TITLE: CANDIDA INFECTIONS - TREATMENT GUIDELINES IN ADULT PATIENTS

GUIDELINES:

These are the 2011 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. 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, such as C. glabrata.

Note: With few exceptions, all antifungal agents require approval from Infectious Diseases prior to use.

PURPOSE:

These guidelines are intended to optimize the use of antifungal therapy, but are not meant to replace clinical judgment.

APPLICABILITY:

Prescribers and pharmacists

PROCEDURE:

1. Usual Susceptibilities of Candida sp. to Antifungal Agents

<table>
<thead>
<tr>
<th>Candida sp.</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>AmphoB</th>
<th>Caspofungin</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>
</tr>
<tr>
<td>C. tropicalis</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>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</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 S-DD</td>
<td>S to S-DD</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 S-DD</td>
<td>S to S-DD</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</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
2. Breakdown of Candida species Isolated from Blood Cultures

NYP/C Milstein Hospital

<table>
<thead>
<tr>
<th>Year</th>
<th>% C. albicans</th>
<th>% C. glabrata</th>
<th>% C. parapsilosis</th>
<th>% C. tropicalis</th>
<th>% C. krusei</th>
<th>% Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>46</td>
<td>30</td>
<td>10</td>
<td>14</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2006</td>
<td>41</td>
<td>25</td>
<td>23</td>
<td>9</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>2007</td>
<td>42</td>
<td>38</td>
<td>12</td>
<td>4</td>
<td>--</td>
<td>5</td>
</tr>
<tr>
<td>2008</td>
<td>31</td>
<td>39</td>
<td>11</td>
<td>13</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2009</td>
<td>46</td>
<td>22</td>
<td>16</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2010</td>
<td>31</td>
<td>43</td>
<td>15</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

NYP/WC

<table>
<thead>
<tr>
<th>Year</th>
<th>% C. albicans</th>
<th>% C. glabrata</th>
<th>% C. parapsilosis</th>
<th>% C. tropicalis</th>
<th>% C. krusei</th>
<th>% Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>61</td>
<td>14</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>2006</td>
<td>60</td>
<td>14.5</td>
<td>9.7</td>
<td>9</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>2007</td>
<td>48</td>
<td>11.1</td>
<td>20.6</td>
<td>12.6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2008</td>
<td>48</td>
<td>17.3</td>
<td>23</td>
<td>13.3</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>2009</td>
<td>43</td>
<td>23</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>2010</td>
<td>31</td>
<td>31</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

3. Algorithm
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 mm Hg or a decrease >30 mm Hg) or signs of inflammation at a Candida-infected site)

**Pre-emptive Antifungal Therapy**
- (Early treatment 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
  - At least TWO of the following risk factors: recent major abdominal surgery, currently receiving total parental nutrition (TPN), currently receiving renal replacement therapy, current central venous catheter (CVC), prolonged ICU stay

**Candiduria**
- (Candida species identified in urine culture)
- **Remove/change urinary bladder catheter if present and repeat urine culture**
- **Persistently positive culture and symptomatic**

**START EMPIRIC ANTIFUNGAL THERAPY**

**Risk factors for fluconazole-resistant *Candida* sp.**
- History/colonization with *C. glabrata*, *C. krusei* or known fluconazole-resistant isolate
- Exposure to azole antifungals (>48 hours in prior 30 days)
- Hematologic malignancy
- HIV positive

**Fluconazole 200 mg PO IV q24h**
- x 5 days
  - *Consider higher dose fluconazole or amphoterin B bladder irrigation for persistent symptomatic candiduria (nystatin and micafungin are NOT expected to achieve adequate concentrations in the urine and should not be used to treat isolated candiduria)*

**Micafungin 100 mg IV q24h**

- **YES**
- Micafungin 100 mg IV q24h
- **NO**
- Hemodynamically unstable
  - Hypotension (SBP <90, or a ≥ 40 mm Hg decrease from baseline in the absence of other causes) despite adequate fluid resuscitation or requiring vaso-active agents

**Fluconazole 400 mg IV q24h**
- (NYW/CIC)
  - OR
  - Fluconazole 800 mg IV q24h
- (NYW/CIC)

**Mycophenolic acid (MPH) 10 mg/kg IV q24h**

**YES**

**NO**

**Fluconazole 400 mg IV q24h**
- (NYW/CIC)
  - OR
  - Lipid Amphoterin B 5 mg/kg IV q24h

**LAST UPDATED 5/25/11**
Candida species identified

Without risk factors for fluconazole resistance (see prior page)

Candida albicans
Candida parapsilosis
Candida tropicalis

Candida glabrata

Candida krusei

Candida lusitaniae
OR other species

Fluconazole 400 mg
(6 mg/kg) IV q24h

Fluconazole MIC
≤ 8 mg/mL
(S)

Fluconazole 400 mg
(6 mg/kg) IV q24h

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

Fluconazole MIC
≥ 64 mg/mL
(R)

Mycophenolate 100 mg IV q24h
OR
Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h

Mycophenolate 100 mg IV q24h

Voriconazole 6 mg/kg
PO q12h x 2 doses, then 4 mg/kg PO q12h

Voriconazole 6 mg/kg
PO q12h x 2 doses, then 4 mg/kg PO q12h

PO therapy

PO therapy encouraged whenever possible. Most oral antifungal agents recommended above have very good oral bioavailability (>55%) and initiation of IV therapy is not always necessary unless patient is hemodynamically unstable and/or GI absorption cannot 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. There is no need to re-load a patient with PO therapy, but just convert the maintenance therapy.

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 5/25/11
4. Antifungal agents comparisons

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Amphotericin B products</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage forms</strong></td>
<td>IV/PO</td>
<td>PO</td>
<td>IV/PO</td>
<td>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>
<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>? decreased with PPI</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>N/A</td>
<td>N/A</td>
<td>Unknown, expected poor</td>
</tr>
<tr>
<td><strong>Elimination route</strong></td>
<td>Renal</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Unknown</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td>Yes¹</td>
<td>No</td>
<td>No²</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hepatic dose adjustment</strong></td>
<td>No</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>No</td>
<td>No</td>
<td>No⁵</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>GI Hepatotoxicity</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>
<td>+</td>
</tr>
<tr>
<td><strong>Induction/inhibition</strong></td>
<td>Inhibits CYP3A4 and other CYP isoforms</td>
<td>Substrate and inhibitor of CYP3A4</td>
<td>Substrate and inhibitor CYP2C19&gt;CYP2 C9&gt;CYP3A4</td>
<td>Inhibits 3A4</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

1 Fluconazole requires dose adjustment in renal dysfunction. For estimated CrCl <30mL/min or receiving hemodialysis or 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 Caution with use of IV formulation in patients with CrCl <50mL/min as cyclodextrin component accumulates (assessment of risk vs. benefit should be made)
3 Itraconazole has been associated with severe hepatotoxicity, including liver failure and death. Itraconazole use should be carefully monitored in patients with hepatic dysfunction.
4 Voriconazole requires dose adjustment in patients with hepatic dysfunction. For Child-Pugh Class A and B, reduce maintenance dose by ½ following usual loading dose. Use is not recommended in Child-Pugh Class C.
5 Micafungin pharmacokinetic data is unavailable for severe hepatic impairment
5. Cost comparisons of antifungal agents.

### Approximate Antifungal Daily Costs - 2011

<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>$8</td>
<td>400 mg IV q24h</td>
<td>$8</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>$19</td>
<td>200 mg PO q12h</td>
<td>$38</td>
</tr>
<tr>
<td>Voriconazole 200 mg PO</td>
<td>$45</td>
<td>200 mg PO q12h</td>
<td>$90</td>
</tr>
<tr>
<td>Voriconazole 280 mg IV</td>
<td>$184</td>
<td>280 mg IV q12h</td>
<td>$368</td>
</tr>
<tr>
<td>Micafungin 100 mg IV</td>
<td>$98</td>
<td>50 mg IV q24h</td>
<td>$98</td>
</tr>
<tr>
<td>Amphotericin B conventional 70 mg IV</td>
<td>$17</td>
<td>70 mg IV q24h</td>
<td>$17</td>
</tr>
<tr>
<td>Amphotericin B Lipid (Abelcet®)</td>
<td>$305</td>
<td>350 mg IV q24h</td>
<td>$305</td>
</tr>
<tr>
<td>Posaconazole 400 mg PO</td>
<td>$50</td>
<td>400 mg PO q12h</td>
<td>$100</td>
</tr>
</tbody>
</table>

**RESPONSIBILITY:**

Joint Subcommittee on Anti-Infective Use

**POLICY/GUIDELINE DATES:**

- Issued: April 2005
- Reviewed: May 2010
- Revised: May 2011

Medical Board Approval: