

Fungal Infections After Liver Transplantation: Incidence and Outcome

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ABSTRACT

Background. Fungal infections, although less frequent than bacterial infections, represent a severe comorbidity with an exponential increase in mortality rate in liver transplantation patients. The incidence of invasive fungal infections (IFIs) after solid organ transplantation ranges from 7% to 42%, with *Candida* spp. and *Aspergillus* spp. as the most common pathogens. Fungal infections in liver transplant recipients have been associated with poor outcome and mortality rates ranging from 65% to 90% for invasive aspergillosis and 30% to 50% for invasive candidiasis. The results largely depend on early diagnosis and early initiation of specific treatment for IFIs. Therefore, the diagnosis must be prompt, preferably based on microbiological data, both cultures and biomarkers, and/or based on clinical features and known risk factors.

Materials and Methods. This study evaluated the incidence of fungal infections in patients after liver transplantation in our center between January 2003 and December 2012. The retrospective analysis of 215 consecutive liver transplantation patients was undertaken to estimate incidence, risk factors, and clinical courses of IFIs in the first 3 months after liver transplantation.

Results. Candidemia and invasive candidiasis microbiologically proven were found in 26 patients (12%), whereas in 6 patients (2.8%) invasive fungal infections from other non-*Candida* fungi developed: *Aspergillus* (4 cases: 2 *A. fumigatus*, 2 *A. terreus*), *Fusarium oxysporum* (1 case), and *Rhodotorula rubra* (1 case). Two patients with *Aspergillus* and the patient with *Fusarium* died. The patient with *Rhodotorula* as well as 22 of the patients with candidemia (85%) survived. All of the episodes developed during the first 3 months posttransplantation. All cases have followed a previous polymicrobial bacterial infection (especially in the biliary tract) with large use of combined antibiotic therapies.

Conclusions. The rate of fungal infection was found to increase in parallel with the number of risk factors. Prophylactic strategies can decrease the risk of fungal infections. Early detection and treatment with adequate early empiric therapy is the key to obtaining a better outcome in liver transplantation patients.

LIVER transplantation is a lifesaving procedure for the treatment of many end-stage liver diseases. However, infections and acute rejection episodes are still the main causes of morbidity and mortality [1]. The incidence of invasive fungal infections (IFIs) after solid organ transplantation overall ranges from 7% up to 42%, with *Candida* spp. and *Aspergillus* spp. as the most common pathogens [2]. Fungal infections in liver transplant recipients have been associated with poor outcome and mortality rates ranging from 65% to 90% for invasive aspergillosis and 30% to 50% for invasive candidiasis [2,3].

Advances in immunosuppression have decreased the incidence of rejection, but also have placed liver transplant recipients at increased risk for both typical and atypical infections. Although the incidence of invasive fungal infection after liver transplantation has declined since the

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mid-1990s [4–6], such infections still develop in approximately 5% to 20% of the patients [7].

Approximately 80% of solid organ transplant recipients suffer at least 1 significant episode of infection during the first year after transplantation, especially in the first 3 months after the surgical procedure. Infections are notoriously difficult to diagnose because the usual signs and symptoms of infection, such as fever and leukocytosis, may be masked or absent in immunosuppressed liver transplant recipients. Bacterial infections remain the most frequently occurring infectious complications in the first 3 months after liver transplantation and are the leading causes of morbidity and mortality in this set of patients [8,9]. Fungal infections, although less frequent than bacterial infections, represent a very severe comorbidity with an exponential increase in mortality rate.

Although various fungal species infect liver transplant recipients, by far the most common is the *Candida* species, which constitutes the predominant causative fungal pathogen, accounting for more than 80% of IFIs [10], followed by the *Aspergillus* species and other rare fungi. The incidence of candidemia among transplant recipients ranges between 2% and 8% [11,12], and the overall mortality associated with invasive fungal presentation has been reported to be as high as 77% [13]. *Aspergillus*-associated mortality has been found to approach 100% if untreated [2,13–16]. Candidiasis and aspergillosis typically occur early posttransplantation [7,17], the time at which the intensity of immunosuppressive regimens is highest and the immune status of the recipient is weakened by illness, the surgical procedure, and the hospital microbiological environment. Delayed diagnosis of fungal infections is a major complicating factor, and in fact is associated with a poor prognosis in liver transplant recipients.

Many risk factors associated with fungal infections have been documented in numerous studies and include renal insufficiency especially on dialysis, rejection treatment, cytomegalovirus viremia or disease, indwelling vascular or urinary catheter, biliary tract manipulation and biliary complications, acute hepatic insufficiency, early graft failure, lengthy operation time, retransplantation, prolonged preoperative hospitalization, prolonged intensive care unit (ICU) stay, preoperative use of broad-spectrum antibiotics, substantial intraoperative infusions of cellular blood products, fungal colonization, and repeat laparotomies after transplantation [2,13,18–20]. The identification of risk factors for IFIs in liver transplant recipients could facilitate the timely use of antifungal prophylactic or pre-emptive agents, thereby preventing the development of an invasive or disseminated fungal infection.

However, recent advances in effective antimicrobial prophylactic strategies have led to a decline in the incidence of opportunistic postoperative infections. In fact, despite the absence of a real consensus, short-term antifungal prophylaxis is currently recommended after liver transplantation, at least in patients considered to be at high risk for fungal infection [21,22].

MATERIALS AND METHODS

Setting

This study was conducted at the Agostino Gemelli Hospital of the Catholic University, a 1300-bed teaching medical center in Rome.

Study Design and Patients

The computerized database of our mycology laboratory was searched to identify infections occurring in the first 3 months among 215 consecutive adult patients who underwent liver transplantation between January 2003 and December 2012. Table 1 shows the demographic characteristics and the etiology of the initial liver disease. All livers came from cadaveric donors, and all recipients underwent liver transplantation using an end-to-end choledochcholedochostomy with external drainage of bile through a Kehr T-tube. Seven patients (4.6%) had a retransplantation, and a Roux-en-Y hepaticojejunostomy was performed as biliary reconstruction. The median Model for End-Stage Liver Disease (MELD) score was 20 (6 to 42).

RESULTS

Samples comprised blood, bile, drains, urine, and bronchoalveolar lavage (BAL) and central venous catheter tip cultures. Culture and identification of the isolated fungi was done in accordance with standard mycological procedures. Cultures from BAL and urine as well as from drains from the abdominal cavity were considered colonization instead of infections.

Candidemia and invasive candidiasis microbiologically proven were found in 26 patients (12%), whereas in 6 patients (2.8%) invasive fungal infections from other non-*Candida* fungi developed: *Aspergillus* (4 cases: 2 *A fumigatus*, 2 *A terreus*), *Fusarium oxysporum* (1 case), and *Rhodotorula rubra* (1 case). Two patients with *Aspergillus* and the patient with *Fusarium* died. The patient with *Rhodotorula* as well as 22 of the patients with candidemia (85%) survived.

Candidemia always was observed after some type of bacterial infection (primarily biliary infections) and exposure to multiple antibiotic therapies, and some types after previous exposure to fluconazole (especially in the cases of non-*albicans Candida*). Table 2 shows the *Candida* spp. isolated in the blood in this series of liver transplantation patients.

Table 1. Demographic Characteristics of the Study Population (215 Consecutive Patients)

Recipient age (median)	54 (14–67)
Sex	
Male	168 (78.1%)
Female	47 (21.9%)
Etiology	
Hepatitis B virus	29 (13.5%)
Hepatitis C virus	72 (33.5%)
Hepatocellular carcinoma	37 (17.2%)
Alcohol	55 (25.6%)
ALF	17 (7.9%)
Other	23 (10.7%)
Retransplantation	9 (4.2%)
Model for End-Stage Liver Disease score (median)	20 (6–42)

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