Invasive Fungal Infections after Liver Transplantation

An Essay
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First thanks to **ALLAH** *to whom I relate any success in achieving any work in my life.*

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Dedication

This work is dedicated to . . .

My beloved father, to whom I owe everything I ever did in my life and will achieve. There are not enough worlds I can describe just how important my father was to me. Good bless you my father.

My mother for always being there for me and all the nights she stayed with me.

My wife dr nehad for being the light of my life and God's gift to me, my backbone. I just wanted to let you know that you fill my heart with joy and happiness e

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List of Abbreviations

Abb.	Full term
AIDS	*Acquired immune-deficiency syndrome*
AmB	*Amphotericin b*
AmB-d	*AmB deoxycholate*
AUC	*Area under curve*
BAL	*Bronco-alveolar lavage*
CF	*Complement fixation*
CMV	*Cytomegalo virus*
CNS	*Central nervous system*
CSF	*Cerebrospinal fluid*
CT	*Computed tomography*
CXR	*Chest radiography*
DNA	*Deoxyribonucleic acid*
EIA	*Enzyme immunoassay*
FDG	*Fluoro-deoxy glucose*
GC-MS	*Gas chromatography-mass spectrometry*
GM	*Galactomannan*
HIV	*Human Immunodeficiency Virus*
HSCT	*Hematopoietic stem cell transplant*
IA	*Invasive aspergillosis*
ICP	*Intracranial pressure*
ICU	*Intensive care unit*
ID	*Immune-diffusion*
IDSA	*Infectious Diseases Society of America*
IFI	*Invasive fungal infection*
IgG	*Immunoglobulin G*
IgM	*Immunoglobulin M*
IMIs	*Invasive mold infections*
IPA	*Invasive pulmonary aspergillosis*
ITS	*Internal transcribed spacer*
LFAmB	*Lipid formulations of AmB*
MIC	*Minimum inhibitory concentration*
MRI	*Magnetic resonance imaging*
NMR	*Nuclear magnetic resonance*

List of Abbreviations **cont...**

Abb.	Full term

OLT..... *Orthotropic liver transplantation*
PCP..... *Pneumocystis carinii (jirovecii) pneumonia*
PCR..... *Polymerase chain reaction*
PET..... *Positron emission tomography*
RNA..... *Ribonucleic acid*
SOT..... *Solid organ transplantation*
SP..... *Species*
TNF..... *Tumor necrosis factor*
US..... *Ultrasound*

Abstract:

Introduction: Liver transplantation is one of the most effective therapeutic options for patients with certain acute and chronic end-stage liver diseases, 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.so the clinical diagnosis and treatment of fungal infections after liver transplantation is very important in decreasing mortality in transplant recipients, Prevention and management of Invasive fungal infection in the immunocompromised patient has proven remarkably challenging.

Objectives: This review aims to highlight the different types of invasive fungal infections, risk factors, diagnosis, early detection and antifungal prophylaxis and treatment after liver transplantation

Data Sources: Medline databases (PubMed, Medscape, ScienceDirect. EMF-Portal) and all materials available in the Internet till 2017.

Study Selection: This search presented 144 articles. The articles studied the role of angiogenesis in dermatological diseases and to purify the most recent studies in this field.

Data Extraction: If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and defined assessment measures.

Data Synthesis: Comparisons were made by structured review with the results tabulated.

Conclusions: Given the increased risk and poor outcomes in liver transplant recipients who develop fungal infections, early diagnosis and aggressive antifungal prophylaxis should be considered upfront in high-risk patients.The early identification of patients at high risk of developing fungal infections may improve outcomes. Further research is needed to determine the benefits of new molecular and immunological diagnostic assays Concerns about identifying high risk transplant recipients and selecting appropriate antifungal agents are very relevant, and the potential advantages of prophylaxis should be measured against the potential harm.

Key words: Invasive fungal infection - Orthotropic liver transplantation

INTRODUCTION AND AIM OF THE WORK

Liver transplantation is one of the most effective therapeutic options for patients with certain acute and chronic end-stage liver diseases, such as acute liver failure, hepato-cellular carcinoma, hepato-lenticular degeneration, severe hepatitis, and decompensated cirrhosis. Liver transplantation is a lifesaving procedure. Since the first successful liver transplantation by ***Dr. Starzl in 1963,*** there has been tremendous and dynamic progress of surgical and postoperative protocols leading to 1-year and 5-year post transplant survival rates at 88% and 74%, respectively ***(Rock-ville et al., 2012).***

The steady increase in the number of liver transplant recipients means hospitals are treating more immune-compromised patients; this can be associated with increased infection-related morbidity and mortality and higher hospital care costs ***(Rosenhagen et al., 2009).***

Infections have been recognized as a frequent complication with bacterial pathogens playing a major role in the immediate postoperative period followed by viral and fungal organisms. Among these fungal infections candida species and aspergillus species are the most common pathogens and

described as the most devastating complications contributing to significant morbidity and mortality ***(Watt et al., 2010).***

Although the incidence of invasive fungal infection following liver transplantation has declined since the mid-1990s ***(Hadley et al., 2009),*** such infections still develop in approximately 5-20% of patients and represent a significant burden in terms of mortality and morbidity ***(Pappas et al., 2010).***

Candida and aspergillus infections account for 70-90% of invasive fungal infections in solid organ transplant recipients with liver transplant patients showing a particularly high susceptibility to candida species ***(Grossi, 2009).***

Candidiasis and aspergillosis typically occur early post-transplant 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. Despite the absence of a real consensus, short-term antifungal prophylaxis is recommended after liver transplantation in patients considered to be at high risk for fungal infection. The criteria for identifying high-risk recipients, however, remains unclear. In the mid-1990s, a series of analyses identified a range of possible risk factors for invasive fungal infections, including pre-transplant or early post-transplant bacterial colonization, poor pre-transplant renal function, a complex transplant procedure as indicated by high

use of blood products, choledochojejunostomy anastomosis or long surgical time, and a difficult post-operative course with extended stay in the intensive care unit (ICU) or bacterial infection ***(Pappas and Silveira, 2009).***

This review aims to highlight the different types of invasive fungal infections, risk factors, diagnosis, early detection and antifungal prophylaxis and treatment after liver transplantation.

INCIDENCE AND RISK FACTORS OF INVASIVE FUNGAL INFECTION AFTER LIVER TRANSPLANTATION

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. 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 mid-1990s, such infections develop in approximately 5% to 20% of the patients ***(Pappas et al., 2010).***

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.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 ***(Sganga et al., 2013).***

Fungal infections, although less frequent than bacterial infections, represent a very severe comorbidity with an exponential increase in mortality rate ***(Sganga et al., 2014).***

Incidence of fungal infection

Fungal infections are a major cause of morbidity and mortality among patients undergoing orthotropic liver transplantation (OLT). Improved surgical techniques and immunosuppressive regimens have reduced mechanical complications and rejection episodes in liver transplant recipients; however, as many as 42% of liver transplant recipients develop invasive fungal infections (IFIs). The mortality associated with these infections can reach 100%, especially in cases of invasive aspergillosis ***(Cruciani et al., 2006).***

Fungal infections most frequently affect the lung and urinary tract.Candida species, especially candida albicans, account for the majority of all fungal infections, followed by aspergillus species, cryptococcus neoformans, other molds, and histoplasma capsulatum. Fung found fungal infections in 55 (6.6%) of 834 adults who underwent orthotopic liver transplantation (OLT) between 1989 and 1992: 65% had candida, 16% had aspergillus, 16% had cryptococcus, and 2% had phaeohyphomycetes. The mortality for these infections was 54.5 %**(fung, 2002).** As surgical methods and techniques have become increasingly sophisticated and postoperative care has improved, the incidence of fungal infections had significantly decreased ***(Cuellar et al., 2009).***

Advances in immunosuppressive management have reduced the use of corticosteroids or have even eliminated their use, increasing the risk of opportunistic infections. However,