TIMM
Trends in Medical Mycology

M.6 Meet-the-expert sessions

Solid organ transplant patients

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Conflict of interest disclosure

- In the past 5 years, J.M.A. has received grant support from **Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, and Pfizer.**
- He has been an advisor/consultant to **Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, and Pfizer.**
- He has been paid for talks on behalf of **Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Astellas Pharma.**

Some Issues

- Importance of the problem
- Differences neutropenic patients
- Some comments regarding treatment
- Difficulties in prophylaxis

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IFI in SOT

IFI	Kidney 1330	Liver 979	Heart 283	Lung 167	Pancreas 53	Total 2812
Candida spp	41 (3%)	30 (3,1%)	11 (3,8%)	6 (3,6%)	2 (3.7%)	90 (3.2%)
Aspergillus spp	2 (0,15%)	5 (0.5%)	3 (1%)	10 (5.9%)	2 (3.7%)	22 (0.8%)
Global	43 (3.2%)	35 (3.6%)	14 (4.9%)	16 (9.6%)	4 (7.5%)	112 (4%)

RESITRA Network (1-09-03 / 01-03-05)

Mortality of IA in SOT

Global: 119/156; 76.3%

Kidbey-pancreas:	2/2	100%
Liver:	67/80	83,7%
Lung:	12/17	70,6%
Kidney:	7/10	70%
Heart:	31/47	65,9%

O. Len y RESITRA. ICAAC. Chicago IL. Abstract M-999

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Variable Utility Galactomannan

Host	Sensibility	Specificity
Neutropenic	96%	96%
HSCT	70%	91%
Liver transplant	57%	94%
ICU	38%	100%
CGD	24%	95%

Maertens, Blood 01; Bretagne CID 98; Fortun, Transplant 01; Walsh, ICAAC 02

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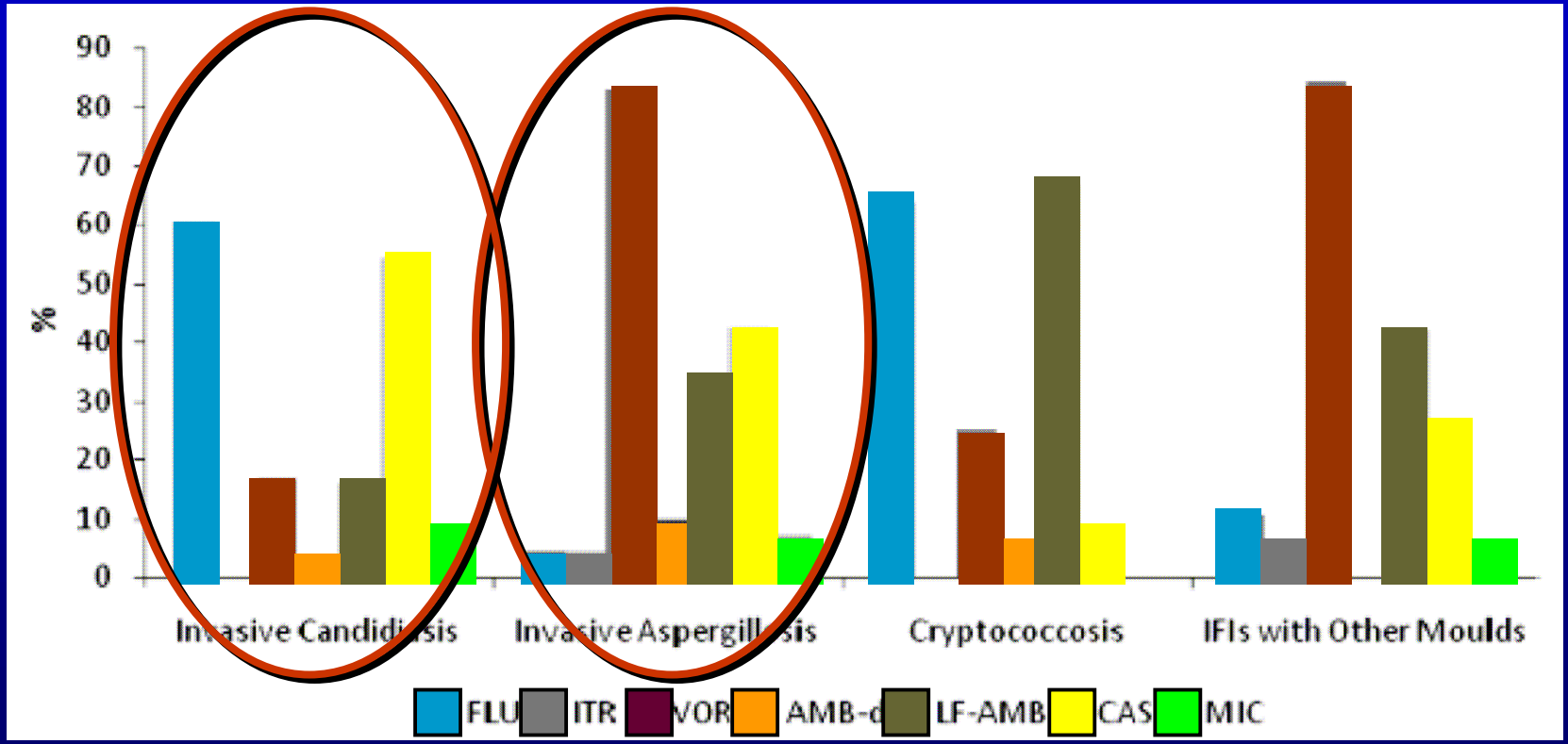
IFI: treatment limitations in SOT

- **Amphotericin B**: Nephrotoxicity, interference with CsA, confusion with rejection
- **Azoles**: Pharmacological interferences, hepatotoxicity, risk of rejection
- **Echinocandins**: Interference caspofungina with CsA

PATH (Prospective Antifungal Therapy Alliance): 2004 – 2007. 515 IFIs en 429 TOS



Neofytos D et al. *Transplant Infectious Diseases* 2010

Caspofungin in SOT

- Multicentric study (13 centers) observational: 2004-2007.
- 81 patients (APACHE: 23): candidiasis 79% and aspergilosis 27%
- No severe AE. No CASPO discontinuation

	Monotherapy	Combination
Aspergillus spp	7/9 (78%)	7/10 (70%)
C. albicans	24/26 (92%)	8/10 (80%)
C. no-albicans	19/20 (95%)	4/5 (80%)

Winkler et al. *Transpl Infect Dis 2010*

Micafungin in SOT

Transplant recipients included in Clinical Trials:

Kuse et al (Lancet 2007): 70 SOT (36 with MICA). No data

Pappas et al (CID 2004): 35 SOT (16 with MICA). No data

Forrest et al (Transplantation 2006)

18 Transplant recipients (7 TOS) MICA 100 mg. (11 días)

Candidemia (5), peritonitis (2)

Success 100%.

Adequate levels: CSA (100%), TAC (97%), SIR (75%)

Anidulafungin in SOT

Transplant recipients included in Clinical Trials:

Reboli et al (N Engl J Med 2007):	12 SOT (7 with ANIDULA)
Krause et al (CID 2004):	? SOT
Krause et al (AAC 2004):	? SOT

Brielmaier et al (Pharmacother 2008)

13 TOS con IFI	Efficacy 77%
	1 breakthrough candidemia (*C. parapsilosis*)
	No interaction
	No liver toxicity

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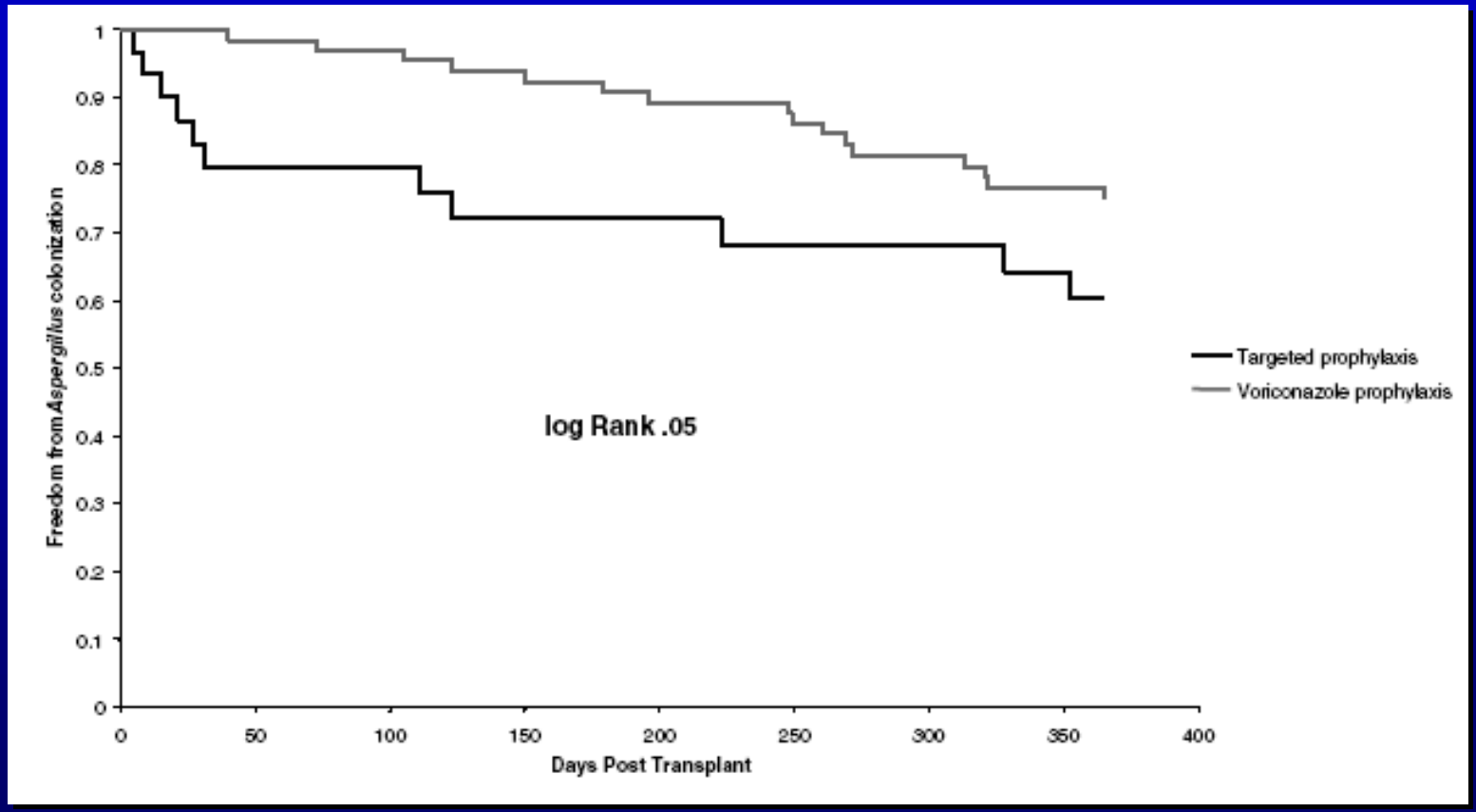
IFI Prophylaxis in SOT

	Kidney	Liver	Heart	Lung	Pancreas	Bowel
Universal				X	X	X
Risk factores	X	X	X			

Lung TX. Inhaled Ampho B

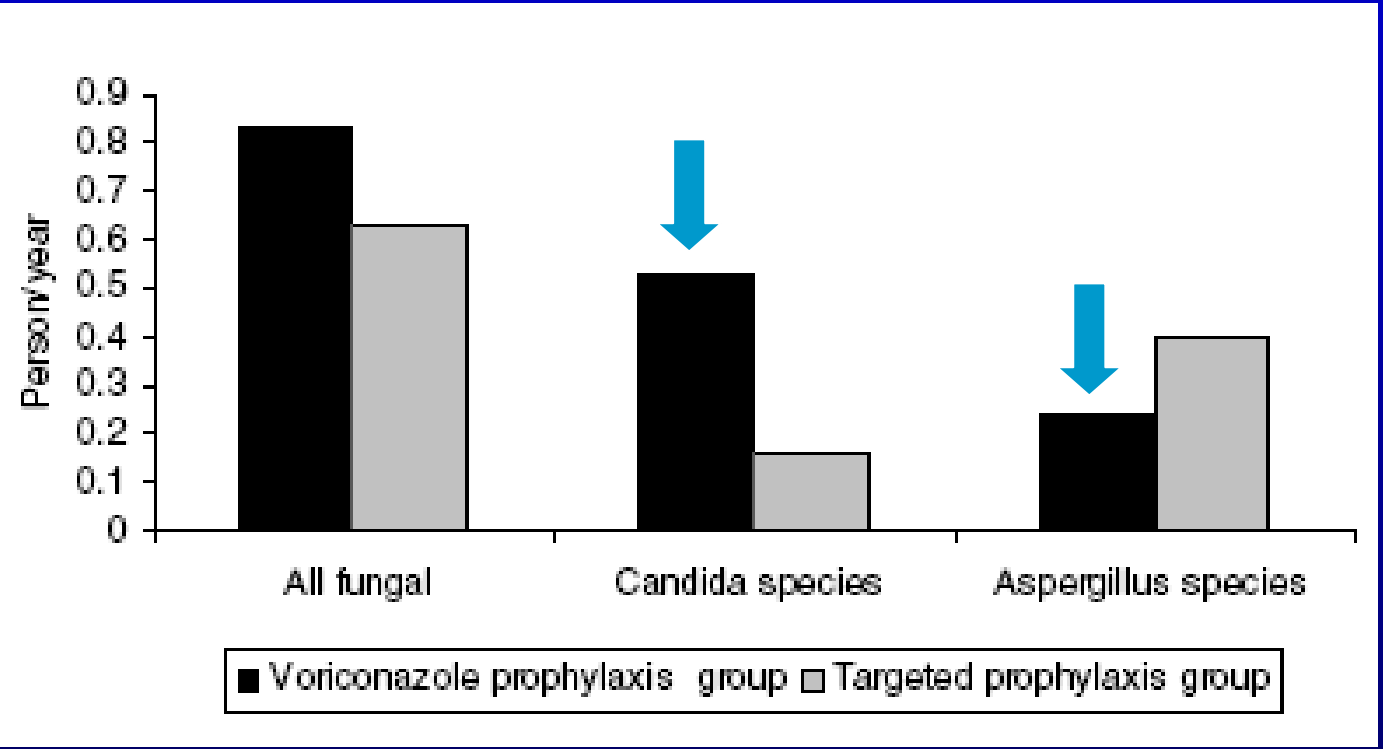
	Nº pat.	Dosage	Result
Monforte *2001*	44	FUNGIZONA 6 mg/8h, 120d 6 mg/d, undefined	AI: 14,4% (control: 33%)
Palmer 2001	51	ABELCET 50 mg/d, 4 days 50 mg/wk, 8 wk	IFI: 12% Tolerance: 98%
Drew 2004	100	a) ABELCET vs. b) FUNGIZ a: 50 mg/wk b: 25 mg/wk	IFI: 11,8% vs. 14,3% (ns) (most Candida) Intolerance: 5,9% VS 12,2%
Lowry 2007	38	a) ABELCET vs. b) FUNGIZ	[ ] serum < 0,2 μg/ml
Borro 2008	60	ABELCET (+ FLU) 50 mg/48 h. 4 days 50 mg/wk, 13 wk	IFI: 2% (1 Aspergillus) Tolerance: 93%
Monforte 2009	27	AMBISOME 25 mg/ 3 x wk, 60 d 25 mg/ wk , 180 d	IA: 0 (4 colon.) Scedosporium: 1 [ ] serum = 0

Voriconazole Prophylaxis in Lung TX



Husain et al. Am J Transplantation 2006

Voriconazole Prophylaxis in Lung TX



Husain et al. Am J Transplantation 2006

Liver Transplantation

1010 Liver TX recipients. RESITRA Network

Universal Prophylaxis (FLU) (3/12 centers):
109 pts. 1 IFI (0,9%)

Selective Prophylaxis (9/12 centers):
429 pts. 6 IFI (1,4%)

(p:NS)

San Juan et al. ICAAC, San Francisco 2009

IFI Prophylaxis in SOT

	Kidney	Liver	Heart	Lung	Pancreas	Bowel
Universal				X	X	X
Risk factores	X	X	X			

Risk Factors of IA in SOT

- **Liver transplant recipients**
  - Retransplantation (OR 29.9)
  - Dialysis (OR 14.5 to 24.5)
  - *Antigen Aspergillus* (OR 50.0)

  Fortún , Liver Transplant 02
  Singh , Transplantation 01

- **Heart transplant recipients**
  - Retransplantaion (RR 5.8)
  - Dialysis (RR 4.9)
  - CMV Disease (RR 5.8)

  Muñoz P, *Am J Transplant 04. Transplantation. 2013*

Lipidic Amphotericin B. Liver TX

	Risk factor	Dosage	Outcome
Singh *Transplantation 2001*	High risk (Dialysis)	AmBisome 5 mg/kg, 4 sem.	IFI: 0 % IA: 0 (control: 36% y 32%) (p<.05)
Fortún *JAC 2003*	High risk	AmBisome 1 mg/kg, 10 days	IFI: 14 % IA: 5 % (control: 36 % y 23 %) (p<.05)
Reed *Liver Transpl 2007*	High risk	Abelcet 5 mg/kg, 5 days	IFI: 3% AI: 0 (control: 16% y 3,5% (p<0,05)
Singhal *Liver Transpl 2000*	ICU >5 d	Abelcet 1 mg, 2,5 mg, 5 mg	No IFI
Castroagudín *Transpl Proc 2005*	High risk	AmBisome 1mg/kg, 7 days	Candidiasis: 0 AI: 2 cases (1 fatal)
Hadley *Traspl Inf Dis 2009*	High risk	AmBisome 2 mg/kg (35 p) Fluconazole (6 mg/kg) (29 p) 14 days	IFI: 10 pat (5% vs 6%) (9 *Candida*, 1 *Cryptococcus*) Antifungal: (23% vs 14%) (p: ns)

Prophylaxis With Caspofungin for Invasive Fungal Infections in High-Risk Liver Transplant Recipients

Major criteria:

- a) Re-transplantation
- b) Dialysis
- c) Fulminant hepatitis

Minor criteria (≥ 2):

- d) Creatinine clearance < 50 ml/min)
- e) Transfusion ≥ 40 unit CBP,
- f) Choledochojejunostomy (Y-Roux)
- g) Multiple colonization *Candida* spp (±48h Tx)
- h) Re-intervention (5 days Tx)

Fortun J et al. Transplantation 2009; 87:424-35

Favorable response (MITT) (primary objective): 63/71 (88.7%)

IFI	**2/71 (2.8%)**
-Surgical infection by *Mucor* spp.	**1**
- Surgical infection by *Candida albicans*	**1**

Caspofungin discontinuation due to clinical adverse effects	**0**
Caspofungin discontinuation due to analytical adverse effects	**6 (8.4%)**
Analytical alteration, toxicity grade IV	**27.7%**

Fortun J et al. Transplantation 2009; 87:424-35

Distribution and metabolism of echinocandins

	Caspo	Mica	Anidula
Metabolism and excretion	Hepatic Renal	Hepatic	Non hepatic (chemical degradation)
Half-life (h)	12-14	12-18	25
Clearance	Fast	Fast	No dose adjustment

Safety of Anidulafungin in Solid Organ Transplant Recipients

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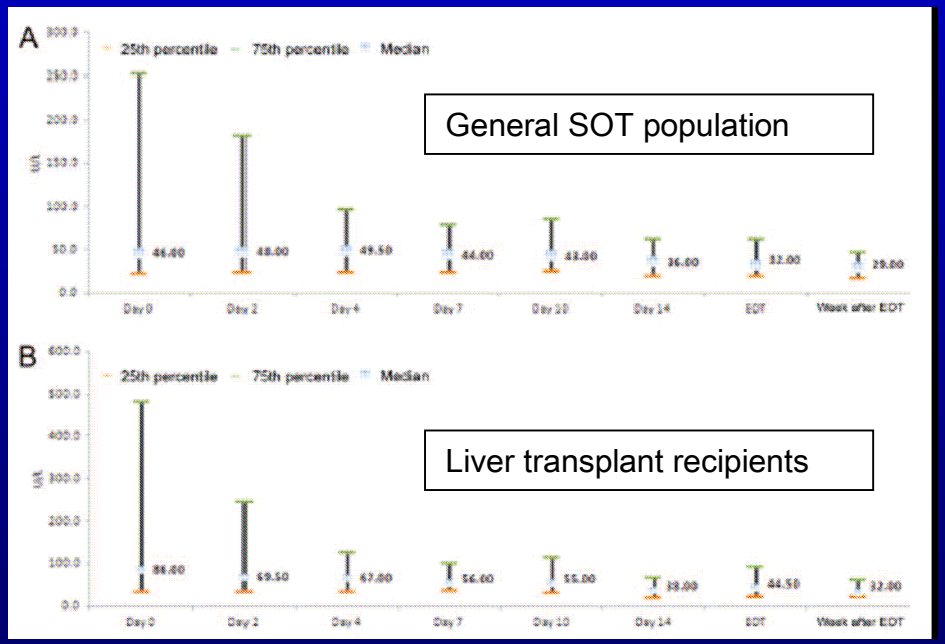
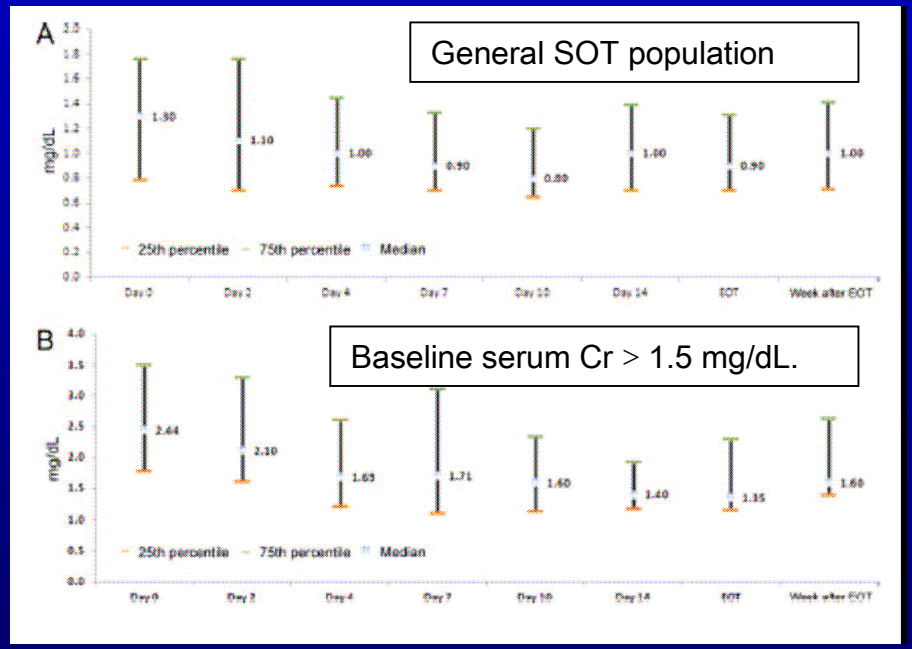


Transaminase levels



Serum creatinine levels

Liver Transpl. 2012;18:680-5

Spanish Society of Infectious Diseases & Clinical Microbiology
-Anti-Fungal prophylaxis Guidelines in SOT-

Transplant	Recommendations
Liver	Targeted Prophylaxis in HR-LTR; -Caspofungin (B-II) ,lipidic amphotericin B (B-II), micafungin (CIII), anidulafungin (CIII),
Lung	Universal prophylaxis -Nebulized amphotericin B (B-II) -Complementary: VCZ if Aspergillus spp colonization or chronic rejection (B-III)
Pancreas	Universal prophylaxis -FCZ (B-II) or lipidic amphotericin B (C-III)
Small bowel	Universal prophylaxis -FCZ (B-II) or lipidic amphotericin B (C-III)
Heart	Targeted Prophylaxis in HR-HTR; -ITZ, VCZ (C-III)
Kidney	No prophylaxis (D-III)

Fortun et al. Enf Infec Microbiol Clin 2011

Thank you very much for your attention

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