New Challenges in Fungal Infections in SOT

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New challenges in fungal infections in SOT

1. **Challenges in epidemiology and clinical presentation**
2. New diagnostic methods
3. Prophylaxis
4. Therapy

Epidemiology of IFI in SOT

- **We have witnessed a shift in pathogens**
  - Significant reduction of *Candida* (advances in technical skills) and *Aspergillus* infections (less CMV)
  - Emergence of new pathogens
    - Zygomycetes, *Fusarium*, *Scedosporium*
  - Virtual disappearance of *P. jiroveci*

- **Delay in the onset of IFI**
  - Fewer complications in the postoperative period
  - Delayed onset of CMV infection, HCV post-transplant reinfection

Challenges in IFI **epidemiology** in SOT

1. **Incidence** of *Candida* infections is increasing in some centers: LT allocated by MELD

Table 2 Fungal infections according to allocation era.

	Pre-MELD era (n = 210)	MELD era (n = 175)	P
Patients with invasive fungal infections	25 (11.9)	42 (24.0)	0.002
Candida colonisation	27 (12.9)	43 (24.6)	0.003
Candida infection	19 (9.0)	33 (18.9)	0.005
Proven Aspergillosis	2 (1.0)	3 (1.7)	0.51
Probable Aspergillosis	11 (5.2)	11 (6.2)	0.66

Data are presented by number (%).

Pts with a higher MELD:

- **More re-transplantation**
- **More renal failure**
- **Longer operation times**
- **More intraoperative blood transfusions**

Lichtenstern C, et al. Mycoses 2013;56:350–7

Challenges in IFI **epidemiology** in SOT

2. Importance of **antifungal resistance** in *Candida* / Not yet a problem with *Aspergillus*

TRANSNET STUDY IN USA

KNOW YOUR EPIDEMIOLOGY

	Fluconazole	Itraconazole	Voriconazole
All (n=383)	**16%**	**17%**	**3%**
***C. albicans* (154)**	1	2	1
***C. glabrata* (119)**	**23**	**52**	**8**
***C. parapsilosis* (48)**	0	0	0
***C. krusei* (32)**	100	0	0
***C. tropicalis* (21)**	5	5	5

Spanish study: 2% of voriconazole-R *Aspergillus* infections (does not include SOT recipients)

Lockhart SR, J Clin Microbiol 2011 / Escribano P, Antimicrob Agents Chemother 2013.

Challenges in IFI **epidemiology** in SOT

3. *Aspergillus* is appearing later and with uncommon clinical presentations

ELSEVIER

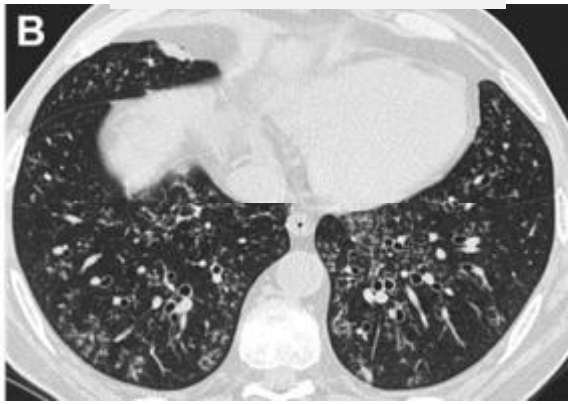
The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

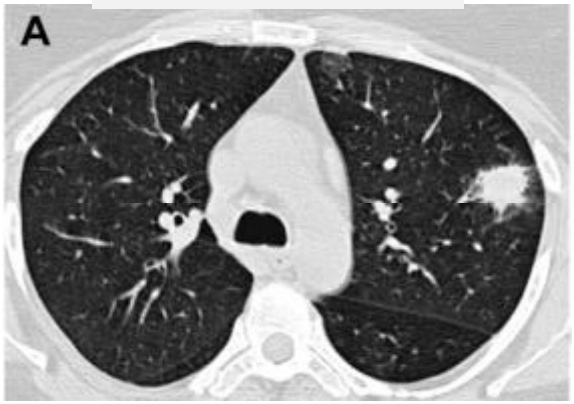
Invasive pulmonary aspergillosis in heart transplant recipients: Two radiologic patterns with a different prognosis

Patricia Muñoz, MD, PhD,[a,b,c] Antonio Vena, MD,[a] Ines Cerón, MD,[a] Maricela Valerio, MD,[a] Jesús Palomo, MD,[d] Jesús Guinea, MD,[a] Pilar Escribano, MD,[a] Manuel Martínez-Sellés, MD,[d,e] and Emilio Bouza, MD[a,b,c] for the PROMULGA Project Group

AIRWAY INVASIVE



ANGIO INVASIVE



- **37%** of IA in HT recipients present with an **airway-invasive** radiological pattern

- **Delayed diagnosis**
  - More mechanical ventilation
  - Increased mortality rate

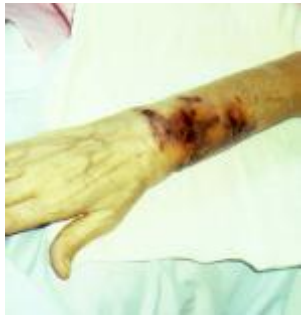
Muñoz P. JHLT 2014

Challenges in IFI **epidemiology** in SOT

4. Emerging fungi have to be considered, mainly in patients on prophylaxis or travel history

- ***Fusarium* and *Scedosporium***
  - Lung transplantation
  - Resistance to antifungals
  - High mortality

- ***Mucormycosis***
  - Previous antifungals (voriconazole, caspofungin)
  - Other RFs (retransplantation, diabetes, rejection, renal failure)
  - Uncommon localization: Soft tissue 22%, Gastrointestinal 12%
  - High mortality



Challenges in IFI **epidemiology** in SOT

6. ***P. jiroveci*** has experienced substantial decrease in the era of TMP-SMX prophylaxis (5-15% to 0.3-2.6%)

- May cause outbreaks in TX units: **BE AWARE**

- Since the generalized use of prophylaxis
  - May appear late (>1 yr)
  - Risk factors: **Age >65 years, CMV infection and total lymphocyte count <750/mm^3 for one month**

  - **Lymphocyte count may help to guide the indication for chemoprophylaxis**

Iriart X, Am J Transp 2015.

Conclusions

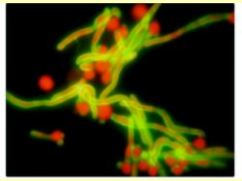
- Overall, candidiasis and aspergillosis are decreasing, pneumocystis has practically disappeared.
- New emergent fungi are appearing in the era of antifungal prophylaxis.
- Resistance to azoles has increased due to the increasing incidence of non-albicans *Candida*, resistance to azoles in *Aspergillus* is not a major problem in Spain but we must be aware of it.

Challenges in fungal infections in SOT

- Changes in epidemiology and clinical presentation
- **New diagnostic methods**
- Prophylaxis
- Therapy

Changes in the diagnosis of IFI in SOT

- **Culture based diagnostic techniques**
  - Traditional cultures
  - Rapid identification with MALDITOF
  - Rapid susceptibility information with E test
  - Molecular methods
    - identification of isolates
    - genotyping of outbreak isolates
    - identification of resistance



- **Non-Culture based diagnostic techniques**
  - **<u>NEW</u> Biomarkers in serum (B-D-glucan, CAGTA, Platelia *Candida*)**
  - Biomarkers already used in clinical practice (Platelia *Aspergillus*)
  - Molecular identification of fungal DNA (PCR, T2 MRI)

1. *Candida* biomarkers may help to identify the origin of the candidemia

- 50 candidemias: 29 deep-seated IC and 21 Catheter-related or primary

- A positive CAGTA suggests that the origin of the candidemia is not the catheter

Potential role of *Candida albicans* germ tube antibody in the diagnosis of deep-seated candidemia

	CAGTA +	CAGTA -
Deep- seated candidemia	20 (68%)	9 (31%)**
Catheter or primary candidemia	**1 (5%)** **Immunosuppressed**	**20 (95%)**
P < 0.001		

Martinez-Jiménez M, Muñoz P, et al. Medical Mycology, 2014

2. A combination of two *Candida* biomarkers (CAGTA + BDG) has a very great NPV in patients with candidemia

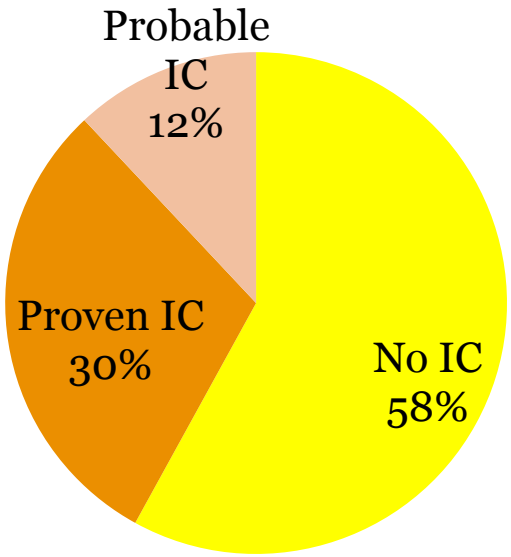
   - CAGTA 1/80 + BDG 80: **S 96.8%** and Sp 84%

   - **S 100%** for *C. albicans, C. tropicalis,* and *C. parapsilosis*

Martinez-Jiménez M. JAC 2015 in press

3. CAGTA + BDG could be a safe indicator to stop empirical antifungal therapy

- 100 patients included
  - 63 ICU
  - 37 non-ICU
- Type of patients
  - High-risk gastrointestinal surgery
  - Sepsis in non-surgical patients
- Final diagnosis
  - No-IC 58%, proven IC 30%, probable IC 12%



- CAGTA 1/160 + BDG 80: **NPV 97%** (100% in ICU patients)

Martínez-Jiménez, M. Carmen, Submitted to CID

4. Spanish in-house *Candida* PCR is very promising

Clinical validation of a multiplex real-time PCR assay for detection of invasive candidiasis in intensive care unit patients

J. Fortún[1]*, Y. Meije[1], M. J. Buitrago[2], S. Gago[2], L. Bernal-Martinez[2], J. Pemán[3], M. Pérez[4], E. Gómez-Gª Pedrosa[5], N. Madrid[1], V. Pintado[1], P. Martín-Dávila[1], J. Cobo[1], G. Fresco[1], S. Moreno[1] and M. Cuenca-Estrella[2]

Table 2. Performance of diagnostic procedures in patients with IC, candidaemia and deep-seated candidiasis (analysis per patient)

	IC (cases, 27; population, 103)	Candidaemia (cases, 21; population, 97)	Deep-seated candidiasis (cases, 11; population, 87)	IC among highly colonized patients (Pittet index ≥0.5) (cases, 16; population, 30)
Blood culture				
sensitivity	77.7% (21/27)	—	45.4% (5/11)	87.5% (14/16)
specificity	100% (76/76)	—	100% (76/76)	100% (14/14)
PPV	100% (21/21)	—	100% (5/5)	100% (14/14)
NPV	92.7% (76/82)	—	92.7% (76/82)	87.5% (14/16)
RT-PCR				
sensitivity	96.3% (26/27)	95.2% (20/21)	90.9% (10/11)	93.7% (15/16)
specificity	97.3% (74/76)	97.3% (74/76)	97.4% (74/76)	100% (14/14)
PPV	92.8% (26/28)	90.9% (20/22)	83.3% (10/12)	100% (15/15)
NPV	98.7% (74/75)	98.7% (74/75)	98.7% (74/75)	93.3% (14/15)

J Antimicrob Chemother 2014; 69: 3134–3141

5. New diagnostic techniques have been developed

T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Eleftherios Mylonakis,[1] Cornelius J. Clancy,[2] Luis Ostrosky-Zeichner,[3] Kevin W. Garey,[4] George J. Alangaden,[5] Jose A. Vazquez,[6] Jeffrey S. Groeger,[7] Marc A. Judson,[8] Yuka-Marie Vinagre,[9] Stephen O. Heard,[10] Fainareti N. Zervou,[1] Ioannis M. Zacharioudakis,[1] Dimitrios P. Kontoyiannis,[11] and Peter G. Pappas[12]

- First fully automated detection of *Candida*
- Blood specimens **without the need for prior isolation**
  - Results in 4 hours
  - **NPV: 99.5%-99.0%**
- Clinical impact needs to be assessed

Mylonakis E. Clin Infect Dis. 2015

Conclusion

- Regarding diagnosis we still depend on culture based methods, but we have new techniques that provide a faster identification and antifungal susceptibility information.
- Non-culture based methods are emerging and using them in combination could increase its NPV.
- However, biomarkers need to be tested in solid organ transplant recipients.
- We need to improve our ability to identify patients at risk and maybe biomarkers could help us in this field.

Challenges in fungal infections in SOT

- Changes in epidemiology and clinical presentation
- New diagnostic methods
- **Prophylaxis** { Indications, Drug, Duration
- Therapy

Challenges in the prophylaxis of IFI in SOT

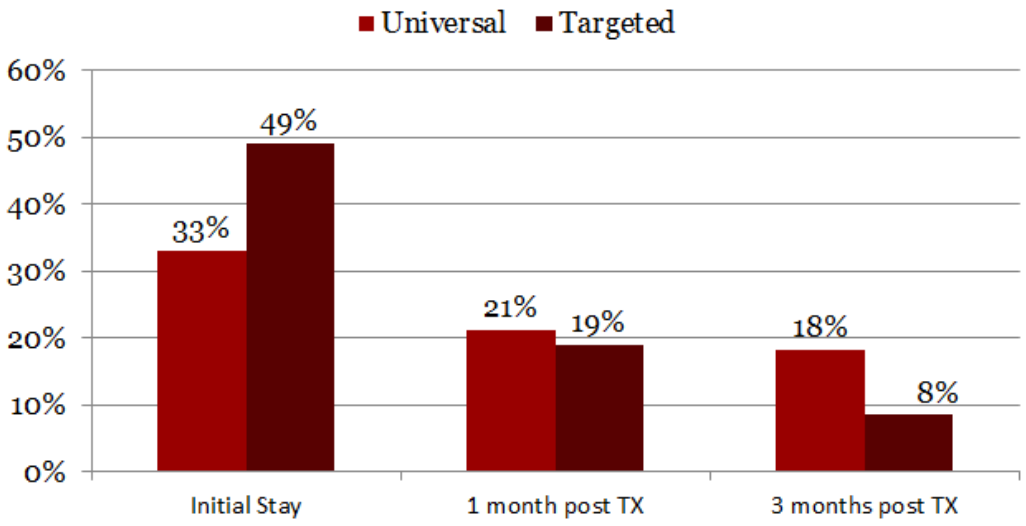
- **Indication**
  - Targeted therapy for most SOT is based on classical and new risk factor

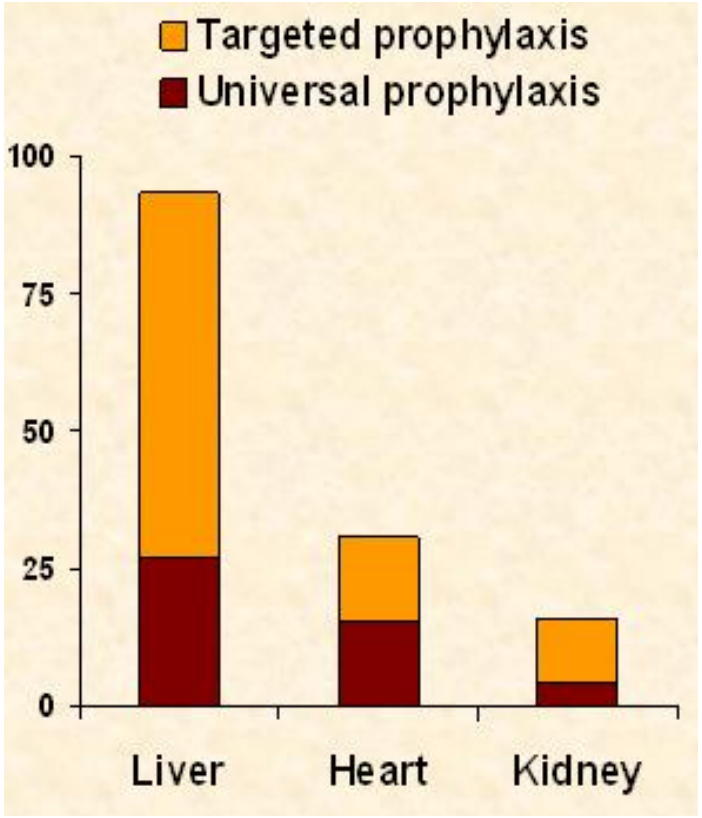
	Kidney	Liver	Heart	Lung	Pancreas	Intestine
Universal				X	X	X
Risk factors	X	X	X			

  - We do not follow guidelines
- **Drug**
  - In liver Tx Candins vs Azoles. Not clear yet.
- **Duration**
  - “Magical numbers” vs risk-factor based duration

1. **In real life, AF prophylaxis is not adjusted to guidelines:** universal prophylaxis is widely used. Broad variety of drugs and different durations.

- Universal Prophylaxis
  - 28% LT in US
  - 32% Spain





Singh N. Am J Transplant 2008 / Muñoz P. *Clin Transplant* 2012

2. **A European consensus** provides information on AF therapy and prophylaxis in SOT recipients.

Risk factors for *Candida* infections

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

Gavaldá J. Clin Microbiol Infect 2015

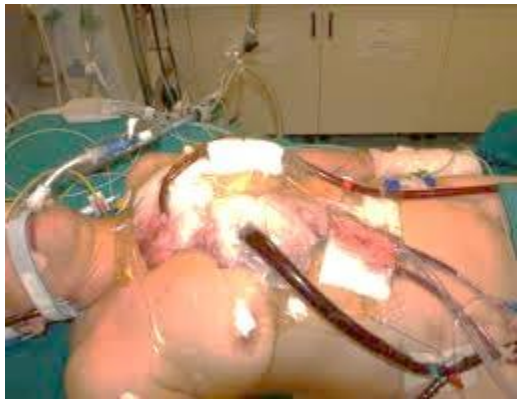
Risk factors for invasive aspergillosis

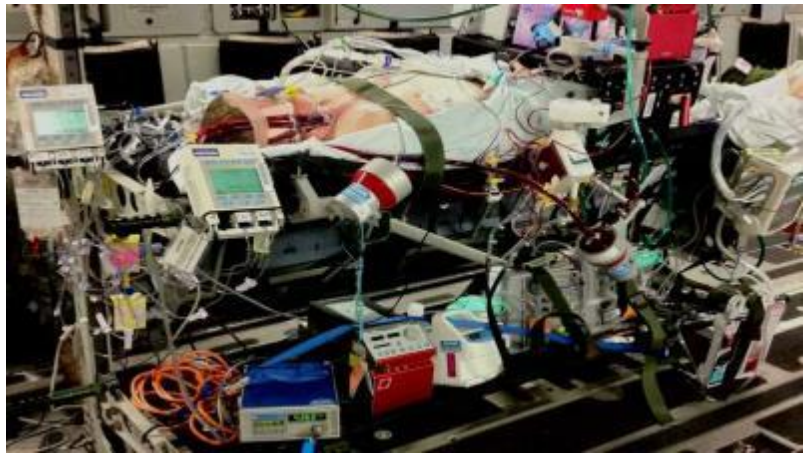
	Early IA	Late IA (> 3 months post-transplant)
Liver Transplant	Re-transplantation Kidney failure, especially post-transplant Haemodialysis Fulminant hepatic failure Complicated surgery or reoperation	More than 6 g of accumulative prednisone in the third month after transplantation Post-transplant renal failure Post-transplant haemodialysis Leukopenia (<500/mm^3) Chronic graft dysfunction
Lung Transplant	Bronchial anastomotic ischemia 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 Hypogammaglobulinemia (IgG < 400 mg/dl)	ICU readmission Kidney transplantation > 2 acute rejection episodes
Kidney Transplant	Graft lost and haemodialysis Haemodialysis Prolonged high corticosteroid doses	
	CMV Infection **Over-immunosuppression**	

Gavaldá J. Clin Microbiol Infect 2014.

3. **New risk factors for IFI** have to be promptly detected and incorporated into our guidelines.

- In HT recipients: post-transplant extracorporeal membrane oxygenation **(ECMO)** was identified as the strongest predictor for fungal infection (**OR, 29.9**; 95% CI, 1.5-592.5, P=0.03)





Tissot F. Transplantation 2013

4. It is not clear which drug is best for antifungal prophylaxis

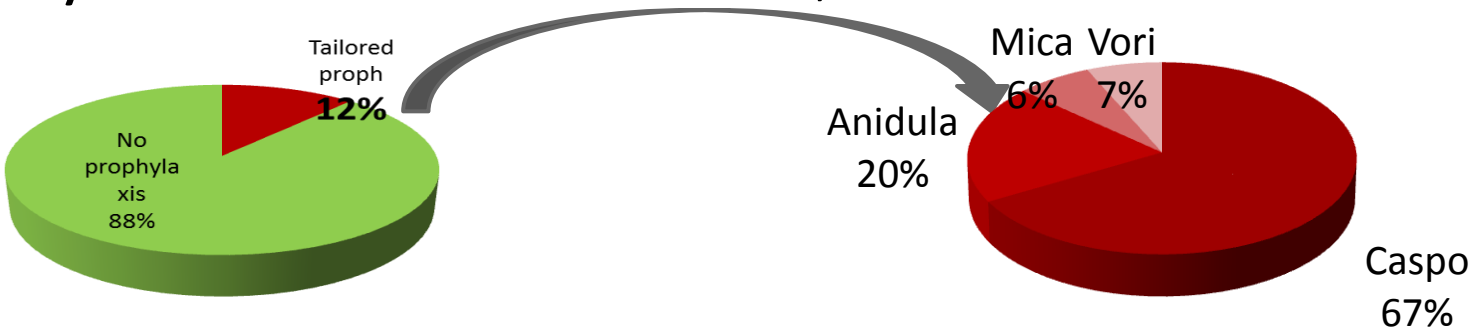
- Risk factors for *Candida* and *Aspergillus* are similar
- Candins are safe and well tolerated and have fewer interactions
  - TENPIN study (Micafungin vs standard therapy in liver tx)
    - Effective and well tolerated: **98.6% Mica** vs **99.3% Std. of care**
  - Clinical trial (Anidulafungin vs fluconazole in liver tx)
    - Incidence of IFI was similar in both groups

Fortún J, Transplantation 2009; Aguado JM. Transplantation 2012; Saliba F. CID 2014; Winston DJ. Am J of Transp 2014

Targeted Antifungal Prophylaxis in Heart Transplant Recipients

Patricia Muñoz,[1,4,5,6,7,9] Maricela Valerio,[1] Jesús Palomo,[2] Maddalena Giannella,[1] Juan F. Yañez,[2] Manuel Desco,[3,8] and Emilio Bouza[1,4,5,6,7]

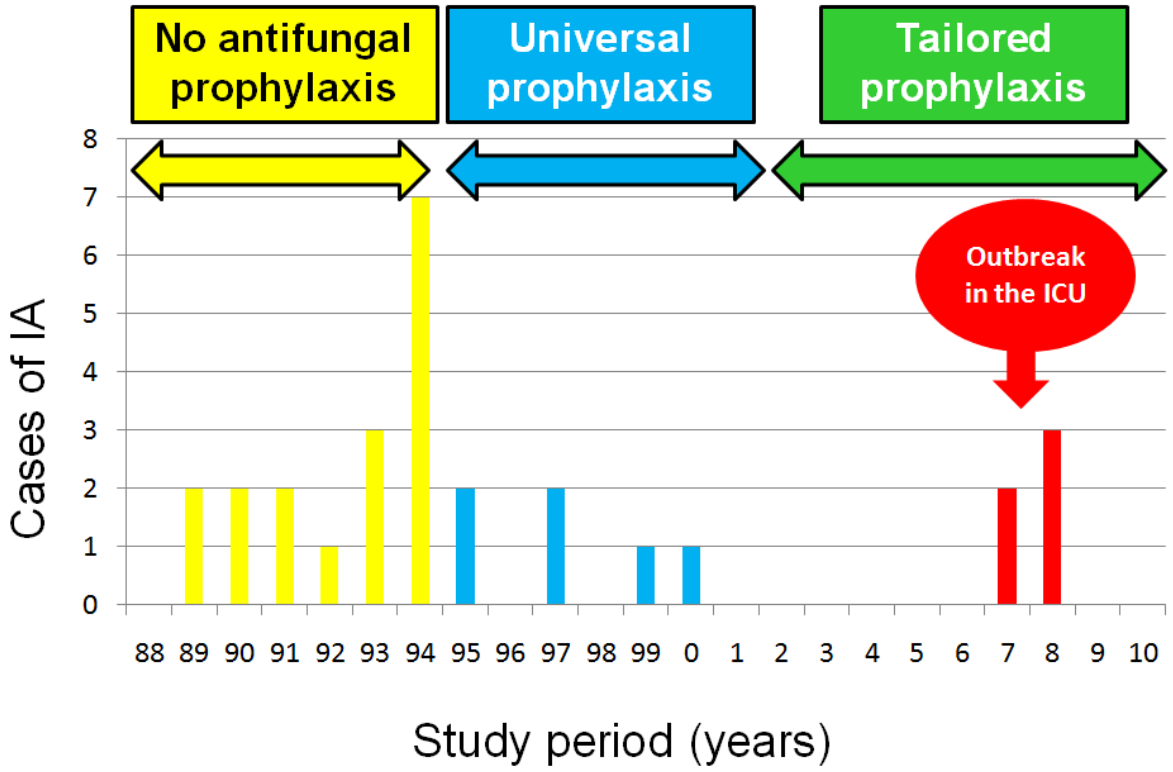
- Prospective study 2003 - 2010
- **Targeted prophylaxis: only if a RF is present**
  - Hemodialysis
  - CMV infection
  - Re-intervention
- **Length of prophylaxis**: depends on the patient (15 days after the RF resolution)



12% HT recipients required prophylaxis according to our RFs

Muñoz P. Transplantation 2013;96: 664-669

5. **If you use targeted AF prophylaxis it is possible to eliminate IA-but be careful with the quality of your hospitals' air**



Muñoz P. JHLT 2014; Muñoz P. Transplantation 2013

Challenges in fungal infections in SOT

- Changes in epidemiology and clinical presentation
- New diagnostic methods
- Prophylaxis
- **Therapy**

1. The role of combination antifungal therapy for IA is not yet clear.

- Updated guidelines of the IDSA suggest reserving this option for salvage therapy.

- Some evidence suggesting voriconazole + caspofungin could diminish mortality in SOT .

Singh N. Transplantation 2006.

Annals of Internal Medicine ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

- Randomized multicenter trial
- Hematological malignancies and HSCT
- **Voriconazole + Anidulafungin (1-2 wks)** vs **Voriconazole**
- No significant difference in mortality at 6 weeks
  - 15.7% combo vs 27.3% voriconazole
- Post-hoc analysis:
  - Benefit in probable IA diagnosed with GM

Marr K. Annals of Int Med. Jan 2015.

2. An Antifungal Stewardship in SOT units is clearly needed

RESEARCH ARTICLE Open Access

How much European prescribing physicians know about invasive fungal infections management?

Maricela Valerio[1,2], Antonio Vena[1,2,3], Emilio Bouza[1,2,3], Nanna Reiter[4], Pierluigi Viale[5], Marcel Hochreiter[6], Maddalena Giannella[5], Patricia Muñoz[1,2,3*] and on behalf the COMIC study group (Collaborative group on Mycosis)

PARTICIPATING COUNTRIES

- Physicians taking the survey did not use antifungals properly.
- 29% used a combination as their 1st choice
  - L-AmB + voriconazole
  - voriconazole + caspofungin

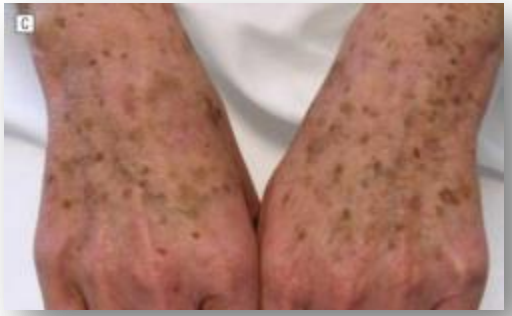
3. ISAVUCONAZOLE is an interesting new drug

- Novel triazole /prolonged half-life
- Once daily IV and oral
- *Candida*, *Aspergillus*, *Cryptococcus* and Mucormycosis.
- Underlying hematological malignancy and a proven/ probable IFI
- **EFFECTIVE:** Isavuconazole is as effective as voriconazole
- **SAFER**: Fewer adverse events

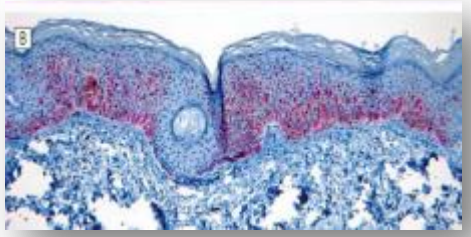
A. J. Ullmann et al. ICAAC 2014 / K. Marr et al. ICAAC 2014

3. Never forget its potential toxicity

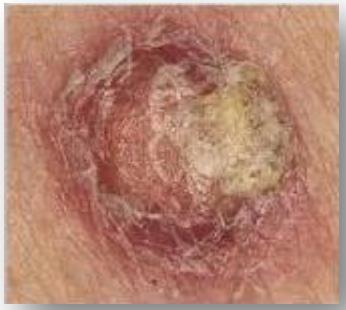
- Independent RF for the development of cutaneous malignancy in lung tx recipients.
- The mechanism of voriconazole-induced skin cancer is still unknown.
- It may have a cumulative effect.



Accelerated photoaging



Melanoma in situ



Squamous cell carcinomas

Arch Dermatol. 2010;146(3):300-304

Williams K. CID 2014

Conclusions

- We still need to know which is the antifungal of choice in each type of SOT and for how long is it suitable for our patients.
- With regards to invasive aspergillosis, more clinical trials in SOT populations are needed to prove its superiority and to evaluate the optimal duration of time.
- Never forget that antifungals could be harmful.
- New azoles with a wide spectrum and fewer adverse events are coming in the next years.

CLINICAL MICROBIOLOGY MYCOLOGY LAB MOLECULAR BIOLOGY LAB

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COMIC STUDY GROUP

SOT AND HSCT TEAMS

Hematology, Hepatology, Cardiology, Nephrology, Surgical teams, Anestesiologists and Intensivists.

INFECTIOUS DISEASE ATTENDINGS

Emilio Bouza, Patricia Muñoz, Ana Fernández-Cruz, Belén Padilla, Paloma Gijón, Mar Sánchez, Alia Eworo, Antonio Vena

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