Antifungals for Candidiasis and Aspergillosis

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Disclosures

No potential conflicts of interest.
3/3 blood cultures are positive for an unidentified yeast……..

Which is the most appropriate initial empirical therapy in a candidemic patient?

1. An echinocandin
2. Liposomal amphotericin
3. Fluconazole
4. Voriconazole
Changing Prevalence of Candidemia

<table>
<thead>
<tr>
<th></th>
<th>Atlanta</th>
<th>Baltimore</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Non-albicans Candida</td>
<td>48%</td>
<td>60%</td>
</tr>
</tbody>
</table>

*(Clin Infect Dis 2012; 55: 1352)*

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole (% R)</th>
<th>Voriconazole (% R)</th>
<th>Echinocandin (% R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0-0.2%</td>
</tr>
<tr>
<td>(n=1405)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>8.8%</td>
<td>10.5%</td>
<td>1.2-1.8%</td>
</tr>
<tr>
<td>(n=571)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>1.3%</td>
<td>0.3%</td>
<td>0%</td>
</tr>
<tr>
<td>(n=318)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>2.1%</td>
<td>0.2%</td>
<td>0-0.5%</td>
</tr>
<tr>
<td>(n=565)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>NA</td>
<td>1.3%</td>
<td>0%</td>
</tr>
<tr>
<td>(n=79)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Azoles

- Fluconazole (Diflucan®)
- Voriconazole (Vfend®)
- Posaconazole (Noxafil®)
- Isavuconazole (Cresemba®)

Fluconazole vs AMB in the Treatment of Candidemia

- 237 patients enrolled with candidemia
- Successfully treated (14 days after last positive blood culture):
  - AMB: 81/103 (79%)
  - FLU: 72/103 (70%)
- Predominantly *C. albicans*
- Intravascular catheters most frequent source of candidemia
- Less toxicity with fluconazole (and PO administration) than with amphotericin B.
Voriconazole vs Amphotericin followed by Fluconazole for Candidemia

- Non-neutropenic patients with candidemia randomized 2:1 ratio to voriconazole (n=283) or amphotericin followed by fluconazole (n=139)
- Primary efficacy analysis: clinical and mycological response 12 weeks after end of treatment (VOR: 41%; AMB/FLU: 41%)
  (Kullberg et al. Lancet 2005; 366: 1435)

Caspofungin vs Amphotericin for Invasive Candidiasis

- Caspofungin 70 mg loading dose IV, then 50 mg IV daily
- Amphotericin: if not neutropenic, patients were given 0.6-0.7 mg/Kg/D IV; if neutropenic, patients were given 0.7-1.0 mg/Kg/D IV
- Minimum of 10 days of intravenous therapy and 14 days total therapy after most recent positive culture
- Fluconazole 400 mg PO QD after IV therapy (no neutropenia, improved clinical condition, negative cultures for 48hrs, NOT C. glabrata or C. krusei)
Caspofungin vs Amphotericin for Invasive Candidiasis

• Modified intention to treat analysis demonstrated similar efficacy between groups
  – Caspofungin: 73.4%
  – Amphotericin: 61.7%

• Prespecified criteria for evaluation:
  – Caspofungin: 80.7%
  – Amphotericin: 64.9% (p=0.03)

Caspofungin vs Amphotericin for Invasive Candidiasis

• Fever, chills, infusion-related events
  – Caspofungin: 0.9%
  – Amphotericin: 32%

• Nephrotoxicity
  – Caspofungin: 8.4%
  – Amphotericin: 24.8%

• Hypokalemia
  – Caspofungin: 9.9%
  – Amphotericin: 23.4%
Micafungin vs Liposomal Amphotericin

- RCT comparing micafungin 100 mg/D versus liposomal amphotericin 3 mg/Kg/D
- Candidemia and invasive candidiasis
- Treatment success in 89.6% of micafungin-treated patients and 89.5% liposomal amphotericin-treated patients
- Significantly more increases in serum creatinine, back pain, infusion reactions with liposomal amphotericin
  (Lancet 2007; 369: 1519-1527)

Anidulafungin versus Fluconazole for Invasive Candidiasis

- RCT of patients with invasive candidiasis
- Anidulafungin 200 mg on day 1 and 100 mg daily versus fluconazole 800 mg on day 1 and 400 mg daily
- Patients in both groups could be switched to PO fluconazole after 10 days of intravenous therapy
<table>
<thead>
<tr>
<th></th>
<th>Fluconazole (N=118)</th>
<th>Anidulafungin (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of IV therapy</td>
<td>60.2%</td>
<td>75.6%*</td>
</tr>
<tr>
<td>End of all therapy</td>
<td>56.8%</td>
<td>74.0%*</td>
</tr>
<tr>
<td>2 week follow-up</td>
<td>49.2%</td>
<td>64.6%*</td>
</tr>
<tr>
<td>6 week follow-up</td>
<td>44.1%</td>
<td>55.9%</td>
</tr>
</tbody>
</table>


**2016 IDSA Candidemia Practice Guidelines**

- An echinocandin (anidulofungin, caspofungin, micafungin) is recommended as initial therapy
- Fluconazole 800 mg loading dose, then 400 mg daily is an acceptable alternative to an echinocandin in selected patients, including those “who are not critically ill and are considered unlikely to have a fluconazole-resistant Candida species.”
2016 IDSA Candidiasis Practice Guidelines

- Transition from an echinocandin to fluconazole is recommended for patients with isolates susceptible to fluconazole (i.e. \textit{C. albicans})

- Voriconazole offers little advantage over fluconazole for most Candida infection (and is better used for other fungal infections)

Fluconazole-resistant \textit{C. glabrata} and Echinocandin Resistance

<table>
<thead>
<tr>
<th>Dates</th>
<th>Isolates (N)</th>
<th>Drug</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2004</td>
<td>110</td>
<td>Anidulafungin</td>
<td>2 (1.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>Caspofungin</td>
<td>4 (3.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>Micafungin</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2006-2010</td>
<td>162</td>
<td>Anidulafungin</td>
<td>6 (3.7%)</td>
<td>15 (9.3%)</td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>Caspofungin</td>
<td>6 (3.7%)</td>
<td>15 (9.3%)</td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>Micafungin</td>
<td>8 (4.9%)</td>
<td>13 (8.0%)</td>
</tr>
</tbody>
</table>

Risk factors for echinocandin nonsusceptible *C. glabrata*

- Hospitalization in prior 90 days (OR: 1.9)
- Previous candidemia (OR: 2.5)
- Prior echinocandin (OR: 18.9)
- Fluconazole resistance (OR: 6.0)


2016 IDSA Candidiasis Practice Guidelines

- Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant Candida isolates
- Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and infection due to *C. glabrata* or *C. parapsilosis*
What is the optimal therapy of asymptomatic urinary catheter-related funguria due to *C. glabrata*?

1. Fluconazole
2. Voriconazole
3. Caspofungin
4. Amphotericin bladder wash
5. No pharmacological therapy

Candiduria in Renal Transplant Patients

- Case-control study of renal transplant patients over an 8 year period
- 1738 transplants, 192 of whom had 276 episodes of candiduria
- Independent risk factors: female gender, ICU, antibacterial use, indwelling catheter, diabetes, neurogenic bladder, malnutrition

Candiduria in Renal Transplant Patients

• 192 case patients with candiduria (97 treated and 95 not treated)
  – 59/97 (61%): fluconazole
  – 58/97 (60%): amphotericin bladder irrigation
  – 119 cases (62%) had catheter removed within 1 week after diagnosis of candiduria

2016 IDSA Candidiasis Practice Guidelines: Asymptomatic Candiduria

- Elimination of predisposing factors (indwelling urinary catheter)
- Treatment with antifungals **not recommended** unless a patient at “high risk for dissemination”, i.e. “neutropenic patients, very low-birth-weight infants and patients who will undergo urologic manipulation”

Oral fluconazole is the treatment of choice for vaginal candidiasis in pregnant women. True or False?

1. True
2. False
### Oral fluconazole and spontaneous abortion

<table>
<thead>
<tr>
<th></th>
<th>Abortion (FLU)</th>
<th>Total # pregnancies (FLU)</th>
<th>Abortion (Control)</th>
<th>Total # pregnancies (Control)</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole vs topical azole</td>
<td>130</td>
<td>2823</td>
<td>118</td>
<td>2823</td>
<td>1.62 (1.26-2.07)</td>
</tr>
<tr>
<td>Fluconazole vs B-lactam</td>
<td>140</td>
<td>3018</td>
<td>143</td>
<td>3018</td>
<td>1.44 (1.14-1.82)</td>
</tr>
<tr>
<td>Fluconazole during pregnancy vs not</td>
<td>92</td>
<td>2338</td>
<td>107</td>
<td>2338</td>
<td>1.23 (0.93-1.62)</td>
</tr>
</tbody>
</table>

(JAMA 2016; 315: 58-67)

### The treatment of choice for disseminated aspergillosis is which of the following?

1. Lipid-based amphotericin B
2. Echinocandin
3. Voriconazole
4. Posaconazole
5. Isavuconazole
6. Combination voriconazole (or posaconazole or isavuconazole) + echinocandin
Lipid-based Amphotericin

- ABLC (Abelcet®)
- Liposomal amphotericin (Ambisome®)

Both products are less nephrotoxic, but perhaps more hepatotoxic, than conventional amphotericin B. Ambisome is less nephrotoxic than ABLC. Ambisome has less infusion-related side effects compared with ABLC, however 10-15% of patients have muscular, dystonic reaction preventable with diphenhydramine pre-administration and slowing of infusion.
Azoles

- Fluconazole (Diflucan®)
- Voriconazole (Vfend®)
- Posaconazole (Noxafil®)
- Isavuconazole (Cresemba®)

Azoles: Spectrum of activity against moulds and dimorphic fungi

- Voriconazole and posaconazole and isavuconazole are active vs Aspergillus, whereas fluconazole is not.
- Voriconazole and posaconazole and (maybe) isavuconazole have some promise in the treatment of Scedosporium and Fusarium.
- Posaconazole and (maybe) isavuconazole are the most active azoles vs zygomycetes (Absidia, Mucor, Rhizmucor, Rhizopus).
- Animal model suggests amphotericin superior to posaconazole.
Azoles: Pharmacokinetics

- Voriconazole, fluconazole, isavuconazole have an oral bioavailability of >90% and are not affected by increases in gastric pH
- Posaconazole suspension bioavailability is increased 2-4 fold when administered with food

Impact of Food Upon Posaconazole Suspension Oral Bioavailability

Top to bottom: suspension with high-fat meal, tablet with high fat meal, suspension with non-fat meal, suspension fasted

(Br J Pharmacol 2004; 57: 218)
Impact of Food Upon Posaconazole Delayed Release Tablet Oral Bioavailability

Antimicrob Agents Chemother 2015; 59: 3385-9

Posaconazole prescribing errors

• Background: Oral suspension approved in 2006 and delayed release tablet in 2013
• FDA: 11 reports of wrong oral formulation being prescribed: 1 died of stroke associated with aspergillosis (received the suspension, rather than the tablet); others with nausea, vomiting, hypokalemia)
  
  (Medscape Jan 4, 2016)
Azoles: Pharmacokinetics

- Voriconazole and fluconazole, but not posaconazole, achieve therapeutic CSF concentrations.
- Fluconazole and voriconazole have low plasma protein binding, whereas posaconazole and isavuconazole are quite high (>95%).

Azoles: Pharmacokinetics

- Fluconazole is dependent upon the kidney for route of elimination. Normal half-life is approximately 24 hrs, which extends to days in end stage renal disease.
- Voriconazole, posaconazole, isavuconazole are eliminated nonrenally. All are dependent upon CYP 450 3A4, but voriconazole additionally is cleared by CYP2C19, CYP2C9. All produce active metabolites. Voriconazole has considerable metabolic clearance differences due to varying pharmacogenomics (CYP2C19).
Monitoring azole blood levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Efficacy target</th>
<th>Toxicity target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>Lack response, GI dysfunction, co-medication, neurological SEs</td>
<td>Prophylaxis: trough &gt;0.5 mcg/ml</td>
<td>Trough &lt;6 mcg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment: trough &gt;1-2 mcg/ml</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Lack response, GI dysfunction, inability to feed patient, co-medication (particularly PPIs)</td>
<td>Prophylaxis: Trough &gt;0.5 mcg/ml</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment: trough of &gt;0.5-1.5 mcg/ml</td>
<td></td>
</tr>
</tbody>
</table>

(Antimicrob Agents Chemother 2009; 53: 24-34)

Azoles: Adverse effects

- Dose related upper gastrointestinal
- Altered LFTs (particularly voriconazole)
- Visual disturbances (voriconazole)
- Photosensitivity (voriconazole)
- Nephrotoxicity (voriconazole)?
- Alopecia (voriconazole)
- Squamous cell carcinoma (voriconazole)
- Periostitis (voriconazole)
Azoles: drug interactions

- Antacids, H2 blockers, omeprazole do not impact fluconazole or voriconazole bioavailability. However, PPI reduces oral bioavailability of posaconazole.
- Enzyme inducers (rifampin) increase both gut and hepatic metabolism of azoles resulting in reducedazole serum levels.
- Azoles (vori>posa>flu) inhibit cytochrome P 450 system, increasing levels of sirolimus, cyclosporine, tacrolimus, benzodiazepines, glucocorticoids, warfarin.

Voriconazole for Invasive Aspergillosis

- Voriconazole 6mg/Kg/dose Q 12 H IV on day 1, then 4 mg/Kg/dose Q 12 H for at least 7 days, then voriconazole 200 mg PO BID (if patient able to take PO) OR IV amphotericin 1-1.5 mg/Kg/D.
- Patients with intolerance to one therapy could be switched to the other.
Voriconazole for Invasive Aspergillosis: Efficacy

• Week 12: successful outcomes in 52.8% of voriconazole patients (20.8% complete response and 31.9% partial response) versus 31.6% successful outcome in the AMB group (15.0% complete response and 21.2% partial response)

• Survival at 12 weeks: VOR (70.8%) versus AMB (57.9%)


Voriconazole for Invasive Aspergillosis: Safety

• Visual disturbances
  – VOR 44.8%, AMB 4.3%

• Chills and fever
  – VOR 3.1%, AMB 24.9%

• Skin reactions
  – VOR 8.2%, AMB 3.2%

Voriconazole in Renal Dysfunction

- Intravenous voriconazole reconstituted in cyclodextrin, accumulates in renal insufficiency; recommended not to be given intravenously to patients with Clcr< 50 ml/min
- Cyclodextrin is associated with mild kidney toxicity in rats (but none in dogs)
- 166 patients retrospectively evaluated with assessment of risk factors for renal dysfunction:
  - Hematologic malignancy, other drugs (fluconazole, penicillins, fluoroquinolones, immunosuppressants) liver impairment all risk factors for renal dysfunction
  - Intravenous administration of voriconazole not associated with renal dysfunction
    (Clin Infect Dis 2012; 54: 913-21)

Voriconazole and Squamous Cell Carcinoma

- Long term therapy associated with SCC
- France: nationwide call for notification of skin cancers and other lesions in voriconazole-treated patients
- In 14 of 17 SCC patients, a multistep process was observed: acute photosensitivity (6 months) actinic keratosis (30 months), and SCC (≥ 3yrs)
  (Clin Infect Dis 2013; 57: e182-8)
Isavuconazole vs voriconazole for Aspergillosis (and other filamentous fungi)

(Lancet published online Dec 9, 2015)

Treatment-emergent adverse events

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole (n=257)</th>
<th>Voriconazole (n=259)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and SQ tissue disorders</td>
<td>86 (33%)</td>
<td>110 (42%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>39 (15%)</td>
<td>69 (27%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>23 (9%)</td>
<td>42 (16%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

(Lancet published online Dec 9, 2015)
The Role of Combination Therapy in the Treatment of Aspergillosis

Experimental Pulmonary Aspergillosis: Synergy

- Experimental invasive pulmonary aspergillosis in a persistently neutropenic rabbit model
- Micafungin versus ravuconazole versus combination
- Outcome measures: residual fungal burden, survival, pulmonary infarct score, lung weight, CT scores, serum galactomannan index

(J Infect Dis 2003; 187: 1834)
Antifungal Combinations Versus Aspergillus: Clinical Studies

- 47 patients who failed AMB and received either VOR (n=31) or VOR + CASP (n=16) as salvage therapy
- Univariable analysis: Reduced mortality with combination compared with VOR (HR 0.42; 95% CI, 0.17-1.1; p=0.048)
- Multivariable analysis: Reduced mortality with combination compared with VOR (HR 0.28; 95% CI, 0.28-0.92; p=0.011)
  
  (Clin Infect Dis 2004; 39: 797)
**IDSA Recommendations for the Treatment of Invasive Aspergillus**

- Voriconazole 6 mg/kg IV every 12 hrs for 1 day, followed by 4 mg/kg IV every 12 hrs; oral dosage is 200mg every 12 hrs
- Alternatives: lipid-based amphotericin products, caspofungin, posaconazole
- Primary combination therapy is not routinely recommended based on lack of clinical data. “The efficacy of primary combination antifungal therapy requires a prospective, controlled clinical trial to justify this approach.”

  (Clin Infect Dis 2008; 46 Feb 1)

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**Combination versus Monotherapy for Aspergillus**

“Clinical data on combination antifungal therapy for invasive aspergillosis are limited but encouraging… but (these studies) involved a small number of patients, were noncontemporaneous…other host and infection-related factors may have influenced the outcome. A randomized trial comparing voriconazole with voriconazole plus anidulafungin has begun.”

Combination therapy: a critical analysis

• “Several clinical trials have been registered; however, in most cases, their final results have not been made available.”

• “There is an imbalance between the lack of published evidence regarding the benefits of combination therapy and its extensive and increasing use in current clinical practice, despite its associated cost.”


Combination Antifungal Therapy for Invasive Aspergillosis: A Randomized Trial

Combination Antifungal Therapy for Invasive Aspergillosis: A Randomized Trial Combination Therapy for Invasive Aspergillosis

A man in his 50s with history of degenerative lumbar disk disease presented with HA, neck pain worsening over 8 days. Physical exam was notable for meningismus. CSF: protein 147, glucose 31, WBC 2304 (72% polys).

Antibacterials and glucocorticoids were started; steroids were stopped after routine blood cultures returned negative. His symptoms improved and he was discharged home to complete a course of antibacterials.
The patient re-presented 1 week after discharge with HA, low back pain, agitation and incomprehensible speech. CSF: protein 319, glucose 2, WBC 4422 (89% polys).

After treatment with antibacterials, his mental status was markedly improved.

By day 6, he was noted to have increased somnolence, intermittent staring spells and a transient right facial droop. Head CT demonstrated mild hydrocephalus. Empirical liposomal amphotericin was started and the CSF sample from this hospital admission grew *Aspergillus fumigatus*.

Despite optimization of therapy, the patient developed uncontrollable seizures, cerebral and cerebellar infarcts and life support ultimately was discontinued.
Four weeks before his first presentation, the patient had received the latest in a series of epidural injections of methylprednisolone for low back pain (originating from New England Compounding Center).

Fungal Infections Associated with Contaminated Methylprednisolone Injections

- As of Oct 30, 2015, 753 cases in 20 states with an associated 61 (8%) deaths
- Laboratory evidence of *Exserohilum rostratum* in 153 (20%) of case patients and one case of Aspergillus (the index case)
- Of the 78% evaluable patients, 31% had meningitis
- Median age was 64yo and median incubation was 47 days from the last injection
  (Morb Mort Week Rep 2015; 64: 1200-1)
Exserohilum rostratum

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC range</th>
<th>MIC mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>1-4 mcg/ml</td>
<td>1-2 mcg/ml</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>0.03-2 mcg/ml</td>
<td>0.4 mcg/ml</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.5-1 mcg/ml</td>
<td>0.5 mcg/ml</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.25-4 mcg/ml</td>
<td>0.5 mcg/ml</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

(N Engl J Med 2013; 368: 2495)

Treatment of Exserohilum rostratum in the outbreak

• Initial recommendations were combination of high dose lipsomal amphotericin and voriconazole
• Considering the large number of patients with subsequent amphotericin toxicity and identification of Exserohilum as the primary pathogen, the regimen was modified to voriconazole monotherapy

(N Engl J Med 2013; 368: 2495)
Treatment of Exserohilum rostratum

- Voriconazole 6 mg/Kg BID for spine infection/meningitis, 4 mg/Kg BID (other disease) with serum trough levels 2-5 mcg/ml for minimum of 3 months (meningitis) and ≥ 6 months for osteomyelitis
  - IV and PO options; excellent bioavailability
  - Clinical experience with serious mold infection
  - Excellent CSF penetration (50% of serum) achieving levels generally above the MIC
  (N Engl J Med 2013; 368: 2495)