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Safety and Efficacy Updates in the Management of Invasive Fungal Infections

Scott J. Bergman, Pharm.D., BCPS (AQ ID), FIDSA
Kayla R. Stover, Pharm.D., BCPS (AQ ID)

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

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

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Safety and Efficacy Updates in the Management of Invasive Fungal Infections

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University of Nebraska Medical Center, College of Pharmacy

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

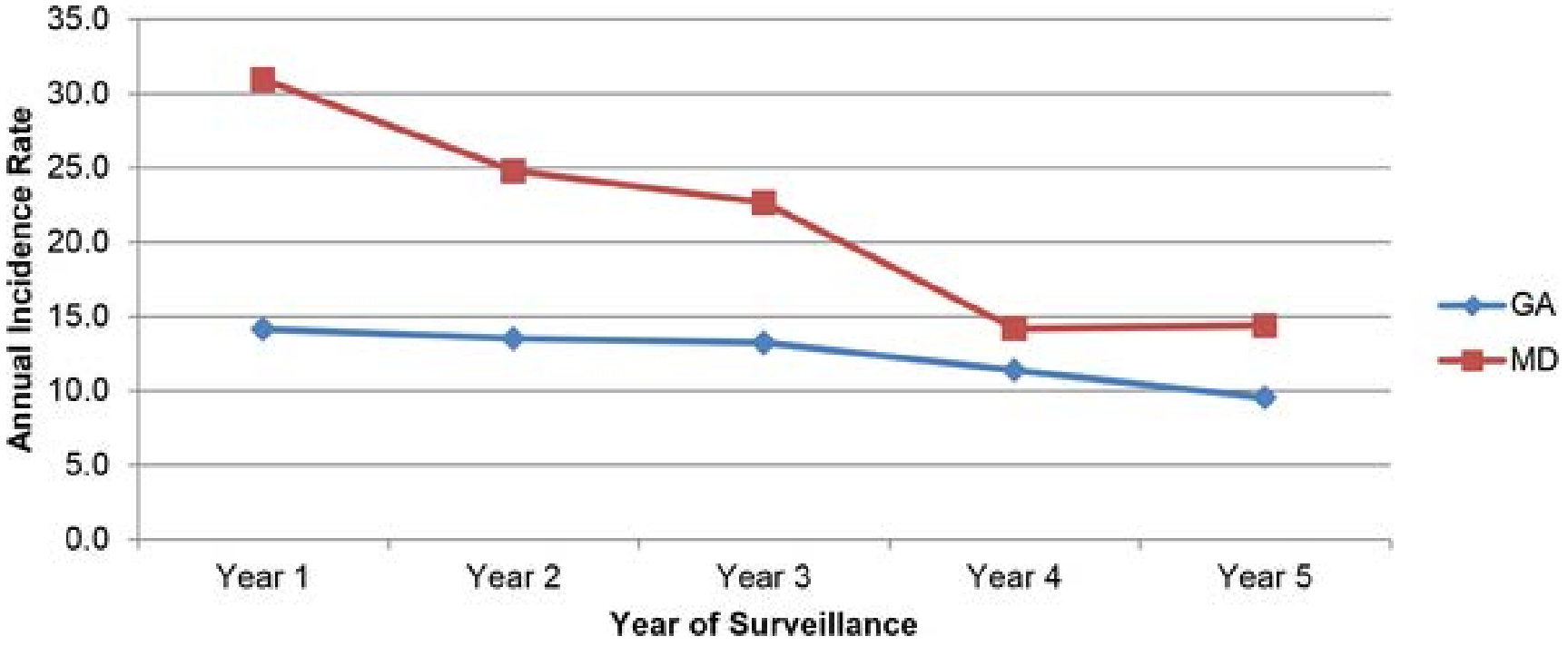
- Over 15 different Candida species exist
- Five account for >90% of bloodstream infections
  - *C. albicans* (37-45%)
  - *C. glabrata* (20-25%)
  - *C. parapsilosis* (13-17%)
  - *C. tropicalis* (8-11%)
  - *C. krusei* (1-2%)

Cleveland AA, et al. PLOS One. 2015; 10(3): e0120452.

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.



Cleveland AA, Harrison LH, Farley MM, Hollick R, Stein B, et al. (2015) Declining Incidence of Candidemia and the Shifting Epidemiology of Candida Resistance in Two US Metropolitan Areas, 2008–2013: Results from Population-Based Surveillance. PLoS ONE 10(3): e0120452. doi:10.1371/journal.pone.0120452 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)

Pappas, et al. Clin Infect Dis. 2016; 62 (4) e1-e50.

Candidiasis Treatment Meta-analysis

Overall Mortality 31.4%

Improved survival (OR)

- Removal of central venous catheter (0.5)
- Echinochandin treatment (0.65)

Predict treatment failure

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

Andes DR, et al. Clin Infect Dis. 2012; 54 (8) 1110-1122.

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 <u>all bloodstream</u> and other clinically-relevant isolates
  - Rapid identification of species is important

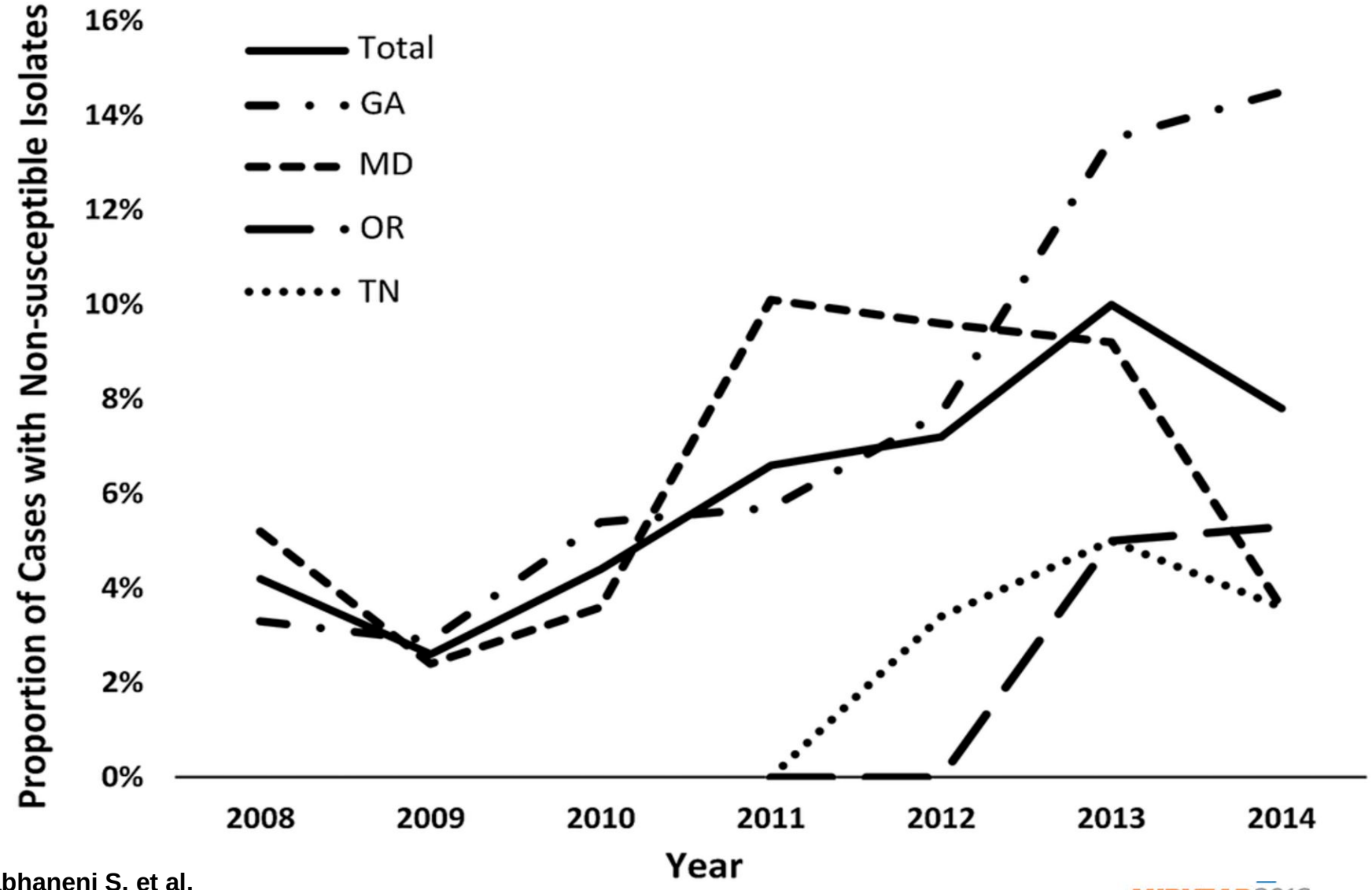
Pappas, et al. Clin Infect Dis. 2016; 62 (4) e1-e50.

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

Alexander BD, et al. Clin Infect Dis. 2013; 56: 1724-32

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



Vallabhaneni S, et al.
Open Forum Infect Dis 2015;2:ofv163

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

Pappas P, et al. Clin Infect Dis. 2016; 62 (4) e1-e50.
Chiotos K, et al. J Antimicrob Chemother. 2016; ahead of print

Overall Resistance

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

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

Cleveland AA, et al. PLOS One. 2015; 10(3): e0120452.

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

Patterson TF, et al. Clin Infect Dis. 2016; ahead of print

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

Patterson TF, et al. Clin Infect Dis. 2016; ahead of print
Marr KA, et al. Ann Int Med. 2015; 162: 81-89

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

Patterson TF, et al. Clin Infect Dis. 2016; ahead of print

Isavuconazole

Isavuconazonium (Cresemba)

- Azole antifungal prodrug
  - Isavuconazonium sulfate → 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

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

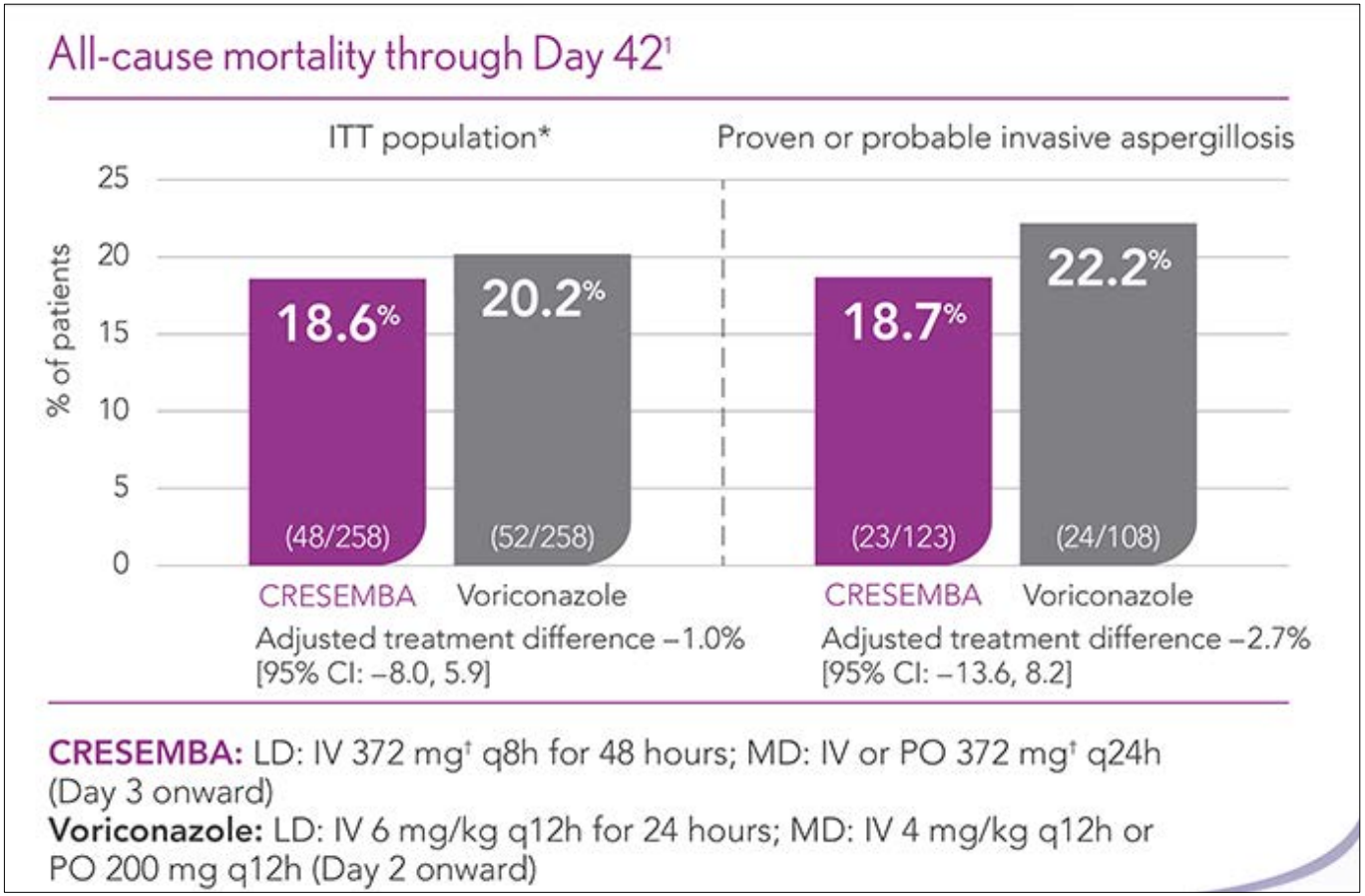
Maertens JA et al. Lancet. 2016 (Feb);387:760-769.

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



Prescribing Information [Cresemba]. Astellas. Northbrook, IL. https://www.cresemba.com/invasive-aspergillosis 2016.

Safety

Disorder	Isavuconazole	Voriconazole	P value
Gastrointestinal	96%	98%	0.122
Skin	33%	42%	0.037
Psychiatric	27%	33%	0.151
Ocular	15%	27%	0.002
Hepatobiliary	9%	16%	0.016

Maertens JA et al. Lancet. 2016;387:760-769.

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

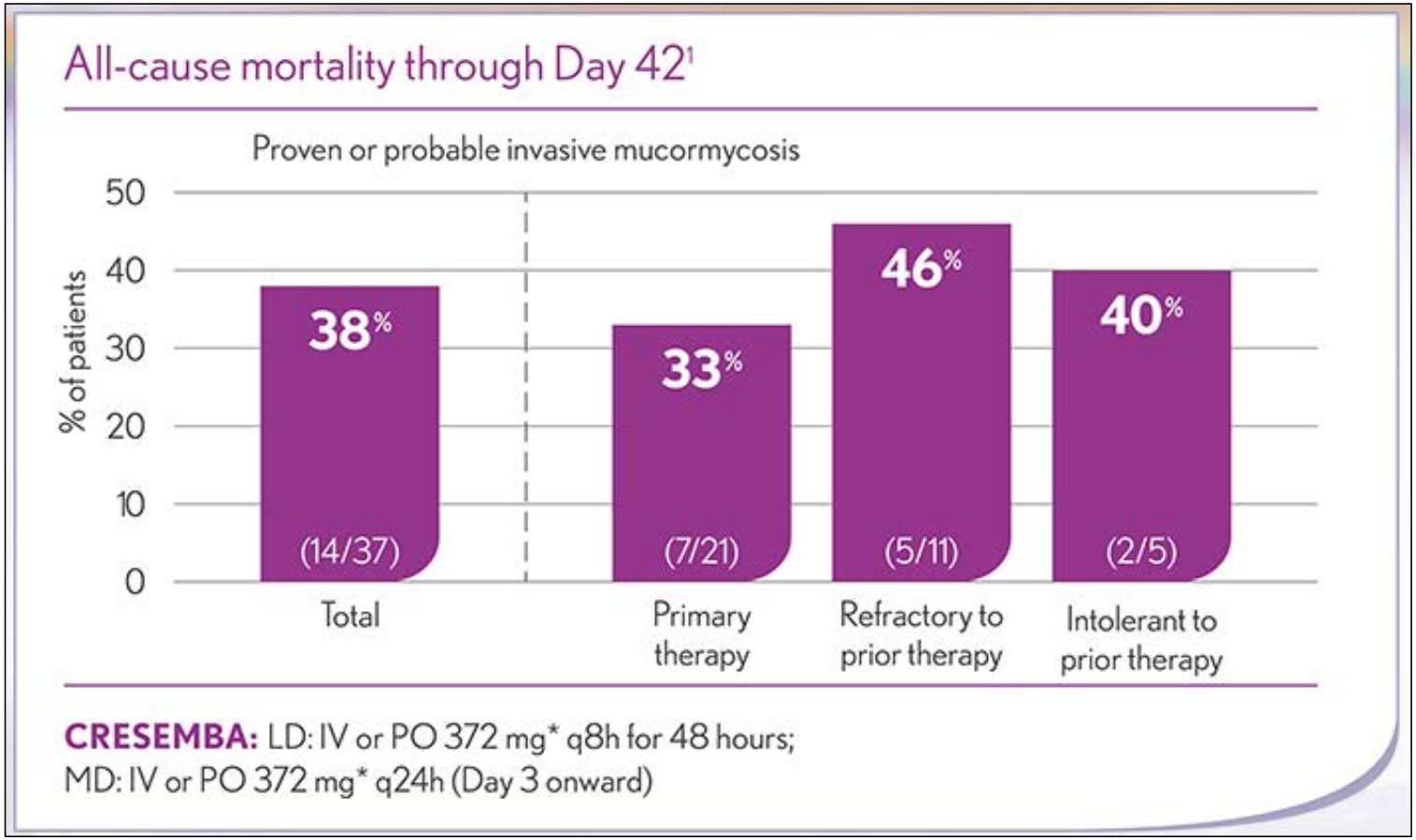
Marty FM, et al. Lancet Infect Dis. 2016 (July);16:828-37

Baseline Characteristics

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

Marty FM, et al. Lancet Infect Dis. 2016 (July);16:828-37

Primary Outcome



Prescribing Information [Cresemba]. Astellas. Northbrook, IL. https://www.cresemba.com/invasive-mucormysosis. 2016.

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

Marty FM, et al. Lancet Infect Dis. 2016 (July);16:828-37
Lanternier J, et al. J Antimicrob Chemother 2015.

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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Safety and Efficacy Updates in the Management of Invasive Fungal Infections

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Associate Professor of Pharmacy Practice
University of Mississippi School of Pharmacy

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

Botero Aguirre. Cochrane Database Syst Rev. 2015;11:CD010481.
Bicanic T. Antimicrob Agents Chemother. 2015;59(12):7224-31.
Oude Lashof AM. Antimicrob Agents Chemother. 2012;56(6):3133-7.

Common Adverse Reactions

- Azoles
  - Hepatotoxicity
  - QT prolongation
  - Teratogenic in animals
- Echinocandins
  - Infusion-site reactions
  - Histamine reactions
    - Rapid infusion

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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

Proposed Mechanism	Author	Citation
CLT causes vasodilation	Tofukuji	J Surg Res 1998
CLT inhibits calcium channels	Fearon	Br J Pharmacol 2000
CLT decreases potassium	Tian	Br J Pharmacol 2006
Econazole inhibits contractions	Tunctan	Life Sciences 2000
ITZ causes CHF	Ahmad	Lancet 2001
VCZ causes Torsades de pointes	Philips	Transplant Infect Dis 2007
AmB overdose & cardiac arrest	Cleary	Ann Pharmacother 1993
AmB causes dilated CM	Danaher	J Antimicrob Chemother 2004
AmB causes hyperK & cardiac arrest	Groot	Neth J Med 2009

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

Pham CP. Ann Pharmacother. 2006;40(7-8):1456-61.
Tatetsu H. Am J Hematol. 2006;81(5):366-9.
Panos G. Am J Case Rep 2016;17:295-300.
Brown JD. Med Mycol Case Rep. 2014;4:23-5.
Frommeyer G. Eur J Pharmacol. 2016;776:185-90.
Uludag D. Ped Hematol Oncol. 2013;30:674-6.

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

Qu Y. Toxicol Applied Pharmacol. 2013;268:113-122.
Cleary JD. Pharmacol Pharm. 2013;4:362-8.

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

Biswal S. J Pharmacol Pharmacother 2012;3(4):342-4.
Shah PJ. J Clin Pharm Ther 2016; 41(3):362-4.

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)

Cleary JD. Clin Infect Dis 2015;61(S6):S662-8.
Stover KR. Expert Opin Drug Saf 2013;13:5-14.
Stover KR. J Pharm Pharmacol 2015;67:1279-83.

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)

Hindahl CB. J Clin Pharm Ther 2012;37:491-3.
Fink M. J Clin Pharm Ther 2013;38:241-2.
Lichtenstern C. J Clin Pharm Ther 2013;38:429-31.
Stover KR. J Clin Pharm Ther 2014;39:1-3.

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

Lahmer T. Infection 2015;43:723-7.

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.

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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

Wagner JL. J Pharmacol Pharmacother 2016;7(2):112-4.

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

Lo Re V 3rd. Am J Med 2016;129(3):283-91.
Raschi E. World J Hepatol 2014;6(8):601-12.

Newer Reports- Azoles

- Hepatotoxicity in rats:
  - Fluconazole: No significant increases in transaminases
    - Mild degenerative changes on histology
  - Itraconazole: Statistically sign 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

Somchit N. Hum Exp Toxicol. 2004;23(11):519-25.
Wang Y. Pharmacother. 2016;36(7):757-65.

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

Wang JL. Antimicrob Agents Chemother 2010;54(6):2409-19.
Jung DS. J Antimicrob Chemother 2015;70(11):3100-6.

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

Luque S. Enferm Infecc Microbiol Clin. 2015 Apr 13.
Schneeweiss S. J Antimicrob Chemother 2016;71(10):2938-44.

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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

Meulendyke JA. J Neurovirol 2014;20(6):591-602.
Osato Y. Gan To Kagaku Ryoho 2011;38(10):1667-72.
Jain S. Ped Blood Cancer 2010;54(5):783.

Newer Reports- Azoles

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

Haylett AK. Br J Dermatol 2013;168(1):179-85.
Willis ZL. J Pediatric Infect Dis Soc 2015;4(2):e22-4.
Singh H. Indian J Pharmacol 2015;47(3):332-3.
Pea F. Ther Drug Monitor 2009;31(1):135-6.

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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

Oude Lashof AM. Antimicrob Agents Chemother 2012;56(6):3133-7.
Kim SH. Mycoses 2016;59(10):644-51.
Turner RB. Int J Antimicrob Agents 2015;46(4):362-6.

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)

Schneeweiss S. J Antimicrob Chemother 2016;71(10):2938-44.

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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

Maertens JA. Lancet 2016;387:760-9.

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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