The Epidemiology, Prevention and Diagnosis of Fungal Infections in Solid Organ Transplant Recipients

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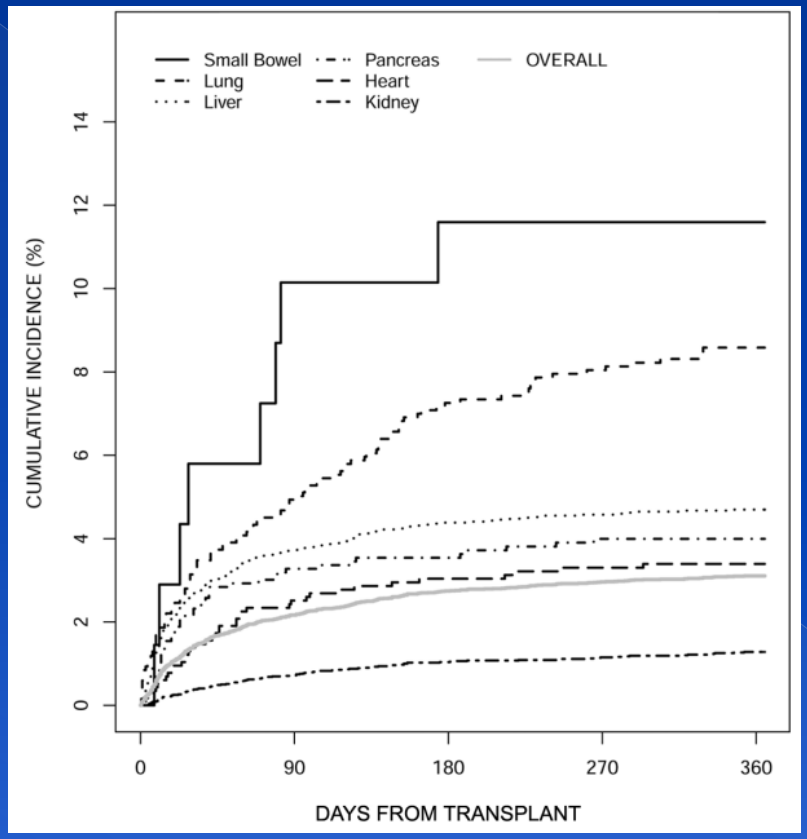
MULTI ORGAN Transplant PROGRAM

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Objectives

- To understand the current epidemiology & risk factors of fungal infections in solid organ transplant (SOT) recipients
- To understand utility of currently available antifungal tests (anti mold) in solid organ transplant recipients.
- To review the role of antifungal prophylactic strategies in SOTs

Cumulative Incidence of IFI in Solid Organ Transplantation



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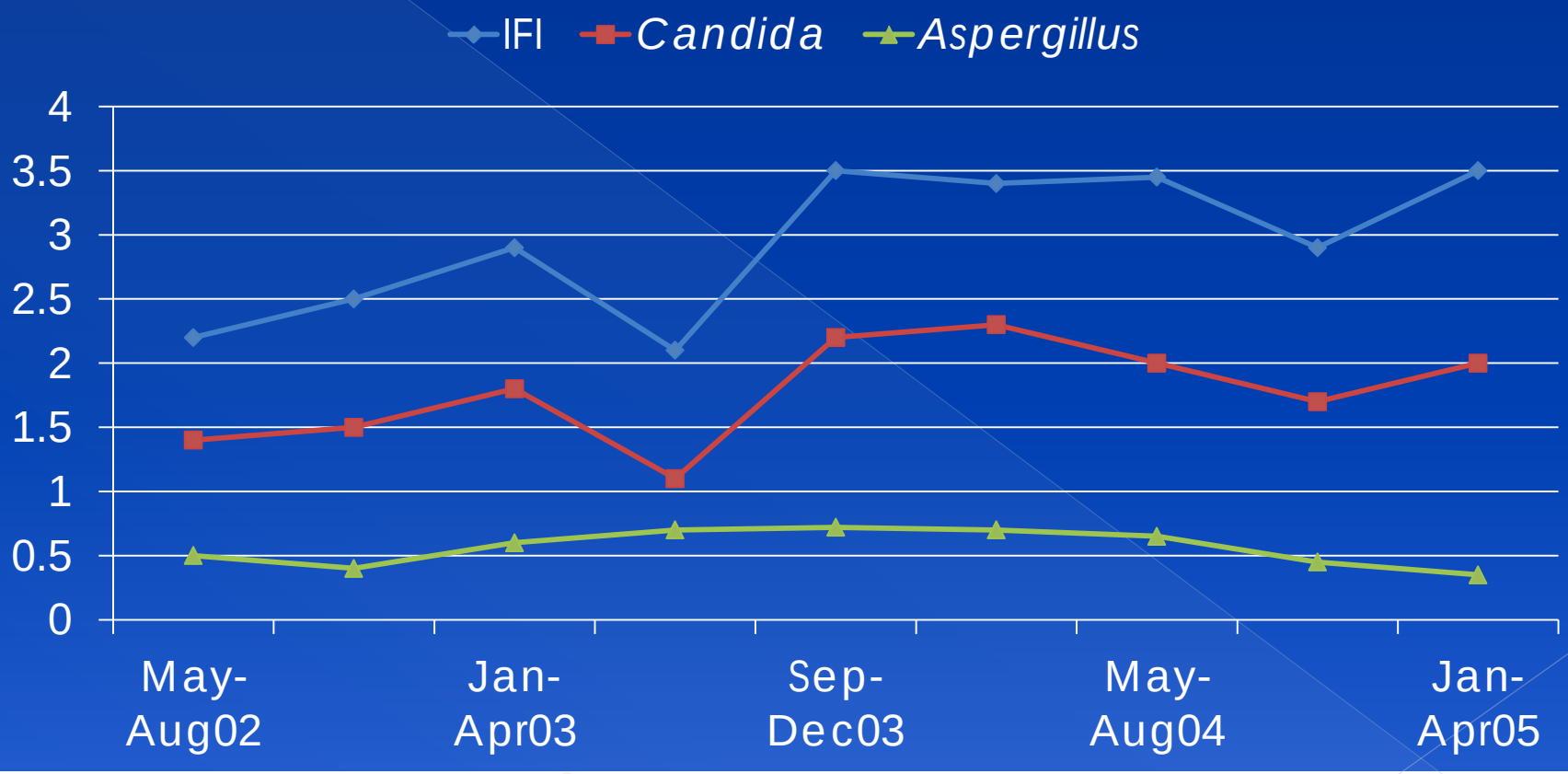
Pappas P et al. Clin Infect Dis 2010;50(8):1101-11

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



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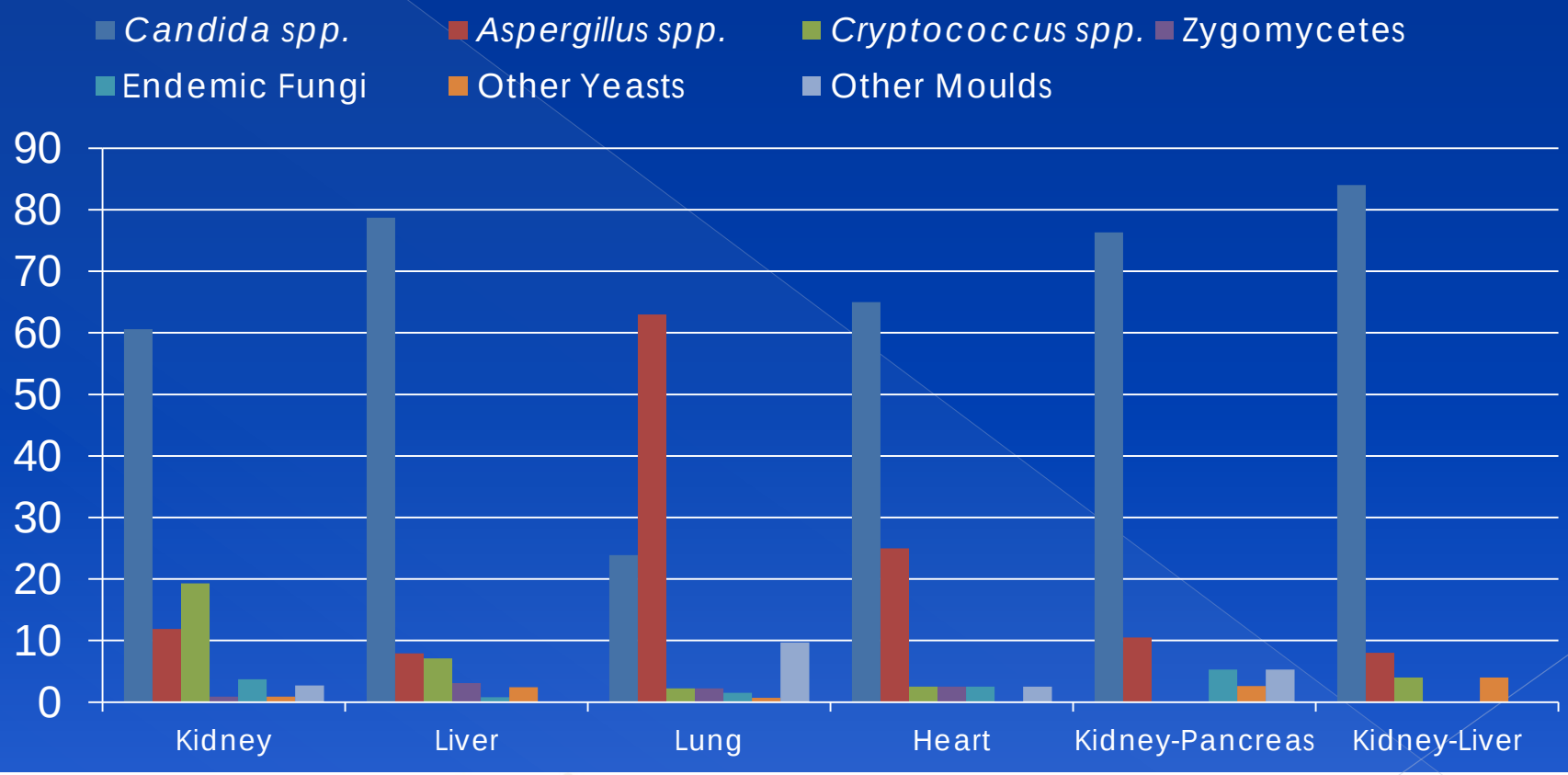
Pappas P et al. Clin Infect Dis 2010;50(8):1101-11

Data on Distribution of IFI in Solid Organ Transplantation



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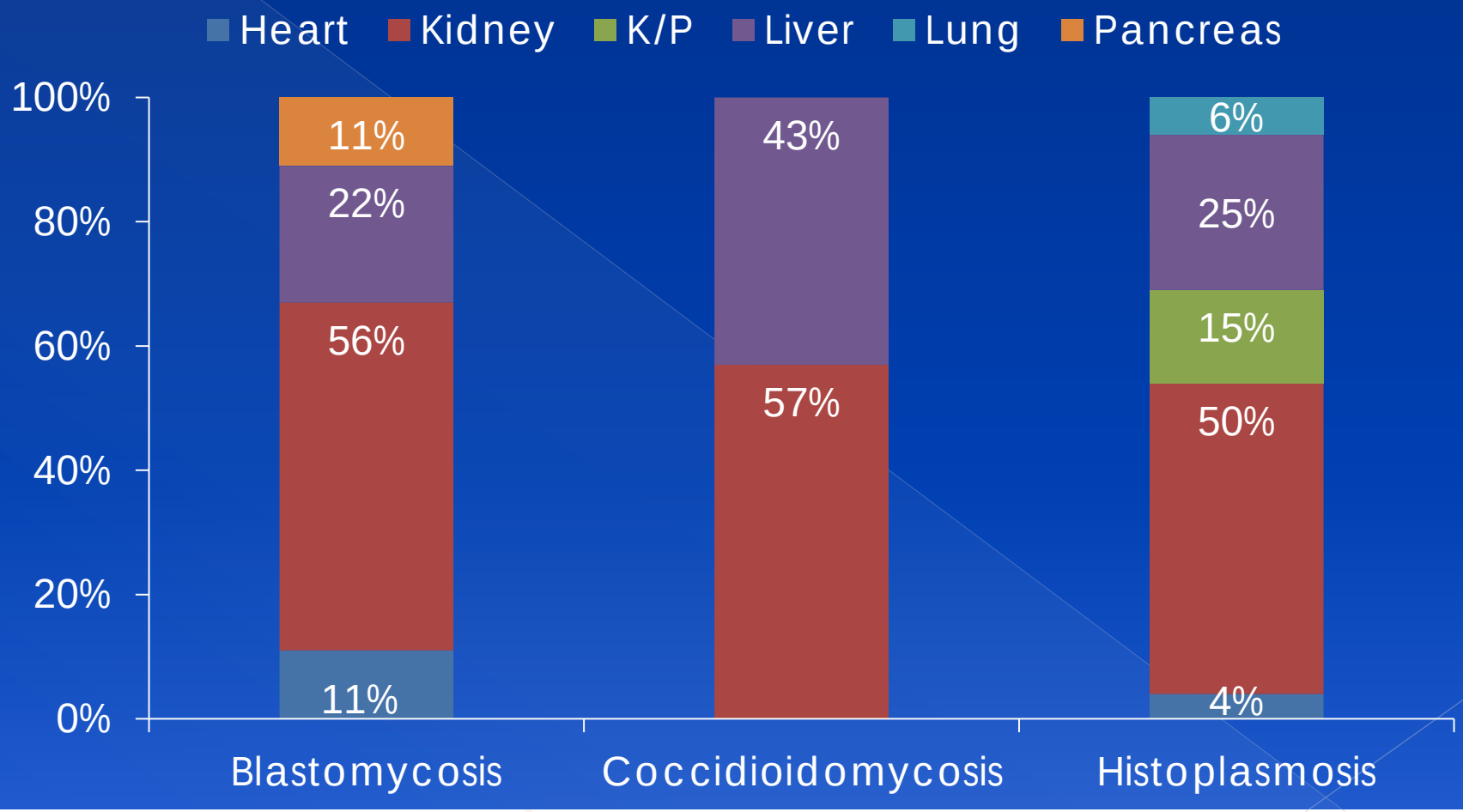
Neofytos D et al. Transplant Infect Dis 2010;12(3):220-9

Endemic FI in SOTR



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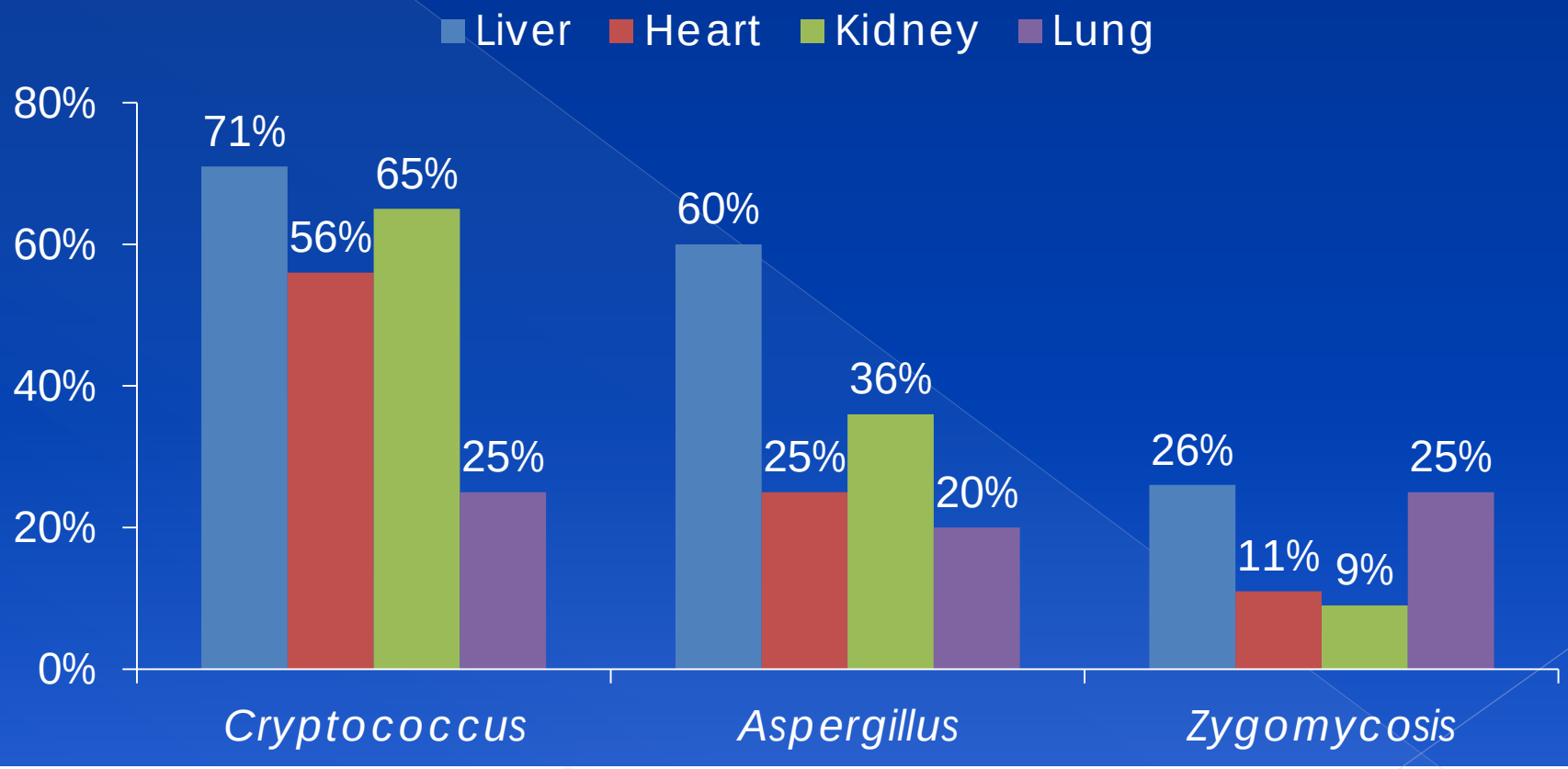
Kauffman CA et al. Transpl Infect Dis 2014;16:213-24

Phaeohyphomycosis

- 30 solid organ transplant (SOT) recipients.
- Median time to diagnosis post-transplant was SOT 685 days.
- Cutaneous infection was more common in SOT (23.1%).
- Overall mortality was 25% and was higher in SCT than in SOT (42% vs 10%; P = <.001).

McCarty TP et al. Med Mycol 2015 [epub ahead of print]

Disseminated Invasive Fungal Infection in Liver Transplantation



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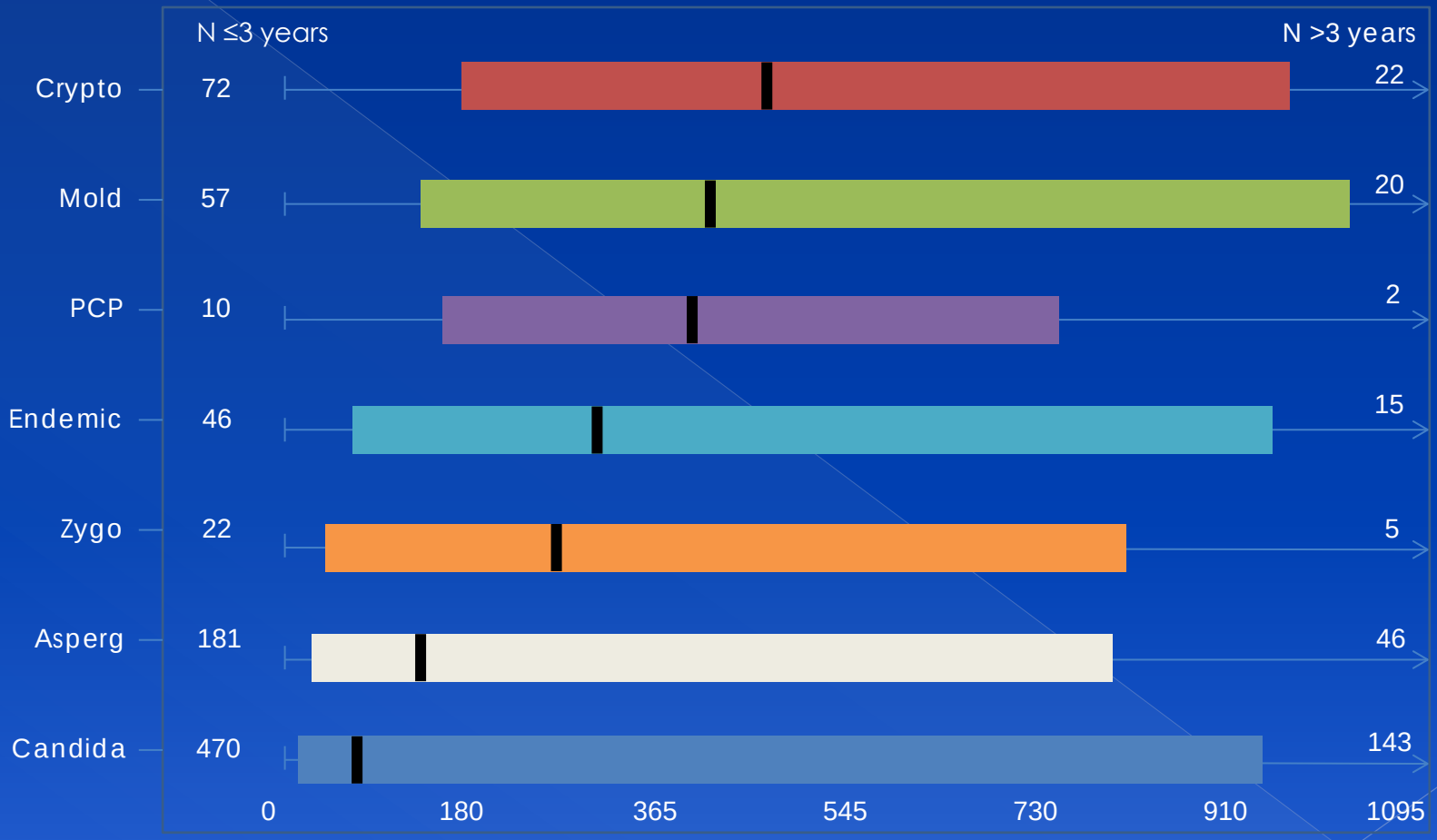
Singh N et al. Liver Transpl 2008;14:1249-55

Timing of IFIs



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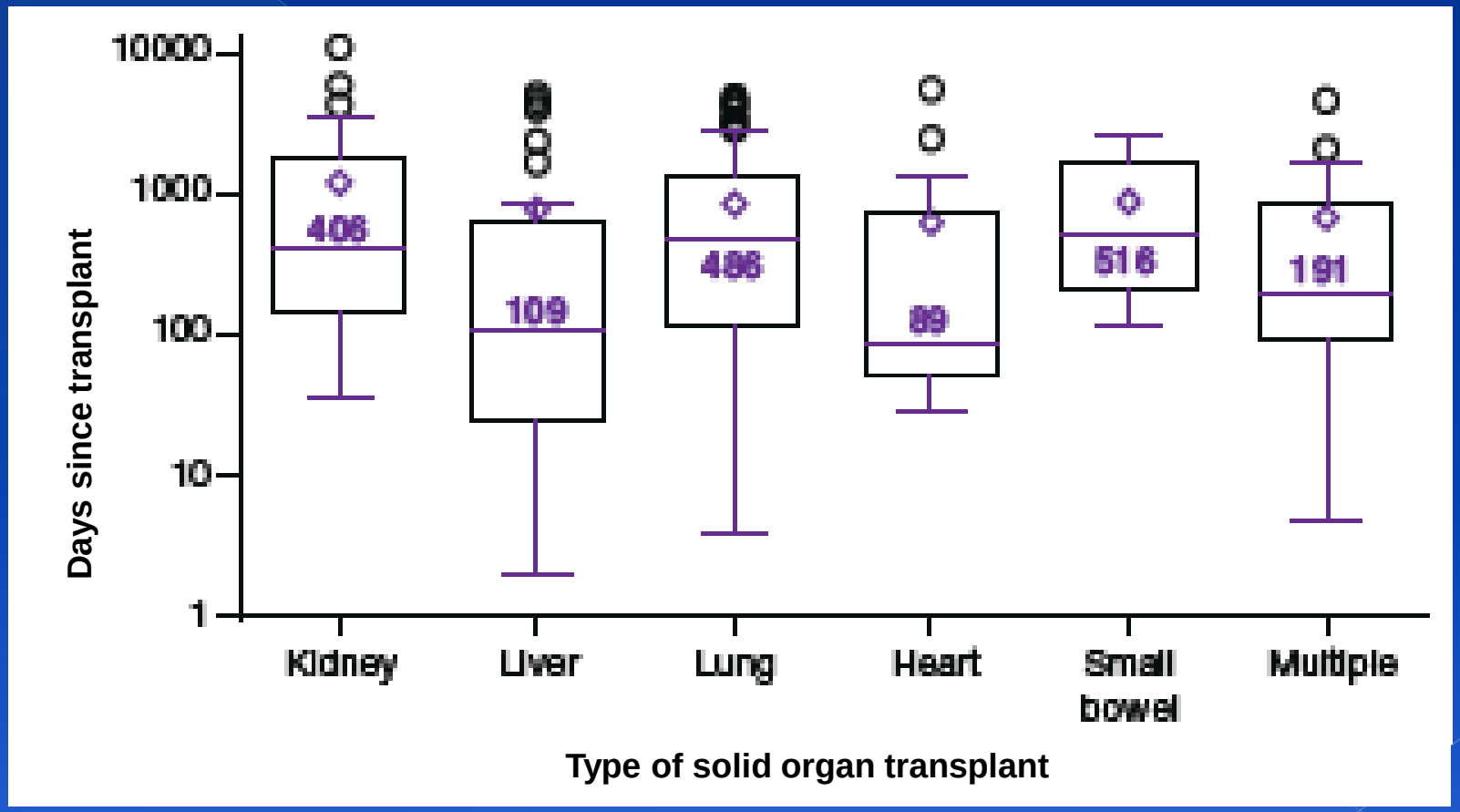
Pappas P et al. Clin Infect Dis 2010;50(8):1101-11

Box and Whisker Plot Indicating Time to IMI Since SOT



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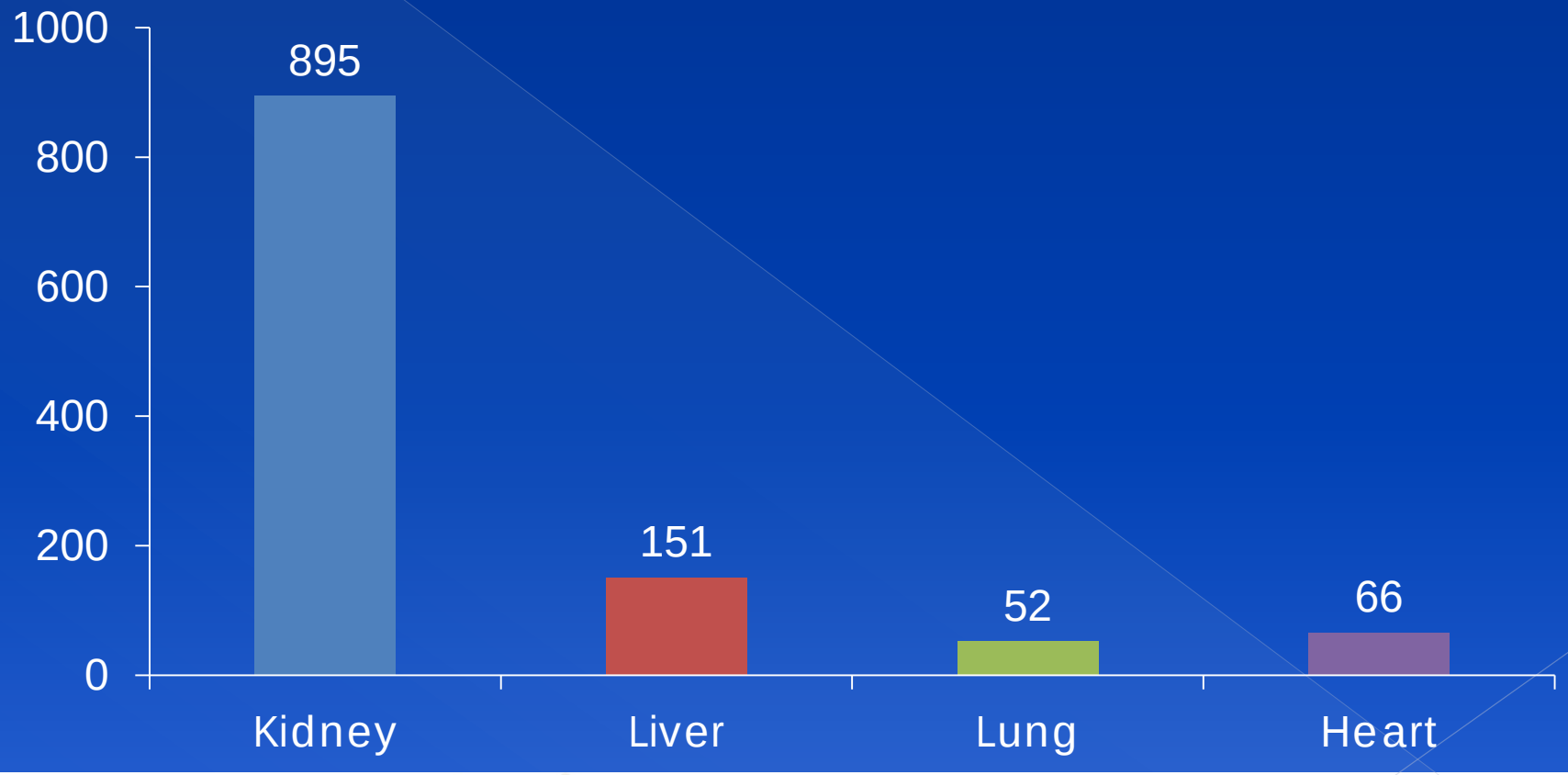
Husain S IDSA 2011

Invasive Candidiasis in Solid Organ Transplantation

- *C. albicans* was the most common species, noted in 46.3% of patients
- Patients who received prior antifungal therapy had a higher likelihood of developing *C. glabrata* or *C. krusei*
  - Majority on prophylaxis
- Mortality of 45.8% in liver transplants

Neofytos D et al. Transplant Infect Dis 2010;12(3):220-9

Median Time to Onset to Invasive Candidiasis in SOT



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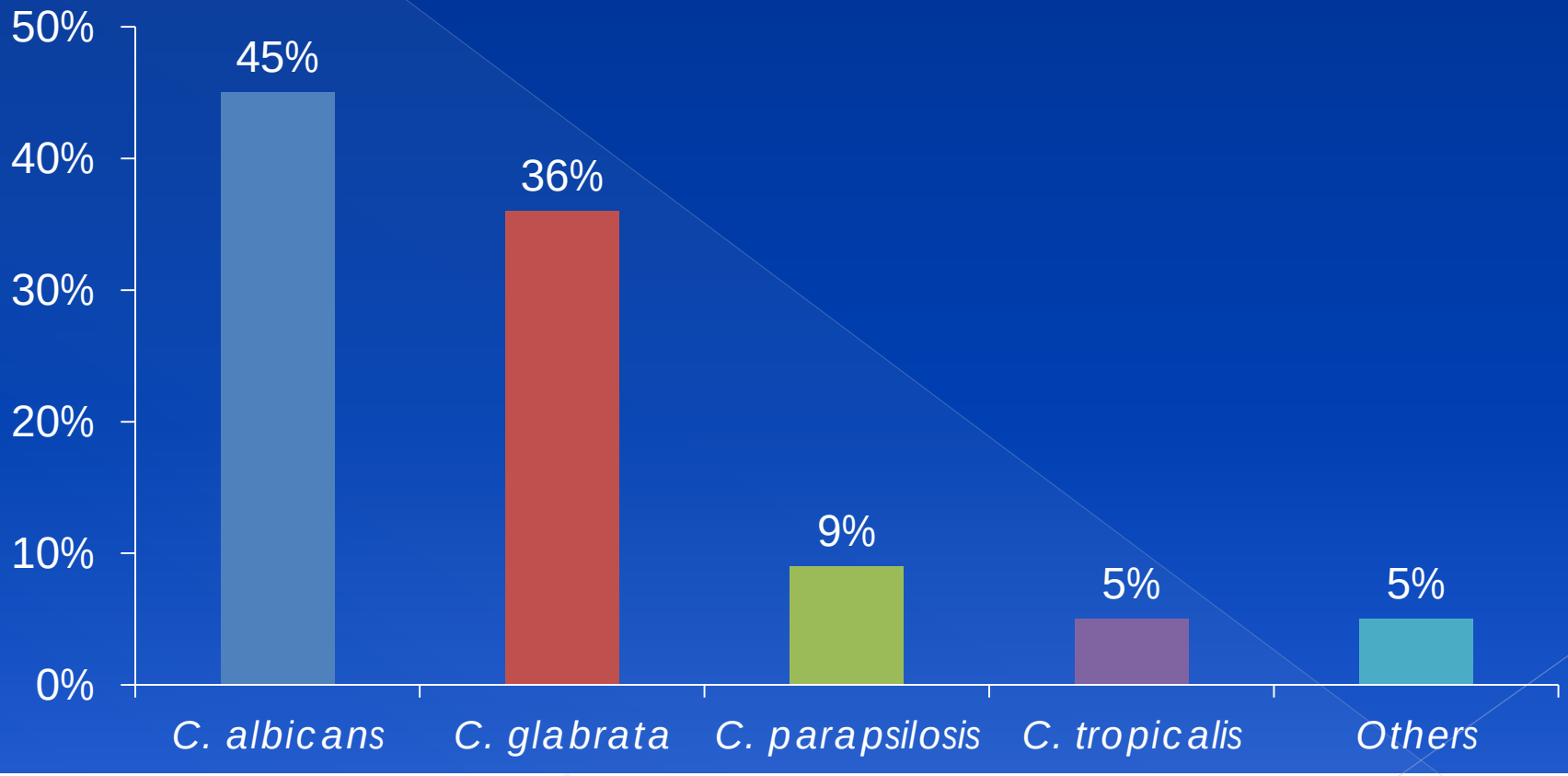
Neofytos D et al. Transplant Infect Dis 2010;12(3):220-9

Distribution of *Candida* Species in Solid Organ Transplantation



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Neofytos D et al. Transplant Infect Dis 2010;12(3):220-9

Another Cohort Study

- The incidence of IFIs was 12%
- Non-albicans *Candida* species accounted for 55% of IFIs
  - 50% of these were *C. parapsilosis*
- Only 43% of *Candida* isolates were fluconazole-susceptible (MIC 8 l/mL)
- All *C. parapsilosis* isolates were fluconazole-resistant which coincided with a surge of these isolates during a peak period of liver transplants

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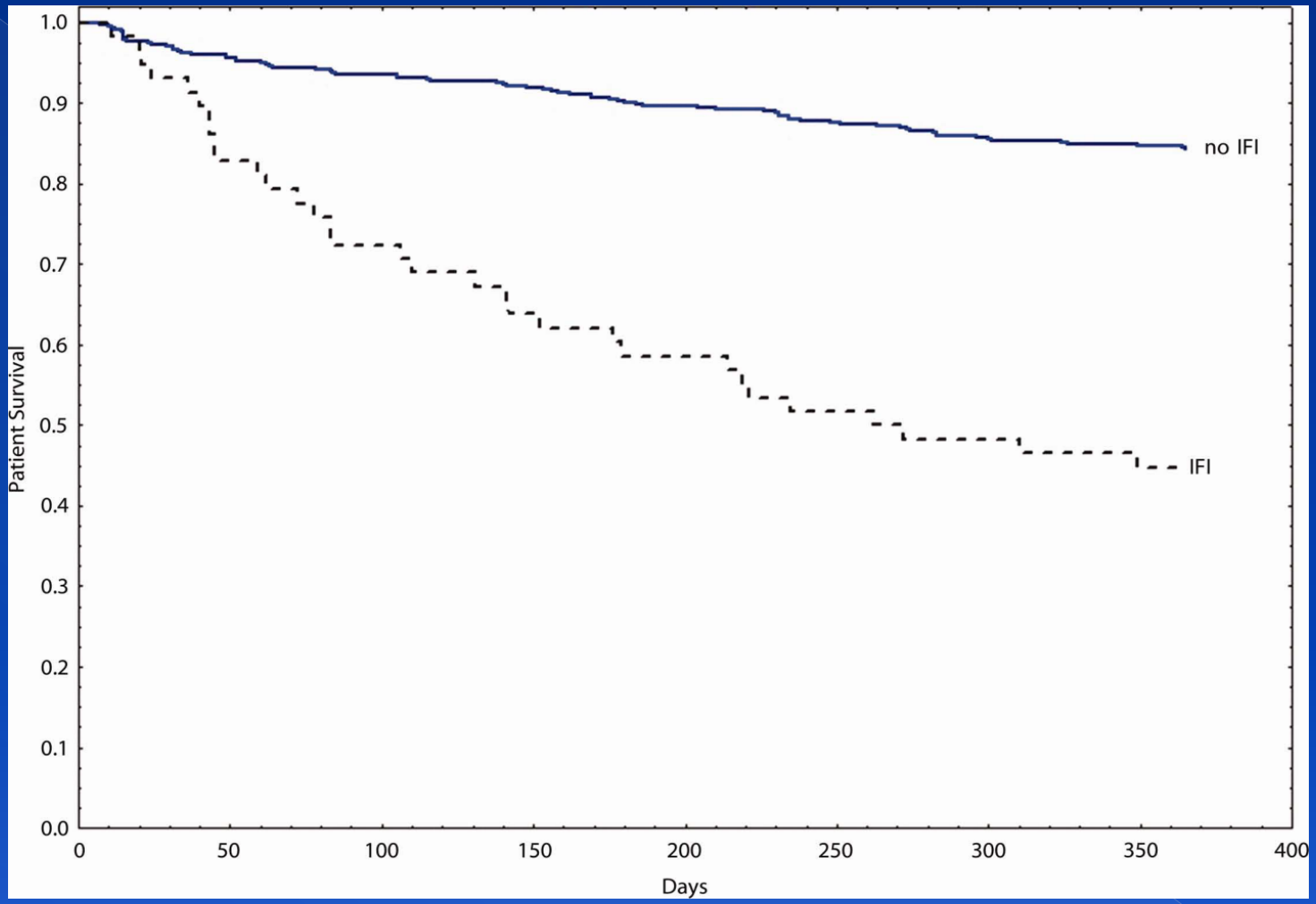
Raghuram A et al. Liver Transpl 2012;18:1100-9



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Raghuram A et al. Liver Transpl 2012;18:1100-9

Risk Factors

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Risk Factors for IFI Common to All Solid Organ Transplantation

- Technical/anatomical abnormalities
  - Skill in operative/perioperative management
  - Vascular access devices (VADs)
  - 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

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

Prospective Study: Lower Risk (<4 %) with Only One Risk Factor

- Choledochojejunostomy anastomosis
- Retransplantation
- Intraoperative 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 orthotopic liver transplantation (OLT)
- *Candida* species isolated from surveillance culture between 48h prior until 48h post-OLT
- Return to OR within 5 days of OLT for laparotomy
- Primary graft non-function

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

Risk Factors for Invasive Fungal Infections

Factors	Univariate			Multivariate
	IFI (n=20)	No IFI (n=362)	*P* value, odds ratio (95% CI)	*P* value, odds ratio (95% CI)
Living donor	35% (7/20)	12% (42/362)	0.008, 4.10 (1.55-10.86)	0.04, 2.96 (1.05-8.40)
Bile leaks within 30 days posttransplant	30% (6/20)	4% (16/362)	0.004, 9.27 (3.15-27.29)	0.001, 7.13 (2.31-22.04)

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Eschenauer GA et al. Am J Transplant 2015;15:180-189

Variables Associated with Fungal Infection in Living Donor Liver Transplantation

Variable	Odds ratio	95% CI	*P* value
Reoperation	6.92	1.82-26.27	0.004
Posttransplant dialysis	5.62	1.517-20.887	0.009
Bacterial infection	3.94	1.02-15.26	0.04

Ohkubo T et al. J Hepatobiliar Pancreat Sci 2012;19(4):382-8

Univariate & Multivariate Analyses of Factors Associated with IFIs

	Univariate Analyses				
	IFI group (n=58)	Non-IFI group (n=444)	Odds ratio	*P* value	95% CI
Creatinine level >2 mg/mL	28/58	103/444	2.4	0.01	1.2-5.0
Fungal colonization	25/58	39/443	7.0	<0.001	3.2-15.3
Calculated MELD score >25	**32/58**	**119/444**	**2.4**	**0.02**	**1.2-4.9**
Postoperative factors (n/N)					
Fluconazole dosage <200 mg daily	12/56	52/426	2.8	0.03	1.1-7.4

	Multivariate Analyses		
	Odds ratio	*P* value	95% CI
Fungal colonization	**7.8**	**<0.001**	**3.9-16.2**

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Raghuram A et al. Liver Transpl 2012;18(9):1100-9

Risk Factors for Late Onset Invasive Aspergillosis in SOT

Variables	Multivariate analysis	
	Odds ratio (95% CI)	*P* value
SOT at age >50 years	2.5 (1.3-5.1)	.009
Renal failure after SOT	3.9 (1.9-7.8)	<.0001
Blood levels of Tac >15 ng/mL or CyA >500 ng/mL at month 3	2.5 (1.2-5)	.011
Use of Tac and CyA for the same patient	3.2 (1.1-9.4)	.032
>1 episode of bacterial infection	7.5 (3.2-17.4)	<.0001
Significant leukopenia (<3000 leukocytes/mm^3)	1.9 (0.9-3.7)	.056
Immunosuppression-related neoplasm	69.3 (6.4-753)	<.0001
Chronic graft rejection	5 (1.9-13)	.001

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Gavalda J et al. Clin Infect Dis 2005;41(1):52-9

Unique Factors Contributing to Risk of Infection in Lung Transplantation

Continuous contact with pathogens

Higher state of immunosuppression

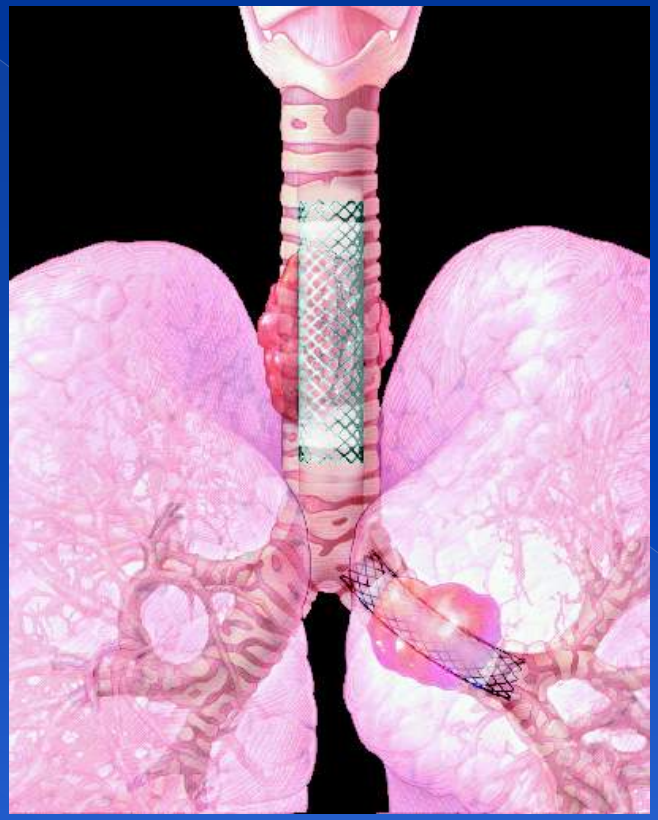
Airway colonization

Pulmonary stent

The native lung

Hypogammaglobulinemia

CARV Infection



Denervation

Impaired cough reflex

Ischemic reperfusion injury

Decrease mucociliary clearance

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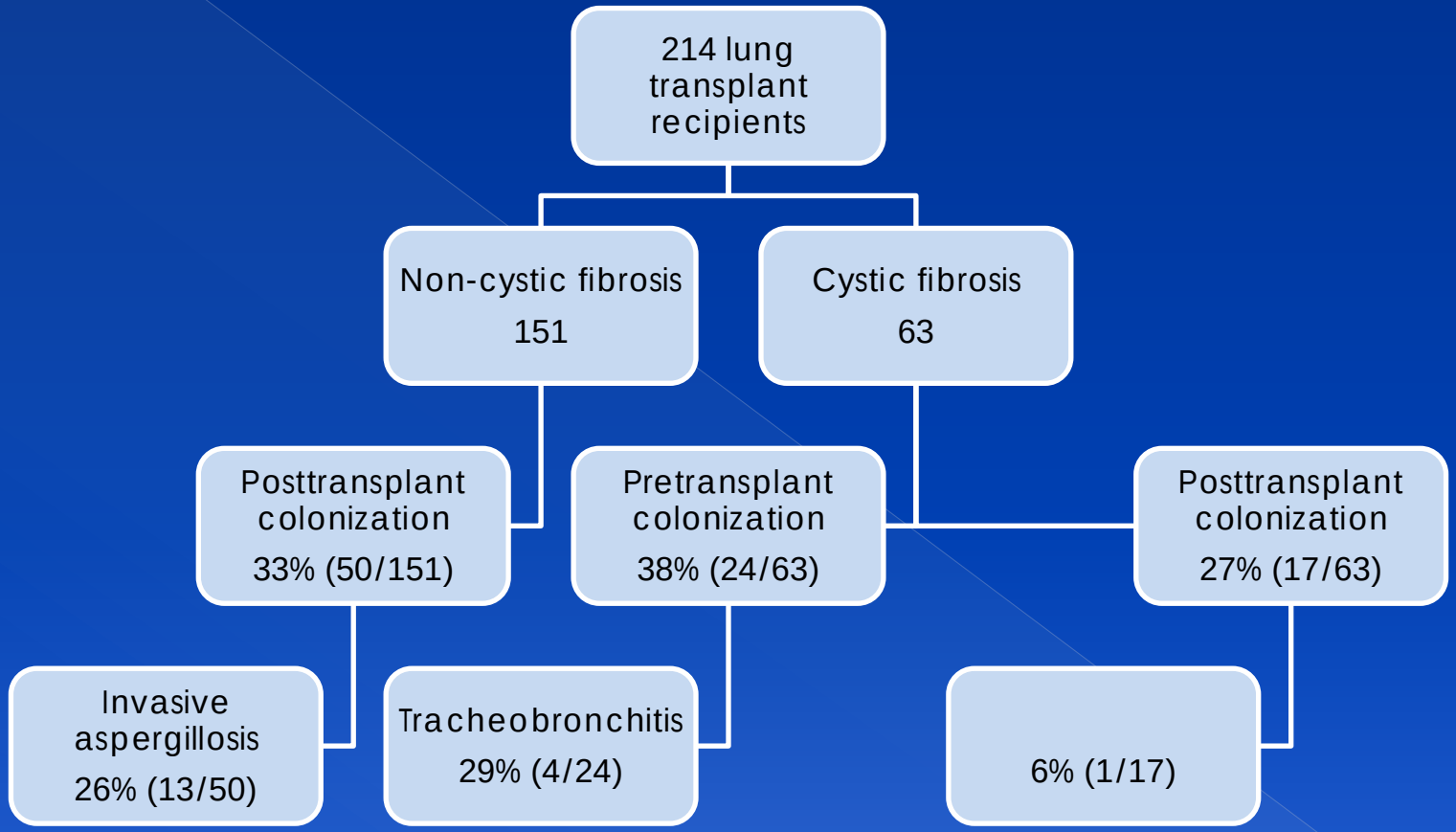
Husain S. Clin Chest Med 2009;30(2):307-13

Colonization



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

Risk Factors for Invasive Aspergillosis in Heart Transplant Recipients

- Heart
  - Isolation of Aspergillus species in respiratory tract cultures
  - Reoperation
  - CMV disease
  - Post-transplant hemodialysis
  - Episode of IA in the program, 2 months before or after heart transplant

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

Predictors of IFI in Univariate Analysis (2004-2010)

Variable	IFI (n=6)	No IFI (n=53)	Odds ratio	95% CI	*P* value
Male sex	5 (83)	40 (75)	0.61	0.66-5.76	0.67
Age >55	5 (83)	20 (38)	8.24	0.89-75.79	0.06
Thymoglobulin	4 (67)	41 (82)	0.44	0.69-2.78	0.38
RRT	5 (83)	12 (23)	17.08	1.81-160.68	0.01
ECMO	4 (67)	8 (15)	11.25	1.76-72.01	0.01
VAD	0	12 (23)	---	---	---
Reoperation during week 1	4 (67)	15 (28)	5.06	0.84-30.64	0.08
Aspergillus species colonization	2 (33)	3 (6)	8.33	1.06-65.3	0.04
Antifungal prophylaxis	0	8 (15)	---	---	---

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Tissot F et al. Transplantation 2014;97:1192-7

Severity of Fungal Disease

Mortality

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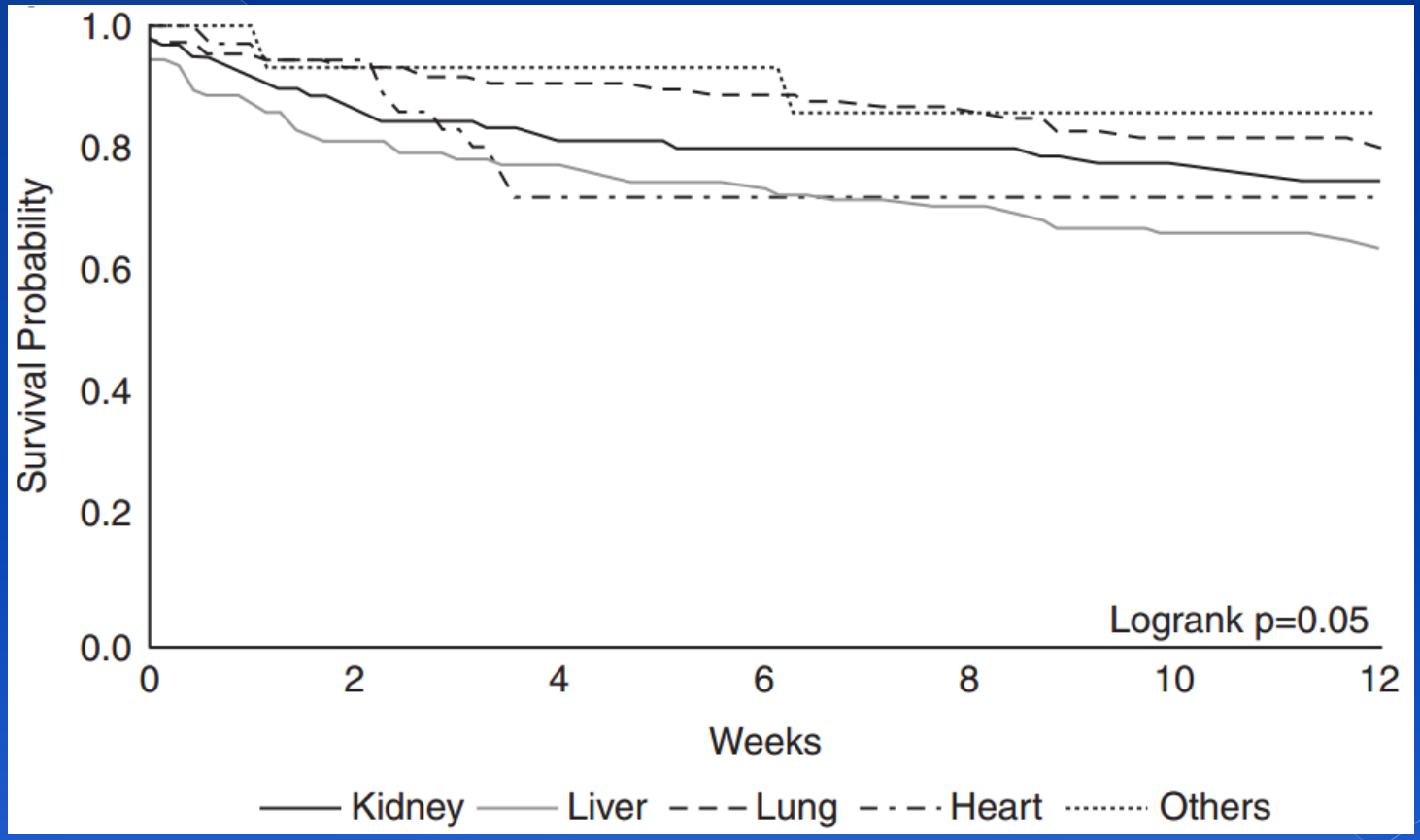
Mortality Associated with IFI in Solid Organ Transplantation



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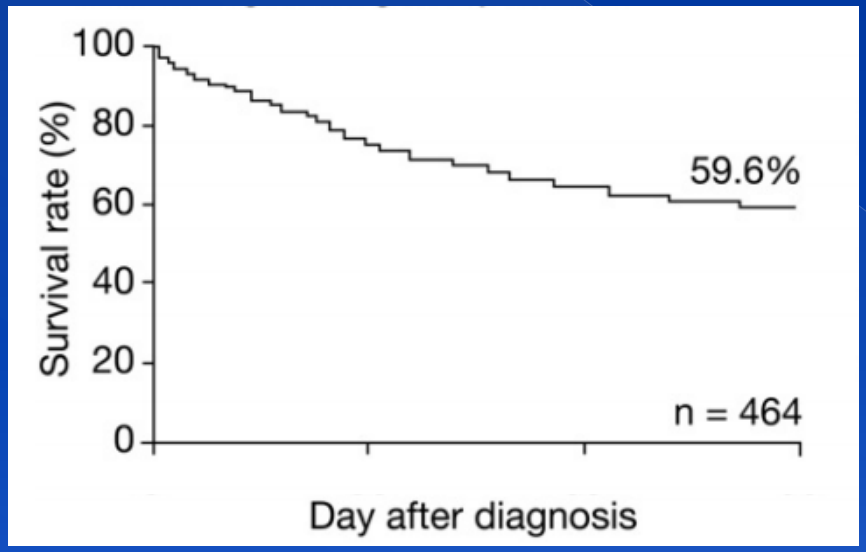
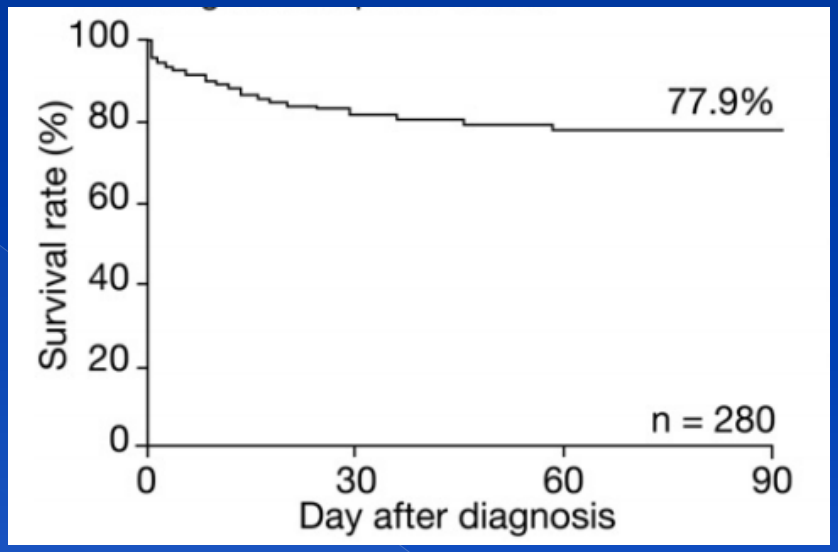
Neofytos D et al. Transplant Infect Dis 2010;12(3):220-9

Mortality with Invasive Aspergillosis

Hematologic malignancy cohort



Solid organ transplant cohort



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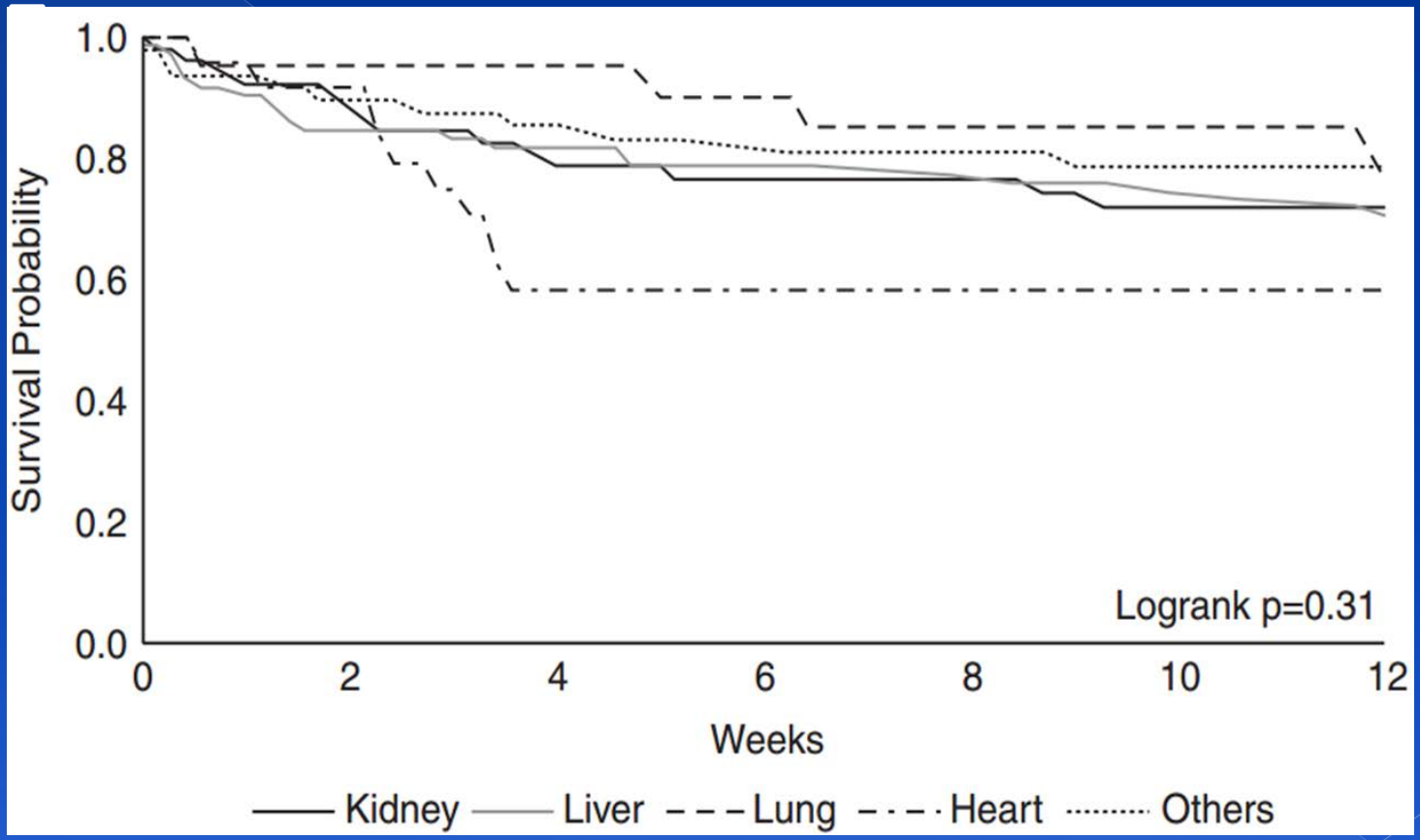
Steinbach WJ et al. J Infect 2012;65(5):453-64

Mortality Associated with Candidiasis in SOT



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Diagnosis

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Serum GM: Cut-off

- Initial controversy regarding optimal cut-off
- Cochrane Database Systematic Review
  - 30 studies

Cut-off	Sensitivity (95%CI)	Specificity (95%CI)	No patients (No. studies)	Median prevalence	FN/FP
>0.5	0.79 (0.61-0.93)	0.82 (0.71-0.92)	901 (7)	9.9 (0.8-34)	2/17
>1.0	0.71 (0.61-0.81)	0.90 (0.87-0.94)	1744 (12)	12.4 (0.8-44)	2/9
>1.5	0.62 (0.45-0.79)	0.95 (0.92-0.98)	2600 (17)	7.4 (0.8-34)	3/5

Leeflang et al. Cochrane Database Syst Rev 2008;8(4):CD007394

Serum GM: Population

- Serum GM performs well in BMT and hematologic cancer pts
- Serum GM not sensitive for the diagnosis of IA in SOT

Metanalysis of 27 studies

Studies	Cases of proven IA				Cases of proven or probable IA			
	TP/(TP + FP)	Pooled sensitivity (95% CI)	TN/(TN + FP)	Pooled specificity (95% CI)	TP/(TP + FN)	Pooled sensitivity (95% CI)	TN/(TN + FP)	Pooled specificity (95% CI)
All	163/229	0.71 (0.68–0.74)	3601/4055	0.89 (0.88–0.9)	250/407	0.61 (0.59–0.63)	2839/3060	0.93 (0.92–0.94)
Studies limited to patients with hematological malignancy	106/152	0.70 (0.62–0.77)	2570/2808	0.92 (0.90–0.93)	177/304	0.58 (0.52–0.64)	2324/2457	0.95 (0.94–0.96)
Studies limited to patients undergoing BMT	49/60	0.82 (0.70–0.90)	722/843	0.86 (0.83–0.88)	32/49	0.65 (0.60–0.78)	17/26	0.65 (0.44–0.83)
Studies limited to solid-organ transplant recipients	2/9	0.22 (0.03–0.60)	180/215	0.84 (0.78–0.88)	9/22	0.41 (0.21–0.64)	210/247	0.85 (0.80–0.89)

	Organ	Incidence	Cut-off	Sensitivity	Specificity
Fortun et al. Transplant 2009	Liver (240)	5.8	OD > 0.5	55.6	93.9
Husain et al. AJT. 2004	Lung (70)	17.1	OD> 0.5	30	93
Kwak et al. JCM. 2004	Liver (154)	0.6	OD > 0.5	NA	87%

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Pfeiffer et al. CID 2006;42:1417-27

What About BAL GM?

BAL GM in SOT

Authors	Patients	Cut-off	Sens(%)	Spec(%)	PPV(%)	NPV(%)	Ref
Pasqualotto A	60 lung TX, 8 IPA	≥1.5	100	90.4	51.5	100	Transpl 2010 15;90(3):30
Husain S	196 lung TX, 11 IPA	≥0.5	81.8	95.8	50.6	99	Clin and Vacc Imm 2008:1760–1763
Husain S	116 Lung Tx ,6 IPA	≥0.5	66.6	98.3	57.1	98	Transpl 2007 27;83(10):1330
Luong M	137Lung tx 16 IPA	≥0.5	93	89	48	99	CID 2011:52
		≥1.0	67	97	71	96	

BAL GM: Cut-off

Studies	No. studies	Pooled SEN (95% CI)	Pooled SPE (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)
Overall analyses	13	0.90 (0.79-0.96)	0.94 (0.90-0.96)	14.87 (8.89-24.90)	0.10 (0.04-0.24)
Cutoff of 0.5 for positivity	8	0.86 (0.70-0.94)	0.89 (0.85-0.92)	7.69 (5.75-10.28)	0.15 (0.07-0.35)
Cutoff of 1.0 for positivity	11	0.85 (0.72-0.93)	0.94 (0.89-0.97)	14.29 (8.33-24.50)	0.16 (0.08-0.31)
Cutoff of 1.5 for positivity	9	0.70 (0.49-0.85)	0.96 (0.93-0.98)	18.97 (10.93-32.93)	0.31 (0.17-0.57)
Cutoff of 2.0 for positivity	5	0.61 (0.38-0.80)	0.96 (0.92-0.98)	16.13 (8.07-32.25)	0.40 (0.23-0.70)

- BAL GM is superior to serum GM for IA
  - BMT and hematologic cancer patients
  - SOTs
- High rate of false positive results
- Better performance using higher cut-off value (>1.0?)

Guo YL. Chest 2010;138(4):817-24

Performance of BAL PCR and GM Assays in the Diagnosis of IPA

Assay result	Performance, % (95% CI) [no. of samples]		Likelihood ratio
	Sensitivity	Specificity	
BAL PCR	100 (79-100) [16/16]	88 (79-92) [118/134]	8.4
BAL GM index ≥1.0	67 (38-88) [10/15]	97 (92-99) [129/133]	22.2
BAL GM index ≥0.5	93 (68-100) [14/15]	89 (82-93) [118/133]	8.3

Luong et al. CID 2011:52

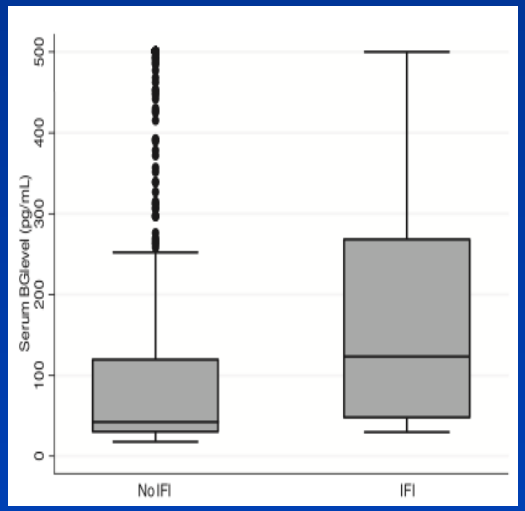
Unanswered Questions in Fungal PCR

- Diagnostic utility as compared to existing serological markers
- Cost utility
- Prognostic utility
- Role in colonization in lung transplantation
- More data in immunocompromised hosts

(1→3) β-D-Glucan

BDG Assay – Clinical Validity (SOT)

- 73 lung transplant patients monitored prospectively
  - 14 IA
- FungiTell assay in serum
- Accuracy of BDG in lung transplant is marginal
  - 90% of lung transplant patients without an IFI had at least 1 positive BDG result



Glucan positive cutoff (pg/ml)	% (95% confidence interval)			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
60	70.7 (54.5, 83.9)	58.7 (55.1, 62.3)	8.5 (5.8, 12.0)	97.4 (95.4, 98.6)
70	63.4 (46.9, 77.9)	62.6 (59.0, 66.0)	8.4 (5.6, 12.0)	96.9 (95.0, 98.3)
80	63.4 (46.9, 77.9)	65.9 (62.4, 69.3)	9.2 (6.1, 13.1)	97.1 (95.2, 98.4)
100	58.5 (42.1, 73.7)	71.3 (67.9, 74.5)	9.9 (6.5, 14.5)	96.9 (95.1, 98.2)

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Alexander et al. JCM 2010

Comparison of MAP and GM Assays on Serum Samples

Parameter	Test result % (95% CI) by:		P value
	MAP	GM	
Sensitivity	46.7 (28.3-65.7)	50.0 (31.3-68.7)	n.s.
Specificity	97.6 (87.4-99.9)	95.1 (83.5-99.4)	n.s.
PPV	93.3 (68.1-99.8)	88.2 (63.6-98.5)	n.s.
NPV	71.4 (57.8-82.7)	72.2 (58.4-83.5)	n.s.

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Pini P et al. Eur J Clin Microbiol Infect Dis 2015;34:131-6

Lateral-Flow Device Test

Medical center/SOT	Sensitivity	Specificity	PPV	NPV	DOR (95% CI)
Innsbruck	100 (3/3)	79 (11/14)	50 (3/6)	100 (11/11)	29 (1.2-700)
Vienna	100 (6/6)	81 (13/16)	67 (6/9)	100 (13/19)	50 (2.2-1121)
Graz	50 (1/2)	100 (6/6)	100 (1/1)	86 (6/7)	13 (0.34-505)
Overall (all 3 centers)	91 (10/11)	83 (30/36)	63 (10/16)	97 (30/31)	50 (5.4-467)
LuTx	100 (5/5)	86 (18/21)	63 (5/8)	100 (18/18)	58 (2.6-1307)

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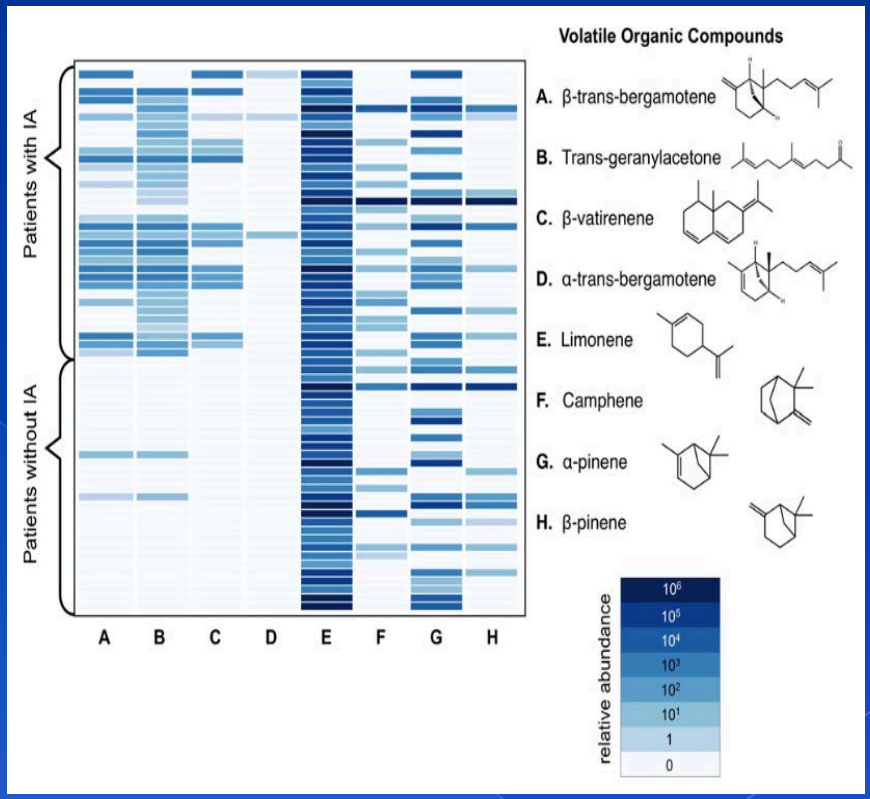
Willinger B et al. Transplantation 2014;98(8):878-902

A Breath Fungal Secondary Metabolite Signature to Diagnose IA

- Thermal desorption-gas chomatography/mass spectrometry to characterize the in-vitro volatile metabolite profile of *Aspergillus fumigatus*
  - Assessed volatile organic compounds (VOCs) profiles of pathogenic *Aspergillus* species in-vitro
  - Assessed whether they could identify evidence of *Aspergillus* metabolism in the breath of patients undergoing evaluation for IA
- Prospectively collected breath samples from 64 patients from 2011 to 2013
- α- and β-pinene, limonene and α- and β-trans-bergamotene
- Identified IA patients with 94% sensitivity and 93% specificity



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Effectiveness of Antifungal Prophylaxis

Meta-analysis of Antifungal Prophylaxis in LTRs

Outcomes	Cruciani RR (95% CI), n=698	Playford EJ RR (9% 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 colonization	**---**	**1.57 (0.76-3.24)**
Mortality	**1.06 (0.69-1.64)**	**0.84 (0.54-1.30)**

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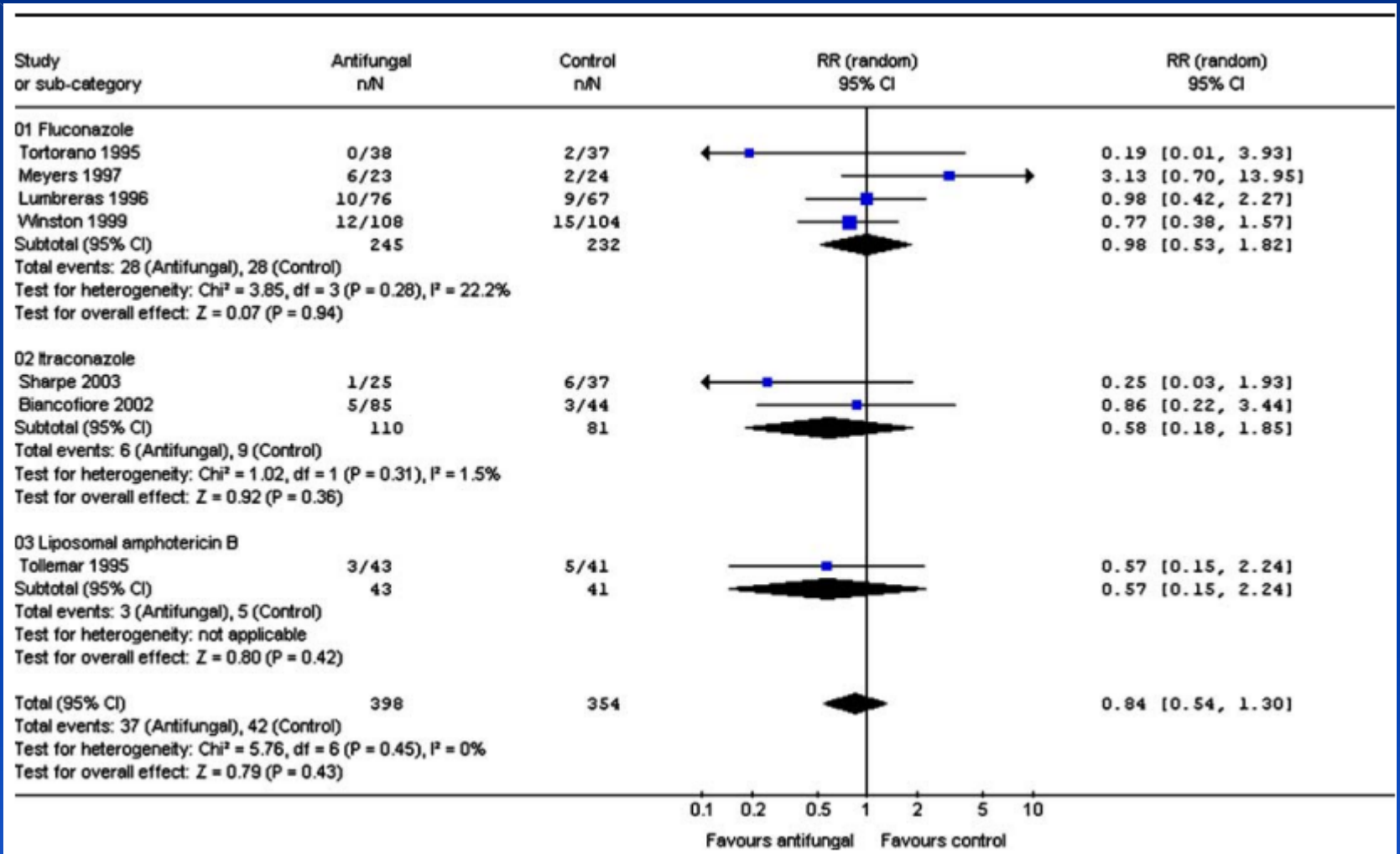
Cruciani M et al. Liver Transpl 2006;12:850-8
Playford EG et al. Eur J Clin Microbiol Infect Dis 2006;25:549-61



Although fewer data on prophylactic itraconazole and LAmB were available, indirect comparisons and three direct comparative trials suggested similar efficacy.

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

Meta-analysis Results: Systemic Prophylaxis Versus Placebo

Outcome	Patients	Studies	Odds ratio (CI)	*P* value	Cochran Q *P* value	I^2 (%)
Proven IFI	745	7	0.37 (0.19-0.72)	0.003	0.44	24.5
Proven or suspected IFI	616	6	0.40 (0.25-0.66)	0.003	0.78	0
Superficial fungal infection	464	4	0.19 (0.08-0.43)	<0.0001	0.38	29.2
Fungal colonization	489	4	0.28 (0.17-0.49)	<0.0001	0.13	44.83
Adverse events	696	6	0.11 (0.48-2.55)	0.81	0.86	0
Mortality attributed to fungal infection	670	5	0.32 (0.10-0.83)	0.02	0.61	2.6
Overall mortality	752	7	0.87 (0.54-1.39)	0.55	0.46	0
Aspergillus IFI	755	7	0.95 (0.35-2.58)	0.92	0.80	0

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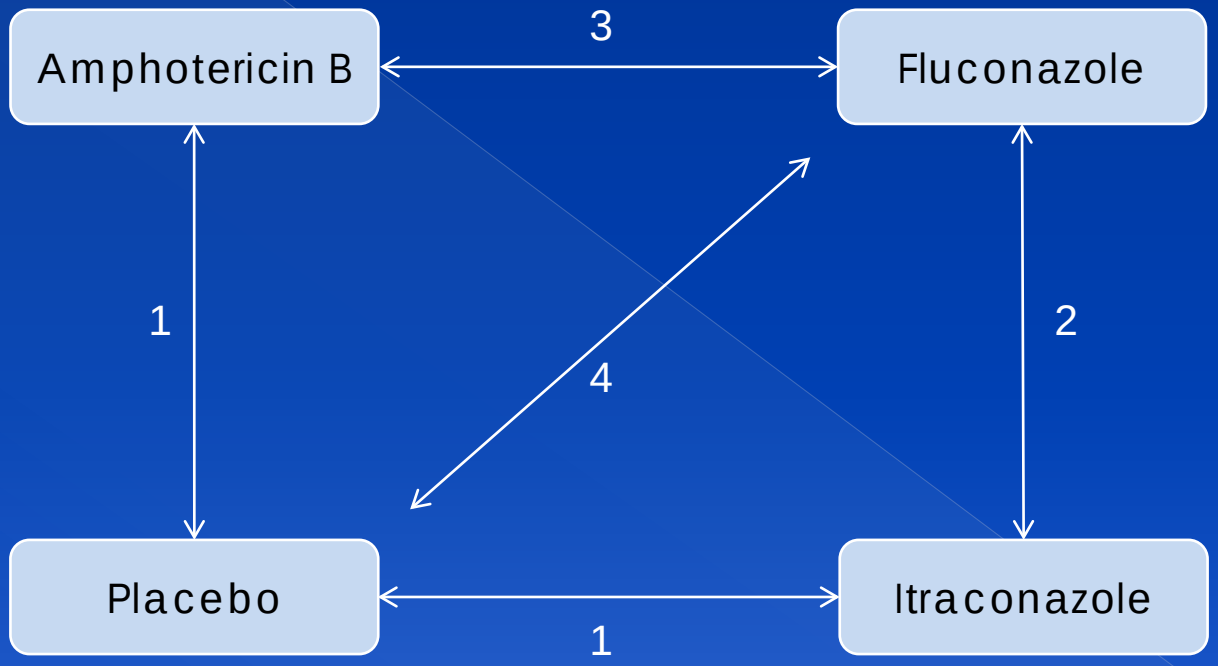
Evans JDW et al. Am J Transplant 2014;14(12):2765-76

Network of Trials Use in the Mixed Treatment Comparison



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Evans JDW et al. Am J Transplant 2014;14(12):2765-76

Bayesian Mixed Treatment Comparison: Relative Effects of Each Treatment on the Odds of IFI

Amphotericin B	1.00 (0.32, 2.90)	0.60 (0.09, 4.15)	**0.21 (0.05, 0.71)**
1.00 (0.35, 3.08)	**Fluconazole**	0.61 (0.12, 3.02)	**0.21 (0.06, 0.57)**
1.67 (0.24, 11.40)	1.65 (0.33, 8.31)	**Itraconazole**	0.36 (0.04, 2.21)
4.70 (1.42, 20.01)	**4.65 (1.75, 15.91)**	2.80 (0.45, 22.27)	**Placebo**

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Evans JDW et al. Am J Transplant 2014;14(12):2765-76

Odds of IFI with Anidulafungin vs. Fluconazole in Prespecified High-risk Groups

Prespecified risk group (n=number of patients)	Odds of any IFI with anidulafungin vs. fluconazole in specified risk group, OR (95% CI), *P* value	Odds of breakthrough IFI with anidulafungin vs. fluconazole in specified risk group, OR (95% CI), *P* value
MELD ≥30 (n=146)	0.34 (0.08-1.35), 0.11	0.00 (0.00-0.70), 0.02
Renal replacement therapy (n=119)	0.45 (0.11-1.87), 0.26	0.00 (0.00-1.05), 0.056
Fulminant hepatic failure (n=5)	No IFI	No IFI
Pre-tx corticosteroids (n=6)	No IFI	No IFI
Pre-tx *Candida* colonization (n=7)	One IFI	No IFI
Pre-tx ICU stay >48 h (n=79)	0.67 (0.15-2.92), 0.59	0.00 (0.00-1.99), 0.14
Pre-tx systemic antifungal agent (n=25)	0.21 (0.02-2.70), 0.18	0.00 (0.00-0.87), 0.04
Repeat liver transplant (n=25)	1.66 (0.12-22.52), 0.70	1.66 (0.12-22.52), 0.70
Repeat abdominal surgery (n=75)	0.49 (0.80-2.88), 0.42	0.00 (0.00-1.96), 0.16
Blood loss >15 U PRBC during transplant surgery (n=142)	0.47 (0.12-1.91), 0.28	0.00 (0.00-0.85), 0.03

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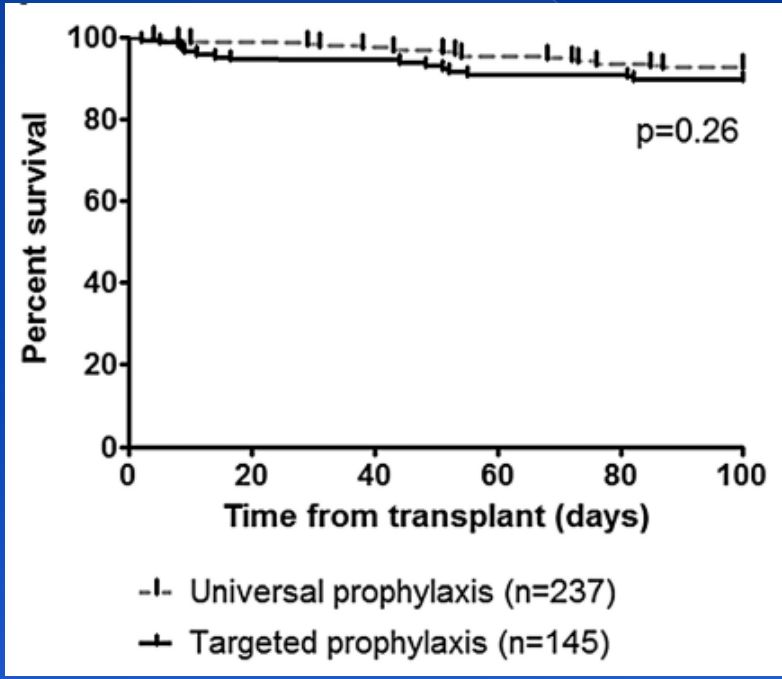
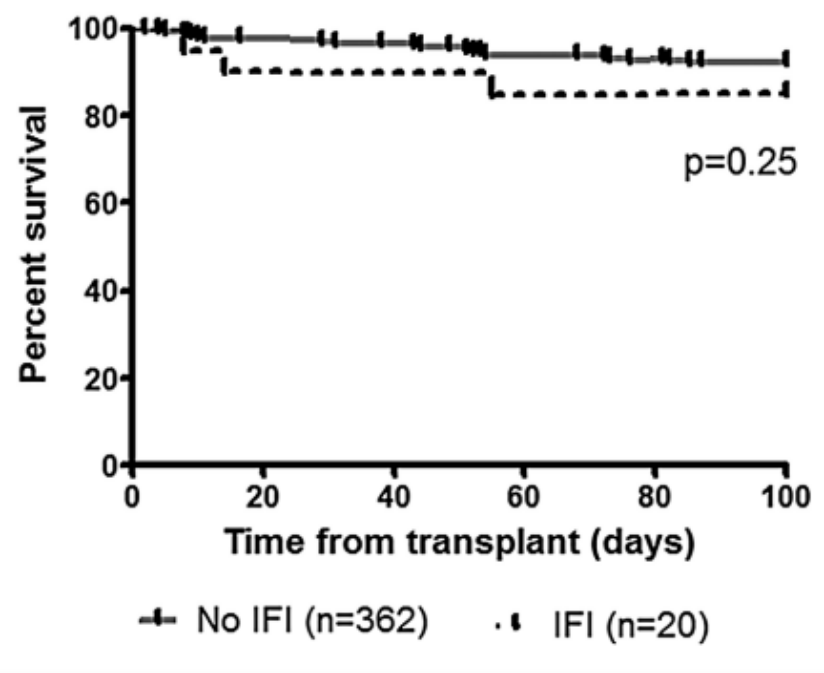
Winston DJ et al. Am J Transplant 2014;14:2758-64

Survival Among LTRs

Stratified by type of antifungal prophylaxis



Stratified by presence or absence of IFIs



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Eschenauer GA et al. Am J Transplant 2015;15:180-189

Targeted Antifungal Prophylaxis in Heart Transplant Recipients

- In a prospective cohort, 2003-10, prophylaxis with an echinocandin was administered only to patients with risk factors (13/133) and duration was personalized, starting with the risk factor (reoperation CMV, MCD infection) and was continued a median of 20 days after resolution
- Antifungal prophylaxis was prescribed only in 9.8% of recipients and effective in all but one patient who should have received a higher dose of caspofungin due to his obesity
- Despite suffering an outbreak of IA in the ICU due to an extremely high concentration of airborne spores (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)

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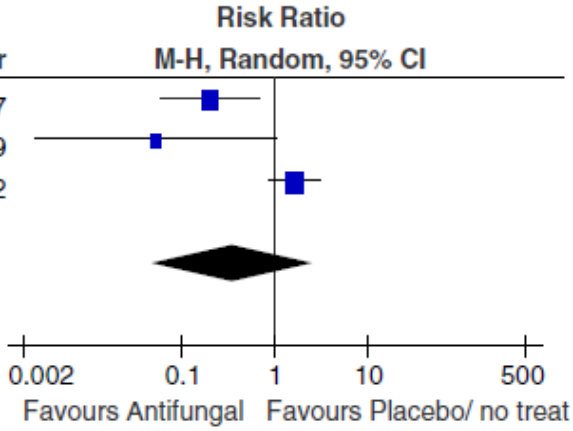
Munoz P et al. Transplantation 2013;96(7):664-9

Overall Estimate of IA in Comparative Studies: Comparing 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: $Tau^2 = 2.41$; $Chi^2 = 13.28$, df = 2 (P = 0.001); $I^2 = 85\%$

Test for overall effect: Z = 1.02 (P = 0.31)



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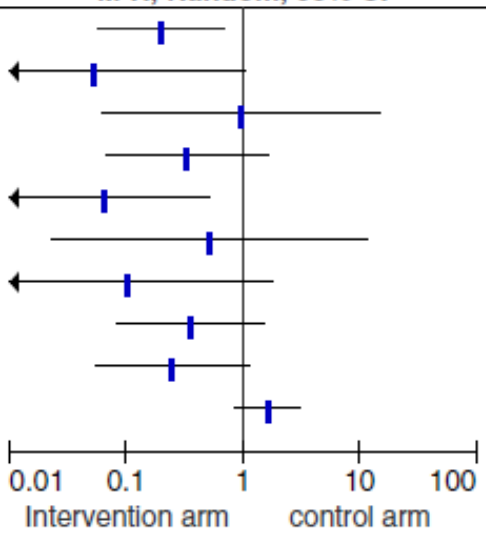
Bhaskaran A, Mumtaz K, Husain S. Curr Infect Dis Rep 2013;15(6):514-25

Effect Sizes of Comparative Studies Using Various Antifungals for Preventing Invasive Aspergillosis

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



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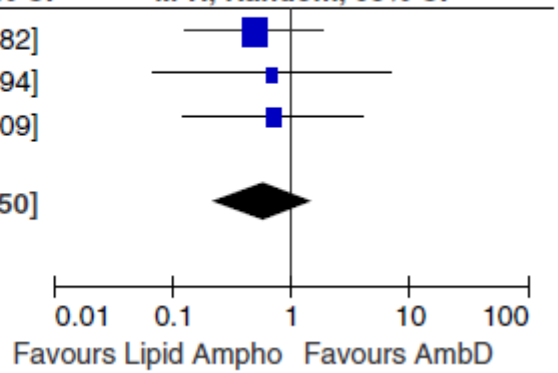
Bhaskaran A, Mumtaz K, Husain S. Curr Infect Dis Rep 2013;15(6):514-25

Overall Estimate of Discontinuation Rates of Different Amphotericin B Formulations in Comparative Studies

Study or Subgroup	Lipid Amphotericin Events	Total	AmbD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Drew 2004	3	51	6	49	52.7%	0.48 [0.13, 1.82]
Lowry 2007	1	20	2	27	17.2%	0.68 [0.07, 6.94]
Monforte 2010	3	104	2	49	30.2%	0.71 [0.12, 4.09]
Total (95% CI)		**175**		**125**	**100.0%**	**0.57 [0.22, 1.50]**
Total events	7		10			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 2 (P = 0.93); $I^2 = 0\%$

Test for overall effect: Z = 1.13 (P = 0.26)



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Bhaskaran A, Mumtaz K, Husain S. Curr Infect Dis Rep 2013;15(6):514-25

Effect of Antifungal Prophylaxis on Colonization

- No difference in the incidence of *Aspergillus* colonization with universal voriconazole and no prophylaxis (21%(12/57) vs 28%(23/28);p=0.48)
- The indirect comparison involving >637 patients, the incidence of *Aspergillus* colonization employing universal prophylaxis with various antifungals and no prophylaxis did not yield significant results

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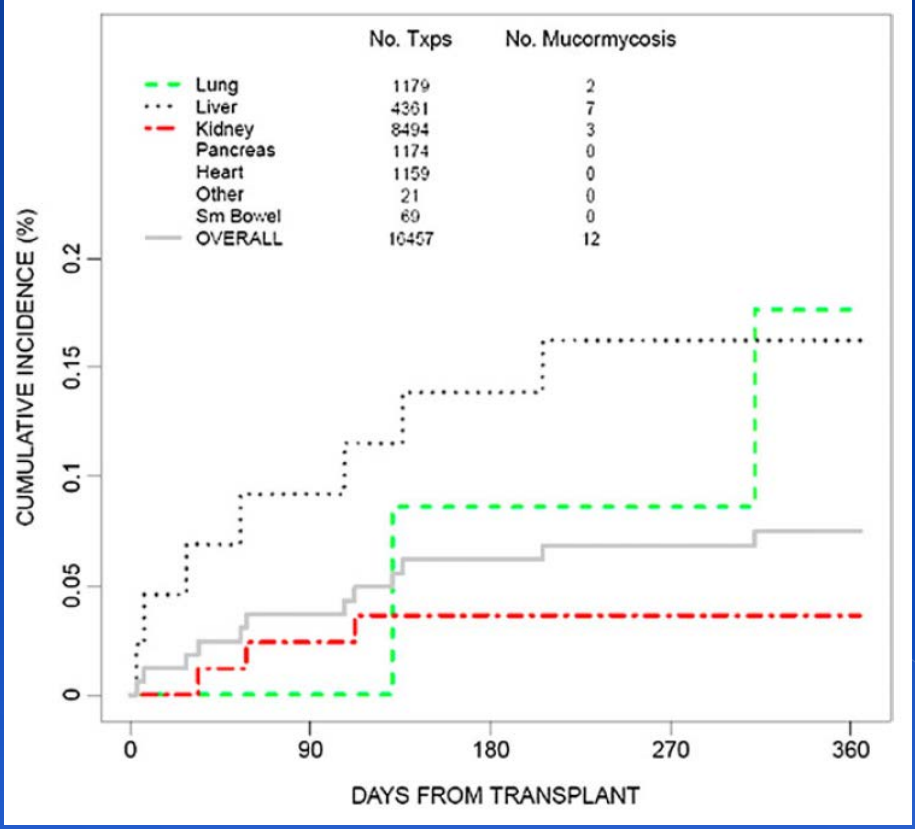
Tofte N Scand J Infect Dis. 2012 Nov;44(11):835-41
Bhaskaran A, Mumtaz K, Husain S. Curr Infect Dis Rep 2013;15(6):514-25

TRANSNET Study: 12-month Cumulative Incidence of Mucormycosis Among HSCT & SOTR



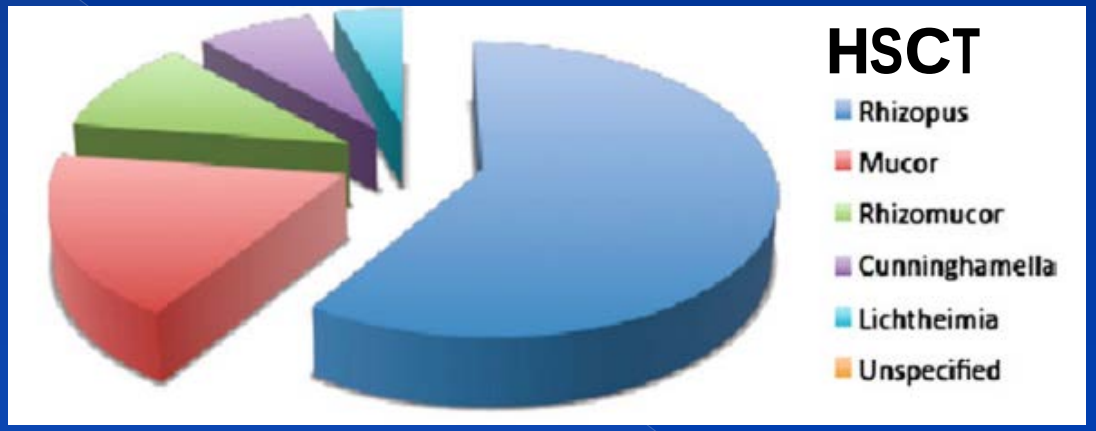
Mucormycosis
2% IFI TRANSNET

0.07%

THE TORONTO TRANSPLANT ID PROGRAM *for infection-free transplantation*

Park. Emerg Infect Dis 2012; Husain CID 2003

TRANSNET Study: Distribution of *Mucorales* Among HSCT & SOTR



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Lanternier F et al. Clin Infect Dis 2012;54(11):1629-36

Clinical Manifestations in Solid Organ Transplantation

Clinical manifestation	Heart (n=18)	Lung (n=4)	Liver (n=19)	Kidney (n=75)	Total (n=116)
Rhino-sinusitis ± orbits	1 (5.5%)	1 (25%)	3 (15.8%)	15 (20%)	20 (17/2%)
Rhinocerebral	2 (11%)	0	1 (5.3%)	13 (17.3%)	16 (13.8%)
Pulmonary	7 (38.8%)	2 (50%)	0	19 (25.3%)	28 (24.1%)
Gastrointestinal	4 (22.2%)	0	2 (10.5%)	7 (9.3%)	13 (11.2%)
Cutaneous	2 (11.1%)	0	8 (42.1%)	8 (10.6%)	18 (15.5%)
Renal	0	0	0	6 (8%)	6 (5.2%)
Disseminated	2 (11.1%)	1 (25%)	5 (26.3%)	7 (9.3%)	15 (12.9%)
Median time of onset days (range)	60 days (range 6-912)	180 days (range 30-730)	18.5 days (range 1-1095)	60.5 days (range 7-2920)	60 days (range 1-2920)

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Almyroudis NG et al. Am J Transplant 2006;6:2365-2374

Risk Factors for Zygomycosis in Solid Organ Transplantation

- Matched case control study with 50 cases of zygomycosis

Risk factors	Odds ratio	*P* value
Renal failure (baseline)	3.17	0.10
Diabetes mellitus	8.11	<0.001
Prior VRC or caspofungin use	4.41	0.021
Tacrolimus	0.23	0.002

Singh N. J Infect Dis 2009;200:1002–11

Risk Factors of Disseminated Disease

- Univariate
  - *Absidia* species
  - Early onset
  - Liver transplant
  - Prior use of antifungal agent
- Multivariate
  - Early onset

Sun HY. Am J Transplant 2009;9(9):2166-71

Moving Target

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thank you

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