The evolving fungal landscape
New developments, challenges and approaches

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Aspergillus infections in the ICU

Changing epidemiology –
Aspergillosis in ICU patients
Increasing incidence of invasive Aspergillosis in the ICU: Risk Stratification

- High Risk
  - Neutropenia
  - Hematological malignancy
  - Stem cell transplant
- Intermediate Risk – ICU patients
Increasing incidence of invasive Aspergillosis in the ICU: Risk Stratification

- High Risk
  - Neutropenia
  - Hematological malignancy
  - Stem cell transplant

- Intermediate Risk
  - Corticosteroids!
  - Severe influenza (H1N1) in the ICU!
  - COPD
  - Immunosuppressants for systemic disease
  - Liver cirrhosis
  - Solid organ cancer
  - HIV
  - Lung transplant

- Low Risk
  - Heart/kidney/liver transplant
  - Malnutrition
  - Prolonged ICU stay

Invasive aspergillosis

Hemato-oncology
Typical signs

ICU patients
Nonspecific

Halo sign
Air crescent sign

# Aspergillosis in ICU patients: BAL Galactomannan

<table>
<thead>
<tr>
<th></th>
<th>Proven Invasive Aspergillosis</th>
<th>No Aspergillosis</th>
<th>Specificity 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>26</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><strong>BAL culture/stain positive</strong></td>
<td>15 (58%)</td>
<td>14 (30%)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum Galactomannan positive</strong></td>
<td>11 (42%)</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>BAL Galactomannan positive</strong></td>
<td>23 (88%)</td>
<td>6 (13%)</td>
<td>Sensitivity 88%</td>
</tr>
<tr>
<td><strong>GM cutoff: 0.5</strong></td>
<td></td>
<td></td>
<td>Specificity 87%</td>
</tr>
</tbody>
</table>

Meersseman et al. AJRCCM 2008
H1N1 Influenza and Invasive Aspergillosis in the ICU

- Belgium 2009-2011: 9 cases of Influenza pneumonia and 25 cases of Invasive aspergillosis.
- Netherlands 2016: 40 cases of Influenza pneumonia and 110 cases of Invasive aspergillosis.

Wauters et al, Intens Care Med 2012
Van de Veerdonk et al, 2016 submitted
H1N1 Influenza and Invasive Aspergillosis in the ICU

Netherlands, 2016 flu season
- 8 University Medical Centers
- 110 confirmed influenza pneumonias in ICU
- 25 proven/probable invasive aspergillosis (EORTC-MSG criteria)
- Corticosteroid use, 80%
- Sensitivity:
  - BAL culture 84%
  - BAL Galactomannan 89%
  - Serum Galactomannan 67%
- Mortality 56%
- Azole resistance, 31%
H1N1 Influenza and Invasive Aspergillosis in the ICU

- Onset of influenza
- ICU Admission
- Start of Mechanical Ventilation
- Chest X-ray infiltrate
- Aspergillus diagnosis
- Antifungal therapy

- Survived
- Died

Diagnosis of influenza
Green - survivors
Red - non survivors

Time (days) between influenza diagnosis and antifungal therapy

Van de Veerdonk et al, 2016 submitted
Diagnosis of invasive aspergillosis in the ICU: BAL Galactomannan and risk factors

Positive culture
  +
Risk factor (COPD, steroids, influenza)
  +
Any sign (e.g., infiltrate)
  =
Obtain BAL
Galactomannan
  +
Treat

Positive BAL
Galactomannan
  +
Risk factor (COPD, steroids, influenza)
  =
Treat
Isavuconazole equivalent to voriconazole for invasive aspergillosis

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole</th>
<th>Voriconazole</th>
<th>Δ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT population (proven/prob/possible IA)</strong></td>
<td>258</td>
<td>258</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality (6wk; primary outcome)</strong></td>
<td>19%</td>
<td>20%</td>
<td>-1.6% (-7.8, 5.7)</td>
</tr>
<tr>
<td><strong>mITT population (proven/prob IA)</strong></td>
<td>143</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality (6wk)</strong></td>
<td>20%</td>
<td>23%</td>
<td>-2.6% (-12.2, 6.9)</td>
</tr>
<tr>
<td><strong>Overall Response (EOT)</strong></td>
<td>35%</td>
<td>36%</td>
<td>1.6% (-9.3, 12.6)</td>
</tr>
<tr>
<td><strong>Drug-related adverse events</strong></td>
<td>42%</td>
<td>60%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>• Hepatobiliary</td>
<td>9%</td>
<td>16%</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>• Eye</td>
<td>15%</td>
<td>27%</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>• Skin/SCT</td>
<td>33%</td>
<td>42%</td>
<td>P = 0.037</td>
</tr>
</tbody>
</table>

Voriconazole 6mg/kg bid → 4mg/kg bid or 200 po bid vs. Isavuconazole 200mg tid x2d → 200mg qd iv or po

Maertens et al, Lancet 2016; 387: 760-9
**Combination therapy for invasive aspergillosis**

### Annals of Internal Medicine

#### Combination Antifungal Therapy for Invasive Aspergillosis
**A Randomized Trial**

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole + anidulafungin</th>
<th>Voriconazole</th>
<th>Δ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>135</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Mortality (6wk; primary outcome)</td>
<td>19.5%</td>
<td>27.8%</td>
<td>-8.3% (-19, 1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.087</td>
</tr>
<tr>
<td>Mortality (12wk)</td>
<td>29.3%</td>
<td>39.4%</td>
<td>-10.1% (-21.4, 1.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.077</td>
</tr>
<tr>
<td>Post-hoc analysis</td>
<td>Voriconazole + anidulafungin</td>
<td>Voriconazole</td>
<td>Δ (95%CI)</td>
</tr>
<tr>
<td>Galacominan-positive pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>108</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Mortality (6wk)</td>
<td>15.7%</td>
<td>27.3%</td>
<td>-11.6% (-22.7, -0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.037</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td>HR 2.71 (1.32, 5.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.007</td>
</tr>
</tbody>
</table>

Azole-Resistant *Aspergillus* strains

Environmental Route

Hospital Route

TR$_{34}$/L98H
TR$_{53}$
TR$_{46}$/Y121F/T289A

Azole therapy
Aspergillosis – Azole resistance

1998 34 bp L98H

2006 53 bp -

2009 46 bp Y121F/T289A


308 Soil samples collected
10 of 308 (3.25%) A. fumigatus azole-resistant
8/10 TR34/L98H
2/10 G54R

Thailand 2016

Tangwattanachuleeporn et al. Med Mycol 2016, in press

Azole resistant *Aspergillus* spp

Overall 7.2%

Local resistance rates 24-30%

<table>
<thead>
<tr>
<th>Region</th>
<th>Resistance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td>4.9%</td>
</tr>
<tr>
<td></td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td>19.2%</td>
</tr>
<tr>
<td></td>
<td>9.4%</td>
</tr>
</tbody>
</table>

NethMap 2015
Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

Radboudumc
Environmental sampling – Resistant *Aspergillus* strains
Think Aspergillus

- Invasive aspergillosis in apparently immunocompetent ICU patients
  - COPD, corticosteroids and severe influenza as emerging risk factors

- BAL galactomannan is the preferred diagnostic technique in the ICU

- Voriconazole or isavuconazole are therapy of choice
  - Voriconazole + echinocandin for severe cases
  - L-AmB second line therapy

- Increasingazole resistance rates – Also in SE-Asia
Cryptococcus
Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial

**Summary**

**Background** Early drug treatments in cerebrospinal fluid support the use of flucytosine, and fluconazole. We compared the fungicidal activity of five drugs for initial therapy of meningitis.

**Early fungicidal activity (EFA)**

Figure 3: Fall in CSF CFU over time by treatment group

Combination antifungal therapies for HIV-associated cryptococcal meningitis

Early fungicidal activity (EFA)

Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis

- Randomized trial in Uganda & South Africa (COAT trial)
  ART initiation within 2 weeks vs. > 5 weeks
  HIV-infected patients with documented cryptococcal meningitis
  R/ Amphotericin B 0.7-1.0 mg/kg/d + fluconazole 800 mg/d

- Planned enrollment n=500
  Terminated early by DSMB after 177

- Primary endpoint: 26 weeks’ mortality
  Early ART 40/88 (45%)
  Deferred ART 27/89 (30%)

Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis

- Deferring ART until 5 weeks after start of AmB improves survival
- Highest death risk in patients with low CSF white cell counts and early ART
- Adverse effect of early ART probably related to IRIS
Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis


ABSTRACT

BACKGROUND
Cryptococcal meningitis associated with human immunodeficiency virus (HIV) infection causes more than 600,000 deaths each year worldwide. Treatment has changed little in 20 years, and there are no imminent new anticryptococcal agents. The use of adjuvant glucocorticoids reduces mortality among patients with other forms of meningitis in some populations, but their use is untested in patients with cryptococcal meningitis.

METHODS
In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphotericin

- Randomized trial in SE-Asia & Africa (CryptoDex trial)
  Dexamethasone vs. placebo x6 wk
- HIV-infected patients with documented cryptococcal meningitis
  R/ Amphotericin B 1.0 mg/kg + fluconazole 800 mg
- Planned enrollment n=880
  Terminated early by DSMB after 451
- Primary endpoint: 10 weeks’ mortality
  Dexamethasone 47%
  Placebo 41%

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

- Survival at 10 weeks and 6 months N.S.
- CFU clearance (EFA) 21 vs. 31\(^\text{§}\) (P<0.001)
- Disability at 10 wks
  - Good outcome 13\% vs. 25\%\(^\text{§}\) (P<0.001)
- Clinical adverse events 667 vs. 404\(^\text{§}\) (P = 0.01)
  - Infection\(^\text{§}\) 48 vs. 25 (P = 0.003)
  - Renal events\(^\text{§}\) 22 vs. 7 (P = 0.004)
  - Cardiac events\(^\text{§}\) 8 vs. 0 (P = 0.004)
  - IRIS 7 vs. 6 (N.S.)

Early fungicidal activity (EFA) P<0.001

\(^\text{§}\) Dexamethasone vs. Placebo

HIV-associated cryptococcal meningitis

- Early fungicidal activity (EFA) in a marker of treatment efficacy.
- AmB + flucytosine is associated with lower mortality than AmB monotherapy.
- AmB + fluconazole is an acceptable alternative.
- Deferred (>5 wks) initiation of ART is associated with lower mortality.
- Dexamethasone does not improve survival and is associated with slower fungal clearance, and higher adverse events and disability rates.
Mucormycosis
Treatment of Mucormycosis

- **Background**
  - Mucormycosis associated with 40% mortality (Haem. malignancy, SOT, DM, trauma)
  - Amphotericin B, posaconazole, isavuconazole are the only active agents

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23
Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis

Background

- Mucormycosis associated with 40% mortality (Haem. malignancy, SOT, DM, trauma)
- Amphotericin B, posaconazole, isavuconazole are the only active agents
- High-dose L-AmB suggested in animal model (Lewis 2010), and in Phase I-II (Walsh 2001)

Methods

- Prospective open label study of L-AmB 10 mg/kg/day x 4 weeks in patients with proven/probable Mucormycosis (+/- surgery)
- Primary endpoint: Overall response at Week 4
- Single arm, open label; powered for a precision of ±15%, N=44

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23
Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis

Patients: 34 eligible
29 proven (85%)
9 probable

<table>
<thead>
<tr>
<th>Proven/probable mucor</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint, Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– complete response</td>
<td>12/33 (36%)</td>
<td>14/31 (45%)</td>
</tr>
<tr>
<td>– partial response</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Mortality</td>
<td>21%</td>
<td>38%</td>
</tr>
<tr>
<td>Creatinine doubling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Treatment interruption</td>
<td>16/40 (40%)</td>
<td></td>
</tr>
<tr>
<td>– Treatment discontinuation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23
An Open-Label Phase 3 Study of Isavuconazole (VITAL):

- Phase 3 open label trial of isavuconazole for rare fungi (EORTC/MSG)
- Primary or salvage therapy – ISA 200mg qd (loading 200mg tid, days 1-2), maximum 180 days
- Of 149 patients enrolled, 37 mucormycosis (32 proven, 5 probable)
- Matched historical controls (AmB)

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole</th>
<th>Amphotericin B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude all-cause mortality, n/N (%)</td>
<td>7/21 (33%; 14.6–57.0)</td>
<td>13/33 (39%; 22.9–57.9)</td>
<td>p=0.775†</td>
</tr>
<tr>
<td>Weighted all-cause mortality (%)</td>
<td>33%; 13.2–53.5</td>
<td>41%; 20.2–62.3</td>
<td>p=0.595$</td>
</tr>
<tr>
<td>Crude mortality by matching covariates, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>5/11 (45%)</td>
<td>7/18 (39%)</td>
<td>NA</td>
</tr>
<tr>
<td>Severe disease¶</td>
<td>6/12 (50%)</td>
<td>8/13 (62%)</td>
<td>NA</td>
</tr>
<tr>
<td>Surgical treatment¶¶</td>
<td>4/9 (44%)</td>
<td>3/13 (23%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Candidemia and Invasive Candidiasis
Invasive candidiasis

- Prophylaxis or early detection of candidiasis in the ICU
# Candida prophylaxis trials in the ICU

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient selection</th>
<th>Invasive candidiasis (prophylaxis/controls)</th>
<th>Mortality (prophylaxis/controls)</th>
</tr>
</thead>
</table>
| Ostrosky-Zeichner 2014 | 186/16,000 high risk, Selected by prediction rule                               | 10% / 17%  
\( P = 0.14 \)  
N.S.                         | 17% / 14%  
N.S.                         |
| Pelz 2001          | 260/1282 high-risk, >3 days ICU                                                   | 8.5% / 15%  
\( P = 0.01 \)  
N.S.                         | 11% / 12%  
N.S.                         |
| Garbino 2002       | 220/5241 highest risk, >3 days ICU, ventilated >2d                               | 4% / 10%  
\( P = 0.02 \)  
N.S.                         | 39% / 41%  
N.S.                         |
| Eggimann 1999      | 49 extremely high risk, Intestinal suture leak requiring relaparotomy             | 2% / 9%  
\( P = 0.06 \)  
N.S.                         | 30% / 50%  
N.S.                         |

# Candida prophylaxis trials in the ICU

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient selection</th>
<th>Invasive candidiasis (prophylaxis/controls)</th>
<th>Mortality (prophylaxis/controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostrosky-Zeichner 2014</td>
<td>186/16,000 high risk, Selected by prediction rule</td>
<td>10% / 17%</td>
<td>17% / 14%</td>
</tr>
<tr>
<td>Pelz 2001</td>
<td>260/1282 high-risk, &gt;3 days ICU</td>
<td>8.5% / 15%</td>
<td>11% / 12%</td>
</tr>
<tr>
<td>Garbino 2002</td>
<td>220/5241 highest risk, &gt;3 days ICU, ventilated &gt;2d</td>
<td>4% / 10%</td>
<td>39% / 41%</td>
</tr>
<tr>
<td>Eggimann 1999</td>
<td>49 extremely high risk, Intestinal suture leak requiring relaparotomy</td>
<td>2% / 9%</td>
<td>30% / 50%</td>
</tr>
</tbody>
</table>

**Conclusion:** No support for antifungal prophylaxis among IC patients other than high-risk groups previously identified in the guidelines.
How to select patients for empirical therapy?

Patients admitted to ICU for >7 days (Spain)

Risk factors for developing invasive candidiasis

Develop Candida score

- Multifocal colonization: 1 point
- Total Parenteral Nutrition: 1 point
- Surgery: 1 point
- Severe sepsis: 2 points

If ≥ 3 points → start treatment

Sensitivity 60-80%, specificity 74-86%

León et al, Crit Care Med 2006
León et al, Crit Care Med 2009
Predictive models depend on prevalence of candidiasis

- Geographical variability in epidemiology of IC, case-mix & medical practices
- Validation in Australia:

<table>
<thead>
<tr>
<th>León model</th>
<th>As reported in Spain (prevalence = 5.8%)</th>
<th>Applied to Australian data (prevalence = 0.2 to 2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>81%</td>
<td>15-26%</td>
</tr>
<tr>
<td>Specificity</td>
<td>74%</td>
<td>98%</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Comments</td>
<td>Application to patients with ICU LOS ≥7d excludes ⅓-½ cases</td>
<td></td>
</tr>
</tbody>
</table>

Playford et al. Int Care Med 2009
Candida Biomarkers – Not ready for prime time

Single or combined biomarker screening in prospective ICU cohort (candidiasis incidence, 13%)

Patients with (medical or surgical) severe abdominal condition, and expected ICU stay ≥7 days

<table>
<thead>
<tr>
<th>Controls</th>
<th>Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not colonized</td>
</tr>
<tr>
<td></td>
<td>N = 48</td>
</tr>
<tr>
<td>BDG ≥ 80 pg/mL, no. (%)</td>
<td>16/46 (34.8)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAGTA positive, no. (%)</td>
<td>10/47 (21.3)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mannan-Ag positive, no. (%)</td>
<td>10/48 (20.8)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mannan-Ab positive, no. (%)</td>
<td>6/48 (12.5)</td>
</tr>
<tr>
<td>C-PCR positive, no. (%)</td>
<td>14/23 (60.9)</td>
</tr>
</tbody>
</table>

- Single assays are highly nonspecific (≈80% of positive results are false)
- Sensitivity is not good enough in high-risk population (≈50% of cases are missed)
- With positive test: chance of candidiasis approx. 1/5 (without testing: 1/7 =13%)

Combining 2 or 3 assays
- "Best" combined assays still is highly nonspecific (81% of positives are false)
- Sensitivity still too low for targeted testing in very high risk (≈30% of cases missed)
- A negative test does not rule out candidiasis in a high-risk patient

BDG, β-D-glucan
CAGTA, Candida albicans germ tube antibodies
Mannan Ag, antigen; Ab, antibodies
C-PCR, Candida multiplex real time whole blood qPCR

León et al, Crit Care 2016; 20: 149
Empiric echinocandin therapy in ICU patients following surgery for intraabdominal infection (INTENSE)

Randomized, double-blind, multicenter study of micafungin vs. placebo

<table>
<thead>
<tr>
<th>Randomized, N=252</th>
<th>Micafungin</th>
<th>Placebo</th>
<th>Difference (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline invasive candidiasis</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Full analysis cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No baseline candidiasis, ≥1 dose</td>
<td>124</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Proven invasive candidiasis (IDRB)</td>
<td>11.1%</td>
<td>8.9%</td>
<td>2.24 (-5.52, 10.20)</td>
</tr>
<tr>
<td>Mortality</td>
<td>4.3%</td>
<td>0.8%</td>
<td>$P = NS$</td>
</tr>
</tbody>
</table>

Conclusion: No support for post-operative empiric/preemptive treatment

1 IDRB, independent data review board

How to select patients for presumptive therapy?
An expert-based view

Severe sepsis?

One or more of:
- Gastrointestinal surgery
- Multifocal *Candida* colonization
- Total parenteral nutrition
- No response to broad spectrum antibiotics
- Surrogate marker (β-D-Glucan, Mannan)

Start Echinocandin

discussed in:
If prophylaxis/empirical therapy are a delusion, how can we make a change?

Invasive candidiasis
If prophylaxis/empirical therapy are a delusion, how can we make a change?

✓ The evidence is in the treatment guidelines

- IDSA Clinical Practice Guideline for Management of Candidiasis 2016
- ESCMID Diagnostic & Management Guidelines for 
  *Candida* Diseases 2012
### ESCMID 2012:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recommendation</th>
<th>References</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin 200→100 mg</td>
<td>AI</td>
<td>Reboli NEJM 2007</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 70→50 mg</td>
<td>AI</td>
<td>Mora-Duarte NEJM 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pappas Clin Infect Dis 2007</td>
<td></td>
</tr>
<tr>
<td>Micafungin 100 mg</td>
<td>AI</td>
<td>Kuse Lancet 2007</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pappas Clin Infect Dis 2007</td>
<td></td>
</tr>
</tbody>
</table>

### IDSA 2016:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Comment</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anidulafungin 200→100 mg</td>
<td></td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Caspofungin 70→50 mg</td>
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<td>Micafungin 100 mg</td>
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</table>
**Initial therapy**

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<th>Compound</th>
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<td>Caspofungin 70→50 mg</td>
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</tbody>
</table>

**Acceptable alternatives**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Comment</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 800→400 mg</td>
<td>Selected patients – Not critically ill and unlikely to have FLU-resistant <em>Candida</em></td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Voriconazole 6→3 mg/kg bid*</td>
<td>Little advantage over FLU as initial therapy</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>L-Amphotericin B 3 mg/kg</td>
<td>Reasonable alternative if intolerance, limited availability, or resistance to other antifungal agents</td>
<td>Strong</td>
<td>High</td>
</tr>
</tbody>
</table>

*Licensed dose: 6 mg/kg q12h for the first 24 hours, followed by 4 mg/kg BID. Voriconazole is indicated in the treatment of candidaemia in non-neutropenic patients (adults & children ≥2 yrs)

Echinocandin superior to Fluconazole: Anidulafungin invasive candidiasis trial

<table>
<thead>
<tr>
<th></th>
<th>Anidulafungin 200→100mg</th>
<th>Fluconazole 400→800mg</th>
<th>Estimated difference % (95%CI; P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success Rate (MITT; EOivT) N=245</td>
<td>76%</td>
<td>60%</td>
<td>15.4% (3.9, 27.0; P&lt;0.02)</td>
</tr>
<tr>
<td>Crude Mortality (8 wks)</td>
<td>23%</td>
<td>31%</td>
<td>P=0.13</td>
</tr>
</tbody>
</table>

Both arms allowed to switch to oral fluconazole after ≥10 days

MITT. modified intent-to-treat population; EOivT, End of intravenous Treatment

Radboudumc

Anidulafungin candidemia study

Success difference driven by C. albicans infections*

*Patients with a single baseline pathogen

New data 2009–2016?

Are echinocandins really superior to fluconazole?

Mycoses Study Group MSG-02 Pooled Analysis

- 1915 patients - Individual patient-level pooled analysis
  - Overall mortality 31.4%
  - Treatment success (EOT) 67.4%

30-day mortality endpoint:

Increased mortality: OR P
- Age 1.01 0.02
- APACHE II score 1.11 0.0001

Decreased mortality:
- Echinocandin antifungal 0.65 0.02
- CVC removal during therapy 0.50 0.0001

1. Treat early
2. Remove catheter
3. Start with echinocandin

**A second azole vs. echinocandin trial**

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Compare the efficacy of <strong>isavuconazole vs caspofungin</strong> in patients with candidemia or other invasive <em>Candida</em> infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multinational, double-blind, randomized, non-inferiority study Switch to oral treatment &gt;Day 10</td>
</tr>
<tr>
<td>Study population</td>
<td>450 adult patients with candidemia/invasive candidiasis</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>&gt;85% power to demonstrate non-inferiority of isavuconazole to caspofungin at a non-inferiority margin of 15%</td>
</tr>
</tbody>
</table>

Kullberg et al. ECCMID 2016, Abstr. 1239; 11 April 2016
# Isavuconazole vs. Caspofungin study

## Efficacy outcomes

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Isavuconazole (n = 199)</th>
<th>Caspofungin (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful overall response at EOivT*</td>
<td>120 (60.3)</td>
<td>143 (71.1)</td>
</tr>
<tr>
<td>Successful overall response at EOT + 2 weeks</td>
<td>109 (54.8)</td>
<td>115 (57.2)</td>
</tr>
<tr>
<td>All-cause mortality Day 14</td>
<td>29 (14.6)</td>
<td>25 (12.4)</td>
</tr>
<tr>
<td>All-cause mortality Day 56</td>
<td>61 (30.7)</td>
<td>60 (29.9)</td>
</tr>
</tbody>
</table>

*Stratified by geographical region and baseline neutropenia status

Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

Kullberg et al. ECCMID 2016, Abstr. 1239; 11 April 2016
Second azole vs. echinocandin trial – similar difference

Success (%)

- Anidulafungin: 75.6% (n=96)
- Fluconazole: 60.2% (n=71)
- Caspofungin: 71.1% (N=201)
- Isavuconazole: 60.3% (N=199)

Reboli 2007
Kullberg 2016

References:
Summary thoughts

- Candidemia / invasive candidiasis emerge from intestinal colonization
- Prophylaxis and empirical or biomarker-driven therapy in the ICU are not supported by published trial data
- Supporting data show superiority of echinocandins
- IDSA 2016 and ESCMID 2012 prioritized echinocandins as the first choice for treatment of candidemia/invasive candidiasis

The evolving fungal landscape
New developments, challenges and approaches

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