Is it applicable, when, how?

Antifungal de-escalation. The case for antifungal stewardship.

- Dr. Rafael Zaragoza
Conflicts:

- Pfizer
- Astellas
- MSD
- Gilead
- Cephalon
SECOND RECOMMENDATION:

- Enjoy City of Sciences and arts
  - Opera house
  - Hemisferic
  - Sciences museum
  - Agora
Allá vamos....
A new scheme…
Invasive Candidiasis in ICU.
The case for antifungal stewardship

• Introduction and definition. How to do it?
• Is de-escalation a real practise?
• Is an early broad spectrum antifungal treatment needed?
• Do we need it? Fluconazole
• Which situations?
  • NEVER?
  • SOMETIMES?
  • ALWAYS?
• When can we step down?
  – If case of proven IC.
  – If IC are not proven.
• Take home messages
Antimicrobial optimization strategies in ICU.

- Guidelines/Protocols
- Restricting the hospital formulary
- Scheduled changes in antibiotic
- Combining antibiotic therapy
- Antibiotic rotation
- Area-specific antimicrobial therapy
- Antimicrobial de-escalation

Kollef MH. Crit Care 2001;5:189-95
INTRODUCTION.

- Antimicrobial stewardship (AMS) has overwhelmingly focussed on antibiotics while antifungal agents have been largely neglected despite the few published audits of antifungal drug use demonstrating clear deficiencies in prescribing behavior.
- Invasive fungal diseases (IFDs) have a lower institutional incidence relative to infections caused by multiresistant bacteria, but their health and economic burden are substantial.
- Pharmacy costs inclusive of antifungal agents are a major determinant of IFD-attributable hospital cost. High drug costs and the toxicities of antifungal agents are the principal rationale for AFS while antifungal resistance is an emerging but less prevalent issue.
- Nonculture-based tests may enhance AFS, but refinement of both target populations and clinical pathways incorporating their use is required. Performance indicators including structural, process and outcome measures are integral for demonstrating the value of AFS programmes.

De-escalation of antibiotic therapy

*Concept*

“Could be considered as a strategy to balance the need to provide adequate initial antibiotic treatment of high risk patients with the avoidance of unnecessary antibiotic utilization, which promotes resistance”
Inadequate empirical antibitibic therapy and ICU-Bacteremia

%IEAT = 29.9%

N = 492

* p < 0.001

Ibrahim et al; Chest 2000; 118: 146-155
Inadequate empirical antibitibic therapy and ICU-Bacteremia

N=166

%IEAT = 23.5%

CNS
Acinetobacter baumannii
Pseudomonas aeruginosa
Candida spp

% Related mortality

p>0,05

APPROACH TO ANTIFUNGAL TREATMENT:  
Pre-emptive and Empirical Therapy: IC/Cd

¿Previous azoles use +/- clinical unstable (MOF, severe sepsis) +/- suspected or previous infection by *C. krusei* o *C. glabrata* +/- multiple colonization by *no-C. albicans* spp +/- ICU stay and risk factors (drug-interactions, kind of patient, p.e. transplantation, peritonitis)?

- Anidulafungin: 200 mg/24 (d1)+100 mg d  
  - Caspofungin: 70 mg/24 h (d1) + 50 mg d  
  - Micafungina: 150 mg/24 hs  
  - Amphotericin B-Lipidic Complex: 3-5 mg/kg/d  
  - Amphotericin B- Liposomal: 3 mg/kg/d  
  - Voriconazol e iv: 6 mg/kg/12h (d1) + 4 mg/kg/12h

**Yes**
We must considered AF: rapid, broad spectrum and PK/PD optimized

**NO**
- Fluconazole: 400-800 mg IV/d.  
  If possible switching to oral therapy (400 mg/d)

**EVEN POSSIBLE: DE-ESCALATION**

Antifungal de-escalation strategy

Initially a broad spectrum antifungal treatment is administrated until the agent of infection was identified:
- Echinocandins
- AMPHOTERICINS

Microbiological data

Maintenance of broad spectrum combination

Patient’s physician criteria

Switching to a narrow spectrum
Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment

Invasive Candidiasis

Hemodynamic stability?

Yes

High probability of azole resistance?
(Local epidemiology, colonisation with fluconazole resistant strains, or recent exposure)

Yes

• Echinocandins
• Alternative: LFA

No

• Fluconazole
• Alternative: Echinocandins
  Voriconazole
  Amphotericin B

Discuss step-down attitude according to the species of Candida isolated (Fluconazole or alternatives)
De-escalation: even it`s possible (I-A)
<table>
<thead>
<tr>
<th>Compound</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Anidulafungin 200/100 | A   | I   | Reboli NEJM 2007         | • Broad spectrum
• Resistance rare
• Fungicidal
• Local epidemiology
• *C. parapsilosis, C. krusei*
• Safety profile
• Less drug-drug interactions than caspofungin |
| Caspofungin 70/50   | A   | I   | Mora-Duarte NEJM 2002 Pappas CID 2007 | • Largely as above |
| Micafungin 100      | A   | I   | Kuse Lancet 2007 Pappas CID 2007 | • Largely as above
• Consider EMA warning label |
Increasing incidence of *Candida parapsilosis* candidemia with caspofungin usage

Graeme N. Forrest a,*, Elizabeth Weekes b, Jennifer K. Johnson c

**Table 1** Rates per 1000 patient-days of the 5 major *Candida* species causing candidemia by fiscal year (FY)

<table>
<thead>
<tr>
<th>Species</th>
<th>FY02</th>
<th>FY03</th>
<th>FY04</th>
<th>FY05</th>
<th>FY06</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>0.28</td>
<td>0.40</td>
<td>0.31</td>
<td>0.39</td>
<td>0.48</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>0.23</td>
<td>0.17</td>
<td>0.21</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>0.05</td>
<td>0.06</td>
<td>0.12</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0.09</td>
<td>0.09</td>
<td>0.06</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>C. krusei</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall</td>
<td>0.69</td>
<td>0.73</td>
<td>0.71</td>
<td>0.80</td>
<td>0.95</td>
</tr>
</tbody>
</table>

**Table 2** Defined daily doses per 1000 patient-days of antifungals by fiscal year

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>FY02</th>
<th>FY03</th>
<th>FY04</th>
<th>FY05</th>
<th>FY06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>3.91</td>
<td>4</td>
<td>6.96</td>
<td>11</td>
<td>6.61</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.39</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>84.2</td>
<td>86.2</td>
<td>104.4</td>
<td>84.4</td>
<td>85.7</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0</td>
<td>47.6</td>
<td>80.1</td>
<td>61.3</td>
<td>72.5</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>23.8</td>
<td>13.9</td>
<td>3.2</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>31.6</td>
<td>27</td>
<td>18</td>
<td>16.6</td>
<td>10.9</td>
</tr>
</tbody>
</table>
Recent Exposure to Caspofungin or Fluconazole Influences the Epidemiology of Candidemia: a Prospective Multicenter Study Involving 2,441 Patients

Olivier Lortholary,1,2,3 Marie Desnos-Ollivier,1,2 Karine Sitbon,1,2 Arnaud Fontanet,4 Stéphane Bretagne,1,2,5 Françoise Dromer,1,2,6 and the French Mycosis Study Group†

27 hospitales

2,618 aislamientos

fluconazol

C. albicans

C. parapsilosis

C. glabrata

C. tropicalis

C. krusei

n = 159

n = 61

DE ESCALATION THERAPY AND CANDIDIASIS

1 ORIGINAL ARTICLE found.
Evaluation of antifungal therapy in patients with candidaemia based on susceptibility testing results: implications for antimicrobial stewardship programmes

D. N. Shah, R. Yau, J. Weston, T. M. Lasco, M. Salazar, H. R. Palmer and K. W. Garey*

Conclusions: Using antifungal susceptibility testing, patients given fluconazole with fluconazole-resistant Candida species were identified. Less than 40% of echinocandin-treated patients with fluconazole-susceptible organisms were de-escalated to fluconazole. Antifungal susceptibility testing may help to identify patients in need of clinical intervention.
What did happen in the last trials?

**WAY OF DE-ESCALATION**

- **ICE STUDY:** Patients could be switched to oral voriconazole or fluconazole at the discretion of the investigator, after a minimum of 10 days’ anidulafungin treatment, if they had 2 subsequent negative blood cultures and resolution of C/IC signs and symptoms.

- **REBOLI STUDY:** All patients could receive oral fluconazole (400 mg daily) at the investigators’ discretion after at least 10 days of intravenous therapy if the patients were able to tolerate oral medication, if they had been afebrile for at least 24 hours, if the most recent blood culture was negative for candida species, and if there was clinical improvement.

**IMPLEMENTATION**

- **ICE STUDY:** 53 patients were switched to an oral azole: 41 to fluconazole (mean duration, 11.7 days; range, 3-44) and 12 to voriconazole (mean duration, 11.2 days; range, 5-20).

- **REBOLI STUDY:** 33 patients FROM EACH GROUP were switched to an oral FLUCONAZOLE

Reboli A et al. NEJM 2007
Ruhnke M et al. CMI in press
Is early treatment needed for Invasive Candidiasis in critically ill patients?
Yes.....of course......
Difficulties in Establishing a Diagnosis for Candidemia

- No disease
- Cultures/Antigen
- Signs and symptoms
- Cultures/histopathology
- Sequelae

Prophylaxis
Preemptive
Empirical
Treatment
Morbidity/Mortality

Crude Mortality 40%
Delaying the Empiric Treatment of Candidemia
An Independent Risk Factor for Hospital Mortality

Multivariate analysis of independent risk factors for hospital mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>1.24</td>
<td>(1.18-1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior antibiotics</td>
<td>4.05</td>
<td>(2.14-7.65)</td>
<td>0.028</td>
</tr>
<tr>
<td>Delay in antifungal therapy</td>
<td>2.09</td>
<td>(1.53-2.84)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Table 3. Multivariate model of independent risk factors for hospital mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from culture date to start of fluconazole therapy, days</td>
<td>1.50 (1.09–2.09)</td>
<td>.0138</td>
</tr>
<tr>
<td>APACHE II score, 1-point increments</td>
<td>1.13 (1.08–1.18)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Septic shock developed in 23% (31 of 135) patients with CBSI. In-hospital mortality was 68%.

Appropriate antifungal therapy was administered to 24 patients; 15 (63%) of these patients died.

Patients who received appropriate antifungal therapy within 15 hours of collecting the first positive Candida blood culture had improved survival ($P = 0.03$).
Figure 1. Proportion of patients and time required to achieve clinical stability.

2Western Uni Orange, CA!

*Correspo

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(28 versus 21 days; P=0.007), compared with EI (n=107).

Conclusions: Non-albicans Candida species accounted for the majority of IC in caspofungin-treated patients. Improved outcomes were observed for patients initiated with caspofungin within 72 h of positive culture compared with those who received delayed therapy.

Keywords: antifungals, initiation, prompt
Relationship between “Candida score” and risk for developing IC in surgical patients

% IC in surgical patients according CS

Current diagnostic approaches to invasive candidiasis in critical care settings

Javier Pemán and Rafael Zaragoza

1Servicio de Microbiología. Hospital Universitario La Fe. Valencia. Spain and 2Servicio de Medicina Intensiva. Hospital Universitario Dr. Peset. Valencia. Spain

*NCMT: Non-culture microbiological tools [(1,3)-b-D-glucan, Candida albicans germ tube antibodies or PCR]
Fluconazole, To be or not to be
Fluconazole improves survival in septic shock: A randomized double-blind prospective study

Sydney Jacobs, MB, ChB, FRCA; David A. Price Evans, MD, DSc, PhD, FRCP; Mohammed Tariq, PhD, FRCPaPath; Nasser Fawzan Al Omar, MSc

71 septic shock patients (Pneumonia=37; y Intrabdominal=34) Randomized: (32 pts) 200 mg fluconazole i.v. vs (39 pts) placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pneumonia</th>
<th>Intra-Abdominal Sepsis</th>
<th>Combineda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole (%)</td>
<td>Placebo (%)</td>
<td>Fluconazole (%)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>5 (28)</td>
<td>8 (42)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Survivors</td>
<td>13 (72)</td>
<td>11 (58)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (100)</td>
<td>19 (100)</td>
<td>14 (100)</td>
</tr>
</tbody>
</table>

*p valueb* .495 .013 .015

*aPneumonia and intra-abdominal sepsis; bFisher’s exact test (two-sided by summation).
**Epidemiological trends in nosocomial candidemia in intensive care**

Matteo Bassetti*1, Elda Righi1, Alessandro Costa2, Roberta Pasce2, Maria Pia Molinari2, Raffaella Rosso1, Franco Bobbio Pallavicini2 and Claudio Viscoli1

Address: Infectious Diseases Department, S. Martino Hospital and University of Genoa, Genoa, Italy; and Intensive Care Unit, S. Martino Hospital, Genoa, Italy.

Email: Matteo Bassetti - mmbb@tin.it; Elda Righi - mmbb@tin.it; Alessandro Costa - mmbb@tin.it; Roberta Pasce - mmbb@tin.it; Maria Pia Molinari - mmbb@tin.it; Raffaella Rosso - mmbb@tin.it; Franco Bobbio Pallavicini - mmbb@tin.it; Claudio Viscoli - mmbb@tin.it

* Corresponding author

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**Figure 2**

Line plot representation of *Candida albicans* and *Candida non-albicans* isolates rates during the study period.

**Figure 3**

Correlation using logistic regression between percentage reduction of *C. albicans* isolation rates and fluconazole use [DDD per year].
Epidemiological trends in nosocomial candidemia in intensive care

Bassetti M et al. BMC Infectious Diseases 2006;6:80
Candidemias in ICU. HUDP 1996-2007

Mortality in C. no albicans episodes > C. albicans (12.5% vs 46.6%; p = 0.03)

N = 397

95%
5%

N = 31

Mortality in C. no albicans episodes > C. albicans (12.5% vs 46.6%; p = 0.03)

N = 397

M = 31

Candida albicans
Candida glabrata
Candida parapsilopsis
Otras

M = 397

Candida albicans
Candida glabrata
Candida parapsilopsis
Otras

19%
48%
23%
10%

N = 271

Reduced susceptibility to fluconazole 17.1%

Desescalated 37.1%


CANDIPOP Study (752 episodes)

12 months of candidemias in Spain (2010-2011)

Overall rate of fluconazole resistance (MIC > 4 μg/ml) was 14.6%.
Risk factors for fluconazole-resistant *Candida glabrata* bloodstream infections.

<table>
<thead>
<tr>
<th>Fluco R</th>
<th>OR (95%IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous use of fluconazole</td>
<td>2.3 (1.3-4.2)</td>
</tr>
<tr>
<td>Previous use of linezolid</td>
<td>4.6 (2.2-9.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluco S</th>
<th>OR (95%IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous use of cefepime</td>
<td>2.2 (1.2-3.9)</td>
</tr>
<tr>
<td>Previous use of metronidazol</td>
<td>2 (1.1-3.5)</td>
</tr>
</tbody>
</table>

- 76 *C. glabrata* R fluconazole
- 68 *C. glabrata* S fluconazole
- 512 controls

**Risk Factors for Fluconazole-Resistant Candidemia**


- Prospective study including adult patients with candidemia (226 episodios)
  - Non-*albicans*: 53%
  - Potentially fluconazole resistant: 18%
- Isolates microbiologically confirmed fluconazole resistance: 13%

<table>
<thead>
<tr>
<th>INDEPENDENT PREDICTORS</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>4,94</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>4,82</td>
</tr>
<tr>
<td>Previous Fluconazole exposure</td>
<td>5,09</td>
</tr>
</tbody>
</table>

*C. glabrata* (14)  
*C. krusei* (14)  
*C. tropicalis* (2)

*Previous fluconazole exposure* is an independent risk factor for candidemia caused by microbiologically confirmed fluconazole resistant species, but not for bloodstream infection caused by non-*albicans Candida* spp. or by potentially fluconazole-resistant *Candida* spp (C. glabrata and C. krusei). Our findings may be of value for selecting empirical antifungal therapy.
Comparison of *albicans* vs. *non-albicans* candidemia in French intensive care units

Olivier Leroy¹, Jean-Paul Mira²,³, Philippe Montravers⁴,⁵, Jean-Pierre Gangneux⁶,⁷, Olivier Lortholary⁸,⁹,¹⁰ for the AmarCand Study Group

**Conclusions:** Although patients infected with *Candida albicans* differed from patients infected with *non-albicans* *Candida* species for a few characteristics, no clinical factor appeared pertinent enough to guide the choice of empirical antifungal therapy in ICU.
Association of Fluconazole Pharmacodynamics with Mortality in Patients with Candidemia

John W. Baddley,¹,³* Mukesh Patel,¹,³ Sujata M. Bhavnani,⁴ Stephen A. Moser,² and David R. Andes⁵

Department of Medicine, Division of Infectious Diseases,¹ and Department of Pathology,² University of Alabama at Birmingham, Birmingham, Alabama; Birmingham Veterans Administration Medical Center, Birmingham, Alabama; Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York⁴; and Department of Medicine and Medical Microbiology and Immunology, University of Wisconsin, Madison, Wisconsin⁵

Received 25 January 2008/Returned for modification 21 March 2008/Accepted 23 June 2008

FIG. 1. Relationship between the fluconazole 24-h AUC/MIC and survival in patients with candidemia ($n = 84$).

$p=0.009$
Global mortality 28% (n=84)

p = 0.02
Association of Fluconazole AUC/MIC and Dose/MIC Ratios with Mortality in Non-neutropenic Patients with Candidemia

A new scheme…
Invasive Candidiasis in ICU.
The case for antifungal stewardship

- Introduction and definition. How to do it?
- Is de-escalation a real practise?
- Is an early broad spectrum antifungal treatment needed?
- Do we need it? Fluconazole
- **Which situations?**
  - NEVER ?
  - SOMETIMES ?
  - ALWAYS ?
- When can we step down?
  - If case of proven IC.
  - If IC are not proven.
- Take home messages
NEVER USE DE-ESCALATION STRATEGY, NEVER STEP DOWN TO FLUCONAZOLE.....if

- CRRT
- AVOID INTERACTIONS specially with inmunossuppresive agents
- Hepatic failure
- *C. glabrata* & *C. krusei* ETIOLOGY.
Fluconazole dosing in continuous venovenous haemofiltration (CVVHF): need for a high daily dose of 800 mg

Raoul Bergner¹, Martin Hoffmann¹, Klaus-Dieter Walter E. Haefeli², Michael Uppenkamp¹ and Ingrid Schmid-Champain¹

¹Medical Department A, Klinikum der Stadt Ludwigshafen, Medicine VI, Clinical Pharmacology and Pharmacoepidemiology

Table 1. Individual and mean values of fluconazole plasma peak concentrations (Cmax) and time of peak (Tmax), and minimal fluconazole plasma concentration (C24h), AUC0−24, extracorporeal clearance (CLCVVHF), total body clearance (CLTOTAL), volume of distribution (Vd), and terminal elimination half-life (t1/2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tmax (min)</th>
<th>Cmax (µg/ml)</th>
<th>C24h (µg/ml)</th>
<th>AUC0−24 (min·µg/ml)</th>
<th>CLTOTAL (ml/min/m²)</th>
<th>CLCVVHF (ml/min)</th>
<th>Vd (l)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>40</td>
<td>27.77</td>
<td>6.60</td>
<td>21.031</td>
<td>38.0</td>
<td>4.31</td>
<td>31.92</td>
<td>13.16</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>31.27</td>
<td>22.86</td>
<td>30.204</td>
<td>22.1</td>
<td>11.85</td>
<td>24.90</td>
<td>45.12</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>31.52</td>
<td>12.64</td>
<td>28.458</td>
<td>28.1</td>
<td>9.97</td>
<td>29.81</td>
<td>23.16</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>28.21</td>
<td>14.92</td>
<td>28.02</td>
<td>27.8</td>
<td>12.31</td>
<td>30.07</td>
<td>28.48</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>32.32</td>
<td>26.59</td>
<td>32.76</td>
<td>21.2</td>
<td>20.90</td>
<td>24.24</td>
<td>66.90</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>21.83</td>
<td>9.00</td>
<td>18.089</td>
<td>44.2</td>
<td>18.38</td>
<td>44.15</td>
<td>22.91</td>
</tr>
<tr>
<td>Mean</td>
<td>60</td>
<td>28.82</td>
<td>15.42</td>
<td>28.39</td>
<td>30.24</td>
<td>11.79</td>
<td>30.85</td>
<td>33.29</td>
</tr>
<tr>
<td>SD</td>
<td>31</td>
<td>3.90</td>
<td>7.91</td>
<td>7.86</td>
<td>9.09</td>
<td>5.34</td>
<td>7.20</td>
<td>19.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tmax (min)</th>
<th>Cmax (µg/ml)</th>
<th>C24h (µg/ml)</th>
<th>AUC0−24 (min·µg/ml)</th>
<th>CLTOTAL (ml/min/m²)</th>
<th>CLCVVHF (ml/min)</th>
<th>Vd (l)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60</td>
<td>18.26</td>
<td>7.74</td>
<td>18.432</td>
<td>43.4</td>
<td>12.59</td>
<td>39.16</td>
<td>16.87</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>24.21</td>
<td>3.27</td>
<td>19.178</td>
<td>41.7</td>
<td>31.63</td>
<td>20.97</td>
<td>4.47</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>32.24</td>
<td>15.13</td>
<td>30.06</td>
<td>30.7</td>
<td>10.21</td>
<td>31.69</td>
<td>29.83</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>17.69</td>
<td>7.82</td>
<td>19.045</td>
<td>53.2</td>
<td>11.03</td>
<td>54.89</td>
<td>25.79</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>26.45</td>
<td>9.50</td>
<td>20.627</td>
<td>38.8</td>
<td>32.23</td>
<td>39.73</td>
<td>22.41</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>17.12</td>
<td>9.60</td>
<td>19.824</td>
<td>20.1</td>
<td>n.d.</td>
<td>21.79</td>
<td>54.67</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>24.84</td>
<td>12.30</td>
<td>19.525</td>
<td>41.0</td>
<td>17.10</td>
<td>37.56</td>
<td>25.15</td>
</tr>
<tr>
<td>Mean</td>
<td>60</td>
<td>29.04</td>
<td>15.14</td>
<td>21.042</td>
<td>37.48</td>
<td>17.80</td>
<td>27.40</td>
<td>17.71</td>
</tr>
<tr>
<td>SD</td>
<td>165</td>
<td>6.37</td>
<td>7.74</td>
<td>7.72</td>
<td>10.04</td>
<td>9.33</td>
<td>11.27</td>
<td>13.84</td>
</tr>
<tr>
<td>P-value</td>
<td>0.11</td>
<td>0.26</td>
<td>0.13</td>
<td>0.11</td>
<td>0.55</td>
<td>0.35</td>
<td></td>
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</tr>
</tbody>
</table>
TIME TO STEP DOWN

- 5 DAYS
- 10 DAYS
- I DO NOT KNOW BUT PROBABLY....

Personal opinion
USE DE-ESCALATION STRATEGY, WITHDRAW ANY ANTIFUNGAL DRUG

....if

- Documentation of another etiology
- Or
- Documentation of other sources of infection
- Or
- No positive result of Platelia after 10 days and improvement of scores
  PCT > 5.5 ng/ml on day 5

Personal opinion
USE DE-ESCALATION STRATEGY, STEPING DOWN TO FLUCONAZOLE.....if

If invasive candidiasis is confirmed by positive blood culture or sterile site after knowing susceptibility to fluconazole and the patient has recovered from MOF
**Blood cultures** = 50% sensitivity

<table>
<thead>
<tr>
<th>SUMMARY of Bloodculture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number: 3 (2 to 4)</td>
</tr>
<tr>
<td>Timing: Obtain blood cultures, one right after the other, from different sites</td>
</tr>
<tr>
<td>Site: Venipuncture</td>
</tr>
<tr>
<td>Volume: Children &lt;2kg, 2 to 4 mL, between 2 and 12 kg, 6 mL, between 12 and 36, 20 mL. At least 60 mL for adults</td>
</tr>
<tr>
<td>Frequency: Daily when candidaemia is suspected</td>
</tr>
<tr>
<td>Incubation time: At least five days</td>
</tr>
<tr>
<td>Performance: 50-75% S (neutropenic, species)</td>
</tr>
<tr>
<td>ID is mandatory (yeast in BC is not always <em>Candida</em>). Lysis-centrifugation (if older BC systems are used)</td>
</tr>
</tbody>
</table>
¿What can we do? ?

Figure 1 Different antifungal strategies for treatment in invasive fungal infections based on diagnostic stage.

Serum procalcitonin measurement contribution to the early diagnosis of candidemia in critically ill patients

Retrospective study
50 bloodstream infections: 15 candidemias (11 patients) y 35 bacteremias (33 patients)

PCT > 5.5 ng/ml NPV for candidemia
"Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts?"

Rafael Zaragoza, Javier Pemán, Miguel Salavert, Ángel Viudes, Amparo Solé, Isidro Jarque, Emilio Monte, Eva Romá, Emilia Cantón.

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<th>Antifungal agent</th>
<th>References</th>
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<td>Prophylaxis</td>
<td>No generally recommended. Patients with upper gastrointestinal perforation, heavy <em>Candida</em> colonization or with severe acute pancreatitis might be benefit</td>
<td>Fluconazole (Pelz et al. 2001) (Garbino et al. 2002) (De Waele et al. 2003; Piarroux et al. 2004)</td>
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<tr>
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<td>Use of “Candida score” or the Ostrosky-Zeichner prediction rule</td>
<td>De-escalation therapy (*), the choice of antifungal drug must be based on the individual characteristics of the patient (Leon et al. 2006; Ostrosky-Zeichner et al. 2007)</td>
</tr>
<tr>
<td>Pre-emptive</td>
<td>Based on detection of galactomannan, (1,3)-β-D-glucan or <em>C. albicans</em> germ tube antibodies or PCR.</td>
<td>De-escalation therapy (*), the choice of antifungal drug must be based on the individual characteristics of the patient (Meersseman et al. 2008; Ostrosky-Zeichner et al. 2005; Zaragoza et al. 2006)</td>
</tr>
<tr>
<td>Targeted</td>
<td>Based on sterile site culture results</td>
<td>De-escalation therapy(*), the choice of antifungal drug must be based on the individual characteristics of the patient (**)(Kullberg et al. 2005; Kuse et al. 2007; Mora-Duarte et al. 2002; Pappas et al. 2007; Phillips et al. 1997; Rex et al. 1994; Zaragoza &amp; Peman 2006)</td>
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## What are the best tests for diagnosing candidaemia? 2

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Test</th>
<th>Considerations</th>
<th>Remarks/Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Mannan and Anti-Mannan</td>
<td>• Combined detection</td>
<td>RECOMMENDED Serial determinations may be necessary. High NPV</td>
</tr>
<tr>
<td></td>
<td>Other antibodies (such as Serion ELISA classic)</td>
<td>• Limited data for candidemia</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>β-D-Glucan</td>
<td>• Not specific for Candida</td>
<td>RECOMMENDED (for Fungitell) No recommendation for other tests. Serial determinations are recommended (twice a week). High NPV. Not validated in children</td>
</tr>
<tr>
<td></td>
<td>Septifast</td>
<td>• Limited data for candidemia</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>In house PCR</td>
<td>• No third party validation data available</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>
Kinetic Patterns of *Candida albicans* Germ Tube Antibody (CAGTA) in Critically Ill Patients: Influence on Mortality

Rafael Zaragoza,¹ Javier Pemán,³ Guillermo Quindós,⁵ Josep C. Bescós,⁵ Paula Ramírez,⁴ Maria D. Gómez,³ Juan J. Camarena,² Ana Cascón,¹ and Francisco Pérez-Atayde,¹ on behalf of the *Candida albicans* Germ Tube Antibody (CAGTAUCI) Study Group

Intensive Care Unit¹ and Department of Microbiology,² Hospital Universitario La Fe, Valencia, Spain; Department of Microbiology³ and Intensive Care Unit,⁴ Hospital Universitario La Fe, Valencia, Spain; Intensive Care Unit, Hospital Universitario Cruces, Bilbao, Spain⁵; Intensive Care Unit, Hospital Universitario de Oña, León, Spain

Received 6 May 2009/Accepted 28 July 2009

**TABLE 1.** Mortality of CAGTA-positive patients according to their dynamic patterns and the administration of antifungal treatment

<table>
<thead>
<tr>
<th>Dynamic pattern</th>
<th>No. (%) of patients with indicated outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>CAGTA positive</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Not determinable</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Increasing titers</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>No change</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Decreasing titers</td>
<td>8 (36.3)</td>
</tr>
</tbody>
</table>
CAGTA
Monitorizing the treatment

USE DE-ESCALATION STRATEGY, STEPPING DOWN TO FLUCONAZOLE.....if

If IC is not confirmed (one of them):

- Improvement of scores (SOFA and CS)
- Negative result of Platelia (if any previous sample was positive) or another biomarker
- No positive result of Platelia on days 5 or 10 or another biomarker
TAKE HOME MESSAGES.

1. TREAT AS SOON AS POSSIBLE WITH A BROAD SPECTRUM ANTIFUNGAL DRUG

2. FOLLOW A DE-ESCALATION PROTOCOL. COMBINE CLINICAL AND MICROBIOLOGICAL DATA

3. DO NOT WORRY ABOUT WITHDRAW IF YOU ARE SURE

4. USE FLUCONAZOLE WHEN THE SITUATION OF THE PATIENT ALLOW YOU TO DO IT.
Nike

I HOPE YOU AGREE WITH ME
Fifth recommendation

- Do not wait for last talk