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Fungal Infection in Liver Transplant Patients

Essay

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Mahmoud Ahmed Alii-Eldin

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List of Abbreviations

Abbreviation	Meaning
AmB	Amphotericin B
CD	Cluster of differentiation
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
FDA	Food and drug administration
HHV-6	Human herpes virus 6
HIV	Human immunodeficiency virus
IA	Invasive aspergillosis
ICU	Intensive care unit
IFI	Invasive fungal infection
IRIS	Immune reconstitution inflammatory syndrome
LT	Liver transplantation
MELD	Model of end stage liver disease
MIC	Minimum inhibitory concentration
PCR	Polymerase chain reactions
PNA FISH	Peptide nucleic acid Fluorescence in situ hybridization
SOT	Solid-organ transplantation

Introduction

Liver transplantation has become a widely accepted treatment for a variety of liver diseases, such as viral and alcoholic cirrhosis, liver malignancy, acute liver failure, and many metabolic abnormalities. The operative procedure is extensive, complex, and technically challenging with multiple vascular transections and anastomoses ***(Feltracco et al., 2011)***.

Due to heavy immunosuppression, the early post-operative period poses greater risks of infection ***(Blair and Kusne, 2005)***. Infection is a leading cause of postoperative mortality and morbidity after liver transplantation ***(Li et al., 2012)***. Monitoring immune status in transplant recipients is essential for predicting the risk of infections ***(Zhou et al., 2011)***.

Invasive fungal infections are seen in 4.7-42% of liver transplant recipients and are associated with high mortality ***(Raghuram et al., 2012).*** The mortality associated with fungal infection is between 25% and 69% ***(Eschenauer et al., 2007)***. Moreover, the mortality of patient with *aspergillus* has been found to approach 100% if untreated ***(Liu et al., 2011)***.

Fungal infections usually develop as a consequence of depressed host defenses and environmental exposure. The risk of fungal infections increases when acute rejection episodes are treated with high dose of corticosteroids or antilymphocyte agents. Predisposing factors for fungal infections include preoperative renal dysfunction, fungal colonization at baseline, severity of end stage cirrhosis, retransplantation, perioperative massive transfusion, need for extracorporeal renal assistance, prolonged ICU stay, and reintubation. Both Aspergillus and Candida species can be found after liver transplantation. As a general rule, if *Candida* species grow from two or more sites, even if not from blood, the condition should be managed as a systemic infection. Although antifungal prophylaxis has been widely studied, no consensus exists on which patients should receive it. The presence of the above risk factors likely indicates the need for antifungal prophylaxis ***(Eschenauer et al., 2007)***.

Aim of the Work

The aim of this essay was to revise the updates on fungal infection in liver transplant patients, its incidence, predisposing factors, diagnosis, prophylactic measures and treatment.

Incidence and Factors Predisposing to Fungal Infection in Liver Transplant Patients

The incidence of fungal infections in organ transplant patients ranges from 2% to 50% depending on the type of organ transplanted, kidney recipients being the least frequent and liver recipients having the highest rate of infection. New antifungal medications and immunosuppressants have changed the spectrum of fungal treatment and prevention ***(Hagerty et al., 2003).***

Invasive fungal infections have been reported in 5% to 42% of liver transplant recipients with an associated mortality rate of 25% to 71% ***(Neofytos et al., 2010).*** In United States of America, one-year cumulative incidences of the first invasive fungal infection (IFI) were 4.7%, for liver transplant recipients. One-year incidence was highest for invasive candidiasis (1.95%) and aspergillosis (0.65%). Trend analysis showed a slight increase in cumulative incidence from 2002 to 2005 ***(Pappas et al., 2010)***

Identification of the factors that may cause postoperative fungal infections is important to transplant surgeon ***(Ohkubo et al., 2012).*** The risk of developing early postoperative complications is associated with the patient's preoperative condition, the quality of the donor liver, the quality of the donor and recipient procedure, initial graft function, and

perioperative anesthesiological and intensive care management ***(Mueller et al., 2004).***

Risk factors to fungal infection relate to transplantation factors, donor and recipient factors. Transplant factors include ischemia-reperfusion damage, amount of intra-operative blood transfusion, level and type of immunosuppression, rejection, and complications, prolonged intensive care stay with dialysis or ventilation, type of biliary drainage, repeat operations, re-transplantation, antibiotics, antiviral regimen, and environment. Donor risk factors include infection, prolonged intensive care stay, quality of the donor liver (e.g. steatosis), and viral status. For the recipient, the most important are model of end stage liver disease (MELD) score >30, malnutrition, renal failure, acute liver failure, presence of infection or colonisation, and immune status for viruses like cytomegalovirus. In recent years it has become clear that genetic polymorphisms in innate immunity, especially the lectin pathway of complement activation and in Toll-like receptors importantly contribute to the infection risk after liver transplantation. Therefore, the risk for infections after liver transplantation is a multifactorial problem and all factors need attention to reduce this risk ***(Hoek et al., 2012).***

Several baseline and post-transplantation variables have been identified as risk factors of invasive fungal infections. These include retransplantation, abdominal surgery after transplantation, a lengthy

transplant operation, class 2 human leukocyte antigen (HLA) mismatch, fulminant hepatic failure, renal dysfunction, dialysis, hyperglycemia requiring insulin therapy, post-transplantation bacterial infection, symptomatic cytomegalovirus infection, prolonged stay in the intensive care unit, prolonged or multiple antibiotic therapy, multiple blood or plasma transfusions, low pretransplantation serum albumin levels ***(Husain et al., 2003)***, number of days of intubation, hepatic artery thrombosis, bile leaks and respiratory failure ***(Gladdy et al., 1999)***. Human herpes virus 6 (HHV-6) viremia was an independently significant predictor of invasive fungal infections and was associated with late mortality in liver transplantation recipients ***(Jeffrey et al., 2000).***

Surgical factors, including the technical complexity of surgery, have been shown to be the most significant variables influencing the frequency of invasive candidiasis after liver transplantation ***(Shahid et al., 2003)***. Factors associated with IFIs included pretransplant fungal colonization, and a daily prophylactic fluconazole dosage < 200 mg. Invasive fungal infection after liver transplantation (especially non-albicans Candida species and fluconazole-resistant C. parapsilosis) were associated with reduced survival. The identification of pretransplant fungal colonization may allow for risk modifications before or at the time of liver transplantation (LT). Additionally, the number of LT procedures and prophylactic strategies may affect institutional outbreaks of resistant Candida strains ***(Raghuram et al., 2012)***.

Survival analysis demonstrated that 36% of patients with Cytomegalovirus (CMV) disease developed invasive fungal disease within the first year post-transplant compared with 8% of those without CMV disease. A multivariable, time-dependent analysis demonstrated that being a CMV-seronegative recipient of a CMV-seropositive donor organ and having bacteremia were independently associated with invasive fungal disease ***(George et al., 1997)***.

Use of Alemtuzumab for treatment of acute graft rejection, conferred and increased risk of invasive fungal infections, mostly esophageal candidiasis within 3 months after the start of therapy ***(Peleg et al., 2007)***.

There are several lines of evidence suggesting that iron overload might predispose to invasive fungal infections. First, iron is known to be an essential growth factor for many pathogenic fungi, and limiting iron availability to medically important fungi can render an otherwise virulent strain unable to cause disease in animal models **(*Weinberg, 1999)***. Second, deletion of the gene for fungal iron uptake protein has been shown to inhibit pathogenicity ***(Ramanan and Wang, 2000).*** Finally, Hepatic iron overload is strongly and independently associated with post-transplantation invasive fungal infections ***(Alexander et al., 2006)***.

Hepatic iron overload is associated with decreased survival after liver transplantation. The results of a large multicenter study showed that

long-term survival after liver transplantation was worse in patients with hepatic iron overload, regardless of whether they had hereditary hemochromatosis ***(Kowdley et al., 2005)***. Iron overload has been implicated as a risk factor for infections due to a variety of fungi, including Aspergillus, Candida, Cryptococcus, Histoplasma, Paracoccidioides, Pneumocystis, Pythium, Rhizopus, Trichosporon, and Zygomycetes ***(Altes et al., 2004).***

Two potential mechanisms by which excess of iron increases the risk of fungal infections have been described. As an important cofactor for enzymes involved in many basic cellular functions and metabolic pathways, iron is as essential a nutrient for the fungi as it is for humans ***(Schaible and Kaufmann, 2004)***. The growth of a wide range of fungi in body fluids, cells, tissues, and intact vertebrate hosts has been shown to be stimulated by excess iron ***(Weinberg, 1999)***. Second, a virtually iron-free environment is required for the proper function of innate and acquired immune responses ***(Bullen et al., 2005)***. Thus, iron excess leads to direct impairment of the natural defense systems of body. Many fungi have developed sophisticated mechanisms for acquiring iron **(*Howard, 1999)***. When excess iron is available, fungal virulence is enhanced, and immune response is impaired ***(Bullen et al., 2005).***