

Management of Invasive Fungal Infections: Applying Evidence-based Strategies and Individualizing Antifungal Therapy

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On-demand Activity

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Agenda

- 11:30 a.m. – 11:40 a.m. **Welcome and Introduction**
Peggy L. Carver, Pharm.D., FCCP
- 11:40 a.m. – 12:15 p.m. **Systemic *Candida* Infection: Rapid Diagnostics and Evolving Resistance and Treatment**
Kevin W. Garey, Pharm.D., M.S., FASHP
- 12:15 p.m. – 12:50 p.m. **Diagnosis and Treatment of Aspergillosis and Therapeutic Drug Monitoring (TDM)**
Peggy L. Carver, Pharm.D., FCCP
- 12:50 p.m. – 1:00 p.m. **Faculty Discussion and Audience Questions**
All Faculty

Faculty

Peggy L. Carver, Pharm.D., FCCP, Activity Chair

Associate Professor of Pharmacy
University of Michigan College of Pharmacy
Clinical Pharmacist, Infectious Diseases
University of Michigan Health System
Ann Arbor, Michigan

Kevin W. Garey, Pharm.D., M.S., FASHP

Professor and Chair
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

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- Peggy L. Carver, Pharm.D., FCCP, serves on the speakers bureau for Merck and Astellas, Inc.
- Kevin W. Garey, Pharm.D., M.S., FASHP, has received research grants from Astellas, Inc. and T2 Biosystems.
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Activity Overview

As the 3rd most common cause of bloodstream infections in the intensive care unit, and the fourth most common cause of nosocomial bloodstream infections, invasive candidiasis is common and deadly. While *C. albicans* remains the most prevalent species in the USA, the prevalence of non-*albicans Candida* species has increased since 2004, and *C. parapsilosis* and *C. glabrata* each comprise approximately 15% of all *Candida* isolates. Because aspergillosis is not a reportable infection in the United States, the exact number of cases is difficult to determine. Prospective surveillance among transplant recipients performed during 2001-2006 found that invasive aspergillosis was the most common type of fungal infection among stem cell transplant recipients and was the second-most common type of fungal infection among solid organ transplant recipients, with a 12-month cumulative incidence of 19%.

The wider availability and use of newer agents over the past decade has resulted in additional choices of antifungal agents, but also in the incidence of antifungal resistance, in particular for *C. glabrata* to azoles and (of recent concern) to echinocandins.

Faculty will discuss current antifungal therapies for the treatment of candidemia and aspergillosis infections, focusing on recent studies that affect the interpretation and use of treatment guidelines and the importance of using local epidemiology and resistance patterns. Management principles for the identification, monitoring, and management of antifungal adverse effects, drug interactions, and therapeutic drug monitoring will also be highlighted.

Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review rapid diagnostics and their roles for diagnosis and treatment of systemic *Candida* infections.
- Recommend treatment options and describe evolving resistance mechanisms and changing paradigms for treating systemic candidiasis or candidemia infections.
- Discuss indications for antifungal therapeutic drug monitoring.
- Compare and contrast the limitations, efficacy and safety profiles of newer antifungal agents.
- Identify current therapeutic options for the diagnosis and treatment of aspergillosis infections.

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- **Available in 2015**
 - **Ask the Experts Webinar.** Our expert faculty will focus on key questions received after the Midyear symposium. If you miss the live webinar in early 2015, plan to view the on-demand archive version later in 2015.
 - **On-Demand Archive.** Captures the faculty presentations from the live symposium for those unable to attend the Midyear Clinical Meeting (1.5 hours CPE; individuals claiming CPE for the live activity or webinar are ineligible to claim credit for this activity).

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The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-704-L01-P for the live activity and ACPE activity #0204-0000-14-704-H01-P for the on-demand activity).

Participants will process CPE credit online at <http://elearning.ashp.org/my-activities>, with the option of printing a CE certificate. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of a live activity or completion of a home study activity.

Management of Invasive Fungal Infections: Applying Evidence-based Strategies and Individualizing Antifungal Therapy

Peggy L. Carver, Pharm.D., FCCP, Activity Chair

Associate Professor of Pharmacy
University of Michigan College of Pharmacy
Clinical Pharmacist, Infectious Diseases
University of Michigan Health System
Ann Arbor, Michigan

Peggy Carver, Pharm.D., FCCP, is Associate Professor of Pharmacy in the Department of Clinical Sciences at the College of Pharmacy, University of Michigan, and Clinical Pharmacist in Infectious Diseases in the Department of Pharmacy Services, University of Michigan Health Systems, Ann Arbor, Michigan. Dr. Carver earned her Doctor of Pharmacy degree and served a residency at the University of California School of Pharmacy in San Francisco, California. She also completed a fellowship at Hartford Hospital in Hartford, Connecticut.

Dr. Carver is the author of the chapter on invasive fungal infections in eight editions of *Pharmacotherapy: A Pathophysiologic Approach*, a widely used and respected book and has extensively published on the topic of antifungals and antifungal therapy. She is a recipient of the University of Michigan College of Pharmacy Teaching Excellence Award, and has been an invited presenter at numerous national and international medical meetings and continuing education conferences. She is a fellow of the American College of Clinical Pharmacy and past president of the Society of Infectious Diseases Pharmacists.

Dr. Carver's research focuses on the pharmacokinetics, pharmacodynamics, and drug interactions of antifungal agents and the role of metal ions in the development of infectious diseases.

Management of Invasive Fungal Infections: Applying Evidence-based Strategies and Individualizing Antifungal Therapy

Kevin W. Garey, Pharm.D., M.S., FASHP

Professor and Chair

Department of Clinical Sciences and Administration

University of Houston College of Pharmacy

Houston, Texas

Kevin W. Garey, Pharm.D., M.S., FASHP is Professor at the University of Houston College of Pharmacy and Chair of the Department of Clinical Sciences and Administration at the University of Houston College of Pharmacy in Houston, Texas. Dr. Garey is an Adjunct Professor at the University of Texas School of Public Health and a Clinical Specialist and Researcher at Baylor St. Luke's Medical Center in Houston, Texas. He received a Bachelor of Science in Pharmacy degree from Dalhousie University in Halifax, Nova Scotia, Canada, a Doctor of Pharmacy from the State University of New York in Buffalo, New York, and Master of Science in Biometry from the University of Texas School of Public Health in Austin, Texas. He completed a pharmacy practice residency at Bassett Healthcare, Cooperstown, NY and infectious disease specialty residency and fellowship training at the University of Illinois at Chicago College of Pharmacy in Chicago, Illinois.

Dr. Garey has numerous publications in infectious diseases topics and has presented extensively at national and international professional conferences. He has received numerous professional awards including the ASHP Drug Therapy Research Award, ASHP Best Practices Award in Health-System Pharmacy, the Society of Infectious Diseases Pharmacists Impact Paper in Infectious Diseases Pharmacotherapy Award and the University of Houston Faculty Leadership award. He is a Fellow of ASHP.

Dr. Garey's research interests involve clinical and translational research involving healthcare-associated infections including post-surgical infections, candidemia, and *Clostridium difficile* infection.

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CE IN THE MIDDAY

Management of Invasive Fungal Infections: Applying Evidence-based Strategies and Individualizing Antifungal Therapy

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- Review rapid diagnostics and their roles for diagnosis and treatment of systemic *Candida* infections.
- Recommend treatment options and describe evolving resistance mechanisms and changing paradigms for treating systemic candidiasis or candidemia infections.
- Discuss indications for antifungal therapeutic drug monitoring.
- Compare and contrast the limitations, efficacy, and safety profiles of newer antifungal agents.
- Identify current therapeutic options for the diagnosis and treatment of aspergillosis infections.

Systemic *Candida* Infection: Rapid Diagnostics and Evolving Resistance and Treatment

Kevin W. Garey, Pharm.D., M.S., FASHP

Chair, Department of Clinical Sciences
and Administration
Professor of Pharmacy Practice
University of Houston College of Pharmacy
Houston, TX

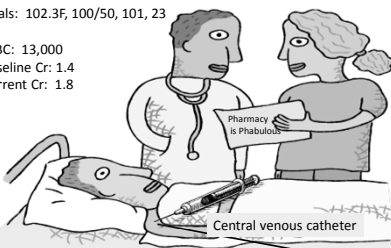
Topics

- Highlight the role of rapid *Candida* diagnostics in the treatment of *Candida* infections
- Provide a summary of treatment recommendations for systemic candidiasis or candidemia
- Discuss appropriate dosing of fluconazole and echinocandins as it relates to
 - Clinical success, overall mortality, antifungal resistance
 - Animal / in-vitro models and human evidence

Systemic *Candida* Infections

Vitals: 102.3F, 100/50, 101, 23

WBC: 13,000
Baseline Cr: 1.4
Current Cr: 1.8



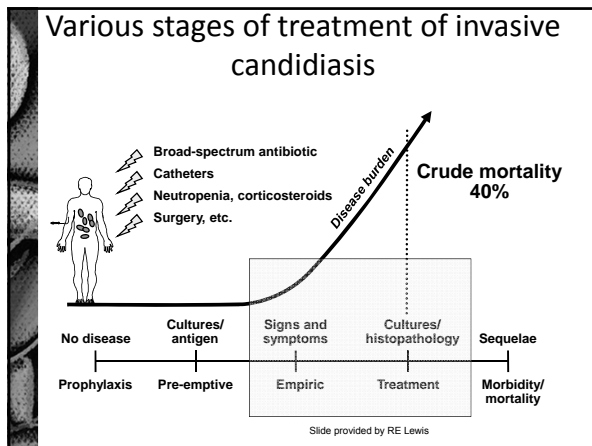
Send Blood samples
Start therapy (micafungin)

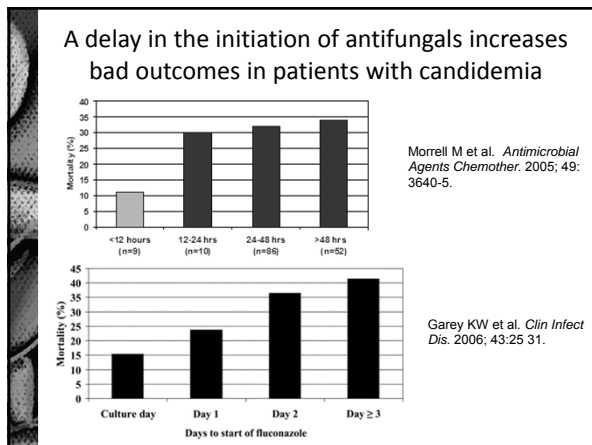
Diagnosis: Suspected systemic candidiasis!!!

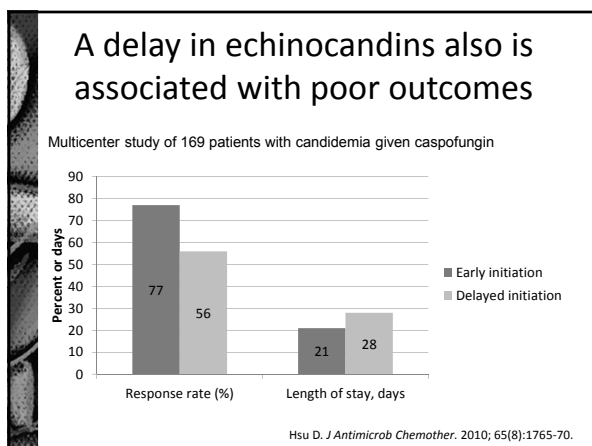
67 year old white male
past admission acute
pancreatitis

Central venous
catheter associated for
TPN

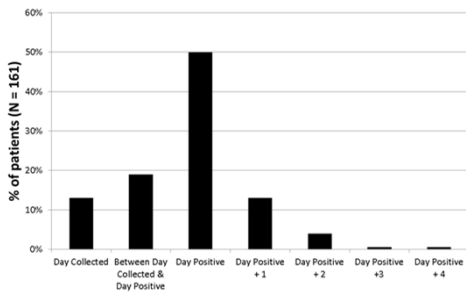
Also received
antibiotics for
pancreatitis







Update 2014: We are still not starting antifungals in a timely manner



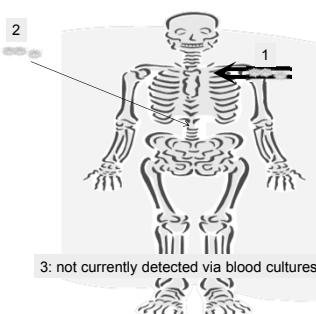
Shah DN et al. *J Antimicrob Chemother.* 2011;66:2146-51.

Why do we need a new diagnostic test for *Candida*?

- Bottom line: We are simply not good enough at predicting clinically who will have candidemia
- But: why aren't blood cultures adequate?
 - To answer this question, we need a better understanding of invasive systemic candidiasis

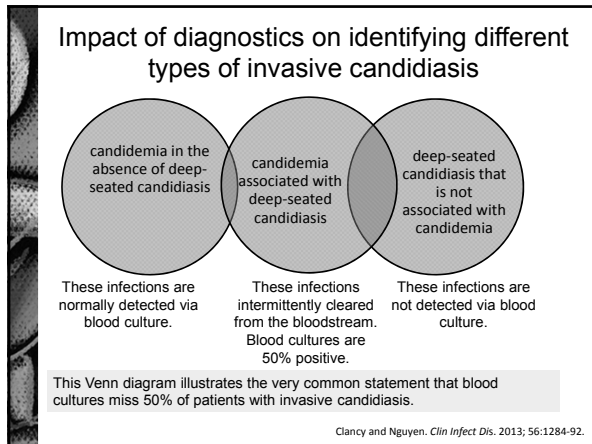
The three definitions of invasive candidiasis

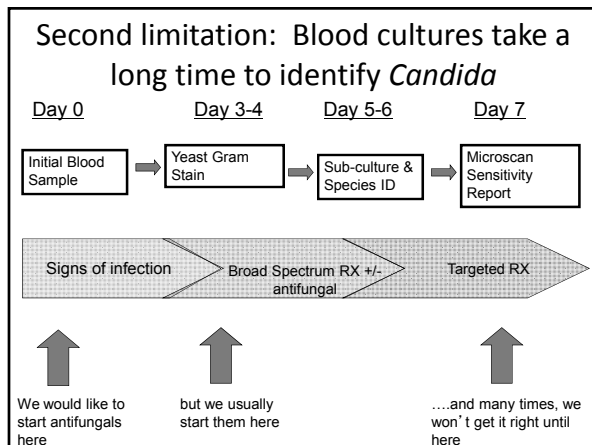
Invasive candidiasis encompasses candidemia and deep-seated candidiasis

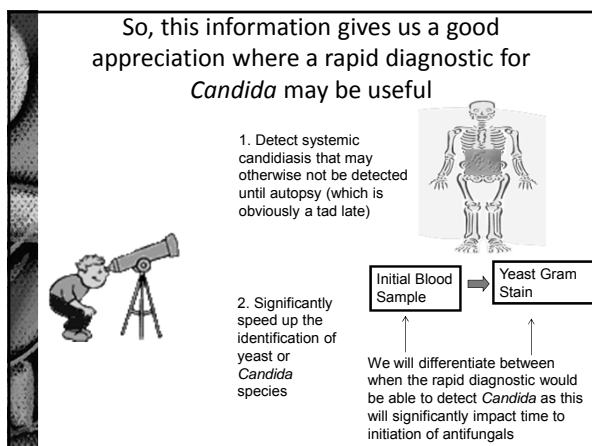


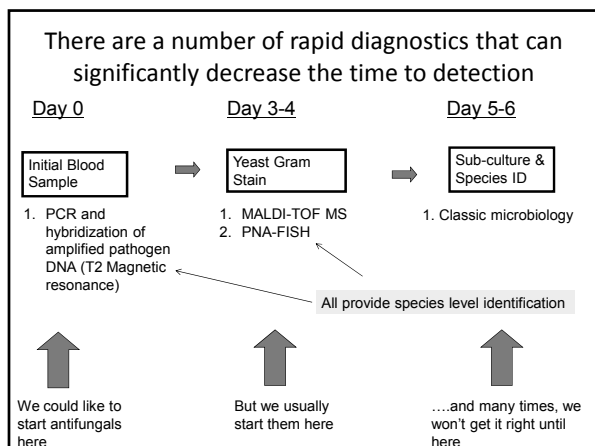
In diagnosing invasive candidiasis, there are 3 entities that must be considered

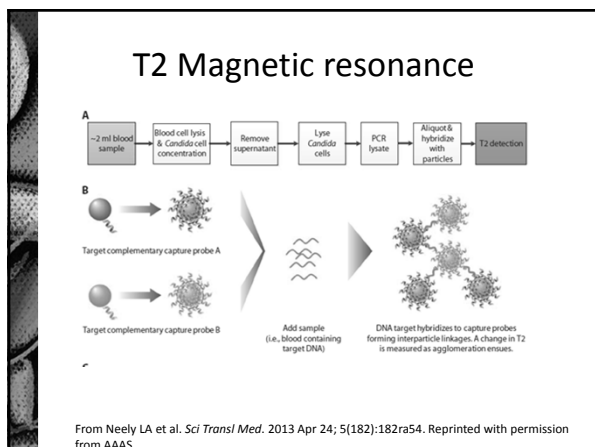
- (1) candidemia in the absence of deep-seated candidiasis
- (2) candidemia associated with deep-seated candidiasis
- (3) deep-seated candidiasis that is not associated with candidemia











You might expect a diagnostic from pure blood to have a tough time detecting the pathogen

Comparison of the *Candida* spp. detection and time to detection between the Bactec 9050 and T2Candida assay run on the T2DX. Whole blood samples spiked with *Candida* species (1-10 CFU/mL)

<i>Candida</i> spp.	Instrument	No. samples	Detection of <i>Candida</i> spp.		Time to detection	
			% positive*	P value	Median h (± SD)	P value
<i>C. albicans</i>	Bactec 9050	20	100%	1.0	106 ± 5.26 h	<0.001
	T2DX	20	100%		3.85 ± 0.29 h	
<i>C. glabrata</i>	Bactec 9050	20	0%		NA	NA
	T2DX	20	100%		3.6 ± 0.27 h	
<i>C. parapsilosis</i>	Bactec 9050	20	100%	1.0	78.25 ± 4.46 h	<0.001
	T2DX	18	100%		3.6 ± 0.3 h	
<i>C. tropicalis</i>	Bactec 9050	20	100%	1.0	30.58 ± 2.15 h	<0.001
	T2DX	13	100%		3.57 ± 0.32 h	
<i>C. krusei</i>	Bactec 9050	20	100%	1.0	40.5 ± 2.23 h	<0.001
	T2DX	19	100%		3.83 ± 0.27 h	

Beyda ND et al. *Diagn Microbiol Infect Dis*. 2013; 77:324-6.

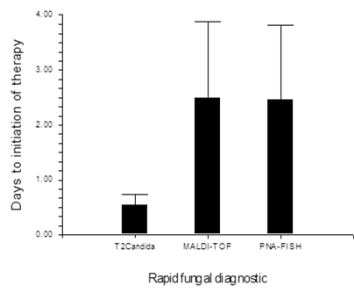
See page 38 for enlarged view

Implications for pharmacy practice

- I think ID/antimicrobial stewardship pharmacists are going to become “react to positive diagnostic test” pharmacists

Monte Carlo simulation on days to initiation of therapy using three rapid diagnostics for *Candida*.

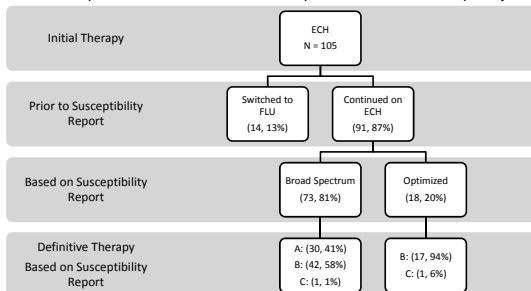
Traditionally, patients start antifungal therapy in 3.5 ± 2.1 days



Aitken SL et al. *Ann Pharmacother.* 2014; 48:683-90.

These rapid diagnostic tests will only be good if someone looks at the results.

Treatment patterns of echinocandin-treated patients based on susceptibility

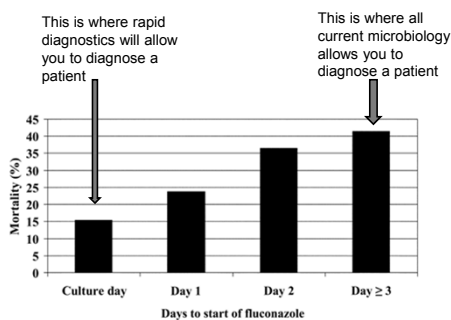


A. Switched to fluconazole; B. Continued on echinocandin; C. No definitive therapy
Shah DN et al. *J Antimicrob Chemother.* 2011; 66:2146-51.

But, when a stewardship pharmacist is involved, good things happen!

- PNA-FISH and *Candida*
 - Pharmacist reacted to results
 - \$1729 saved per patient
 - Forrest GN et al. *J Clin Microb.* 2006; 44:3381-3.
- MALDI-TOF and (Gram-negative)
 - Pharmacist reacted to results
 - Approximately \$12k saved per patient
 - Perez KK et al. *Arch Pathol Lab Med.* 2012; 137: 1247-54..

Rapid diagnostics will decrease mortality rates due to systemic candidiasis



Systemic *Candida* Infections

Vitals: 102.3F, 100/50, 101, 23

WBC: 13,000
Baseline Cr: 1.4
Current Cr: 1.8



Send Blood samples using a rapid diagnostic

Diagnosis: Systemic *Candida* infection!!!

67 year old white male- past admission acute pancreatitis

Central venous catheter associated for TPN

Also received antibiotics for pancreatitis

How do we make our decision about what antifungal to use?

Which antifungal regimen would you choose to treat the patient?



- a. Fluconazole 400mg IV once daily
- b. Fluconazole 6 mg/kg IV once daily
- c. An echinocandin (your choice) FDA indicated fixed dose
- d. An echinocandin (your choice) using a mg/kg once daily dose

If you were choosing using general susceptibility to antifungals

<i>Candida</i> species	FLUC	ECH	AMP B
<i>C. albicans</i>	S	S	S
<i>C. tropicalis</i>	S	S	S
<i>C. parapsilosis</i>	S	S to R	S
<i>C. glabrata</i>	S-DD to R	S	S to I
<i>C. krusei</i>	R	S	S to I

S = susceptible; S-DD = susceptible dose – dependent; R = resistant

FLUC = fluconazole; AMP B = amphotericin B; ECH = caspofungin, micafungin, anidulafungin

Pappas PG et al. *Clin Infect Dis*. 2009; 48:503-35

If you were choosing based on highest level of RCT evidence: Microbiologic response at the end of IV therapy

Pathogen	Successful microbiologic response		p value
	Anidulafungin	Fluconazole	
<i>C. albicans</i>	95%	81%	0.01
<i>C. glabrata</i>	75%	60%	0.37
<i>C. parapsilosis</i>	69%	88%	0.36
<i>C. tropicalis</i>	87%	64%	0.35
All <i>Candida</i> species	88%	76%	0.02

Non-inferiority trial (n=245, double-blind, RCT). 245 patients given fluconazole 800 mg LD then 400 mg daily or anidulafungin 200 mg LD then 100 mg daily.

Reboli AC et al. *N Engl J Med*. 2007; 14:2472-82.

IDSA Guideline Recommendations:
Initial therapy with fluconazole vs. an echinocandin

Fluconazole	An Echinocandin
Less critically ill	Moderately severe to severe illness
No recent azole exposure	Recent azole exposure

Pappas PG et al. Clin Infect Dis. 2009; 48:503-35.

Recent European *Candida* Guidelines

- Highlights
 - Use amphotericin B or echinocandins preferentially if catheters cannot be removed
 - Switch to oral therapy after 10 days of I.V. therapy (systemic candidiasis)
 - Daily blood cultures until negative

Cornely OA et al. Clin Microbiol Infect. 2012; 18:19-37.

How long to continue treatment for candidemia?

2 weeks*

* No obvious metastatic complications

When to start counting treatment days?
After documented clearance of *Candida* species from bloodstream

Pappas PG et al. Clin Infect Dis. 2009; 48:503-35.

Bottom line

- So this is pretty simple
 - Everyone is pretty much moderately or severely ill (at least in the hospital)
 - Start an echinocandin
 - When there is improvement ,switch to fluconazole
 - Treat for 2 weeks after blood cultures are negative
- Where do pharmacists come in?
 - Appropriate dosing!

IDSA guidelines recommendation on management of candidemia in non-neutropenic patients

Initial (empiric) therapy options

Fluconazole

Loading dose of 800 mg (12 mg/kg) → 400 mg (6 mg/kg) daily

An Echinocandin

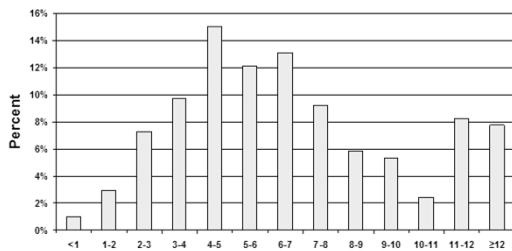
Caspofungin
Loading dose of 70 mg → 50 mg daily

Micafungin 100 mg daily

Anidulafungin
Loading dose: 200 mg → 100 mg daily

Pappas PG et al. *Clin Infect Dis*. 2009; 48:503-35.

Histogram of fluconazole dose (mg/kg) adjusted for renal dysfunction given to 206 nonneutropenic patients with candidemia.



48% of patients received an initial dose <6 mg/kg

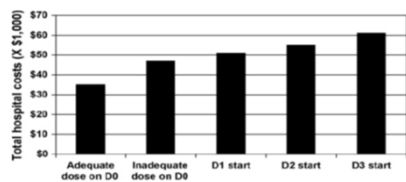
Garey KW et al. *Pharmacoepidemiol Drug Saf*. 2007; 16:919-27.

Fluconazole

- Dose: 6 mg/kg (*C. glabrata*: 12 mg/kg)
- Pharmacodynamics
 - Dose: MIC or AUC:MIC
- Animal models support an AUC/MIC breakpoint of 25-50 (remember that number)
- Thus: appropriate dosing should affect outcomes

Lewis RE. *Mayo Clin Proc.* 2011; 86: 805-17.
Andes D et al. *Antimicrob Agents Chemother.* 1999; 43:2116-20.

An inappropriate fluconazole dose increases hospital costs



Total hospital costs stratified by adequate fluconazole dose given at the onset of symptoms (Day 0) or later.

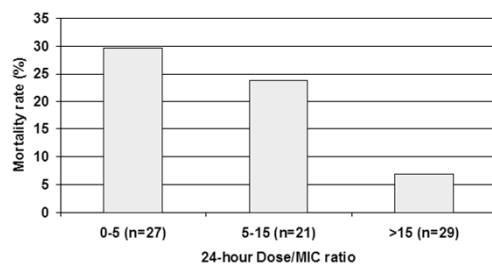
Garey KW et al. *Int J Antimicrob Agents.* 2007; 29:557-62.

Mortality rate stratified by tertiles and fluconazole Dose (mg/kg) / MIC at 24 hours ($p=0.03$ using logistic regression controlling for time to initiation of fluconazole therapy)

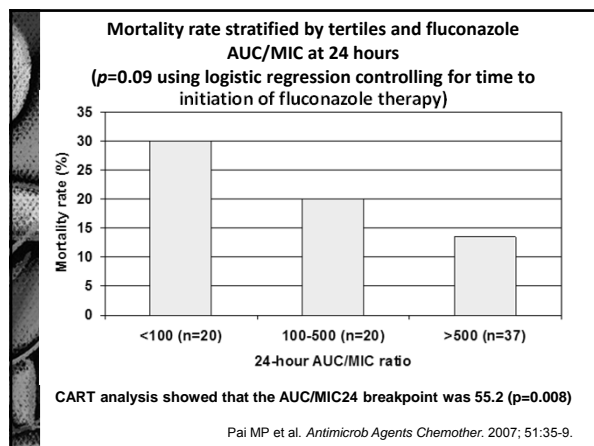
77 isolates from candidemia study available for MIC determination

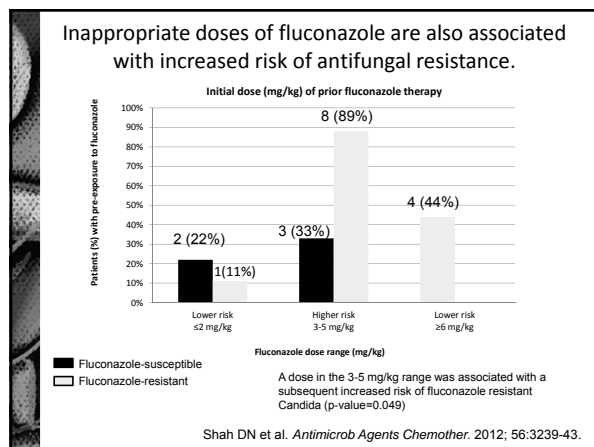
-AUC/MIC and Cmax/MIC ratio calculated for each patient

-Breakpoint analysis via CART analysis



Pai MP et al. *Antimicrob Agents Chemother.* 2007; 51:35-9.





Fluconazole Dose

- Human evidence suggests that the appropriate dose of fluconazole is associated with:
 - Better treatment outcomes
 - Reduced mortality
 - Decreased resistance
- What fixed dose would we have to give to make sure the majority of patients get at least 6 mg/kg?

Distribution of fluconazole dose (mg/kg) based on the fixed dose of fluconazole divided by the patient weight. Results are adjusted based on patients' renal dysfunction

	Corresponding dose divided by patients body weight (mg/kg)										
Dose of fluconazole given to patients	<4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	>12	
<400 mg	94%	3%	3%								
400 mg	11%	29%	24%	22%	11%	4%					
600 mg				38%	50%	13%					
800 mg				5%	7%	11%	18%	8%	28%	23%	
>800 mg										100%	

Echinocandins

- Block glucan synthesis needed for fungal cell walls
 - Caspofungin 70 mg LD then 50 mg daily
 - Micafungin 100 mg daily
 - Anidulafungin 200 mg LD then 100 mg daily
- This is easy, fixed dosing!
- But: is this correct?
- PD predictors:
 - AUC:MIC > 20 (unbound) or Cmax:MIC > 10

Andes D et al. *Antimicrob Agents Chemother.* 2010; 56:2497-506.
Lewis RE. *Mayo Clin Proc.* 2011; 86:805-17.

However, there are no dose-response studies with echinocandins as we always give a fixed dose!

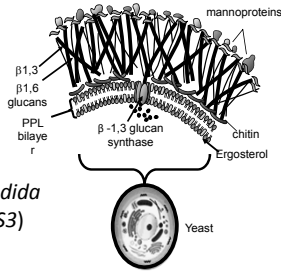
- With very low MICs, the PD targets are very achievable with standard dosing regimens
- Update 2014: FKS resistance!

Echinocandins inhibit glucan synthase

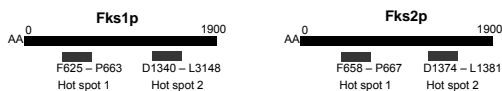
- Inhibit β -1,3-glucan synthase enzyme

– Catalytic subunit (Fks1p/2p)

– Encoded by 3 *FKS* related genes in *Candida* spp. (*FKS1*, *FKS2*, *FKS3*)



FKS mutations are associated with reduced echinocandin susceptibility



- Two regions (HS1 and HS2) of Fks1/2p are associated with echinocandin resistance
- Prominent mutations typically confer cross-resistance to all echinocandins

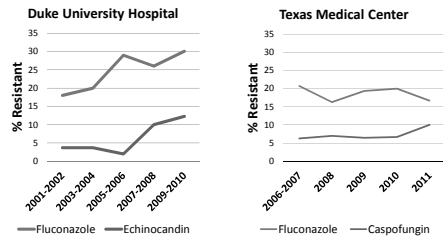
Echinocandin resistance relatively uncommon globally

- Susceptibility patterns of 3,107 *Candida* species from 34 countries
- 38% cross-resistance to fluconazole

	Rates of resistance (varies by region)
All <i>Candida</i> species	Up to 1.7%
<i>Candida albicans</i>	Up to 0.6%
<i>Candida glabrata</i>	Up to 3.8%

Pfaller MA et al. *J Clin Microbiol.* 2013; 51:390-2.

Emergence of echinocandin resistance in *C. glabrata*



Alexander BD et al. *Clin Infect Dis*. 2013; 56:1724-32.
Beyda ND et al. *Clin Infect Dis*; 2014; 59:819-25.

Will echinocandin resistance make us change to a more individualized dosing strategy?

	Beyda et al. (2014) (n = 78)	Alexander et al. (2013) (n = 278)	Shields et al. (2011) (n = 39)
Risk factors for FKS mutant <i>C. glabrata</i>			
Prior echinocandin therapy	OR 10.65; 95%CI 2.51- 45.24	OR 19.65; 95%CI 7.19-58.1	P=0.0001
Prior episode of candidemia	OR 18.59; 95%CI 1.56 – 221.69	P = < 0.05	---
Risk factors for echinocandin treatment failure			
Prior echinocandin therapy	OR 9.17; 95%CI 1.9 – 44.46	P = < 0.05	P = 0.008
Presence of an FKS mutation	P = 0.033	P = 0.0391	OR 41.7; 95%CI 3.96- 445.7

Alexander BD et al. *Clin Infect Dis*. 2013; 56:1724-32.
Beyda ND et al. *Clin Infect Dis*; 2014; 59:819-25.
Shields et al. *Antimicrob Agents Chemother*. 2011;

Conclusion

- Pharmacists reacting to rapid diagnostic tests for systemic candidiasis could significantly improve patient care
- Fluconazole
 - At least 6 mg/kg (800 mg for all?)
 - Improved benefit (treatment success, mortality, and resistance)
 - No brainer: Do it (not many do)
- Echinocandins:
 - Fixed doses are great with low MICs
 - Did this fixed dosing strategy encourage resistance?
 - Individualized dosing strategy needs further study

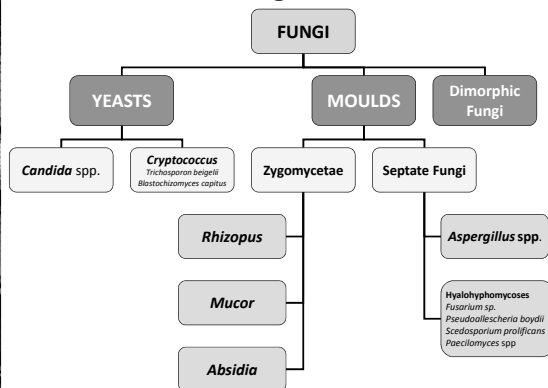
Diagnosis and Treatment of Aspergillosis and Therapeutic Drug Monitoring (TDM)


Peggy L. Carver, Pharm.D., FCCP

Activity Chair

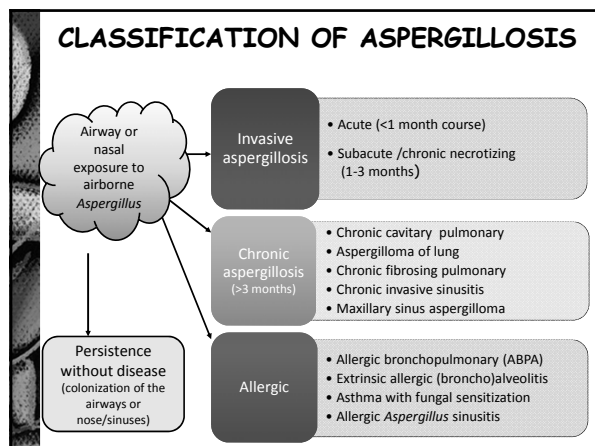
Associate Professor of Pharmacy
The University of Michigan College of Pharmacy
Ann Arbor, Michigan

The Fungal World



Which of the following statements is correct? 

- a. Aspergillosis is rarely difficult to diagnose.
- b. Aspergillosis should always be treated with a combination of antifungal agents.
- c. Aspergillosis is most often treated with voriconazole, amphotericin B or echinocandins.



Patient case – diagnosis of aspergillosis

- AR is a 42-year-old male, post-HSCT for AML, complicated by grade II GVHD, who presents with cough, dyspnea with pulmonary nodules 3 weeks post-transplant.
- Invasive pulmonary aspergillosis was diagnosed via:
 - chest CT (nodules with halo)
 - positive galactomannan antigen tests (levels 3.2, 1.9)
 - a needle biopsy which grew *A. fumigatus*.


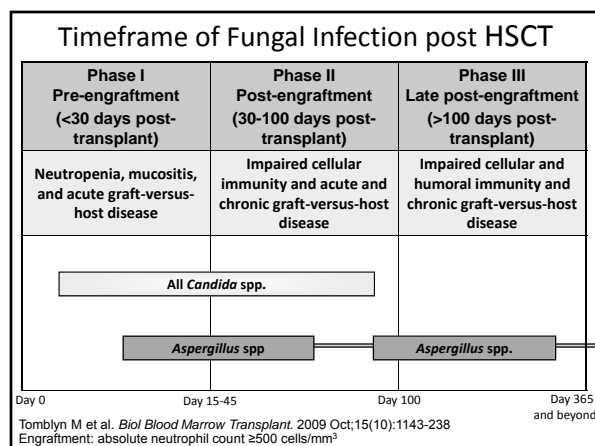
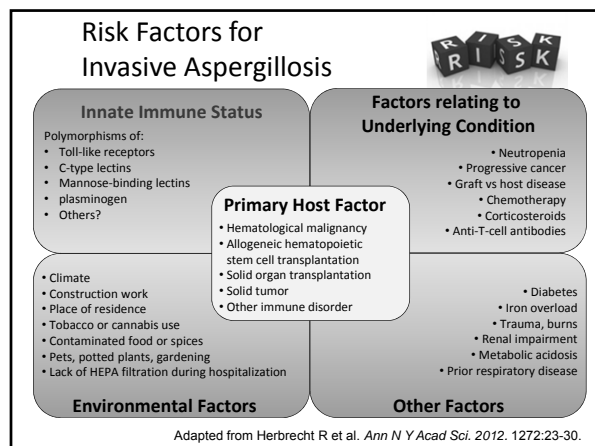


Image provided by Dr. Carver

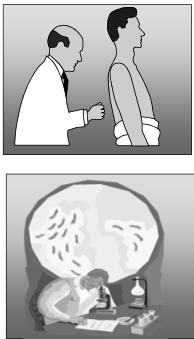
AML = acute myeloid leukemia; GVHD = graft-versus-host-disease; HSCT=Hematopoietic Stem Cell Transplantation





See page 38 for enlarged view

Difficulties in the Diagnosis of Invasive Aspergillosis

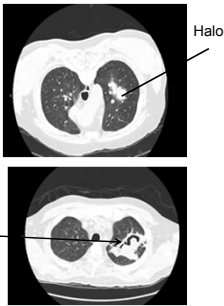


- Clinical/patient
 - nonspecific symptoms
 - tissue biopsies difficult to obtain
- Microbiological
 - Tissue cultures often unavailable
 - Difficult to differentiate colonization vs. infection
 - Blood cultures rarely positive

Radiological Difficulties in the Diagnosis of Invasive Aspergillosis

- “Halo sign”
 - very sensitive but non specific
 - perimeter of ground-glass opacity surrounding hemorrhagic nodular lesion
 - small vessel angioinvasion → thrombosis of small/medium sized vessels → ischemic necrosis
 - seen EARLY in disease; lasts <5 days
- “Air-crescent” Sign
 - crescent of gas above a soft tissue sequestrum within a nodular or cavitary lesion; due to tissue contraction
 - not useful for early diagnosis
 - seen LATE in angioinvasive IA
 - correlates with recovery of neutrophils

CT Scan



Images provided by Dr. Carver

http://www.medscape.org/viewarticle/444470_4,
 Pinto PS. *Radiology.* 2004; 230: 109-110.

The search for fungal biomarkers for invasive aspergillosis

- Galactomannan antigen
 - Detects *Aspergillus* species (also *Penicillium* spp)
 - good negative predictive value, but low positive predictive value
 - test performs less well in solid organ transplant patients
 - Cross-reactivity with pip/tazo
- β -D-glucan
 - nonspecific for *Candida*
 - ‘pan’ fungal **except** cryptococcus and zygomycetes
- PCR
 - Species specific
 - Simple, sensitive but potential for contamination
- Novel methods under development
 - monoclonal antibody JF5
 - *Aspergillus* nucleic acids
 - siderophore detection
 - MALDI-TOF

Johnson G, et al. *Biomark Med.* 2014; 8:429-51.
Horton CR. 2014. *Exp Rev Clin Imm* 10(6):771-80.

Treatment of Aspergillosis

Patient case – initial therapy of aspergillosis

- AR was initiated on voriconazole, but he experienced visual hallucinations, which responded to a dosage reduction, and then a severe rash.
- Therapy was changed to Liposomal-AmB (5 mg/kg/day IV).

Image provided by Dr. Carver

X = no in vitro activity; ✓ = in vitro activity; R = resistance
AmB = amphotericin B; Flucon = fluconazole; Itra = itraconazole; Posa = posaconazole; Vori = voriconazole;
Echino = echinocandins (caspofungin, micafungin, anidulafungin)

A
A
A
E
C
A

¹Walsh
²Maer
AmbB

¹Walsh TJ et al. Clin Infect Dis 2008; 46:32-60; ²Prentice AG et al. http://www.bcsghguidelines.com/documents/fungal_infection_bcsgh_2008.pdf accessed 10/24/14; ³Maertens J et al. Bone Marrow Transpl 2011; 46:709-18; ⁴Bohme A et al. Ann Hematol 2009;88:97-110; ⁵Thursky KA et al. Intern Med J 2008;38:496-520. AMB = amphotericin B, d-AMB = deoxycholate AMB, L-AMB = liposomal AMB, ABLC = AMB lipid complex; ABCD = AmBiscol AMB colloid dispersion

OLA ⁺ Lipid d-An	% Surviving
0	100
1	100
2	100
3	100
4	100
5	100
6	100
7	100
8	100
9	100
10	100
11	100
12	100
13	100
14	100
15	100
16	100
17	100
18	100
19	100
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92	100
93	100
94	100
95	100
96	100
97	100
98	100
99	100
100	100



What if the patient doesn't respond to Voriconazole?

- Causes of antifungal therapy failure
 - Host factors (severity of illness, immune suppression)
 - Primary or acquired drug resistance
 - Wrong diagnosis or mixed infection
 - Pharmacokinetic factors
 - complex pharmacokinetics of antifungal agents
 - Drug-drug or drug-food interactions
 - adherence
- Treatment options - **salvage therapy** of aspergillosis
 - CONTINUE with the same agent, or another agent in the same class with a broader spectrum
 - CHANGE to a different antifungal class
 - COMBINE antifungal drugs

Nucci M. et al. *Clin Infect Dis* 2008;1426-33.

Patient case – salvage therapy of aspergillosis

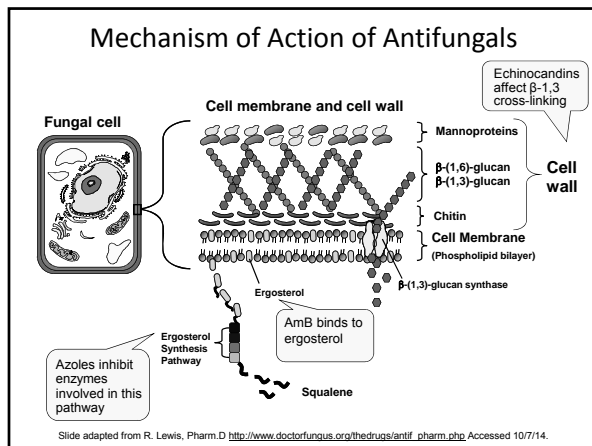
- AR's aspergillosis progressed despite 11 days of L-AmB
- Caspofungin was added in combination with L-AmB for 6 months, with a complete response

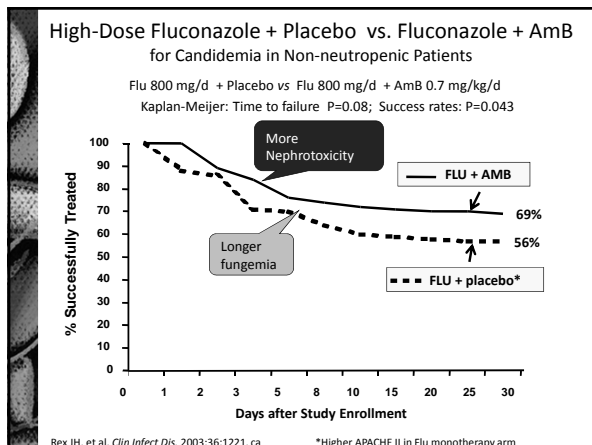


Image provided by Dr. Carver

Invasive Aspergillosis

Combination Antifungal Therapy





Should we use Combination Antifungal Therapy ?

The Case FOR


The Case AGAINST

The Case FOR Combination Therapy	The Case AGAINST Combination Therapy
<ul style="list-style-type: none"> Mortality rates are HIGH Enables \uparrow spectrum of activity More rapid killing \downarrow chances of developing resistance No overlapping toxicities 	<ul style="list-style-type: none"> Lack of <ul style="list-style-type: none"> correlation between <i>in vitro</i> data, animal models, and clinical experience solid clinical data Possibility of antagonism \uparrow risk of drug interactions and toxicities

Combination Therapy for Invasive Aspergillosis		
Regimen	Study Design	Main outcomes
CASPOFUNGIN + L-AmB		
Aliff 2003	• Retrospective study in leukemics (N=30) • Salvage therapy with L-AmB + caspo	• Favorable response in 60% (18/30)
Kontoyannis 2003	• Retrospective, heme patients (N=48) • Salvage therapy of caspo addition after ≥7 d L-AmB	• Only 18% response to combo therapy
Caillot 2007	• Prospective, open label in heme patients (N=30) • L-AmB 3 mg/kg/d + caspo vs L-AmB 10 mg/kg/day	• "CombiStrat" study. More favorable responses (partial or complete) in combo tx group
CASPOFUNGIN or ANIDULAFUNGIN + VORICONAZOLE		
Marr 2004	• Vori (prior to 2001) vs vori + caspo (after 2001) after progression of disease on ≥7 d AmB	• combo therapy pts had a significantly lower rate of mortality vs vori monotherapy
Maertens 2006	• Salvage therapy with caspo + another 'mold-active' agent in patients refractory to or intolerant of standard antifungal therapy (N=53)	• Success = 55% & 49% (at end of combo therapy & Day 84, respectively). • Day 84 survival = 55%.
Singh 2006	• Prospective, randomized, MC, observational • Vori or caspo (N=40) 1 st therapy vs historical control (N=47) of L-AmB therapy in SOT	• No difference in 90 day survival overall, although in pts with renal failure or <i>A. fumigatus</i> , combo therapy was associated with ↑ survival
Upton 2007	• Retrospective in HSCT (N=405); Vori + caspo vs caspo alone	• No difference in clinical outcomes of Vori + caspo as primary therapy vs vori monotherapy
Marr 2012	• Prospective, randomized, MC study in heme ± HSCT (N=277) • Vori alone vs vori + anidula; 1 st endpoint = 6 wk survival	• trend toward ↑ 6 wk survival with combination of vori + anidula vs vori monotherapy.

Aliff. Cancer 2003;4:1025-32; Kontoyannis. Cancer 2003;2:292-9; Caillot D. Cancer 2007; 110:2740; Marr et al. CID 2004;39:797-802; Maertens et al. Cancer 2006;107:2888-97; Singh. Transplantation 2008; 81(3): 320-6; Upton. CID 2007;44:531; Marr K. Presented at: 22nd ECCMID, London, UK, 3/31/12-4/3/12.
MC = multicenter; SOT = Solid organ transplant; HSCT = hematopoietic stem cell transplant; heme = hematological malignancy; L-AmB = liposomal amphotericin B; Vori = voriconazole; anidula = anidulafungin; caspo = caspofungin; micamicalungin

See page 39 for enlarged view



Patient case – salvage therapy of aspergillosis

- AR's aspergillosis progressed despite 11 days of L-AmB
- Caspofungin was added in combination with L-AmB for 6 months, with a complete response
- AR was continued on oral itraconazole maintenance therapy.





Image provided by Dr. Carver



Antifungal Therapeutic Drug Monitoring (TDM)

Plasma level monitoring of antifungals:



- is rarely necessary unless toxicity is observed.
- should probably be performed in all patients receiving long term voriconazole therapy for aspergillosis.
- is required for fluconazole, voriconazole, and caspofungin because the efficacy of these agents correlates with peak levels.

Therapeutic drug monitoring (TDM) of antifungals ?

- When is TDM needed?
 - An established relationship exists between *plasma drug concentrations* and:
 - efficacy
 - toxicity
 - Recommended for drugs with:
 - narrow therapeutic index
 - variable pharmacokinetics
 - questionable compliance, absorption, or drug-drug interactions

Plasma Concentration Monitoring of Antifungals

Drug	Serum concentration monitoring necessary?	Target concentrations for Treatment & Prophylaxis	Timing of sample
Itraconazole	Yes, to ensure absorption & efficacy	Trough > 0.5 µg/mL	Trough after 7 days therapy
Voriconazole	Yes <ul style="list-style-type: none"> variable metabolism due to nonlinear PK & genetic variability in CYP2C19 → unpredictable dose-exposure relationship low concs are assoc with poor outcome; high concs are assoc with adverse effects. 	<ul style="list-style-type: none"> Wide range of recs due to heterogeneous study designs. Troughs >1-2 µg/mL; concs >2.05 µg/mL assoc with improved outcome; 2-5.5 µg/mL probably best target Concs >5.5 µg/mL assoc with ↑ risk of visual & hepatic adverse events 	<ul style="list-style-type: none"> Trough after 5 days therapy? Nonlinear metabolism, so time to SS is unpredictable
Posaconazole suspension & tablets	Maybe <ul style="list-style-type: none"> Outcomes (but not adverse events) correlate with higher plasma concs in prophylaxis & possibly treatment 	<ul style="list-style-type: none"> Treatment: not well studied concs >1.25 mg/L needed? Prophylaxis: >700 ng/mL ? 	<ul style="list-style-type: none"> Random level at SS (>7 days therapy). Long $t_{1/2}$ ensures little fluctuation in peaks & troughs at SS.
Flucytosine	Yes <ul style="list-style-type: none"> high concs are assoc with toxicity 	Peak conc < 100 µg/mL	2 hours post-dose peak

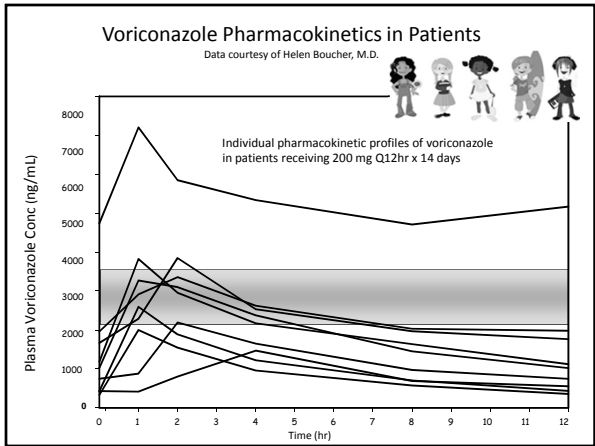
Adapted from: Dodds-Ashley ES et al. Clin Infect Dis. 2006;43 suppl 1:S28-39. ; Smith J et al. Antimicrob Agents Chemother. 2006; 50:1570-2. ; Jang SH et al. Clin Pharmacol Ther. 2010; 88:115-9. ; Hussaini T et al. Pharmacotherapy 2011;31(2):214-25.
NA = not applicable or not known; concs = concentrations; SS=steady state

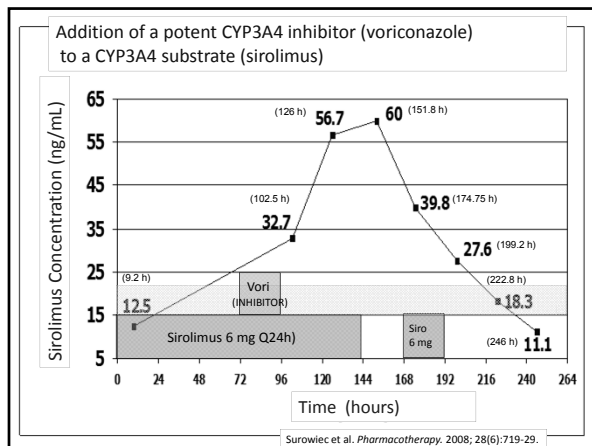
See page 39 for enlarged view

Adverse Effects and Drug Interactions

	Drug Interactions with Azole Antifungals			
	CYP enzymes		P-glycoprotein	
	Substrate	Inhibitor	Substrate	Inhibitor
Fluconazole	3A4	3A4 (++) 2C9, 2C19 (++)	Yes	No
Itraconazole	3A4	3A4 (+++)	Yes	Yes
Voriconazole	3A4 2C9, 2C19 (for N-oxide metabolite)	3A4 (+) 2C9 (++) 2C19 (++)	No	No
Posaconazole	NOT a substrate of CYPs; metabolized via UGT pathway	3A4 (++)	Yes	Yes

UGT = UDP-glucuronidation; CYP = cytochrome P450; CYP interactions are classified as
+++ = strong; ++ = moderate; + = weak. Saad AH, et al. 2006. Pharmacotherapy 26(12):1730-44.





Can voriconazole & sirolimus be safely co-administered?

- **Yes !**
 - as long as you evaluate:
 - which agent the patient receives first
 - the sirolimus dosage
 - sirolimus levels
 - concurrent disease states
 - CYP3A isoenzyme inhibitors
 - Sirolimus levels should be closely and routinely monitored before, during, and after coadministration of voriconazole and other CYP3A isoenzyme inhibitors.

Side Effects of Systemic Antifungal Agents

Adverse Effect	AmB	Flucon	Itra	Vori	Posa	Echino
Nephrotoxicity	✓	X	X (possible with IV)	X (possible with IV)	X	X
Abdominal Discomfort	X	✓	✓	✓	✓	X
↑ Hepatic Transaminases	✓	✓	✓	✓	✓	✓
Rash, photosensitivity	X	✓	✓	✓ (vori - malignancy)	✓	✓
Infusion-related Reactions / Histamine Release	✓	X	X	X	X	✓
CNS & Visual Disturbances	X	X	X	✓	X	X
Cardiomyopathy (itra), ↑ QT (azoles), ? echinos	X	✓	✓	✓	✓	?

Adapted from Lewis RE. *Mayo Clin Proc*. 2011;86(8):805-817

Long-term adverse effects of antifungals

- Long-term use of antifungals is common
 - Prophylaxis
 - Treatment of aspergillosis
- Voriconazole
 - Alopecia
 - Phototoxicity
 - skin cancer
 - photosensitivity
 - Periostitis/Fluoride toxicity

Conclusions

- Aspergillosis remains difficult to diagnose
- Although aspergillosis is most often treated with voriconazole, amphotericin B, and echinocandins are often utilized in therapy, in particular as salvage therapy or as part of combination therapy
- Adverse effects and drug interactions remain problematic with antifungals
- The role of therapeutic drug monitoring of antifungals remains controversial; however, voriconazole (and perhaps posaconazole) should be monitored

You might expect a diagnostic from pure blood to have a tough time detecting the pathogen

Comparison of the *Candida* spp. detection and time to detection between the Bactec 9050 and T2Candida assay run on the T2DX. Whole blood samples spiked with *Candida* species (1-10 CFU/mL)

<i>Candida</i> spp.	Instrument	No. samples	Detection of <i>Candida</i> spp.		Time to detection		
			% positive*	P value	Median h (± SD)	P value	
<i>C. albicans</i>	Bactec 9050	20	100%	1.0	106 ± 5.26 h	<0.001	
	T2DX	20	100%		3.85 ± 0.29 h		
<i>C. glabrata</i>	Bactec 9050	20	0%		NA	NA	
	T2DX	20	100%		3.6 ± 0.27 h		
<i>C. parapsilosis</i>	Bactec 9050	20	100%	1.0	78.25 ± 4.46 h	<0.001	
	T2DX	18	100%		3.6 ± 0.3 h		
<i>C. tropicalis</i>	Bactec 9050	20	100%	1.0	30.58 ± 2.15 h	<0.001	
	T2DX	13	100%		3.57 ± 0.32 h		
<i>C. krusei</i>	Bactec 9050	20	100%	1.0	40.5 ± 2.23 h	<0.001	
	T2DX	19	100%		3.83 ± 0.27 h		

Beyda ND et al. *Diagn Microbiol Infect Dis.* 2013; 77:324-6.

Risk Factors for Invasive Aspergillosis



Innate Immune Status

- Polymorphisms of:
- Toll-like receptors
 - C-type lectins
 - Mannose-binding lectins
 - plasminogen
 - Others?

Factors relating to Underlying Condition

- Neutropenia
- Progressive cancer
- Graft vs host disease
- Chemotherapy
- Corticosteroids
- Anti-T-cell antibodies

Primary Host Factor

- Hematological malignancy
- Allogeneic hematopoietic stem cell transplantation
- Solid organ transplantation
- Solid tumor
- Other immune disorder

- Climate
- Construction work
- Place of residence
- Tobacco or cannabis use
- Contaminated food or spices
- Pets, potted plants, gardening
- Lack of HEPA filtration during hospitalization

Environmental Factors

- Diabetes
- Iron overload
- Trauma, burns
- Renal impairment
- Metabolic acidosis
- Prior respiratory disease

Other Factors

Adapted from Herbrecht R et al. *Ann N Y Acad Sci.* 2012. 1272:23-30.

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