Timing of Susceptibility-Based Antifungal Administration in Patients with *Candida* Bloodstream Infection

BY

SHELLEE GRIM
B.S., Washington State University, 2001
Pharm.D., Washington State University, 2001

THESIS

Submitted as fulfillment of the requirements for the degree of
Masters of Science in Clinical and Translational Science
in the Graduate College of the
University of Illinois at Chicago, 2012

Chicago, Illinois

Defense Committee:

Jack Zwanziger, Chair
Nina Clark
Jennifer Layden

ACKNOWLEDGEMENTS

I would like to thank my thesis committee, Drs. Jack Zwanziger, Nina Clark, and Jennifer Layden for their support and mentorship with this project. In addition, I would like to recognize the important contributions to this work of Drs. Karen Berger, Sandeep Gupta, and William Janda and Ms. Christine Teng.

I would like to thank Drs. John Garofalo, Andy Donnelly, Jan Engle, and Jerry Bauman for their support and encouragement throughout this program.

SAG

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
BSI	Bloodstream Infection
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICU	Intensive Care Unit
MIC	Minimum Inhibitory Concentration
SE	Standard Error of the Regression
SDD	Susceptible Dose-Dependent

SUMMARY

We sought to determine the impact of timing of appropriate antifungal therapy, as assessed by susceptibility results, on patient survival after candidemia. Patients 16 years of age or older with first episodes of candidemia from 2001–2009 were included. Clinical data were collected retrospectively, including time to appropriate antifungal therapy and patient survival.

The study population included 446 patients (243 [54%] female, mean age 53 years) with candidemia, 380 (85%) of whom had antifungal susceptibility data. *Candida albicans* was the most common pathogen (221, 50%) followed by *C. glabrata* (99, 22%), *C. parapsilosis* (59, 13%), *C. tropicalis* (48,11%), and *C. krusei* (6,1%). Thirty-day mortality was 34% (151 out of 446 patients) and there was not a clear relationship between time from positive culture to receipt of appropriate antifungal therapy and 30-day survival. On multivariable Cox regression, increased Acute Physiology and Chronic Health Evaluation (APACHE) II score (hazard ratio [HR] 1.11, 95% confidence interval [CI] 1.09–1.13, p≤0.001), cirrhosis (HR 2.15, 95% CI 1.48–3.13, p≤0.001), and Human Immunodeficiency Virus (HIV) infection (HR 2.03, 95% CI 1.11–3.72, p=0.02), were independent predictors of mortality. A secondary analysis requiring patients in the early treatment group to have received at least 24 hours of effective antifungal therapy did show a significant mortality benefit to receiving antifungal treatment within 72 hours of a positive blood culture being drawn (30-day mortality for early treatment: 27% versus 40%, p=0.004; HR for mortality with delayed treatment on multivariable analysis: 1.41, 95% CI 1.01–1.98, p=0.045).

Candida bloodstream infection is associated with high mortality, despite timely receipt of appropriate antifungal therapy.

I. BACKGROUND

A. *Candida* Species

One of the five kingdoms of life, fungi include unicellular yeasts and multicellular molds, the large majority of which are beneficial to humankind. These fungi exist in the environment and are responsible for degradation and recycling of organic matter. Given their cellular likeness to humans, fungi have been used in science by molecular biologists to study eukaryotic processes. Additionally, some fungal metabolites have led to the development of antibiotic and immunosuppressive medications (Ryan, 2010). Although most fungi are harmless, there has been a dramatic increase in human infections caused by fungal organisms in the past three decades (Groll et al., 1996; Jarvis, 1995; McNeil et al., 2001; Zilberberg et al., 2008). Infections caused by *Candida* species have accounted for the majority of these infections, although its relative incidence is decreasing to due to increased infections caused by *Aspergillus* species and other molds (Groll et al., 1996; Pappas et al., 2009).

Of the more than 150 *Candida* species identified, less than 10 have been implicated as common causes of human infection (Pappas et al., 2009; Ryan, 2010). *Candida albicans* is the most frequently isolated species followed by *C. glabrata*. Other common *Candida* species include *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, *C. krusei*, *C. guilliermondii*, and *C. dubliniensis*. *Candida* species are spherical, unicellular organisms that are common endogenous flora of the skin, oropharyngeal and gastrointestinal tracts, and the female genitourinary tract. *Candida* species may cause superficial or invasive infection when physical and/or immunological barriers are compromised. The focus of this work is on patients with invasive infection, namely *Candida* bloodstream infection.

B. Pathogenicity and Risk Factors for Invasive Candidiasis

As described above, *Candida* is a common component of human skin, oral, intestinal, and female genitourinary flora. A mucosal disruption such as from trauma or chemotherapy-induced mucositis may allow for invasion by endogenous *Candida*. The utilization of antibiotics, especially broad-spectrum antibiotics, destroy bacterial flora thus promoting an environment in which yeasts may overgrow (Pappas et al., 2009; Ryan, 2010). The pathogenesis of invasive *Candida* infections is multifactorial; the primary determinants include *Candida* colonization, disruption of skin and mucosal integrity, and an immunocompromised state such as chemotherapy-induced neutropenia, receipt of corticosteroids and other immunosuppressive medications, and HIV infection (van de Veerdonk et al., 2010). Thus, risk factors for invasive candidiasis include the use of a central venous catheter, receipt of parenteral nutrition, acute renal failure and receipt of dialysis, burns, surgery (especially abdominal surgery), malignancy, receipt of chemotherapy, neutropenia, mucositis, transplantation, receipt of corticosteroids and/or other immunosuppressive medications, receipt of antibiotics (especially prolonged courses), increased hospital length of stay, *Candida* colonization, and diabetes mellitus (Pappas et al., 2003; Pappas et al., 2009; Ryan, 2010).

C. Epidemiology

From 2000 to 2005, the incidence of candidemia-related hospitalization per 100,000 population in the United States increased by more than 50% (Zilberberg et al., 2008). *Candida* is the fourth most common causative pathogen of nosocomial bloodstream infection (BSI) after coagulase-negative staphylococci, *Staphylococcus aureus,* and *Enterococcus* species (National Nosocomial Infections Surveillance Systems Report, 1999) and invasive candidiasis is associated with high mortality (Gudlaugsson et al., 2003; Sispas et al., 2009; Walsh and Groll, 1999). Although *C. albicans* remains the most common cause of invasive candidiasis, its relative proportion of *Candida* epidemiology has decreased. In a cohort study from Atlanta and

San Francisco from 1992–1993, *C. albicans* and *C. glabrata* were responsible for 52% and 12%, of bloodstream infections, respectively (Kao et al., 1999). Less than 10 years later in the states of Connecticut and Maryland, the relative proportion of bloodstream infections due to *C. albicans* had decreased to 45% whereas those due to *C. glabrata* had increased to 24% (Hajjeh et al., 2004). The results from *Prospective Antifungal Therapy Alliance* database, which reported data from over 2,000 patients with candidemia from 23 North American medical centers from 2004 to 2008, similarly found that the *C. albicans* and *C. glabrata* comprised 46% and 26%, of bloodstream infections, respectively (Horn et al., 2009). This changing epidemiology was further confirmed by recently published data by Lockhart et al (Lockhart et al., 2012). The investigators reported on *Candida* bloodstream isolates from 2008–2011 in Atlanta and Baltimore. The most commonly isolated species were *C. albicans* (38%), *C. glabrata* (29%), *C. parapsilosis* (17%), and *C. tropicalis* (10%). The specific *Candida* species isolated is important for treatment because species is closely linked to antifungal drug susceptibility (Pappas et al., 2009).

D. Manifestations

1. Clinical presentation

Infection from *Candida* species develops when there is a breach of host physical and/or immunological defenses. Invasive candidiasis typically presents as a BSI, although the candidemia may not be detected. The clinical manifestations of *Candida* bloodstream infection are non-specific and include fever and possibly increased white blood cell count (depending on host immune status), which may progress to sepsis and multi-organ failure. Patients with candidemia present similarly to patients with bacterial BSI except that given the nature of the infection and associated risk factors, they may already be receiving empiric or directed therapy toward bacterial pathogens. Once *Candida* has established invasive infection, the organism has the predilection to disseminate and cause organ infection in the eyes, heart, brain, and kidneys. To assess for these possible sites of infection, it is routine to perform dilated funduscopic

examinations and echocardiograms on all patients diagnosed with *Candida* bloodstream infection (Pappas et al., 2009; Ryan, 2010).

2. **Outcome**

Invasive *Candida* infection has been shown to detrimentally impact patient outcomes with a reported attributable mortality as high as 49% noted by Gudlaugsson et al (Gudlaugsson et al., 2003). More recent data has estimated attributable mortality to range from 15%–25% for adults with *Candida* bloodstream infection (Morgan et al., 2005; Zaoutis et al., 2005). Additionally, an episode of candidemia is estimated to add an estimated $40,000 to the costs of hospitalization (Morgan et al., 2005; Fridkin 2005).

E. Diagnosis

Isolation of *Candida* species from the bloodstream is diagnostic for invasive *Candida* infection. Although culture methods have improved (Ericson et al., 2012), routine blood cultures may fail to diagnose candidemia (Pappas et al., 2009). New tests such as the detection of ß-D-glucan and real-time polymerase chain reaction tests show promise in the diagnosis of invasive candidiasis (McMullan et al., 2008; Obayashi et al., 2008) and may prove to be useful diagnostic aids in the future.

F. Treatment

1. Antifungal agents

Developed in 1958, amphotericin B deoxycholate remains the broadest spectrum antifungal agent currently available. Amphotericin B has activity against all *Candida* species with the exception of *C. lusitaniae*, of which some strains have developed resistance. Its use is limited by toxicities, namely nephrotoxicity and infusion-related toxicities such as rigors and chills (Pappas et al., 2009). In the mid-1990s, the pharmaceutical industry released three lipid formulations of Amphotericin B that retained the broad spectrum antifungal activity and had less

nephrotoxicity compared to the conventional formulation (Bowden et al., 1996; Johnson et al., 2002; Sharkey et al., 1996; Walsh et al., 1998). The two most often used lipid-based products, amphotericin B lipid complex and liposomal amphotericin B, have replaced amphotericin B deoxycholate for most adult patients (Pappas et al., 2009).

Fluconazole, introduced in 1990, revolutionized the treatment of invasive candidiasis. The drug is available intravenously and in highly bioavailable oral formulations, thus providing a reliable oral option for the treatment of systemic disease. Fluconazole absorption is not impacted by gastric acidity or food consumption, further making it a convenient therapy. Similar to other azoles, fluconazole is an inhibitor of cytochrome P450 3A4 enzymes, which may cause significant drug interactions in particular with transplant recipients receiving calcineurin-inhibitors and HIV seropositive patients receiving antiretroviral medications. Fluconazole also exhibits the class triazole toxicities such as hepatotoxicity, skin rash, and QTc prolongation, though to lesser degrees than the other triazoles (Pfizer, 2010). Fluconazole is inherently resistant to *C. krusei* and has developed increasing resistance, some of which may be overcome by increasing the dose, to *C. glabrata* (Pappas et al., 2009; Pfaller et al., 2007). Importantly, fluconazole has minimal resistance among other *Candida* species such as *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae* (Pappas et al., 2009).

Itraconazole has similar anti-*Candida* activity to fluconazole and has with more drug interactions and less reliable absorption; it is not used preferentially over fluconazole for the treatment of invasive candidiasis (Pappas et al., 2009). Voriconazole and posaconazole also exhibit more class triazole toxicities than fluconazole, but they add slightly to the anti-*Candida* activity of fluconazole. Despite inherent fluconazole resistance, both drugs retain activity against *C. krusei* (Pappas et al., 2009). In addition, voriconazole and posaconazole are likely to retain susceptibility to isolates of *C. glabrata* with increased fluconazole Minimum Inhibitory Concentrations (MICs) to the susceptible dose-dependent (SDD) range (MICs = 16–32 mcg/mL) (Pappas et al., 2009). However, fluconazole-resistant *C. glabrata* isolates (MIC ≥ 64 mcg/mL),

are less likely to be susceptible to either drug (Pfaller et al., 2007). Among the azoles, fluconazole is the drug of choice for fluconazole-susceptible *Candida* infections. Voriconazole and posaconazole may provide an advantage over fluconazole in the treatment of *C. krusei* and for *C. glabrata* with decreased fluconazole activity that retain susceptibility to the newer azoles (Pappas et al., 2009).

The echinocandins, caspofungin, anidulafunigin, and micafungin, are only available in the intravenous formulation. As a class, the echinocandins are well tolerated and have minimal drug interactions. The echinocandins also have the broadest anti-*Candida* spectrum of all antifungals with the possible exception of *C. parapsilosis* (Pappas et al., 2009). In-vitro data have shown that *C. parapsilosis* has higher MIC values, albeit still within the susceptible range, than the other *Candida* species (Pfaller et al., 2008). Higher failure rates with *C. parapsilosis* have not been observed (Bennett, 2006) and most experts agree that echinocandins need not be avoided for the treatment infections due to *C. parapsilosis*; however, their use may not be necessary since this species is most often susceptible to fluconazole. Of note, among the echinocandins, no one agent has been shown to be superior to the others for the treatment of invasive candidiasis and they may be used interchangeably (Pappas et al., 2009).

First-line therapy for suspected or documented *Candida* BSI consists of fluconazole or an echinocandin. An echinocandin is preferred for moderately to severely ill patients, for patients with recent triazole exposure, and for infections caused by *C. glabrata* and *C. krusei*. Fluconazole is recommended for less severely ill patients without recent triazole exposure. In addition, it is recommended to modify therapy based on the results of antifungal susceptibility testing, including narrowing from an echinocandin to fluconazole when appropriate. Voriconazole and posaconazole are not recommended as routine first-line therapy given the marginal additional anti-*Candida* activity over fluconazole. Amphotericin B is generally not given for first-line therapy for uncomplicated infections but is the drug of choice for central nervous system infections and infective endocarditis. Notably, the approved antifungal medications have

been studied for invasive candidiasis in a heterogeneous manner with various antifungal comparators and definitions of success (Anaissie et al., 1996; Kullberg et al., 2005; Mora-Duarte et al., 2002; Pappas et al., 2007; Reboli et al., 2007); it is impossible to determine a superior agent from the published data. Thus, the guidelines recommend targeted antifungal therapy to the specific *Candida* species and susceptibility tests if available (Pappas et al., 2009).

2. Timing of antifungal therapy

Timely therapy of bacterial BSI is of critical importance and inadequate initial therapy adversely impacts hospital mortality (Ibrahim et al., 2000; Leibovici et al., 1998). Furthermore, fungal BSIs are associated with higher rates of inadequate initial antimicrobial treatment than bacterial BSIs (Ibrahim et al., 2000) and carry high mortality rates (Gudlaugsson et al., 2003; Sipsas et al., 2009; Walsh and Groll, 1999). The importance of early treatment of candidemia has been suggested by some investigators (Garey et al., 2006; Morrell et al., 2005). However, there are limited data definitively demonstrating that early therapy for candidemia benefits patients. The results of studies addressing this question are conflicting (Fernandez et al., 2009; Garey et al., 2006; Hsu et al., 2010; Morrell et al., 2005; Klevay et al., 2008; Kludze-Forson et al., 2010; Parkins et al., 2007; Patel et al., 2009; Taur et al., 2010; Zilberberg et al., 2010) and most of these studies have not employed in vitro antifungal susceptibility results to assess the appropriateness of therapy (Fernandez et al., 2009; Garey et al., 2006; Hsu et al., 2010; Morrell et al., 2005; Patel et al., 2009; Taur et al., 2010; Zilberberg et al., 2010). The purpose of the present study is to investigate the impact of timing of appropriate antifungal therapy, as assessed by antifungal drug susceptibility results, on mortality among patients with *Candida* BSI (Grim et al., 2012).

II. METHODS

A. Study Design

This study was conducted at an urban academic medical center with 489-beds including 52 adult critical care beds, active abdominal solid organ and stem cell transplant programs, and a cancer center (Grim et al., 2012). All patients 16 years of age or older with *Candida* BSI from January 2001 to December 2009 were identified by the clinical microbiology laboratory. Only the first episode of candidemia was included for patients with multiple episodes during the study period. Patients who received appropriate antifungal therapy for 24 hours or longer prior to initial BSI culture were excluded from the analysis. Receipt of inappropriate antifungal therapy for 24 hours or longer prior to initial BSI culture was not a criterion for study exclusion.

B. Data Collection

Data collection was performed retrospectively to obtain the following information: demographics, comorbidities, severity of illness based on APACHE II scores (the most aberrant values within 24 hours prior to the collection of blood samples indicating candidemia were obtained), presence of mechanical ventilation, time of collection of the first positive blood culture for *Candida*, time of initiation of first appropriate antifungal therapy, initial and follow-up blood culture results, microbiologic response to antifungal therapy, and mortality. The difference between the time of collection of the first positive blood culture for *Candida* and receipt of first appropriate antifungal therapy was defined as the time to appropriate antifungal therapy. Receipt of corticosteroids was collected and use of high-dose steroids was defined as a minimum of 15 mg of prednisone equivalents daily.

C. Organism Isolation and Identification

Blood cultures were ordered at the discretion of the primary medical team based on the presence of signs and/or symptoms of BSI. Blood samples were obtained by nursing or phlebotomy personnel following skin and/or catheter sterilization. Blood samples were inoculated into one aerobic and anaerobic bottle each and processed using the BacT/ALERT® 3D (bioMérieux, Inc., Durham, North Carolina) automated microbial detection system. Organism identification was made using the Vitek® 2 Yeast Biochemical Card (bioMérieux, Inc., Durham, North Carolina); API® 20C AUX Yeast Identification Kit (bioMérieux, Inc., Durham, North Carolina) was utilized for organisms that failed identification by the primary method.

D. Definition of Appropriate Antifungal Therapy

Appropriateness of antifungal therapy was based on antifungal susceptibility testing, which became routine at our institution for fluconazole, itraconazole, and flucytosine in 2003, for voriconazole, posaconazole, and amphotericin B in 2007, and for the echinocandins in 2008. Antifungal susceptibilities were determined with the Sensititre® YeastOne® panel (Trek Diagnostic Systems, Inc., Cleveland, Ohio). For fluconazole-susceptible *Candida* isolates (MIC ≤ 8 mg/L) a minimum daily dose of 400 mg was considered appropriate. For fluconazole-SDD (MIC 16–32 mg/L) isolates, a minimum daily dose of 800 mg was considered appropriate (Pappas et al., 2004). For patients with a calculated creatinine clearance (Cockcroft and Gault, 1976) less than 50 mL/min, the daily dose of fluconazole was multiplied by two for assessment of appropriateness based on standard dosing adjustments made in renal dysfunction (Pfizer, 2010).

The appropriateness of dosing of other antifungals was defined as follows (Pappas et al., 2009): amphotericin B deoxycholate greater than or equal to 0.5 mg/kg once daily, lipid formulations of amphotericin B greater than or equal to 3 mg/kg once daily, caspofungin (formulary echinocandin through March 2008) 70 mg x 1 dose followed by 50 mg once daily (or

35 mg once daily for patients with significant liver impairment), micafungin (formulary echinocandin beginning April 2008) 100 mg once daily, and voriconazole 6 mg/kg twice daily x 2 doses then a minimum of 3 mg/kg twice daily. In the absence of antifungal susceptibility testing, the following criteria were used to assess appropriateness of therapy: fluconazole 400 mg daily was deemed appropriate for the treatment of BSI caused by *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. lusitaniae*; a minimum of fluconazole 800 mg daily was defined as appropriate for the treatment of *C. glabrata*; amphotericin B was considered inappropriate for the treatment of BSI caused by *C. lusitaniae*; fluconazole was considered inappropriate for treatment of *C. krusei*; the echinocandins were assessed as appropriate for the treatment of all *Candida* species; voriconazole and posaconazole were considered appropriate for all non-*glabrata Candida* species; and patients receiving voriconazole or posaconazole for *C. glabrata* infection in the absence of antifungal susceptibility testing were excluded from analysis (Table I).

TABLE I

APPROPRIATE ANTIFUNGAL THERAPY

Appropriate therapy	**N=349**
Fluconazole	177
400mg/day[a]	
800mg/day[b]	
Echinocandin (for all *Candida* species)	125
Caspofungin 70mg x 1 then 50mg daily	
Micafungin 100mg daily	
Amphotericin B (for all *Candida* species except for *C. lusitaniae*)	41
≥ 0.5 mg/kg/day amphotericin B deoxycholate	
≥ 3mg/kg/day lipid formulation of amphotericin B	
Voriconazole (for all *Candida* species except for *C. glabrata*)	6
6mg/kg q12h x 2 doses then ≥ 3mg/kg twice daily	
Posaconazole (for all *Candida* species except for *C. glabrata*)	0
Inappropriate therapy	**N=97**
No antifungal therapy	55
Insufficient fluconazole	42
< 400mg/day for fluconazole-susceptible isolate	21
< 800mg/day for fluconazole-SDD isolate	11
< 800mg/day for *C. glabrata* without susceptibilities	3
Fluconazole-resistant isolate	5
Infection caused by *C. krusei*	2
Use of amphotericin B for *C. lusitaniae*	0
Unable to assess appropriateness	**N=1**
Voriconazole for *C. glabrata* without antifungal susceptibilities	1
Posaconazole for *C. glabrata* without antifungal susceptibilities	0

[a] For infection caused by fluconazole-susceptible isolate or by *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. lusitaniae* without susceptibilities

[b] For infection caused by fluconazole-susceptible dose-dependent isolate or by *C. glabrata* without susceptibilities

E. Definition of Response

Microbiological response was defined as culture-confirmed resolution of infection within 7 days of initiation of appropriate antifungal therapy sustained for at least 6 weeks after the original culture date. Persistent *Candida* BSI was defined as more than 7 days of candidemia caused by the initial organism(s) after initiation of appropriate antifungal therapy. Microbiological failure was defined as persistent, recurrent, or new BSI due to *Candida* within 6 weeks of first positive culture. Patients were followed for outcomes after onset of *Candida* BSI. The time to death or loss to follow-up within 30 days after infection was recorded.

F. Statistical Methodology

The Chi-Square test was performed to assess for differences in 30-day mortality based on receipt and timing of appropriate antifungal therapy. A Kaplan-Meier curve was constructed to illustrate the relationship between receipt and timing of appropriate antifungal therapy on survival; the log-rank test was used to assess for statistical differences between groups. Univariable Cox regression was performed to determine patient and infection characteristics associated with 30-day survival. The proportional hazards assumption was tested graphically and with the creation of time-dependent variables. Clinically plausible variables with a p-value of ≤ 0.2 were entered into a multivariable Cox regression model. Statistical analyses were performed with PASW Statistics v. 17.0 (SPSS: An IBM Company, Chicago, Illinois). Institutional review board approval was obtained.

III. RESULTS

A. Study Population

There were 453 patients with first episodes of *Candida* BSI during the study period (Grim et al., 2012). Six patients received at least 24 hours of appropriate antifungal therapy prior to first *Candida* BSI culture and were excluded. One additional patient was excluded because appropriateness of antifungal therapy could not be determined based on a priori definitions; the patient received voriconazole for *C. glabrata* BSI without voriconazole susceptibility testing. The study sample therefore included 446 patients with a mean age of 53 years; 243 (54%) were female and 229 (51%) were Black (Table II). The number of first episodes of *Candida* BSI averaged 49 per year; there were no discernible trends in the number of infections per year. The most common comorbidities were diabetes mellitus (131, 29%), solid tumor (120, 27%), and cirrhosis (72, 16%), and 249 (56%) of patients were in the Intensive Care Unit (ICU) at the time of *Candida* BSI. The mean and median APACHE II score were 18.9 and 17.0, respectively. *Candida albicans* was the most common pathogen (221, 50%), followed by *C. glabrata* (99, 22%), *C. parapsilosis* (59, 13%), *C. tropicalis* (48, 11%), and *C. krusei* (6, 1%). Antifungal susceptibilities were reported for 380/446 (85%) of patients.

B. Antifungal Therapy

Appropriate antifungal therapy consisted of fluconazole (177, 40%), caspofungin or micafungin (125, 28%), amphotericin B (41, 9%), and voriconazole (6, 1%). A relatively high percentage of patients (97, 22%) did not receive appropriate initial antifungal therapy; 55 patients (12%) failed to receive any antifungal therapy, and 42 patients (9%) received insufficient doses of fluconazole (21 received less than 400mg/day for a fluconazole-susceptible isolate, 11 received less than 800mg/day for an SDD isolate, 3 received less than 800mg for *C. glabrata* without

susceptibilities, 5 received fluconazole for a fluconazole-resistant isolate, and 2 received fluconazole for BSI caused by *C. krusei*; Table I).

TABLE II

CHARACTERISTICS OF PATIENTS WITH *CANDIDA* BSI (N=446)

	Antifungal Timing			
Characteristic	≤72 hours n=231 (%)	>72 hours n=215 (%)	Total n=446	p-value
Age [mean (range)]	52.0 (16–92)	54.3 (17–93)	53 (16–93)	0.14
Male (%)	107 (46)	96 (45)	203 (46)	0.72
Race				0.02
Black	112 (49)	117 (54)	229 (51)	
Caucasian	71 (31)	50 (23)	121 (27)	
Hispanic	38 (16)	40 (19)	78 (18)	
Other	10 (4)	8 (4)	18 (4)	
Year of *Candida* BSI				0.39
2001	21 (9)	30 (14)	51 (11)	
2002	24 (10)	20 (9)	44 (10)	
2003	19 (8)	28 (13)	47 (11)	
2004	31 (13)	25 (12)	56 (13)	
2005	20 (9)	19 (9)	39 (9)	
2006	33 (14)	24 (11)	57 (13)	
2007	27 (12)	30 (14)	57 (13)	
2008	36 (16)	24 (11)	60 (14)	
2009	20 (9)	15 (7)	35 (8)	
Underlying condition (%)				
Hematologic malignancy	15 (7)	12 (6)	27 (6)	0.69
Solid tumor	63 (27)	57 (27)	120 (27)	0.86
Allogeneic stem cell transplant	3 (1)	2 (1)	5 (1)	0.71
Solid organ transplant	21 (9)	20 (9)	41 (9)	0.94
HIV infection	12 (5)	10 (5)	22 (5)	0.79
Cirrhosis	36 (16)	36 (17)	72 (16)	0.74
Diabetes mellitus	65 (28)	66 (31)	131 (29)	0.55
Clinical features/risk factors				
Antibiotics within 2 weeks	216 (94)	200 (93)	416 (93)	0.84
ICU	128 (55)	121 (56)	249 (56)	0.85
Mechanical ventilation	85 (37)	83 (39)	168 (38)	0.69
Total parenteral nutrition	87 (38)	65 (30)	152 (34)	0.10
Neutropenia	13 (6)	6 (3)	19 (4)	0.14
Renal replacement therapy	58 (25)	61 (28)	119 (27)	0.44
Serum creatinine ≥ 2.0	75 (33)	97 (45)	172 (39)	0.01
Low-dose steroids	16 (7)	15 (7)	31 (7)	0.98
High-dose steroids	53 (23)	42 (20)	95 (21)	0.38
Surgery within 2 weeks	55 (24)	49 (23)	104 (23)	0.80
Mean APACHE II score (range)	18.3 (3–45)	19.5 (1–50)	18.9 (1–50)	0.15

CHARACTERISTICS OF PATIENTS WITH *CANDIDA* BSI (N=446)

	Antifungal Timing			
Characteristic	≤72 hours n=231 (%)	>72 hours n=215 (%)	Total n=446	p-value
Candida species				<0.001
C. albicans	135 (58)	88 (41)	221 (50)	
C. parapsilosis	31 (13)	28 (13)	59 (13)	
C. tropicalis	25 (11)	23 (11)	48 (11)	
C. krusei	2 (1)	4 (2)	6 (1)	
C. lusitaniae	1 (0.4)	2 (1)	3 (1)	
Other *Candida* species	9 (4)	1 (0.5)	10 (2)	
Appropriate antifungal therapy				0.28
Fluconazole	125 (54)	52 (24)	177 (40)	
Echinocandin	79 (34)	46 (21)	125 (28)	
Amphotericin B	24 (10	17 (8)	41 (9)	
Voriconazole	3 (1)	3 (1)	6 (1)	
None	0	97 (45)	97 (22)	

C. **Outcomes**

Given that the Garey study (Garey et al., 2006) showed a linear relationship between increased time to fluconazole and hospital mortality, our original analysis subdivided patients into 4 timing groups: less than or up to 24 hours, 24–48 hours, 48–72 hours, and greater than 72 hours (Figure 1). Contrary to expected outcomes, numerically the highest 30-day mortality was observed among patients who received the earliest appropriate antifungal therapy. There was no statistical difference in mortality based on timing with the exception of between the less than or up to 24 hour and 48–72 hour groups (44.4% versus 23.8%, p=0.04). Similarly, on univariable Cox regression, with the less than or up to 24h group as a reference, receipt of appropriate antifungal therapy 48–72 hours after the first positive culture was protective against decreased survival (HR 0.43, 95% CI 0.22–0.83, p=0.01). There was concern that the patients in the earliest timing group (less than or up to 24 hours, n=36) may have biased the results. Intuitively, it's logical that more critically ill patients receive more aggressive therapy (i.e., earlier therapy) than less critically ill patients, and it was postulated that there may have been other factors that attributed to increased mortality than just antifungal timing. Since the lowest 30-day mortality was observed in the 48–72 hour group (23.8%), the decision was made to dichotomize the data and perform subsequent analyses comparing the timing of appropriate antifungal therapy based on less than or up to 72 hours and greater than 72 hours. Additionally, revised analyses taking into account early deaths after the receipt of appropriate antifungal therapy were performed.

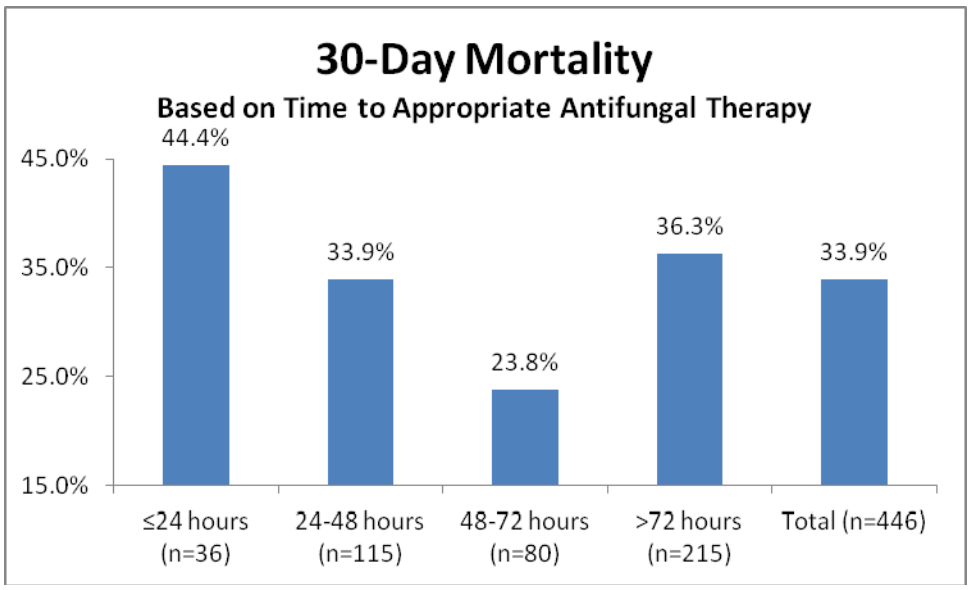

Figure 1. Thirty-day mortality based on the time to initiation of appropriate antifungal therapy in 4 timing groups.

p=0.04 between less than or up to 24 hours and 48–72 hours

Thirty-day mortality was compared based on receipt and timing of appropriate antifungal therapy (Figure 2). Overall mortality was 34% (151/446) with the highest mortality (45%, 44/97) among the 97 patients who failed to receive appropriate antifungal therapy (data not shown). Though still considerable, mortality was significantly lower for those who received appropriate antifungal therapy (31%). There was a slight trend toward lower 30-day mortality for patients who received appropriate antifungal therapy within 72 hours of the collection of a positive blood culture but the difference was not statistically significant (32% versus 36%, p=0.11). We also analyzed survival of the two groups over time according to timing of appropriate antifungal therapy. A Kaplan-Meier 30-day survival curve for these data is illustrated in Figure 3. There was no significant difference in survival between patients who received appropriate antifungal therapy within 72 hours or beyond 72 hours from the initial positive culture being drawn (p=0.18), but again there was a trend toward lower survival over time among the latter group.

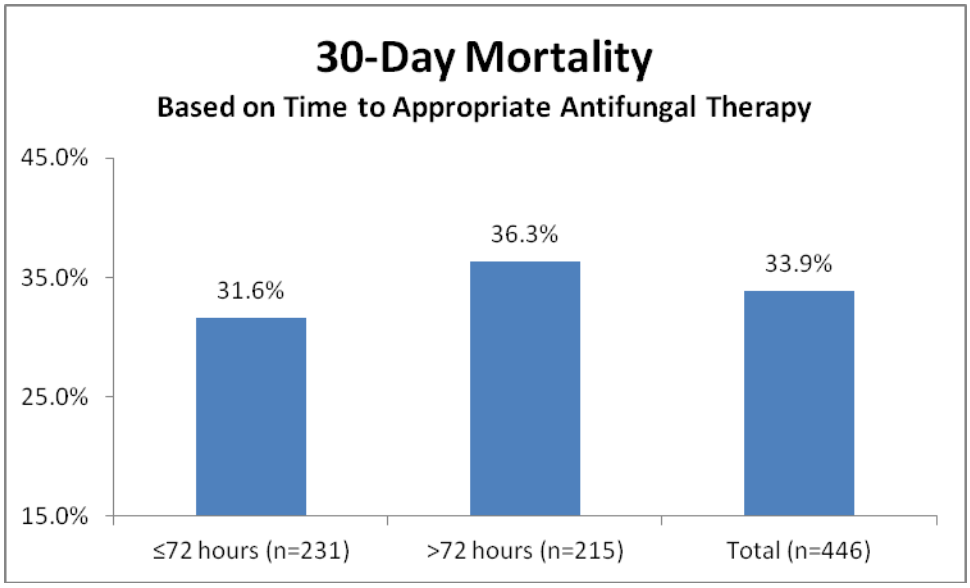

Figure 2. Thirty-day mortality based on the time to initiation of appropriate antifungal therapy in 2 timing groups.

p=0.11 between less than or up to 72 and greater than 72 hours

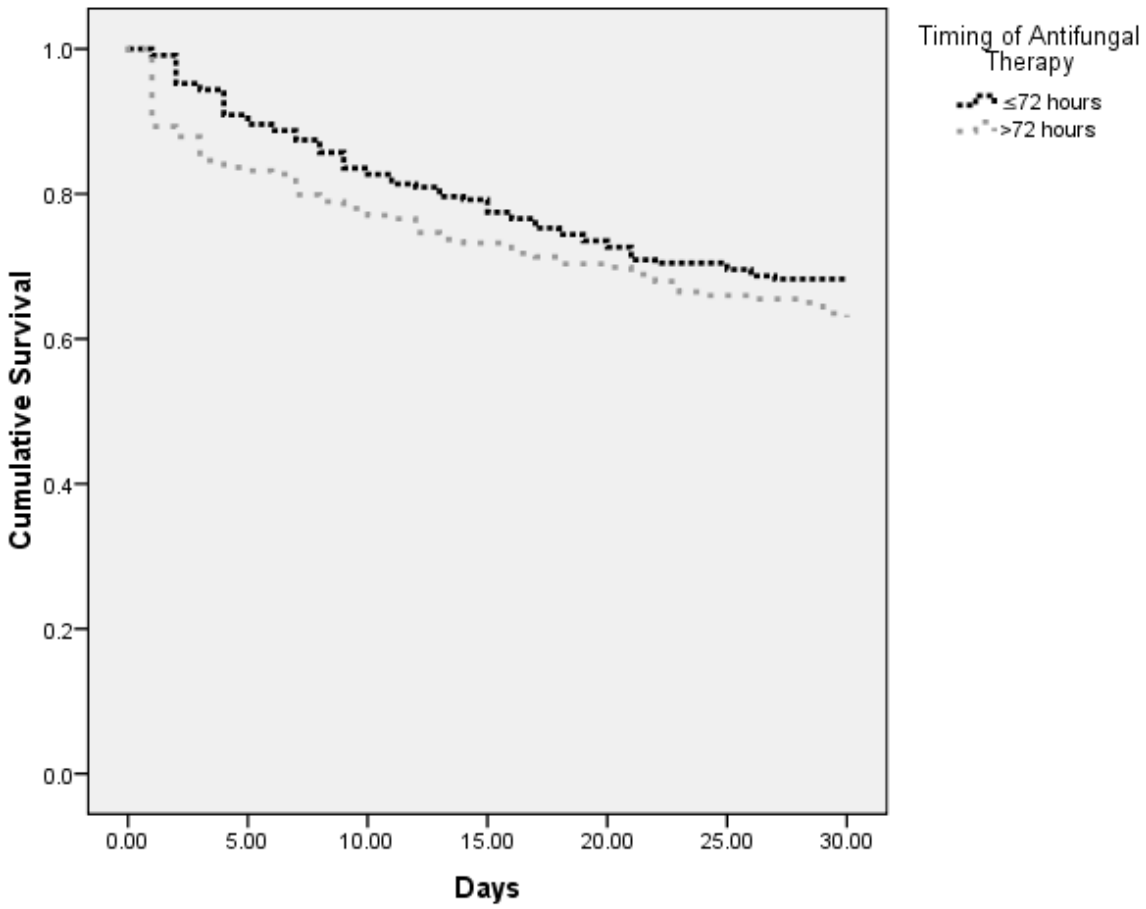

Figure 3. Kaplan-Meier survival curves based on time to initiation of appropriate antifungal therapy.

p=0.18 between less than or up to 72 and greater than 72 hours

D. **Survival Analyses**

Univariable Cox regression analysis (Table III) of all patients with *Candida* BSI (n=446), demonstrated that a number of variables were associated with increased mortality risk including increased age, immunosuppression (e.g., HIV infection, cirrhosis, high-dose steroid therapy), critical illness (e.g., ICU residence at the time of *Candida* BSI, mechanical ventilation, renal dysfunction, increased APACHE II score), and pathogen factors (e.g., BSI caused by *C. glabrata*, and BSI caused by a fluconazole non-susceptible isolate). Microbiological response to treatment could not be assessed in 89 patients but of the remaining 357 patients, 51 (14%) had microbiological failure (22 persistent and 29 new or recurrent BSI). Notably, microbiological clearance of infection was protective against mortality. Receipt of appropriate antifungal therapy more than 72 hours after collection of a positive blood culture was associated with a HR of 1.24 (95% CI 0.90–1.71, p=0.19). On multivariable Cox regression analysis (Table IV), increased APACHE II score (HR1.11, 95% CI 1.09–1.13, p≤0.001), cirrhosis (HR 2.15, 95% CI 1.48–3.13, p≤0.001), and HIV infection (HR 2.03, 95% CI 1.11–3.72, p=0.02) were independent predictors of mortality controlling for age, serum creatinine 2.0 mg/dL or greater, and receipt of appropriate antifungal therapy more than 72 hours after collection of a positive blood culture. When controlling for these other clinical characteristics, the timing of appropriate antifungal therapy was not associated with survival after *Candida* BSI. There was also no association between timing of appropriate antifungal therapy and microbiological resolution of *Candida* BSI, including persistent infection.

TABLE III

UNIVARIABLE COX REGRESSION: PATIENT SURVIVAL (N=446)

Characteristic	Beta	SE	HR	95% CI	p-value
Antifungal timing (reference category ≤ 72 hours)					
> 72 hours	0.22	0.16	1.24	0.90–1.71	0.19
Age by year	0.02	0.01	1.02	1.01–1.03	0.001
Male gender	0.26	0.16	1.30	0.95–1.79	0.11
Race (reference category White)					
Black	-0.23	0.19	0.80	0.55–1.16	0.24
Hispanic	-0.08	0.24	0.74	0.68–1.72	0.74
Asian	-0.65	0.72	0.52	0.13–2.15	0.37
Other	-0.04	0.60	0.96	0.30–3.10	0.95
Culture year					0.65
Underlying condition					
Hematologic malignancy	0.32	0.30	1.37	0.76–2.47	0.29
Solid tumor	-0.02	0.18	0.98	0.69–1.41	0.92
Allogeneic stem cell transplant	0.57	0.58	1.77	0.57–5.56	0.33
Solid organ transplant	-0.71	0.36	0.49	0.24–1.00	0.051
HIV infection	0.67	0.30	1.95	1.08–3.52	0.03
Cirrhosis	1.16	0.18	3.19	2.25–4.52	< 0.001
Diabetes mellitus	0.02	0.18	1.02	0.72–1.48	0.91
Clinical features/risk factors					
Antibiotics within 2 weeks	1.32	0.58	3.73	1.19–11.68	0.02
ICU	0.91	0.18	2.47	1.73–3.53	< 0.001
Mechanical ventilation	0.89	0.16	2.42	1.76–3.34	< 0.001
Total parenteral nutrition	-0.31	0.18	0.74	0.52–1.04	0.09
Neutropenia	0.42	0.34	1.52	0.77–2.98	0.23
Renal replacement therapy	0.58	0.17	1.78	1.27–2.48	0.001
Serum creatinine ≥ 2.0	0.83	0.16	2.30	1.67–3.17	< 0.001
Steroids (reference category no steroids)					
Low-dose	-0.61	0.42	0.55	0.24–1.24	0.15
High-dose	0.37	0.18	1.45	1.01–2.08	0.04
Surgery within 2 weeks	-0.65	0.23	0.52	0.34–0.82	0.004
APACHE II score	0.11	0.00	1.12	1.10–1.14	< 0.001

UNIVARIABLE COX REGRESSION: PATIENT SURVIVAL (N=446)

Characteristic	Beta	SE	HR	95% CI	p-value
Candida species (reference category *C. albicans*)					
C. glabrata	0.40	0.19	1.50	1.02–2.19	0.04
C. krusei	0.46	0.59	1.59	0.50–5.05	0.43
Other *Candida* species	-0.10	0.21	0.90	0.60–1.35	0.62
Fluconazole susceptibility (reference category susceptible)					
Non-susceptible	0.48	0.21	1.61	1.08–2.42	0.02
Antifungal therapy (reference category fluconazole)					
Amphotericin B	0.26	0.30	1.29	0.71–2.45	0.40
Echinocandin	0.36	0.21	1.43	0.95–2.15	0.09
Voriconazole	-0.43	1.01	0.65	0.09 – 4.72	0.67
Microbiological cure (n=357)	-1.10	0.23	0.33	0.21 – 0.52	< 0.001

TABLE IV

MULTIVARIABLE COX REGRESSION: PATIENT SURVIVAL (N=446)

Characteristic	HR	95% CI	p-value
APACHE II score	1.11	1.09 – 1.13	≤ 0.001
Cirrhosis	2.15	1.48 – 3.13	≤ 0.001
HIV infection	2.03	1.11 – 3.72	0.02
Age (in years)	1.01	1.00 – 1.02	0.06
Serum creatinine ≥ 2.0	0.84	0.58 – 1.20	0.34
Antifungal timing (reference category ≤ 72 hours)			
> 72 hours	1.10	0.80 – 1.52	0.57

Because it was possible that patients who died before receiving 24 hours of appropriate antifungal therapy may not have benefitted from this therapy even if treatment was administered in a timely manner, a secondary analysis was performed to account for this possibility. There were 18 patients who died prior to receiving 24 hours of appropriate antifungal therapy, 14 of whom received appropriate therapy within 72 hours of collection of first positive blood culture. These 14 patients were therefore reclassified as having not received timely appropriate therapy given the short duration of antifungal treatment before death (i.e., they were reclassified in the more than 72 hour group). In this analysis, the 30-day mortality was significantly lower among patients who received appropriate antifungal therapy within 72 hours of a positive culture being drawn (27% versus 40%, p=0.004) and the Kaplan-Meier curve revealed a significant difference in survival between the two groups (Figure 4; p=0.001). In addition, on univariable (HR 1.75, 95% CI 1.26–2.43, p=0.001) and multivariable (HR 1.41, 95% CI 1.01–1.98, p=0.045) analyses, delayed receipt of antifungals was associated with decreased survival. An analysis was also performed excluding the 18 patients who died before receiving 24 hours of appropriate antifungal therapy, and 30-day mortality remained significantly lower among patients who received appropriate antifungal therapy within 72 hours of a positive culture being drawn (28% versus 37%, p=0.047; Figure 5).

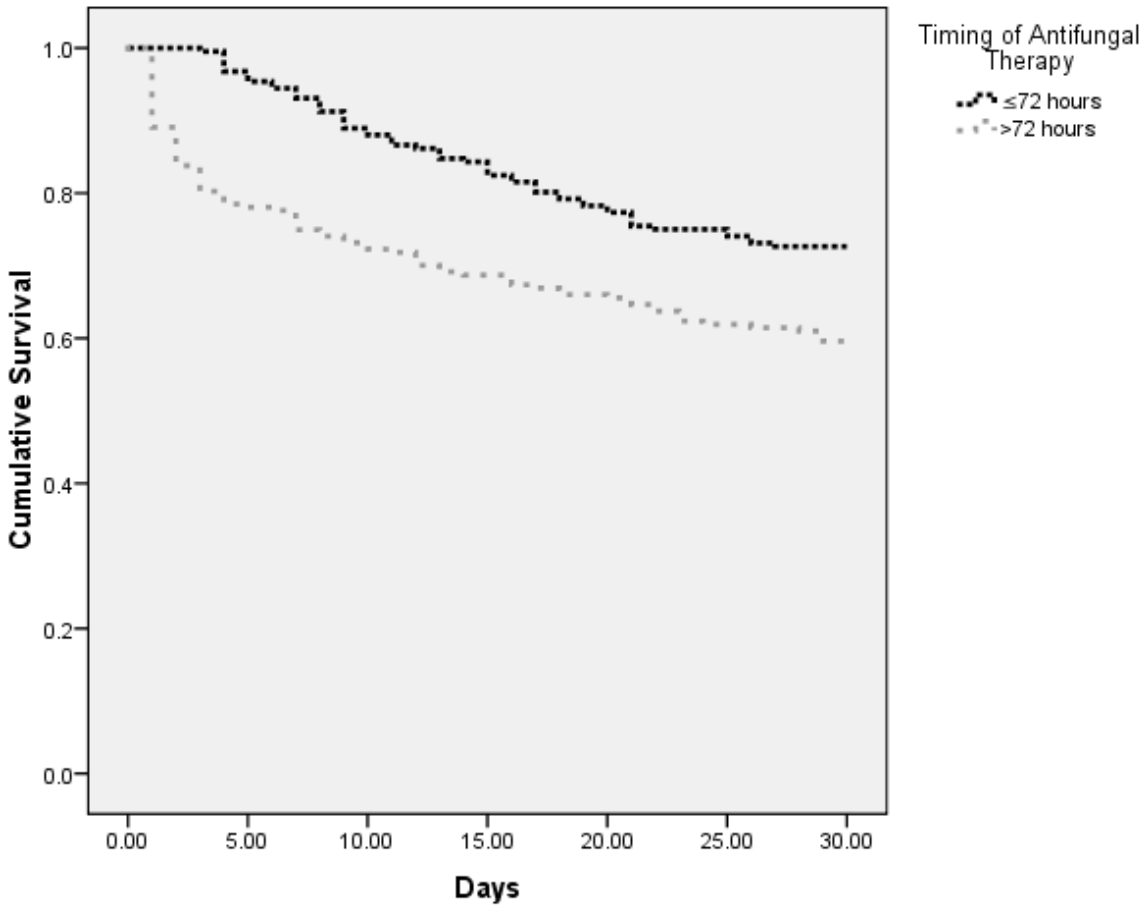

Figure 4. Kaplan-Meier survival curves based on the time to initiation of appropriate antifungal therapy, with patients who received less than 24 hours of appropriate therapy classified in the greater than 72 hour group.

p=0.001 between less than or up to 72 and greater than72 hours

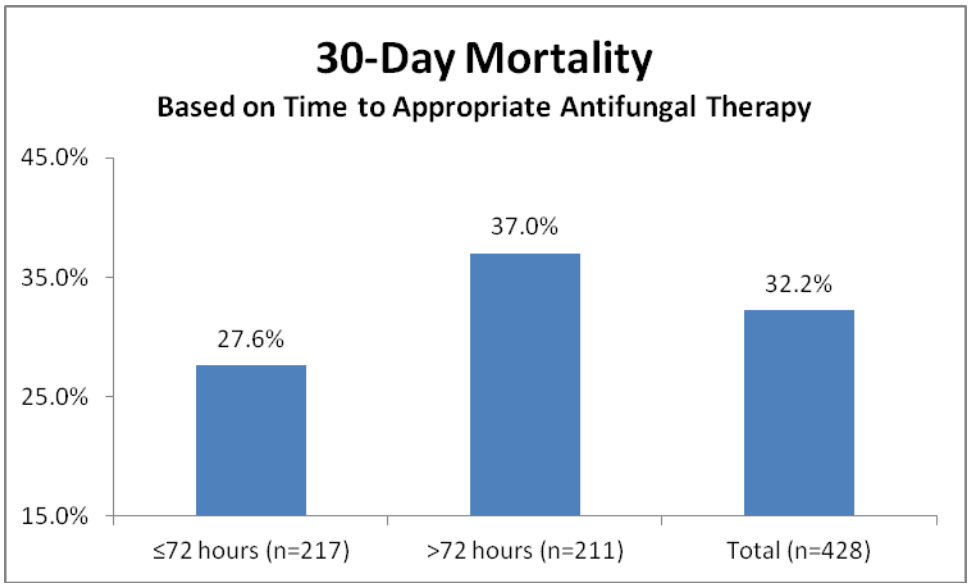

Figure 5. Thirty-day mortality based on the time to initiation of appropriate antifungal therapy excluding patients who received less than 24h of appropriate antifungal therapy

p=0.047 between less than or up to 72 and greater than72 hours

IV. DISCUSSION

A. Clinical Relevance

These data represent the largest study conducted to date assessing the importance of timing of appropriate antifungal therapy and survival after *Candida* BSI (Grim et al., 2012), and one of only 4 similar studies (Grim et al., 2012; Klevay et al., 2008; Kludze-Forson et al., 2010; Parkins et al., 2007) incorporating in vitro susceptibility results to assess appropriateness of therapy. In our primary analysis, we could not demonstrate a significant association between the receipt of early appropriate antifungal therapy and outcomes including mortality, microbiologic response, and persistent infection. However, we also took into account the fact that some patients, although they received antifungal treatment in a timely manner, may not have had an adequate duration of treatment to affect outcome. When we reclassified or excluded patients who died very soon after receiving appropriate therapy, we did find a significant mortality benefit to initiating antifungal therapy within 72 hours of obtaining a positive blood culture.

B. Comparison to Published Data

Our results differ in some respects from those of previous investigators. In 2005 and 2006, two studies demonstrated a clear relationship between delaying the initiation of antifungal therapy and mortality. The first of these by Morrell et al. (2005) concluded that in a retrospective analysis of 157 candidemic patients, administration of antifungal treatment 12 hours or longer after the collection of the first blood culture positive for *Candida* was an independent risk factor for hospital mortality (adjusted odds ratio 2.09; 95% CI1.53–2.84; p=0.018). A major limitation of this study was that only 9 patients received antifungal treatment within 12 hours of having a blood culture positive for *Candida* obtained, limiting the ability to draw firm conclusions regarding the results due to the small sample size. Mortality rates for patients who received therapy at 12–24 hours, 24–48 hours and more than 48 hours after a positive blood culture were

similar and were in the range of overall mortality of our study (32% versus 34%, respectively). Furthermore, routine antifungal susceptibility testing was not performed on *Candida* isolates and thus the appropriateness of therapy could not be assessed.

A second retrospective cohort study examined the mortality associated with timing of fluconazole therapy in 230 patients with candidemia at four medical centers (Garey et al., 2006). Mortality rates were lowest for patients beginning fluconazole on the day the first positive blood culture was drawn, and rates rose progressively with time to initiation of fluconazole. Earlier initiation of fluconazole was also associated with a decreased length of ICU stay. An important limitation of this study, as in that by Morrell et al. (2005), is the lack of antifungal susceptibility testing to assess the appropriateness of therapy. In addition, the study did not examine the effects of newer antifungal agents which are being increasingly used for invasive *Candida* infections (Pappas et al., 2009).

The results of subsequent studies on this topic have yielded conflicting results. Two smaller studies (Patel et al., 2009; Zilberberg et al., 2010) have supported the conclusions of Morrell and Garey. Patel et al. (2009) described increased mortality among 31 patients with *Candida*-associated septic shock when appropriate antifungal therapy was not received within 15 hours of blood sample collection. From the same institution as Morrell, Zilberberg et al. (2010) studied 90 patients with candidemia requiring ICU admission. Eighty out of 90 patients failed to received appropriate antifungal therapy within 24 hours of infection; in this group the hospital mortality was 29% compared to 0% among the 10 patients who received early appropriate therapy (p=0.059). Both studies were limited by the lack of availability of routine antifungal susceptibility testing.

Several more recent studies have failed to find an association between timely receipt of antifungal therapy and mortality after *Candida* BSI (Fernandez et al., 2009; Hsu et al., 2010; Klevay et al., 2008; Kludze-Forson et al., 2010; Parkins et al., 2007; Taur et al., 2010). Taur et al. (2010) studied 106 patients with cancer and *Candida* BSI and reported that a longer period

from the time a positive blood culture was drawn until it became positive ("incubation time") was independently associated with an increased risk of hospital mortality on multivariable analysis. However, the total length of time from when a positive blood culture was drawn to the time of antifungal initiation did not independently affect outcome. From a sample of 96 patients without antifungal susceptibility testing, Fernandez et al. (2009) reported no difference in the time to antifungal therapy among survivors (61 hours) versus non-survivors (59 hours) of *Candida* BSI. Hsu et al. (2010) investigated patients who received an echinocandin for *Candida* BSI; early (less than 3 days, n=107) versus late (more than 3 days, n=62) initiation of caspofungin for candidemia was associated with improved overall response (77% versus 57%, p=0.006), but it was not associated with infection-related or all-cause hospital mortality. Parkins et al. (2007) analyzed 199 patients with invasive candidiasis, and although appropriate empiric antifungal therapy was protective against hospital mortality, there was no association between timing of antifungal administration and mortality. In this study, antifungal susceptibility testing was available for 89% of the study participants. Klevay et al. (2008) and Kludze-Forson et al. (2010) reported antifungal susceptibilities for 100% of their study patients. Klevay et al conducted a matched study of patients with BSI caused by *C. albicans* (n=54) or *C. glabrata* (n=54) and found that patients with *C. glabrata* were not less likely to receive appropriate antifungal therapy and that there was no association between timing of therapy and 30-day mortality. Similarly, Kludze-Forson et al. reported the absence of an association between the timing of appropriate antifungal therapy and hospital mortality among 123 candidemic patients; increased severity of illness score was the only independent predictor of mortality.

C. **Discordant Results**

The reason for differing results among various studies investigating the impact of timing of antifungal therapy on outcomes is unknown but multiple complex factors are likely responsible. Study design details such as the size of study populations and subgroups,

differences in patient comorbidities and illness severity, and variations in antifungal drugs studied may all have affected the ability to discern the true effect of appropriate early antifungal therapy. With the exception of the study by Patel et al. (2009), our study population had the highest mean APACHE II scores. It is possible that results obtained in the studies by Morrell et al. (2005) and Garey et al. (2006) may not be as applicable to a more critically ill population of patients. Importantly, we obtained different findings when reclassifying the small subgroup of patients who died before receiving 24 hours of effective antifungal therapy as having never received appropriate therapy; in this analysis, the 30-day mortality and survival results are more consistent with the original findings by Morrell et al. and Garey et al., showing an impact of earlier antifungal therapy on outcome. None of the previous studies assessing the timing of therapy in candidemia have performed a similar analysis and this may be an important consideration in any future studies of this type. Finally, the biggest difference may be the fact that many earlier studies did not employ the routine use of antifungal susceptibility testing to assess appropriateness of therapy. In any case, it may be that patient comorbidities and critical illness, or pathogen factors may be just as important if not more important in determining mortality than early administration of antifungal therapy.

D. **Limitations and Strengths**

The strengths of the current study are its size, use of antifungal susceptibility data, strict criteria for assessing appropriateness of therapy and inclusion of detailed information about study patients including multiple severity of illness indicators. However, it is important to recognize that the retrospective design did not allow the capture of all possible data that could have been important in assessing outcomes, such as symptom onset. In addition, the study was conducted at a single center and therefore may not be directly applicable to other institutions or settings. Finally, it is assumed in the study design that blood cultures were drawn at the first suspicion of infection but it is possible that time to appropriate antifungal therapy was longer for

some patients than was assessed if there was a delay in obtaining blood cultures in candidemic patients. This type of bias could explain higher than expected mortality in patients who appeared to receive early appropriate antifungal therapy. Despite these limitations our data are consistent with prior studies indicating a high mortality rate among hospitalized patients with candidemia as well as a particularly high mortality rate among those who never receive appropriate antifungal therapy. Furthermore, we confirmed that BSI due to *C. glabrata* or fluconazole non-susceptible *Candida* isolates are associated with a higher mortality (Choi et al., 2009; Dimopoulos et al., 2008; Kovacicova et al., 2000; Slavin et al., 2010) as are those BSI due to *C. krusei* where fluconazole therapy is administered (Choi et al., 2009; Krcmery et al., 1999).

E. **Conclusions**

In conclusion, among a large group of patients with *Candida* BSI, we did not find a survival benefit to early appropriate antifungal therapy when analyzing the study population as a whole, but noted that outcomes could be affected by whether patients had received a certain minimum duration of antifungal therapy. Our results are supported by the inclusion of routine antifungal susceptibility testing to optimally assess the appropriateness of treatments and the fact that the use of newer antifungal medications was included in the analysis. Given the high mortality seen in most studies of candidemic patients, additional maneuvers are needed to try to improve outcomes in these patients.

CITED LITERATURE

Anaissie, E. J., Darouiche, R. O., Abi-Said, D., Uzun, O., Mera, J., Gentry, L. O., Williams, T., Kontoyiannis, D. P., Karl, C. L., and Bodey, G. P.: Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin Infect Dis* 1996;23:964–72.

Bennett, J. E.: Echinocandins for candidemia in adults without neutropenia. *N Engl J Med* 2006;355:1154–9.

Bowden, R. A., Cays, M., Gooley, T., Mamelok, R. D., and van Burik, J. A.: Phase I study of amphotericin B colloidal dispersion for the treatment of invasive fungal infections after marrow transplant. *J Infect Dis* 1996;173:1208–15.

Choi, H. K., Jeong, S. J., Lee, H. S., Chin, B. S., Choi, S. H., Han, S. H., Kim, M. S., Kim, C. O., Choi, J. Y., Song, Y. G., and Kim, J. M.: Blood stream infections by Candida glabrata and Candida krusei: a single-center experience. *Korean J Intern Med* 2009;24:263–9.

Cockcroft, D. W. and Gault, M. H.: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.

Dimopoulos, G., Ntziora, F., Rachiotis, G., Armaganidis, A., and Falagas, M. E.: Candida albicans versus non-albicans intensive care unit-acquired bloodstream infections: differences in risk factors and outcome. *Anesth Analg* 2008;106:523–9.

Ericson, E. L., Klingspor, L., Ullberg, M., and Orenci, V.: Clinical comparison of the Bactec Mycosis IC/F, BacT/Alert FA, and BacT/Alert FN blood culture vials for the detection of candidemia. *Diag Microbiol Infect Dis* 2012;73:153–6.

Fernandez, J., Erstad, B. L., Petty, W., and Nix, D. E.: Time to positive culture and identification for Candida blood stream infections. *Diag Microbiol Infect Dis* 2009;64:402–7.

Fridkin, S. K.: The changing face of fungal infections in health care settings. *Clin Infect Dis* 2005;41:1455–60.

Garey, K. W., Rege, M., Pai, M. P., Mingo, D. E., Suda, K. J. Turpin, R. S., and Bearden, D. T.: Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006;43:25–31.

Grim, S. A., Berger, K., Teng, C., Gupta, S., Layden, J. E., Janda, W. M., and Clark, N. M.: Timing of susceptibility-based antifungal drug administration in patients with Candida bloodstream infection: correlation with outcomes. *J Antimicrob Chemother* 2012;67:707–14.

Groll, A. H., Shah, P. M., Mentzel, C., Schneider, M., Just-Neubling, G., and Huebner, K.: Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996;33:23–32.

Gudlaugsson, O., Gillespie, S., Lee, K., Vandeberg, J., Hu, J., Messer, S., Herwaldt, L., Pfaller, M., and Diekema, D.: Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* 2003;37:1172–7.

Hajjeh, R. A., Sofair, A. N., Harrison, L. H., Lyon, G. M., Arthington-Skaggs, B. A., Mirza, S. A., Phelan, M., Morgan, J., Lee-Yang, W., Ciblak, M. A., Benjamin, L. E., Sanza, L. T., Huie, S., Yeo, S. F., Brandt, M. E., and Warnock, D. W.: Incidence of bloodstream infections due to Candida species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. *J Clin Microbiol* 2004;42:1519–27.

Horn, D. L., Neofytos, D., Anaissie, E. J., Fishman, J. A., Steinbach, W. J., Olyaei, A. J., Marr, K. A., Pfaller, M. A., Chang, C. H., and Webster, K. M.: Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis* 2009;48:1695–703.

Hsu, D. I., Nguyen, M., Nguyen, L., Law, A., and Wong-Beringer, A.: A multicentre study to evaluate the impact of timing of caspofungin administration on outcomes of invasive candidiasis in non-immunocompromised adult patients. *J Antimicrob Chemother* 2010;65:1765–70.

Ibrahim, E. H., Sherman, G., Ward, S., Fraser, V. J.,and Kollef, M. H.: The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;118:146–55.

Jarvis, W. R.: Epidemiology of nosocomial fungal infections, with emphasis on Candida species. *Clin Infect Dis* 1995;20:1526–30.

Johnson, P. C., Wheat, L. J., Cloud, G. A., Goldman, M., Lancaster, D., Bamberger, D. M., Powderly, W. G., Hafner, R., Kauffman, C. A., and Dismukes, W. E.: Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med* 2002;137:105–9.

Kao, A. S., Brandt, M. E., Pruitt, W. R., Conn, L. A., Perkins, B. A., Stephens, D. S., Baughman, W. S., Reingold, A. L., Rothrock, G. A., Pfaller, M. A., Pinner, R. W., and Hajjeh, R. A.: The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. *Clin Infect Dis* 1999;29:1164–70.

Klevay, M. J., Ernst, E. J., Hollanbaugh, J. L., Miller, J. G., Pfaller, M. A., and Diekema, D. J.: Therapy and outcome of Candida glabrata versus Candida albicans bloodstream infection. *Diag Microbiol Infect Dis* 2008;60:273–7.

Kludze-Forson, M., Eschenauer, G. A., Kubin, C. J., Della-Latta, P., and Lam, S. W.: The impact of delaying the initiation of appropriate antifungal treatment for Candida bloodstream infection. *Med Mycol* 2010;48:436–9.

Kovacicova, G., Krupova, Y., Lovaszova, M., Riodova, A., Trupl, J., Liskova, A., Hanzen, J., Milosovic, P., Lamosova, M., Macekova, L., Szovenyiova, Z., Purgelova, A., Obertik, T., Bille, J., and Krcmery, V.: Antifungal susceptibility of 262 bloodstream yeast isolates from a mixed cancer and non-cancer patient population: is there a correlation between

in-vitro resistance to fluconazole and the outcome of fungemia? *J Infect Chemother* 2000;6:216–21.

Krcmery, V., Jr., Spanik, S., Kunova, A., Trupl, J., Grausova, S., Krupova, I., Mateicka, F., Pichnova, E., Grey, E., and Sabo, A.: Nosocomial Candida krusei fungemia in cancer patients: report of 10 cases and review. *J Chemother* 1999;11:131–6.

Kullberg, B. J., Sobel, J. D., Ruhnke, M., Pappas, P. G., Viscoli, C., Rex, J. H., Cleary, J. D., Rubinstein, E., Church, L. W., Brown, J. M., Schlamm, H. T., Oborska, I. T., Hilton, F., and Hodges, M. R.: Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005;366:1435–42.

Leibovici, L., Shraga, I., Drucker, M., Konigsberger, H., Samra, Z., and Pitlik, S. D.: The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;244:379–86.

Lockhart, S. R., Iqbal, N., Ahlquist, A. M., Farley, M. M., Harrison, L. H., Bolden, C. B., Baughman, W., Stein, B., Hollick, R., Park, B. J., and Chiller, T.: Species Identification and Antifungal Susceptibility of Candida Bloodstream Isolates from Population-based Surveillance in Two US Cities: 2008-2011. *J Clin Microbiol* 2012 Aug 8 [epub ahead of print].

McNeil, M. M., Nash, S. L., Hajjeh, R. A., Phelan, M. A., Conn, L. A., Plikaytis, B. D., and Warnock, D. W.: Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. *Clin Infect Dis* 2001;33:641–7.

Mora-Duarte, J., Betts, R., Rotstein, C., Colombo, A. L., Thompson-Moya, L., Smietana, J., Lupinacci, R., Sable, C., Kartsonis, N., and Perfect, J.: Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002;347:2020–9.

Morgan, J., Meltzer, M, I., Plikaytis, B. D., Sofair, A. N., Huie-White, S., Wilcox, S., Harrison, L. H., Seaberg, E. C., Hajjeh, R. A., and Teutsch, S. M.: Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. *Infect Control Hosp Epidemiol* 2005;26:540–7.

Morrell, M., Fraser, V. J., and Kollef, M. H.: Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005;49:3640–5.

McMullan, R., Metwally, L., Coyle, P. V., Hedderwick, S., McCloskey, B., O'Neill, J. H., Patterson, C. C., Thompson, G., Webb, C. H., and Hay, R. J.: A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. *Clin Infect Dis* 2008;46:890–6.

National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990-May 1999, issued June 1999. *Amer J Infect Control* 1999;27:520–32.

Obayashi, T., Negishi, K., Suzuki, T., and Funata, N.: Reappraisal of the serum (1-->3)-beta-D-glucan assay for the diagnosis of invasive fungal infections--a study based on autopsy cases from 6 years. *Clin Infect Dis* 2008;46:1864–70.

Pappas, P. G., Rex, J. H., Lee, J., Hamill, R. J., Larsen, R. A., Powderly, W., Kauffman, C. A., Hyslop, N., Mangino, J. E., Chapman, S., Horowitz, H. W., Edwards, and J. E., Dismukes, W. E.: A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* 2003;37:634–43.

Pappas, P. G., Rex, J. H., Sobel, J. D., Filler, S. G., Dismukes, W. E., Walsh, T. J., and Edwards, J. E.: Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;38:161–89.

Pappas, P. G., Rotstein, C. M., Betts, R. F., Nucci, M., Talwar, D., De Waele, J. J., Vazquez, J. A., Dupont, B. F., Horn, D. L., Ostrosky-Zeichner, L., Reboli, A. C., Suh, B., Digumarti, R., Wu, C., Kovanda, L. L., Arnold, L. J., and Buell, D. N.: Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis* 2007;45:883–93.

Pappas, P. G., Kauffman, C. A., Andes, D., Benjamin, D. K., Calandra, T. F., Edwards, J. E., Filler, S. G., Fisher, J. F., Kullberg, B. J., Ostrosky-Zeichner, L., Reboli, A. C., Rex, J. H., Walsh, T. J., and Sobel, J. D.: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:503–35.

Parkins, M. D., Sabuda, D M., Elsayed, S., and Laupland, K. B.: Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive Candida species infections. *J Antimicrob Chemother* 2007;60:613–8.

Patel, G. P., Simon, D., Scheetz, M., Crank, C. W., Lodise, T., and Patel, N.: The effect of time to antifungal therapy on mortality in candidemia associated septic shock. *Amer J Ther* 2009;16: 508–11.

Pfaller, M. A., Messer, S. A., Boyken, L., Rice, C., Tendolkar, S., Hollis, R. J., and Diekema, D. J.: Use of fluconazole as a surrogate marker to predict susceptibility and resistance to voriconazole among 13,338 clinical isolates of Candida spp. Tested by clinical and laboratory standards institute-recommended broth microdilution methods. *J Clin Microbiol* 2007;45:70–5.

Pfaller, M. A., Boyken, L., Hollis, R. J., Kroeger, J., Messer, S. A., Tendolkar, S., and Diekema, D. J.: In vitro susceptibility of invasive isolates of Candida spp. to anidulafungin, caspofungin, and micafungin: six years of global surveillance. *J Clin Microbiol* 2008;46:150–6.

Pfaller, M. A., Castanheira, M., Messer, S. A., Moet, G. J., and Jones, R. N.: Variation in Candida spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from the SENTRY Antimicrobial Surveillance Program (2008-2009). *Diag Micro Infect Dis* 2010;68:278–83.

Pfizer: Prescribing information for Diflucan. New York: 2010.

Reboli, A. C., Rotstein, C., Pappas, P. G., Chapman, S. W., Kett, D. H., Kumar, D., Betts, R., Wible, M., Goldstein, B. P., Schranz, J., Krause, D. S., and Walsh, T. J.: Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007;356:2472–82.

Ryan, K. J.: *Sherris Medical Microbiology*, eds. K. J. Ryan, C. G. Ray, N. Ahmad, W. L. Drew, and J. J. Plorde. McGraw-Hill Companies, Inc., 2010.

Sharkey, P. K., Graybill, J. R., Johnson, E. S., Hausrath, S. G., Pollard, R. B., Kolokathis, A., Mildvan, D., Fan-Havard, P., Eng, R. H., Patterson, T. F., Pottage, J. C., Simberkoff, M. S., Wolf, J., Meyer, R. D., Gupta, R., Lee, L. W., and Gordon, D. S.: Amphotericin B lipid complex compared with amphotericin B in the treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* 1996;22:315–21.

Slavin, M. A., Sorrell, T. C., Marriott, D., Thursky, K. A., Nguyen, Q., Ellis, D. H., Morrissey, C. O., and Chen, S. C.: Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. *J Antimicrob Chemother* 2010;65:1042–51.

Sipsas, N. V., Lewis, R. E., Tarrand, J., Hachem, R., Rolston, K. V., Raad, I. I., and Kontoyiannis, D. P.: Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001-2007): stable incidence but changing epidemiology of a still frequently lethal infection. *Cancer* 2009;115:4745–52.

Taur, Y., Cohen, N., Dubnow, S., Paskovaty, A., and Seo, S. K.: Effect of antifungal therapy timing on mortality in cancer patients with candidemia. *Antimicrob Agents Chemother* 2010;54:184–90.

van de Veerdonk, F. L., Kullberg, B. J., and Netea, M. G.: Pathogenesis of invasive candidiasis. *Curr Opin Crit Care* 2010;16:453–9.

Walsh, T. J., Hiemenz, J. W., Seibel, N. L., Perfect, J. L., Horwith, G., Lee, L., Silber, J. L., DiNubile, M. J., Reboli, A., Bow, E., Lister, J., and Anaissie, E. J.: Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998;26:1383–96.

Walsh, T. J. and Groll, A. H.: Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. *Transpl Infect Dis* 1999;1:247–61.

Zaoutis, T. E., Argon, J., Chu, J., Berlin, J. A., Walsh, T. J., and Feudtner, C.: The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. *Clin Infect Dis* 2005;41:1232–9.

Zilberberg, M. D., Shorr, A. F., and Kollef, M. H.: Secular trends in candidemia-related hospitalization in the United States, 2000-2005. *Infect Control Hosp Epidemiol* 2008;29:978–80.

Zilberberg, M. D., Kollef, M. H., Arnold, H., Labelle, A., Micek, S. T., Kothari, S., and Shorr, A. F.: Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. *BMC Infect Dis* 2010;10:150.

VITA

Name Shellee A. Grim, Pharm.D., BCPS

Education and Training

2006–present	Masters in Clinical and Translational Research University of Illinois at Chicago School of Public Health, Chicago, Illinois Anticipated completion: December 2012
2003	Infectious Diseases Specialty Residency University of Kentucky Chandler Medical Center, Lexington, Kentucky
2002	Pharmacy Practice Residency University of Kentucky Chandler Medical Center, Lexington, Kentucky
2001	Doctor of Pharmacy Washington State University College of Pharmacy, Pullman, Washington
2001	Certificate of Completion with International Emphasis Washington State University Honors College, Pullman, Washington
2001	Bachelor of Science, General Studies (Biological Sciences) Washington State University College of General Studies, Pullman, Washington

Academic Appointments

2010–present	Clinical Associate Professor, Department of Pharmacy Practice University of Illinois at Chicago, Chicago, Illinois
2004–2005	Clinical Assistant Professor, Department of Internal Medicine, Section of Infectious Diseases University of Illinois at Chicago, Chicago, Illinois
2003–2010	Clinical Assistant Professor, Department of Pharmacy Practice University of Illinois at Chicago, Chicago, Illinois

Professional Experience

2003–present	Clinical Pharmacist, Transplant Infectious Diseases University of Illinois Medical Center, Chicago, Illinois

Teaching Activities

University of Illinois at Chicago College of Pharmacy

Preceptor

2008–present	Experiential V (PHAR 357)
2005–present	Advanced Specialty Clerkship Rotation (PMPR 388)--Research
2004–present	Advanced Medicine Clerkship Rotation (PMPR 387)—Infectious Diseases

2004–present	Pharmacy Practice Resident Rotation (PGY1)—Infectious Diseases
2004–present	Specialty Resident Rotation (PGY2)—Infectious Diseases

Lecturer

2011–present	Fundamentals of Drug Action III (PHAR 333) "Mycology" 2 contact hours/year
2008–present	Principles of Drug Action and Therapeutics III (PHAR 403) "Therapeutics of Invasive Fungal Infections" 2 contact hours/year
2007–present	Applied Pharmacokinetics (PMPR 440) "Pharmacokinetics of Antifungal Agents" 2 contact hours/year
2005–2010	Fundamentals of Drug Action III (PHAR 333) "Virology" and "Mycology" 6 contact hours/year
2005–2010	Principles of Drug Action and Therapeutics VII (PHAR 407) "Transplant Infectious Diseases" 1 contact hour/year
2005–2007	Principles of Drug Action and Therapeutics VI (PHAR 406) "Systemic Antifungal Agents" 2 contact hours/year
2005–2006	Applied Pharmacokinetics (PMPR 440) "Extended-Interval Aminoglycosides" 1 contact hour/year

Small Group Facilitator

2003–2005	Experiential II (PHAR 352) 10 contact hours/year
2003–2005	Experiential III (PHAR 453) 2 contact hours/year
2003	Principles of Drug Action and Therapeutics VI (PHAR 406) 21 contact hours

<u>University of Illinois College of Medicine</u>

Lecturer

2005–present	Infectious Diseases Fellowship Conference "Aminoglycosides: Pharmacokinetics and Dosing" "Anti-Infective Considerations: Pregnancy and Lactation" 2 contact hours/year
2005–2008	M3 Clerkship Core Lecture Series "Antimicrobial Resistance" 4 contact hours/year

<u>University of Kentucky College of Pharmacy</u>

Course Instruction/Co-Coordination

2001	Medical Spanish for Pharmacists (PHR 895-03) 30 contact hours

Lecturer

2002–2003	Contemporary Aspects of Pharmacy Practice III (PHR 949) "Essential Elements of Study Design" 3 contact hours/year
2002	Introduction to Antibiotics (PHR 913) "Macrolides," "Tetracyclines" and "Aminoglycosides" 3 contact hours
2002	Integrated Therapeutics I (PHR 951) "Infective Endocarditis" 2 contact hours

Washington State University College of Pharmacy

Teaching Assistant

1999	Pharmaceutics Compounding Laboratory (PharS 437) 36 contact hours

Publications

Articles - Refereed

Rowe, J., Grim, S. A., Peace, D., Lai, C., Sweiss, K., Layden, J. E., and Clark, N. M.: The significance of cytomegalovirus (CMV) viremia at day one hundred or more following allogeneic hematopoietic stem cell transplantation (HSCT). *Biol Blood Marrow Transplant* (submitted).

Santayana, E., Grim, S. A., Janda, W. M., Layden, J. E., Lee,T. A., and Clark, N. M.: Risk factors and outcomes associated with vancomycin-resistant *Enterococcus* (VRE) infections with reduced susceptibility to linezolid. *Diagn Micro Infect Dis* 2012 Jun 29 (Epub).

Grim, S. A., Berger, K., Teng, C., Gupta, S., Layden, J. E., Janda, W. M., and Clark N. M.: Timing of susceptiblity-based antifungal drug administration in patients with *Candida* bloodstream infection: correlation with outcomes. *J Antimicrob Chemother* 2012;67(3):707–14.

Layden, J. E., Cotler, S. J., Grim, S. A., Fischer, M. J., Lucey, M. R., and Clark, N. M.: The impact of donor and recipient race on survival after hepatitis C-related liver transplantation. *Transplantation* 2012;93(4):444–9.

Grim, S. A., Proia, L., Miller, R., Alhyraba, M., Costas-Chavarri, A., Oberholzer, J., and Clark, N. M.: A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. *Transplant Infect Dis* 2012;14(1):17–23.

Heinrich, L., Tokumaru, S., Clark, N. M., Garofalo, J., Paek, J., and Grim, S .A.: Development and implementation of a piperacillin-tazobactam extended infusion guideline. *J Pharm Pract* 2011;24(6):571–6.

Culos, K. A., Cannon, J. P., and Grim, S. A.: Alternative agents to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. *Amer J Ther* 2011 Jun 3 (Epub).

Grim, S. A. and Clark, N. M.: Management of infectious complications in solid organ transplant recipients. *Clin Pharmacol Ther* 2011;90(2):333–42.

Jarrett, O., Grim, S. A., Benedetti, E., and Clark, N. M.: Gastrointestinal tuberculosis in renal transplant recipients: case report and review of the literature. *Transplant Infect Dis* 2011;13(1):52–7.

Grim, S. A., Pereira, E., Guzman, G., Clark, N. M.: CMV PCR as a diagnostic tool for CMV gastrointestinal disease after solid organ transplantation. *Transplantation* 2010;90(7):799–801.

Grim, S. A. and Clark, N. M.: The role of adjuvant agents in treating fungal diseases. *Curr Fungal Infect Reports* 2009;3(2):117–26.

Reid, G. E., Grim, S. A., Sankary, H., Benedetti, E., Oberholzer, J., and Clark, N. M.: Early intraabdominal infections associated with orthotopic liver transplantation. *Transplantation* 2009;87(11):1706–11.

Grim, S. A., Hong, I., Freeman, J., Edwards, C., and Clark, N. M.: Daptomycin for the treatment of vancomycin-resistant enterococcal infections. *J Antimicrob Chemother* 2009;63(2):414–6.

Grim,S. A., Rene, L., Gupta, S., and Clark, N. M.: Safety of linezolid in patients with baseline thrombocytopenia. *J Antimicrob Chemother* 2008;62(4):850–1.

Alhyraba, M., Grim, S. A., Benedetti, E., and Clark, N. M.: Unusual presentation of cytomegalovirus enteritis after liver and kidney transplantation. *Transplant Infect Dis* 2007;9:343–6.

Grim, S. A., Pham, T., Thielke, J., Sankary, H., Oberholzer, J., Benedetti, E., and Clark, N. M.: Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients. *Clin Transplant* 2007;21(5):628–32.

Reid, G. E., Grim, S. A., Aldeza, C. A., Janda, W. M., and Clark, N. M.: Rapid development of tigecycline resistance in *Acinetobacter baumannii*. *Pharmacotherapy* 2007;27(8):1198–201.

Grim, S. A., Slover, C. M., Sankary, H., Oberholzer, J., Benedetti, E., and Clark, N. M.: Risk factors for wound healing complications in sirolimus-treated renal transplant recipients. *Transplant Proc* 2006;38:3520–3.

Jain, R., Clark, N. M., Diaz-Linares, M., and Grim, S. A.: Limitations of current antiretroviral agents and opportunities for development. *Curr Pharm Des* 2006;12(9):1065–74.

Grim, S. A., Rapp, R. P., Martin, C. A., and Evans, M. E.: Trimethoprim/sulfamethoxazole: Is this a viable agent for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus*? *Pharmacotherapy* 2005;25(2):253–64.

Miles, M. V., Tang, P. H., Ryan, M. A., Grim, S. A., Fakhoury, T. A., Strawsburg, R. H., deGrauw, T. J., and Baumann, R. J.: Feasibility and limitations of oxcarbazepine monitoring using salivary monohydroxycarbamazepine (MHD). *Ther Drug Monitor* 2004;26(3):300–4.

Grim, S. A., Romanelli, F., Jennings, P. R., and Ofotokun, I.: A case of late-onset drug fever associated with minocycline use: report and review of the literature. *Pharmacotherapy* 2003;23(12):1659–62.

Ryan, M., Grim, S., Miles, M. V., Tang, P. H., Fakhoury, T. A., Strawsburg, R. H., deGrauw, T. J., and Baumann, R. J.: Correlation of lamotrigine concentrations between serum and saliva. *Pharmacotherapy* 2003;23(12):1550–57.

Miles, M. V., Tang, P. H., Glauser, T. A., Ryan, M. A., Grim, S. A., Strawsburg, R. H., deGrauw, T. J., and Baumann R. J.: Topiramate concentration in saliva: an alternative to serum monitoring. *Ped Neurol* 2003;29:143–7.

Grim, S. A., and Romanelli, F.: Viread® (tenofovir disoproxil fumarate). *Ann Pharmacother* 2003;37:849–59.

Grim, S. A., Ryan, M., Miles, M. V., Tang, P. H., Strawsburg, R. H., deGrauw, T. J., Fakhoury, T. A., and Baumann, R. J.: Correlation of levetiracetam concentrations between serum and saliva. *Ther Drug Monitor* 2003;25:61–6.

Grim, S. A., Smith, K. M., Romanelli, F., and Ofotokun, I.: Treatment of azole resistant oropharyngeal candidiasis with topical amphotericin B. *Ann Pharmacother* 2002;36:1383–6.

Articles – Non-Refereed

Grim, S. A., Contributor. :The Eighth Annual HIV Drug Guide. Positively Aware 2004;15(1):16–40.

Rapp, R. P. and Grim, S. A.: A rational approach to issues surrounding vancomycin resistance. *Pharmacy Practice News* 2003, 67–72.

Published Abstracts

Reid, G., Grim, S., Layden, J., Akkina, S., Tang, I., Adams, W., Campara, M., Janda, W., and Clark, N.: The use of fosfomycin (FOS) to treat urinary tract infections (UTIs) in renal transplant recipients (RTRs). Poster presentation: American Transplant Congress, Boston, Massachusetts, June 2012, abstract 614; published in *Am J Transplant* 2012;12(Suppl 3):212.

Kitazano, H., Rog, D., Clark, N. M., Grim, S. A., and Reid, G. E.: *Acinetobacter baumannii* infection among solid organ transplant recipients. Poster presentation: American Transplant Congress, San Diego, California, May 2010, abstract 1351; published in *Am J Transplant* 2010;10(Suppl 4):425-6.

Grim, S., Alhyraba, M., Costas, A., Oberholzer, J., Benedetti, E., Sankary, H., and Clark, N.: Endemic fungal infections (EFI) following solid organ transplantation (SOT). Poster presentation: American Transplant Congress, Boston, Massachusetts, June 2009, abstract 1624; published in *Am J Transplant* 2009;9(Suppl 2): 640.

Grim, S., Pereira, E., Guzman, G., and Clark, N.: Cytomegalovirus (CMV) polymerase chain reaction (PCR) assay as a diagnostic tool in CMV enteritis (CMVE) after transplantation. Poster presentation: American Transplant Congress, Boston, Massachusetts, May 2009, abstract 1281; published in *Am J Transplant* 2009;9(Suppl 2): 549.

Reid, G. E., Grim, S. A., Sankary, H., Oberholzer, J., Benedetti, E., and Clark, N. M.: Early intraabdominal infections (IAI) associated with liver transplantation (LT). Poster presentation: American Transplant Congress, San Francisco, California, May 2007, abstract 1391; published in *Am J Transplant* 2007;7(Suppl 2):504.

Grim, S., Slover, C., Sankary, H., Oberholzer, J., Benedetti, E., and Clark, N.: Risk factors for wound healing complications in sirolimus-treated renal transplant recipients. Poster presentation: World Transplant Congress, Boston, MA, July 2006, abstract 1225; published in *Am J Transplant* 2006;6(Suppl 2):481.

Grim, S. A., Gupta, S., Holloway, M., Sankary, H., Oberholzer, J., Benedetti, E., and Clark, N. M.: Characteristics of invasive *Candida* infections in solid organ transplant recipients. Poster presentation: 14th International Symposium on Infections in the Immunocompromised Host, Crans-Montana, Switzerland, July 2006, abstract 42; published in *Int J Infect Dis* 2006;10(Suppl 1):S23.

Grim, S., Pham, T., Thielke, J., Sankary, H., Oberholzer, J., Testa, G., Benedetti, E., and Clark, N.: Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients. Platform presentation: American Transplant Congress, Seattle, Washington, May 2005, abstract 1384; published in *Am J Transplant* 2005;5(Suppl 11):508.

Grim, S. A., Jaffe,H. A., and Clark, N. M.: A case of BK virus-associated hemorrhagic cystitis in a lung transplant recipient and review of the literature. Poster presentation: 13th International Symposium on Infections in the Immunocompromised Host, Granada, Spain, June 2004, abstract 26; published in *Int J Infect Dis* 2004;8:S13–4.

Grim, S. A., Record, K. E., Lewis, D. A., and Smith, K. M.: Impact of low molecular weight heparins on acute venous thromboembolism prophylaxis: a case-control analysis. Poster presentation: American College of Clinical Pharmacy Annual Meeting, Albuquerque, NM, October 2002; abstract 121; published in *Pharmacotherapy* 2002;22(10):1344.

Grim, S. A., Ryan, M., Miles, M. V., Tang, P. H., Strawsburg, R. H., deGrauw, T. J., and Baumann R. J.: Correlation of levetiracetam concentrations between serum and saliva. Poster presentation: American College of Clinical Pharmacy Annual Meeting, Albuquerque, NM, October 2002, abstract 187; published in *Pharmacotherapy* 2002;22(10):1354.

Ryan, M., Grim, S. A., Miles, M. V., Tang, P. H., Strawsburg, R. H., deGrauw, T. J.,and Baumann R. J.: Correlation of lamotrigine concentrations between serum and saliva. Poster presentation: American College of Clinical Pharmacy Annual Meeting, Albuquerque, NM, October 2002, abstract 188; published in *Pharmacotherapy* 2002;22(10):1354.

Clinical Studies

A Prospective, Randomized Trial Comparing the Efficacy of Anidulafungin and Voriconazole in Combination to that of Voriconazole Alone when used for Primary Therapy of Proven or Probable Invasive Aspergillosis (Pfizer, Inc.)
Co-Investigator (PI: N. Clark), 5% effort, 3/09 – 2/11 $104,784 direct costs

Timing of Antifungal Drug Administration in Patients with *Candida* Bloodstream Infection: Correlation with Outcomes and Antifungal Susceptibility Data (Merck & Co., Inc.)
Co-Principal Investigator, 15% effort, 2/07 – 3/11 $25,775 direct costs

Anidulafungin Pharmacokinetics in Patients with Septic Shock and Hypoalbuminemia (Pfizer, Inc.)
Co-Investigator (PI: E. Tesoro), 3% effort, 7/06 – 1/10 $34,467 direct costs

A Randomized, Double-Blind Study to Assess the Efficacy and Safety of Prophylactic Use of Maribavir Versus Oral Ganciclovir for the Prevention of Cytomegalovirus Disease in Recipients of Orthotopic Liver Transplants (ViroPharma Incorporated, 1263-301)
Co-Investigator (PI: N. Clark), 4% effort, 1/08 – 6/09 $62,838 direct costs

Chicago-Area Review of the Use, Efficacy, and Tolerability of Novel Antifungals in the Clinical Setting (Pfizer, Inc.)
Co-Principal Investigator, 15% effort, 5/06 – 5/08 $40,000 direct costs

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Comparative Study of Micafungin (FK 463) Versus Caspofungin as Antifungal Treatment in Patients with Invasive Candidiasis or Candidemia (Astellas Pharma US, Inc., 03-0-192)
Co-Investigator (PI: N. Clark), 4% effort, 2/06 – 4/07 $5,200 direct costs

A Review of the Epidemiology of Invasive *Candida* Infections, Antifungal Drug Utilization and Susceptibility Patterns (Merck & Co., Inc.)
Co-Principal Investigator, 12% effort, 2/05 – 1/06 $14,460 direct costs

A Prospective, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of the Safety and Efficacy of Three Days Continuous Infusion of GR270773 in the Treatment of Suspected or Confirmed Gram-Negative Severe Sepsis in Adults (GlaxoSmithKline EMD20001)
Co-Invesigator (PI: N.Clark), 3% effort, 5/04 – 3/06 $8,023 direct costs

A Randomized, Double-Blind, Placebo-Controlled Trial of Caspofungin vs. Placebo as Prophylaxis of Invasive Candidiasis in High-Risk Adults in the Critical Care Setting (Bacteriology-Mycology Study Group BAMSG 2-01)
Co-Investigator (PI: N. Clark), 5% effort, 11/04 – 1/06 $11,187 direct costs

CLEAR II®: Collaborative Exchange of Antifungal Research (Enzon Pharmaceuticals)
Co-Investigator (PI: N. Clark), 3% effort, 11/04 – 3/05 $18,000 direct costs

Presentations

International

November 2006 — "Current Concepts in Infectious Diseases Pharmacotherapy and Rational Use of Anti-Infective Agents." Two-day, team taught educational program for pharmacists in Hong Kong. Co-facilitator. Hong Kong, China
Lectures given: Introduction to Selection of Appropriate Anti-Infective Agents,
Application of the Antibiogram: Applying Microbiology Data at the Patient's Bedside, Update in Antifungal Agents, Management of Infection Related Disease States

November 2006 — "Antimicrobial Stewardship Focus Group." Two-day, team taught educational program for pharmacists specializing in infectious diseases in Hong Kong. Co-facilitator, Hong Kong, China
Lectures given: Focus on Broad Spectrum Antibiotics, Conducting Medication Use Evaluations, Establishing an

	Anti-Infective Stewardship Team, Developing Anti-Infective Pathways
March 2005	"Current Concepts in Infectious Diseases Pharmacotherapy and Rational Use of Anti-Infective Agents." Two-day, team taught educational program for pharmacists in Hong Kong. Co-facilitator. Hong Kong, China Lectures given: Management of Infections in Immunocompromised Hosts, Management of Febrile Neutropenia, Treatment of Invasive Fungal Infections, Management of Infection Related Disease States, The Pharmacist's Role in Reducing Antimicrobial Resistance
<u>National</u>	
May 2005	"Infectious Complications Associated with the Use of Rituximab for ABO-Incompatible and Positive Cross-Match Renal Transplant Recipients," Platform presentation, American Transplant Congress, Seattle, Washington
May 2003	"Optimizing Medication Adherence in Highly Non-Adherent HIV-Seropositive Patients," Research presentation, Star of the North Fellowship Forum, Brainerd, Minnesota
<u>Regional</u>	
January 2012	"*Klebsiella pneumoniae* Carbapenemase (KPC)-Producing *K. pneumoniae* Infections in Solid Organ Transplantation," Multidisciplinary transplant journal club, University of Illinois Medical Center at Chicago, Chicago, Illinois
November 2010	"Antifungals: Treatment Strategies for Emerging Disease," Infectious Diseases Research Frontiers: ICAAC Review, Midwestern University, Downers Grove, Illinois (ACPE-accredited)
May 2010	"Optimization of Antifungal Therapy in Hospitalized Patients," MedAssets Midwest Regional Meeting, Northwestern University, Chicago, Illinois (ACPE-accredited)
January 2008	"Antifungals: A View from the Front Lines of Research," Infectious Diseases Research Frontiers: ICAAC Review, Midwestern University, Downers Grove, Illinois (ACPE-accredited)
January 2008	"Host Genetic Determinants of Outcome in *Candida* Bloodstream Infection (CBSI)", Works in Progress Research Seminar Series, Clinical Research Training Program, University of Illinois at Chicago, Chicago, Illinois

March 2007	"Update in the Pharmacotherapy of Invasive Fungal Infections", Spring meeting of the Illinois Council of Health-System Pharmacists and Missouri Society of Health-System Pharmacists, St. Charles, Missouri (ACPE-accredited)
April 2004	"Voricaspoamphofungin: What's New in the Antifungal Armamentarium?", Pharmacy Continuing Education Series, University of Illinois Medical Center at Chicago, Chicago, Illinois (ACPE-accredited)
December 2003	"Current Topics in HIV/AIDS Treatment", Pharmacy Continuing Education Series, University of Illinois Medical Center at Chicago, Chicago, Illinois (ACPE-accredited)
May 2003	"Optimizing Medication Adherence in Highly Non-Adherent HIV-Seropositive Patients", Southeastern Residency Conference, Athens, Georgia
April 2002	"Saliva Monitoring of Antiepileptic Drugs", Southeastern Residency Conference, Athens, Georgia

Poster presentations

Grim SA, Santayana E, Janda WM, Clark NM. Risk factors and outcomes associated with vancomycin-resistant Enterococcus (VRE) infections with reduced susceptibility to linezolid (LZD). The 48th Annual Meeting of the Infectious Diseases Society of America, Vancouver, British Columbia, Canada, October 2010, abstract 3025.

Santayana E, Grim SA, Janda W, Clark NM. Risk factors associated with the development of infection or colonization with linezolid-resistant, vancomycin-resistant *Enterococcus* (LR-VRE). Proceedings of the Great Lakes Residency Conference, West Lafayette, IN, April 2009.

Heinrich L, Tokumaru S, Grim S, Paek J, Garofalo J, Clark N. Implementation and evaluation of an extended infusion piperacillin-tazobactam protocol. Proceedings of the Great Lakes Residency Conference, West Lafayette, IN, April 2009.

Grim SA, Clark NM, Dai Y, Dumanski J, Reid GE, Williamson PR. Host genetic determinants of outcome in *Candida* bloodstream infection (CBSI). US Critical Illness and Injury Trials Group, Bethesda, MD, November 2008, abstract 16.

Cannon JP, Clark NM, Lee T, Setlak P, Grim SA. The incidence of carbapenem (CBP)-related seizures: a meta-analysis. American College of Clinical Pharmacy Annual Meeting, Denver, Colorado, October 2007, abstract 288.

Grim SA, Hanes SD, Teng C, Gupta S, Janda WM, Clark NM. Timing of antifungal (AF) administration in *Candida* bloodstream infection (CBSI): correlation with outcomes. The 45th Annual Meeting of the Infectious Diseases Society of America, San Diego, California, October 2007, abstract 1665.

Grim S, Gupta S, Holloway M, Lee T, Paek J, Janda W, Clark N. *Candida* bloodstream infections (CBSI) at a University Hospital 2001-2004. The 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, Ontario, Canada, October 2006, abstract 549.

Grim S, Cannon J, Lee T, Crank C, Patel G, Proia L, Labuszewski L, Mullane K, Jancel T, Clark N. Utilization of newer antifungals in a large metropolitan setting. Focus on Fungal Infections, Las Vegas, Nevada, March 2006, abstract 19.

Slover CM, Grim SA, Clark NM. Risk factors for wound healing complications in patients treated with sirolimus post-kidney transplantation. Proceedings of the Great Lakes Residency Conference, West Lafayette, IN, April 2005.

Fernandez C, Morris J, Grim S, Clark N. Use of the novel antifungals in a clinical setting: a retrospective evaluation. Proceedings of the Infectious Diseases Pharmacotherapy Fellowship Forum, Vail, CO, June 2004.

Morris JL, Fernandez C, Grim S, Gunderson S, Paek J, Schreckenberger P, Clark N. Use, efficacy, and safety of novel antifungals in the clinical setting: a retrospective analysis. Proceedings of the Great Lakes Residency Conference, West Lafayette, IN, April 2004.

Grim, SA, Romanelli F, Rapp RP, Thornton AC. Optimizing medication adherence in highly non-adherent HIV-seropositive patients. Proceedings of the Star of the North Fellowship Forum, Brainerd, MN, May 2003.

Grim, SA, Romanelli F, Rapp RP, Thornton AC. Optimizing medication adherence in highly non-adherent HIV-seropositive patients. Program and Abstracts of the Thirty-Fourth Annual Southeastern Residency Conference, Athens, GA, May 2003.

Gerard LN, Martin C, Grim S, Ryan M, Rapp R. Antimicrobial use as a causative factor of vancomycin-resistant Enterococci (VRE) infection. Program and Abstracts of the Thirty-Fourth Annual Southeastern Residency Conference, Athens, GA, May 2003.

Cuellar S, Grim S, Kuhn RJ. Performance assessment of patient counseling skills after a medical Spanish course for pharmacists. Program and Abstracts of the Thirty-Third Annual Southeastern Residency Conference, Athens, GA, April 2002.

Grim SA, Ryan M, Baumann R, Miles MV, Tang PH. Saliva monitoring of antiepileptic drugs. Program and Abstracts of the Thirty-Third Annual Southeastern Residency Conference, Athens, GA, April 2002.

Grim SA, Terriff CM. Pharmacologic preparedness for bioterrorism: estimating antidote quantities and cost. American Society of Health-System Pharmacists Midyear Clinical Meeting, Las Vegas, NV, 2000.

Administrative Activity and Service

University of Illinois Medical Center at Chicago

2004–present	Member, UIH Infection Control Committee
2004–2006	Member, Community Acquired Pneumonia Taskforce

2003–present	Member, Bone Marrow Transplant Unit Protocol Committee
2003–present	Member, Solid Organ Transplant Protocol Committee
2003–present	Co-Chair, Anti-Infective Subcommittee of the Hospital Pharmacy & Therapeutics Committee

University of Illinois College of Pharmacy

2011–present	Academic Faculty Mentor, Department of Pharmacy Practice
2010–present	Member, Department of Pharmacy Practice Promotion and Tenure Committee
2005–2010	Member, Residency Seminar Committee
2004–present	Member, Pharmacy Practice Residency Recruitment Committee

Extracurricular

2010–present	Member, Recognition Awards Society of Infectious Diseases Pharmacists
2006–2007	Member, Inhalational Antibiotics Working Group Society of Infectious Diseases Pharmacists
2006–2007	Member, Program Committee Society of Infectious Diseases Pharmacists
2006	Member, Paul F. Parker Award Selection Committee University of Kentucky

Community Service

2012	Scholarship reviewer, WSU Alumni Association--Midwest Chapter
2011–present	Volunteer, Recovery on Water (ROW), Chicago, IL
2010–present	Faculty Judge, UIC College of Pharmacy Research Day, Chicago, IL
2007–present	Student mentor, Illinois Council of Health-System Pharmacists, Chicago, IL
2007, 2009	Volunteer, Habitat for Humanity, St. Clement Church, Chicago, IL
2002	Brown bag medication review, Lexington Senior Citizens Center, Lexington, KY
2000–2001	Poison prevention program, Pullman Public Schools District, Pullman, WA
1999	Fundraiser/Marathoner, Leukemia Society of America, Washington-Alaska Chapter

Ad Hoc Reviewer

2012	Future Microbiology
2011	Journal of Pharmacy Practice
2011	Scandanavian Journal of Infectious Diseases
2009–2010	Pharmacotherapy
2009	Nephrology Dialysis Transplantation Plus
2009	Phytomedicine
2009	Kidney
2008–2012	Journal of Antimicrobial Chemotherapy
2008–2009	Critical Care Medicine
2008	Infection
2008	Mycology
2008	American Journal of Nephrology
2008	Recent Patents on Anti-Infective Drug Discovery
2008	Saudi Medical Journal
2006	Novation/University HealthSystem Consortium Drug Monograph Series
2006	Pharmacotherapeutics: Clinical Reasoning in Primary Care
2002–2005	Pharmacotherapy
2002–2003	Annals of Pharmacotherapy
2002	Journal of Pharmaceutical Technology

Professional Affiliations

2007–present	Infectious Diseases Society of America
2007–2009	Illinois Council of Health-System Pharmacists
2004–present	International Immunocompromised Host Society
2003–2005	American Association of Colleges of Pharmacy
2002–present	Society of Infectious Disease Pharmacists
2001–present	American College of Clinical Pharmacy
2001–present	American Society of Microbiology
1998–2011	American Society of Health-System Pharmacists
1997–2005	American Pharmaceutical Association

Certifications and Licensure

2012–present	APhA Pharmacy-Based Immunization Delivery Certificate Program
2004–present	Board Certified Pharmacotherapy Specialist, Board of Pharmaceutical Specialties
2003–present	Illinois Board of Pharmacy (#289617)
2001–present	Kentucky Board of Pharmacy (#012149)
2001–present	Washington Board of Pharmacy (#40273)
2002	HIV/AIDS Pharmacotherapy Traineeship, American Society of Consultant Pharmacists
2002	Scholarship of Teaching and Learning Certificate Program, University of Kentucky
2001–2005	Advanced Cardiac Life Support, American Heart Association
2000–present	Basic First Aid and CPR Certification, American Heart Association

Honors and Awards

2008	Rho Chi Honor Society, University of Illinois at Chicago Chapter
2007	Academic Employee of the Month, Hospital Pharmacy Services, University of Illinois at Chicago
2007	Professor Recognition Award Nominee, University of Illinois at Chicago
2006	Professor Recognition Award Nominee, University of Illinois at Chicago
2001	Mortar and Pestle Professionalism Award, Washington State University
2000	President's Leadership Award, Washington State University
1999	President's Leadership Award, Washington State University