

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

Live Webinar

Wednesday, March 18, 2015
1:00 p.m. – 2:00 p.m. ET

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On-demand Activity

Live webinar recorded and archived to be watched at your convenience



Planned by ASHP Advantage and supported by an educational grant from Merck.

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

Activity Overview

This activity will focus on current issues related to the management of antifungal infections in hospitalized patients, especially related to antifungal stewardship. The faculty will address these issues and provide practice pearls for pharmacists.

The content of this activity is based on questions raised by participants in a recent educational symposium on this topic as well as clinical aspects of treating patients with antifungal infections that faculty want to discuss further.

Learning Objectives

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

- Distinguish how and when to incorporate rapid diagnostics into appropriate treatment guidelines of systemic candidiasis.
- Choose correct antifungal treatment, including appropriate dosing, in patients with suspected/proven fungal infections.
- Examine a bundled stewardship approach to antifungal stewardship.

Continuing Education Accreditation



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 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-15-423-L01-P for the live activity and ACPE activity #0204-0000-15-423-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 the live activity or completion of a home study activity.

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

Activity 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

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.

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

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.

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

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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.
- All other planners report no financial relationships relevant to this activity.

CE IN THE MIDDAY

Ask the Experts: Antifungal Stewardship from Diagnosis to Treatment and Beyond

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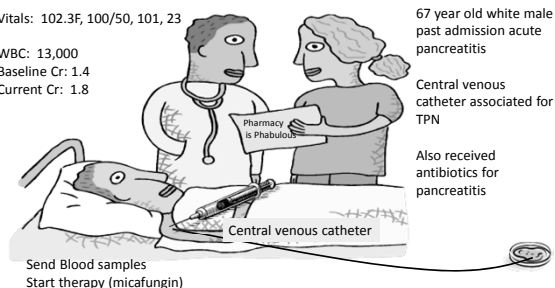
Learning Objectives

- Distinguish how and when to incorporate rapid diagnostics into appropriate treatment guidelines of systemic candidiasis.
- Choose correct antifungal treatment, including appropriate dosing, in patients with suspected/proven fungal infections.
- Examine a bundled stewardship approach to antifungal stewardship.

Systemic *Candida* Infections

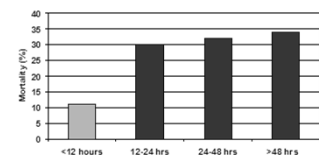
Vitals: 102.3F, 100/50, 101, 23

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

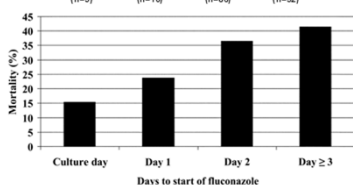


Diagnosis: Suspected systemic candidiasis!!!

A delay in the initiation of antifungals increases bad outcomes in patients with candidemia



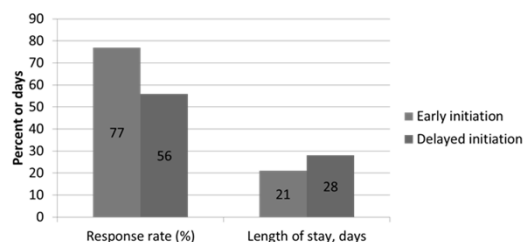
Morrell M et al. *Antimicrobial Agents Chemother.* 2005; 49: 3640-5.



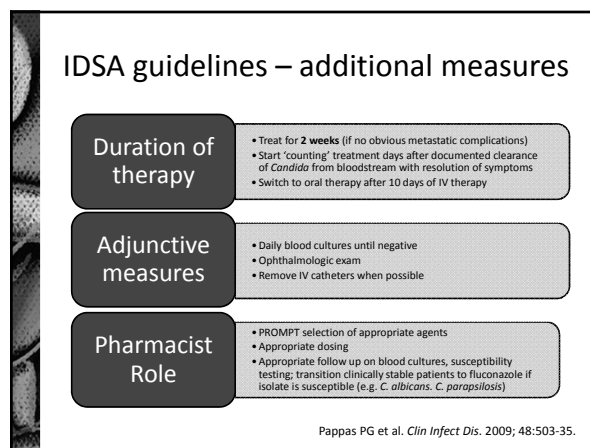
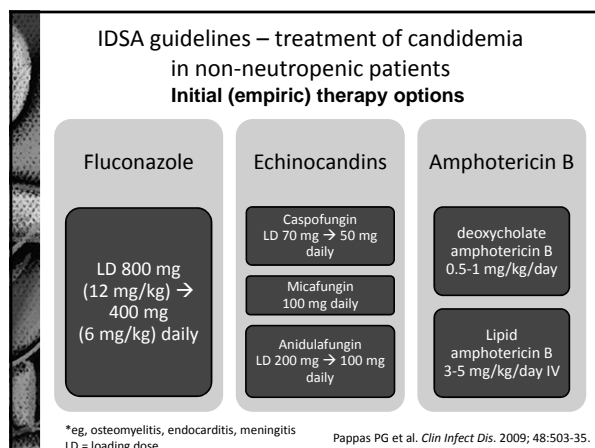
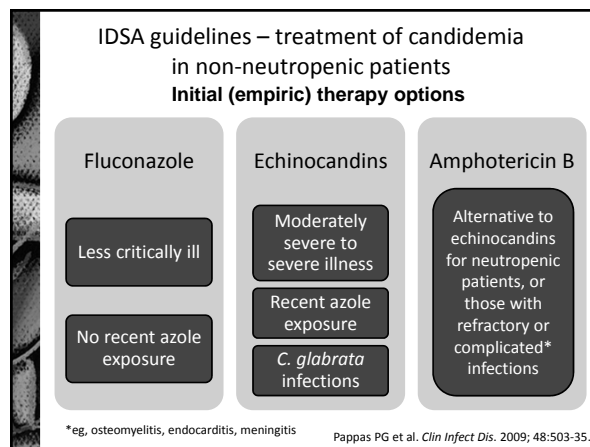
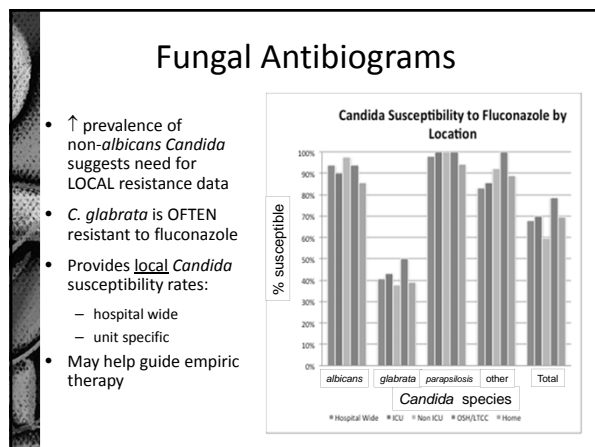
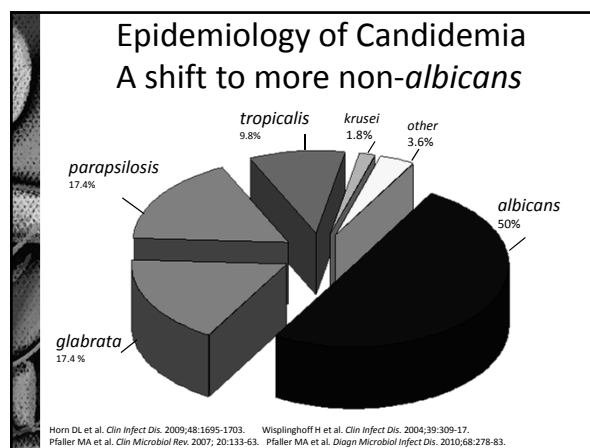
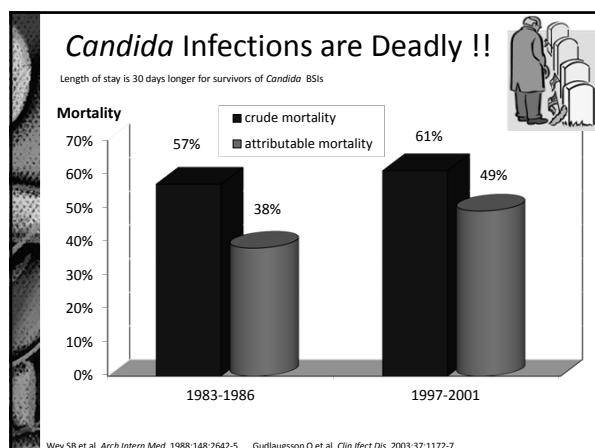
Garey KW et al. *Clin Infect Dis.* 2006; 43:25-31.

A delay in echinocandins also is associated with poor outcomes

Multicenter study of 169 patients with candidemia given caspofungin



Hsu D. *J Antimicrob Chemother.* 2010; 65(8):1765-70.



Highlights of Recent Studies and European *Candida* Guidelines

- For moderately or severely ill patients
 - Start with an echinocandin or amphotericin B if catheters cannot be removed
 - Severity of illness and choice of antifungal predict response in patients with *C. glabrata* fungemia, but do not influence mortality
 - When there is improvement, switch to fluconazole (if the pathogen is susceptible), and to PO therapy after 10 days of IV therapy
 - Treat for 2 weeks after blood cultures are negative
- New CLSI fluconazole susceptibility breakpoints for *C. glabrata* are predictive of response when fluconazole is dosed appropriately.
- Where do pharmacists come in?
 - Appropriate dosing!

Cornely OA et al. *Clin Microbiol Infect.* 2012; 18:19-37. Andes DR et al. *Clin Infect Dis.* 2012;54:1110-22. Eschenauer GA et al. *J Antimicrob Chemother.* 2013;68(4):922-6.

What is new since the guidelines

- Antifungal resistance (the bad news)
 - echinocandin-resistant *Candida*
- Rapid *Candida* diagnostics (the good news)
- Antifungal stewardship bundles (the solution?)

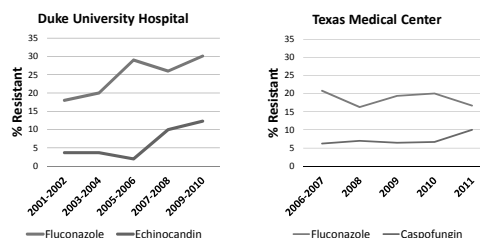
Echinocandin resistance relatively uncommon globally

- 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.

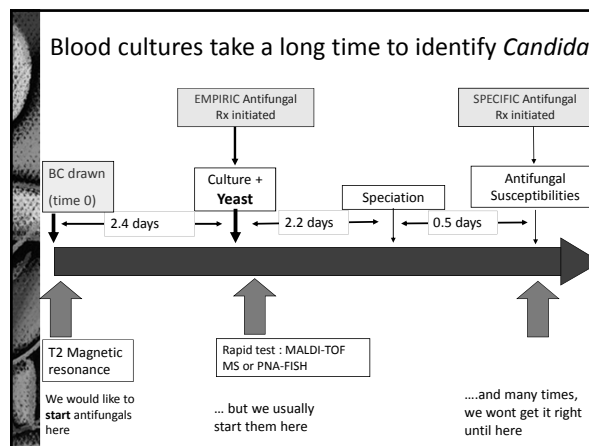
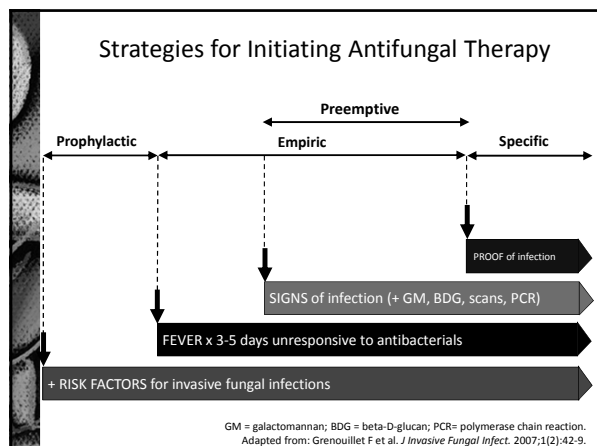
The biggest predictor of echinocandin resistance is prior use of an echinocandin!

	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.

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, and the timeline for diagnosis of infections



Beyond blood cultures:

Options for the rapid detection of *Candida*

Which 'rapid diagnostic test' does your hospital utilize?

- None, or Germ tube testing
- PNA-FISH
- MALDI TOF
- T2 Magnetic resonance
- I have no idea...

Germ Tube Test

- Presumptive identification of *C. albicans* vs. non-*albicans* spp.
- Simple, rapid (2-3 hr), reliable, economical
- Evaluates *Candida* hyphae (germ tube) formation at 37°C in pooled human sera

+ germ tube → *C. albicans* or *C. dubliniensis*
 Ø germ tube → Non-*albicans Candida*
 (Caution: rarely, some *C. albicans* will not show hyphal formation)

Do you fish? (PNA-FISH®)

- Fluorescence in-situ hybridization (FISH)
- A drop from positive blood culture is fixed onto a microscope slide
- PNA probe hybridizes to the *C. albicans* & *C. glabrata* rRNA

http://www.atsd.com/pubs/2014/04/20140401_atsd_mediapub_c_401

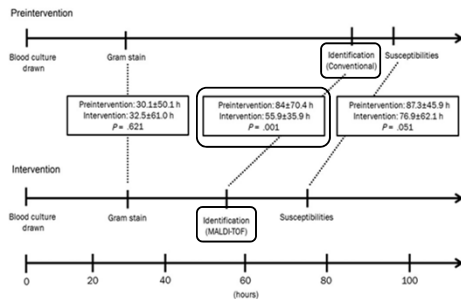
PNA FISH (+ stewardship) did not decrease the time to optimal therapy with *C. glabrata*

	NO fluconazole susceptibility testing NO PNA FISH® Phase 1 N=41	+ fluconazole susceptibility testing NO PNA FISH® Phase 2 N=35	+ fluconazole susceptibility testing + PNA FISH® Phase 3 N=47
EVENT	Time (days) (Range) IQR		
appropriate AF therapy for <i>C. glabrata</i>	2.4 ± 2.8 [0-6.6]	4.6 ± 4.2 [0-11.2]	2.9 ± 2.2 [0-6.3]
optimal AF therapy for <i>C. glabrata</i>	2.4 ± 2.8 [0-6.6]	5.0 ± 4.5** [0-11.2]	3.8 ± 3.0 [0-8.9]

** = P<0.05

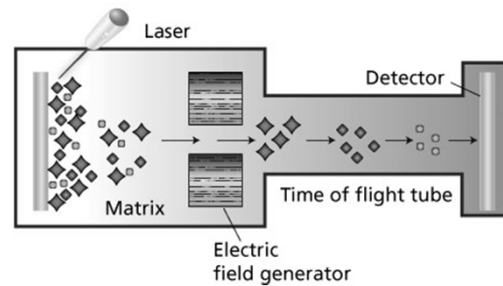
Carver et al. IDSA Annual Meeting 2010, Poster #616.

Use of MALDI TOF + real-time stewardship interventions



Huang AM, et al. Clin Infect Dis 2013;57(9):1237-45.

Maldi TOF

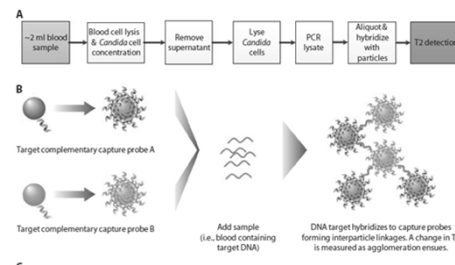


MALDI-TOF with AST intervention decreased time to organism identification and time to effective and optimal antibiotic therapy

- 'real-time' pages and email alerts 24 hrs/day
 - allowed for AST review of pertinent electronic medical records and
 - intervention at the time of all organism identification, reporting of susceptibility results, and the majority of Gram stain results.
- All patients with + blood cultures (bacteria & yeast)
- Provided prescribers with pre-established, evidence-based antibiotic recommendations in accordance with institutional guidelines

Huang AM et al. Clin Infect Dis. 2013; 57(9):1237-45.

T2 Magnetic resonance



From Neely LA et al. Sci Transl Med. 2013 Apr 24; 5(182):182ra54. Reprinted with permission from AAAS.

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)

Candida spp.	Instrument	No. samples	Detection of Candida 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 hr	<0.001
	T2DX	20	100%		3.85 ± 0.29 hr	
<i>C. glabrata</i>	Bactec 9050	20	0%		NA	NA
	T2DX	20	100%		3.6 ± 0.27 hr	
<i>C. parapsilosis</i>	Bactec 9050	20	100%	1.0	78.25 ± 4.46 hr	<0.001
	T2DX	18	100%		3.6 ± 0.3 hr	
<i>C. tropicalis</i>	Bactec 9050	20	100%	1.0	30.58 ± 2.15 hr	<0.001
	T2DX	13	100%		3.57 ± 0.32 hr	
<i>C. krusei</i>	Bactec 9050	20	100%	1.0	40.5 ± 2.23 hr	<0.001
	T2DX	19	100%		3.83 ± 0.27 hr	

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

Multicenter clinical trial of T2MR

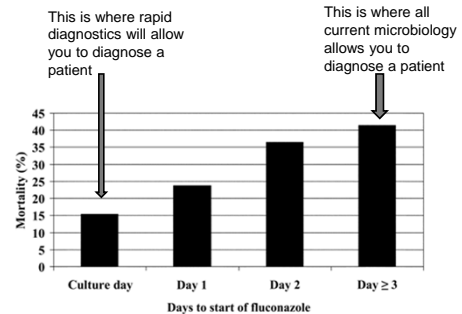
- Fully automated; Direct analysis of whole blood specimens
- Mean time to:
 - negative result = 4.2 ± 0.9 hrs
 - detection and species identification = 4.4 ± 1.0 hrs
- Overall
 - specificity = 99.4% (95% CI 99.1%-99.6%)
 - sensitivity = 91.1% (95% CI 86.9%-94.2%)
- Specificity of individual species:
 - *C. albicans* / *C. tropicalis* 98.9% (95% CI 98.3%-99.4%)
 - *C. parapsilosis* 99.3% (95% CI 98.7%-99.6%)
 - *C. krusei* / *C. glabrata* 99.9% (95% CI 99.7%-100.0%)

Mylonakis E et al. Clin Infect Dis. 2015; 60: 892-9.

Implications for pharmacy practice

ID/antimicrobial stewardship
pharmacists are likely to become
“react to positive diagnostic test”
pharmacists

Rapid diagnostics will decrease mortality rates due to systemic candidiasis



Beyond blood cultures: Options for the rapid detection of *Candida*

Which ‘rapid diagnostic test’ would you LIKE your hospital to utilize?

- a. None, or Germ tube testing
- b. PNA-FISH
- c. MALDI TOF
- d. T2 Magnetic resonance
- e. I have no idea...

Why Antifungal Stewardship ?

- Antimicrobial stewardship has overwhelmingly focused on antibiotics
- Antifungal agents have been largely neglected, despite deficiencies in prescribing behavior
- High drug cost
- Potential for toxicities, esp with long term use

Ananda-Rajah M et al. *Curr Opin Infect Dis.* 2012;25:107-115.

Antifungal Stewardship Activities in Common with Antibiotic Stewardship

- Guidelines for antifungal use in institution
- Recommendations for empiric therapy
 - Use of local epidemiology to determine empiric therapy
 - Susceptibility testing
 - Rapid diagnostic tests
- De-escalation of empiric therapy
- Dosing /dose adjustments

Ananda-Rajah M et al. *Curr Opin Infect Dis.* 2012;25:107-115.

What Did We Discover By Constructing A Fungal Antibigram at our Hospital?

- Although *C. glabrata* BSIs continue to be highly resistant to fluconazole, resistance has not changed significantly in the last 8 years.
- Spending time in the ICU is not predictive of fluconazole susceptibility at our hospital.

Care Bundles

- Used to systematically manage specific diagnoses in order to improve patient quality of care
- Defined elements of care monitored to ensure compliance
- Ensure patients consistently receive optimal treatment
- 'All or none' philosophy

Cooke FJ et al. *Int J Antimicrob Agents*. 2007; 30:25-9.
Antworth A et al. *Pharmacotherapy*. 2013; 33: 137-43.

Implementation of a *Candidemia* Care Bundle Improved Compliance with Key Care Elements

Key Bundle Element	Control group (%)	AST intervention group (%)	P value
Compliance with all candidemia care bundle endpoints	40	78	0.0016
Rates of ophthalmological consult	75.7	97.6	0.01
Selection of appropriate antifungal therapy	86.5	100	0.0488
Compliance with an appropriate duration of therapy	67.7	97.6	0.0012
Excess total days of therapy	83 antifungal days	5 antifungal days	---

Antworth A et al. *Pharmacotherapy*. 2013; 33: 137-43.

Better Outcomes when Compliant with *Candidemia* Bundles

- Nation-wide study in Japan (N=608)
- Significant difference in clinical success between patients with and without bundle compliance [92.9% versus 75.8% (P = 0.011)].
- Bundle compliance (after exclusion of step down to PO therapy) was an independent predictor of:
 - clinical success (OR 4.42, 95% CI 2.05 – 9.52)
 - mortality (OR 0.27, 95% CI 0.13 – 0.57),
- Independent individual elements contributing to clinical success were
 - removal of central venous catheters within 24 h,
 - assessment of clinical efficacy on the 3rd to the 5th day
 - at least 2 weeks of therapy after clearance of candidemia.

Takesue Y et al. *Journal Antimicrob Chemother*. 2015; 70:587-93.

Conclusions

- Pharmacists reacting to rapid diagnostic tests for systemic candidiasis could significantly improve patient care
- Fluconazole:
 - Give a loading dose, then at least 6 mg/kg (800 mg for all?)
 - Improved outcomes (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
- Antifungal stewardship
 - EARLY initiation of therapy
 - RESPOND to diagnostic tests, don't just do them
 - De-escalate when susceptibility data is available
 - Consider a 'bundle' approach