Infection Risk Modeling in Solid Organ Transplantation: The Fungal Problems

Shahid Husain, MD, MS
Associate Professor of Medicine
Director, Transplant Infectious Diseases
University Health Network, University of Toronto

You Might Look in the Crystal Ball But We Are Scientists

Unfortunately Our Model is Not Giselle Rather…

$$\begin{cases} y_1 = f_1(x_1,\ x_2\ \ldots,\ x_n), \\ y_2 = f_2(x_1,\ x_2; \ldots,\ x_n), \\ \ldots, \\ y_i = f_i(x_1,\ x_2; \ldots,\ x_n), \\ \ldots, \\ y_m = f_m(x_1,\ x_2; \ldots,\ x_n), \end{cases}$$

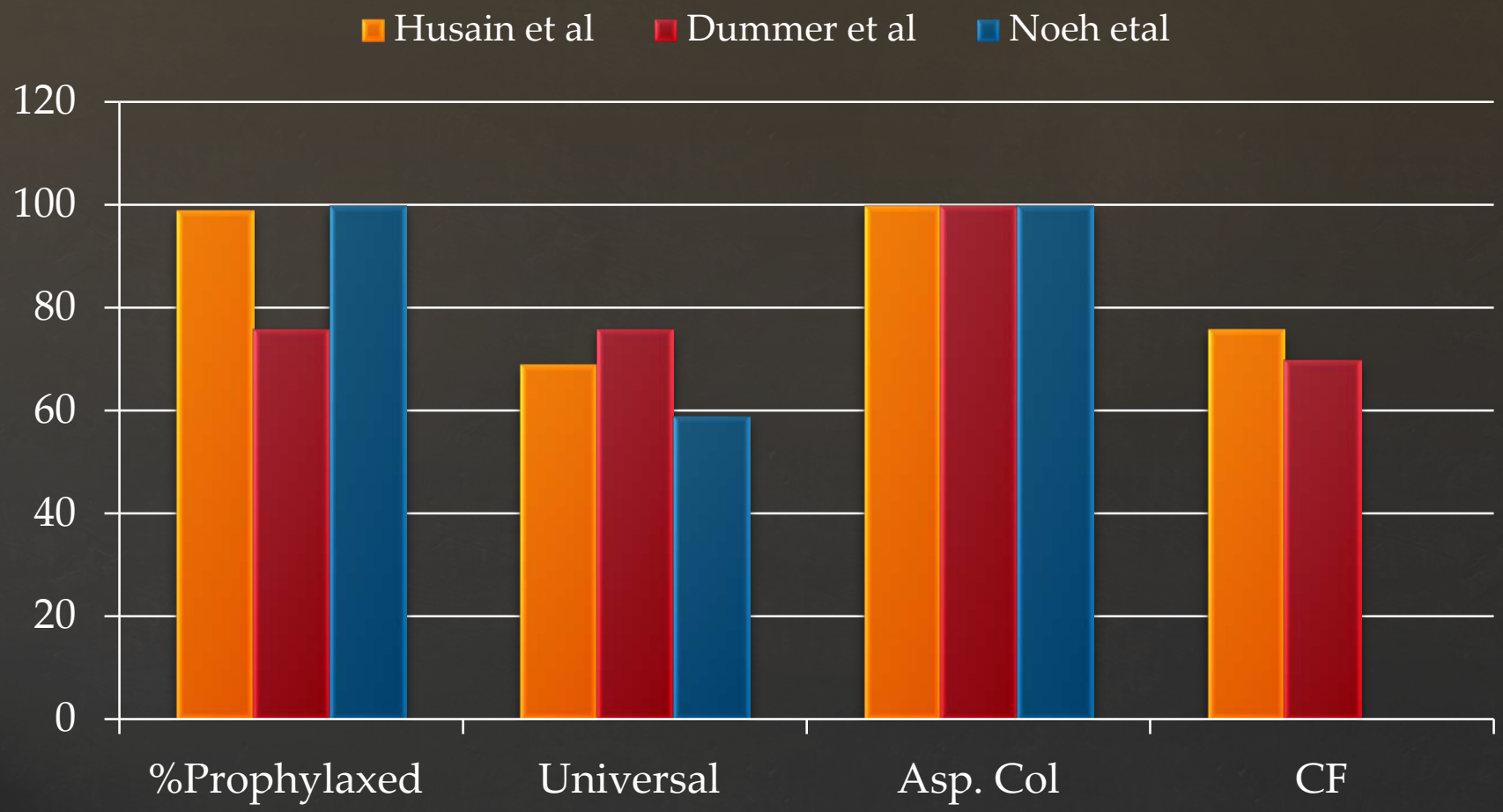
Why We Should Build a Risk Model

Antifungal Prophylaxis in Liver Transplants

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

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

Antifungal Prophylaxis in Lung Transplant

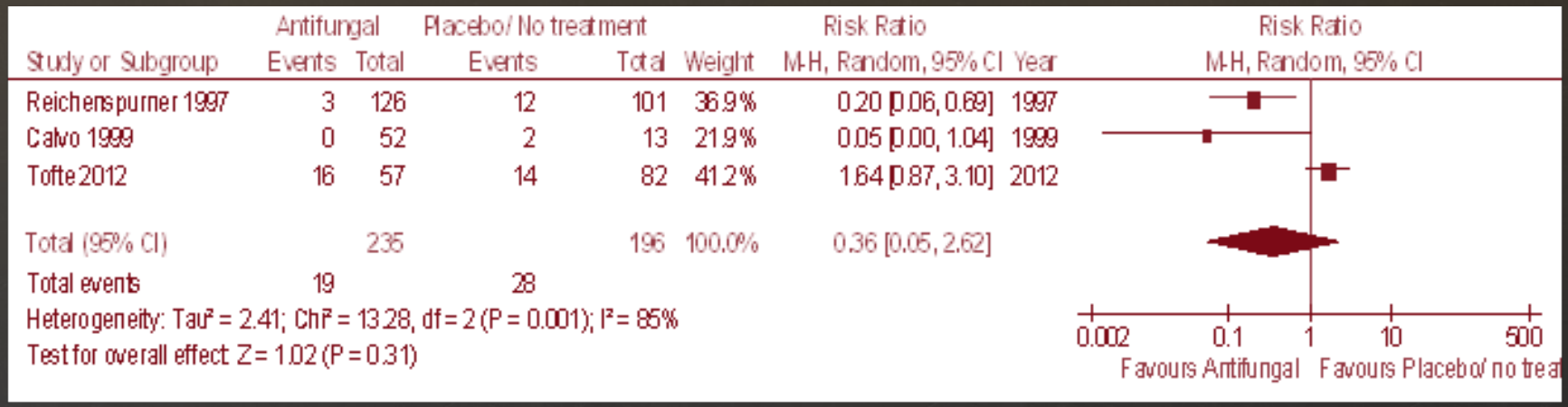


Meta-Analyses of Antifungal Prophylaxis in LTRs

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)**

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

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

Consequences

- Non-albicans *Candida* species accounted for 55% of IFIs; 50% of these IFIs were *Candida parapsilosis*
- Only 43% of *Candida* isolates were fluconazole-susceptible (minimum inhibitory concentration 8 l/mL)
- All *C. parapsilosis* isolates were fluconazole-resistant, .

Raghuram A, Liver Transpl 2012;18:1100-1109

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

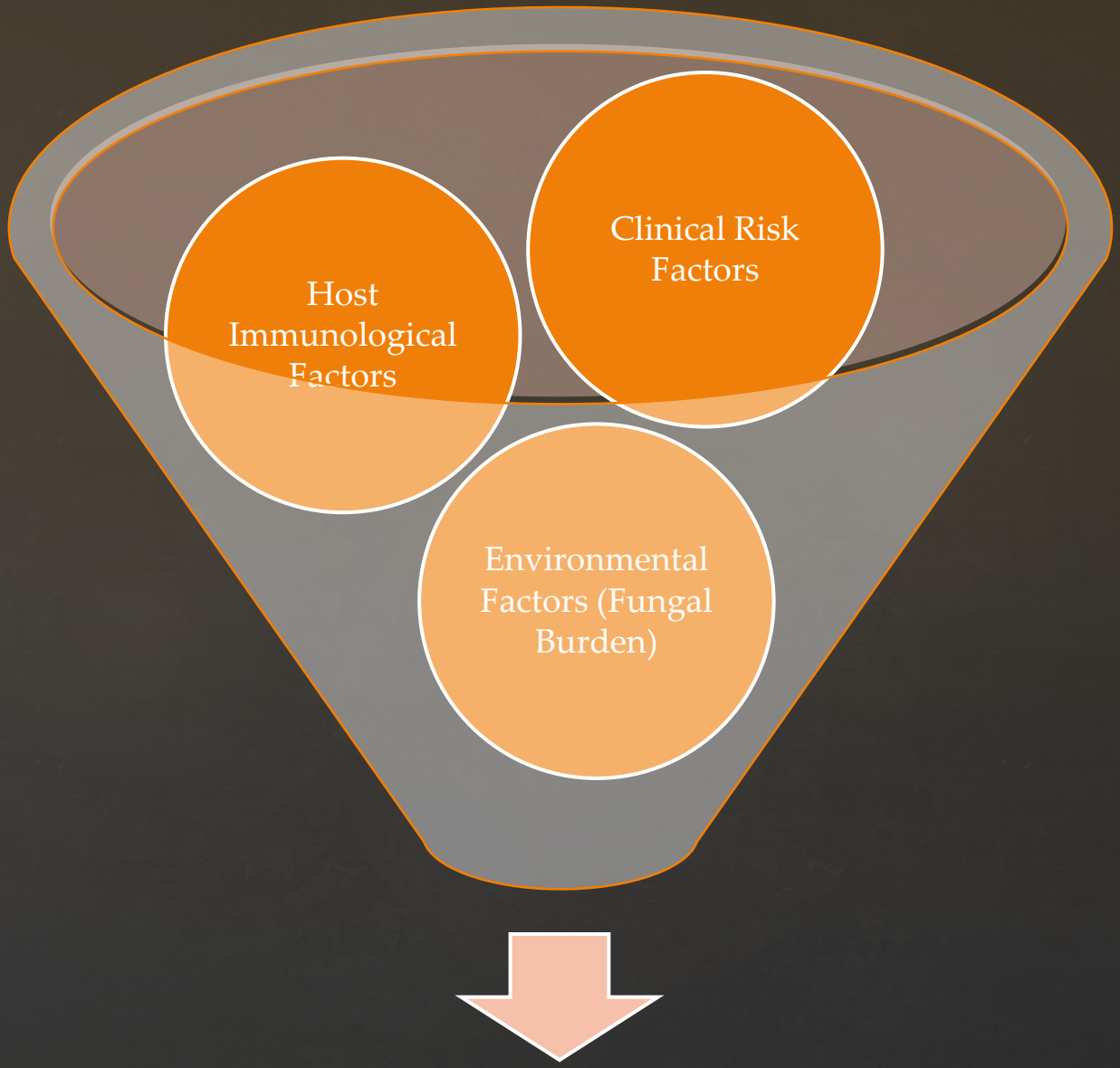
Bhaskaran A. Semin Respir Crit Care Med 2013;34(3)

The Best Utility of Fungal Infection Model would be

Targeted antifungal prophylaxis:
Refers to an antifungal medication started in the post-operative period, prior to any post-transplant isolation of a fungal pathogen, which is prescribed only to patients deemed higher risk for IFI.

Pre-emptive antifungal therapy:
Refers to an antifungal medication started after a post-transplant isolation of a fungal pathogen or diagnostic marker in the absence of any evidence for invasive fungal infection.

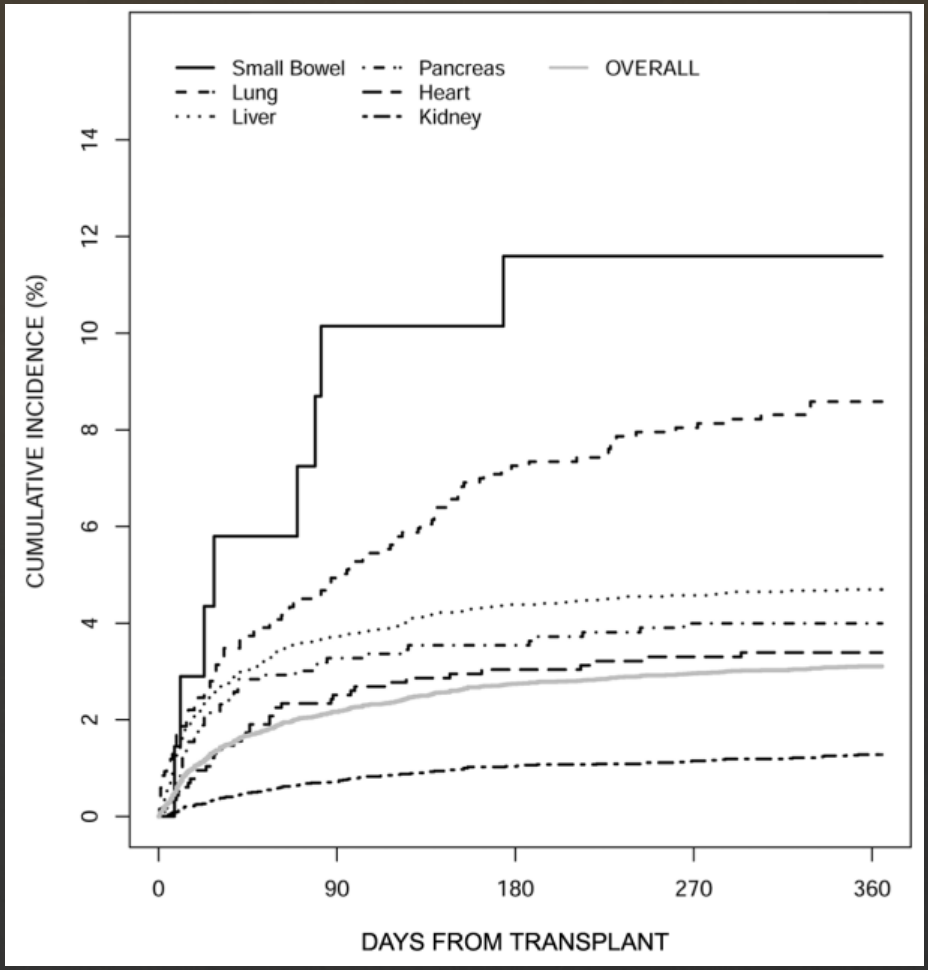
What Should Be Used in Modelling The Risk of Fungal Infections in SOT



IFI in the IC Host

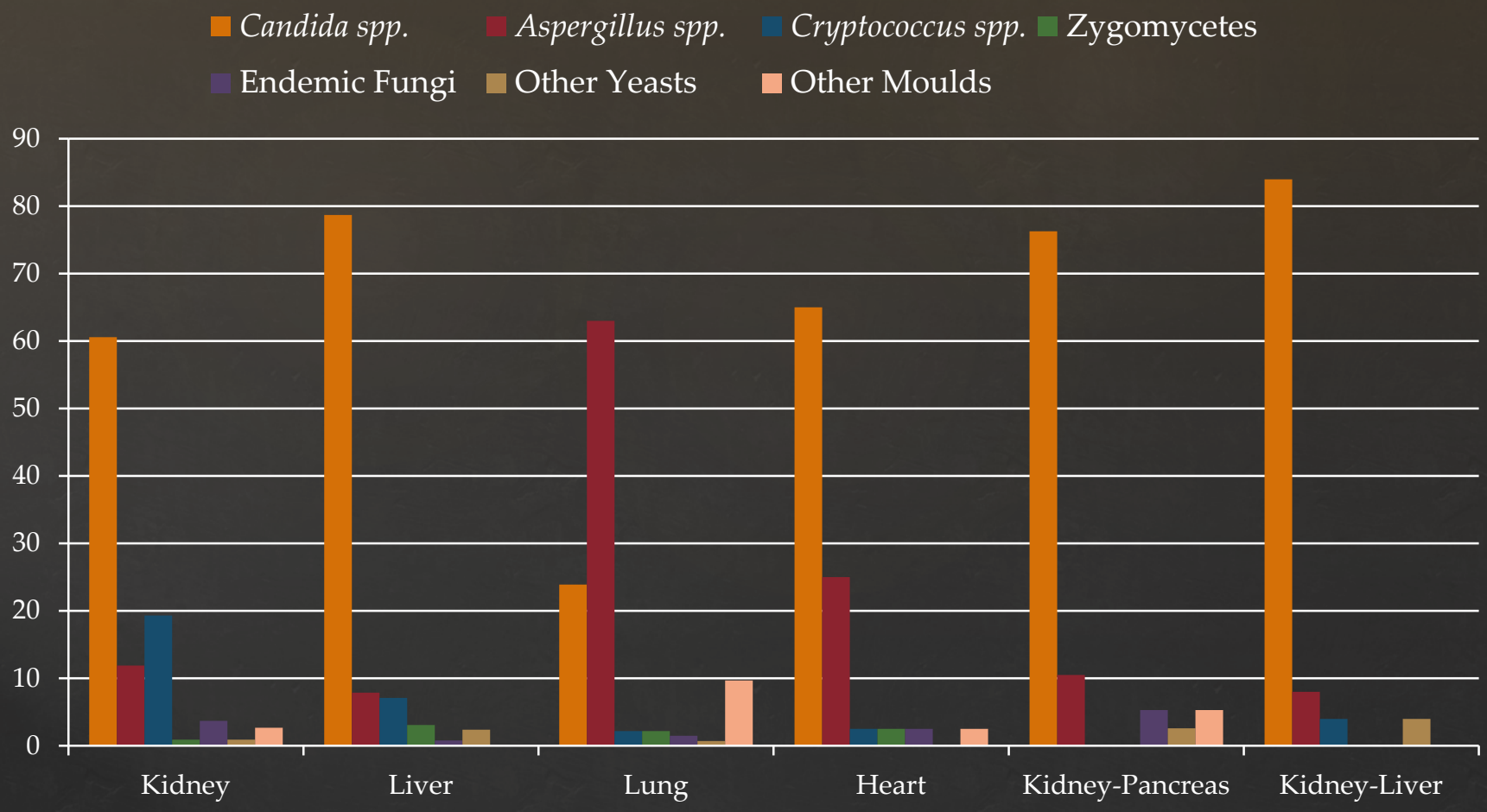
The Clinical Risk of Fungal Infection

Type of Transplant



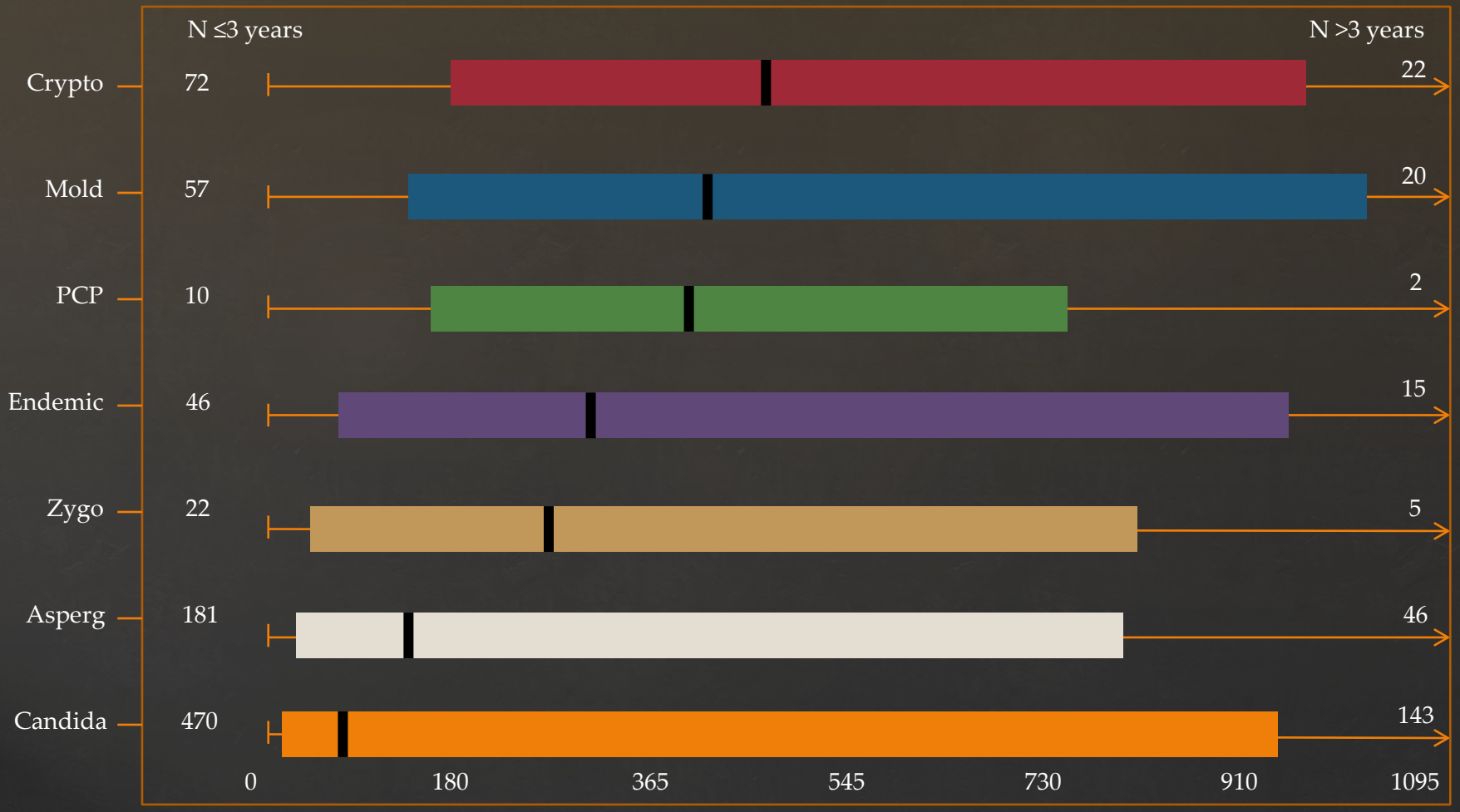
Pappas P. Clin Infect Dis 2010;50(8):1101-11

Distribution of IFI in SOT



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

Timing of IFI



Pappas P. Clin Infect Dis 2010;50

Lower Risk (< 4%) with Only One Risk Factor

- Choledochojejunostomy anastomosis
- Re-transplantation
- Intra-operative administration of ≥40 units of cellular blood products
- Pre-operative 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 non-function

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

Newly Established Risk Factors in Liver Transplantation

- MELD score >25
- Preceding bacterial infection
- Prolonged ICU stay
- Fulminant hepatic failure

Lichtenstern C. Mycoses 2013;56:350–357

Raghuram et al. Liver Transpl 2012

Saliba F. Clin Transplant 2013;27:E454–61

Unique Factors Contributing to the Risk of Infection in LT

Continuous contact with pathogens

Higher state of immunosuppression

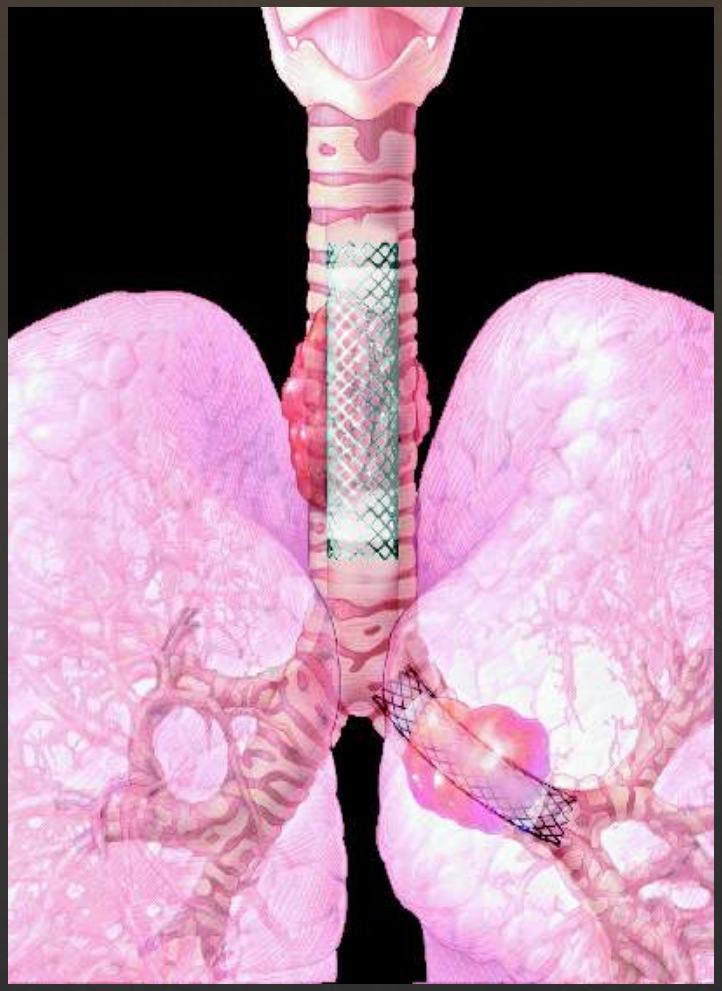
Airways colonization

Pulmonary stent

The native lung

Hypogamma-globulinemia

CARV Infection



Denervation

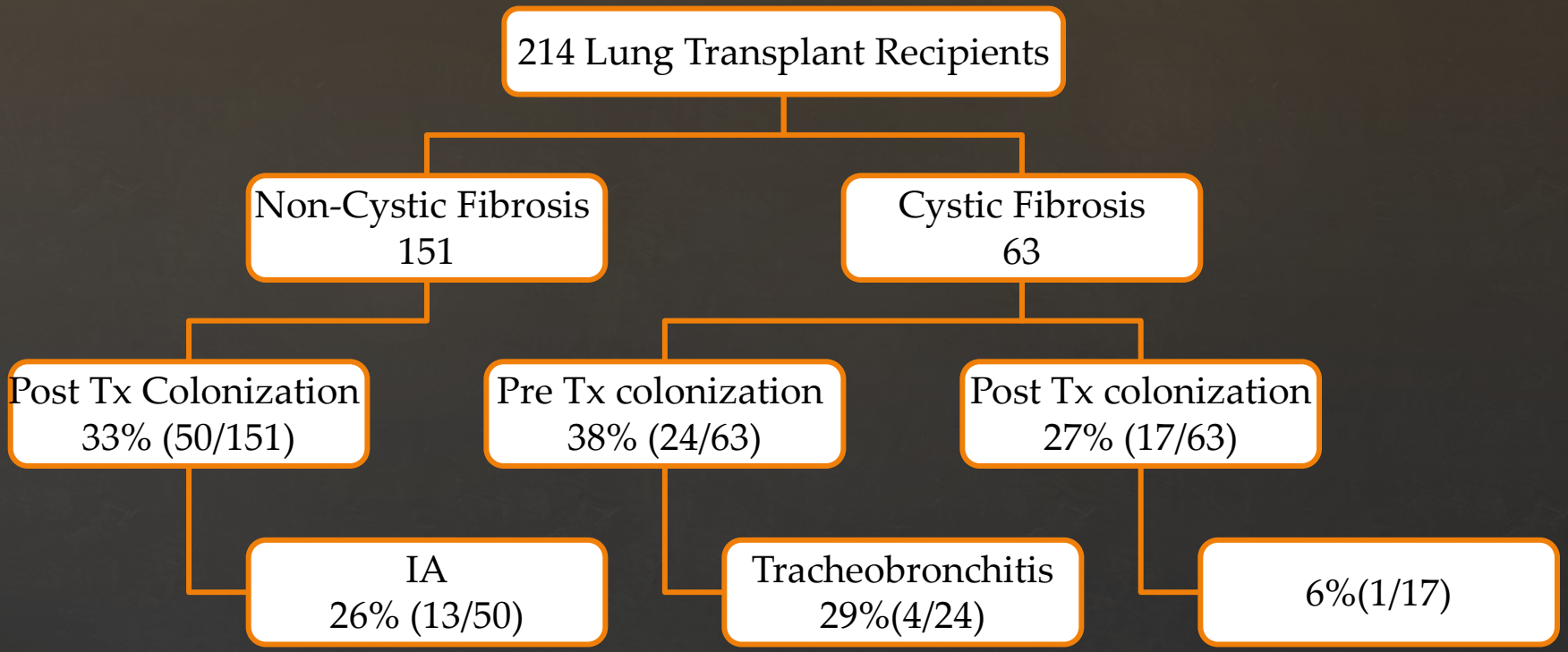
Impaired cough reflex

Decrease mucociliary clearance

Ischemic reperfusion injury

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

Colonization

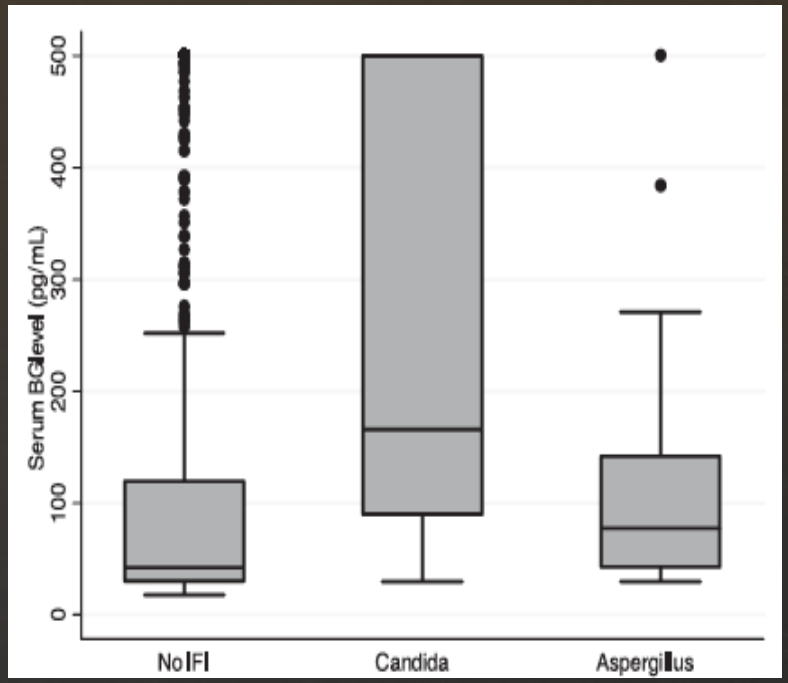


Helmi M. Chest 2003 Mar;123(3):800-8; Nunley. Chest 1998 Nov;114(5):1321-9

Diagnostic Biomarkers

Role of Serum (1→3) β-D-Glucan to Diagnose IFI?

- 1 study in LTRs assessed the utility of serial serum BDG monitoring for diagnosis of IFI (including IA and IC)
- Fungitell test, cut-off 60 pg/mL
  - Sensitivity 71%
  - Specificity 59%
  - Test positive in 4/7 IA cases
- Serum BDG test has marginal accuracy for the diagnosis of IFI in LTRs



Alexander et al. JCM 2010;48:4083-88

Role of Serum GM to Diagnose IA in SOT Recipients?

- 3 studies conducted in SOTR have shown that serum GM testing is associated with an unacceptably low sensitivity for the diagnosis of IA

	Organ	Incidence	Cut-off	Sensitivity	Specificity
Fortun et al. Transplantation, 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	N/A	87

Role of BAL GM in Diagnosing IA in CTT Recipients?

- BAL GM was shown to be useful for diagnosis of IA
  - More sensitive than serum GM
- 3 meta-analyses evaluated the utility of BAL GM for diagnosing IA
  - Sensitivity of BAL GM 82-86% (using cut-off >0.5)
  - Specificity of BAL GM 89-92% (using cut-off >0.5)

	Guo. Chest. 2010	Zou. PlosOne. 2012	Heng. Clin Rev Micro. 2013
Number of studies	**13**	**30**	**16**
Pooled Sensitivity GM >0.5	86 (70-94)	87 (79-92)	82 (70-91)
Pooled Sensitivity GM >1.0	85 (72-93)	96 (76-92)	75 (55-88)
Pooled Sensitivity GM >1.5	70 (49-85)	85 (71-96)	92 (48-99)
Pooled Specificity GM >0.5	89 (85-92)	89 (85-92)	92 (85-96)
Pooled Specificity GM >1.0	94 (89-97)	95 (91-97)	95 (87-98)
Pooled Specificity GM >1.5	96 (93-98)	95 (90-97)	98 (78-100)

Guo et al. Chest.2010;138(4):817-24; Zou et al. PlosOne. 7(8):e43347; Heng et al. Clin Rev Microbiol 2013;Epub

Role of BAL *Aspergillus* PCR in Diagnosing IA?

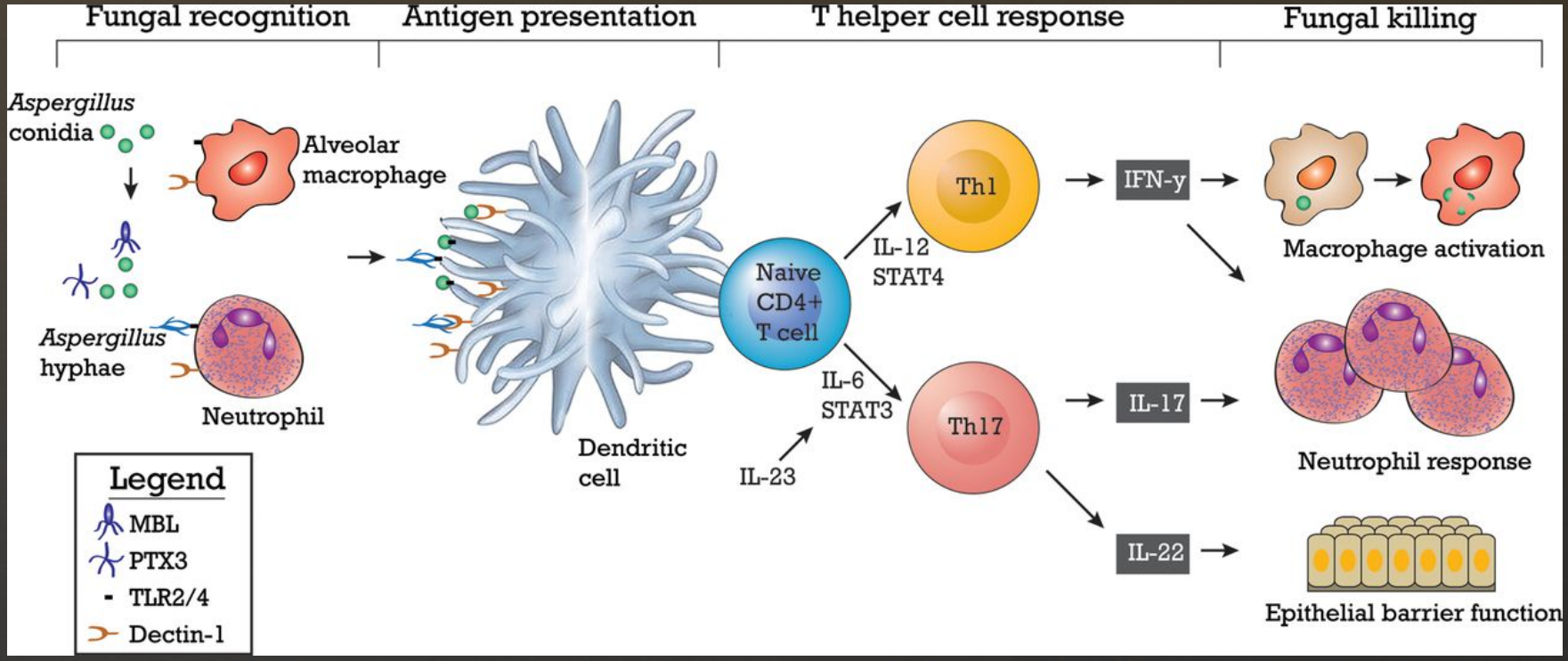
- 1 study evaluated the Viracor PCR in BAL for diagnosis of IA among 137 LTRs
  - Sensitivity 100%; superior to BAL GM (100% vs. 93%)
  - Among LTRs with colonization, BAL GM was more specific than BAL PCR (92% vs. 50%)
- No data on the performance of MycAssay in CT recipients

Test	Sensitivity	Specificity	PPV	NPV
BAL PCR	100 (79-100)	88 (79-92)	50 (30-65)	100 (97-100)
BAL GM > 0.5	93 (68-100)	89 (82-93)	48 (29-97)	99 (95-100)
BAL GM > 1.0	67 (38-88)	97 (92-99)	71 (42-92)	96 (92-99)

Luong et al. CID 2011;10:1218-1222

Biomarkers in Invasive Fungal Infections

Protective Immunity Against *Aspergillus*



Camargo JF and Husain S. Clin Infect Dis 2014;59:569-577

Selected Genetic Polymorphisms Associated with IA

Gene	Patient population	SNP		Risk of IA OR (95%CI)	Ref
		Position	Nucleotide substitution		
MBL2	HSCT	-	-	7.3 (1.9-27.3)	Granell M, Exp Hematol 2006
TLR4	HSCT	−2604	A/G	3.22 (1.02–10.16)	Bochud P, NEJM 2008
		+1363	C/T	4.96 (1.52–16.24)	
		+1063 +1363	A/G C/T	6.16 (1.97–19.26)	
CLEC7A	Hematological malignancies	c.714	A/C	3.89 (1.51–9.99)	Cunha C, Blood 2010
		c.255+813	G/T	5.59 (1.37–22.77)	Sainz J, Plos One 2012
		c.375-1404	C/G	4.91 (1.52–15.89)	
PTX3	HSCT	+281	A/G	2.92 (1.69–5.05)	Cunha C, NEJM, 2014
		+734	A/C	2.62 (1.52–4.54)	
		+281G +734A	A/G A/C	3.08 (1.47–6.44)	
DC-SIGN	Hematological malignancies	c.2797	A/G	2.75 (1.27–5.95)	Sainz J, Plos One 2012

Camargo JF and Husain S. Clin Infect Dis 2014;59:569-577

Common Genetic Variants Candidiasis I

Gene	SNP (rs-number)	Phenotype	Disease
Dectin-1	Y238X (rs16910526)	Decreased IL-1β and Th17 responses	*Candida* colonization
DEFB1	-44C/G (rs1800972)	Unknown	*Candida* carriage
IL-4	-589T/C (rs2243250) -1098T/G (rs2243248), -589C/T (rs2243250), -33C/T (rs2070874)	Increased vaginal IL-4, reduced NO and MBL levels Unknown	RVVC Chronic disseminated candidiasis
IL-10	-1082A/G (rs1800896)	Higher *Candida*-induced IL-10 production	Persisting candidemia
IL-12B	2724INS/DEL (rs17860508)	Lower *Candida*-induced IFN-γ production	Persisting candidemia
MBL2	Variable number of tandem repeats in intron 4	Reduced vaginal MBL levels	RVVC
NLPR3	Length polymorphism	Impaired IL-1β production	RVVC

Smeekens SP. EMBO Mol Med 2013;5:805-13

Common Genetic Variants Candidiasis II

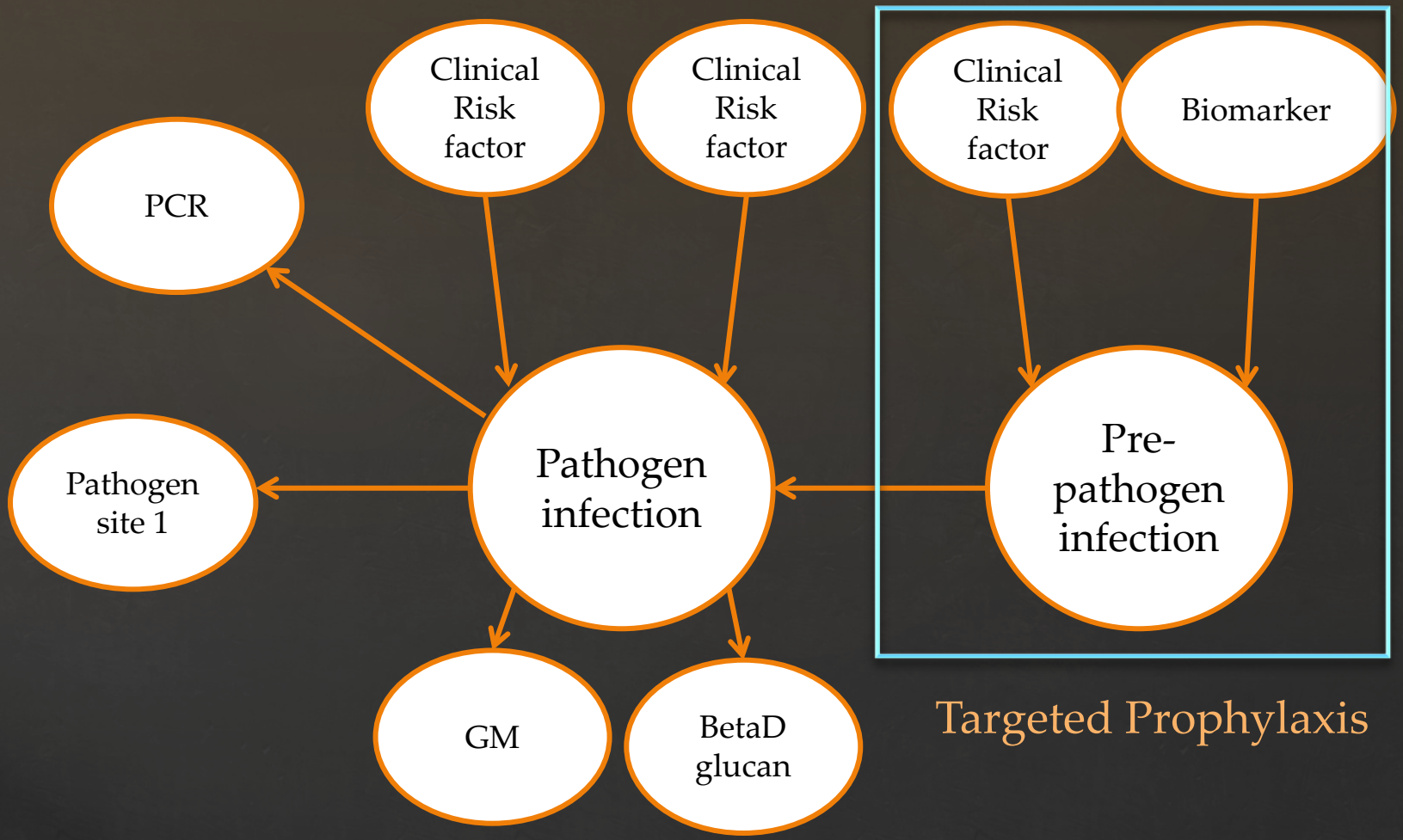
Gene	SNP (rs-number)	Phenotype	Disease
PTPN22	R620W (rs2476601)	Unknown	Increased risk for CMC
TLR1	R80T (rs5743611), S248N (rs4833095), I6025 (rs5743618)	Decreased production of IL-1β, IL-6 and IL-8 after TLR1-TLR2 stimulation	Increased susceptibility to candidemia
TLR2	R753Q (rs5743708)	Decreased levels if IFN-γ and IL-8	Increased susceptibility to candidemia
TLR3	L412F (rs3775291)	Decreased IFN-γ levels	Increased risk for CMC
TLR4	D299G (rs4986790), Y399I (rs4986791)	Increased IL-10 production	Increased susceptibility to candidemia

Smeekens SP. EMBO Mol Med 2013;5:805-13

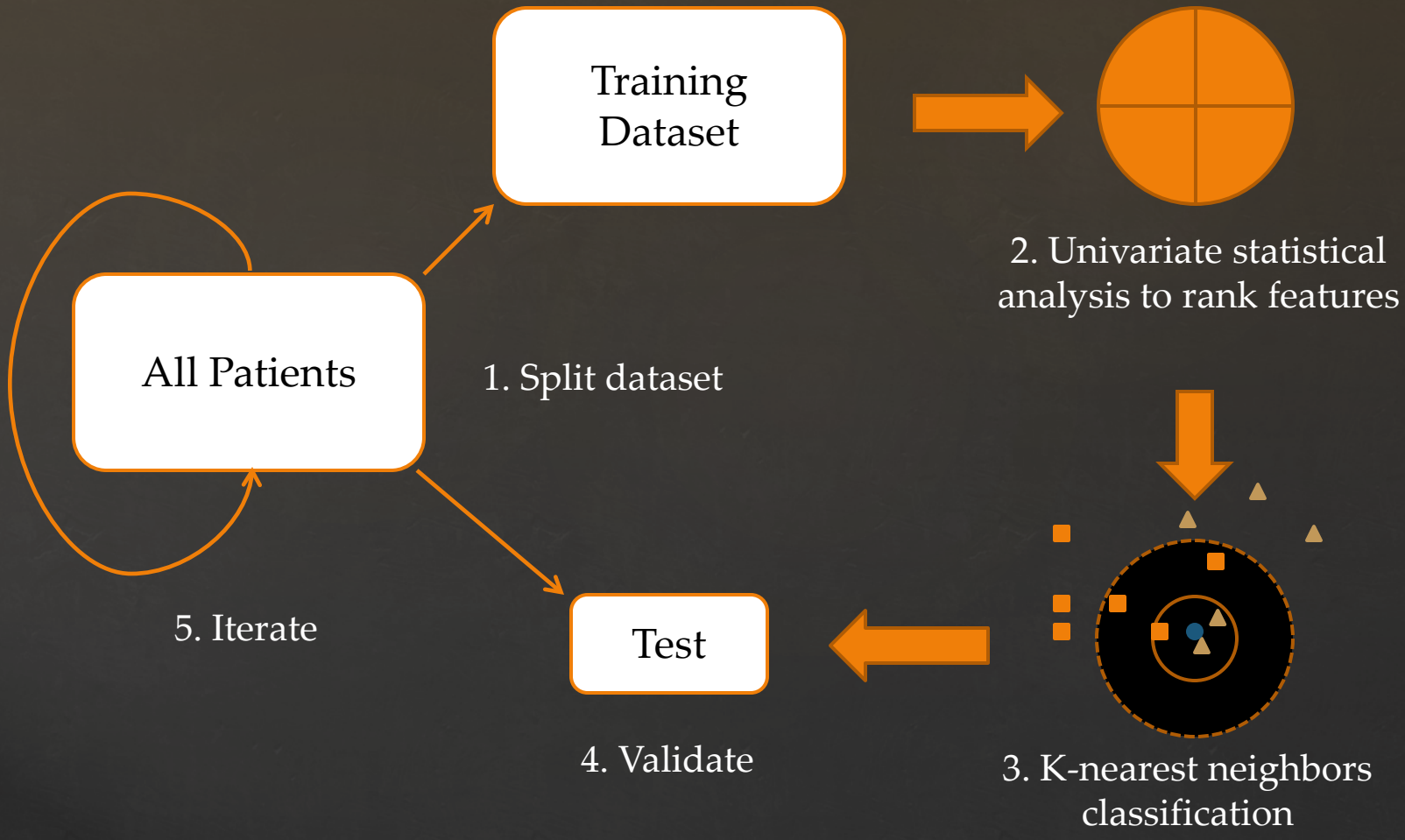
Effect of Commonly Used Immunosuppressives and Antifungal Drugs on Biomarkers

	PTX3	Dectin-1	DC-SIGN	TLR2	TLR4	NFAT	IL-17
Steroids	↓	↓	↓				↓
Tacrolimus		↓			↓	↓	↓
Cyclosporin		↓		↓	↓	↓	↓
Mycophenolic acid							↓
Rapamycin		↓		↓	↓	↓	
D-AmB				↑			
L-AmB					↑		
Voriconazole				↑			
Echinocandins		↑					?↑

Bayesian Model for Infection Risk Modelling in Future



K-Nearest Neighbor Algorithm



Conclusions

- Current clinical risk stratification of IFI in SOTRs are based on older studies and continues to evolve. Further delineation of clinical risk factors in current era is required

- There is a emerging data on the diagnostic markers (β-D-Glucan , GM and PCR) of IFI in SOT. They can be employed in pre-emptive setting

- Immunological markers for IFIs are not well studied in SOT their role in targeted prophylaxis remains to be defined

- Decision making models for SOT from large cohort studies need to incorporate diagnostic and immunological markers for IFIs

Transplant Infectious Disease Team