

Liver Transplantation

Review of Literature and update

Essay

Submitted for partial fulfillment of M.Sc Degree
In Internal Medicine

Presented by:

Waleed Amr Fateen

M. B. B. Ch

Under Supervision of:

Prof. Dr. Mohsen Maher

Professor of Internal Medicine
Ain Shams University

Prof. Dr. Mahmoud El Meteini

Professor of General Surgery
Ain Shams University

Prof. Dr. Hossam El Deen Abdel Aziz

Assistant professor of Internal Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2008

Contents:

Acknowledgements.....	3
List of Tables.....	4
List of figures.....	5
List of Abbreviations.....	6
Introduction.....	10
Aim of the Work.....	14
List of Chapters	
1. History of liver transplantation.....	15
2. Egyptian experience with liver transplantation....	21
3. Indications for liver transplantation.....	34
4. Pretransplantation Work up.....	70
5. Operation.....	98
6. Immunosuppression.....	110
7. Postoperative Care.....	155
8. English summary.....	219
9. References.....	226
10. Arabic summary.....	276

Acknowledgements:

Professor **Dr. Mohsen Maher**, professor in internal medicine, Ain Shams university, has been providing constant encouragement and constructive guidance which were of paramount importance for the initiation, progress and completion of this work.

Professor **Dr. Mahmoud El Meteini**, professor of surgery, Ain Shams university and chief transplant surgeon at Wadi El Neel hospital, gave me the chance of a lifetime to become a member of his team at Wadi el Neel hospital and regularly attend rounds and clinics. This had a great impact on my perception of the practice. He is my mentor and his supervision is the cornerstone for this work.

Without the help of **Dr. Hossam Abdel Aziz** assistant professor of internal medicine, Ain Shams university I would have never finished this work on time. His constant guidance gave a deep meaning to this work.

My father and my Professor **Dr. Amr Fateen**, professor of internal medicine, Ain Shams university, he taught me A B Cs in alphabet, life, medicine and hepatology. I am the luckiest person in the world to be his son.

Professor **Dr. Osama Gaber** director of Transplantation and Vice-Chair for administration and faculty affairs, department of surgery The Methodist Hospital / Cornell University is the person who first injected me with the poison of admiration to the concept of liver transplantation when I first traveled for an internship at his previous center in Memphis, Tennessee in 2001. He is my role model. I learned so much from him. I wish this work would make him proud.

I would like to express my gratitude and appreciation to **Dr. Rasha Refaie** transplant hepatologist at Wadi El Neel Hospital for her meticulous supervision of this work apart from the constant guidance and support during training in Wadi el Neel hospital.

List of Tables:

- **Table 1:** The first seven human liver recipients. **Page: 17**
- **Table 2:** Milestones of liver transplantation. **Page: 20**
- **Table 3:** Risk factors for recurrence of HCC for patients transplanted in Wadi el Neel Center. **Page: 30**
- **Table 4:** Contraindications to LDLT according to UNOS. **Page: 50**
- **Table 5:** Child-Turcotte-Pugh Classification. **Page: 59**
- **Table 6:** MELD data must be recertified at certain intervals. **Page: 61**
- **Table 7:** UNOS listing status. **Page: 62**
- **Table 8:** Relationship between MELD and 3-month mortality in hospitalized cirrhotic patients. **Page: 63**
- **Table 9:** Pretransplant Evaluation. **Page: 77**
- **Table 10:** Nutritional recommendations for a liver transplantation candidate. **Page: 82**

List of figures:

- **Figure 1:** Relationship between the 3-month survival rates and MELD score in patients with cirrhosis. **Page: 63**
- **Figure 2:** Waiting list removal because of death or patient being “too sick” for the year before and immediately after implementation of the MELD system. **Page: 64**
- **Figure 3:** The donor procedure. University of Wisconsin solution. **Page: 101**
- **Figure 4:** The recipient procedure. **Page: 105**
- **Figure 5:** The living donor right lobe procedure. **Page: 109**
- **Figure 6:** T-cell activation **Page: 113**
- **Figure 7:** T-cell co-stimulatory and cytokine activation pathways. **Page: 114**
- **Figure 8:** Mechanisms of action of immunosuppressive agents **Page: 117**
- **Figure 9:** Targets of immunosuppressive agents. **Page: 137**

List of Abbreviations:

6-MP:	6-mercaptopurine
AB:	Antibody
ABG:	Arterial Blood Gases
ACE:	Angiotensin-converting enzyme
ACR:	Acute Cellular Rejection
AFP:	Alpha feto protein
AIDS:	Acquired Immunodeficiency Syndrome
AIH:	Autoimmune Hepatitis
ALF:	Acute Liver Failure
ALG:	Anti lymphocyte globulin
AMA:	Anti Mitochondrial Antibody
ANA:	Anti Nuclear Antibody
Anti SM Ab:	Anti Smooth muscle Antibody
ALT:	Alanine Aminotransferase
APACHE:	Acute Physiology and Chronic Health Evaluation
AP:	Activated Protein
APC:	Antigen Presenting Cell
AST:	Aspartate Aminotransferase
ATN:	Acute Tubular Necrosis
BCS:	Budd Chiari Syndrome
BMI:	Body Mass Index
BMD:	Bone Mineral Density
BUN:	Blood Urea Nitrogen
CAD:	Coronary Artery Disease
CBC:	complete blood count
CEA:	Carcinoembryonic Antigen
CLD:	Chronic Liver Disease
CNC:	Clinical nurse Coordinator
CNI:	Calcineurin Inhibitors
CT:	Computerized Tomography
CTP:	Child-Turcotte-pugh
CMV:	Cytomegalovirus
CPM:	Central pontine myelinosis
CR:	Chronic Rejection
CRF:	Chronic Renal Failure
CVA:	Cerebro-Vascular Accident

List of Abbreviations

CVD:	Cardiovascular Disease
CXR:	Chest X-Ray
DDLT:	Deceased donor liver transplantation
DEXA:	dual energy x-ray absorptiometry
DLT:	Domino Liver Transplantation
DNA:	Deoxyribonucleic acid
EBV:	Epstein Barr Virus
ECG:	Electrocardiography
EEG:	Electroencephalography
EIA:	Enzyme-linked Immunosorbent Assay
ERCP:	Endoscopic Retrograde Cholangio Pancreatography
ESLD:	End stage liver disease
ESRD:	End Stage Renal Disease
FAP:	Familial Amyloid Polyneuropathy
FKBP:	FK Binding Protein
GBWR:	Graft to body weight ratio
GFR:	Glomerular Filtration Rate
GVHD:	Graft versus Host Disease
HAART:	Highly active Anti retro viral Therapy
HAT:	Hepatic artery thrombosis
HAV:	Hepatitis A Virus
HBcAb:	Hepatitis B core Antibody
HBeAg:	Hepatitis B e Antigen
HBeAb:	Hepatitis B e Antibody
HBIG:	Hepatitis B immune globulin
HBsAg:	Hepatitis B surface Antigen
HBsAb:	Hepatitis B surface Antibody
HBV:	Hepatitis B virus
HCC:	Hepatocellular carcinoma
HCIG:	Hepatitis C virus immunoglobulin
HCV:	Hepatitis C Virus
HDV:	Hepatitis D (delta) virus
HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
HPS:	hepatopulmonary syndrome
HRQOL:	Health related quality of life
HRS:	Hepato renal syndrome
HSV:	Herpes Simplex Virus
HTN:	Hypertension

List of Abbreviations

HVT:	Hepatic venous thrombosis
ICOS:	Inducible Co-stimulatory Molecule
ICU:	Intensive Care Unit
IFN:	Interferon
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IL:	Interleukin
IM:	Intramuscular
IV:	Intravenous
INR:	International Normalized Ratio
JAK:	Janus Kinase
LCF:	Liver Cell Failure
LDLT:	Living donor liver transplantation
LFT:	Liver Function Tests
LKM AB:	Liver Kidney Microsomal AB
LT:	Liver Transplant
MAP:	Mitogen Activating Protein
MELD:	Model for End-Stage Liver Disease
MESOT:	Middle Eastern Society of Organ Transplantation
MHC:	Major Histocompatibility Complex
MHV:	Middle hepatic vein
MMF:	Mycophenolate Mofetil
MRA:	Magnetic Resonance Angiography
MRCP:	Magnetic Resonance Cholangio Pancreatography
MRI:	Magnetic Resonance Imaging
MRV:	Magnetic Resonance Venography
mTOR:	Mammalian Target of Rapamycin
NAFLD	Non Alcoholic Fatty Liver Disease
NASH:	non-alcoholic steatohepatitis
NF:	Nuclear Factor
NFAT:	Nuclear Factor of Activated T cells
NOS:	not otherwise specified
OKT3:	Muromonab CD-3
OPTN:	Organ Procurement and Transplantation Network
OLT:	Orthotopic liver transplantation
PBC:	primary biliary cirrhosis
PCP:	Pneumocystis carinii
PCR:	Polymerase Chain Reaction
PELD:	Pediatric end-stage liver disease

List of Abbreviations

PFT:	Pulmonary Function Test
PG:	Prostaglandin
PIP3:	Phosphatidylinositol-4,5-triphosphate
PNF:	Primary Graft non function
PPD:	Purified Protein Derivative
PPH:	Porto pulmonary Hypertension
PPS:	Porto pulmonary syndrome
PSC:	primary sclerosing cholangitis
PTC:	percutaneous transhepatic cholangiography
PTDM:	Post transplant diabetes mellitus
PVT:	portal venous thrombosis
QOL:	Quality of Life
RIBA:	Recombinant Immuno Blotting Assay
RNA:	Ribonucleic acid
SBP:	spontaneous bacterial peritonitis
SF-36:	short-form health survey
SO ₂ :	Saturation of Oxygen
SRL:	Sirolimus
SRTR:	Scientific Registry of Transplant Recipients
STAT:	Signal Transducer and Activator of Transcription
SVR:	Sustained Virological Response
TAC:	Tacrolimus
TB:	Tuberculosis
TCR:	T cell Receptor
TIPS:	Transjugular Intrahepatic Porto systemic Shunt
TNF:	Tumor Necrosis Factor
UNOS:	United Network Organ Sharing
U/S:	Ultra Sound
UCDA:	Ursodeoxycholic acid
US:	United States
UW:	University of Wisconsin
VSV:	Varicella Zoster Virus

Introduction

Introduction:

No sense of accomplishment can exceed that of seeing a robust liver transplant recipient who, a few weeks earlier, was seemingly near death from end-stage hepatic failure.

Witnessing such miraculous transitions was what sustained efforts to replace the liver in the 1960s and 1970s when therapeutic triumph was not the usual outcome. Although 2 years ago the longest surviving liver recipient was in her 36th post transplant year, the high mortality and morbidity in the early experience suggested that liver transplantation was a feasible, but not practical, form of treatment. Huge changes occurred with the advent in 1980 of cyclosporine, and again a decade later with the arrival of tacrolimus (Busuttil and Klintmalm, 2005).

Despite continued advances in antiviral therapy and the medical management of chronic liver disease, liver transplantation remains the only prospect for long-term survival in patients with decompensated cirrhosis, unresectable primary hepatic malignancies, and fulminant hepatic failure in which spontaneous recovery is not anticipated.

The availability of a wider array of immunosuppressive agents has now made graft rejection a lesser concern than disease recurrence. Recurrence of hepatitis C virus (HCV) infection has become a major problem in the care of transplant recipients (Schrem, et al., 2008).

The unremitting shortage of deceased-donor organs continues to be reflected in deaths on the liver

transplantation waiting list. Concerns about lack of an equitable system of allocation of available organs has led to implementation of the Model for End-Stage Liver Disease (MELD), which may have achieved its stated aim of reducing deaths on the waiting list (Jung, et al., 2008).

This method of allocation assigns organs to recipients on the basis of an objective, continuous measure of the severity of their liver disease. Extension of live-donor transplantation to adult recipients has increased the organ pool. Other innovations such as splitting deceased-donor grafts to benefit two recipients and use of so-called marginal grafts, including those from older and non-heart-beating donors also have modestly expanded the organ supply. Unfortunately, the shortage of deceased-donor organs will continue to be the rate-limiting step in substantially increasing the number of transplant recipients (Busuttil and Klintmalm, 2005).

Despite ongoing debates about organ allocation and concerns about recurrence of disease, the prospects for long-term survival are very good to excellent for most liver transplant recipients, who otherwise would succumb to their liver disease. For instance, the likely 1-year survival rate for patients with decompensated cirrhosis is less than 10% without liver transplantation but approximately 85% to 90% at 1 year and 75% at 5 years after transplantation for most indications (Schrem, et al., 2008).

In Egypt, the very high prevalence of HCV and the relatively high prevalence of Hepatitis B virus (HBV) has lead to a towering number of patients with end stage liver disease (ESLD) and Hepatocellular carcinoma

(HCC). Cadaveric liver transplantation is not permissible in Egypt. This all throws the light on the extreme importance of living donor liver transplantation (LDLT) as the only cure for the very high incidence of ESLD in our country.

A completely devoted team, believing, accepting & capable of defending the expected difficulties and logistics is fortunately currently found in Egypt and yielding decent results since the start of the program in 2001.

Cadaveric liver transplantation has been and is still the backbone of liver transplantation to broaden our experience, to serve a bigger number of patients and to backup living related liver transplantation a cadaveric donor program should be started in Egypt.

Aim of the Work:

This review article was designed to throw the light on some of the basics of liver transplantation in an evidence based fashion. Liver transplantation is a very raw and open field for research. There is a lot of dispute over so many issues related to liver transplantation; this essay presents the recent evidence with and against many of the controversial subjects.

The goal of this text is to provide a comprehensive and up to date essay covering many aspects of liver transplantation.

Chapter 1

History of liver transplantation