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Candida bloodstream infections in hemodialysis recipients

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Abstract

Candidemia is a major cause of morbidity and mortality in patients undergoing hemodialysis but it has not been well defined in this patient population. We performed a retrospective case-control study to characterize the epidemiology, microbiology, and outcomes of hemodialysis-associated candidemia. All cases of candidemia at our institution were evaluated from 1 January 2000 until 1 September 2004. For each case, two non-candidemic dialysis patients served as controls. Among 350 cases of candidemia, 78 (22%) occurred in adult hemodialysis patients. Cases and controls were similar with respect to age, corticosteroid, antibiotics use, prevalence of diabetes mellitus, liver cirrhosis, surgical procedures, and cancer. Multivariate analysis found total parenteral nutrition (TPN) (19.5% vs. 1.3%; $P < 0.0001$) and dialysis through a vascular catheter (74% vs. 46.8%; $P = 0.0001$) to be independently associated with candidemia. Non-*C. albicans* *Candida* spp. particularly *C. glabrata* and *C. krusei* were more common in hemodialysis recipients than in candidemic patients not receiving hemodialysis (31% vs. 17% $p = 0.009$). In-hospital mortality was significantly elevated for candidemic vs. non-candidemic hemodialysis recipients (51.9% vs. 7.8%; $P < 0.0001$). Candidemia in hemodialysis recipients is frequently caused by non-*C. albicans* *Candida* species, is associated with TPN and dialysis via a vascular catheter (vs. shunt or fistula) and carries a high mortality rate.

Keywords

Candidemia; hemodialysis; infection; epidemiology

Introduction

In the hemodialysis population, infections are second only to cardiovascular disease as the leading cause of morbidity and mortality [1]. Although staphylococcal septicemia is the

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most common cause of bloodstream infections in this population, candidemia is an important complication of renal failure and of hemodialysis [2–4]. Among critically ill patients, renal failure was associated with a relative risk of 4.2 for developing candidemia. The fourth most common cause of bloodstream infections in all hospitalized patients in the US are *Candida* species [5]. In one study, approximately one-third of candidemia cases were estimated to be of community onset [6]. In this group of patients, 55% had a central venous catheter present at the time of candidemia. More than 15% of all patients receiving central venous catheters suffer adverse events linked to the catheters, these most frequently being infections [7].

Although renal failure is a recognized risk factor for candidemia, little is known about the risk factors for candidemia in these patients receiving hemodialysis. We therefore studied the epidemiology, microbiology and outcomes of hemodialysis-associated candidemia by retrospectively analyzing a cohort of adult patients with and without infection.

Materials and methods

Patients and study setting

This was a retrospective case control study conducted at the Washington Hospital Center (WHC), a 907-bed tertiary care center in Washington, DC. Patients were identified by review of infection control databases. All culture proven cases of candidemia occurring from 1 January 2000 to 1 September 2004 were evaluated. The institutional review board of the WHC approved this study and requirement for informed consent was waived.

Microbiology

Fungal isolates from blood cultures were identified to the species level by use of the germ tube test and either the VITEK 2 ID-YST (bioMérieux, Durham, NC, USA) or API 20C AUX (bioMérieux) tests.

Case definitions and data extraction

The three populations observed from 2000–2004 and defined in this study were: (i) all patients with candidemia, (ii) all patients on hemodialysis without candidemia, and (iii) all patients on hemodialysis who developed candidemia. Cases were defined as adult patients with hemodialysis who had developed candidemia. Patients were included only once during their hospitalization if they developed candidemia and any subsequent positive cultures with the same species were considered as part of the same candidemia episode. For each case, two non-candidemic adult hemodialysis patients who were admitted to the hospital during a contemporaneous three month interval were chosen as controls. Medical records were abstracted for timing of candidemia, demographics, underlying illnesses, neutropenia (defined as an absolute neutrophil count of less than 500 cells/ μ l), surgery (defined as any procedure performed in an operating room), and use of TPN and immune suppressive medications and antibiotics. When possible, the mode of hemodialysis (fistula, graft, implanted vascular catheter) was ascertained. Infections acquired within 48 hours of hospital admission were considered community acquired. All others were classified as nosocomially acquired. Crude mortality was assessed at the end of hospitalization.

Statistical analysis

Univariate analysis using Epi Info (CDC; Atlanta, GA) version 6.04b was performed to determine odds ratios and chi-square values for categorical variables. The two-tailed significance level was set at $P=0.05$. SPSS (Chicago, IL) version 10.1 was used to perform multiple logistic regression with forward stepwise entering of all variables found to be significant by univariate analysis ($P<0.3$).

Results

Patient population

During the study period, 350 cases of candidemia were identified, of which 78 (22%) occurred in 77 adult hemodialysis patients. Of these individuals 18 (23%) had acute renal failure. All candidemic hemodialysis recipients (cases) and 154 contemporaneous non-candidemic hemodialysis patients (controls) were included in the study. Clinical characteristics are summarized in Table 1. Twenty-one infections (27%) within the hemodialysis population were community-acquired candidemia while 57 (73%) were hospital acquired.

Risk factors for candidemia

Several variables were strongly associated with candidemia in hemodialysis recipients (Table 1). Cases and controls were similar with respect to age, gender, receipt of corticosteroids, prevalence of diabetes mellitus, hepatic cirrhosis, surgical procedures or cancer. Those variables reaching statistical significance included dialysis through a catheter, TPN, antibiotic use and neutropenia. Following multivariate analysis, two variables remained statistically significant: TPN use and dialysis through a catheter (Table 1). Antibiotic use, which was significant in univariate analysis, appeared not to be an independent risk factor for candidemia in hemodialysis patients following multivariate analysis.

Outcomes

In-hospital mortality of cases was 40/77 (51.9%) compared with 113/283 (40%) for candidemic non-hemodialysis patients ($P=0.058$). Mortality was also significantly elevated for patients with candidemia receiving hemodialysis compared with non-candidemic hemodialysis recipients (12/154; 7.8%) ($P<0.0001$). Among patients with hemodialysis-associated candidemia, nosocomially acquired infections carried a higher mortality when compared to community acquired infections (61 vs. 24%; $P=0.0026$).

Microbiology

The distribution of *Candida species* causing bloodstream infection among patients with and without hemodialysis is shown in Table 2. Bloodstream infections due to *C. albicans* were more common in non-hemodialysis patients (23% vs. 53%; $P<0.0001$). Infections caused by *C. glabrata* and *C. krusei* were more commonly associated with hemodialysis vs. non-hemodialysis, respectively (31% vs. 17%; $P=0.015$). The rate of *C. parapsilosis* was higher

among hemodialysis recipients vs. non-hemodialysis (23% vs. 15%) but this difference did not achieve statistical significance.

Discussion and conclusion

To our knowledge, this is the first study of the epidemiology of candidemia in the population of patients with hemodialysis. Hemodialysis predisposes patients to candidemia by disrupting anatomic barriers. In our cohort of 231 hemodialysis recipients, we found that use of a catheter for dialysis (Table 1) (vs. native graft or fistula) was an independent risk factor for candidemia (Odds Ratio [OR] 3.24). Dialysis via a catheter is used mainly, but not exclusively as a temporary measure. Catheters may be utilized for extended periods of time until an alternative access has matured or for ongoing hemodialysis access. In this study, 74% of hemodialysis associated candidemia and 47% of non-candidemic hemodialysis patients were dialyzed via catheters. Dialysis via a catheter is more frequent in the inpatient population and may be a marker for more severe underlying illness, but it is also a risk for infection, as intravascular devices are independently associated with candidemia irrespective of renal function [3,10–12]. The amount of dialysis delivered may be inadequate when catheters are used [13]. Suboptimal dialysis with resultant ongoing uremia may thus contribute to phagocyte dysfunction and possibly elevate rates of candidemia [14].

Use of TPN is a major risk factor for candidemia [2,15–17]. TPN requires vascular access catheters that may become contaminated during frequent manipulation. Contaminating fungi can persist and grow within TPN solutions, especially in lipid-containing formulations [18–20]. In our study, the rate of candidemia among hemodialysis recipients was significantly elevated as an independent risk factor (OR 18.39) when TPN was used. Patients with multiple risk factors for candidemia such as TPN and renal failure may be particularly vulnerable to infection. In surgical ICU patients, any combination of diabetes mellitus, new onset hemodialysis, use of TPN, or receipt of broad-spectrum antibiotics was associated with an invasive candidiasis rate of 16.6% [21].

Neutropenia is an established risk factor for invasive *Candida* infections [3]. In our study, neutropenia was associated with four cases of candidemia in the hemodialysis population and none of the non-candidemic hemodialysis recipients.

In most series, *C. albicans* remains the most frequently isolated species but non-*C. albicans* *Candida* species are increasing in frequency [22]. The prevalence of infection and relative distribution of the different species is influenced by host and environmental factors including geographic locale, exposure to antimicrobial agents and underlying illness [23–26].

Previously described risk factors for non-*C. albicans* candidemia include exposure to antifungal agents, neutropenia, and extremes in age [24,27–31].

Candida albicans was the most common cause of candidemia (53%) in patients not on hemodialysis, but *C. glabrata* (26%) was the most common pathogen among the hemodialysis recipients. These differences in this hemodialysis population may be related to gaps in infection control measures, frequent exposure to the health system (e.g., thrice weekly hemodialysis), high prevalence of vascular catheters and subsequent colonization

with non-*C. albicans Candida* species. Over the last several years, there has been a shift in the epidemiology of candidemia toward the non-*C. albicans Candida* species that is confirmed in this study [22]. Our study suggests that hemodialysis also predisposes to infection with non-*C. albicans Candida* species. Knowledge of the prevalence of different *Candida* species in this population may have implications upon antifungal selection for prevention and early treatment of candidemia since *C. krusei* and *C. glabrata* are more frequently resistant to fluconazole.

Candidemia has been associated with crude mortality rates of 30–60% [32–34]. In our study, in-hospital crude mortality rates for adult hemodialysis recipients with and without candidemia were 51.9% and 7.8%, respectively (OR 12.79). Within the hemodialysis group, nosocomially acquired candidemia was associated with significantly higher mortality when compared with community acquired infections. Candidemia is associated with attributable mortality rates of 14–49% [32,33]. As a group, candidemic hemodialysis recipients in our study were likely to be more severely ill at baseline than their non-candidemic counterparts as suggested by higher rates of TPN, dialysis via catheters, and neutropenia. The high mortality rate in our candidemic hemodialysis patients likely reflects the impact of *Candida* sepsis upon a severely ill and vulnerable population.

Patients with renal failure are particularly prone to developing bloodstream infections and hemodialysis is a known risk factor for candidemia. In a multivariate analysis, patients with history of hemodialysis had an odds ratio of 18.3 for development of nosocomial candidemia [2]. Uremia per se may contribute to development of candidemia. Renal failure is associated with phagocyte dysfunction [35–38]. Mononuclear cells from uremic patients have decreased responsiveness to *Candida* antigens and uremic plasma inhibits phagocytosis of *C. albicans* by previously healthy monocytes [37–39]. Hemodialysis predisposes patients to candidemia by disrupting anatomic barriers during angioaccess and perhaps by inducing immune dysfunction via monocyte apoptosis with resultant inhibition of *Candida* growth [40]. Thus, the high rate of candidemia in this population reflects a combination of factors including co-morbid conditions such as diabetes mellitus, broad exposure to antibacterial agents, underlying renal dysfunction, and the dialysis process.

In summary, hemodialysis represents a significant risk factor for the development of candidemia with dialysis via a catheter and use of TPN identified as major independent risk factors. In-hospital mortality rates are high, and infections are likely to be due to non-*C. albicans Candida* species, which may require alterations in the choice of empirical antifungal agents.

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Table 1

Factors associated with candidemia in hemodialysis patients.

Variable	Cases n = 77 (%)	Controls n = 154 (%)	P-value	Odds Ratio
Implantable vascular catheter*	57 (74)	72 (46.8)	<0.0001	3.24 (1.78–5.91)
TPN	15 (19.5)	2 (1.3)	<0.0001	18.38 (4.08–82.79)
Neutropenia	4 (5.2)	0	0.01 [‡]	
Surgery	38 (49.4)	73 (47.4)	0.88	1.08 (0.62–1.87)
Corticosteroids	10 (13)	17 (11)	0.82	1.20 (0.52–2.77)
Diabetes mellitus	45 (58.4)	99 (64.3)	0.74	0.78 (0.43–1.42)
Cirrhosis	3 (3.9)	6 (3.9)	1.01	1.01 (0.19–4.67)
Cancer	8 (10.4)	8 (5.2)	0.11	2.12 (0.76–5.87)
Antibiotic use	64 (83.1)	106 (68.8)	0.03	2.23 (1.12–4.43)
Mortality	40 (51.9)	12 (7.8)	<0.0001	12.79 (5.78–28.8)
Multivariate analysis				
Implantable catheter	57 (74)	72 (46.8)	0.0001	3.25 (1.71–6.19)
TPN	15 (19.5)	2 (1.3)	<0.0001	18.39 (3.85–120.13)
Antibiotic use	64 (83.1)	106 (68.8)	0.13	0.67 (0.39–1.17)

* Includes tunneled and non-tunneled catheters

[‡] odds ratio was not determined as no patients in the control group had neutropenia.

Table 2

Distribution of infecting species in candidemic patients with and without hemodialysis.

Organism	HD n = 78 (%)	Non HD n = 272 (%)	P-value
<i>C. albicans</i>	18 (23)	144 (53)	<0.0001
<i>C. glabrata</i>	20 (26)	44 (16)	0.057
<i>C. parapsilosis</i>	18 (23)	41 (15)	0.399
<i>C. tropicalis</i>	18 (23)	33 (12)	0.107
<i>C. krusei</i>	4 (5)	4 (1)	0.06
Other (<i>C. guilliermondii</i> and unidentified species)	0 (0)	6 (2)	0.345

HD = hemodialysis.