New Challenges in Fungal Infections in SOT

Maricela Valerio
Clinical Microbiology and Infectious Diseases Department
Hospital General Universitario Gregorio Marañón
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
1. **Incidence** of *Candida* infections is increasing in some centers: LT allocated by MELD

### Table 2: Fungal infections according to allocation era.

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

Pts with a higher MELD:
- More re-transplantation
- More renal failure
- Longer operation times
- More intraoperative blood transfusions

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

### Challenges in IFI epidemiology in SOT

 Transitional Study in USA

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=383)</td>
<td>16%</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td><em>C. albicans</em> (154)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>C. glabrata</em> (119)</td>
<td>23</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td><em>C. parapsilosis</em> (48)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>C. krusei</em> (32)</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>C. tropicalis</em> (21)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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

Challenges in IFI epidemiology in SOT

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

- Delayed diagnosis
  - More mechanical ventilation
  - Increased mortality rate

37% of IA in HT recipients present with an airway-invasive radiological pattern
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/mm³ for one month**

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

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**
  - **NEW** 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

<table>
<thead>
<tr>
<th></th>
<th>CAGTA +</th>
<th>CAGTA -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep-seated candidemia</td>
<td>20 (68%)</td>
<td>9 (31%)**</td>
</tr>
<tr>
<td>Catheter or primary</td>
<td>1 (5%)</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>candidemia</td>
<td></td>
<td>Immunosuppressed</td>
</tr>
</tbody>
</table>

P < 0.001

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

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*
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)
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. Fortún¹, Y. Meije², M. J. Buitrago², S. Gago², L. Bernal-Martínez², J. Pemán³, M. Pérez⁴, E. Gómez-Gó Pedrosa⁵, N. Madrid¹, V. Pintado¹, P. Martín-Dávila¹, J. Cobo¹, G. Fresco¹, S. Moreno¹ and M. Cuenca-Estrella²

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

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

J Antimicrob Chemother 2014; 69: 3134–3141
5. New diagnostic techniques have been developed

- 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

<table>
<thead>
<tr>
<th></th>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Lung</th>
<th>Pancreas</th>
<th>Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Risk factors</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

![Graph showing the comparison between targeted and universal prophylaxis across different transplant types: Liver, Heart, and Kidney. The bars indicate the percentage of patients treated with targeted and universal prophylaxis at different time points: Initial Stay, 1 month post-TX, and 3 months post-TX.](image)
2. A European consensus provides information on AF therapy and prophylaxis in SOT recipients.

**Risk factors for *Candida* infections**

<table>
<thead>
<tr>
<th>Transplant type</th>
<th>Target Population</th>
</tr>
</thead>
</table>
| 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, choledochojunostomy (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 |
## Risk factors for invasive aspergillosis

<table>
<thead>
<tr>
<th>Early IA</th>
<th>Late IA (&gt; 3 months post-transplant)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver Transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Re-transplantation</td>
<td></td>
</tr>
<tr>
<td>Kidney failure, especially post-transplant</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td></td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Complicated surgery or reoperation</td>
<td></td>
</tr>
<tr>
<td><strong>Lung Transplant</strong></td>
<td>Chronic graft dysfunction</td>
</tr>
<tr>
<td>Bronchial anastomotic ischemia or bronchial stent placement</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td></td>
</tr>
<tr>
<td>Single-lung transplant</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> spp. colonization before or during first year post-transplant</td>
<td></td>
</tr>
<tr>
<td><strong>Heart Transplant</strong></td>
<td>ICU readmission</td>
</tr>
<tr>
<td><em>Aspergillus</em> spp. colonization of the respiratory tract</td>
<td></td>
</tr>
<tr>
<td>Re-operation</td>
<td>&gt; 2 acute rejection episodes</td>
</tr>
<tr>
<td>Post-transplant haemodialysis</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinemia (IgG &lt; 400 mg/dl)</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney Transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Graft lost and haemodialysis</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td></td>
</tr>
<tr>
<td>Prolonged high corticosteroid doses</td>
<td></td>
</tr>
<tr>
<td><strong>CMV Infection</strong></td>
<td></td>
</tr>
</tbody>
</table>
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)*
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

Targeted Antifungal Prophylaxis in Heart Transplant Recipients

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.
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

2. An Antifungal Stewardship in SOT units is clearly needed

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

Maricela Valerio¹², Antonio Vena¹², Emilio Bouza¹², Nanna Reiter², Pierluigi Viale⁵, Marcel Hochreiter⁵, Maddalena Giannella⁵, Patricia Muñoz¹² and on behalf the COMIC study group (Collaborative group on Mycosis)

- 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

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.

*Arch Dermatol.* 2010;146(3):300-304
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.
Carlos Sánchez, Teresa Peláez, Jesús Guinea, Pablo Martín Rabadán, Pilar Escribano, Roberto Alonso.

Maria Sanjurjo, Carmen Rodríguez, Betsabé Cáliz

SOT AND HSCT TEAMS
Hematology, Hepatology, Cardiology, Nephrology, Surgical teams, Anestesiologists and Intensivists.

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