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Factors Associated with the Development of Candidemia and Candidemia-Related Death Among Liver Transplant Recipients

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Objective

The authors' objective was to identify factors associated with candidemia and candidemia-related death among adult liver transplant recipients.

Summary Background Data

Invasive candidiasis is the most common severe fungal infection occurring after liver transplantation and is associated with high morbidity and mortality rates. Although candidemia is not always found during invasive candidiasis, it has been considered as an indicator of invasive candidiasis in immunocompromised patients.

Methods

A time-matched case–control study of 26 patients with candidemia, which was defined as the isolation of *Candida* from at least one blood culture, and 52 control patients without candidemia was reported. Two control patients were matched with each case patient regarding time of transplantation and duration of follow-up.

Results

Between December 1985 and December 1992, candidemia developed in 1.4% of adult liver transplant recipients a median of 25 days after transplantation (range, 2–1690 days). The overall mortality rate among patients with candidemia was 81%, and 71% of these deaths were related to candidemia. Conditional logistic regression analysis was used to identify factors associated with candidemia, which were 1) hyperglycemia treated with insulin up to 2 weeks before candidemia (odds ratio [OR], 16.15; $p = 0.002$), and 2) exposure to more than three different intravenous antibiotics before development of candidemia (OR, 11.15; $p = 0.005$). The variables predictive of death related to candidemia were abdominal surgery performed up to 1 week before candidemia (relative risk [RR], 7.25; $p = 0.02$), high white blood cell count (RR, 1.10; $p = 0.01$), lower platelet count (RR, 0.99; $p = 0.02$), and elevated AST with candidemia (RR, 1.001; $p = 0.01$).

Conclusions

Hyperglycemia that requires insulin and exposure to more than three antibiotics are the factors associated with the development of candidemia in liver transplant recipients. When candidemia develops shortly after abdominal surgery and in patients with elevated AST, high white blood cell count, or low platelet count, it is associated with a high mortality rate.

Invasive candidiasis is the most common severe fungal infection to occur after liver transplantation.[1] It is known to occur in patients who have difficult and prolonged surgery, who are immunosuppressed, and who have received intensive antibiotic therapy,[2-9] factors common to many liver transplant recipients. Development of invasive candidiasis after liver transplantation is associated with a high mortality rate (70%)[10,11] due to the difficulty in making an early diagnosis of the disease.

The *Candida* species is not always found in the bloodstream of patients with invasive candidiasis. However, candidemia has been considered a good indicator of disseminated *Candida* infection among immunocompromised patients.[12-14] In a recent study, fungemia due to *C. albicans* was associated with a poor prognosis compared with other *Candida* species.[15] The authors concluded that even a single blood culture positive for *Candida* species should raise the suspicion of invasive infection, particularly in immunocompromised hosts.[15]

The purpose of this retrospective matched case–control study was to identify factors associated with the development of candidemia and candidemia-related mortality among adult liver transplant recipients. Although several studies have identified risk factors for candidemia in different populations, none have involved its development after liver transplantation. The number of liver transplants is increasing each year, and the optimum cost-benefit of transplantation will depend largely on prevention of infectious complications, such as candidiasis.

MATERIAL AND METHODS

Patient Selection

From December 1985 to December 1992, a total of 197 adult patients developed candidemia at Presbyterian University Hospital in Pittsburgh. Of these, 36 (18.3%) were liver transplantation recipients. Complete medical records were available for 26 patients, who constituted the study group. During the same time period, a total of 2621 adult patients underwent liver transplantation at the same institution. To assemble a homogeneous control group with respect to duration of exposure to the risk factors, we selected for each candidemia patient two control patients who were at risk for candidemia at the time each patient's condition was diagnosed. Control patients were matched with case patients with respect to time of transplantation and duration of follow-up to the day of the first blood culture indicative of *Candida* species. A patient was not eligible to be a control patient if he or she did not survive at least as long as the matched case patient and if autopsy or another histologic specimen revealed invasive candidiasis.

Definitions

We defined candidemia as the isolation of *Candida* species from at least one blood culture. *Candida* endophthalmitis was diagnosed when on evaluation by an ophthalmologist, the patient was found to have characteristic lesions. Death related to candidemia was defined by autopsy findings showing invasive candidiasis or, if an autopsy was not performed, the patient's dying within 2 weeks of development of candidemia.

Microbiologic Studies

Surveillance cultures for fungi were not performed systematically. However, specimens were submitted for fungal culture when any infectious complication was clinically suspected.

Treatment and Immunosuppression

Orthotopic liver transplantation was performed according to the standard techniques described by Starzl et al.[16] Cefotaxime and ampicillin were administered intravenously as antibacterial prophylaxis for the first 3 days after transplantation. Nystatin (500,000 units four times/day) was given orally for *Candida* prophylaxis. In several cases involving difficult and prolonged surgery, low-dose amphotericin B (10–20 mg/day) administered intravenously was used for fungal prophylaxis, beginning at the time of surgery and continuing for 2 to 4 weeks. Primary prophylaxis for *Pneumocystis carinii* with trimethoprim-sulfamethoxazole was given routinely.

Two immunosuppressive regimens were used. The first included cyclosporine A (Sandoz Co., East Hanover, NJ) and corticosteroids. Cyclosporine was initially administered intravenously (3 mg/kg/day). Oral cyclosporine was initiated with the return of bowel function and was overlapped briefly with the intravenous dose. An intravenous intraoperative dose of 1 g methylprednisolone was followed by a 5-day tapering of the drug from 200 mg to 20 mg. The second regimen included tacrolimus (FK506; Fujisawa Pharmaceutical Co, Osaka, Japan) and corticosteroids. Tacrolimus was started intrave-

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nously (0.05–0.1 mg/kg/day) and was converted to an oral dose of 3 mg/kg/day with the return of bowel function. An intraoperative dose of 1 g methylprednisolone administered intravenously was followed by low-dose corticosteroids (20 mg/day) beginning immediately after transplantation. Subsequent adjustments of the immunosuppressive dose were guided by the quality of the graft, the presence of rejection, toxicity, and cyclosporine/tacrolimus plasma trough levels. Azathioprine was also administered to some case patients. Rejection episodes occurring with the use of either regimen were treated with increased doses of corticosteroids using either a 1-g "pulse" dose or a 5-day tapering of the methylprednisolone dose. Corticosteroid-resistant rejection was treated with intravenous OKT3 monoclonal antibody (Ortho Pharmaceuticals Co., Raritan, New Jersey).

Variables Analyzed

Exposures were ascertained up to the day of the first positive *Candida* blood culture among case patients (i.e., first day of candidemia) and at the corresponding follow-up interval among control patients. The variables compared between case patients and the matched control patients have been used in an earlier analysis of fungal infection after liver transplantation.[17] The variables analyzed can be classified into the following categories: 1) demographic: sex, age, liver disease (hepatocellular, cholestatic, others); 2) surgical: number of transplantations, total surgical time, abdominal surgery performed up to 1 week before candidemia, type of biliary anastomosis; 3) nosocomial: duration of stay in the intensive care unit; number of days of exposure to total parenteral nutrition (TPN); use of urinary catheter, endotracheal tube, hemodialysis, and central lines and number of central lines; 4) antimicrobials: number of days of exposure to intravenous antibiotics; exposure to fewer or more than 3 different antibiotics (median number of antibiotics received for case and control patients) for more than 1 day; duration of exposure to vancomycin or third-generation cephalosporins; and prophylaxis with trimethoprim-sulfamethoxazole, mycostatin, and amphotericin B; 5) immunosuppressive therapy: exposure to tacrolimus, cyclosporine, azathioprine and OKT3 and number of corticosteroid boluses; 6) amount of blood products given: red blood cells, fresh-frozen plasma, platelets; 7) laboratory values before transplantation and at development of candidemia, including white blood cell count, hematocrit, platelet count, albumin, creatinine, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and prothrombin time; 8) others: hyperglycemia requiring insulin therapy occurring after transplantation and up to 2 weeks before candidemia, and other infections that developed before candidemia.

Because cultures for fungi were not obtained systematically, *Candida* colonization was not included among the variables analyzed.

Statistical Analysis

Conditional linear logistic regression was used to identify risk factors for candidemia, and the odds ratio (OR) was computed as an estimate of the relative risk.[18] An odds ratio greater than 1 suggested increased risk, whereas an odds ratio less than 1 suggested a protective effect. The interpretation of the odds ratio depends on the scale of measurement of the exposure. For exposures defined on a continuous scale (*e.g.*, age), the odds ratio indicates the change in the odds of disease for an increase of 1 unit in the exposure. For exposures defined on a nominal scale (*e.g.*, sex), the odds ratio indicates the odds of disease in the exposed group relative to the unexposed group. The analysis was done in two stages. First, univariate analyses were performed to identify candidate risk factors for candidemia. These factors were entered into a multivariate analysis if the probability value was less than 0.25.[19] Second, a stepwise multivariate conditional logistic regression (forward inclusion method) was used to assess simultaneously the effect of each exposure and to identify those factors that are independently associated with candidemia. The score was used to assess the importance of each factor at each stepwise run. The statistical significance level required for inclusion was set at 0.05. The analyses were performed with use of the statistical software package EGRET.[20] Kahn's method was used to compute approximate 95% confidence intervals (CI) for unadjusted as well as adjusted odds ratios.[21]

Patient survival was calculated from the date of the first orthotopic liver transplantation until death, and cumulative survival rates were calculated with the Kaplan–Meier (product-limit) method. Univariate Cox's proportional hazards model was used to identify factors with potential prognostic significance and to calculate the relative risk (RR) of death. The outcome of interest was death associated with candidemia. Those deaths not associated with candidemia were censored at time of failure but were included with patients who survived for estimation of overall survival. On the basis of univariate analyses, a multivariate stepwise Cox's regression (forward-inclusion method) was performed to identify those factors independently associated with candidemia-related mortality.

RESULTS

Clinical Findings

Between December 1985 and December 1992, candidemia developed in 36 of the 2621 patients (1.4%) who

Table 1. CLINICAL PRESENTATION (26 CASES)

	No. (%)
Primary candidemia	4 (15)
Peritonitis	12 (46)
Wound infection	1 (4)
Kidney fungus ball	1 (4)
Line sepsis	5 (19)
Abdominal abscess	3 (12)

underwent liver transplantation at our institution. Complete medical records were available for the 26 case patients. The most common isolate found was *C. albicans* (19 patients [73%]). The other isolates included *C. glabrata* (3 patients), *C. tropicalis* (1), *C. stellatoidea* (1), *C. pseudotropicalis* (1), and *C. parapsilosis* (1). Candidemia was diagnosed at a median of 25 days after transplantation (range, 2–1690 days) and in 12 patients (46%) developed more than 1 month after transplantation. For 10 patients, *Candida* species were isolated from the blood for more than 1 day (38%). Only 2 of 24 case patients (8%) who were examined by an ophthalmologist developed *Candida* endophthalmitis. No significant difference was observed in number of deaths between case patients who developed candidemia secondary to *C. albicans* (84%) and those with other isolates (71%). Candidemia was treated in all cases with 0.5 to 0.7 mg/kg/day amphotericin B administered intravenously to a cumulative dose of 1 to 2 g.

Table 1 shows the clinical source of infection. Most candidemia episodes originated from intra-abdominal infections (58%), usually secondary to peritonitis, or from infected intravenous lines (19%). Four patients (15%) had primary candidemia without an identified secondary site of infection. *Candida* species identical to that found in the blood were isolated before development of candidemia in 20 patients (77%) at a median of two other colonizing sites (range, 1 to 8) and at a median of 9 days (range, 1 to 424 days) before fungemia.

Twenty-one case patients (81%) died at a median of 12 days (range, 3–615 days) after development of candidemia. Eleven of these patients had an autopsy performed (52%), and the results showed evidence of invasive candidiasis in nine cases (82%). Six patients who died up to 2 weeks after development of candidemia did not have an autopsy performed. Therefore, a total of 15 deaths (71%) were associated with candidemia. Figure 1 shows the time of diagnosis of candidemia and patient survival after transplantation. Nine cases of candidemia (35%) developed up to 2 weeks after liver transplantation and were associated with a 100% mortality rate. In three of five survivors (60%), the cause of candidemia was a line sepsis.

Factors Associated with the Development of Candidemia

Twenty-one variables were found to be eligible for a multivariate analysis by our criterion ($p < 0.25$), as follows: female sex, more than one liver transplantation, undergoing abdominal surgery up to 1 week before candidemia, duration of total surgical time, duration of stay in the intensive care unit, duration of exposure to a urinary catheter, duration of exposure to central venous lines, duration of exposure to a respirator, number of days receiving dialysis, duration of TPN therapy, exposure to more than three different antibiotics administered intravenously, number of days of intravenous antibiotic use, use of amphotericin B prophylaxis, use of tacrolimus, use of azathioprine, use of OKT3, higher creatinine levels before transplantation, higher bilirubin levels before transplantation, hyperglycemia developing up to 2 weeks before development of candidemia, hyperglycemia developing at or immediately after transplantation, and previous infections.

Five of the 52 control patients (10%) and 9 of the 26 case patients (35%) received prophylaxis with low-dose amphotericin B (10–20 mg/day). The use of amphotericin B prophylaxis was found to be associated with the development of candidemia. However, because the decision to use this prophylaxis was based on clinical suspicion, it was not included in the multivariate analysis. This was done to avoid a selection bias in the estimation of the odds ratio.

Table 2 shows the variables found to be simultaneously associated with candidemia in a multivariate analysis. These variables were hyperglycemia requiring insulin treatment occurring up to 2 weeks before development of candidemia (OR = 16.15; 95% CI = 2.77–94.07; $p = 0.002$) and use of more than three different antibiotics administered intravenously before development of candidemia (OR = 11.15; 95% CI = 2.04–61.02; $p = 0.005$).

Predictors of Candidemia-Related Death

We identified predictors of candidemia-related death by comparing cases of death related to candidemia ($n = 15$) with cases of death not related to candidemia ($n = 6$) and with survivors ($n = 5$). The variables significant in the univariate analysis were entered into a multivariate Cox's regression analysis. These variables were total hours of surgery; abdominal surgery performed up to 1 week before candidemia; and the number of days of exposure to central venous lines, urinary catheters, and

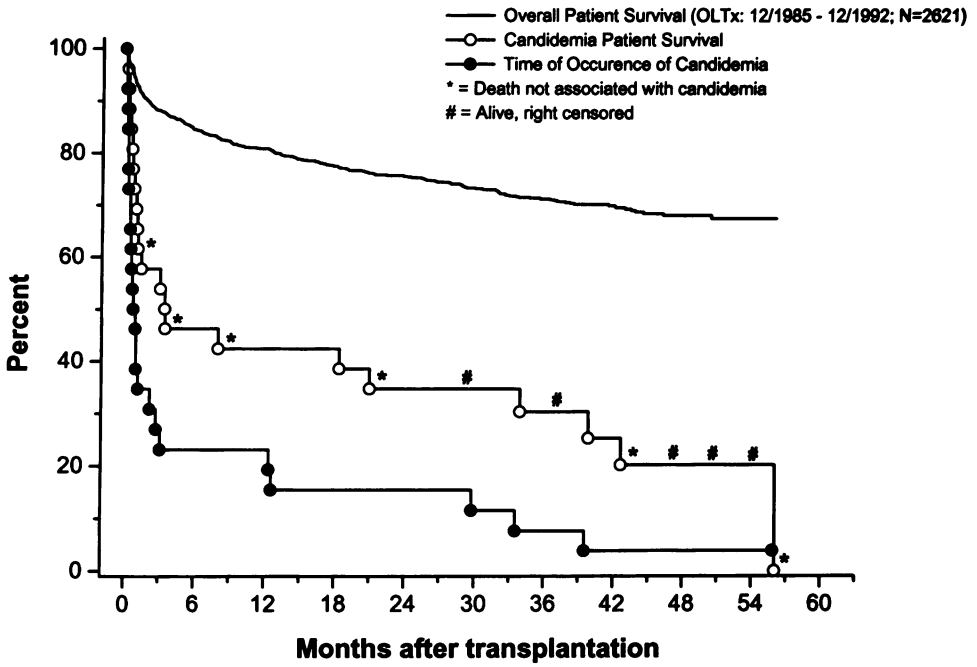

Figure 1. Time of occurrence of candidemia and actuarial patient survival (Kaplan–Meier) after liver transplantation in patients with candidemia and in the entire cohort.

antibiotics. With the development of candidemia, the variables were white blood cell count, hematocrit, platelet count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and prothrombin time. However, the only variables associated with death-related candidemia according to the multivariate analysis were abdominal surgery performed up to 1 week before candidemia (RR = 7.25; 95% CI = 1.36–38.64; p = 0.02), high white blood cell count at diagnosis of candidemia (RR = 1.1; 95% CI = 1.02–1.19; p = 0.01), lower platelet count at candidemia (RR = 0.988; 95% CI = 0.978–0.998; p = 0.02), and elevated aspartate aminotransferase at candidemia (RR = 1.001; 95% CI = 1.0008–1.0011; p = 0.01) (Table 2).

DISCUSSION

This study confirms previous reports suggesting that in immunocompromised patients even an isolated episode of candidemia should not be considered a benign transient condition. Two patients with isolated candidemia and with no evidence of previous colonization died within 14 days of developing candidemia. For one of these patients, the autopsy results showed disseminated

Table 2. FACTORS ASSOCIATED WITH CANDIDEMIA AND CANDIDEMIA RELATED MORTALITY

Variable	Odds Ratio	Relative Risk	95% Confidence Interval		p-Value
			Lower	Upper	
Candidemia					
Hyperglycemia within 2 weeks of candidemia	16.15	—	2.77	94.07	0.002
Exposure to more than three antibiotics	11.15	—	2.04	61.02	0.005
Candidemia Mortality					
Abdominal surgery within 1 week before candidemia	—	7.25	1.36	38.64	0.02
WBC at candidemia	—	1.1	1.02	1.19	0.01
Platelet count at candidemia	—	0.988	0.978	0.988	0.02
AST at candidemia	—	1.001	1.0008	1.0011	0.01

WBC = white blood cell count; AST = aspartate aminotransferase.

candidiasis. Intra-abdominal infection, particularly peritonitis, was the most common source of candidemia after orthotopic liver transplantation, thus suggesting that surgical complications play an important role in its origin. Additionally, our study showed the difficulty in making the diagnosis of invasive candidiasis. *Candida* endophthalmitis has been considered to be a marker of dissemination in nonimmunosuppressed patients.[22,23] However, only 8% of our patients with candidemia who had undergone an eye examination had endophthalmitis. These data correlate with experimental studies that have demonstrated a decreased incidence of ophthalmoscopicaly detectable endophthalmitis with immunosuppressive therapy.[24] In these conditions, the inflammatory response is minimal, as has been shown in patients with acquired immunodeficiency syndrome who may have disseminated mycoses with only mild or no clinical symptoms.[25]

Hyperglycemia that required insulin treatment was one of two factors found to be associated with development of candidemia after liver transplantation. Diabetes mellitus has been identified as an important underlying condition in *Candida* infections, from mucocutaneous infection to invasive disease.[6,26,27] Our study confirms earlier observations that hyperglycemia influences the development of candidemia.[11,28] Hyperglycemia is thought to impair several nonspecific mechanisms of the host defense[29] and to increase virulence of *C. albicans*. In a hyperglycemic environment, *C. albicans* overexpresses a C3-receptor-like protein that impairs phagocytic recognition and promotes the adhesion of the fungus to endothelial, mucosal, or foreign surfaces.[30]

The cause of hyperglycemia development after liver transplantation is multifactorial and may be due to glucocorticoid therapy, stress of surgery, TPN, cyclosporine, or tacrolimus.[31] Total parenteral nutrition therapy had been directly associated with the development of *Candida* endophthalmitis and candidemia,[28,32,33] particularly among patients who have received broad-spectrum antibiotics.[28] However, in recent studies researchers could not demonstrate a direct association between TPN and candidemia.[7-9,34] It was assumed that the association between TPN and candidemia was secondary to the use of central venous catheters, rather than to TPN *per se*.[9,35] However, none of these studies included hyperglycemia as a variable in the analysis of possible factors associated with candidemia. In our study, 65% of patients who developed candidemia and who were receiving TPN required insulin, in contrast to 27% of control patients. No significant difference was found between the case and control patients, in the number of patients who received TPN but not insulin, and the between the number of patients who received insulin but not TPN. This suggests that hyperglycemia requiring insulin is a key factor in the development of candidemia during TPN therapy.

The number of antibiotics given intravenously as well as longer treatment courses of antibiotics has been associated with development of candidemia.[7-9] In our study, only the number of antibiotics administered was associated with development of candidemia. It had been established that the use of broad-spectrum antibiotics, particularly those that inhibit gram-negative anaerobic bacteria, results in a substantially greater concentration of *Candida* species in the gut.[36] The administration of three or more antibiotics to our patients most likely markedly reduced the anaerobic gut flora. We recently demonstrated that candidates for liver transplantation are have high yeast colonization in the gut before transplantation.[37] When these patients with yeast colonization in their gut received broad-spectrum antibiotics after transplantation, *Candida* colonization increased even further.

The mortality rate associated with candidemia was 71%, which is higher than that recently reported in a study of patients with cancer (42%) that covered a similar time period.[15] The most important predictor of candidemia-related death was abdominal surgery performed up to 1 week before development of candidemia. Possibly, bowel manipulation during abdominal surgery of patients with heavy colonization releases large amounts of yeast into the bloodstream. This may produce a more intense inflammatory response, resulting in a more severe disease and death.[38]

Although amphotericin B is still considered the drug of choice for treatment of invasive candidiasis, its toxicity is a significant limitation. Fluconazole, a triazole, has recently been found to be effective for the treatment of candidemia in patients without major immunodeficiency and without neutropenia.[39] Additional comparative trials are needed to study the effectiveness of fluconazole among immunosuppressed patients.

In summary, candidemia is associated with a high mortality rate in liver transplant recipients, particularly when it occurs shortly after abdominal operations. We identified two factors associated with the development of candidemia: treatment with multiple antibiotics and hyperglycemia requiring insulin. Therapeutic modalities to be evaluated in prospective trials should include the use of higher doses of amphotericin B prophylaxis and the use of new antifungal agents for prophylaxis.

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