Journal of Infection (2008) **56**, 126–129

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Increasing incidence of *Candida parapsilosis* candidemia with caspofungin usage

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Accepted 30 October 2007
Available online 21 December 2007

KEYWORDS
Candidemia;
Caspofungin;
Candida parapsilosis;
Candida tropicalis

Summary *Objectives:* To determine the impact on the change in epidemiology of *Candida* species at our institution since the introduction of caspofungin.
Methods: A 5-year retrospective review of all candidemia at a major tertiary care center. Only one episode of candidemia per patient per admission was counted. All antifungal defined daily doses were also collected in this same time period. Regression analysis was performed on the data and correlation statistics among antifungal use and *Candida* species were assessed using a Pearson correlation analysis.
Results: There were 469 individual episodes of candidemia between fiscal year 2002 and 2006 with the rate increasing every year. On regression analysis there was a significant increase in *Candida parapsilosis* candidemia ($R^2 = 0.90$, $p = 0.02$) and significant increase in caspofungin usage ($R^2 = 0.80$, $p < 0.01$), with a correspondingly significant decline in conventional ($R^2 = -0.77$, $p < 0.01$) and lipid amphotericin B ($R^2 = -0.95$, $p < 0.05$) usage. We found correlations between increased caspofungin usage ($R^2 = 0.94$, $p = 0.017$) and increased *C. parapsilosis* candidemia and decreased *Candida tropicalis* candidemia ($R^2 = 0.92$, $p < 0.05$) and a trend towards decreased *Candida glabrata* ($R^2 = 0.64$, $p = 0.1$).
Conclusions: We showed significant correlations between increased caspofungin usage and an increased incidence of *C. parapsilosis* candidemia and reduction in *C. tropicalis* candidemia, with a trend towards less *C. glabrata* candidemia.

Introduction

Since the echinocandins were introduced into the management of invasive candidiasis, they have provided a highly effective, less toxic therapy compared to amphotericin B and also an effective alternative therapy to azole-resistant

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0163-4453/$30
doi:10.1016/j.jinf.2007.10.014

Candida species.[1–4] Importantly, documented emergence of echinocandin resistant *Candida* organisms have been rare and often limited to the failure to remove infected hardware or collections.[5,6] However breakthrough *Candida* infections while on echinocandin therapy have been reported.[7,8] We report on the impact of the echinocandins since their introduction for the treatment of candidemia on the epidemiology of the *Candida* species isolated from blood stream infections over the last 5 years.

Methods

This was a 5-year retrospective review of all Candidemia events that occurred at the University of Maryland Medical Center between Fiscal Year 2002 (FY02) and FY06 (July 1, 2001 to June 30, 2006). This review was approved by the University of Maryland Institutional Review Board.

Setting and patients

The University of Maryland is a 600 bed inner-city tertiary care teaching hospital. Cultures obtained from the Shock Trauma center and the Pediatric units were excluded from this review because the patients are not evaluated by the hospital's Antimicrobial Team, which consist of an infectious disease physician and clinical pharmacist. Only one episode of candidemia per patient per admission was counted. Recurrent candidemias with either the same or different *Candida* species in the same patient were excluded from analysis to eliminate duplication of data where repeated isolation of the same uncommon organism from the same patient could cause an unexpected incidence shift. Also, *Candida* species with an incidence of less than 1% a year over the 5-year review were excluded.

Antifungal data

The total antifungal usage was obtained from the UMMC pharmacy database and was converted to defined daily doses (DDD) per World health Organization guidelines.[9] The time period selected for evaluation was based on the fact that caspofungin was not approved for the treatment of invasive candidiasis by the Food and Drug Administration (FDA) until early 2003, although it had prior availability as a salvage therapy for invasive aspergillosis. We expected off-label use in this preceding period at low levels with a rapid increase after the indication. Other factors in selecting this range were a national shortage of caspofungin during FY01 that limited its use and also our pharmacy changed to a new interface at the end of FY01, making collecting prior year antifungal data inaccurate. The lipid amphotericin B products were combined for analysis.

Fluconazole susceptibility testing was performed using 25-μg fluconazole disk diffusion (Pfizer, New York, NY) on Mueller Hinton agar supplemented with glucose and methylene blue and interpreted according to CLSI M27-A guidelines only during FY05 and FY06.[10] Fluconazole resistance was interpreted when there was a minimum inhibitory concentration (MIC) >64 μg/ml.

Statistical analysis

To assess the effects of the relationship between caspofungin usage and candidemias we compared the annual rates of candidemia per 1000 patient-days with the DDD/1000 patient-days of drug in the at risk population. Data analysis was performed using SPSS version 15 (SPSS, Chicago, IL). To compare variables between groups a one-way ANOVA was performed. Correlations among antifungal use and *Candida* species were assessed by Pearson correlation analysis. Dependent variables were assessed using a linear regression model. The level of statistical significance was set at <0.05.

Results

There were 469 individual episodes of candidemia identified in the review period. The rate of candidemia per 1000 patient-days, with a breakdown by fiscal year and individual *Candida* sp. is in Table 1. Between FY02 and FY06, there was an increase in the incidence of candidemia within the institution from a rate of 0.69 episodes/1000 patient-days to 0.95 episodes/1000 patient-days ($R^2 = 0.88$, $p = 0.06$) Using regression analysis, from FY02 to FY06 there was a significant increase in the incidence of *C. parapsilosis* candidemia ($R^2 = 0.90$, $p = 0.02$) while the increase in *C. albicans* ($R^2 = 0.6$) was not significant. Also, there was a significant decline seen in *C. tropicalis* ($R^2 = -0.90$, $p < 0.05$) and a trending decline with *C. glabrata* candidemia ($R^2 = -0.30$, $p = 0.10$), respectively, in this period. The incidence of *Candida krusei* candidemia remained unchanged. Fluconazole resistance among *Candida* sp. remained unchanged in the only 2 fiscal years that were tested, with 4 out of 79 (5%) isolates (2 *C. glabrata* and 2 *C. albicans*) with fluconazole resistance in FY05 and 8 out of 121 (6%) isolates (5 *C. glabrata* and 3 *C. krusei*) in FY06 ($p = 1$).

There were changes in antifungal usage during the review period (Table 2). On regression analysis, there was no change in fluconazole (both intravenous and oral) usage ($R^2 = 0.005$, $p = 1$). There was a significant increase in the usage of caspofungin ($R^2 = 0.8$, $p < 0.01$) while there was a trend towards increased voriconazole (IV and PO) usage ($R^2 = 0.63$, $p = 0.2$). There was a correspondingly significant decline in conventional ($R^2 = -0.77$, $p < 0.01$) and lipid amphotericin B ($R^2 = -0.95$, $p < 0.05$) usage. Micafungin was only introduced during FY06 and itraconazole which was rarely used after FY02 had too little data to evaluate.

Table 1 Rates per 1000 patient-days of the 5 major *Candida* species causing candidemia by fiscal year (FY)

Species	FY02	FY03	FY04	FY05	FY06
C. albicans	0.28	0.40	0.31	0.39	0.48
C. glabrata	0.23	0.17	0.21	0.19	0.20
C. parapsilosis	0.05	0.06	0.12	0.17	0.19
C. tropicalis	0.09	0.09	0.06	0.05	0.04
C. krusei	0.02	0.01	0.01	0	0.02
Overall	0.69	0.73	0.71	0.80	0.95

Table 2 Defined daily doses per 1000 patient-days of antifungals by fiscal year

Antifungal	FY02	FY03	FY04	FY05	FY06
Caspofungin	3.91	4	6.96	11	6.61
Micafungin	0	0	0	0	2.39
Fluconazole	84.2	86.2	104.4	84.4	85.7
Voriconazole	0	47.6	80.1	61.3	72.5
Amphotericin B	23.8	13.9	3.2	3.5	3.8
Amphotericin B lipid formulation	31.6	27	18	16.6	10.9

While both caspofungin and voriconazole had the largest percent increase use within the hospital, voriconazole was restricted to use in the cancer center, while caspofungin and micafungin were rarely used in the cancer center during this period.

Correlations

We assessed correlations between antifungal usage and the emergence of *C. parapsilosis* and reduction of *C. tropicalis* candidemia within our institution. We found a strong correlation between caspofungin usage ($R^2 = 0.94$, $p = 0.014$) and the increased *C. parapsilosis* candidemia observed. Also, when micafungin was incorporated into the analysis, this correlation remained intact ($R^2 = 0.91$, $p = 0.017$) (Fig. 1). There was also a significant reduction in *C. tropicalis* candidemia with increased caspofungin usage ($R^2 = 0.92$, $p = 0.05$) while there was a trend towards reduced *C. glabrata* candidemia ($R^2 = 0.64$, $p = 0.1$). There were no correlations between the other antifungals and *C. parapsilosis* candidemia or any other species. Of interest, both caspofungin or micafungin use was less than 2% of their combined DDD in the cancer center in the time period analyzed, and there were only 2 cases of *C. parapsilosis* candidemia, both had received an echinocandin during their stay prior to their candidemia.

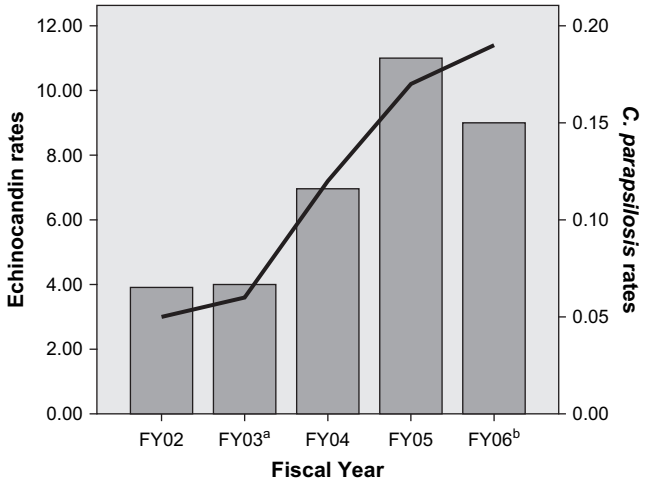

Figure 1 Graph showing increased rates of echinocandin (DDD/1000 patient-days) usage with associated increase rates of *C. parapsilosis* candidemia/1000 patient-days. Shaded bars = Caspofungin DDD/1000 patient-days. Black line = *Candida parapsilosis*/1000 patient-days. [a]Caspofungin received FDA approval for the treatment of invasive candidiasis during FY03. [b]includes micafungin DDD/1000 patient-days.

Discussion

There have been many reports published on the selection pressures of fluconazole and non-*albicans* species, in particular *C. glabrata*.[11–13] This is the first published report suggesting a statistical correlation between the increased use of caspofungin and increased incidence of *C. parapsilosis* candidemia. Also, we have shown a correlation between the increased usage of echinocandins and a significant reduction in *C. tropicalis* candidemia. There appears to be a couple of associated secondary effects with the increased echinocandin usage including decreased usage of all formulations of all amphotericin B and a trend towards decreased *C. glabrata* candidemia, which both could be interpreted as positive effects.

C. parapsilosis is frequently associated with outbreaks especially in neonatal centers, burns units and intensive care settings.[14–16] It has been shown to be spread by hands in these settings, and this was a concern from our analysis, and a reason to investigate why we were identifying an almost 400% increase in cases. Within the same time period of this study, we had implemented rigorous infection control measures within the institution and a measure of this is that nosocomial methicillin resistant *Staphylococcus aureus* (MRSA) blood stream infection (BSI) rates had decreased 32% from 0.4 cases per 1000 patient-days in FY04 to 0.27 cases per 1000 patient-days in FY06, while vancomycin resistant enterococcal (VRE) BSI rates decreased by 15%. Although not absolute, if the increase of *C. parapsilosis* candidemia was due to nosocomial transmission, we should expect MRSA and VRE BSI rates to have also increased. Secondly, *C. parapsilosis* prevalence in hospitals has been associated with regional variations.[17,18] Sofair et al. recently reported that *C. parapsilosis* was associated with community onset disease in Maryland, however, this data was collected before caspofungin was widely used and our rates for *C. parapsilosis* were less than 10% during the same period as their review.[19] We can only hypothesize why we have seen this increase despite the rates of fluconazole use being unchanged, however, the close MIC to therapeutic effect of the echinocandins towards *C. parapsilosis* has been implicated in the presumed selection pressure for this organism.[4,20,21] However, the effect of decreasing *C. tropicalis* candidemia with the increased use of echinocandins is intriguing and may be due to their increased potency against this organism. Although caspofungin was predominantly used in this time period, the switch to micafungin during FY06 did not change the incidence of *C. parapsilosis*, but it is too early to tell. We do not expect changing echinocandins will affect the trend of increasing incidence of *C. parapsilosis* candidemias as it may be a species-specific phenomenon with this class of antifungals.

There are several limitations to these data that include the retrospective statistical analysis of hospital data, the lack of information regarding the clinical factors and outcomes, and separating nosocomial versus imported

candidemia from the community setting to definitively determine cause and effect. Despite these limitations, we have evaluated a large time period from prior to the widespread use of caspofungin and other echinocandins and we have shown that there has been a statistically significant correlation with their use and the increase in *C. parapsilosis* candidemias that should warrant further investigation, although the benefits of less amphotericin B usage and reductions in *C. tropicalis* and *C. glabrata* infections may also appear to be advantageous.

Acknowledgement

Results from this study were presented in part at the 15th Focus on Fungal Meeting [Abstract 62], San Diego, CA, March 8, 2007.

Financial support: none.

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