Overcoming Challenges in the Management of Invasive Fungal Infections

This session is supported by an educational grant from Astellas.

Faculty

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Faculty Disclosure

Dr. Lewis: Consultant—Accelerate Diagnostics, Allergan, Astellas, The Medicines Company, Merck & Co., Inc.

Learning Objectives

- Describe the current challenges associated with the management of IFI
- Compare clinical data of available antifungal therapies, including differences in the spectrum of activity, mechanisms-of-action, PK and PD, tissue penetration, and adverse effects
- Implement timely and informed clinical decisions that incorporate the latest evidence with respect to prophylactic, empiric, preemptive, and targeted antifungal treatment
- Lead the healthcare team in ensuring appropriate IFI treatment monitoring and modification, medication reconciliation, and prevention of drug toxicities and interactions

IFI = invasive fungal infection; PK = pharmacokinetics; PD = pharmacodynamics.

Patient Case

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Receiving piperacillin-tazobactam and vancomycin
- Doing well in the surgical intensive care unit until hospital day 5
- Increasing fevers, increasing white blood cell counts
- Abdominal imaging suggests a new fluid collection
- What organisms are you concerned about?

Pathogens Associated with Healthcare-Associated Infections

Pathogen	All Healthcare-Associated Infections (N=504) No. (%)	Pneumonia (N=110)	Surgical Site Infections (N=110)	Gastrointestinal Infections (N=86)	Urinary Tract Infections (N=65)	Bloodstream Infections (N=50)
Clostridium difficile	61 (12.1)	0	0	61 (70.9)	0	0
Staphylococcus aureus	54 (10.7)	18 (16)	17 (16)	1 (1)	2 (3)	7 (14)
Klebsiella pneumoniae or Klebsiella oxytoca	50 (9.9)	13 (12)	15 (14)	1 (1)	15 (23)	4 (8)
Escherichia coli	47 (9.3)	3 (3)	14 (13)	1 (1)	18 (28)	5 (10)
Enterococcus species	44 (8.7)	2 (2)	16 (15)	5 (6)	11 (17)	6 (12)
Pseudomonas aeruginosa	36 (7.1)	14 (13)	7 (6)	1 (1)	7 (11)	2 (4)
Candida species	32 (6.3)	4 (4)	3 (3)	3 (4)	3 (5)	11 (22)

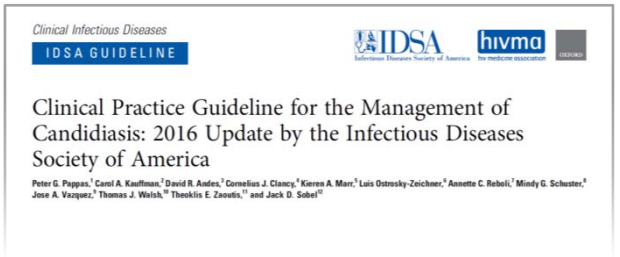
Magill SS, et al. *N Engl J Med.* 2014;370:1198.

The Impact of Candidemia

- Fourth most common bloodstream isolate
- Leading fungal pathogen in US hospitals
- 14.5% attributable increase in mortality in adults
- 10.1-day increased length of stay
- Approximately $60,000 increase in hospital charges

Zaoutis TE, et al. *Clin Infect Dis.* 2005;41(9):1232-1239. Weinberger M, et al. *J Hosp Infection.* 2005;61(2):146-154. Bilir SP, et al. *Future Microbiol.* 2015;10:1133-1144. Moran C, et al. *Am J Infect Control.* 2010;38:78-80.

New Guidelines


Clinical Infectious Diseases

IDSA GUIDELINE

IDSA hivma

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

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

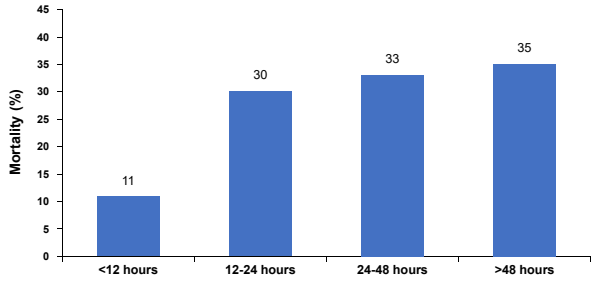
Invasive Candidiasis: Who Is at Risk?

Risk Factors
Central venous catheters
Candida species colonization
Increasing severity of illness
Exposure to broad-spectrum antibiotics
Recent major surgery, especially abdominal
Necrotizing pancreatitis
Hemodialysis
Parenteral nutrition
Corticosteroids

- A subset of postsurgical patients may be at uniquely high risk of candidiasis
  - Recurrent gastrointestinal perforation
  - Anastomotic leaks
  - Acute necrotizing pancreatitis

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

Candidemia: Time to Initiation of Therapy and Mortality



Is your team thinking about *Candida* species in high-risk patients?

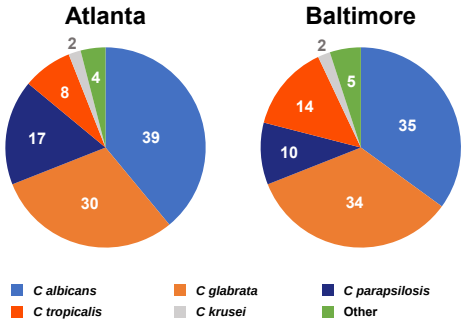
Morrell M, et al. *Antimicrob Agents Chemother*. 2005;49:3640-3645.

General Susceptibility Patterns of *Candida* Species

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Candins	AmB
Candida albicans	S	S	S	S	S	S
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I
Candida tropicalis	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S to R	S
Candida krusei	R	S-DD to R	S	S	S	S to I

AmB = amphotericin B; S = susceptible; S-DD = susceptibility-dose dependent; R = resistant; I = intermediate.
Pappas PG, et al. *Clin Infect Dis*. 2009;48(5):503-535.

Current *Candida* Species Epidemiology



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

Patient Case (cont)

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Receiving piperacillin-tazobactam and vancomycin
- Results from blood cultures drawn on hospital day 5 now positive for yeast
- What therapy should this patient receive?

Candidemia in Non-Neutropenic Patients

- Echinocandin is recommended as initial therapy
  - Strong recommendation; high-quality evidence
- Fluconazole, IV or PO, 800-mg (12 mg/kg) load, then 400 mg (6 mg/kg) daily is an acceptable alternative in select patients
  - Not critically ill
  - Not likely to have a fluconazole-resistant *Candida* species
    - Strong recommendation; high-quality evidence

IV = intravenous; PO = oral.
Pappas PG, et al. *Clin Infect Dis*. 2016;62:e1-e50.

Amphotericin B vs Fluconazole vs Echinocandin: Which One Is Best for Candidemia?

- Patient-level review of recent randomized trials for candidemia
- Data for all 3 classes of drugs used
- Data from 1915 patients, 7 trials
- Overall mortality rate was 31.4%
- Treatment success rate was 67.4%

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

Bad Prognostic Signs

Predictors of Mortality using Logistic Regression

Predictor	OR	95% CI
Increasing age	1.01	1.00-1.02
Higher APACHE II score	1.11	1.08-1.14
Immunosuppressive therapy	1.69	1.18-2.44
Infection with *C tropicalis*	1.64	1.11-2.39

OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation.
Andes DR, et al. *Clin Infect Dis*. 2012;54(8):1110-1122.

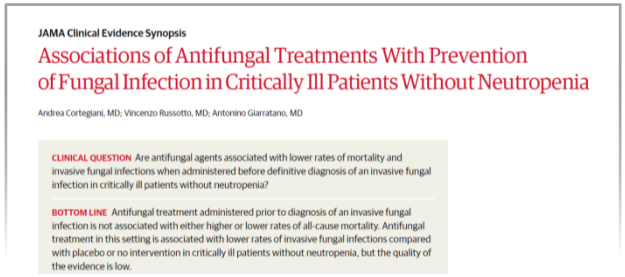
Predictors of a Good Outcome

- Removal of central venous catheter
  - OR=0.50, 95% CI=.35-.72, *P*=.0001
- Treatment with an echinocandin
  - OR=0.65, 95% CI=.45-.94, *P*=.02
- Similar findings using the clinical success endpoint

Assessment of lines should be a consideration for the entire team!

Andes DR, et al. *Clin Infect Dis*. 2012;54(8):1110-1122. Clancy CJ, et al. *Clin Infect Dis*. 2012;54(8):1123-1125.

Prophylaxis/Early Empiric Therapy



JAMA Clinical Evidence Synopsis

Associations of Antifungal Treatments With Prevention of Fungal Infection in Critically Ill Patients Without Neutropenia

Andrea Cortegiani, MD; Vincenzo Russotto, MD; Antonino Giarratano, MD

CLINICAL QUESTION Are antifungal agents associated with lower rates of mortality and invasive fungal infections when administered before definitive diagnosis of an invasive fungal infection in critically ill patients without neutropenia?

BOTTOM LINE Antifungal treatment administered prior to diagnosis of an invasive fungal infection is not associated with either higher or lower rates of all-cause mortality. Antifungal treatment in this setting is associated with lower rates of invasive fungal infections compared with placebo or no intervention in critically ill patients without neutropenia, but the quality of the evidence is low.

No decrease in mortality, fewer invasive fungal infections…
very unrewarding!

Cortegiani A, et al. *JAMA*. 2017;317:311-312.

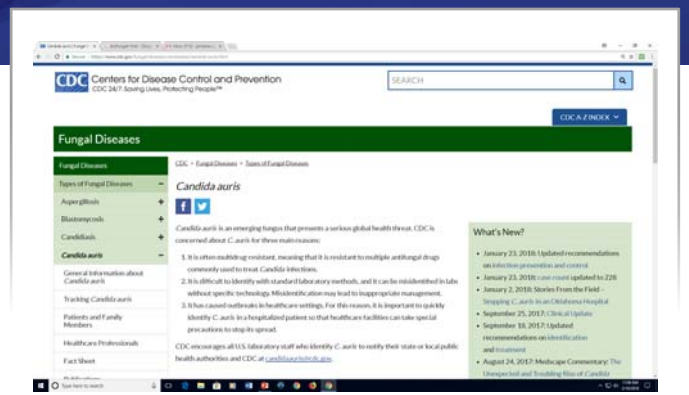
Susceptibility Testing

- Testing for azole susceptibility is recommended for:
  - All bloodstream isolates
  - Other clinically relevant *Candida* species isolates
- Testing for echinocandin susceptibility should be considered:
  - In patients who have had prior treatment with an echinocandin
  - Among those who have had infection with *C glabrata* or *C parapsilosis* (strong recommendation; low-quality evidence)

Pappas PG, et al. *Clin Infect Dis*. 2016;62:e1-e50.

Patient Case (cont)

- A 62-year-old woman with a history of diverticulitis
- Admitted because of possible perforation of the bowel
- Patient returns to the operating room for repair of the leak and drainage of the abscess
- She has been receiving micafungin for 6 days
- She has improved clinically
- Her blood cultures grew *C albicans*
- Should she have received empiric therapy?



CDC [website]. Fungal Diseases. https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris.html. Accessed February 8, 2018.

Candida Species: Conclusions

- Echinocandins are first-line choice in 2018
- Pull the lines when possible
- Epidemiology appears stable
- Know your institutional epidemiology
- Emergence of multidrug-resistant *C glabrata*?

Aspergillus Species and the Azoles

Clinical Infectious Diseases

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

- Primary treatment with voriconazole still recommended
- Initiate therapy early
- Alternatives to voriconazole for primary therapy
  - Isavuconazole
  - Lipid formulations of AmB
- Echinocandins are NOT recommended for primary therapy

Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-e60.

Patient Case

- A 53-year-old man with acute myeloid leukemia
- Normal cytogenetics
- Admitted for induction therapy
- Planning to be followed up to undergo a stem-cell transplantation
- What fungal infections do you need to consider?
- what drug classes are options?

Voriconazole: Strengths

- The current gold standard for IA?
- Broad spectrum – but NO mucormycosis
- IV and PO formulations
- Oral formulation now generic
- High oral bioavailability
- Penetrates human brain tissue and abscess material, achieving peak concentrations similar to or even exceeding those seen in plasma
- Agent of choice for central nervous system aspergillosis

IA = invasive aspergillosis.
Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-60. Dodds-Ashley ES, et al. *Clin Infect Dis*. 2006;43:S28-S39. Felton T, et al. *Clin Microbiol Rev*. 2014;27(1):68-88.

Voriconazole: Weaknesses

- Increasing concern over the risk of skin cancer
- Is the bioavailability as good as we thought?
- Cytochrome P450 nightmares continue
- When and when not to weight-based dose
- Toxic at high levels?
  - Liver function tests
  - Hallucinations

Kuklinski LF, et al. *J Am Acad Dermatol*. 2017;77(4):706-712. Pascual A, et al. *Clin Infect Dis*. 2012;55(3):381-390.

Posaconazole: Strengths

- Broad-spectrum azoles (>vori – zygomycetes)
- Mortality benefit in select populations
- Well-tolerated
- Solid tablet formulations and IV formulations
  - No treatment indications
  - Enhanced bioavailability solid oral dosage form – daily dosing!
  - IV (highly wallet toxic!)
- Penetrates into the inflamed eye
- Concentration within the human dermis comparable to that in plasma

Krishna G, et al. *J Antimicrob Chemother*. 2012;67(11):2725-2730. Felton T, et al. *Clin Microbiol Rev*. 2014;27(1):68-88.

Posaconazole: Weaknesses

- Kill the oral suspension! – Dosing differences
- Tablets are a marked improvement
- Once daily! Tablets and IV only!
- Saturable absorption – Not an issue with tablets?
- Erratic absorption – Only with the liquid
- Drug interactions – CYP3A4
- pH issues – Fewer with tablets

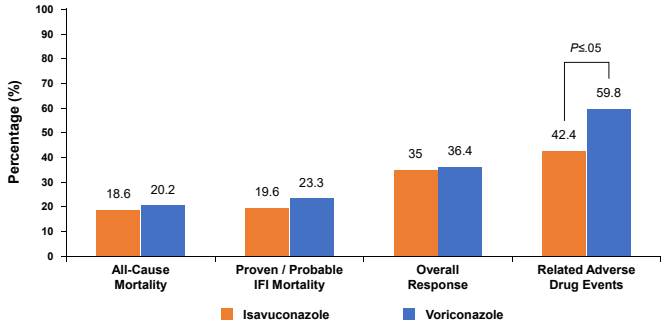
Pham A, et al. *Mycoses*. 2016;59:226-233.

Isavuconazole

- Spectrum very similar to posaconazole
- Broad in vitro activity against a range of medically important fungi (eg, *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*)
- Once daily and a prodrug – Loading doses required
- IV and PO
- No cyclodextrin in the IV
- Treatment indications – Very little prophylaxis data
- Indicated for the treatment of mucormycosis
- Issues with *Candida* species data

US Food and Drug Administration [website]. Drugs. https://google2.fda.gov/search?q=isavuconazole&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&requiredfields=-archive%3AYes&output=xml_no_dtd&getfields=*. Accessed February 13, 2018. Warn PA, et al. *Antimicrob Agents Chemother*. 2009;53(8):3453-3461.

Voriconazole vs Isavuconazole: IA and Other Mold

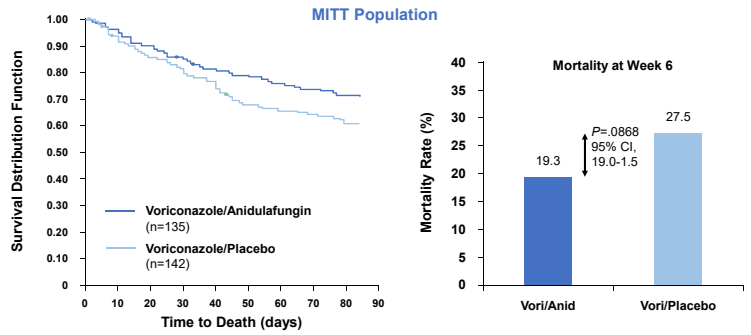


Maertens JA, et al. *Lancet*. 2016;387:760-769.

Patient Case (cont)

- A 53-year-old man with acute myeloid leukemia
- Normal cytogenetics
- Admitted for induction therapy
- Patient underwent induction therapy, neutrophils recovered on day 26, and patient was discharged on day 29
- Readmitted to undergo allogeneic (brother) hematopoietic stem-cell transplantation, which was successful, and then discharged home
- Readmitted with pleuritic chest pain, dry cough, and new 1-cm nodule noted on chest computed tomographic scan

Voriconazole + Anidulafungin vs Voriconazole Monotherapy for IA: MITT Population Crashing



MITT = modified intent-to-treat.
Marr KA, et al. Presented at 22nd European Congress of Clinical Microbiology and Infectious Disease, April 2, 2012, London, United Kingdom. Abstract LB 8212. Marr KA, et al. *Ann Intern Med*. 2015;162(2):81-89. Patterson TF, et al. *Clin Infect Dis*. 2016;63:e1-e60.

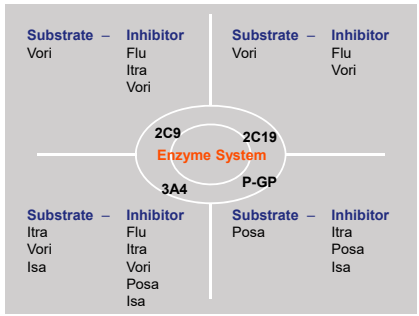
The Anti-*Aspergillus* Azoles: Toxicity and Monitoring

- Voriconazole is not benign
  - Unpredictable pharmacokinetics
  - Skin cancer
  - Hallucinations
  - Monitoring required: Trough >1-6
  - Do all practitioners seeing the patient know what to look for?
- Posaconazole tablets: Do they even need monitoring?
- Isavuconazole: Role should be clarified by further studies

Williams K, et al. *Clin Infect Dis*. 2014;58:997-1002. Moon WJ, et al. *Clin Infect Dis*. 2014;59:1237-1245. Pascual A, et al. *Clin Infect Dis*. 2012;55:381-390. Andes D, et al. *Antimicrob Agent Chemother*. 2009;53:24-34. Pham A, et al. *Mycoses*. 2016;59:226-233. Miceli MH, et al. *Clin Infect Dis*. 2015;61(10):1558-1565.

Drug Interaction Challenges: An Issue for the Healthcare Team

- "New information is emerging rapidly, and thus, this review is by its very nature incomplete"
- Medication reconciliation has increased in importance since the passage of the Patient Protection and Affordable Care Act in 2010
- The role of each healthcare provider, including the pharmacist, in the medication reconciliation continuum should be clearly defined
- Medication assessment and reconciliation by pharmacists 3-7 days post-discharge can decrease readmissions and provide cost savings



P-GP = P-glycoprotein.
Bruggemann RJM, et al. *Clin Infect Dis*. 2009;48:1441. US Food and Drug Administration. Advisory Committee Briefing Document. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/UCM430748.pdf. Accessed February 29, 2016. Splawski J, et al. *P T*. 2016;41(3):176-178. Kilcup M, et al. *J Am Pharm Assoc*. 2013;53:78-84.

So…Advanced Azoles 2018

- And then there were 3:
  1. Voriconazole
  2. Posaconazole
  3. Isavuconazole
- How different are they?
  - Excellent tissue penetration
- Do the indications matter?
- How different are the spectrums and pharmacokinetics/ pharmacodynamics?
- Are they interchangeable?

Questions?