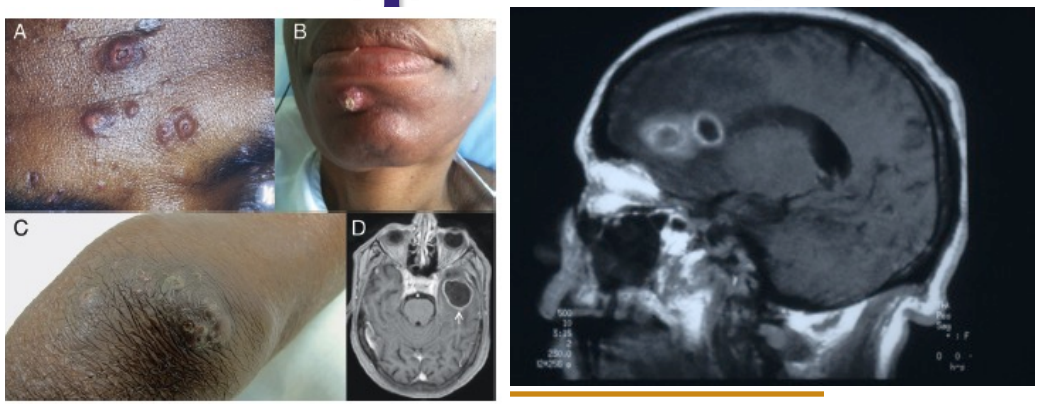
Fungal infections following solid organ transplantation



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Université Paris Descartes, Hôpital Necker Enfants malades,

IHU Imagine Paris, France.

Varese, May 19th, 2017

PARIS DESCARTES

FONDATION imagine INSTITUT DES MALADIES GÉNÉTIQUES

Necker ENFANTS MALADES

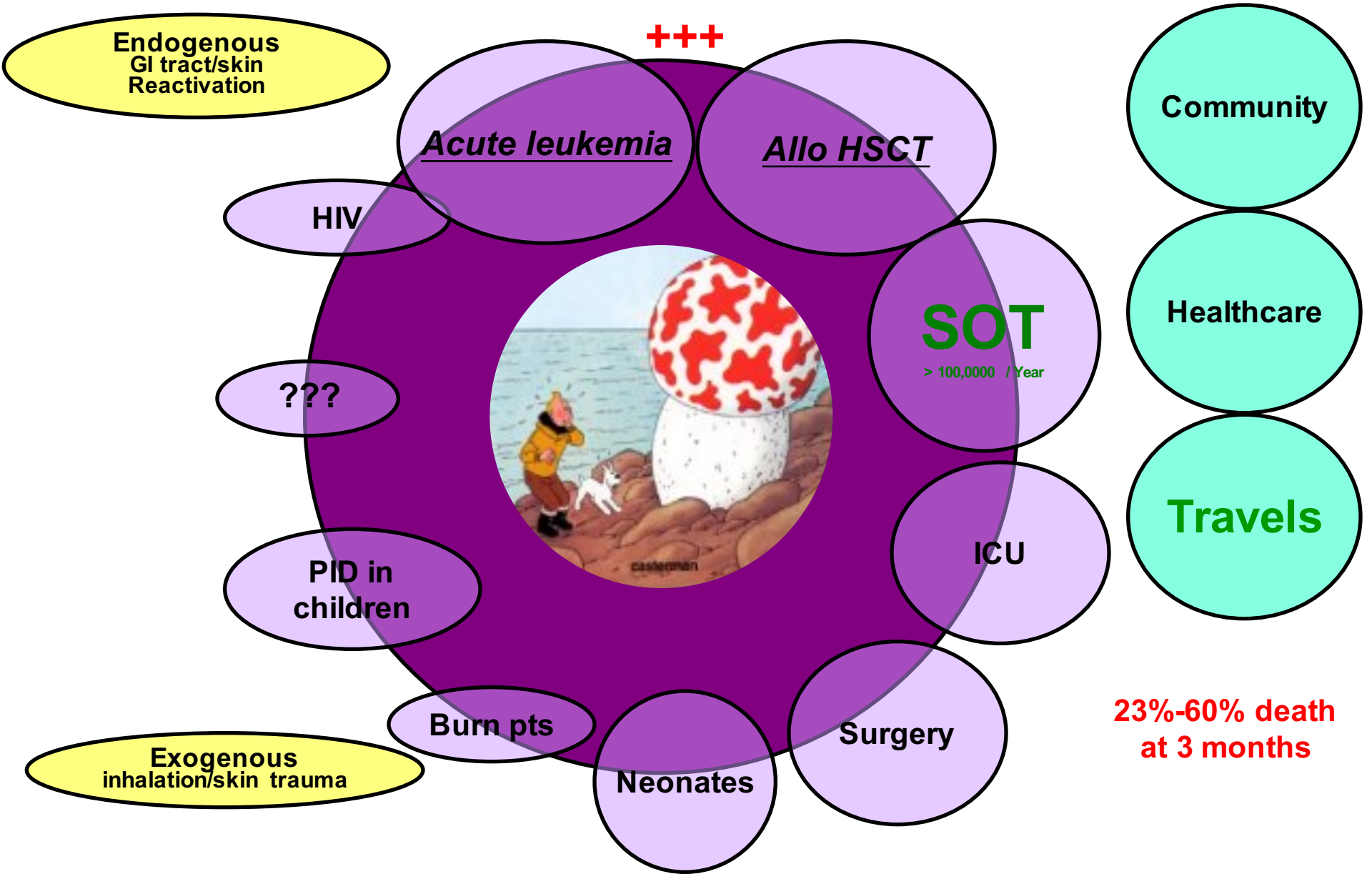
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Institut Pasteur

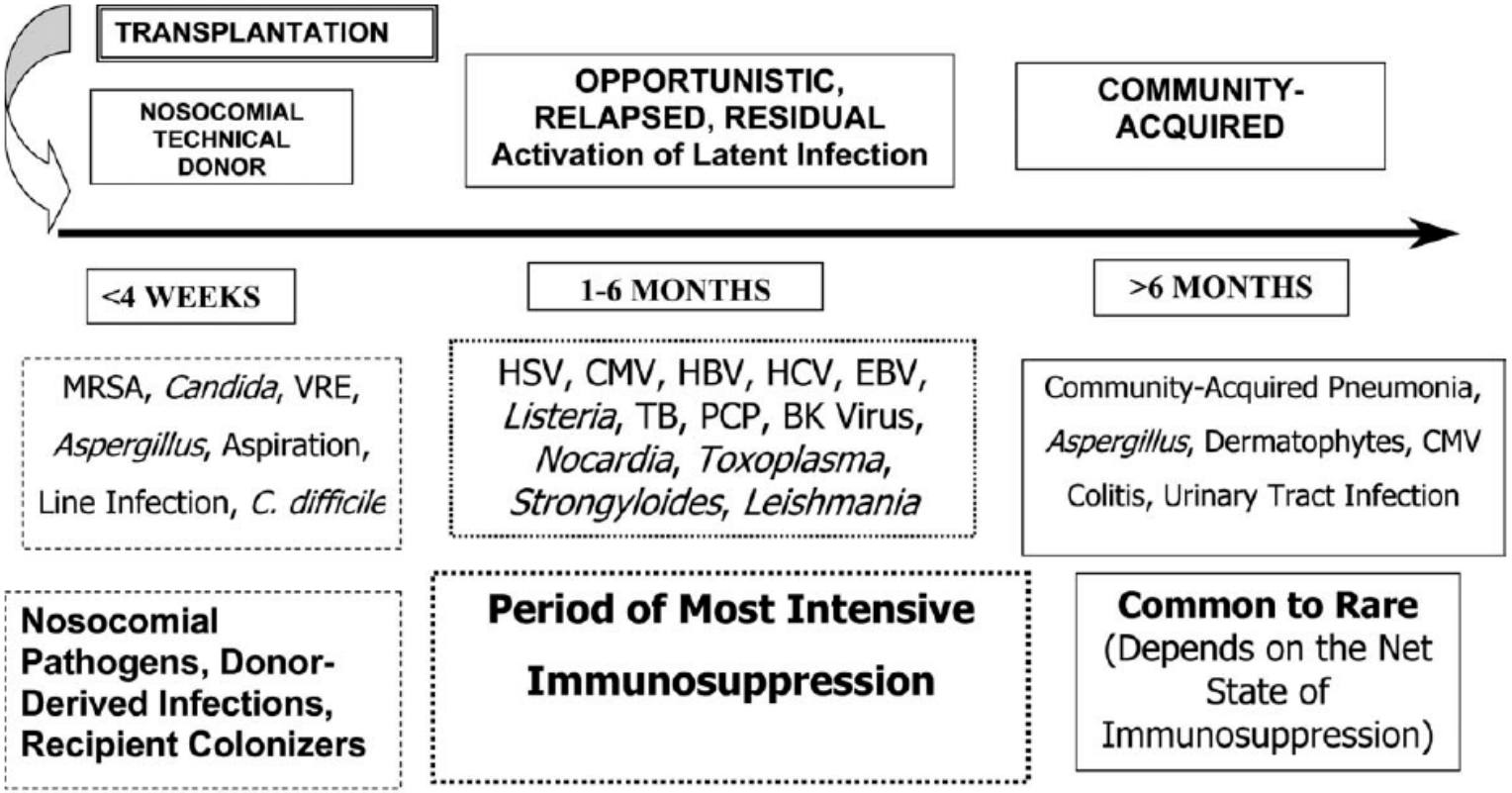
What will not be covered….!

- **Diagnosis of IFI:** See Schelenz et al. Lancet ID 2015
- **Prophylaxis:** See Gavalda et al. CMI 2014
- ***Pneumocystis jirovecii* :** See ECIL, J Antimicrob Chemother 2016
- **Cutaneous/subcutaneous infections:** See Guegan et al. Curr Opin Infect Dis 2016
- **Organ transmitted IFI:** See AST recommendations; Albano et al. CID 2010; Brugières TID 2010

Risk Factors for IFI



Time dependent infectious risk in SOT



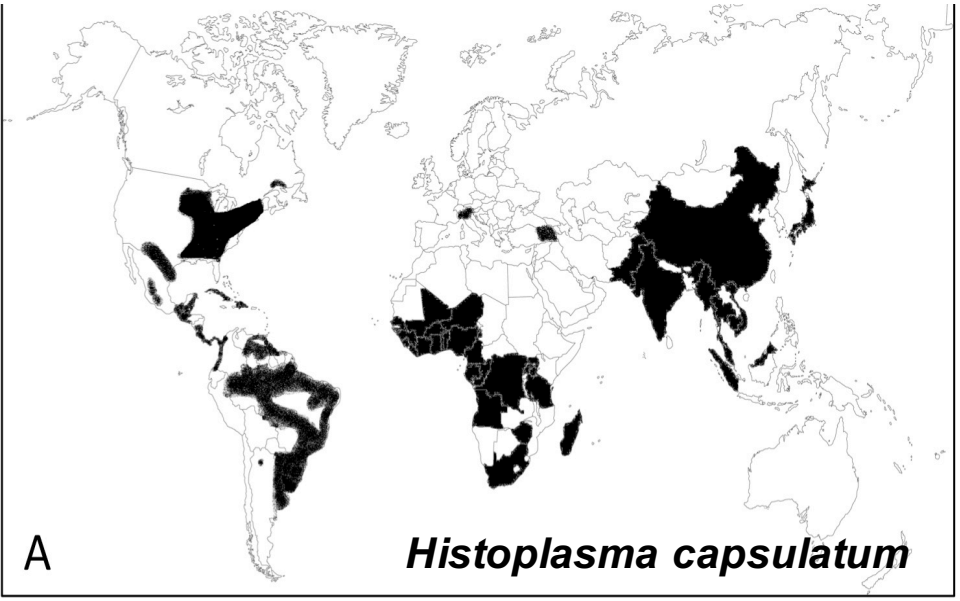
COMMON VARIABLES IN IMMUNOSUPPRESSION

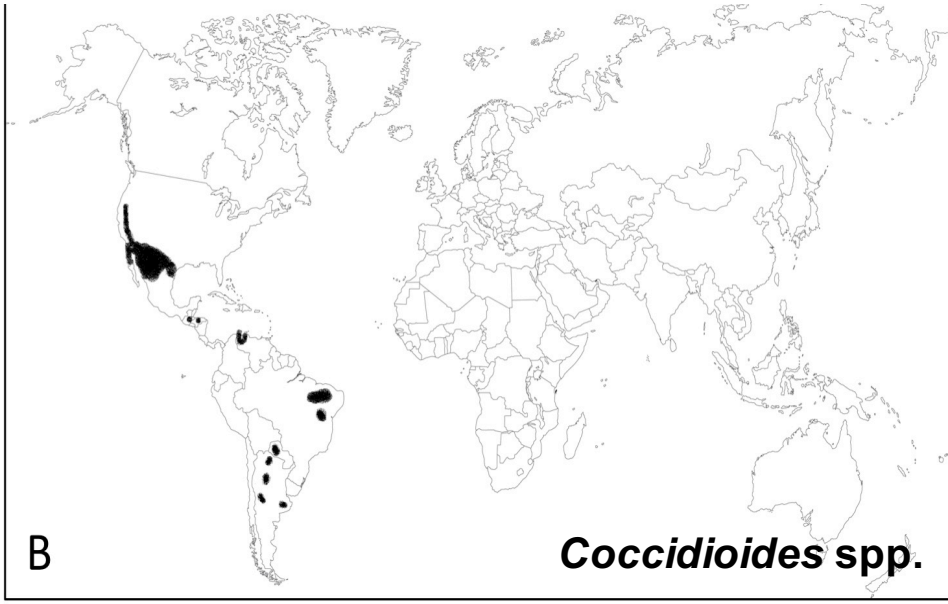
- ☹ **Antirejection therapy (anti-lymphocyte sera) and new agents for immunosuppression**
- ☹ **Neutropenia and lymphopenia**
- ☹ **Immunomodulatory viral infections (CMV, HCV, and EBV)**

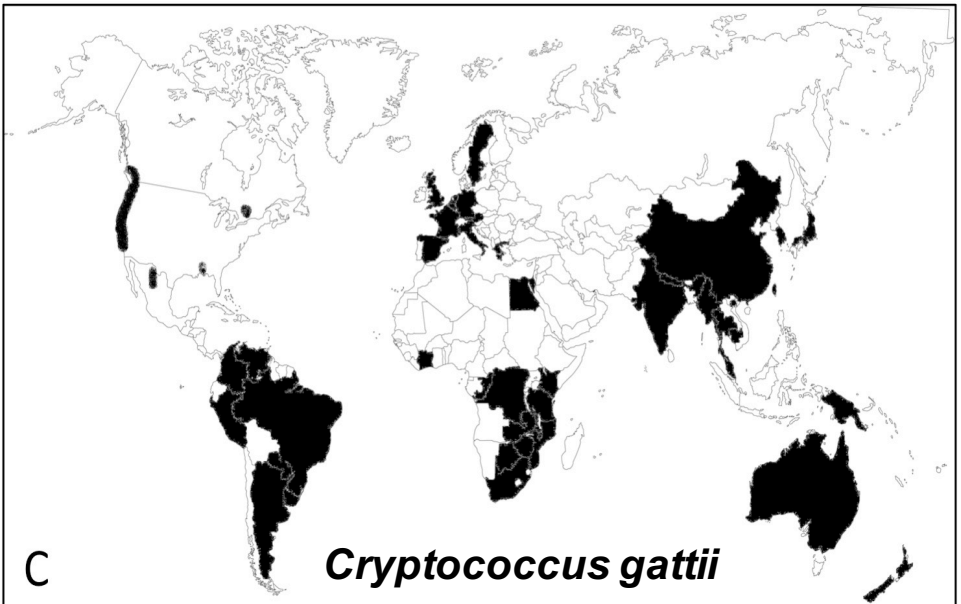
Fishman, 2011, Liver Transplantation

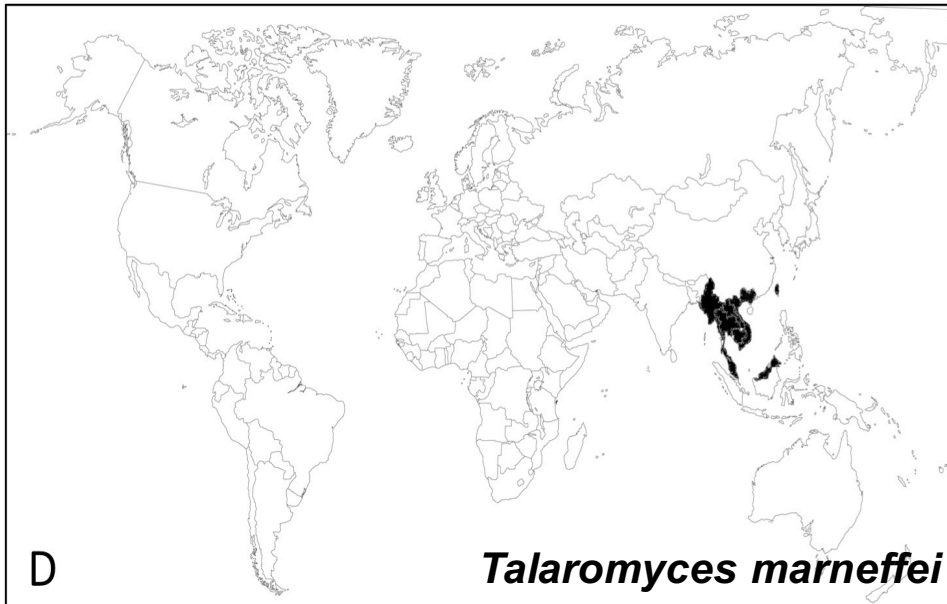
Immunocompromised SOT and worldwide fungal risk

Lortholary O *et al.* CID 2013





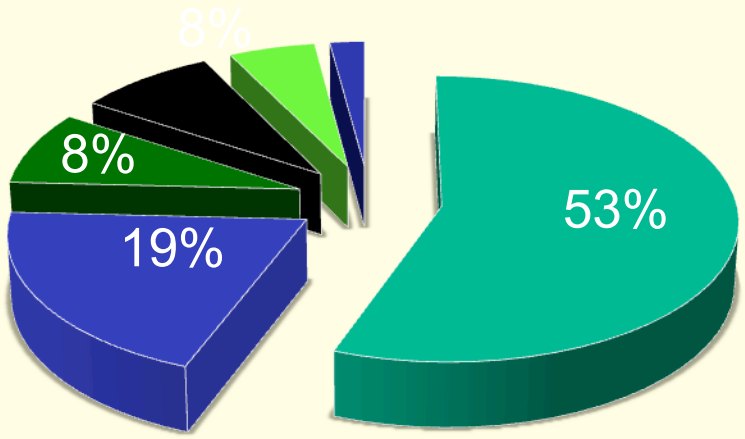




Major IFI diagnosed in SOT recipients

TRANSNET data

1208 IFI in 1063 organ transplant recipients



- Candidiasis
- Aspergillosis
- Cryptococcosis
- Non-Asp moulds
- Endemic fungi
- Mucormycosis

Median time post-transplant

- Candidiasis ⟷ 103 d
- Aspergillosis ⟷ 184 d
- Cryptococcosis ⟷ 575 d

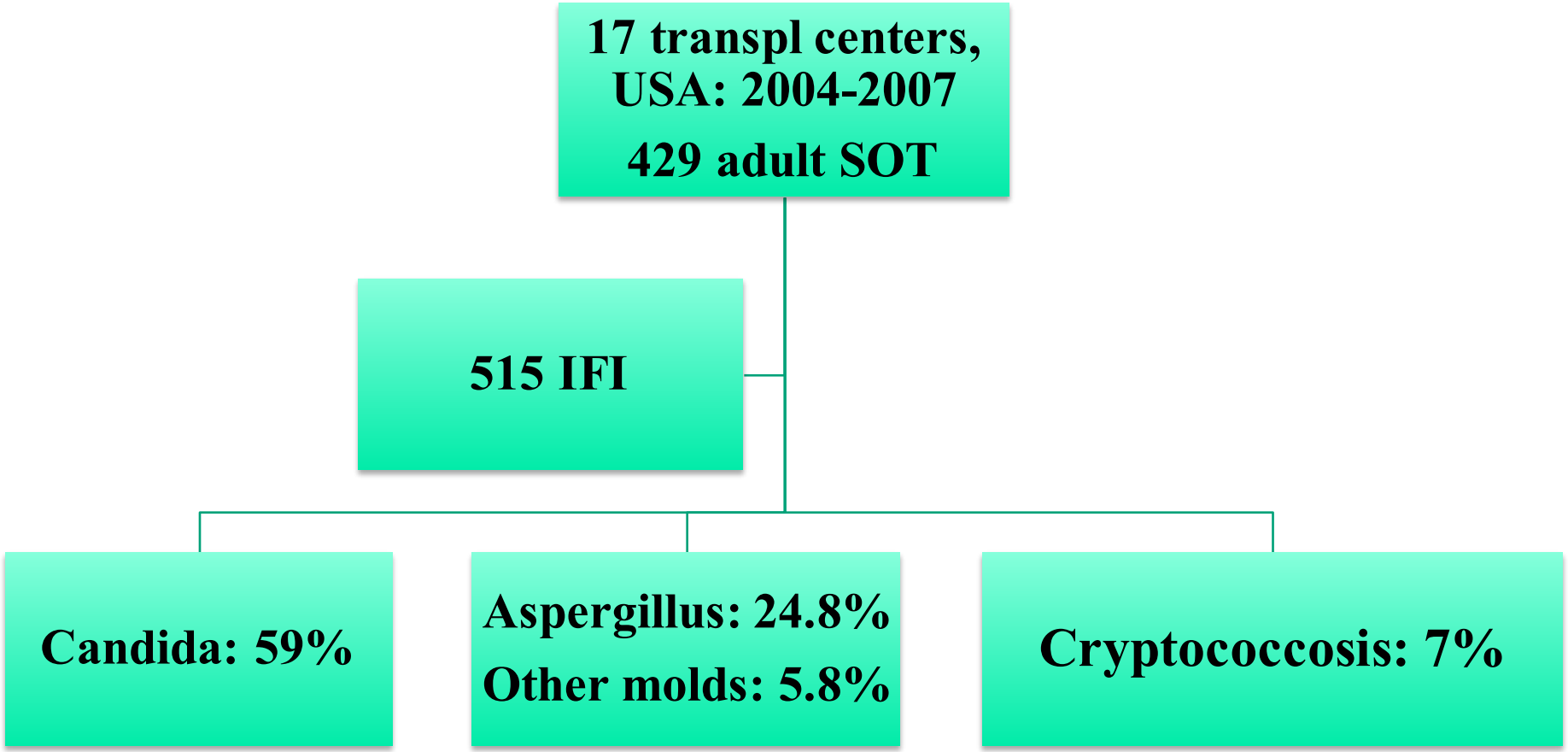
Pappas, Clin Infect Dis 2010

Invasive fungal diseases 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)

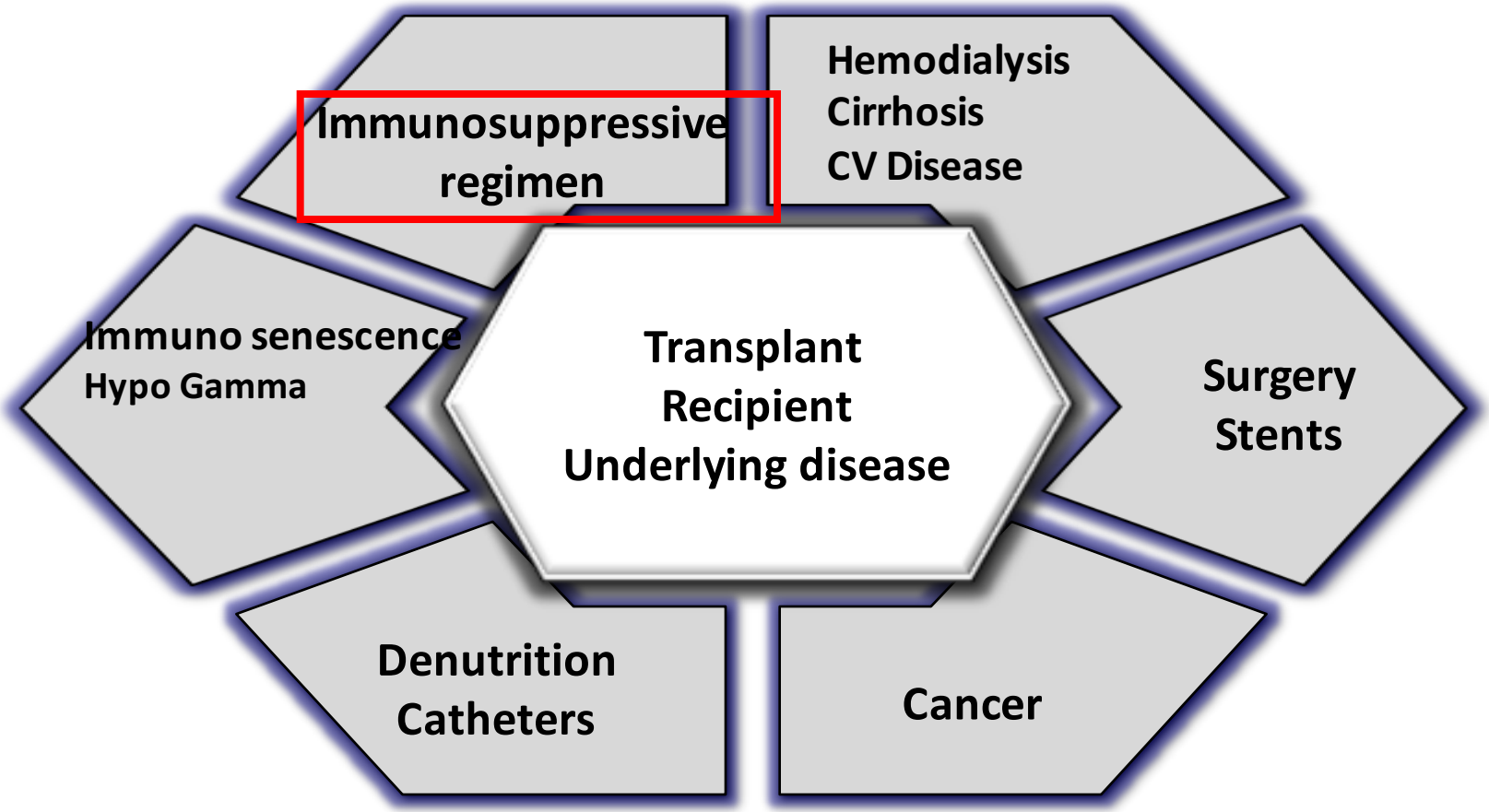
Pappas Clin Infect Dis 2010

Major IFD diagnosed in SOT recipients



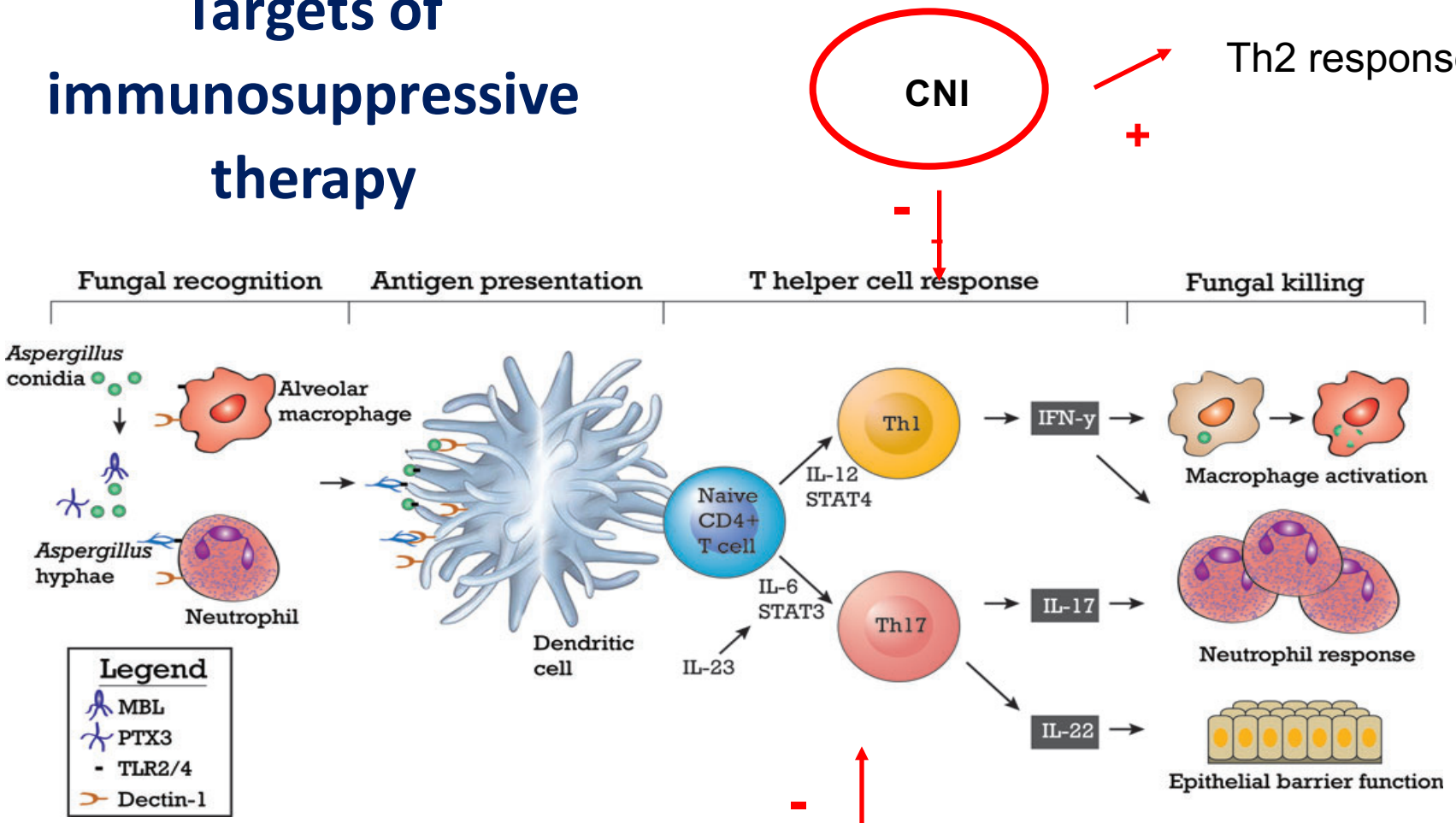
Neofytos, Transpl Infect Dis 2010

Vulnerability of transplant recipients to IFD



Burden of immunosuppressive therapy?

Targets of immunosuppressive therapy



Steroids

CNI

mTORi

MPA

Steroids

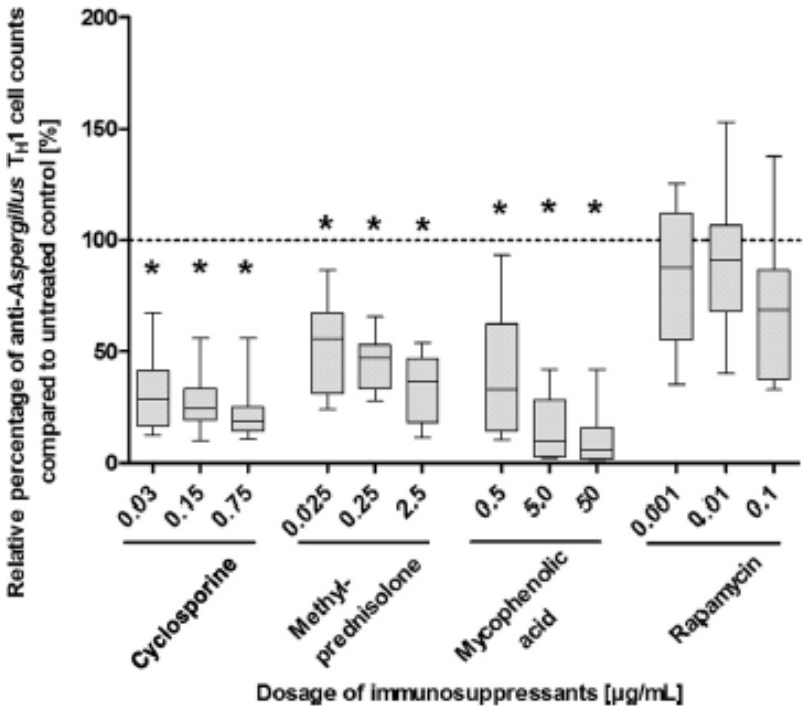
Steroids

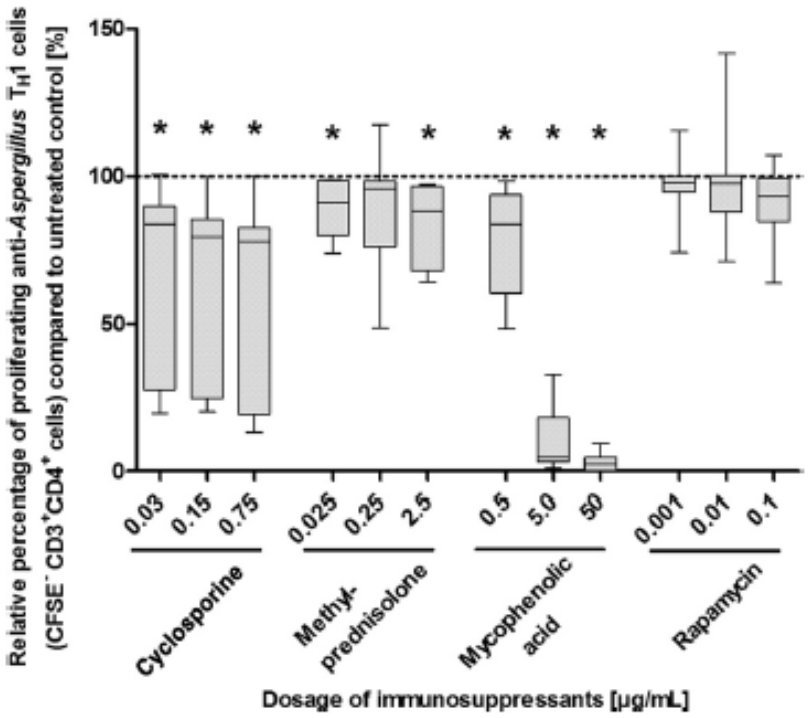
MPA

Corticosteroids

CNI

Decreased anti-Aspergillus Th1 immunity with immunosuppressant





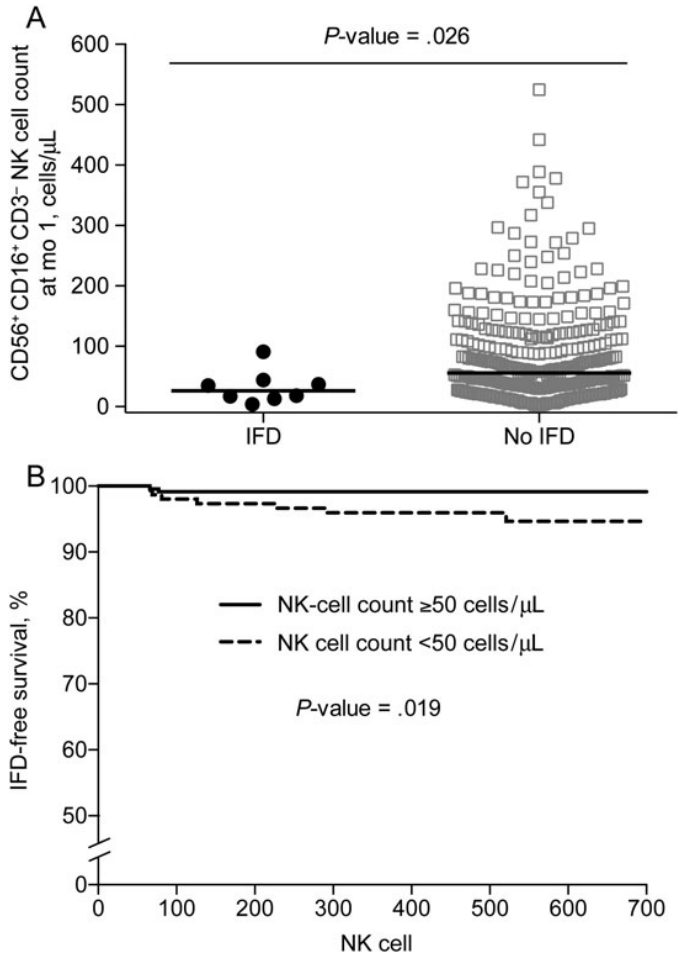
Decreased anti-Aspergillus Th1 cells count and proliferation

CsA decreases INF-γ release by Th1 cells (not shown)

Tramsen, 2014

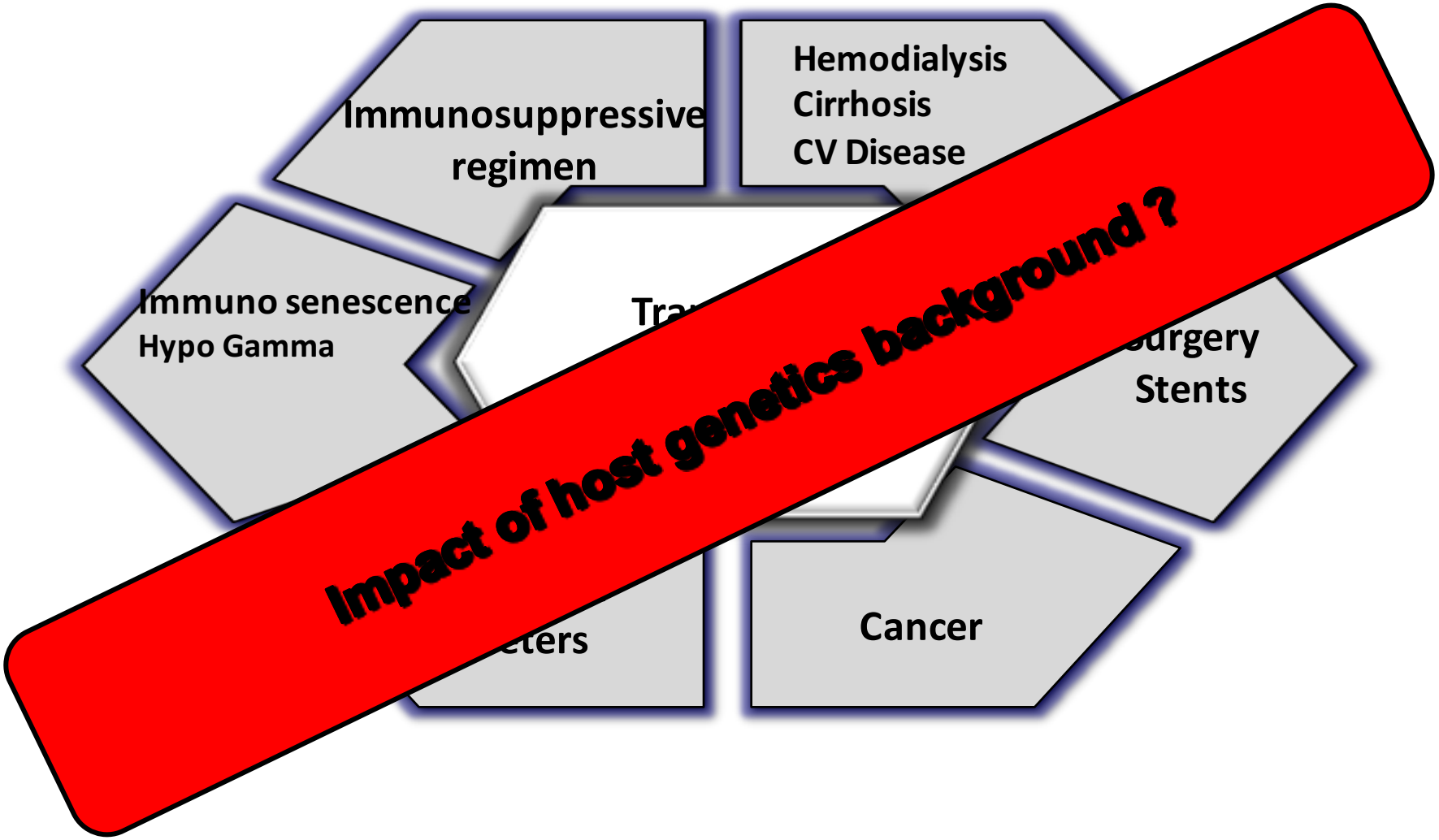
Decreased post-operative NK cell count predisposes to IFD in SOT

396 SOT
10 IFI, median 79 d



Fernandez Ruiz JID 2016

Vulnerability of transplant recipients to IFD



Independent factors associated with mold colonization or infection in SOT

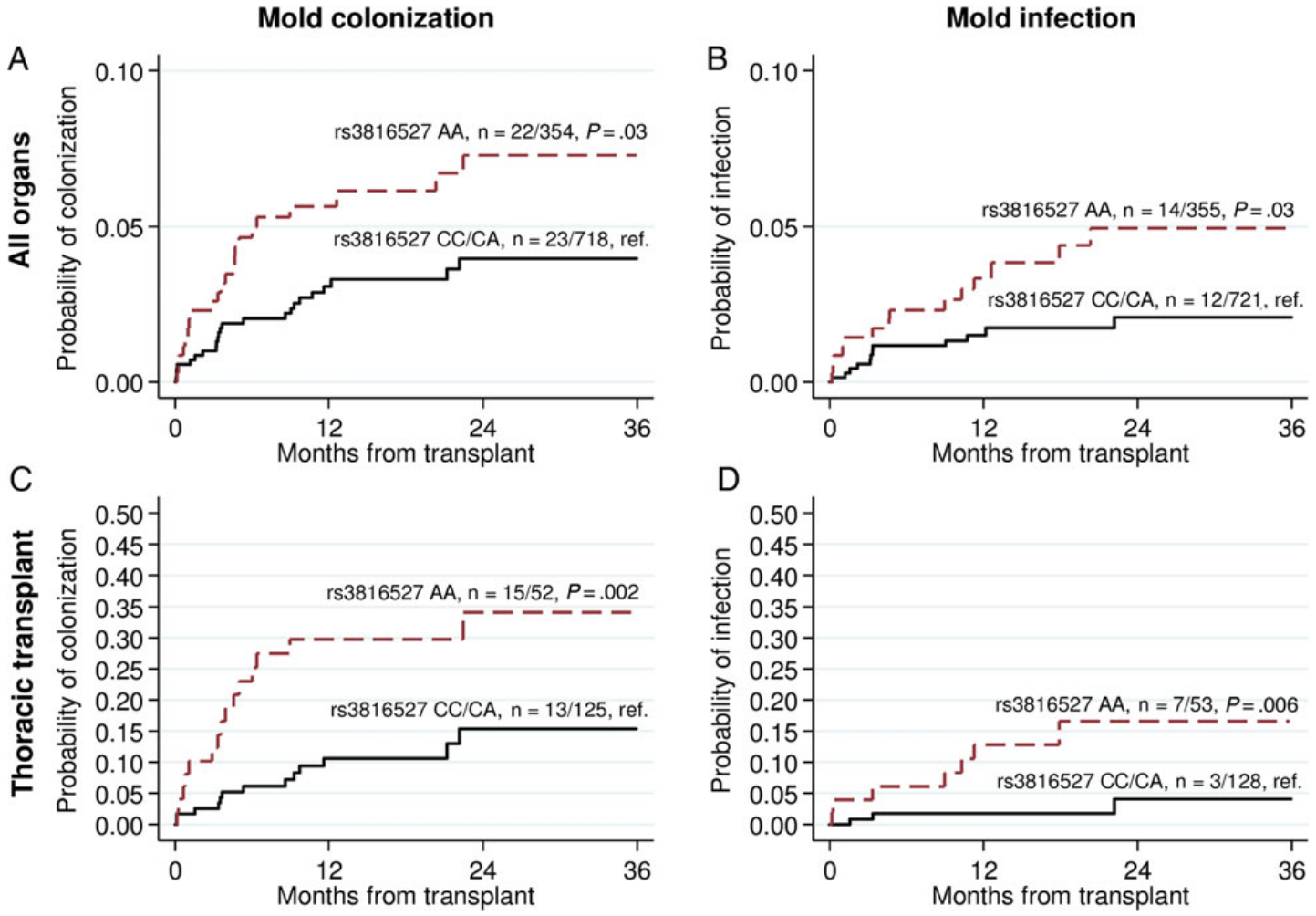
Swiss Cohort: 1101 SOT, 2008-2011
24 SNPs

	Mold Colonization (n = 42)		IMI (n = 25)	
Variable	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[a]
IL1B rs16944 (TT vs CC/CT)[b]	2.52 (1.18–5.36)	.02	4.29 (1.71–10.8)	.002[c]
DEFB1 rs1800972 (CC vs GG/GC)[b]	6.11 (2.28–16.4)	.0003[d]	4.73 (1.46–15.3)	.01
IL1RN rs419598 (CC vs TT/TC)[b]	3.35 (1.31–8.58)	.01	2.50 (.75–8.29)	.1
Lung or heart transplantation	11.5 (5.83–22.6)	<.0001	3.12 (1.21–8.03)	.02
MMF	0.32 (.16–.63)	.001	0.14 (.06–.33)	<.0001
Tacrolimus	0.52 (.27–1.03)	.06	0.45 (.19–1.09)	.1
Corticosteroids	. . .	. . .	3.03 (.67–13.7)	.1
Acute/chronic rejection	. . .	. . .	2.35 (.94–5.83)	.07
CMV infection/disease	1.83 (.89–3.72)	.1	2.68 (1.11–6.50)	.03
Recipient age (per year)	1.04 (1.01–1.06)	.008	1.06 (1.02–1.10)	.004

Wojtowicz, JID 2015

Pentraxin 3 rs3816527 single nucleotide polymorphism associated with mold colonization or infection in SOT

Swiss Cohort: 1101 SOT, 2008-2011



Wojtowicz, CID 2015

Risk factors for candidiasis in SOT

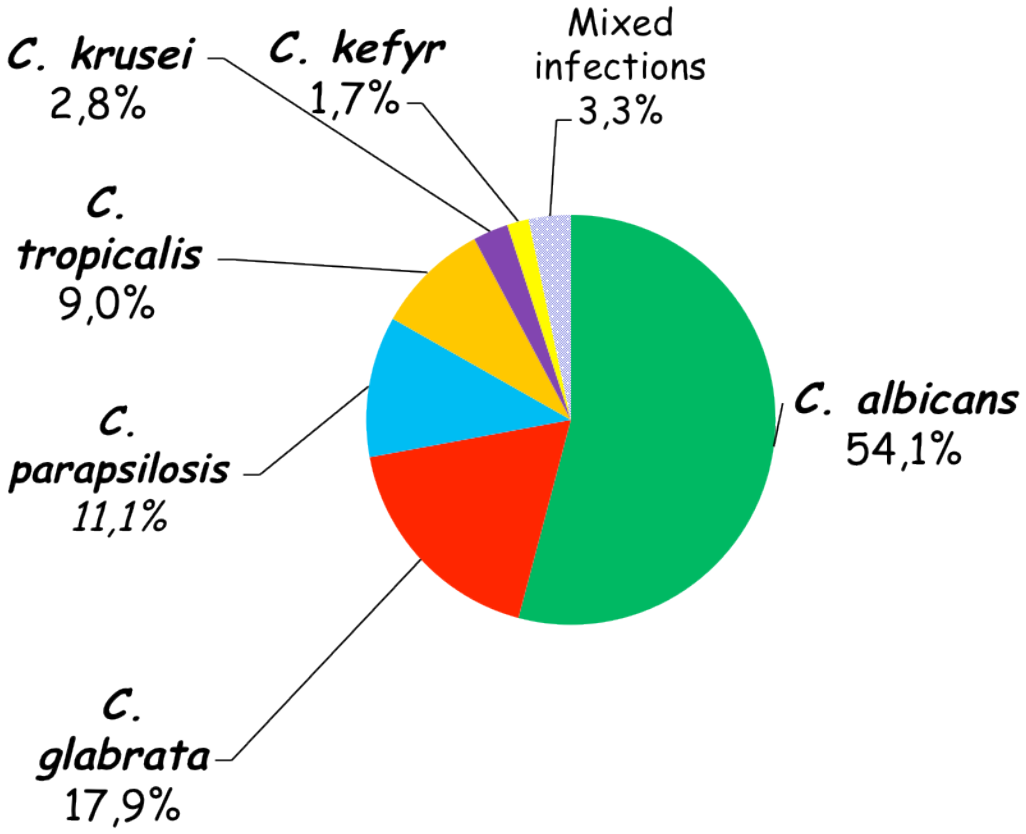
Transplant type	Target population
Liver	**High-risk liver transplant recipients:** **Major:** MELD score >30 Re-transplantation, fulminant hepatic failure, Renal failure requiring replacement therapy, **Minor:** MELD score 20–30, split, living-donor >40 transfusion blood products, choledochojejunostomy (Roux-en-Y) Renal failure not requiring replacement therapy (CrCl <50 mL/min) Early re-intervention, multifocal colonization/infection by *Candida* spp.
Pancreas	Post-perfusion pancreatitis, acute rejection and poor initial allograft function Vascular thrombosis, enteric drainage, anastomotic problems, haemodialysis Laparotomy after transplantation
Intestinal	Acute rejection and poor initial allograft function, haemodialysis, laparotomy after transplantation, anastomotic problems, over-immunosuppression
Heart	Acute rejection, haemodialysis, re-exploration after transplantation

Cr CL, creatinine clearance; MELD, model for end-stage liver disease; over-immunosuppression (high immunosuppression drug levels, under corticoid bolus).

ESCMID recommendations
Gavalda et al. CMI 2014

Characteristics of 2507 patients with candidemia: species involved

Patients' characteristics (N=2507)	
Male gender	60,3%
Mean age (± sd) years	60 (± 17)
Intensive care unit	48.1%
Malignancy	50.3%
Prior surgery (30 days)	38.7%
Central venous catheter	74%



2571 isolates in 2507 incident episodes
(2424 single, 83 mixed infections)

SOT : 10.5% candidemia in ICU
2.7% outside ICU

Lortholary et al. ICM sept 2014

Risk of candidemia due to fluconazole non-susceptible isolates

- **Candipop study, 29 hospitals, Spain 2010-2011**:

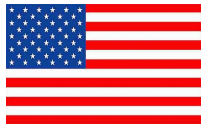
617 patients (21.7% FCZ non-susceptible)

- **Independent factors with FCZ-NS**:
  - **Transplant recipient (AOR 2.13; 95% CI 1.01-4.55)**
  - Hospitalization in a unit with high prevalence (≥ 15%) of FCZ-NS strains (7.53; 4.68-12.10)
  - Previous azole therapy (≥ 3d, within 30 d) (2.04; 1.16-3.62)

- **Definition and validation of a predictive score**

Cuervo *et al*. CMI 2015

Echinocandin resistant / MDR Candida glabrata isolates (2012-2014)



Does exist in the absence of prior exposure !

% Echinocandin R	% MDR (azoles & echinocandins)	Reference
	1	CDC Sentry, Pfaller JCM 2012
	1	Pham AAC 2014
11 (18% *FKS* mutants)	-	Beyda CID 2014
6.7 (increase 2001-2010)	3.5	Alexander CID 2013
10.3	6.8	Farmakiotis EID 2014
	2.6	Cleveland PLoS ONE 2015

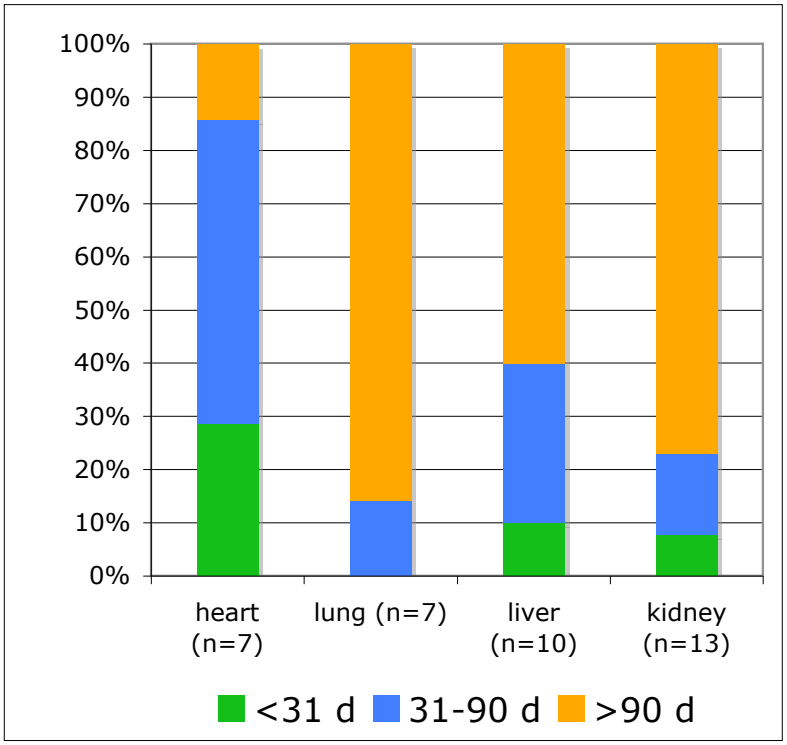
Risk factors for invasive aspergillosis in SOT

	Early IA	Late IA (>3 months post-transplant)
Liver transplant	Re-transplantation Kidney failure, especially post-transplant Haemodialysis Fulminant hepatic failure Complicated surgery or reoperation	More than 6 g of accumulative prednisone in the third month after transplantation Post-transplant renal failure Post-transplant haemodialysis Leukopenia (<500/mm^3) Chronic graft dysfunction
Lung transplant	Bronchial anastomotic ischaemia or bronchial stent placement Acute rejection Single-lung transplant *Aspergillus* spp. colonization before or during first year post-transplant	Chronic graft dysfunction
Heart transplant	*Aspergillus* spp. colonization of the respiratory tract Re-operation Post-transplant haemodialysis Hypogammaglobulinaemia (IgG < 400 mg/dl)	ICU readmission Kidney transplantation >2 acute rejection episodes
Kidney transplant	Graft lost and haemodialysis Post-transplant haemodialysis Prolonged high corticosteroid doses	
	CMV infection Over-immunosuppression	

ESCMID recommendations
Gavalda et al. CMI 2014

Incidence of invasive aspergillosis in SOT recipients in France

- **Incidence**
  - **Heart 4.8 % (7/146) *(1)***
    - **1-14% *(2)***
    - **10 per 1000 person-years *(3)***
  - **Lung 4.1 % (7/172) *(1)***
    - **6-16% *(2)***
    - **49 per 1000 person-years *(3)***
  - **Liver 0.8 % (9/1067) *(1)***
    - **1-8 % *(2)***
    - **11 per 1000 person-years *(3)***
  - **Kidney 0.3 % (13/3157) *(1)***
    - **0.4-5% *(2)***
    - **2 per 1000 person-years *(3)***
- **Late complication excepted for heart transplantation**



Tracheobronchitis
44% SOT, ++ ulcerations
Fernandez Ruiz Medicine 2012

(1) Lortholary, CMI 2011; (2) Fernanda, Med Mycol 2007; (3) Neofytos TID 2013 [IMI]

Recent case control studies of IA in kidney transplant recipients

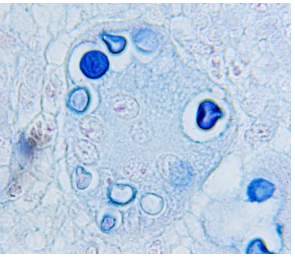
- **16 adults, Paris 2003-2013**
- 81% limited to lungs
- 12 week mortality 6%
- 1 year mortality 19%
- Cardiovascular diseases pretransplant, delayed graft function and opportunistic infections increase occurrence of IA
- IA reduces overall survival and graft survival

- **41 adults, Leuven 1995-2013**
- Early onset (≤ 3 months)
  - Duration of replacement therapy pretransplant
  - Leukopenia
- Late onset (> 3 months)
  - Donor CMV seropositivity
- 12 week mortality 39%
- Dissemination, leukopenia and height of GM index increase risk of death

Desbois , Transplantation Direct, in press

Heylen CID 2015

C. neoformans infection pathogenesis during SOT



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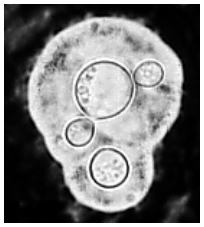


Environment

LUNGS
(Alveolar Mphages)

SKIN

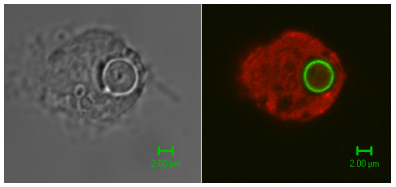
cn

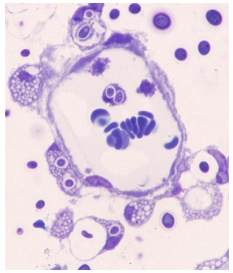
GRAFT

Latency (CD4/Th1 cytok)

Immune deficiency

Blood (PBMC)





CNS Organs

PRIMARY INF

REACTIVATION

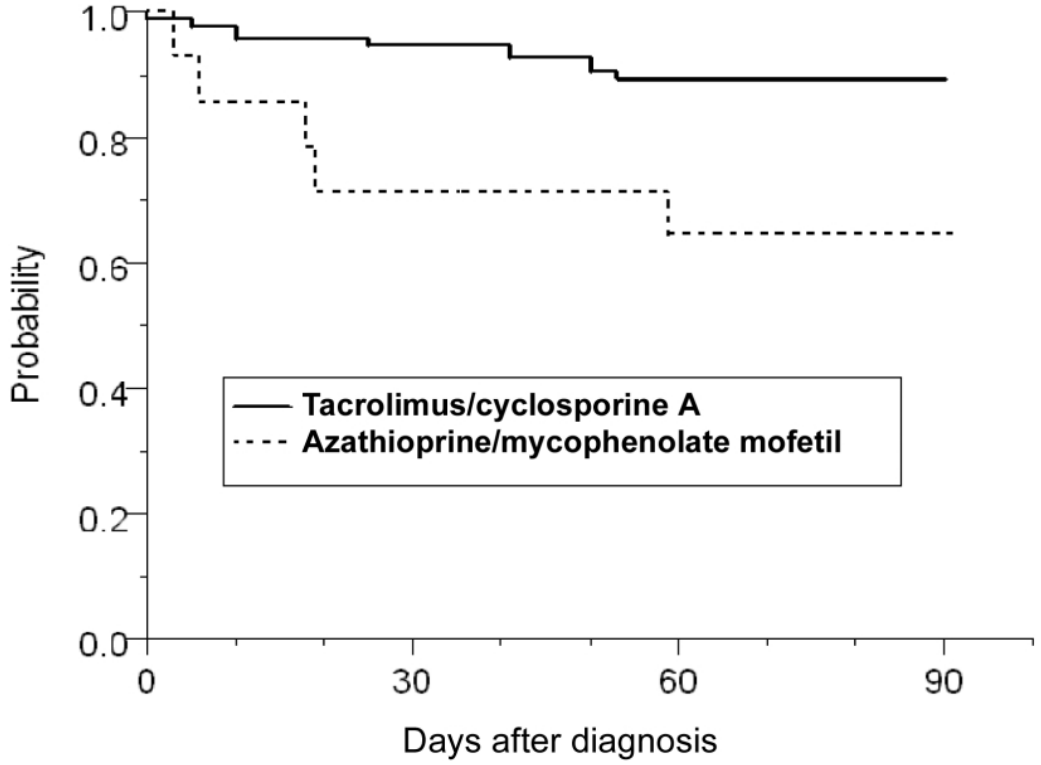
MULTIPLE INF

52%

Saha, Clin Vaccine Immmunol 2007

Beneficial roles of calcineurin inhibitors during SOT-associated cryptococcosis

- Less disseminated forms (48 vs 80%, p=0.02)
- More pulmonary forms (37 vs 7%, p=0.02)
- Less death (OR= 0.21, p=0.008)



N=111 SOT

Singh, J Infect Dis, 2007

Calcineurin Inhibitor Agents Interact Synergistically with Antifungal Agents In Vitro against *Cryptococcus neoformans* Isolates: Correlation with Outcome in Solid Organ Transplant Recipients with Cryptococcosis[▽]

Dimitrios P. Kontoyiannis,[1]* Russell E. Lewis,[1] Barbara D. Alexander,[2] Olivier Lortholary,[3] Françoise Dromer,[4] Krishan L. Gupta,[5] George T. John,[6] Ramon del Busto,[7] Goran B. Klintmalm,[8] Jyoti Somani,[9] G. Marshall Lyon,[9] Kenneth Pursell,[10] Valentina Stosor,[11] Patricia Muňoz,[12] Ajit P. Limaye,[13] Andre C. Kalil,[14] Timothy L. Pruett,[15] Julia Garcia-Diaz,[16] Atul Humar,[17] Sally Houston,[18] Andrew A. House,[19] Dannah Wray,[20] Susan Orloff,[21] Lorraine A. Dowdy,[22] Robert A. Fisher,[23] Joseph Heitman,[3] Nathaniel D. Albert,[1] Marilyn M. Wagener,[24] and Nina Singh[24]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2008, p. 735–738

An Immune Reconstitution Syndrome–Like Illness Associated with *Cryptococcus neoformans* Infection in Organ Transplant Recipients

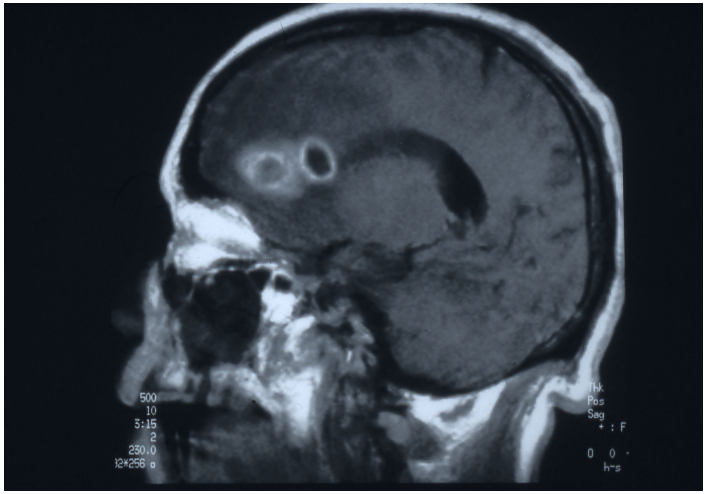
Prospective multicenter cohort: 4.8% pts

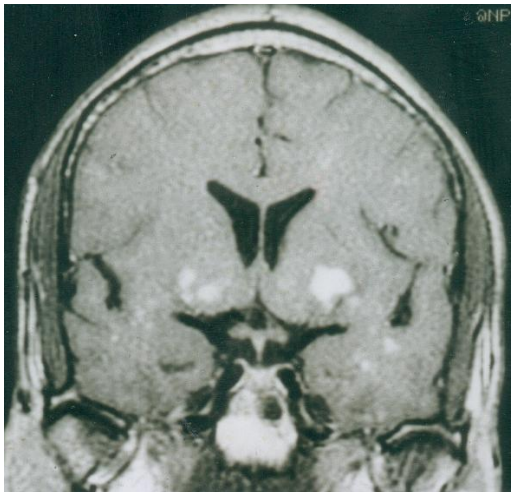
Nina Singh,[1] Olivier Lortholary,[16] Barbara D. Alexander,[2] Krishan L. Gupta,[18] George T. John,[19] Kenneth Pursell,[3] Patricia Munoz,[17] Goran B. Klintmalm,[5] Valentina Stosor,[4] Ramon del Busto,[6] Ajit P. Limaye,[7] Jyoti Somani,[8] Marshall Lyon,[8] Sally Houston,[9] Andrew A. House,[20] Timothy L. Pruett,[11] Susan Orloff,[13] Atul Humar,[21] Lorraine Dowdy,[10] Julia Garcia-Diaz,[14] Andre C. Kalil,[15] Robert A. Fisher,[12] Shahid Husain,[1] and the Cryptococcal Collaborative Transplant Study Group[a]

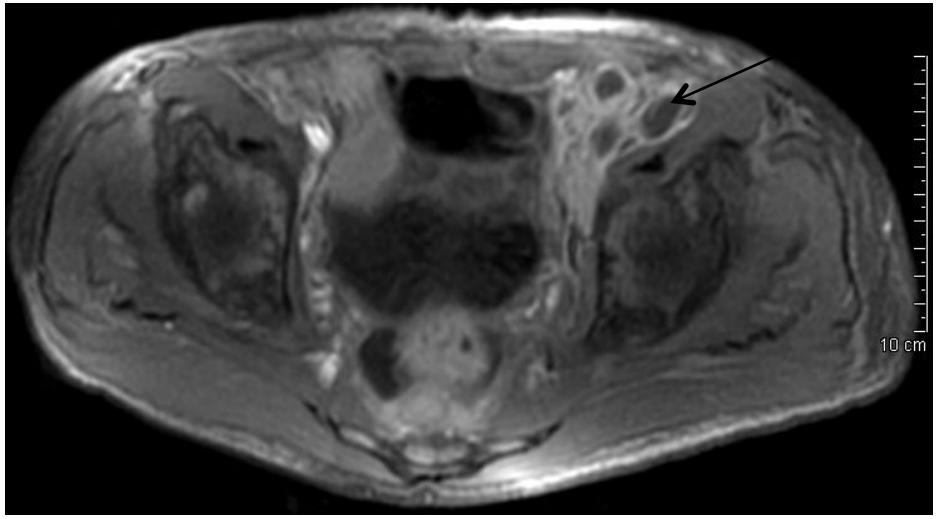
CID 2005

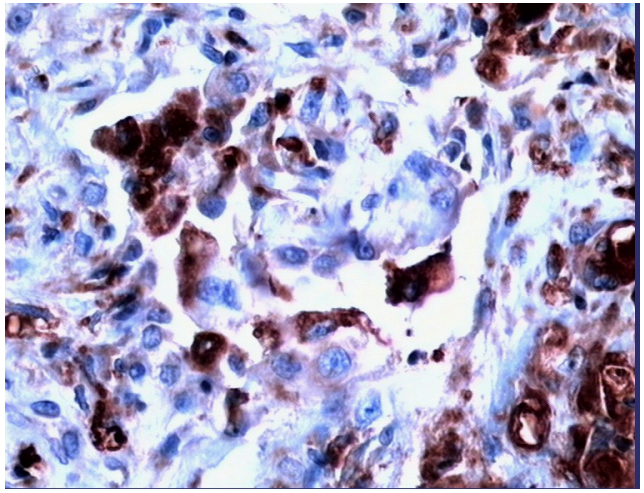
Type of transplant Kidney Kidney-pancreas Liver	 2/4 1/4 1/4
Time to onset of *C.neoformans* infection post-transplant, median (range)	10.5 months (3-29 months)
Immunosuppressive regimen Tacrolimus, mycophenolate mofetil, prednisone	 4/4
Initial sites of involvement Pulmonary (any) Skin, soft tissue (any) Central nervous system (any) Disseminated infection*	 2/4 2/4 2/4 4/4
Time to onset of IRS-like syndrome after antifungal therapy, median (range)	5.5 weeks (4-12 weeks)

Clinical cases of cryptococcal IRIS

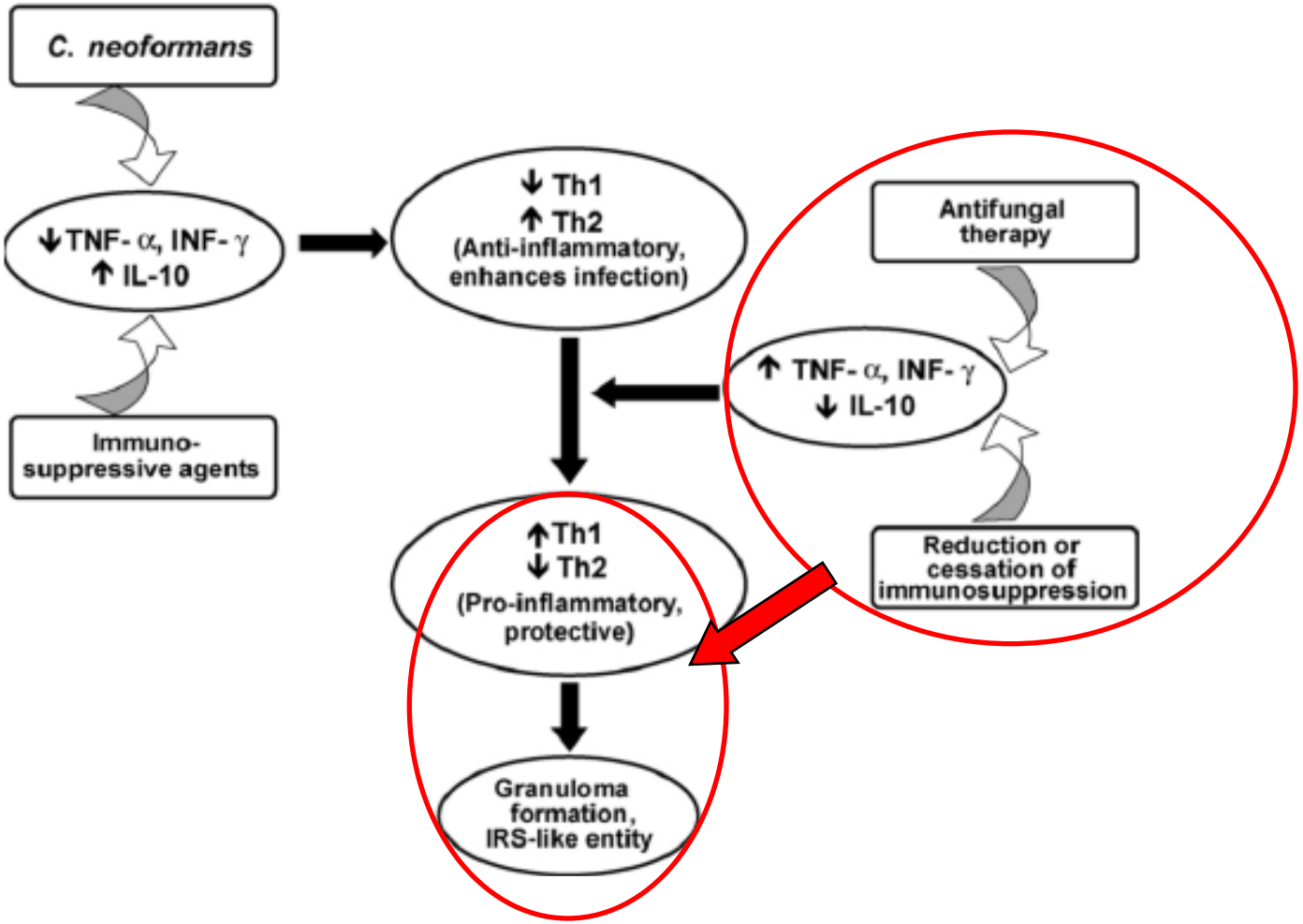








Reversal Th2/Th1 and proinflammatory responses and occurrence of cryptococcal IRIS during SOT ?



Sun, Clin infect Dis 2011

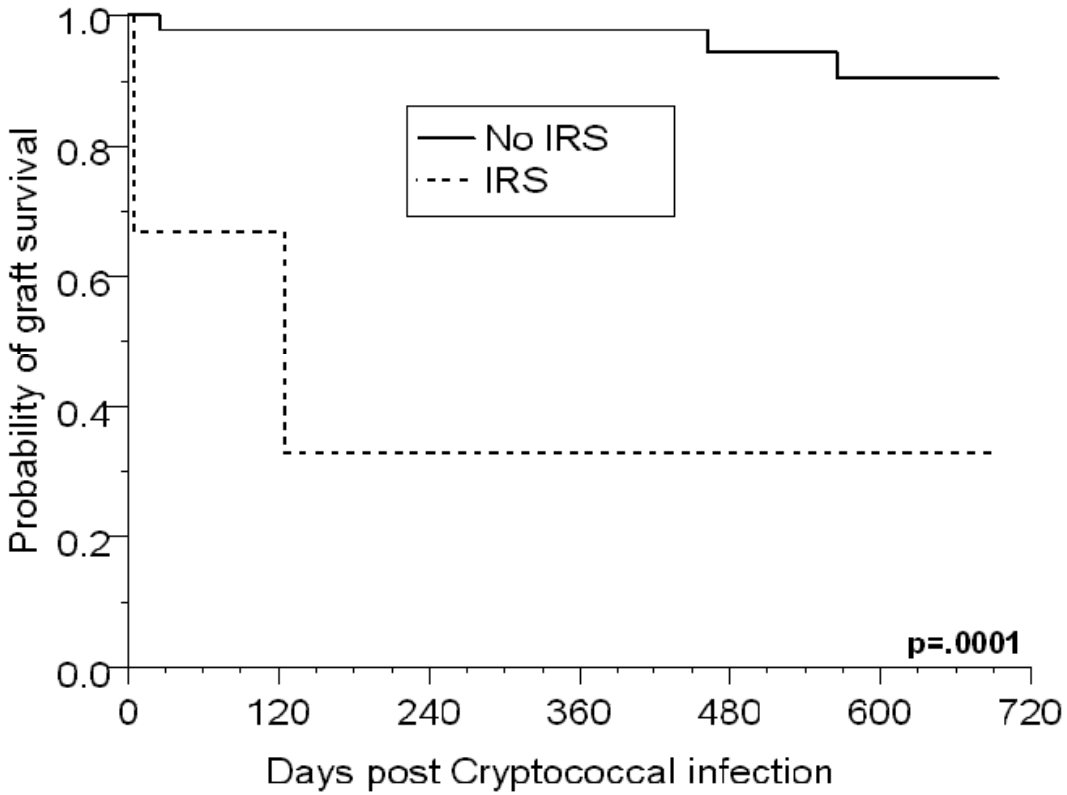
Singh, Clin infect Dis 2005

Predictors of IRIS in SOT with cryptococcosis

Factor	IRS (n = 13)	No IRS (n = 76)	Odds of IRS, OR (95% CI)	Comparison Group	*P* Value
Pulmonary disease only	7.7% (1/13)	45% (34/76)	0.10 (.01–.83)	Extrapulmonary	.033
CNS disease	85% (11/13)	40% (30/76)	8.43 (1.74–40.75)	No CNS	.008
Fungemia	38.5% (5/13)	36% (20/55)	1.09 (.31–3.80)	No fungemia	.888
Disseminated disease	92.3% (12/13)	51.3% (39/76)	11.38 (1.41–91.95)	Local disease	.022
Discontinuation of CNI	50.0% (6/12)	13.8% (9/65)	6.88 (1.91–24.76)	Continue CNI	.008

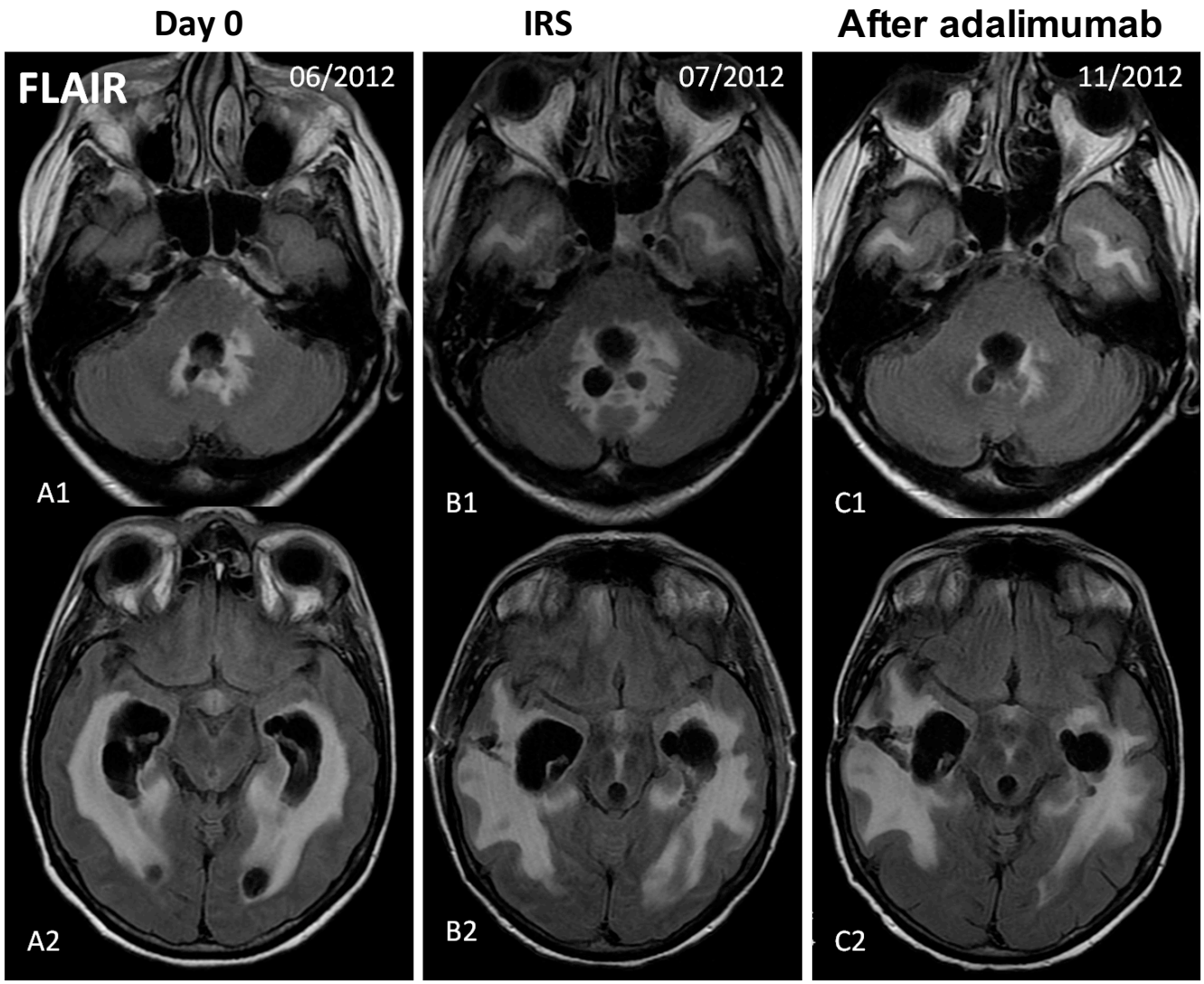
Sun, CID 2015

Probability of graft survival in renal transplant recipients with cryptococcosis according to IRIS



Singh, Lortholary et al. Transplantation 2005

Efficacy of a anti-TNF-α monoclonal antibody during SOT-associated cryptococcal IRIS



Scemla, Am J Transpl, 2015

IFI following SOT !

- Except PjP, first 3 : candidiasis, aspergillosis & cryptococcosis
- Predisposing immune deficiency to be better deciphered
- Influence of host genetic background
- Acquired resistance among *Candida* species
- Influence of immunosuppressive therapy
  - baseline severity and outcome
  - ± synergy with antifungals
  - occurrence of IRIS following discontinuation
- New approaches for the management of fungal IRIS