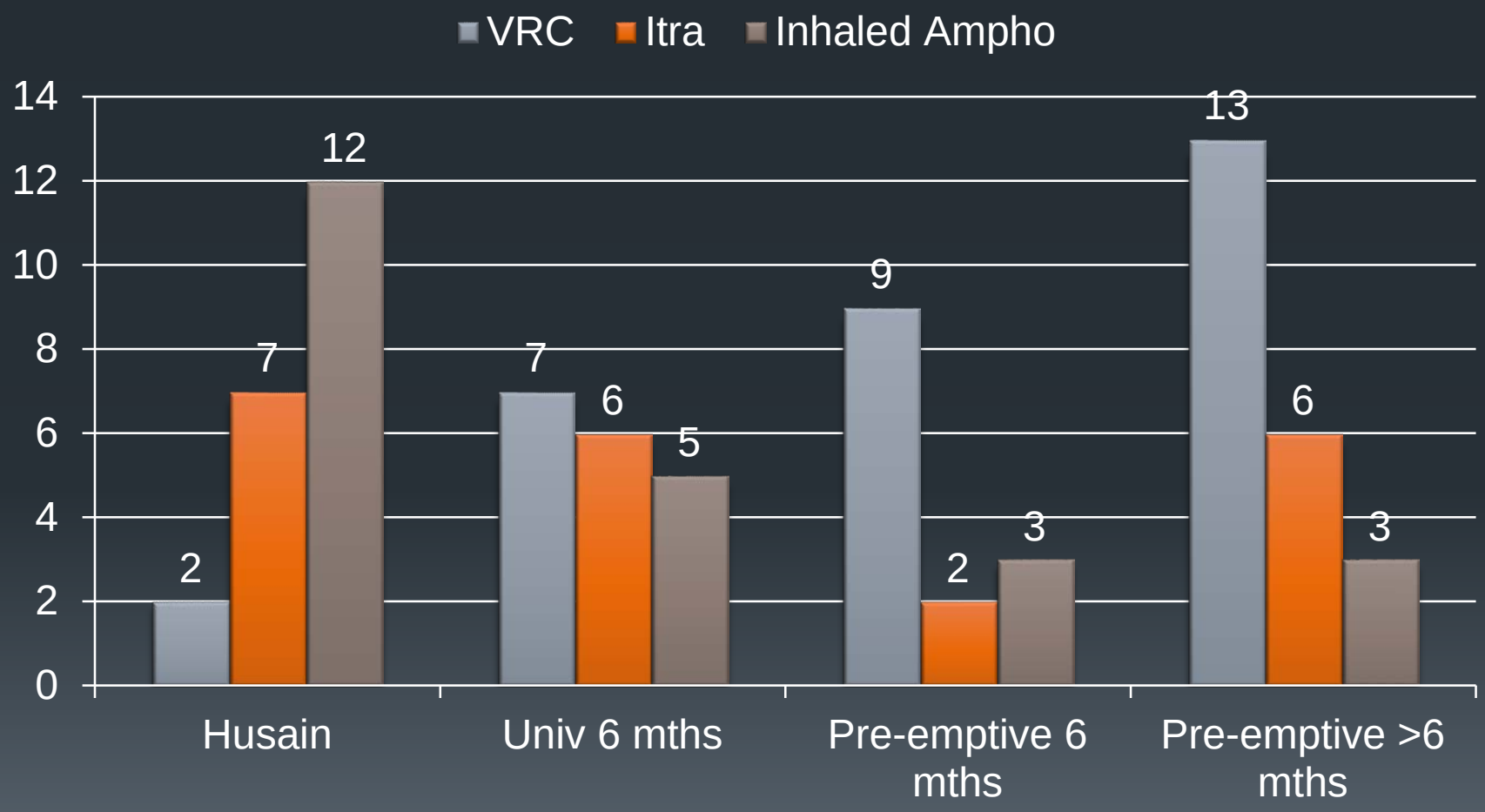


Singh N. Am J Transplant 2008;8(2):426-31

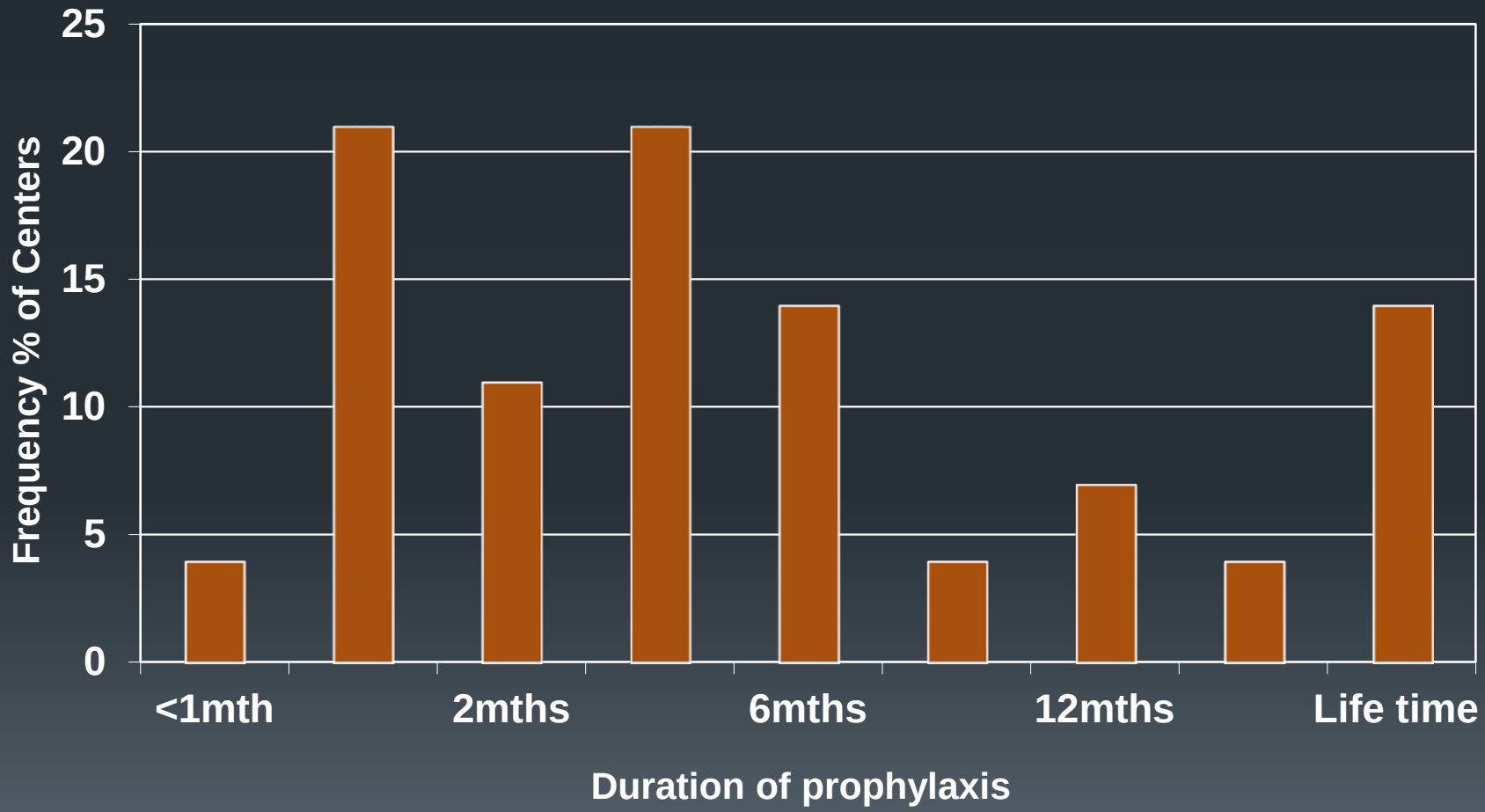
Antifungal Prophylaxis in LT



Choices of Antifungal Agents: Lung



Duration of Post Transplant Antifungal Prophylaxis



Dummer JS. J Heart Lung Transplant 2004;23(12):1376-81

Current Recommendations

General Rules for Antifungal Prophylaxis in SOT

- Targeted prophylaxis in high risk patients
  - Kidney
  - Pancreas
  - Liver
  - Heart
  - Lung
- Universal antifungal prophylaxis
  - Small Bowel

Risk Factors for IA in Organ Transplant Recipients

- Liver
  - Retransplantation
  - Renal failure, particularly requiring renal replacement therapy
  - Transplantation for fulminant hepatic failure
  - Reoperation
- Lung
  - Single lung tx
  - Early airway ischemia
  - CMV infection
  - Rejection and augmented immunosuppression
  - Pre-tx *Aspergillus* colonization
  - Post-tx *Aspergillus* colonization within a year of tx
  - Acquired hypogammaglobulinemia (IgG < 400 mg/dL)

Singh NM, Husain S. Am J Transplant 2013;13:228-41

Risk Factors for IA in Organ Transplant Recipients

- Heart
  - Isolation of *Aspergillus* spp. in respiratory tract cultures
  - Reoperation
  - CMV disease
  - Post-tx hemodialysis
  - Existence of an episode of IA in the program 2 months before or after heart tx
- Kidney
  - Graft failure require hemodialysis
  - High and prolonged duration of corticosteroids

Singh NM, Husain S. Am J Transplant 2013;13:228-41

Recommendations for Prophylaxis for IA in SOTR

Organ	Antifungal prophylaxis	Duration
Liver II-2	Lipid formulation of amphotericin B (3-5 mg/kg/day) OR an echinocandin	Initial hospital stay or for 4 weeks posttransplant
Lung	Inhaled amphotericin B 6 mg/q8 or 25 mg/day OR Inhaled Albelcet 50 mg OR Inhaled Ambisome 25 mg OR Voriconazole 200 mg BID OR Intraconazole 200 mg BID	Preferably guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors Once every 2 wks & then once per week for at least 13 wks Three times/week for 2 months, followed by weekly administration for 6 months and twice per month afterwards 4 months or longer
Heart II-3	Itraconazole 200 mg BID OR Voriconazole 200 mg BID	50-150 days

Singh NM, Husain S. Am J Transplant 2013;13:228-41

Risk Factors for *Candida* Infection

Organ	Risk factors
Liver	Prolonged or repeat operation Retransplantation Renal failure Choledocho-jejunostomy *Candida* colonization High transfusion requirement
Small bowel	Graft rejection/dysfunction Enhanced immunosuppression Anastomotic dysruption Abdominal reoperation Multivisceral transplantation
Pancreas	Enteric drainage Vascular thrombosis Postperfusion pancreatitis

Singh NM, Husain S. Am J Transplant 2013;13:228-41

Recommended Prophylaxis Strategies to Prevent Candida Infection in SOT

Organ	Antifungal prophylaxis	Duration
Liver	Fluconazole 400 mg/day LFAmB 3-5 mg/kg/day	Up to 4 weeks or Until resolution of risk factors
Small bowel	Fluconazole 400 mg/day LFAmB 3-5 mg/kg/day	At least 4 weeks Until healing of anastomosis and absence of rejection
Pancreas	Fluconazole 400 mg/day LFAmB 3-5 mg/kg/day	At least 4 weeks

Silveira FP, Kusne S, AST Infectious Diseases Community of Practice. Am J Transplant 2013;13:220-7

Pancreas Transplantation

Risk factors	Antifungal agent	Duration
Enteric drainage		Duration of prophylaxis will depend on reduction of risk factor
Vascular thrombosis	Fluconazole	
Post perfusion pancreatitis	LFAmB is preferred in centers with a high prevalence of non-albicans spp.	

Pappas G. Am J Transplant 2009;9(S4):S173–9

Coccidioidomycosis: Prophylaxis

- Targeted antifungal prophylaxis with fluconazole
  - Transplant recipients with a past or recent history of coccidioidomycosis or positive *Coccidioides* serologies prior to surgery
  - Active infection or positive serologies in the donor
- Lifelong antifungal prophylaxis is recommended for organ transplant recipients

Proia L. Am J Transplant 2009;9(S4):S199–207

Histoplasmosis

- Patients who have recovered from active histoplasmosis infection, with or without treatment, during the 2 years prior to initiation of immunosuppression may be considered for itraconazole prophylaxis (200 mg daily), although the efficacy and appropriate duration of prophylaxis is unknown (lung tx)

Proia L. Am J Transplant 2009;9(S4):S199–207

Antifungal Prophylaxis: Unanswered Questions

- Risk stratification especially with biomarkers and diagnostics methods to identify highest risk transplant recipients

- Optimal antifungal prophylaxis
  - Universal vs. preemptive
  - Choice of agents
  - Duration of prophylaxis

- Life is an unanswered question, but lets still believe in the dignity and importance of the question

- Tennessee Williams