These are the 2007 Guidelines for the Treatment of Candida species infections in adult patients. These recommendations take into account drugs available on the New York-Presbyterian Hospital Formulary, susceptibility of Candida sp. to antifungal agents, hospital specific Candida sp susceptibilities, toxicities and drug interactions of the antifungals, and cost. These guidelines are intended to optimize the use of antifungal therapy, but are not meant to replace clinical judgement. A patient’s antifungal treatment history, history of positive fungal cultures, end-organ function, drug interaction potential, and level of immunosuppression corresponding to risk of non-Candida invasive fungal infections must always be taken into account. In addition, appropriate dosing for the patient’s weight, end-organ function, site of infection, and drug interactions are essential to improving outcomes and limiting the selection of more resistant Candida species. Historically, lower dosing of fluconazole (100-200 mg daily) for systemic infections has been associated with an increase in the development of azole-resistant Candida species, like C. glabrata.

**Usual Susceptibilities of Candida sp. to Antifungal Agents**

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole (not standardized)</th>
<th>Amphotericin B (not standardized)</th>
<th>Caspofungin (not standardized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</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>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S</td>
<td>S to I (? R)</td>
<td>S</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td>C. krusei</td>
<td>R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
<td>S</td>
</tr>
</tbody>
</table>

S = Susceptible
S-DD = Susceptible-dose dependent (increased MIC may be overcome by higher dosing - e.g. 12 mg/kg/day fluconazole)
I = Intermediate
R = Resistant

**Breakdown of Candida species Isolated from Blood Cultures**

<table>
<thead>
<tr>
<th></th>
<th>NYP / C – Milstein Hospital</th>
<th>NYP / WC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2005</td>
<td>2006&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>% C. albicans</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>% C. glabrata</td>
<td>27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>% C. parapsilosis</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>% C. tropicalis</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>% C. krusei</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> through 10/2006
<sup>b</sup> FLU susceptibility: 21% S, 58% S-DD, 21% R
<sup>c</sup> FLU susceptibility: 23% S, 56% S-DD, 19% R

**Approximate Antifungal Daily Costs - 2007**

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Approximate Cost / Dose</th>
<th>Usual Adult Dose</th>
<th>Approximate Cost / Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 400 mg IV</td>
<td>$15</td>
<td>400 mg IV q24h</td>
<td>$15</td>
</tr>
<tr>
<td>Fluconazole 400 mg PO</td>
<td>$1</td>
<td>400 mg PO q24h</td>
<td>$1</td>
</tr>
<tr>
<td>Itraconazole 200 mg PO solution</td>
<td>$14</td>
<td>200 mg PO q12h</td>
<td>$28</td>
</tr>
<tr>
<td>Voriconazole 280 mg IV</td>
<td>$160</td>
<td>280 mg IV q12h (maintenance)</td>
<td>$320</td>
</tr>
<tr>
<td>Voriconazole 200 mg PO</td>
<td>$25</td>
<td>200 mg PO q12h (maintenance)</td>
<td>$50</td>
</tr>
<tr>
<td>Amphotericin B conventional 70 mg IV</td>
<td>$12</td>
<td>70 mg IV q24h</td>
<td>$12</td>
</tr>
<tr>
<td>Amphotericin B Lipid (Abelcet®)</td>
<td>$260</td>
<td>350 mg IV q24h</td>
<td>$260</td>
</tr>
</tbody>
</table>
Antifungal Therapy for the Treatment of Infections Caused by *Candida* species in Adult Patients

**Candidemia**
(Documented *Candida* species in blood)

**OR**

**Invasive Candidiasis**
(positive Candida culture from sterile site and either fever >38.3°C or hypotension [SBP <90 mmHg or a decrease ≥30 mmHg] or signs of inflammation at a Candida-infected site)

**Pre-emptive Antifungal Therapy**
[prevention of invasive candidiasis on the basis of an individual risk profile]

Criteria:
- Fever >38.3°C on broad spectrum antibiotics, AND
- *Candida* sp. colonization at ≥2 sites, AND
- ≥2 major or ≥3 minor risk factors with no other obvious source of infection

Major risk factors: prolonged antibacterial therapy, immunosuppression, neutropenia, extensive burns, intestinal perforation, major abdominal surgery, diarrhea or ileus, TPN, renal replacement therapy

Minor risk factors: older age, renal insufficiency, ICU stay >10 days, bladder catheter, multilumen CVC, DM, candiduria

**START EMPIRIC ANTIFUNGAL THERAPY**

**Risk factors for fluconazole-resistant *Candida* sp.**
- history/colonization with *C. glabrata, C. krusei* or known fluconazole-resistant isolate
- significant exposure to azole antifungals (e.g. > 2 weeks in the last 90 days)
- hematologic malignancy
- HIV positive

**Caspofungin 70 mg IV x 1, then 50 mg IV daily**

**YES**

**NO**

**Hemodynamically unstable**

Hypotension (SBP <90, or >40 mmHg decrease from baseline in the absence of other causes) despite adequate fluid resuscitation

**Fluconazole 400 mg IV q24h (NYP/WC)**
**OR**
**Fluconazole 800 mg IV q24h (NYP/C)**

**YES**

**NO**

**Caspofungin 70 mg IV x 1, then 50 mg IV daily**
**OR**
**Lipid Amphotericin B 5 mg/kg IV daily**

**Fluconazole 200 mg PO/IV daily**
**x 5 days**

* Consider higher dose fluconazole or amphotericin B bladder irrigation x 3-5 days for persistent symptomatic candiduria

(voriconazole and caspofungin DO NOT achieve adequate concentrations in the urine and should not be used to treat isolated candiduria)

**Candiduria**
(*Candida* species identified in urine culture)

Remove/change urinary bladder catheter if present and repeat urine micro/culture

≥ 10⁵ cfu/mL with pyuria (>10 WBC) or symptomatic

**LAST UPDATED 4/30/07**
Candida species identified

Species

Candida albicans
Candida parapsilosis
Candida tropicalis

Candida glabrata

Fluconazole MIC ≤ 8 mcg/mL
(S)

Fluconazole 400 mg (~6 mg/kg) IV q24h

Fluconazole 800 mg (~12 mg/kg) IV q24h
OR Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h

Candida krusei

Fluconazole MIC 16-32 mcg/mL
(S-DD)

Fluconazole 400 mg (~6 mg/kg) IV q24h

Fluconazole MIC ≥ 64 mcg/mL
(R)

Fluconazole 400 mg (~6 mg/kg) PO q24h

Candida lusitanae
OR other species

Fluconazole 800 mg (~12 mg/kg) PO q24h

Caspofungin 70 mg IV x 1, then 50 mg IV q24h
OR Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h

Voriconazole 200 mg PO q12h
(only if voriconazole MIC reported < 1 mcg/mL)

ID Consult suggested

PO THERAPY
Oral therapy encouraged whenever possible. Most oral antifungal agents recommended above have very good oral bioavailability (>95%) and initiation of IV therapy is not always necessary unless patient is hemodynamically unstable and/or GI absorption can not be ensured. If IV therapy is initiated, the switch to oral or via tube administration is encouraged once the following criteria are met and there is an oral alternative.

Criteria for oral or via tube administration:
- GI absorption likely normal
- Ability to receive oral dosage form (analogous to concomitant oral or via tube administration of any other meds)

LAST UPDATED 4/30/07
<table>
<thead>
<tr>
<th></th>
<th>Fluconazole (Diflucan®)</th>
<th>Itraconazole (Sporanox®)</th>
<th>Voriconazole (Vfend®)</th>
<th>Amphotericin B/ Lipid Amphotericin B (Abelcet®)</th>
<th>Caspofungin (Cancidas®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage forms</strong></td>
<td>IV/PO</td>
<td>PO (IV: Non-Formulary)</td>
<td>IV/PO</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>&gt;90%</td>
<td>55%</td>
<td>&gt;95%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Effect of gastric pH</strong></td>
<td>None</td>
<td>Decreased concentrations</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>CSF penetration</strong></td>
<td>Excellent (~80%)</td>
<td>Poor (&lt;10%)</td>
<td>Good (40-60%)</td>
<td>Poor (&lt;2.5%)</td>
<td>Unknown, expected poor</td>
</tr>
<tr>
<td><strong>Elimination route</strong></td>
<td>Renal</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Unknown</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td>Yes ¹</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hepatic dose adjustment</strong></td>
<td>No</td>
<td>Yes ²</td>
<td>Yes ³</td>
<td>No</td>
<td>Yes ⁴</td>
</tr>
<tr>
<td><strong>Toxicities</strong></td>
<td>Hepatotoxicity (high doses and prolonged therapy)</td>
<td>GI Hepatotoxicity Negative inotropic effects</td>
<td>Visual disturbances Hepatotoxicity Rash Hallucinations</td>
<td>Nephrotoxicity Infusion related reactions Electrolyte abnormalities</td>
<td>Phlebitis/thrombophlebitis Elevated transaminases Histamine release reaction</td>
</tr>
<tr>
<td><strong>Drug interaction potential</strong></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Induction / inhibition</strong></td>
<td>Inhibits CY3A4 and other CYP isoforms; Interactions with enzymes involved with glucuronidation</td>
<td>Substrate and inhibitor of CYP3A4</td>
<td>Substrate and inhibitor CYP2C19 &gt; CYP2C9 &gt; CYP3A4</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

IV = Intravenous; PO = Oral

¹ Fluconazole requires dose adjustment in renal dysfunction. For estimated CrCL < 50 ml/min and patients receiving hemodialysis and peritoneal dialysis, ½ the usual daily dose should be administered. For patients receiving continuous renal replacement therapy (CRRT), the usual dose should be administered.

² Itraconazole has been associated with severe hepatotoxicity, including liver failure and death. Itraconazole use should be carefully monitored in patients with hepatic dysfunction.

³ Voriconazole requires dose adjustment in patients with hepatic dysfunction. For Child Pugh Class A and B, reduce IV and PO maintenance dose by ½ following usual loading dose. Use not recommended in Child Pugh Class C.

⁴ Caspofungin requires dose adjustment in hepatic disease. For Child Pugh Class B, reduce maintenance dose to 35 mg IV daily following usual loading dose. Use not recommended in Child Pugh Class C.