Controversies in Hospital Medicine: Antifungal Therapy

Empiric Therapy, Combination Therapy, and the Question of Central Venous Catheters

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What is the most appropriate antifungal therapy for presumed infections in non-neutropenic patients?

Case: Empiric Therapy

• 52 y.o. female s/p renal transplant in 2009 is admitted for pyelonephritis
• She was admitted two weeks ago with a similar presentation & was treated with cefepime and vancomycin, followed by oral ciprofloxacin
• She is now started on piperacillin/tazobactam + vancomycin, but cultures are negative and she continues to be febrile after 5 days of therapy
• She is to be started on antifungal therapy

Which of the following antifungals should be started?
A. Fluconazole
B. Caspofungin
C. Voriconazole
D. Liposomal amphotericin B
Risk Factors for Invasive Candidiasis

- Prolonged antibiotic use
- Prolonged ICU stay
- High APACHE II score
- Central venous catheter
- Total parenteral nutrition
- Prolonged antibiotic use
- Candida colonization at ≥2 sites
- Broad-spectrum antibiotics

Mortality Due to Invasive Mycoses

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida species</td>
<td>40%*</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>62%**</td>
</tr>
<tr>
<td>Invasive moulds (Aspergillus spp, Fusarium spp, Zygomycetes)</td>
<td>~80%‡</td>
</tr>
<tr>
<td>Scedosporium species</td>
<td>54%†-68%‡</td>
</tr>
</tbody>
</table>

*Adults hospitalized in the US; **Hospitalized patients with IA; †SOT recipients; ‡HSCT recipients.

Prompt Therapy is Crucial in the Management of Candidemia

Hospital mortality in patients with Candida BSI, according to length of delay in starting antifungal treatment (Marr DJ, plate 8, 2008).

BFI: Bloodstream infection.

Data from retrospective cohort analysis of 93 patients with Candida BSI**.

## Candida Species Sensitivity Profile

<table>
<thead>
<tr>
<th>Species</th>
<th>FLUC</th>
<th>ITRA</th>
<th>VOR</th>
<th>POS</th>
<th>5-FC†</th>
<th>AMB</th>
<th>Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>SDD to R</td>
<td>SDD to R</td>
<td>S (to SDD†)</td>
<td>S (to SDD†)</td>
<td>S to I</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>R</td>
<td>R</td>
<td>S (to SDD†)</td>
<td>S (to SDD†)</td>
<td>I to R</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>R</td>
<td>S</td>
<td>S (to SDD†)</td>
<td>I to S (to SDD?)</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>

S=susceptible; SDD=susceptible-dose dependent; R=resistant; I=intermediate

SDD - Susceptibility depends on the dose of the drug and bioavailability (delivery). Maximum tolerated dosages should be used.

Adapted from Ostrosky-Zeichner L, Pappas PG. Crit Care Med. 2006;34:857-863.

## Distribution of Candida Species in Bloodstream Infections

SENTRY 1997-2000: 32 centers in the United States, 23 in Europe, 9 in Latin America, and 7 in Canada

- 54% C. albicans
- 16% C. glabrata
- 15% C. parapsilosis
- 10% C. tropicalis
- 2% C. krusei
- 3% Other

N=2047 bloodstream isolates


## IDSA Clinical Practice Guidelines for the Management of Candidemia

- **Empirical treatment for suspected invasive candidiasis in nonneutropenic patients:**
  - Fluconazole 800 load x 1, then 400 mg (6 mg/kg)/day
  - Caspofungin 70 mg load x 1, then 50 mg/day
  - Anidulafungin 200 mg load x 1, then 100 mg/day
  - Micafungin 100 mg/day
- **Echinocandin preferred for patients with:**
  - Recent azole exposure
  - Moderately severe or severe illness
  - High risk of infection due to C. glabrata or C. krusei

Case: Empiric Therapy

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• She is now started on piperacillin/tazobactam + vancomycin, but cultures are negative and she continues to be febrile after 5 days of therapy

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Which of the following antifungals should be started?

A. Fluconazole  Either may be correct depending on incidence of non-albicans Candida at a specific institution
B. Caspofungin  
C. Voriconazole  
D. Liposomal amphotericin B

Is there an appropriate role for combinations of antifungal agents?
Case: Combination Antifungals

- The 52 y.o. female in the previous case is diagnosed with a *Candida glabrata* bloodstream infection
- She had been previously started on fluconazole but is subsequently changed to caspofungin
- After one week she has failed to respond clinically and blood cultures are still positive for *C. glabrata*
- Addition of second antifungal is considered

Is there an appropriate role for combination antifungals in this patient?
A. No, combination therapy is not appropriate
B. Yes, adding liposomal amphotericin B would be appropriate
C. Yes, adding voriconazole would be appropriate
D. Yes, change to voriconazole + liposomal ampho B

Case Fatality Rates Among Patients with Invasive Aspergillosis

- Therapeutic success rates in invasive fungal infections continue to be suboptimal
- Introduction of echinocandins offered potential for use of drugs with different target site, low toxicity profile
- Data from *in vitro* and animal models have shown some potential for additive or synergistic effects

Rationale for Combination Antifungal Therapy

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Combination Antifungals in Solid Organ Transplantation

- Prospective, multicenter, observation study
- 40 solid organ transplant recipients with proven or probable invasive Aspergillus infection
  - All patients received voriconazole + caspofungin
  - Compared to historical control group of 47 patients receiving lipid amphotericin B (mean 5.2 mg/kg/day)
- Results:
  - 90-day survival not significantly different between combo vs. control groups (67.5% vs. 51.1%, respectively; HR 0.57 (95% CI 0.29-1.1; P = 0.12)
  - Combo therapy independently associated with reduced mortality in two subgroups:
    - Patients with renal failure, HR 0.32 (95% CI 0.12-0.85, P = 0.02)
    - Patients with A. fumigatus, HR 0.37 (95% CI 0.16-0.84; P = 0.019)


Combination Antifungals in Patients with Hematologic Malignancies

- Prospective, randomized, open-label pilot study of patients with proven or probable invasive aspergillosis
- Patients randomized to receive liposomal amphotericin B 3 mg/kg/day + caspofungin 50 mg/day vs. high-dose liposomal amphotericin B (10 mg/kg/day)
- 30 patients (15 in each arm) were treated for median of ~18 days
  - Duration of neutropenia before enrollment = 31.5 days in combo group vs. 15.0 days in high-dose ampho B group (P = 0.015)
- Results
  - Favorable responses:
    - Combination therapy = 10/15 (67%)
    - High-dose ampho B = 4/15 (27%)
    - P = 0.028
  - Survival at 12 weeks:
    - Combination therapy = 100%
    - High-dose ampho B = 80%
- Both regimens were well tolerated overall, but slightly higher rates of AEs in high-dose ampho B group

Combination Antifungals for Aspergillosis in Lung Transplant Patients

- Retrospective review of 15 lung transplant patients treated with voriconazole plus caspofungin
  - 4 patients treated for pre-transplant colonization
  - 11 patients treated for proven or probable invasive aspergillosis
- Patients received voriconazole (median 500 mg/day) × 15 ± 4 days + caspofungin 50 mg/day × 18 ± 3 days
  - Caspofungin stopped after favorable clinical response and switch from IV to PO voriconazole
- Patients with colonization were all culture-negative at 90 days
- 10 of 11 patients (91%) with aspergillosis had complete response
- Combination was well tolerated overall


Recommendations Regarding Combination Antifungal Therapy

- Small studies show improved efficacy with combination regimens in the management of invasive aspergillosis in immunocompromised pts
- Liposomal amphotericin B + echinocandin, voriconazole + echinocandin may be considered in patients with no improvement or disease progression on initial monotherapy
  - Amphotericin B + azole drugs not recommended due to theoretical/potential antagonistic effects
- No current recommendations for combination therapy of invasive candidiasis
  - Switching agents preferred over addition of second drug

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Is the removal of intravenous catheters required for effective treatment of fungal infections?

Case: Catheter Removal
• The 52 y.o. female in the previous case is still being treated for her C. glabrata bloodstream infection as before
• A central line was to be removed when her fungal blood cultures proved positive, but she has very difficult IV access and it was initially decided to leave the catheter in place due to a recent published study showing no benefit to catheter removal

With her continued candidemia, should the central line now be removed?
A. No, there is no proven benefit to removal
B. No, it would have initially been wise but no point now
C. Yes, it should have been removed initially
D. Yes, it was perhaps unnecessary before but is needed now

Risk Factors for Invasive Candidiasis

- Broad-spectrum antibiotics
- Neutropenia
- Immunosuppression
- Prolonged antibiotic use
- Prolonged ICU stay
- High APACHE II score
- Central venous catheter
- Candida colonization at ≥2 sites
- Total parenteral nutrition
- ≥14 days of mechanical ventilation
Rationale for Early Removal of Central Venous Catheters in Patients with Candidemia

- CVCs consistently identified as risk factors for the development of candidemia
- CVCs in patients with candidemia known to harbor Candida biofilms which may impede eradication of infection
- IDSA guidelines on management of candidemia give CVC removal a grade B-III level of evidence
- IDSA guidelines on management of catheter-related bloodstream infections give CVC removal an A-II level of evidence


Early Removal of Central Venous Catheters in Patients with Candidemia

- Subgroup analysis of two Phase III, multicenter, double-blind, randomized, controlled trials of candidemia
  - Liposomal amphotericin B vs. micafungin
  - Caspofungin vs. micafungin 100 mg/d vs. micafungin 150 mg/d
- Inclusion criteria included age >16 years, CVC at diagnosis, receipt of ≥1 dose of study drug
- Early CVC removal = within 24-48 hours of treatment
- Evaluated six treatment outcomes:
  - Treatment success
  - Rate of persistent and recurrent candidemia
  - Time to mycological eradication
  - Survival at 28 days and 42 days


Early Removal of Central Catheters in Patients with Candidemia

Results in 842 patients

- Univariate analysis:
  - Early CVC removal did not improve time to mycological eradication
  - Early CVC removal did not improve rates of persistent or recurrent candidemia
  - Early CVC removal associated with trends toward better treatment success and survival rates
- Multivariate analysis:
  - No benefits to early CVC removal
  - Significant outcome variables = APACHE II score, older age, persistent neutropenia

Early Removal of Central Catheters in Patients with Candidemia

- True benefits of catheter removal are unknown
- Failure to prove benefit in the Nucci study does not prove a true lack of benefit
- Original studies had methodological issues which may have prevented effect of CVC removal from being accurately assessed
- CVC interventions should be individualized to patients needs
  - Removal of unneeded CVCs, or removal in persistent/recurrent infection would still seem prudent

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Summary

- Empiric antifungal therapy in non-neutropenic patients:
  - Fluconazole is most appropriate agent for empiric use in most patients
  - Echinocandins may also be appropriate in high-risk patients or institutions with high incidence of infection with non-albicans Candida
- Combination antifungal therapy:
  - No evidence supporting combinations regimens in invasive Candida infections
  - Reserved for patients failing monotherapy in treatment of invasive Aspergillus, other invasive mould infections
- Removal of infected intravenous catheters:
  - Recent study showing no benefit of CVC removal should be considered hypothesis-generating rather than providing definitive answers
  - CVC removal should still be considered in patients with candidemia