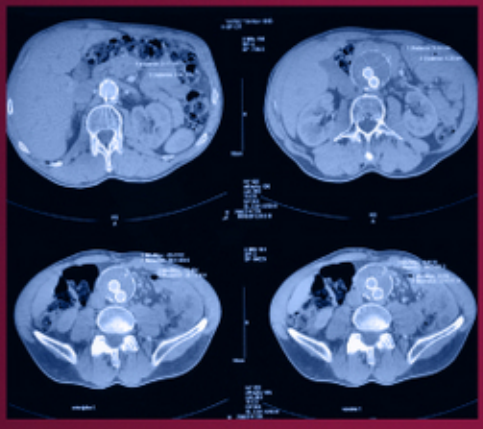
MEDICAL CARE OF THE
Liver Transplant Patient

FOURTH EDITION



EDITED BY
Pierre-Alain Clavien and James F. Trotter

WILEY-BLACKWELL

Medical Care of the Liver Transplant Patient

Medical Care of the Liver Transplant Patient

4th edition

Edited by

Pierre-Alain Clavien MD, PhD
Professor and Chairman
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

James F. Trotter MD
Professor of Medicine
Medical Director of Liver Transplantation
Baylor University Medical Center
Dallas, TX, USA

Associate Editor

Beat Müllhaupt MD
Head, Section of Hepatology
Division of Gastroenterology and Hepatology
University Hospital Zürich
Zürich, Switzerland

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

This edition first published 2012 ©, 2001, 2006, 2012 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Library of Congress Cataloging-in-Publication Data

Medical care of the liver transplant patient / edited by Pierre-Alain Clavien, James F. Trotter ; associate editor, Beat Müllhaupt. – 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4443-3591-0 (hardcover)
ISBN-10: 1-4443-3591-X
1. Liver–Transplantation. 2. Preoperative care. 3. Postoperative care. I. Clavien, Pierre-Alain. II. Trotter, James F.
[DNLM: 1. Liver Transplantation. 2. Patient Selection. 3. Perioperative Care. WI 770]
RD546.M375 2012
617.5'5620592–dc23
2011017804

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 9/11.5pt Sabon by Toppan Best-set Premedia Limited

1 2012

Contents

Contributors, ix
Preface, xv

Part 1 Management of the potential transplant recipient

1 Selection and evaluation of the recipient (including retransplantation), 3
Audrey Coilly and Didier Samuel

2 Monitoring the patient awaiting liver transplantation, 13
Andreas Geier and Beat Müllhaupt

3 Management of portal hypertension, 26
Juan Carlos Garcia-Pagan, Juan G. Abraldes and Jaime Bosch

4 Management of renal disease in the liver transplant candidate, 39
Andrés Cárdenas and Pere Ginès

5 Management of hepatopulmonary syndrome and portopulmonary hypertension, 51
Victor I. Machicao and Michael B. Fallon

6 Psychiatric and substance abuse evaluation of the potential liver transplant recipient, 62
Thomas P. Beresford

7 Organ allocation in liver transplantation: ethics, organ supply, and evidence-based practice, 75
Nicole Siparsky, David Axelrod and Richard B. Freeman

8 Viral hepatitis and transplantation, 88
Geoffrey W. McCaughan

9 Metabolic liver diseases, 97
Maureen M.J. Guichelaar and Michael R. Charlton

10 Cholestatic and autoimmune liver disease, 110
Ulrich Beuers

11 Hepatocellular carcinoma, 121
Maria Reig, Alejandro Forner and Jordi Bruix

12 Cholangiocarcinoma, 133
Howard C. Masuoka, Gregory J. Gores and Charles B. Rosen

13 Rare indications for liver transplantation, 145
Stevan A. Gonzalez

14 Liver transplantation in HIV patients, 155
Marion G. Peters and Peter G. Stock

15 Living-donor liver transplantation, 162
Robert S. Brown Jr

16 Fulminant hepatic failure, 176
Michael A. Heneghan and William Bernal

Part 2 Donor issues and management in the perioperative period

17 Extended-criteria donor, 191
Ashraf Mohammad El-Badry and Mickael Lesurtel

18 Liver transplantation using donors after cardiac death, 201
Paolo Muiesan, Laura Tariciotti and Chiara Rocha

19 Transmission of malignancies and infection through donor organs, 216
Aaron M. Winnick and Lewis Teperman

20 The transplant operation, 229
Philipp Dutkowski, Olivier de Rougemont and Pierre-Alain Clavien

21 Difficult surgical patients, 238
Philipp Dutkowski, Stefan Breitenstein and Pierre-Alain Clavien

22 Domino and split-liver transplantation, 246
Abhideep Chaudhary and Abhinav Humar

23 Surgical aspects of living-donor transplantation, 255
Kelvin K.C. Ng and Sheung Tat Fan

24 Anesthesia, 266
Beatrice Beck-Schimmer

25 Coagulation and blood transfusion management, 276
Herman G.D. Hendriks, Ton Lisman and Robert J. Porte

26 Critical care of the liver transplant recipient, 286
Markus Béchir, Erik Schadde and Philipp Dutkowski

27 Rejection and immunosuppression trends in liver transplantation, 297
James F. Trotter

28 Vascular complications after liver transplantation, 311
Goran Klintmalm and Srinath Chinnakotla

29 Biliary complications following liver transplantation, 319
Sanna op den Dries, Robert C. Verdonk and Robert J. Porte

30 Role of histopathology, 332
Achim Weber

Part 3 Chronic problems in the transplant recipient

31 Medical problems after liver transplantation, 347
Eberhard L. Renner and Marco Puglia

32 Prevention and treatment of recurrent HBV and HCV infection, 361
Ed Gane

33 Recurrence of the original disease, 372
James Neuberger

34 Infections in the liver transplant recipient, 380
Nicolas J. Mueller and Jay A. Fishman

35 Cutaneous diseases in liver transplant recipients, 389
Sylvie Euvrard and Jean Kanitakis

36 Post-transplant lymphoproliferative disorder and other malignancies after liver transplantation, 398
Natasha Chandok and Kymberly D.S. Watt

37 Sexual function and fertility after liver transplantation, 406
Andreas Geier and Beat Müllhaupt

Part 4 Pediatric liver transplantation

38 Special considerations in pediatric liver transplantation, 419
Brandy Ries Lu and Ronald J. Sokol

Multiple choice questions, 431
Answers, 446
Index, 451

Contributors

Juan G. Abraldes MD
Consultant
Liver Unit
Institut Clinic de Malalties Digestives i Metaboliques
Hospital Clinic, and University of Barcelona
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas (CIBERehd)
Barcelona, Spain

David Axelrod MD, MBA
Section of Solid Organ Transplant Surgery
Department of Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, NH, USA

Markus Béchir MD
Consultant
Surgical Intensive Care Unit
University Hospital Zürich
Zürich, Switzerland

Beatrice Beck-Schimmer MD
Professor of Anesthesiology
Institute of Anesthesiology
University Hospital Zürich
Zürich, Switzerland

Thomas P. Beresford MD
Professor of Psychiatry
Department of Veterans Affairs Medical Center
Denver, CO, USA;
School of Medicine University of Colorado
Aurora, CO, USA

William Bernal MD, FRCP
Consultant Intensivist
Institute of Liver Studies
King's College Hospital
London, UK

Ulrich Beuers MD
Professor of gastroenterology and Hepatology
Head of Hepatology
Department of Gastroenterology and Hepatology
Academic Medical Center, University of Amsterdam
Amsterdam, The Netherlands

Jaime Bosch MD, PhD , FRCP
Chair of Medicine
Head, Hepatic Hemodynamic Laboratory
Liver Unit
Hospital Clinic IDIBAPS
University of Barcelona
Director, Biomedical Research Centre Network of Hepatic and Digestive Diseases (CIBERehd)
National Institute of Health Carlos III, Ministry of Science and Innovation Barcelona, Spain

Stefan Breitenstein MD
Clinical Assistant Professor
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Robert S. Brown, Jr. MD, MPH
Frank Cardile Professor of Medicine
Center for Liver Diseases and Transplantation
Columbia University College of Physicians and Surgeons
New York, NY, USA

Jordi Bruix MD
Professor of Medicine BCLC group
BCLC group
Liver Unit
Hospital Clínic
Institut d'Investigacions
Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas(CIBERehd)
University of Barcelona
Barcelona, Spain

Andrés Cárdenas MD, MMSc
GI Unit
Institut Clinic de Malalties Digestives i Metaboliques
Hospital Clinic, and University of Barcelona
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas (CIBERehd)
Barcelona, Spain

Natasha Chandok MD, MPH
Assistant Professor of Medicine
Division of Gastroenterology
Multi-Organ Transplant Program
University of Western Ontario
London, ON, Canada

Michael R. Charlton MB, BS, FRCP
Professor of Medicine
Head of Hepatobiliary Section
Medical Director Liver Transplantation
Division of Gastroenterology and Hepatology
Mayo Clinic
Mayo Clinic Transplant Center
Rochester, MN, USA

Abhideep Chaudhary MBBS, MS
Transplant Fellow
Thomas E. Starzl Transplantation Institute
University of Pittsburgh Medical Center
UPMC Montefiore
Pittsburgh, PA, USA

Srinath Chinnakotla MD
Associate Professor of Surgery and Pediatrics
University of Minnesota Medical School
Clinical Director of Pediatric Transplantation
University of Minnesota Amplatz Children's Hospital
Minneapolis, MN, USA

Pierre-Alain Clavien MD, PhD
Professor and Chairman
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Audrey Coilly, MD
Consultant Hepatologist
Centre Hépato-Biliaire
AP-HP Hôpital Paul Brousse
and Univ. Paris-Sud Faculté de Médecine
Villejuif, France

Olivier de Rougemont MD
Research HPB and Transplant Fellow
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Philipp Dutkowski MD
Professor of Surgery
Head Division of Transplantation Surgery
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Ashraf Mohammad El-Badry MD
Clinical HPB and Transplant Fellow
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Sylvie Euvrard MD
Consultant Physician
Department of Dermatology
Edouard Herriot Hospital Group
Hospices Civils de Lyon
Lyon, France

Michael B. Fallon MD
Professor of Medicine
Director, Division of Gastroenterology, Hepatology and Nutrition
University of Texas Health Science Center at Houston
Houston, TX, USA

Sheung Tat Fan MD, PhD
Sun Chieh Yeh Chair Professor of Surgery
Department of Surgery
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

Jay A. Fishman MD
Professor of Medicine
Harvard Medical School
Associate Director, MGH Transplant Program
Director, Transplant Infectious Disease and Compromised Host Program
Massachusetts General Hospital
Boston, MA, USA

Alejandro Forner MD
BCLC group
Liver Unit,
Hospital Clínic.
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas(CIBERehd)
University of Barcelona
Barcelona, Spain

Richard B. Freeman Jr MD
Allyn Professor and Chair
Department of Surgery
Dartmouth Medical School
Dartmouth Hitchcock Medical Center
Lebanon, NH, USA

Ed Gane MB, ChB, MD, FRACP
Professor
New Zealand Liver Transplant Unit
Auckland City Hospital
Auckland, New Zealand

Juan Carlos Garcia-Pagán MD, PhD
Senior Consultant in Hepatology
Liver Unit
Institut Clinic de Malalties Digestives i Metaboliques
Hospital Clinic, and University of Barcelona
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas (CIBERehd)
Barcelona, Spain

Andreas Geier MD
Consultant, Hepatologist
Division of Gastroenterology and Hepatology
Swiss HPB (Hepato-Pancreato-Biliary) Center
University Hospital Zürich
Zürich, Switzerland

Pere Ginès MD, PhD
Professor of Medicine
Chairman of Liver Unit
Institut Clinic de Malalties Digestives i Metaboliques
Hospital Clinic, and University of Barcelona
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas (CIBERehd)
Barcelona, Spain

Stevan A. Gonzalez MD, MS
Attending Physician, Division of Hepatology
Annette C. and Harold C. Simmons Transplant Institute
Baylor All Saints Medical Center
Fort Worth, TX, USA

Gregory J. Gores MD, FACP
Professor of Medicine
Division of Gastroenterology and Hepatology
The Miles and Shirley Fiterman Center for Digestive Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Maureen M.J. Guichelaar MD, PhD
Consultant, Hepatology / Research collaborator
Mayo Clinic, Rochester MN, USA
Department of Gastroenterology and Hepatology
Medisch Spectrum Twente
Enschede, The Netherlands

Herman G.D. Hendriks MD, PhD
Consultant Anesthesiologist
Department of Anesthesiology
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Michael A. Heneghan MD, MMedSc, FRCPI
Consultant Hepatologist
Institute of Liver Studies
King's College Hospital
London, UK

Abhinav Humar MD
Professor of Surgery
Transplant Surgery
Thomas E. Starzl Transplantation Institute
UPMC Montefiore
Pittsburgh, PA, USA

Jean Kanitakis MD
Professor of Medicine
Hospital Practitioner
Department of Dermatology
Edouard Herriot Hospital Group
Lyon, France

Goran Klintmalm MD, PhD, FACS
Chairman and Chief
Annette C. and Harold C. Simmons Transplant Institute
Baylor University Medical Center
Dallas, TX, USA

Mickaël Lesurtel MD, PhD
Swiss National Fund Professor
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and
Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Ton Lisman PhD
Associate Professor of Experimental Surgery
Surgical Research Laboratory
Department of Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Brandy Ries Lu MD
Sutter Pacific Medical Foundation
California Pacific Medical Center
Pediatric Gastroenterology and Hepatology
San Francisco, CA, USA

Victor I. Machicao MD
Associate Professor of Medicine
Medical Director of Liver Transplantation
Division of Gastroenterology, Hepatology and
Nutrition
University of Texas Health Science Center at
Houston
Houston, TX, USA

Howard C. Masuoka MD, PhD
Transplant Hepatology Fellow and Instructor
Division of Gastroenterology and Hepatology
The Miles and Shirley Fiterman Center for
Digestive Diseases
Mayo Clinic College of Medicine
Rochester, MN, USA

Geoffrey W. McCaughan MBBS, PhD
Professor of Medicine
The AW Morrow Gastroenterology and Liver Centre
Royal Prince Alfred and the University of Sydney
The Centenary Research Institute
Sydney, NSW, Australia

Nicolas J. Mueller MD
Senior Staff Physician
Division of Infectious Diseases and Hospital
Epidemiology
University Hospital Zürich
Zürich, Switzerland

Paolo Muiesan MD
Consultant Surgeon
Liver Transplantation and HPB Surgery
Liver Unit
Queen Elizabeth Hospital
Birmingham, UK

Beat Müllhaupt MD
Professor of Medicine
Head Section of Hepatology
Swiss HPB and Transplantation Centers
Division of Gastroenterology and Hepatology
University Hospital Zürich
Zürich, Switzerland

James Neuberger DM
Consultant Physician
Liver Unit
Queen Elizabeth Hospital
Birmingham, UK;
Associate Medical Director
Organ Donation and Transplantation
NHS Blood and Transplant
Bristol, UK

Kelvin Kwok-Chai Ng MS, PhD, FRCSEd (Gen)
Honorary Clinical Associate Professor
Department of Surgery
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

Sanna op den Dries BSc
Section of Hepatobiliary Surgery and Liver Transplantation
Department of Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Marion G. Peters MD
Professor of Medicine
Chief of Hepatology Research
Division of Gastroenterology
University of California, San Francisco
San Francisco, CA, USA

Robert J. Porte MD, PhD, FEBS
Professor of Surgery
Head of Hepato-Pancreato-Biliary Surgery and Liver Transplantation
Department of Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Marco Puglia MD, FRCPC
Assistant Professor
Department of Medicine
Division of Gastroenterology
McMaster University
Hamilton, ON, Canada

Maria Reig MD
BCLC group
Liver Unit
Hospital Clínic
Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS)
Ciber de Enfermedades Hepáticas y Digestivas(CIBERehd)
University of Barcelona
Barcelona, Spain

Eberhard L. Renner MD, FRCP(C)
Professor of Medicine
Director GI Transplantation
University Health Network
University of Toronto
Toronto, ON, Canada

Chiara Rocha MD
Resident in General Surgery
Liver Unit
Queen Elizabeth Hospital
Birmingham, UK

Charles B. Rosen MN
Professor of Surgery
Chair, Division of Transplantation Surgery
Mayo Clinic and Mayo Clinic College of Medicine
Rochester, MN, USA

Didier Samuel MD, PhD
Professor of Hepatology
Head of the Liver Unit and Liver ICU
Medical Director of the Liver Transplant Program Center
Hépato-Biliaire
AP-HP Hôpital Paul Brousse
Head of the Research Unit 785,
Univ. Paris-Sud and Inserm
Villejuif, France

Erik Schadde MD
Attending Surgeon
Department of Surgery
Swiss HPB (Hepato-Pancreato-Biliary) and Transplantation Center
University Hospital Zürich
Zürich, Switzerland

Nicole Siparsky MD
Section of Solid Organ Transplant Surgery
Department of Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, NH, USA

Ronald J. Sokol MD
Professor and Vice Chair of Pediatrics
Chief, Section of Pediatric Gastroenterology, Hepatology and Nutrition
The Children's Hospital
Aurora, CO, USA

Peter G. Stock MD, PhD
Professor of Surgery
Department of Surgery
Division of Transplantation
University of California San Francisco
San Francisco, CA, USA

Laura Tariciotti MD
Specialist Registrar (Liver Surgery)
Liver Unit
Queen Elizabeth Hospital
Birmingham, UK

Lewis W. Teperman MD
Director of Transplantation
Vice-Chair of Surgery
NYU Langone Medical Center
The Mary Lea Johnson Richards Organ Transplant Center
Department of Surgery
New York, NY, USA

James F. Trotter MD
Professor of Medicine
Medical Director of Liver Transplantation
Baylor University Medical Center
Dallas, TX, USA

Robert C. Verdonk MD, PhD
Department of Gastroenterology and Hepatology
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Kymberly D.S. Watt MD
Associate Professor of Medicine
Division of Gastroenterology/Hepatology
William J von Liebig Transplant Center
Mayo Clinic & Foundation
Rochester, MN, USA

Achim Weber MD
Assistant Professor of Molecular Pathology
Institute of Surgical Pathology
University of Zürich
Zürich, Switzerland

Aaron M. Winnick MD
Fellow, Transplant Surgery
NYU Langone Medical Center
The Mary Lea Johnson Richards Organ Transplant Center
Department of Surgery
New York, NY, USA

Preface

We are pleased to present the 4th edition of ***Medical Care of the Liver Transplant Patient***. The idea to produce such a book started in 1994 at Duke University Medical Center, NC, USA, where a new program for adult and pediatric liver transplantation was developed. The goals were to produce valuable information for any physicians dealing with liver transplantation either in training, established in one field of transplantation or for general praticioners dealing with these patients. Dr Paul Killenberg was the main architect of this project with Dr P-A Clavien, and participated very actively up to the first 3 editions of the book. In 2009, Paul Killenberg died suddenly from a cardio-vascular event, and we would like here to underline his major contributions to the filed of hepatology and this book. Logically, the job of co-editor was taken by James Trotter, who was already involved with the book from his time at Duke University.

Since the 3rd edition published in 2006, there have been a number of novel developments in the field of liver transplantation including, the search to solve the problem of organ shortening with the use of extended criteria donors and particularly donors after cardiac death (DCD), new approaches and indications regarding liver transplantation for malignancies, and the treatment of a variety of infectious diseases. A number of new authors were invited to update previous chapters or write new chapters.

The 4th edition of the book has been extensively revised with many new chapters and was subdivided in four parts covering management of potential transplant recipient (Part 1), donor issue and management in the peri-operative period (Part 2), chronic problems in the transplant recipients (Part 3), and pediatric liver transplantation (Part 4). As new features, we have included learning points for each chapter, and questions to enable the readers to test their understanding of the key information. Sixteen new chapters were added, namely for Part 1: Management of renal disease; Management of hepato-pulmonary syndrome and portal-pulmonary hypertension; Cholestatic and autoimmune liver disease; Cholangiocarcinoma; Rare indications (rare tumors, Budd Chiari, etc); HIV patients; for Part 2: Extended criteria donor; Donation after cardiac death (NHBD); Transmission of malignancies and infection through donor organs; Domino and split transplantation; Coagulation and blood transfusion management; Acute care after liver transplantation; Rejection and immunosuppression; for Part 3: Prevention and treatment of recurrent viral hepatitis; PTLD and other malignancies after liver transplantation; Sexual function and fertility after liver transplantation.

We are grateful to our many colleagues who have agreed to author chapters in this book. We are also grateful to our colleagues at Wiley-Blackwell, Jennifer Seward, Rebecca Huxley, and Kathy Syplywczak, whose interest in this project has been so very important. We would like to also express our greatest gratitude to Madeleine Meyer, from the Zurich office, who played a major role in coordinating and making this edition possible.

P-A Clavien
James Trotter
January 2012

PART ONE

Management of the Potential Transplant Recipient

1 Selection and evaluation of the recipient (including retransplantation)

Audrey Coilly[1,2] *and Didier Samuel*[1,3,4]

[1]AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif; [2]Univ. Paris-Sud, Faculté de Médecine, Paris; [3]Univ. Paris-Sud, UMR-S 785, Villejuif, Paris; and [4]Inserm, Unité 785, Villejuif, France

Key learning points

- Patients should be considered for liver transplantation if they have evidence of life-threatening complications of liver disease including cirrhosis and acute liver failure.
- Indications and contraindications perpetually change with regard to an organ shortage and medical improvements.
- Prioritization for transplantation is now determined by the Model of End Stage Liver Disease (MELD), which lists patients with the greatest risk of short-term mortality.
- At the liver center, a detailed evaluation of the recipient is performed to ensure that transplantation is indicated and feasible.
- Despite a high mortality comparing primary liver transplantation, retransplantation is the only therapy suitable for patients with loss of graft function.

Introduction

Selection and evaluation of a recipient for liver transplantation (LT) has become a great challenge, in the best interest of both the patient and society. Actually, limited organ availability and an increasing demand for organ transplantation has extended transplant waiting times and thus increased morbidity and mortality for potential recipients on waiting lists.

Patients should be referred to transplant centers when a life-threatening complication of liver disease occurs. A detailed medical evaluation is performed to ensure the feasibility of LT. Priority for transplantation has been determined by the MELD score, identifying patients with the highest estimated short-term mortality.

Selection of the recipient: why liver transplantation should be performed

Selection of the recipient is a main challenge for transplant physicians. LT is indicated in end-stage liver disease (ESLD). The most common indication in the adult is cirrhosis but the list of indications is growing. In contrast, the transplant community is currently faced with a major organ shortage; this has put extraordinary pressure on organ allocation programs. Since a successful outcome requires optimal patient

Medical Care of the Liver Transplant Patient, Fourth Edition. Edited by Pierre-Alain Clavien, James F. Trotter.

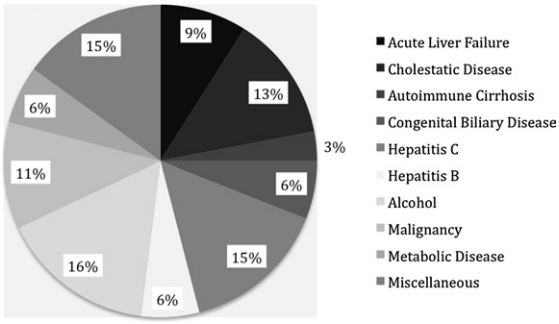


Figure 1.1 Indications for liver transplantation in Europe[38]

selection and timing, the issue of which patients to list for LT and when to transplant cirrhotic patients has generated great interest as well as considerable controversy.

Main indications for LT: complications of ESLD

LT should be considered in any patient with liver disease in whom the procedure would extend life expectancy beyond what the natural history of underlying liver disease would predict or in whom LT is likely to improve quality of life. Patients should be selected if expected survival in the absence of transplantation is 1 year or less, or if the patient has an unacceptable quality of life because of liver disease. Indications for LT in Europe are summarized in Figure 1.1.

Gastroesophageal variceal bleeding

Gastroesophageal varices are found in 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis. Variceal bleeding usually does not occur until the Hepatic Venous Pression Gradient (HVPG) is above 12 mmHg. Each episode of bleeding carries a 20% mortality rate. If the varices are left untreated, after survival from the first episode, the rebleeding risk can be up to 70% within 1 year and is a major cause of death in patients with cirrhosis. Medical treatments are endoscopic variceal ligation and nonselective beta-blockers. Transjugular intrahepatic portosystemic shunt (TIPS) involves establishment of a direct pathway between the hepatic veins and the portal veins to decompress the portal venous hypertension that is the source of the patient's hemorrhage. The procedure is technically challenging, especially in critically ill patients, and has a mortality rate of 30–50% in the emergency setting, but has <90% effectiveness in controlling bleeding from gastroesophageal varices. LT remains the best way to decompress the portal system if other therapy has failed.[1]

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric complication of cirrhosis in which clinical manifestations range from subtle personality changes and sleep disorder to coma. Although treatments have emerged, such as rifaximin to improve recurrence of HE,[2] LT remains the only effective therapy.

Ascites and hepatorenal syndrome

Refractory ascites occurs in 5–10% of cirrhotic patients and carries a mortality rate of >50% at 2 years. Patients are prone to develop gastrointestinal variceal bleeding, hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) and HRS approximately 1 year after the development of ascites, reflecting the poor prognosis of patients with ascites. LT evaluation therefore should be instituted whenever refractory ascites develop.[3]

HRS is characterized by renal vasoconstriction in response to renal hypoperfusion from a low systemic effective circulating volume. The annual incidence of HRS in patients with cirrhosis and ascites is approximately 8%.[4] Two types of HRS are described. Type 1 HRS is characterized by a rapidly progressive impairment of the circulatory and renal functions associated with a very poor prognosis (median survival rate <2 weeks). Type 2 HRS is characterized by a steady impairment of the circulatory and renal function with a median survival rate of 6 months. LT should be considered as soon as a HRS is diagnosed.

Pulmonary complications

Hepatopulmonary syndrome (HPS) is found in 4–47% of patients with cirrhosis and is characterized by intrapulmonary vascular dilatations, especially in the basal parts of the lung. Liver injury and/or portal hypertension trigger the release of endothelin-l, TNF-alpha, cytokines and mediate vascular shear stress and release of nitric oxide and carbon monoxide, all

contributing to intrapulmonary vasodilatation. This results in hypoxemia which may require oxygen therapy. Because it could reverse HPS, LT is the only curative treatment. HPS differs from portopulmonary hypertension (PPHTN) which occurs in 2–8% of patients with cirrhosis. Imbalance between vasodilating and vasoconstrictive agents may be responsible for misguided angiogenesis and pulmonary hypertension. It is associated with a higher risk for LT and increased post-transplantation mortality.

Specific indications for LT

Some indications for LT are specific and vary depending on the underlying liver disease.

Cholestatic diseases

Some criteria for primary biliary cirrhosis (PBC) are specific (see Chapter 10). As survival rate is considerably reduced when the bilirubin level is over 100 µmol/L for <1 year, this level is an indication of LT without any other complication. Uncontrolled and intolerable pruritus or major asthenia, even if isolated, are also indications for LT.

Primary sclerosing cholangitis (PSC) is a rare idiopathic cholestatic disease of unknown cause, characterized by a chronic fibrosing inflammation of the bile ducts (see Chapter 10). There is also an increased risk of cholangiocarcinoma, which is a difficult diagnosis with a prevalence over 30% after a 10-year disease course.[5] Specific indications for PSC are longstanding severe jaundice (bilirubin level over 100 µmol/L), cholestasis and pruritus not related to an acute episode of cholangitis, repeated episodes of cholangitis not controlled by antibiotics, and any suspicion of cholangiocarcinoma.

Autoimmune chronic hepatitis

Autoimmune chronic hepatitis is more common in young women. The clinical presentation of the disease is variable; classically it presents as active chronic hepatitis, but it may also present as established cirrhosis and in few cases as a fulminant course without chronic hepatic disease. A main characteristic of this disease is a good response to immunosuppressive treatment including steroids.[6]

LT is indicated in autoimmune hepatitis for clinical decompensation, despite long-term adequate immunosuppressive treatment, or in fulminant hepatic failure, in which immunosuppressive treatment is usually ineffective and potentially deleterious.

Viral hepatitis

Chronic viral hepatitis due to the hepatitis virus B, C and/or D is one of the most common causes of ESLD worldwide and a frequent diagnosis in patients referred to transplant centers. Viral recurrence after LT is a major issue and graft damage secondary to viral re-infection may lead to graft failure, retransplantation or death.

Alcoholic liver disease

Alcoholic cirrhosis is a common liver disease and a significant number of patients with alcoholic liver disease receive LT. Several centers have developed an evaluation process based on medical and psychiatric criteria to better determine patients who would benefit most from the procedure. Abstinence from alcohol of at least 6 months is usually required to evaluate the need and timing of LT and to obtain better control of alcoholism. This interval is neither a consensus nor an absolute requirement. The risk of recidivism is estimated to be between 15–40% depending on the series, which seems to be related to the duration of follow up after LT and the duration of abstinence before transplantation. Whichever the case, this remains controversial.[7]

Acute alcoholic hepatitis has been considered an absolute contraindication to liver transplantation on the grounds that patients with this disorder have been drinking recently and that a period of abstinence will allow many to recover. Unfortunately, many patients die during this interval. Patients who do not recover within the first 3 months of abstinence are unlikely to survive.[8] Consequently, liver transplantation centers face a dilemma when caring for a patient with alcoholism who has severe alcoholic hepatitis and whose condition deteriorates despite adherence to abstinence, nutritional support, corticosteroids, and other elements of medical management.[9]

Hepatobiliary malignancy

In certain cases, hepatobiliary malignancy is an indication for LT.

Hepatocellular carcinoma (HCC) is the commonest primary malignancy of the liver. LT is a suitable therapeutic option for early, unresectable HCC, particularly in the setting of chronic liver disease. The

study by Mazzaferro in 1996 established LT as a viable treatment for HCC.[10] In this study, the "Milan criteria" were applied, achieving a 4-year survival rate similar to LT for benign disease. Since then various groups have attempted to expand these criteria[11] (see Chapter 11).

Cholangiocarcinoma (CCA) is the second most common cancer among the primary hepatic neoplasm, accounting for 5–20% of liver malignancies.[12] LT for CCA remains a controversial subject (see Chapter 12). A protocol combining neoadjuvant chemoradiation and LT was first used in patients with unresectable hilar CCA. Results have confirmed that this approach leads to significantly lower recurrence rates and higher long-term survival rates than other existing treatment modalities. Despite this, protocols to treat patients with CCA are not widespread, and are available at only a handful of transplant programs.

Other hepatobiliary malignancies may be successfully treated by LT, including without fibrolamellar carcinoma (without metastases), and hemangioendothelioma.

Classically, metastatic tumors of the liver have been considered a poor indication for LT, although some centers have performed this procedure associated with another therapy, such as chemotherapy and radiotherapy. In metastases from neuroendocrine tumors, liver transplantation could be indicated for patients with symptoms related to major hepatomegaly, hormone production, inavailability of effective therapeutic alternatives, diffuse metastases of the liver, slow-growing tumor and absence of extrahepatic disease.[13] Transplant offers the main advantage of a significant improvement of the quality of life in many patients, an alternative to palliative therapy and a possible cure in some patients.

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

In the setting of the metabolic or insulin resistance syndrome (IRS), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are becoming increasingly common medical problems in the developed world. Patients with histological necrotic-inflammatory changes and/or fibrosis may progress to ESLD and require LT (see Chapter 9). It is likely that many potential LT candidates with NASH are excluded from LT due to co-morbid conditions related to IRS.

Fulminant hepatitis

Fulminant hepatitis is an emergency of LT.[14] Viruses (especially hepatitis viruses A and B), drugs, and toxic agents are the most common causes of fulminant hepatitis; its prevalence varies between countries. The prognosis is essentially determined by neurological status, but is also affected very rapidly by damage to other organs. LT has revolutionized the prognosis of fulminant hepatitis, increasing the survival rate from 10–20% (all causes combined) to 75–80% at 1 year and 70% at 5 years (see Chapter 16).

When to perform liver transplantation

The timing of LT is crucial. Physicians have to determine which patients have liver disease that will endanger their lives before life-threatening systemic complications occur. This consideration is balanced by the risk of surgery and immunosuppressive treatment of LT if it is performed too early.

The timing of LT has changed in recent years, reflecting the modification in the method of organ allocation. Up until 2002, a patient's position on the transplant list was determined by their time on the waiting list.[15] The MELD score was implemented for determining organ allocation in 2002 in the USA. This score is an algorithm based on objective measures comprising creatinine, bilirubin and international normalized ratio (INR). The MELD was developed initially to determine the short-term prognosis for patients undergoing TIPS.[16] It was considered to be highly accurate for predicting liver-related death. It was also regarded as a better system because it ignores waiting time and considers actual liver dysfunction.

Implementation of MELD led to an immediate reduction in liver transplant waiting list registrations for the first time in history of LT.[15] Moreover, the median waiting time to LT decreased.[17] In patients with MELD scores ≤14, the mortality rate with transplantation was found to be higher than that of patients with the same MELD score who had not undergone transplantation.[18] Consequently, a MELD score higher than 15 is now considered a valid indication of LT in patients with ESLD. In contrast to the clear benefit of accurately estimating mortality for those patients on the waiting list, MELD has not been found to be as useful in predicting mortality following

LT.[19] Mortality in the post-transplantation period is related not only to the degree of liver dysfunction prior to transplantation, but to other factors, such as donor characteristics, experience of the transplantation team, and random postoperative complications that cannot be predicted.

The MELD scoring system does have limitations. Not all candidates for LT suffer from diseases that carry an immediate mortality risk. These patients would not be well served by a priority system based solely on a mortality risk endpoint. Patients with HCC have relatively preserved synthetic function; they were not given priority in the early years of LT, which led to a high rate of death in these patients prior to LT. The MELD system offers a way to assign priority points for a diagnosis of HCC (see Chapter 11). Seventeen "exceptional diagnoses" have been identified to be underserved by the MELD score allocation system, including pulmonary complications of cirrhosis, hepatic encephalopathy, amyloidosis, and primary hyperoxaluria (Table 1.1). In these cases, extra points could be awarded to certain groups of patients as shown.[20]

Even if the MELD scoring system is well-recognized to be a revolution in the LT era, some studies have tried to improve the model, incorporating values as serum sodium (MELD-Na), and age (integrated MELD). Another example is ΔMELD, using a time-dependent analysis.[21] Some authors compared these models but the MELD score remains the only one used for organ allocation.[22]

Table 1.1 Exceptions to MELD score

Manifestations of cirrhosis
Ascites and hyponatremia
Gastrointestinal bleeding
Encephalopathy
Hepatopulmonary syndrome
Portopulmonary hypertension
Pruritus
Miscellaneous liver diseases
Budd–Chiari syndrome
Familial amyloidosis
Cystic fibrosis
Hereditary hemorrhagic telangiectasia
Polycystic liver disease
Primary hyperoxaluria
Recurrent cholangitis
Unusual metabolic disease
Malignancy
Cholangiocarcinoma and Hepatocellular carcinoma
Unusual tumors
Other
Small-for-size syndrome

Evaluating the recipient: Who shouldn't be transplanted?

Evaluation of the recipient aims to identify contraindications of surgery as well as the contraindications to taking long-term immunosuppressive treatment. This assessment is not consensual and should be discussed in each transplant center. The contraindications to LT are dynamic, ever-changing and vary among liver transplant centers, regarding local expertise. There is an expectation that those transplanted would have a survival probability of at least 50% at 5 years with a quality of life acceptable to the patient. Figure 1.2 shows a sample decision tree for selection and evaluation of an LT recipient.

Assessment of operability

The evaluation of the operability of the candidate requires a cardiovascular and respiratory assessment first.

To evaluate the cardiovascular risk, each patient should undergo an electrocardiogram and a transthoracic echocardiography to identify underlying heart disease. In patients with cirrhosis, increased cardiac output is described and the presence of latent cardiac dysfunction, which includes a combination of reduced cardiac contractility with systolic and diastolic dysfunction. Electrophysiological abnormalities are also noticed. This syndrome is termed "cirrhotic cardiomyopathy".[23] If the patient has multiple cardiovascular risk factors, a stress test should be carried out in order to reveal asymptomatic ischemic heart disease. A thallium stress test is now a minimally invasive and useful examination. In some cases, if coronary disease is suspected during the evaluation in high-risk patients, coronary angiography should be discussed.

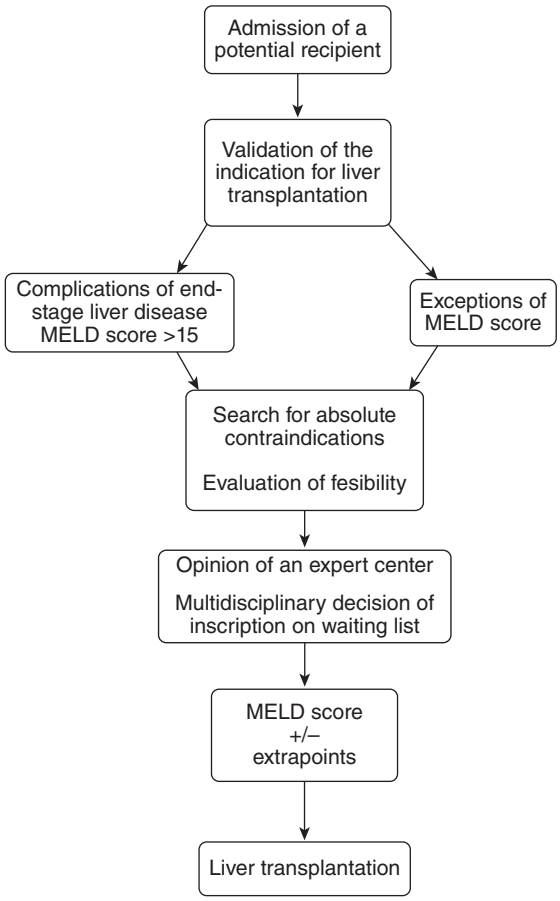


Figure 1.2 Proposed decision tree for selection and evaluation of LT recipient

To evaluate the respiratory risk, a lung function test and a chest X-ray are recommended to screen for lung disease related to cirrhosis or otherwise. When HPS or PPHTN are suspected, further investigation should be performed. The diagnosis of HPS is made by calculating the alveolar-arterial oxygen gradient and performing contrast echocardiography.

A diagnosis of PPHTN is made by performing echocardiography and right-heart catheterization when the systolic pulmonary artery pressure is higher than 30 mmHg on echocardiography.[24] PPHTN used to be an absolute contraindication to LT. The pre-LT management of patients with PPHTN requires early diagnosis and chronic therapy with pulmonary vasodilators such as intravenous epoprostenol to decrease pulmonary vascular resistance. Careful perioperative attention is imperative to avoid right ventricular failure from acutely elevated pulmonary artery pressure or sudden increases in right ventricular preload. With increased surgical and anesthetic expertise, PPHTN is no longer considered an absolute contraindication for LT[25](see Chapter 5).

An evaluation of renal function is essential. HRS, usually a reversible cause of renal failure, has to be differentiated from other causes of chronic kidney disease that are potentially nonreversible and mandate simultaneous liver–kidney transplantations. Estimated renal clearance could be hard to determine in patients with cirrhosis.[26] Performing inulin clearance and renal biopsies might help in the decision-making process. Chronic kidney disease patients with glomerular filtration rates of <30 ml/min, HRS patients requiring renal replacement therapy for >8–12 weeks, and patients with renal biopsy findings of >30% fibrosis and glomerulosclerosis would benefit from receiving both liver and kidney grafts.[27]

The general condition and nutritional status are sometimes difficult to assess in the patient with ESLD. Liver cirrhosis is associated with malnutrition. The clinical and biological parameters used may not apply in cases of severe hepatic insufficiency (body mass index, prealbumin etc.) More studies are needed to develop specific nutritional scores in cirrhosis.

Osteoporosis is also a common complication among patients with cirrhosis and may be detected by bone desitometry which can predict the risk of pathological fracture. An anesthesia consultation is mandatory at the end of this evaluation to assess operational risk. Human leukocyte antigen (HLA) typing and determination of blood group should be included in the general evaluation.

Anatomical evaluation

The surgeon must consider the type of vascularization of the recipient, mainly regarding the hepatic artery and portal system. The presence of shunts, which should be ligated during surgery, or the arcuate ligament are routinely sought. CT angiography of the liver is now performed in all recipients without contraindications. Hepatic arteriography has been largely replaced by CT angiography, but it is still indicated in cases of variant anatomy or previous hepatic surgery including LT.

In the past, portal vein thrombosis (PVT) was considered an absolute contraindication for LT. Thanks to improvement in medical care, surgical techniques and radiological interventions, PVT by itself can represent an indication for LT. Several studies showed that surgical thrombectomy, thromboendovenectomy with venous reconstruction, interposition of vein graft, porto-caval hemitransposition and radiological endovascular interventions can resolve venous obstruction in liver transplant recipients. Interestingly, PVT patients' rates of survival at 1 and 5 years after LT are equal.[28]

Infection screening

Patients with cirrhosis are prone to develop infections that could lead to the development of multiple organ failure and death.[29] Screening for latent infections is required in order to treat a potentially lethal infections before LT and to prevent an exacerbation after LT under immunosuppressive regimens.

A chest radiograph should be performed to identify indirect signs of bacterial or fungal lung infection, including tuberculosis. Some teams recommend conducting a skin test. The search for the tubercle bacillus is not required in the absence of risk factors and with a normal chest radiograph for others.

Examination by an otolaryngologist, and a stomatologist could be required with a nasofibroscopy, a stomatological sinus radiography and panoramic radiographs. Latent dental infection should be treated if possible before LT.

Serologic evaluation for aspergillosis, syphilis, and legionella is often recommended. Hepatitis B and C are systematically sought, even if it is not the cause motivating the transplant. Human immunodeficiency virus (HIV) infection has been considered until recently as a contraindication for LT due to the poor spontaneous prognosis of HIV infection. The advent of highly active antiretroviral drugs (HAART) was a therapeutic breakthrough, and the prognosis has been dramatically improved. The progression of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) seems more rapid in co-infected patients, and a high number of patients will develop life-threatening liver cirrhosis. Patients with a controlled HIV disease are now considered suitable candidates for LT[30] (see Chapter 14).

Serological tests of herpesviridae viruses (Epstein–Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, varicella zoster virus, human herpes virus 6 and 8) are conducted to determine the potential risk of reactivation after LT.

Neoplasia screening

Cancer screening must take into account age, gender, and alcoholic and smoking status of the recipient. If an extrahepatic cancer is an absolute contraindication for LT, a past history of cancer already treated should not disqualify candidates for LT, in accordance, case by case with an oncologist to estimate the survival and risk of recurrence at 1 year, 5 years, and 10 years under long-term immunosuppressive treatment. Actually, the LT should be performed if the risk of recurrence is estimated to be <10%. More often, physicians require a waiting period of 5 years to exclude potential recurrence. This fact should be balanced by the severity of hepatic illness. Colorectal cancer screening is mandatory for any candidate older than 50. If a colonoscopy under general anesthesia is too risky, CT colonography may be an alternative, although its usefulness in cirrhotic patients with ascites has never been demonstrated. The search for pulmonary neoplasia, stomatology, and of the ear–nose–throat (ENT), esophageal and bladder regions is mandatory in cases of alcohol and smoking addiction. An ENT examination is associated with a nasofibroscopy, and an examination of the oral cavity and an upper gastrointestinal endoscopy are recommended.

All women should have regular gynecological care including Papanicolaou test (Pap smear) and mammogram if needed. In men older than 50, screening for prostate disease should be done, including the quantification of PSA and a vesico-prostatic ultrasound.

An examination of the skin is important but skin cancer rarely contraindicates LT.

Special screening for hepatic malignancy

Preoperative baseline metastatic work-up includes a bone scan and chest computed tomography (CT). Recently, a positron emission tomography (PET) scan also tends to be included because of the usefulness to find undetected malignancy and to avoid legal issues.

Social, psychiatric, and addiction assessment

It is important to search for social network problems, psychiatric illness, and addiction in order to evaluate

the adherence of the recipient. In the case of hepatic encephalopathy, neuropsychological testing, CT brain scan, and electroencephalography could help to determine the reversibility of neuropsychiatric troubles. Drug or alcohol abuse is considered to be a contraindication to LT for many reasons: the risk of recidivism, risk of noncompliance, and risk of injury to the graft (see Chapter 6). A period of abstinence from alcohol for at least 6 months is generally a requirement though some teams currently criticize this rule. To date, other models should be defined to evaluate the risk of relapse, including a detailed psychiatric evaluation.

Stably abstinent, methadone-maintained opiate-dependent patients are generally good candidates for LT and show low relapse rates.[31] Current toxicology screening methods provide a positive result of screening for cannabinoids up to 2 months after the patient's last use. Patients who tested positive for marijuana had similar survival rates compared to those with negative test results. Whether patients who regularly use marijuana should be excluded from the waiting list remains a controversial issue.

Pre- and post-transplant smoking rates are high and cause significant morbidity and mortality by cardiovascular events or malignancies. Transplant teams should encourage smoking cessation treatments.

Age

The upper age limit for LT varies; the age of 65 is generally considered to be the upper limit but it has been successfully performed in patients as old as 70. The limit should be determined according to the patient's general medical condition and discussed within each transplant center.

Evaluating and selecting a good recipient for LT requires the collaboration of several specialists. The final decision should be made within each center by expert multidisciplinary staff, considering the benefits and risks for each recipient.

Retransplantation

After LT, graft loss still occurs in 10–20% of adults. The most frequent causes of irreversible graft damage are primary nonfunction, hepatic artery thrombosis, graft rejection and recurrent diseases. Liver retransplantation (re-LT) is the only therapy suitable for patients with loss of graft function after a primary liver transplantation but re-LT carries a high morbidity and mortality rate compared with LT. The 1-, 5-, and 10-year patient survival rates after retransplantation were 61%, 53.7%, and 50.1%, respectively. These percentages were significantly less than those after LT during the same period: 82.3%, 72.1%, and 66.9%. In some centers patients could receive three, four, or more transplants.

Although re-LT is inferior to initial LT, it is the only means of prolonging survival in the patients whose initial graft has failed, making it an important contribution to overall survival.[32]

Primary nonfunction

Primary nonfunction (PNF) is a postoperative condition characterized by absence of hepatic recovery due to various insults during harvesting, preservation or revascularization, unappreciated diseases in the donor, or accelerated rejection. Moderate steatosis of donor liver (30–60%) is associated with an increased incidence of PNF and re-LT rate. PNF, usually defined by the criteria of immediate graft failure with an elevated level of liver enzymes, scarce bile output, encephalopathy, and coagulopathy, is the main indication for re-LT.[33] The incidence is around 6%. In the setting of PNF, re-LT should be undertaken early, within the first 7 days of the primary LT. As shown by multiple studies, re-LT at an intermediate time interval (8–30 d) is associated with a worse prognosis.

Hepatic artery thrombosis

Hepatic artery thrombosis (HAT) after LT can cause significant morbidity or mortality and lead to liver failure or septic complications.[34,35] Allograft rejection is a possible cause of HAT. The incidence is near 3% (see Chapter 28).

Rejection

In the 1980s, acute hepatic allograft rejection occurred in approximately 80% of patients undergoing LT. Chronic rejection is always preceded by one or more episodes of acute rejection, and usually refractory to immunosuppressive therapy. Chronic rejection is an important cause of late graft failure. Despite improve-

ment in immunosuppression therapy, the incidence is still 5% by tacrolimus-based immunosuppressive regimen (see Chapter 27).

Recurrent diseases

Hepatitis C

Approximately 20% or more of HCV-positive transplant recipients will develop allograft cirrhosis within 5 years after LT, and 10% of HCV-infected recipients will die or lose their allograft secondary to hepatitis C-associated allograft failure. The only solution is re-LT[36] but for HCV-positive transplant recipients, re-LT remains highly controversial: patients undergoing re-LT for recurrent HCV have a significantly shorter median survival than those patients undergoing re-LT for other reasons of graft loss (see Chapter 32).

Hepatitis B

The use of hepatitis B immunoglobulin and nucleoside analogues has reduced the risk of HBV recurrence and led to the improvement of patient and graft survival rates.

Other liver diseases

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis have a recurrence rate of 20–30% within 5 years after liver transplantation (see Chapter 33).

Timing for retransplantation

There is no consensus among transplant physicians to define specific re-LT survival outcomes below which re-LT is to be avoided. Only the MELD scoring system for organ allocation provides an objective stratification of retransplant candidates based on severity of illness.

A reduction in short-term survival rate to <60% was observed in all re-LT patients with a MELD score over 25.[37] While mortality was increased in all groups with a concomitant rise in MELD score, patients with a score over 30 had a survival rate of 20–40%. Retransplantation may exhibit survival rates similar to primary transplant in select patients. It is more likely to be successful in healthier recipients with a lower MELD score.

The effect of allograft quality is exceedingly recognized as one of the important parameters that determine success of transplantation in general and re-LT in particular. More studies are needed to clearly define the parameters but older donors and a long, cold ischemia time (>8 hours) seem to be the key factors.

HCV used to be considered as an independent risk factor for higher mortality rate, but several studies have demonstrated that a reasonable rate of survival can be achieved following re-LT and no significant survival differences are observed between HCV-positive, cryptogenic, cholestatic, or alcoholic liver disease patients when adjusted for age and MELD scores.[38,39]

These data suggest that the selection of the recipient should integrate the severity of illness, the interval time since the primary LT and the graft quality more than the cause of retransplantation.

References

1. de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762–8.
2. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–81.
3. Planas R, Montoliu S, Balleste B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006;4:1385–94.
4. Gines A, Escorsell A, Gines P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105: 229–36.
5. LaRusso NF, Shneider BL, Black D, et al. Primary sclerosing cholangitis: summary of a workshop. Hepatology 2006;44:746–64.
6. Czaja AJ, Manns MP. Advances in the Diagnosis, Pathogenesis and Management of Autoimmune Hepatitis. Gastroenterology 2010;139:58–72.
7. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nussler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13: 197–205.
8. Mathurin P, Duchatelle V, Ramond MJ, et al. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. Gastroenterology 1996;110:1847–53.

9. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology 2010;51:307–28.
10. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
11. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502–9; discussion 9–11.
12. Khan SA, Davidson BR, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 2002;51(Suppl 6):VI1–9.
13. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int 2008;21:1107–17.
14. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology 1995;21:240–52.
15. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.
16. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–71.
17. Wiesner R, Lake JR, Freeman RB, Gish RG. Model for end-stage liver disease (MELD) exception guidelines. Liver Transpl 2006;12:S85–7.
18. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307–13.
19. Habib S, Berk B, Chang CC, et al. MELD and prediction of post-liver transplantation survival. Liver Transpl 2006;12:440–7.
20. Freeman RB Jr, Gish RG, Harper A, et al. Model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD Exception Study Group and Conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transpl 2006;12:S128–36.
21. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl 2003;9:12–18.
22. Biselli M, Gitto S, Gramenzi A, et al. Six score systems to evaluate candidates with advanced cirrhosis for orthotopic liver transplant: Which is the winner? Liver Transpl 2010;16:964–73.
23. Moller S, Henriksen JH. Cirrhotic cardiomyopathy. J Hepatol 2010;53:179–90.
24. Umeda N, Kamath PS. Hepatopulmonary syndrome and portopulmonary hypertension. Hepatol Res 2009;39:1020–2.
25. Fix OK, Bass NM, De Marco T, Merriman RB. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. Liver Transpl 2007; 13:875–85.
26. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605–13.
27. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). Am J Transplant 2008;8:2243–51.
28. Ponziani FR, Zocco MA, Campanale C, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16: 143–55.
29. Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. Hepatology 2009;50: 2022–33.
30. Samuel D, Weber R, Stock P, Duclos-Vallee JC, Terrault N. Are HIV-infected patients candidates for liver transplantation? J Hepatol 2008;48:697–707.
31. Lucey MR, Weinrieb RM. Alcohol and substance abuse. Semin Liver Dis 2009;29:66–73.
32. Pfitzmann R, Benscheidt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P. Trends and experiences in liver retransplantation over 15 years. Liver Transpl 2007;13:248–57.
33. Lock JF, Schwabauer E, Martus P, et al. Early diagnosis of primary nonfunction and indication for reoperation after liver transplantation. Liver Transpl 2010;16: 172–80.
34. Gunsar F, Rolando N, Pastacaldi S, et al. Late hepatic artery thrombosis after orthotopic liver transplantation. Liver Transpl 2003;9:605–11.
35. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. Am J Transplant 2009;9:746–57.
36. McCashland T, Watt K, Lyden E, et al. Retransplantation for hepatitis C: results of a U.S. multicenter retransplant study. Liver Transpl 2007;13:1246–53.
37. Watt KD, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? Liver Transpl 2003;9:1019–24.
38. Carrión JA, Navasa M, Forns X. Retransplantation in patients with hepatitis C recurrence after liver transplantation. J Hepatol. 2010;53:962–70.
39. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl 2003;9: 1231–43.