

Echinocandin Use in Hospitalized Patients: A Multi-institutional Study

Kevin W. Garey, PharmD, MS, Samuel L. Aitken, PharmD, Anthony Dima-Ala, PharmD,
Nicholas D. Beyda, PharmD, Kristi Kuper, PharmD, Yang Xie, PhD and Hoonmo L. Koo, MD

Abstract: *Background:* The echinocandin antifungals are recommended as initial therapy in hospitalized patients with candidemia. Contemporary usage rates and indication for use of echinocandins have not been studied in the United States. The purpose of this study was to evaluate echinocandin usage patterns in community and academic teaching hospitals over time and to evaluate dose, duration of therapy and indications for use. *Methods:* This study used hospital pharmacy databases from academic and community hospitals to collect information on adult inpatients given systemic antifungal agents from 2008 to 2012. Patient medical information was also obtained from randomly selected patients given an echinocandin over the same time period. *Results:* Echinocandin use was determined for 4 academic and 34 community hospitals. A significant increase in echinocandin use was observed in academic and community hospitals during the time period ($P < 0.001$). Two hundred forty-two randomly selected patients receiving an echinocandin were retrospectively reviewed. Indications for echinocandin use did not change during the time period and included empiric therapy in a high-risk patient without subsequent mycologic confirmation from a normally sterile site (55%), systemic candidiasis (43%) and prophylactic (2%). Fifty-six percent of patients had at least 1 anatomic site of mycologic growth; most commonly urine only (14%), respiratory only (12%) or blood only (7%). In patients with candidemia, the hospital treatment course with an echinocandin averaged 8.4 ± 7.9 days (range, 1–35 days). *Conclusions:* This study provides useful benchmark data on antifungal use and indications for use that could be used for antifungal stewardship program comparisons.

Key Indexing Terms: Antifungals; Drug evaluation; Yeast; *Candida* species; Usage patterns; Antifungal stewardship. [*Am J Med Sci* 2015;349(4):316–320.]

Candida species are the 4th most common cause of nosocomial bloodstream infections and the most common pathogens responsible for fungal bloodstream infections.¹ Of candidemia episodes, 33% to 55% occur in intensive care units with mortality rates as high as 71%.^{2,3} Candidemia in hospitalized patients has increased in frequency and has been associated with higher mortality, longer length of hospital stay and increased cost compared with bacterial bloodstream infections.⁴ *Candida albicans* is the single most frequently isolated *Candida* species; however, due to shifts in fungal ecology, the incidence of candidemia caused by non-*albicans Candida* species is now greater than the incidence caused by *C. albicans*.⁵

From the Department of Clinical Sciences and Administration (KWG, SLA, AD, NDB, KK), University of Houston College of Pharmacy, Houston, Texas; Merck & Co, Inc (YX), Whitehouse Station, New Jersey; and Section of Infectious Diseases (HLK), Baylor College of Medicine, Houston Texas.

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Correspondence: Kevin W. Garey, PharmD, MS, University of Houston College of Pharmacy, 1441 Moursund Street, Houston, TX 77030 (E-mail: kgarey@uh.edu).

The echinocandin antifungals, caspofungin, micafungin and anidulafungin, act by the inhibition of 1,3- β -D-glucan synthesis in the fungal cell wall.⁶ They have similar broad spectrum of activity and may be used for azole-resistant fungal infections. The 2009 IDSA guideline recommend an echinocandin as initial therapy for candidemia in patients with moderately severe to severe candidiasis and in patients with recent exposure to azole antifungals.⁷ With the favorable safety profile and efficacy benefit of echinocandins, it is likely that the use of echinocandins is increasing sharply in the United States. To the best of our knowledge, studies assessing the rate and indication for echinocandin antifungals in the general hospital population have not been undertaken. The purpose of this study was to perform a contemporary analysis of echinocandin use among hospitalized patients. The specific aims were to evaluate usage patterns in community and academic teaching hospitals over time and to evaluate dose, duration of therapy and indications for use.

METHODS

Data Sources

This study used hospital pharmacy databases and electronic health records to collect information on adult (aged at least 18 years) inpatients given echinocandins at academic and community hospitals from 2008 to 2012. Systemic echinocandin antifungals included caspofungin, micafungin and anidulafungin. Rates and usage patterns of echinocandin use were assessed among several U.S. hospitals. Rates were calculated by aggregating patient level data for echinocandin antifungals from community and academic teaching hospitals and reported as days of therapy (DOT) per 1,000 patient days.⁸ To assess echinocandin usage from academic teaching centers (defined as a health care system with an accredited medical residency program), data were obtained from 4 healthcare systems with medical residency programs over a 12-month time period (CHI St. Luke's Health, Houston, TX and 3 additional health systems reporting information to MedMined [Carefusion, San Diego, CA]). To assess usage in community hospitals (defined as no accredited medical residency program or affiliation), usage data from 27 to 34 community hospitals per year in the United States was obtained from health systems reporting information to Cardinal Health Pharmacy Solutions, Houston, TX. Usage data represent dispensing data obtained from each hospital's pharmacy database. The study was approved by the Institutional Review Board of the University of Houston.

Participating Hospitals

The academic teaching health care centers included a 3-hospital health care system located in Houston, Texas. At the time of this study, this health care system comprised 1 major academic teaching institution and 2 community hospitals (each less than 200 beds and offering general medical and surgical services) located in the suburbs of Houston. The main academic center in the CHI St. Luke's Health System is Baylor St. Luke's

Medical center, a 650-bed tertiary care hospital with large solid organ transplantation and cardiovascular surgery programs. Additionally, Baylor St. Luke's Medical Center has an active antimicrobial stewardship program, including prospective audit and feedback of all patients with a positive sterile site culture for a pathogenic microorganism (including *Candida* species).^{9,10} During the time period of this study, echinocandin usage was not restricted to any specific service or indication at Baylor St. Luke's Medical Center. The 3 additional academic teaching hospitals were greater than 500 beds, 2 of 3 hospitals had either a burn center or cystic fibrosis clinics, and all 3 had solid organ transplant programs. The community hospitals were each general medical/surgical hospitals of less than 200 beds located throughout the United States. Additional information on these hospitals, such as echinocandin formulary restrictions or specific patient treatment details, was not available.

Echinocandin Use Assessment

To assess indications for echinocandin use, the medical charts of patients admitted to an academic 3-hospital health care system (CHI St. Luke's Health, Houston, TX) who were given an echinocandin from 2007 to 2012 were reviewed. Approximately 40 patients per year were randomly selected from the total number of patients given an echinocandin each year by using a random number generator and sort function in MS Excel (Microsoft Corp., Redmond, WA). At this hospital, caspofungin and micafungin were the preferred formulary echinocandin at 2 different time points. Caspofungin was the formulary echinocandin from 2006 to 2009, and micafungin was the formulary agent from 2010 to 2012. Anidulafungin was available as a nonformulary item. Data collected included patient location at the time of antifungal, indication for use, source of infection and culture results and patient comorbidities including the Charlson comorbidity index, an aggregate comorbidity measure.¹¹

Indications for Echinocandin Use

Indications for antifungal use were adapted from the Practice Guidelines for the Treatment of Invasive Candidiasis published by the Infectious Diseases Society of America as previously described.^{7,12} Briefly, prophylactic use was defined as use of an echinocandin in a high-risk patient with no evidence of fungal infection and no signs of infection in addition to medical record documentation of the use of an echinocandins as prophylaxis. Empiric therapy was defined as use of an echinocandin in a high-risk patient with signs of infection (based on documentation in the medical record of suspected infection) but without mycologic evidence of fungal infection in a normally sterile site. Candidiasis was defined as evidence of infection along with *Candida* species isolated from the blood or from another normally sterile body site (eg, surgical or percutaneous drainage from an intra-abdominal site or deep surgical wound exploration). Candidemia was defined as evidence of infection along with *Candida* species isolated from the blood. Antifungal susceptibility from *Candida* bloodstream isolates was performed by the clinical microbiology laboratory using semiautomated broth microdilution Sensititre (Thermo Fisher Scientific, Waltham, MA) per CLSI guidelines as previously described.¹³⁻¹⁵ For the purpose of this analysis, patients given an antifungal empirically or pre-emptively with subsequent growth of *Candida* from the blood or other normally sterile site taken at the time of initiation of echinocandin were categorized as having candidiasis.

Statistical Analyses

Summary statistics were calculated for patient's demographics, hospitalization variables and comorbidities. Data on

length of therapy were assessed using histograms. Changes in DOT over time were assessed using linear regression. The χ^2 and Student's *t*-test were used for comparisons as appropriate. Analyses were performed using SAS version 9.1 (SAS institute, Cary, NC) or STATA version 13.1 (StataCorp LP, College Station, TX). A $P < 0.05$ was considered significant.

RESULTS

Echinocandin Usage Rates

Echinocandin use in academic and community hospitals over time is shown in Figure 1. A significant increase in echinocandin use was observed in academic and community hospitals ($P < 0.001$) during the time period. At academic health centers, monthly usage averaged 26.71 ± 5.50 (Min: 16.06/Max: 48.60) DOT per 1,000 PD per month. At community hospitals, monthly usage averaged 6.96 ± 2.01 (Min: 3.12/Max: 12.70) DOT per 1,000 PD per month.

Echinocandin Indication Analysis—Overall Usage Patterns

Baylor St. Luke's Medical Center was chosen as the site for the more detailed analysis on echinocandin use. At this hospital, 223,046 antifungal DOT were assessed over the study period, of which 33,907 patient days were for echinocandin antifungals. Three thousand seventy-seven patients aged 59 ± 16 years (54% male) received echinocandins during the study time period. Fifty-seven percent of doses were given to patients in an intensive care unit. Eighty-two percent of patients received an echinocandin from an infectious disease consultant. The vast majority of patients received an appropriate dose of micafungin 100 mg (98.2% of all patients receiving micafungin) or caspofungin 70 mg loading dose followed by 50 mg daily dose (92.9% of all patients receiving caspofungin), which were the hospital formulary echinocandins. The average length of echinocandin therapy was 11.9 ± 14.5 days.

Patient Population

Patient medical charts were reviewed for 242 patients given echinocandins aged 59.4 ± 15.6 years (45.4% female).

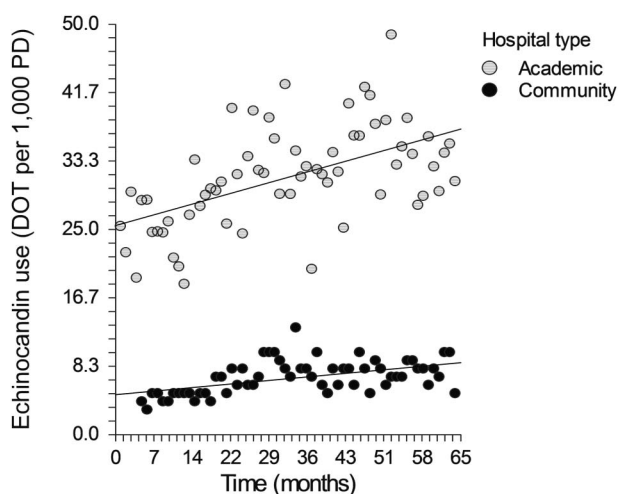


FIGURE 1. Academic medical center health system and community hospital usage of echinocandin antifungals from 2006 to 2012. A significant increase in the use of echinocandins was observed ($P < 0.01$). Echinocandin antifungals included caspofungin, micafungin and anidulafungin. DOT, days of therapy; PD, patient days.

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