

# Challenges in the Management of Serious Fungal Infections



Counteracting the Impact of **Candidemia** in the **Acute-Care Setting**



**CE Credit for Pharmacists**



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**Presenter**

James S. Lewis II, PharmD

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# Challenges in the Management of Serious Fungal Infections

## Counteracting the Impact of Candidemia in the Acute-Care Setting

### Presenter

**James S. Lewis II, PharmD**  
 Infectious Diseases Pharmacy Programs Manager  
 University Health Systems, San Antonio  
 Clinical Assistant Professor  
 University of Texas Health Science Center

### Q&A Cohost

**Elizabeth Dodds Ashley, PharmD, BCPS**  
 Clinical Associate  
 Duke University Medical Center

### Clinical Reviewer

**Nina Singh, MD**  
 Associate Professor of Medicine  
 University of Pittsburgh  
 Chief of Transplant Infectious Diseases  
 VA Medical Center



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### Target Audience

This activity is designed for hospital pharmacists.

### Learning Objectives

At the conclusion of this activity, participants should be able to:

- List the factors that contribute to the prevalence of fungal infections
- Summarize the burden of candidemia in the acute-care setting
- Assess the efficacy, adverse effect profiles, and tolerability of available agents for the treatment of candidemia
- Implement an appropriate treatment algorithm to evaluate optimal management of candidemia in acute-care patients

### Statement of Need

Candidemia is the fourth most common bloodstream infection in the United States and the leading fungal pathogen encountered in US hospitals. Invasive candidiasis is associated with an average increased length of hospital stay of more than 10 days and a mortality rate of up to 30%. Candidemia infections have also been estimated to increase hospital charges by nearly \$40,000 per patient.

Compounding the seriousness of invasive candidiasis is the fact that patients at risk of candidemia are frequently severely ill, including those who spend more than 3 days in an intensive care unit, patients with diabetes, those on dialysis, and patients undergoing gastrointestinal surgery. Furthermore, the most common agent traditionally used for the treatment of patients with invasive candidiasis, amphotericin B deoxycholate, is associated with significant toxicity.

Treatment options for invasive candidiasis have increased considerably in recent years with 2 newer classes of drugs—the azoles (eg, ketoconazole, fluconazole, itraconazole, voriconazole, and posaconazole) and, more recently, the echinocandins (eg, caspofungin, micafungin, and anidulafungin [investigational])—joining amphotericin B deoxycholate as the most common agents for the acute care of patients with candidemia.

Along with the introduction and continued development of newer antifungal therapies, evidence is accumulating regarding the efficacy, tolerability, and cost impact of these agents and their appropriate role in the management of invasive candidiasis. These data are of specific importance to pharmacists who play a critical role in pharmacologic infection control in the hospital setting. Hospital pharmacists require education regarding the clinical and economic burden of invasive candidiasis in the hospital setting, the at-risk patient population, and the latest evidence demonstrating the current and potential role of newer classes of antifungal therapies in the treatment of seriously ill patients with candidemia.

### **CPE Accreditation**

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### **Clinical Review**

This activity was reviewed by Nina Singh, MD, Associate Professor of Medicine, University of Pittsburgh, Chief of Transplant Infectious Diseases, VA Medical Center.

### **Disclosure Information**

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The faculty reported the following:

**Dr. Dodds Ashley:** Consultant/grant support/speakers bureau—Astellas, Enzon, Merck, Pfizer, Schering Plough

**Dr. Lewis:** Consultant/speakers bureau—Astellas Pharma Inc, Pfizer Inc, Schering Plough

**Dr. Singh:** Grant support—Enzon, Schering Plough

The University of Tennessee College of Pharmacy and Princeton Media Associates require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation. Dr. Lewis has disclosed that he will discuss off-label/unapproved uses of the following: prophylaxis of fungal infections in the intensive care unit; the use of micafungin and posaconazole to treat candidemia; real-time polymerase chain reaction testing for diagnosis of candidemia; and the use of recombinant monoclonal antibody targeting heat shock protein 90 for the treatment of candidemia.

## Challenges in the Management of Serious Fungal Infections: Counteracting the Impact of Candidemia in the Acute-Care Setting

James S. Lewis II, PharmD  
 Infectious Disease Pharmacy Programs Manager  
 Clinical Assistant Professor  
 University Health System  
 University of Texas Health Science Center  
 San Antonio

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## Learning Objectives

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## What We Are Going to Cover

- Epidemiology overview
- Susceptibility issues
- Where do the antifungal classes stand?
  - Echinocandins
  - Azoles
  - Polyenes
- Species-specific issues in *Candida* species (sp) infections

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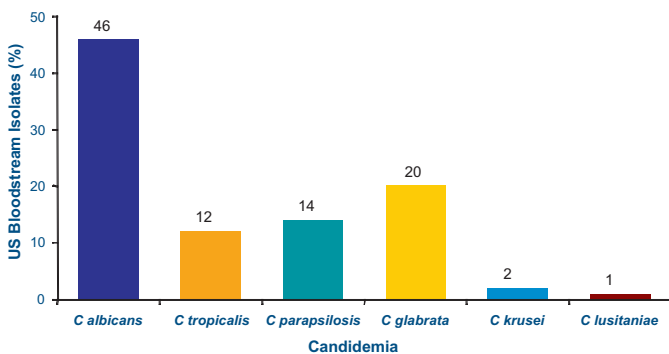
## The Impact of Candidemia

- Fourth most common bloodstream isolate
- Leading fungal pathogen in US hospitals
- 14.5% attributable mortality in adults
- 10.1-day increased length of stay
- \$39,331 increased hospital charges

Zaoutis TE, et al. *Clin Infect Dis*. 2005;41:1232-1239.  
 Weinberger M, et al. *J Hosp Infect*. 2005;61:146.

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## Not Just *Candida albicans*



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## General Susceptibility Patterns of *Candida* Species

Species	Flu	Itra	Vori	Candins	Ampho
<i>albicans</i>	S	S	S	S	S
<i>tropicalis</i>	S	S	S	S	S
<i>parapsilosis</i>	S	S	S	S to I	S
<i>glabrata</i>	S-DD to R	S-DD to R	S to I	S	S to I
<i>krusei</i>	R	S-DD to R	S to I	S	S to I
<i>lusitaniae</i>	S	S	S	S	S to R

Flu=fluconazole; Itra=itraconazole; Vori=voriconazole; Candins=echinocandins; Ampho=amphotericin; S=susceptible; I=intermediate; S-DD=susceptible-dose dependent; R=resistant.  
 Table adapted from Pappas PG, et al. *Clin Infect Dis*. 2004;38:161-189.

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**“Knowledge of the infecting species, however, is highly predictive of likely susceptibility and can be used as a guide to therapy.”**

**Infectious Diseases Society of America  
2004 Guidelines for Treatment of Candidiasis**

Infectious Diseases Society of America. *Clin Infect Dis.* 2004;38:161-189.

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## The Problem with Diagnostics

- **The “gold standard”**
  - Positive culture from sterile site
  - Histopathology
- **Blood cultures—only 50% to 70% sensitive**
- **β-D-glucan assay**
  - Sensitive but how specific?
  - Gram-positive organism interference
- **Real-time polymerase chain reaction—“home brews” no commercial system**

Ostrosky-Zeichner L, et al. *Crit Care Med.* 2006;34:857.  
Pickering JW, et al. *J Clin Microbiol.* 2005;43(12):5957.  
Masai M, et al. *J Clin Microbiol.* 2006;44(1):143.

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## Prophylaxis in the ICU: Where Do We Stand?

- **Decreased infections?**
- **Decreased mortality?**
- **Resistance issues**
- **Tolerability issues**
- **Cost**

Golan Y, et al. *Ann Intern Med.* 2005;143:857.  
Wenzel RP, et al. *Clin Infect Dis.* 2005;41:S389.  
Cruciani M, et al. *Intensive Care Med.* 2005;31:1479.  
Shorr AF, et al. *Crit Care Med.* 2005;33:1928.  
Ostrosky-Zeichner L, et al. *Crit Care Med.* 2006;34:857.

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## The Drugs

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## Echinocandins: Benefits

- **Fungicidal (against many *Candida* sp)**
- **Tolerability**
- **Pharmacokinetics**
- **Few drug-drug interactions**
- **No cross-resistance with azoles**

Boucher HW, et al. *Drugs.* 2004;64:1997.

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## Echinocandins: Limitations

- **Limited spectrum (*Candida* sp, *Aspergillus* sp)**
- **Endemic mycoses (histomycosis, coccidioidomycosis)?**
- **Not effective against *C neoformans*, zygomycetes**
- **Oral formulations not available**
- **Cost**
  - 50 mg caspofungin = \$310.00
  - 100 mg micafungin = \$184.00

Boucher HW, et al. *Drugs.* 2004;64:1997.

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### The Clinical Data: Favorable Responses to Therapy

	Caspofungin (n = 88)	AmB (n = 97)
End of IV Therapy (MITT)	73.4%	61.7%

- However...Toxicity = Failure
- 3 in the caspofungin arm, 19 in the AmB arm (P = .03)
- Take home...both drugs work, 1 is toxic

MITT=modified intention to treat; AmB=amphotericin B. Mora-Duarte J, et al. N Engl J Med. 2002;347:2020.

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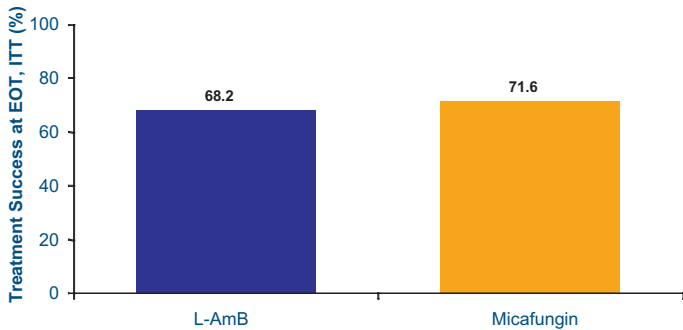
### Micafungin vs Liposomal AmB for Candidemia

- Double-blind, randomized, noninferiority
- Micafungin 100 mg per day
- Liposomal amphotericin B (L-AmB) 3 mg/kg per day
- Neutropenic patients allowed
- 50% ICU patients in both arms

Rhunke M, et al. ICAAC;2005;LB M-722c.

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### Micafungin vs L-AmB



EOT=end of treatment; ITT = intent to treat. Rhunke M, et al. ICAAC;2005;LB M-722c.

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### Adverse Events

	Micafungin N = 264	L-AmB N = 267	P ≤ .05
Fever	8.7%	13.5%	
Back Pain	0.4%	4.5%	X
Abnormal LFTs	4.2%	1.9%	
Hypokalemia	6.8%	12.0%	
Creatinine ↑	1.9%	6.4%	X

LFTs=liver function tests. Rhunke M, et al. ICAAC;2005;LB M-722c.

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### Anidulafungin in Candidemia

- 100 mg anidulafungin vs 400 mg fluconazole
- Randomized, double-blind, noninferiority
- 89% candidemia only
- Patients stratified for
  - Acute Physiology and Chronic Health Evaluation (APACHE) II > or ≤ 20
  - Neutropenia
- 10 days of IV therapy, then oral fluconazole in either arm

Reboli A, et al. ICAAC;2005;Abstract M-718.

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### Anidulafungin in Candidemia: Success in MITT Population (%)

Timepoint	Anidulafungin (N = 127)	Fluconazole (N = 118)	Delta %	95% CI
End of IV Therapy	75.6	60.2	15.42	3.85-26.99
2-Week Follow-Up	64.6	49.2	15.41	3.14-27.68
6-Week Follow-Up	55.9	44.1	11.84	-0.60-24.28

Reboli A, et al. ICAAC;2005;Abstract M-718.

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### Echinocandins: Additional Considerations

- Multi-echinocandin resistance to *C parapsilosis*
- *Antimicrobial Agents and Chemotherapy* 2005 multi-echinocandin resistance to *C parapsilosis*
- Burn ICU in Detroit
- 22 burn patients June through November 2004
- 9/22 colonized with *C parapsilosis*
- MIC 90s
  - Caspofungin = 8
  - Micafungin = 16
  - Anidulafungin = 2

Moudgal V, et al. *Antimicrob Agents Chemother.* 2005;49:767.  
Ghannoum M, et al. ICAAC; 2005;Presentation M-722a.

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### Azole Antifungals

- Inhibit CYP 450 lanosterol 14- $\alpha$  demethylase
- *Candida* sp: Slow killing—considered “static”
- CYP 450 drug interactions
- Oral formulations
- Tolerability?

Boucher HW, et al. *Drugs.* 2004;64:1997.

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### Azoles and Drug Interactions

- Tacrolimus/cyclosporin A/sirolimus
- Rifabutin/rifampin
- Efavirenz (NNRTI), ritonavir (PI)
- Phenytoin/carbamazepine/phenobarbital
- Busulfan, docetaxel, vinca alkaloids, cyclophosphamide, trimetrexate
- HMG CoA—lovastatin/simvastatin/atorvastatin/ cerivastatin

NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A.

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### Fluconazole

- The most used systemic antifungal
- Benefits
  - Lack of toxicity
  - Oral bioavailability is excellent
  - Extremely active against many *Candida* sp
- Limitations
  - Spectrum, often underdosed

Rex J, et al. *N Engl J Med.* 1994;331:1325.

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### Fluconazole Disk Diffusion Testing



Courtesy of James H. Jorgensen, PhD.

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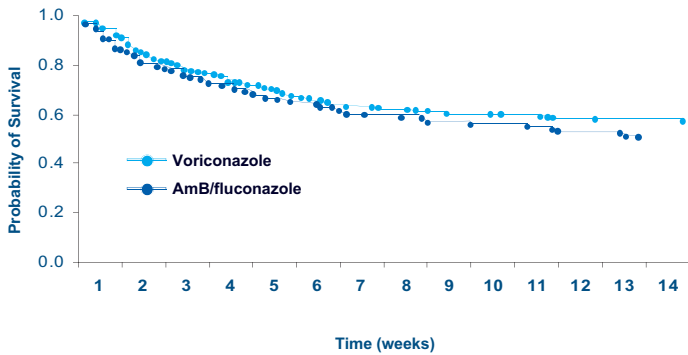
### Fluconazole in 2006

- More *C glabrata*
- Was it as good as amphotericin + fluconazole?
- What about that anidulafungin data?
- Where does it fit?
- *C parapsilosis*?

Pappas DG, et al. *Clin Infect Dis.* 2003;37:634-643.  
Rex J, et al. *Clin Infect Dis.* 2003;36:1221.  
Reboli A, et al. ICAAC;2005;Abstract M-718.  
Spellberg BG, et al. *Clin Infect Dis.* 2006;42:244.

24

### Voriconazole in Candidemia



Kullberg B, et al. *Lancet*. 2005;366:1435.

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### Posaconazole

- Spectrum: voriconazole + zygomycetes
- Currently only oral
- Improved drug interaction profile?
- Well tolerated
- Some great saves!

Greenberg RN, et al. *Antimicrob Agents Chemother*. 2006;50:126.  
Van Burik J-AH. *Clin Infect Dis*. 2006;42:e61.

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### What About Amphotericin?

- Still the “gold standard” comparator
- Toxicity limitations
- Wallet toxicity issues
- Steadily declining use

Ostrosky-Zeichner L, et al. *Clin Infect Dis*. 2003;37:415.

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### *Candida glabrata*

- Rapid and stable fluconazole resistance
- The role of voriconazole?
- Pan-azole resistance?
- High-dose polyene
- Use of echinocandins

Borst A, et al. *Antimicrob Agents Chemother*. 2005;49:783.  
Alexander BD, et al. *Transplantation*. 2005;80:868.  
Imhof A, et al. *Clin Infect Dis*. 2004;39:743.  
Pappas PG, et al. *Clin Infect Dis*. 2004;38:161.

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### *Candida krusei*

- Intrinsically fluconazole resistant
- Rare in most settings
- Lower mortality than *C albicans* fungemia
- Treatment options:
  - Voriconazole
  - Echinocandins
  - AmB products at higher doses (1 mg/kg/d AmB deoxycholate)

Munoz P. *J Antimicrob Chemother*. 2005;55:188.  
Ostrosky-Zeichner L, et al. *Eur J Clin Microbiol Infect Dis*. 2003;22:651.  
Pappas PG, et al. *Clin Infect Dis*. 2004;38:161.

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### *Candida parapsilosis*

- The Achilles heel of the echinocandins?
- Class resistance as a problem
- The caspofungin candidemia study
- The anidulafungin candidemia study
- Experience in a burn unit

Moudgal V, et al. *Antimicrob Agents Chemother*. 2005;49:767.  
Mora-Duarte J, et al. *N Engl J Med*. 2002;347:2020.  
Reboli A, et al. *ICAAC*;2005;Abstract M-718.  
Ghannoum M, et al. *ICAAC*;2005;Presentation M-722a.

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### The Future?

- Recombinant monoclonal antibody targeting heat shock protein 90 (HSP 90)
- In combination with lipid AmB
- Patients with invasive candidiasis

Complete Response	29 (48%)	47 (84%)	5.76	2.41-13.79	<.001
Attributable Mortality	11 (18%)	2 (4%)	0.168	0.036-0.797	.025

OR=odds ratio.  
 Pachi J, et al. *Clin Infect Dis.* 2006;42:1404.  
 Casadevall A. *Clin Infect Dis.* 2006;42:1414.

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### Conclusions

- *Candida* sp in the ICU—a moving target
- The role of prophylaxis
- Which drugs when?
- A changing of the guard?
- What about amphotericin?

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# Challenges in the Management of Serious Fungal Infections

## Post-Test

 This activity is approved for one (1) hour credit (0.1 CEUs) and is cosponsored by the University of Tennessee College of Pharmacy who is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. ACPE Program #064-999-06-234-H01.

To be eligible for a statement of participation, all participants must attend a full teleconference event, complete the 10-question post-test with a score of 70% or better, and complete the evaluation form. Participants who complete the post-test and evaluation form online may immediately print their statement of participation. Those who mail or fax back their successfully completed post-test and evaluation form will receive a statement of participation by mail within 4 weeks.

Participants should select the single most appropriate answer to each of the following questions.

- The length of stay for hospitalized patients who develop candidemia increases by an average of \_\_\_\_\_.
  - 4.3 days
  - 7.5 days
  - 10.1 days
  - 12.2 days
- Which of the following *Candida* species is most frequently resistant to the azoles?
  - C glabrata*
  - C krusei*
  - C albicans*
  - Both a and b
- How sensitive are current blood cultures to detect *Candida* infection?
  - 25% to 30%
  - 50% to 70%
  - 80% to 90%
  - None of the above
- Echinocandins are not effective against which of the following?
  - Aspergillus*
  - C neoformans*
  - Zygomycetes
  - Both b and c
- A study by Rhunke et al comparing L-AmB with micafungin found that all of the following adverse effects occurred more frequently in patients treated with L-AmB, except:
  - Fever
  - Hypokalemia
  - Back pain
  - Abnormal liver function
- According to a study by Reboli et al, at 2 weeks following the end of therapy, anidulafungin exhibited efficacy that was approximately \_\_\_\_ greater than that of fluconazole.
  - 15%
  - 10%
  - 7%
  - 4%
- The azoles have the potential to interact with which of the following agents?
  - Rifabutin
  - Ritonavir
  - Phenytoin
  - All of the above
- Fluconazole is almost uniformly active against which of the following *Candida* species?
  - C parapsilosis*
  - C glabrata*
  - C krusei*
  - All of the above
- Which of the following is susceptible to posaconazole, but not to voriconazole?
  - C krusei*
  - C albicans*
  - Zygomycetes
  - None of the above
- Which of the following statements regarding *C krusei* is not true?
  - C krusei* is intrinsically resistant to fluconazole.
  - C krusei* is associated with a higher mortality rate than *C albicans* fungemia.
  - Voriconazole can be used to effectively treat *C krusei* infection.
  - None of the above

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**www.princetoncme.com**

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**Challenges in the Management of Serious Fungal Infections  
Counteracting the Impact of Candidemia in  
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300 Rike Drive, Suite A  
Englishtown, NJ 07726-8544  
Fax: (609) 371-2733

Please indicate your answers to the continuing education test on the previous page by circling one answer to each question.

- |            |             |
|------------|-------------|
| 1. A B C D | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B C D  |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |

**Challenges in the Management of Serious Fungal Infections  
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Release date: May 15, 2006  
Expiration date: May 15, 2007  
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The University of Tennessee College of Pharmacy would appreciate your comments on the quality of this educational activity. Please rate the following by using a 5-point grading system, with 1 being the lowest rating (strongly disagree/poor rating) and 5 being the highest rating (strongly agree/excellent rating).

1. After reading this educational activity, the participant was able to:

1      2      3      4      5

List the factors that contribute to the prevalence of fungal infections

1      2      3      4      5

Summarize the burden of candidemia in the acute-care setting

Assess the efficacy, adverse effect profiles, and tolerability of available agents for the treatment of candidemia

1      2      3      4      5

Implement an appropriate treatment algorithm to evaluate optimal management of candidemia in acute-care patients

1      2      3      4      5

2. This educational activity was objective, balanced, and free of commercial bias.

1      2      3      4      5

3. Please indicate your overall evaluation of this activity.

1      2      3      4      5

4. Do you intend to make changes in your practice as a result of this activity?

1      2      3      4      5

5. What aspects of this activity were of most interest to you?

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

6. Do you have any comments or suggestions for this or future activities?

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Please complete all sections to be eligible for CE.

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