Safety and Efficacy Updates in the Management of Invasive Fungal Infections

Scott J. Bergman, Pharm.D., BCPS (AQ ID), FIDSA
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Session Objectives

- Discuss updated recommendations for the management of candidiasis from the Infectious Diseases Society of America
- Evaluate the recent reports of toxicity associated with commonly used antifungal agents
- Develop a medication regimen that reflects application of best evidence and current guidelines given a description of a specific patient
Disclosure

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Safety and Efficacy Updates in the Management of Invasive Fungal Infections

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Outline - Efficacy

• Invasive Candidiasis
• Invasive Aspergillosis
• Isavuconazole
Introduction - Case

- 55 year old male presents to emergency room
  - Type 2 diabetes for 15 years, on glyburide/metformin,
  - Poor glycemic control, A1C = 10%
  - No recent hospitalizations
- Complaining of chronic abdominal discomfort – diagnosis of presumptive diverticulitis
  - Fever, hypotension, tachypnea
  - Abdomen distended and tender
- Admitted to medical floor
Introduction - Case

- Initiated on broad-spectrum antibiotics, bowel rest prescribed
  - Central line placed, TPN started
- Fever persists, condition deteriorates, transferred to ICU
  - Blood cultures negative
- Abdominal CT: Small abscesses in peritoneal cavity and significant amount of intraperitoneal fluid
  - Blood cultures repeated
- What risk factors does this patient have for invasive fungal infection?
Introduction - Case

- Interventional radiology drains the peritoneal abscess
  - White blood cell count decreases
  - Fever persists
- Gram stain of peritoneal fluid shows a Gram negative rod and budding yeast
  - Germ tube negative
  - Lactose fermenting Gram-negative rod susceptible to original beta-lactam chosen
- IV catheter removed, tip cultured
- What would you recommend now?
Candidiasis

- Over 15 different Candida species exist
- Five account for >90% of bloodstream infections
  - *C. albicans* (37-45%)
  - *C. glabrata* (20-25%)
  - *C. parapsilosis* (13-17%)
  - *C. tropicalis* (8-11%)
  - *C. krusei* (1-2%)

Candidiasis

- Mucosal
  - Oropharynx (thrush)
  - Esophageal
  - Vulvovaginal
- Invasive
  - Intra-abdominal
  - Candidemia
Annual candidemia incidence rates per 100,000 person-years, by year and location, 2008–2013.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0120452
Invasive Candidiasis Practice Guidelines

- 2016 IDSA Update
- Echinocandins are first-line therapy
  - Caspofungin 70mg x1, then 50mg/d
  - Micafungin 100mg daily
  - Anidulafungin 150mg x1, then 100mg/d
- Non-neutropenic patients (strong, high)
- Neutropenic patients (strong, moderate)

Candidiasis Treatment Meta-analysis

Overall Mortality 31.4%

Improved survival (OR)
- Removal of central venous catheter (0.5)
- Echinochandhin treatment (0.65)

Predict treatment failure
- Increasing age (1.01)
- APACHE II score (1.11)
- Immunosuppresive therapy (1.69)
- *Candida tropicalis* (1.64)

Fluconazole

- Acceptable alternative
  - 800mg (12mg/kg) x 1, then 400mg (6mg/kg) IV/PO daily
  - If not critically ill and considered unlikely to have resistance (strong, high)
- Testing for azole susceptibility is recommended for all bloodstream and other clinically-relevant isolates
  - Rapid identification of species is important

C. glabrata Resistance

- Fluconazole
  - 18% → 30% between 2001 and 2010
  - 14% of these also echinocandin resistant

- Echinocandins
  - 4.9% → 12.3% prevalence
  - FKS mutant
    - 8/10 treated, failed or relapsed
  - Risk factor: prior echinocandin therapy
    - Odds ratio 19.65

Proportion of cases with *Candida glabrata* isolates non-susceptible to echinocandins, by surveillance site and year, 2008–2014

Echinocandin Resistance

- Testing should be considered
- Patients who have had prior treatment with an echinocandin or have *C. glabrata* or *C. parapsilosis*
  - Strong recommendation, low evidence
- *C. parapsilosis* naturally has higher MICs
  - Outcomes are similar between therapies

Overall Resistance

- 7% Fluconazole
- 2% Echinocandin
- 1% multiple drugs

- Amphotericin B lipid formulation 3-5 mg/kg/d

Invasive Aspergillosis
Invasive Aspergillosis Practice Guidelines

- Triazoles are 1st line therapies (strong rec, high evidence)
- Treatment: Voriconazole 6mg/kg IV q12h x 2 doses, then 4mg/kg q12h before switch to oral 200-300mg BID
- Prevention: Posaconazole
- Therapeutic drug monitoring is advised
  - Strong recommendation, moderate evidence
- Antifungal susceptibility testing is not required
  - Reserve for treatment failure or if resistance suspected

Combination Therapy

- Preclinical studies and laboratory testing promising
  - Azoles or polyenes and echinocandins
  - Synergistic or additive effects, but conflicting results
  - Weak recommendation, low-quality evidence
- Voriconazole plus an echinocandin can be considered
  - Weak recommendation, moderate evidence
  - Probable IA mortality 15.7% vs. 27.3%, overall NS
  - Combination AE’s 12.7% vs. 8.4% monotherapy

Alternatives

- **Primary therapy:**
  - Liposomal Amphotericin B 3-5 IV mg/kg/d
  - Isavuconazole IV/PO 200mg q8h x 6, then 200mg/d

- **Salvage therapy:**
  - Amphotericin B Lipid Complex 5mg/kg/d
  - Caspofungin 70mg/d, then 50mg/d
  - Micafungin 100-150mg/d IV
  - Posaconazole 300mg q12h x2, then 300mg/d IV/po XR
  - Itraconazole suspension 200mg po BID

Isavuconazole
Isavuconazonium (Cresemba)

- Azole antifungal prodrug
  - Isavuconazonium sulfate $\rightarrow$ isavuconazole
- FDA indications: invasive aspergillosis & mucormycosis, 2015
- IV = PO
- Load: 372mg (200mg) q8h x 6 doses
- Maintenance: 372mg (200mg) daily
Aspergillosis – SECURE Trial

- Phase 3, randomized, double-blind, controlled, multi-center, noninferiority trial
- Isavuconazole vs. voriconazole in patients with proven, probable, or possible invasive mold disease caused by *Aspergillus* spp. or other filamentous fungi
  - In patients with proven or probable disease, *Aspergillus* spp. were isolated in ~33% of cases
    - *A. fumigatus* most common

Maertens JA et al. Lancet. 2016 (Feb);387:760-769.
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline risk factor in ITT population</th>
<th>Isavuconazole N=258 n(%)</th>
<th>Voriconazole N=258 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>211 (82)</td>
<td>222 (86)</td>
</tr>
<tr>
<td>Allogeneic hematopoietic stem cell transplant (HSCT)</td>
<td>54 (21)</td>
<td>51 (20)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>163 (63)</td>
<td>175 (68)</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>48 (19)</td>
<td>39 (15)</td>
</tr>
<tr>
<td>T-cell immunosuppressant use</td>
<td>111 (43)</td>
<td>109 (42)</td>
</tr>
</tbody>
</table>

Maertens JA et al. Lancet. 2016 (Feb);387:760-769.
Results

- Primary efficacy endpoint: all-cause mortality at day 42 in intention-to-treat population
  - Isavuconazole: 258 patients, 19%
  - Voriconazole: 258 patients, 20%

- Secondary endpoint: overall response in patients with proven or probable disease, determined by data review committee
  - Isavuconazole: 143 patients, 35%
  - Voriconazole: 129 patients, 36%

Maertens JA et al. Lancet. 2016 (Feb);387:760-769.
Results

## Safety

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Isavuconazole</th>
<th>Voriconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>96%</td>
<td>98%</td>
<td>0.122</td>
</tr>
<tr>
<td>Skin</td>
<td>33%</td>
<td>42%</td>
<td>0.037</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>27%</td>
<td>33%</td>
<td>0.151</td>
</tr>
<tr>
<td>Ocular</td>
<td>15%</td>
<td>27%</td>
<td>0.002</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>9%</td>
<td>16%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Mucormycosis – VITAL trial

- Phase 3, open-label, non-comparative trial
  - 34 sites worldwide
- 37 patients with proven or probable mucormycosis, most pulmonary
  - Primary therapy
  - Refractory to prior antifungal therapy
  - Intolerance to prior antifungal therapy

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline risk factors in Mucorales patients</th>
<th>Primary N=21 n(%)</th>
<th>Refractory N=11 n(%)</th>
<th>Intolerant N=5 n(%)</th>
<th>Total N=37 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy</td>
<td>11 (52)</td>
<td>7 (64)</td>
<td>4 (80)</td>
<td>22 (60)</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>4 (19)</td>
<td>4 (36)</td>
<td>5 (100)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (19)</td>
<td>5 (46)</td>
<td>1 (20)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>5 (24)</td>
<td>3 (27)</td>
<td>2 (40)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>T-cell immunosuppressant use</td>
<td>7 (33)</td>
<td>6 (55)</td>
<td>5 (100)</td>
<td>18 (49)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (19)</td>
<td>0</td>
<td>0</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Primary Outcome

Case-control analysis

- Compared to amphotericin B historical matched controls
  - FungiScope registry, primary therapy
  - Severe-CNS/disseminated, hematologic malignancy, surgery within 7 days
  - Mortality: 7/21 (33%) Isavu vs. 13/33 (39%) AmB

- AmBizygo trial = 10mg/kg/d Liposomal Ampho B
  - Similar mortality (38% at 12 weeks)
  - 40% substantial nephrotoxicity

Safety

- 24/37 (65%) discontinued therapy (n)
- Death (11)
- Adverse events (6)
- Non-compliance (4)
- Insufficient response (2)
- Investigator’s choice (1)
Adverse events

- Relapse of progression of malignancy (2)
- Acute liver injury (2)
- Nausea (1)
- *E. coli* bacteremia (1)

- No QT prolongation
Conclusion

- Isavuconazole is effective for invasive aspergillosis and mucormycosis
- Appears safer than comparator agents
- Expensive
Case Revisited

- 55 year old male patient with diabetes
- In ICU from diverticulitis
- On broad-spectrum antibiotics and TPN
- Yeast growing from peritoneal fluid
- Suspect candidemia
- Empiric antifungal therapy needed
Treatment for Invasive Candidiasis

A. Amphotericin B, Liposomal formulation
B. Fluconazole
C. Micafungin
D. Voriconazole
Take away points

- Echinocandins are first-line therapy for candidemia
- Antifungal resistance is on the rise
  - Check with your lab about testing
  - Especially *C. glabrata*
- Invasive aspergillosis treatment/guideline updated
- Isavuconazole is a new option to consider for rare molds
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Safety and Efficacy Updates in the Management of Invasive Fungal Infections

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Self-Reflection Question: Globally, antifungals are associated most frequently with toxicity of which of the following systems?

A. Cardiac  
B. Hepatic  
C. Neuro  
D. Renal
Patient Case: A patient with history of cirrhosis and chronic kidney disease stage 3 presents with disseminated candidiasis with Candida glabrata (susceptibilities pending). Which antifungal would you recommend?

A. Fluconazole
B. Caspofungin
C. Liposomal Amphotericin B
D. Voriconazole
Outline - Safety

- Common Systemic Antifungals
- Newer Reports
  - Cardiac Toxicity
  - Hepatotoxicity
  - Neurotoxicity
  - Renal Toxicity
Common Systemic Antifungals

- Polyenes
  - Amphotericin

- Echinocandins
  - Anidulafungin
  - Caspofungin
  - Micafungin

- Azoles
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
  - Isavuconazole
Polyenes Adverse Reactions

- Infusion-related reactions
  - Better with lipid formulations
    - (ABCD>C-Amb B>ABLC>L-AmB)
  - Pre-treatment helps (acetaminophen, steroids)

- Nephrotoxicity
  - Renal tubular acidosis
  - Azotemia
  - Possibly better with lipid formulations

- Electrolyte changes
  - Hypokalemia, hypomagnesemia
  - Potential for arrhythmias

- Anemia

Common Adverse Reactions

- **Azoles**
  - Hepatotoxicity
  - QT prolongation
  - Teratogenic in animals

- **Echinocandins**
  - Infusion-site reactions
  - Histamine reactions
    - Rapid infusion
Recent Toxicity Reports: Cardiac
Self-Reflection Question:
Antifungals are associated most frequently with which cardiac toxicity?

A. Arrhythmia
B. Changes in contractility
C. Heart failure
### Cardiac Toxicity History

<table>
<thead>
<tr>
<th>Proposed Mechanism</th>
<th>Author</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLT causes vasodilation</td>
<td>Tofukuji</td>
<td>J Surg Res 1998</td>
</tr>
<tr>
<td>CLT inhibits calcium channels</td>
<td>Fearon</td>
<td>Br J Pharmacol 2000</td>
</tr>
<tr>
<td>CLT decreases potassium</td>
<td>Tian</td>
<td>Br J Pharmacol 2006</td>
</tr>
<tr>
<td>Econazole inhibits contractions</td>
<td>Tunctan</td>
<td>Life Sciences 2000</td>
</tr>
<tr>
<td>ITZ causes CHF</td>
<td>Ahmad</td>
<td>Lancet 2001</td>
</tr>
<tr>
<td>VCZ causes Torsades de pointes</td>
<td>Philips</td>
<td>Transplant Infect Dis 2007</td>
</tr>
<tr>
<td>AmB overdose &amp; cardiac arrest</td>
<td>Cleary</td>
<td>Ann Pharmacother 1993</td>
</tr>
<tr>
<td>AmB causes dilated CM</td>
<td>Danaher</td>
<td>J Antimicrob Chemother 2004</td>
</tr>
</tbody>
</table>

CLT: clotrimazole; ITZ: itraconazole; VCZ: voriconazole; AmB: amphotericin B
CHF: congestive heart failure; CM: cardiomyopathy
Newer Reports- Azoles: Arrhythmias

- **Fluconazole**
  - QT prolongation
  - Torsades de pointes
- **Posaconazole**
  - QT prolongation and cardiac arrest with previous risk factors
- **Voriconazole**
  - Torsades de pointes
    - 5 adult and 3 pediatric cases since 2004
    - Most recent: prolonged QT resulting in TdP
  - Bradycardia

Newer Reports- Azoles: Contractility

- Itraconazole
  - Decreases left ventricular contractility
  - Negative inotropic effect
    - Proposed mechanism: direct heart effect

- In animal studies: fluconazole, voriconazole not associated with changes in contractility

Newer Reports- Echinocandins: Arrhythmias

- **Caspofungin**
  - Patient with AML, no past history of cardiac disease
  - Complete heart block and cardiac arrest after first dose
  - Possibly histamine-mediated?

- **Micafungin**
  - Patient with paroxysmal atrial fibrillation, systolic heart failure, peripheral vascular disease, diabetes, hypertension
  - On amiodarone and fluconazole: ventricular fibrillation
  - Switched to micafungin: polymorphic ventricular tachycardia

**Newer Reports- Echinocandins: Contractility**

*Ex vivo* Animal Studies: dose range

- Caspofungin and anidulafungin associated with decreased left ventricular contractility
  - Caspofungin: reversible; mean decrease 40.6±15.6%
  - Anidulafungin: irreversible; mean decrease 77.1±9.4%
- No changes with micafungin

*In vivo* Animal Studies: two clinically relevant doses

- Caspofungin: mean decrease in cardiac output 62.6±13.0%
- Anidulafungin: mean decrease in cardiac output 62.7±19.4%
- No significant change with micafungin (CO: 18% decrease, p = NS)

Newer Reports- Echinocandins: Contractility

- Anidulafungin
  - Flash pulmonary edema
    - Coughing + shortness of breath/chest tightness
  - Severe hemodynamic instability during administration
    - Hypotension, bradycardia
  - Decreased cardiac index (2 to 1.6 L/min/m²)
    - Decreased MAP despite vasopressor support
  - Decreased cardiac index (3.5 to 2.1 L/min/m²)

- Caspofungin
  - Decreased cardiac index (3.2 to 2.7 L/min/m²)

Newer Reports- Echinocandins: Contractility

- Prospective analysis of medical ICU patients receiving antifungals
  - 12 caspofungin
  - 3 anidulafungin
- Monitored using transpulmonary thermodilution
  - Systolic, diastolic, mean arterial, and central venous pressure, HR
- MAP ($p < 0.042$) and DBP ($p < 0.007$) significantly decreased immediately after infusion
  - Not significantly different from baseline at 4 hours

Newer Reports- Echinocandins: Contractility

Micafungin?

- No case reports to date
- Some evidence that it may be safe even at high doses
  - Max tolerated doses in stem cell transplantation
    - 3-8 mg/kg/day from 7-28 days around transplant
    - All 36 patients received at least 8 days (median: 18 days)
    - No patients had Grade 3 or 4 adverse effects

Sirohi B. Bone Marrow Transpl 2006;38:47-51.
Recent Toxicity Reports: Hepatic
Newer Reports - Polyenes

Amphotericin B deoxycholate

- Acute hepatic injury following administration
- Patient had previous hepatic injury but was resolved at time of administration

Newer Reports- Azoles

- Oral azoles and association with liver injury
  - Low for fluconazole, ketoconazole, itraconazole
    - 13; 19.3; 24.5/100 person-years, respectively
  - Higher for voriconazole, posaconazole
    - 181.9; 191.1/100 person-years, respectively
  - Higher association with pre-existing liver disease

- Drug-induced liver injury
  - 2.9% of all reports to AERS are antimycotics
  - 1964 cases, 112 liver failure
  - Keto, vori, posaconazole: disproportionally high incidence

Newer Reports- Azoles

- Hepatotoxicity in rats:
  - Fluconazole: No significant increases in transaminases
    - Mild degenerative changes on histology
  - Itraconazole: Statistically significant difference in ALT/AST
    - Hepatocellular necrosis, degeneration of hepatocytes, biliary cirrhosis histologically

- Voriconazole
  - 63 adults in ICU
  - Increased trough = increased hepatotoxicity
  - Significant difference with trough > 4 vs. < 4 mg/L

Newer Reports- Echinocandins

- Caspofungin vs. azoles and liver injury
  - 9.3% of caspofungin users had increased enzymes
    - No discontinuation of drug
    - Vs. 2% of fluc-; 19.7% of vori-; 17.4% of itraconazole

- Caspofungin vs. anidulafungin with liver dysfunction
  - On concomitant hepatotoxins
  - Switched from caspofungin to anidulafungin
    - Significantly decreased AST/ALT
    - 70% with favorable changes

Newer Reports- Echinocandins

- Micafungin use in pre-existing liver dysfunction: 12 patients
  - Liver function stable or improved in all patients except one

- Micafungin and liver injury vs. other parenteral antifungals
  - 2970 mica recipients vs. 6726 other
  - Hepatic injury rates similar
    - Defined as changes in liver enzymes
    - Mica: 13/100 patients; others: 12/100 patients

Recent Toxicity Reports: Neuro
Newer Reports- Azoles

- Fluconazole and paroxetine combination
  - Found to be neuroprotective despite neuroinflammation

- Itraconazole and vinca alkaloids
  - Neurotoxicity seen with vinca alkaloids
    - Constipation, paralytic ileus
  - Neurotoxicity enhanced by addition of itraconazole

- Posaconazole + vincristine
  - Life-threatening neurotoxicity in a child with ALL

Newer Reports- Azoles

- **Voriconazole**
  - Photosensitivity (UVA) and skin carcinogenesis
  - Case of phototoxicity, pseudoporphyria, photo-onycholysis
  - Psychosis in a patient with AML and febrile neutropenia
  - Hallucinations

Recent Toxicity Reports: Renal
Newer Reports- Azoles

- Voriconazole
  - Safety/tolerability with baseline renal insufficiency
    - 39% worsening renal function with voriconazole
    - Compared to 53% with amphotericin/fluconazole
    - 14 week all-cause mortality: 49% Vori vs. 65% AmB
  - Safety of IV formulation with renal impairment
    - No difference in proportion of troughs in target range between CrCl< 50 and controls
    - No significant decrease in renal function after vori
  - Systematic review found no strong evidence of renal toxicity due to IV voriconazole

Newer Reports- Echinocandins

- Micafungin and renal injury vs. other parenteral antifungals
  - 2970 mica recipients vs. 6726 other
  - Renal injury rates lower with micafungin
    - Defined as changes in GFR
    - Mica: 63/100 patients; others: 65/100 patients
    - HR = 0.93 (CI: 0.87-0.99)

Recent Toxicity Reports: Miscellaneous
Miscellaneous Reports

- Isavuconazole
  - FDA approved in 2015
  - No cardiac, renal, hepatic, neuro adverse effects reported
  - SECURE Trial
    - ADEs similar to voriconazole
    - Similar GI effects, infections reported, administrative site conditions
    - Fewer skin disorders (rash, erythema, drug eruption), cardiac disorders, eye disorders, hepatobiliary disorders

Patient Case: A patient with history of cirrhosis and chronic kidney disease stage 3 presents with disseminated candidiasis with Candida glabrata (susceptibilities pending). Which antifungal would you recommend?

A. Fluconazole
B. Caspofungin
C. Liposomal Amphotericin B
D. Voriconazole
Key Takeaways

- No antifungal is completely “safe”
- Three primary classes (polyenes, azoles, echinocandins) have adverse effects in varying systems within the body
  - Cardiac effects are shared by all three classes
  - Hepatic effects are most common with the azoles, but can occur in the other classes, too
  - Neuro effects are most common with the azoles, particularly voriconazole
  - Renal effects are most common with amphotericin, but probably are not as severe as believed with voriconazole
- It is important to be familiar with the known (and lesser-known) adverse effects
  - May impact agent selection and monitoring
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