PHARMACY LEARNING NETWORK 1-DAY REGIONAL MEETINGS

Ensuring Safe and Effective Treatment of Invasive Fungal Infections

ICHP

Presented in partnership with the ICHP Annual Meeting

Presenter

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Disclosures

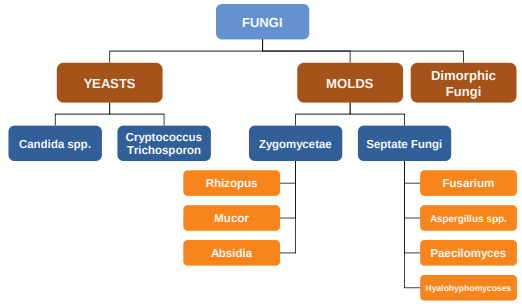
James S. Lewis II, PharmD, FIDSA: Consultant—Accelerate Diagnostics, Allergan, Astellas, The Medicines Company, Merck & Co., Inc.

Objectives

- Describe the mechanisms-of-action, efficacy/safety, and tolerability of available antifungal therapies for IFIs
- Evaluate recent clinical trial data on the benefits and limitations of conventional and newer antifungal agents, including adverse effect profiles and resistance patterns
- Outline best practices for IFI diagnostic testing and monitoring to ensure appropriate and timely treatment, including medication modifications, reconciliation, and prevention of toxicities and drug interactions
- Proactively lead the healthcare team in making informed prophylaxis, empiric, preemptive, and targeted antifungal treatment decisions to improve patient outcomes

IFIs = invasive fungal infections.

The Fungal World



Pathogens Associated with Healthcare Associated Infections (HCAIs)

Pathogen	All HCAIs (N=504) Number/ (%)	Pneumonia (N=110)	Surgical Site Infections (N=110)	GI Infections (N=86)	UTIs (N=65)	Bloodstream Infections
C. difficile	61 (12.1)	0	0	61 (70.9)	0	0
S. aureus	54 (10.7)	18 (16)	17 (16)	1 (1)	2 (3)	7 (14)
K. pneumoniae or *oxytoca*	50 (9.9)	13 (12)	15 (14)	1 (1)	15 (23)	4 (8)
E. Coli	47 (9.3)	3 (3)	14 (13)	1 (1)	18 (28)	5 (10)
Enterococcus	44 (8.7)	2 (2)	16 (15)	5 (6)	11 (17)	6 (12)
P. aeruginosa	36 (7.1)	14 (13)	7 (6)	1 (1)	7 (11)	2 (4)
Candida	**32 (6.3)**	**4 (4)**	**3(3)**	**3 (4)**	**3 (5)**	**11 (22)**

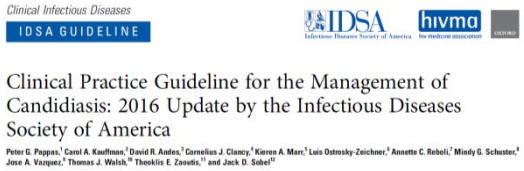
GI = gastrointestinal; UTIs = urinary tract infections.
Magill SS, et al. *N Engl J Med*. 2014;370:1198.

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
- $39,331 increased 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.

Big News!!



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.

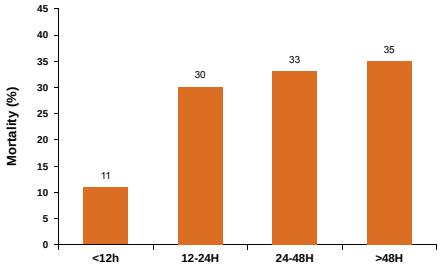
Invasive Candidiasis: Who Is at Risk?

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

- A subset of postsurgical patients may be at uniquely high risk for candidiasis
  - Recurrent GI 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



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

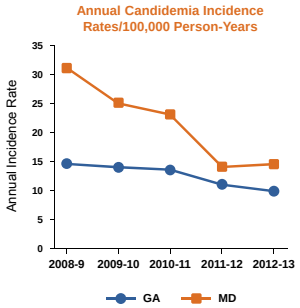
General Susceptibility Patterns of *Candida* spp

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

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

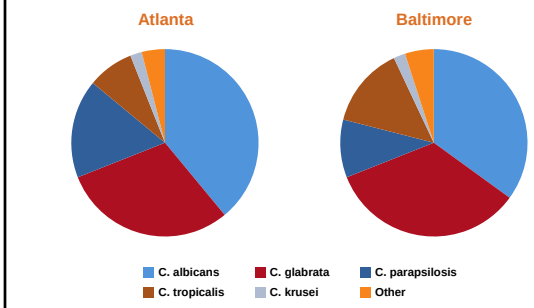
Current Epidemiology

- Most common groups
  - Adults > 65
  - Infants < 1
- Declines across all age groups except age 1-19 in MD
- Fluconazole resistance rates decreased in:
  - GA = -10%
  - MD = -25%
  - Overall rate = 7% resistant



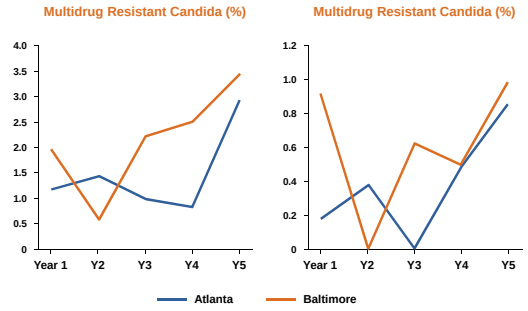
Cleveland AA, et al. *PLoS One*. 2015;10(3);e0120452.

More Epidemiology



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

Worrisome Signs: Echinocandin Resistance



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

Beyond Blood Cultures

- **Blood culture strengths**
  - Recover the infecting organism
  - Allows susceptibility testing
  - Detection of multiple pathogens
- **Blood culture weaknesses**
  - Overall sensitivity for IC ≈50%
  - Time to positivity 2 to 3 days
  - Longer for some species (ie, *Candida glabrata*)

Clancy CJ, et al. *Clin Infect Dis.* 2013;56(9):1284-1292.

Overall Sensitivity and Specificity of the T2 Magnetic Resonance Method

Sensitivity	Number	%	95% CI
Overall per patient	233 / 256	91.0	86.8-94.2
Overall per assay	234 / 257	91.1	86.9-94.2

Specificity	Number	%	95% CI
Overall per patient	1516 / 1545	98.1	97.3-98.7
Overall per assay	5114 / 5146	99.4	99.1-99.6

CI = confidence interval.
Myelonakis E, et al. *Clin Infect Dis.* 2015;60:892-899.

So Where Do We Stand With Diagnostics

- T2 is great… if you can afford it
- Diagnostics will increasingly allow for timely therapy adjustment
- Echinocandin to azole switches
  - When?
  - Who?

The Continuing Challenge of Empiric Therapy

- "…considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever"
- "Preference should be given to an echinocandin in:
  - hemodynamically unstable patients
  - previously exposed to an azole
  - colonized with azole-resistant *Candida* species"
- "Fluconazole may be considered in:
  - Hemodynamically stable patients
  - Colonized with azole-susceptible Candida species
  - No prior exposure to azoles"
- Duration = candidemia if patient responds
- Stop therapy if no clinical response & cultures + surrogate markers negative

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

Prophylaxis – We Still Can't Get it Right

- Caspofungin vs placebo
- 222 patients
- Prediction rule used
- ICU patients at "high-risk"
- Primary endpoint – Proven/probable IC

ICU = intensive care unit.
Ostrosky-Zeichner L, et al. *Clin Infect Dis*. 2014;58(9):1219-1226.

Prophylaxis/MITT Population

Variable	Caspofungin (n=102)	Placebo (n=84)	*P* Value
Incidence of proven/ probable IC (%)	9.8	16.7	.14
Incidence of proven IC (%)	1.0	4.8	.11
Use of antifungals within 7 days of EOT	13.7	17.9	.35
All cause mortality within 7 days of EOT	16.7	14.3	.78

MITT = modified intent-to-treat; IC = invasive candidaisis; EOT = end of therapy.
Ostrosky-Zeichner L, et al. *Clin Infect Dis*. 2014;58(9):1219-1226.

AmB 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 from 7 trials
- Overall mortality was 31.4%
- Rate of treatment success was 67.4%

AmB = amphotericin B.
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
Increasing APACHE 2 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; 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

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

Candidemia in Nonneutropenic 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 selected patients
  - A. Not critically ill
  - B. Not likely to have a fluconazole-resistant Candida species
    - (Strong recommendation; high-quality evidence)

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

Susceptibility Testing

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

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

Candida: Conclusions

- Echinocandins are first-line choice in 2016
- Pull the lines when possible
- Epidemiology appears stable
- Know you institutional epidemiology
- Emergence of multidrug-resistant *C. glabrata*?

Aspergillus 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

- Primary treatment with voriconazole still recommended
- Initiate therapy early
- Alternatives to voriconazole for primary therapy
  - Liposomal AmB
  - Isavuconazole
  - Other lipid amphotericin products
- Echinocandins NOT recommended for primary therapy

Patterson TF, et al. *Clin Infect Dis.* 2016;63(4):e1-e60.

Voriconazole — Strengths

- The current gold standard for IA
- Broad spectrum
- IV and oral formulations
- Oral formulation now generic
- High oral bioavailability

IA = invasive aspergillosis.

Voriconazole — Weaknesses

- Increasing concern over skin cancer risk
- Is the bioavailability as good as we thought?
- P450 nightmares continue
- When to weigh base dose and when to not
- Toxic at high levels?
  - LFTs
  - Hallucinations

Zwald FO, et al. *Dermatol Surg.* 2012;38(8):1369-1374. Pascual A, et al. *Clin Infect Dis.* 2012;55(3):381-390.

Posaconazole

- Strengths
  - The broadest spectrum of the currently available azoles
  - Mortality benefit in select populations
  - Well-tolerated…or is it?
- New formulations available – gamechangers!
  - IV – highly wallet toxic!!
  - Enhanced bioavailability solid oral dosage form – daily!!

Krishna G, et al. *J Antimicrob Chemother.* 2012;67(11):2725-2730.

Posaconazole — Weaknesses

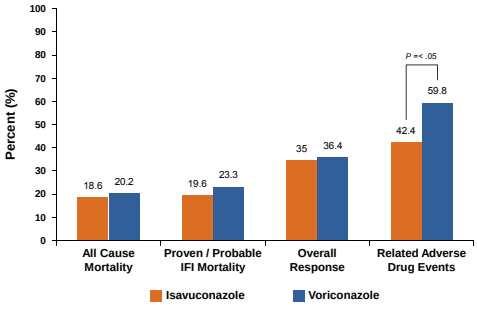
- Kill the oral suspension!!! Exceptions??
- New tablets are a marked improvement
- Once daily! – tablets and IV only!
- Saturable absorption – not an issue with tablets?
- Erratic absorption – tablets?
- Drug interactions – no help there!
- pH issues - appear much less with tablets

Isavuconazole

- Yes that really is the name!
- Spectrum between vori and posa?
- Once daily & prodrug issues
- IV and oral
- No cyclodextrin in the IV
- Better tolerated than voriconazole?
- Treatment indications – no prophylaxis data

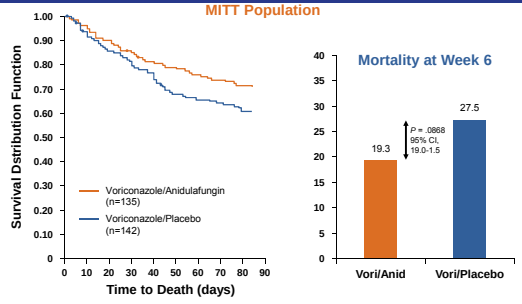
Cresemba [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.

Voriconazole vs Isavuconazole: IA and Other Mold



Maertens JA, et al. *Lancet.* 2015 [epub ahead of print].

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



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.

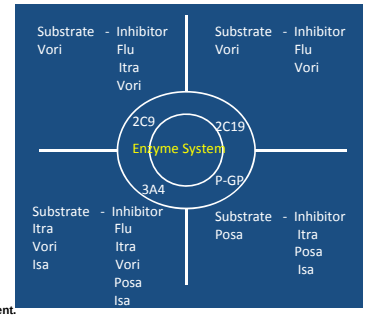
The Anti-Aspergillus Azoles: Toxicity and Monitoring

- Voriconazole is not benign
  - Unpredictable PK
  - Skin cancer
  - Hallucinations
  - Monitoring required – trough >1-6
- Posaconazole tablets – do they even need monitoring?
- Isavuconazole – we don't know what we don't know

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 [epub ahead of print].

Drug Interaction Challenges

"New information is emerging rapidly, and thus, this review is by its very nature incomplete."



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.

So…Advanced Azoles 2016

- And then there were 3
- How different are they?
- Do the indications matter?
- How different are the spectrums and PK/PD?
- Are they interchangeable?