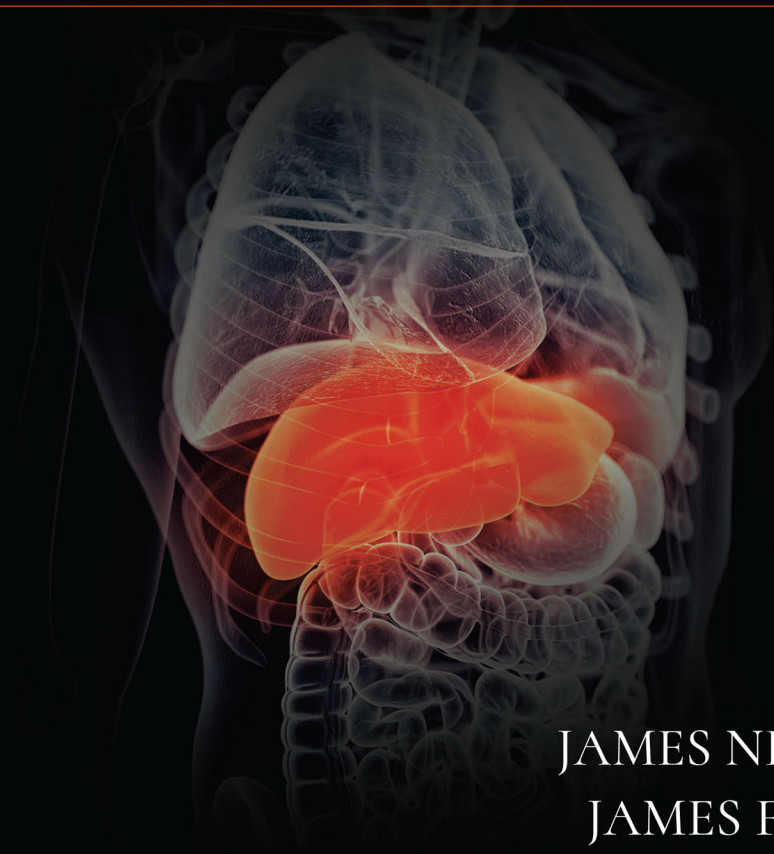
LIVER TRANSPLANTATION

CLINICAL ASSESSMENT AND MANAGEMENT



EDITED BY
JAMES NEUBERGER
JAMES FERGUSON
PHILIP N. NEWSOME
MICHAEL RONAN LUCEY

SECOND EDITION

WILEY Blackwell

Liver Transplantation

Liver Transplantation

Clinical Assessment and Management

Second Edition

Edited by

James Neuberger, DM, FRCP
Honorary Consultant Physician, Queen Elizabeth Hospital, Birmingham, UK

James Ferguson, MD, FRCPE
Consultant Hepatologist, Queen Elizabeth Hospital and Hon Reader in Medicine, University of Birmingham, Birmingham, UK

Philip N. Newsome, PhD, FRCPE
Professor of Experimental Hepatology and Director of the Centre for Liver and Gastrointestinal Research, University of Birmingham and Consultant Transplant Hepatologist, Queen Elizabeth Hospital, Birmingham, UK

Michael Ronan Lucey, MD, FRCPI
Professor of Medicine and Chief, Division of Gastroenterology and Hepatology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

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Contents

List of Contributors

Adebowale A. Adeyemi, MD
Medical Director, Liver Transplant Program
Nemours/Alfred I. duPont Hospital for Children
Wilmington, DE
USA

Matthew J. Armstrong, PhD, MRCP
Consultant in Liver and Transplant Medicine
Queen Elizabeth University Hospital
Honorary Lecturer
National Institute for Health Research Biomedical Research Centre
University of Birmingham
Birmingham, UK

John Ayuk, MD
Consultant Endocrinologist
Queen Elizabeth Hospital
Honorary Senior Lecturer
University of Birmingham
Birmingham
UK

Adiba I. Azad, MD, PhD
Gastroenterology Fellowship
Mayo Clinic
Rochester, MN
USA

Ashley Barnabas, MRCP
Clinical Research Fellow
Institute of Liver Studies
King's College Hospital
London
UK

Patrick Bertolino, MD
Associate Professor
Centenary Institute of Cancer Medicine and Cell Biology
AW Morrow Gastroenterology & Liver Centre
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Francesca Blasi, MD
PhD student
Transplant and HepatobiliaryUnit
Department of Surgery
University of Rome Tor Vergata
Rome
Italy

Patrizio Bo, MD
Gynecologist
Obstetrics and Gynecology Unit
Cittadella Hospital
Cittadella
Padua
Italy

David G. Bowen, MD
Associate Professor of Medicine
Centenary Institute of Cancer Medicine and Cell Biology
AW Morrow Gastroenterology & Liver Centre
Australian National Liver Transplant Unit
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Patrizia Burra, MD, PhD
Professor and Head of Multivisceral Transplant Unit
Department of Surgery, Oncology and Gastroenterology
Padua University Hospital
Padua
Italy

Owen L. Cain, MD, FRCPath
Consultant Histopathologist
Queen Elizabeth Hospital
Birmingham
UK

Andres F. Carrion, MD
Assistant Professor of Clinical Medicine
Division of Gastroenterology and Hepatology
University of Miami Miller School of Medicine
Miami, FL
USA

Carlo D.L. Ceresa, MB, ChB, MRCS, DPhil
MRC Clinical Research Fellow
Nuffield Department of Surgical Sciences, University of Oxford
Oxford University Hospitals NHS Foundation Trust
Oxford
UK

Michael Charlton, MD, FRCP
Professor of Medicine
Director, Center for Liver Diseases
University of Chicago Biological Sciences
Chicago, IL
USA

Miruna David, MRCP, FRCPath
Consultant Microbiologist
Department of Microbiology
Queen Elizabeth Hospital
Birmingham
UK

Brian R. Davidson, MB, ChB, MD, FRCS (Glasg), FRCSEng
Professor of Surgery
University College London
Consultant HPB and Liver Transplant Surgeon
Wellington Hospital and Royal Free Hospital NHS Foundation Trust
London
UK

Jemma Marie Day, DClinPsy
Clinical Psychologist
Department of Child Health
King's College Hospital Foundation NHS Trust
London
UK

Hélène Donnadieu-Rigole, MD, PhD
Consultant and Head of Department
Addiction Unit, CHU Saint Eloi
Montpellier University
Montpellier
France

Ahmed Elsharkawy, MD
Consultant Hepatologist
Liver Unit
Queen Elizabeth Hospital
Birmingham
UK

Stéphanie Faure, MD
Consultant
Hepatology and Liver Transplantation Unit, CHU Saint Eloi
Montpellier University
Montpellier
France

Sandy Feng, MD, PhD
Professor of Surgery
Director of the Abdominal Transplant Fellowship Program
Division of Transplantation, Department of Surgery
University of California–San Francisco
San Francisco, CA
USA

James Ferguson, MD
Consultant Physician and Honorary Reader
Liver Unit
Queen Elizabeth Hospital
Birmingham
UK

Robert J. Fontana, MD
Professor of Medicine and Medical Director of Liver Transplantation
University of Michigan Medical School
Ann Arbor, MI
USA

Peter J. Friend, MD, FRCS
Professor of Transplantation
Nuffield Department of Surgical Sciences, University of Oxford
Consultant HPB and Transplant Surgeon
Oxford University Hospitals NHS Foundation Trust
Oxford
UK

Gregory J. Gores, MD
Consultant
Division of Gastroenterology and Hepatology, Department of Internal Medicine
Executive Dean for Research
Mayo Foundation for Medical Education and Research
Mayo Clinic
Rochester, MN
USA

Arpita Goswami-Banerjee
Penn Transplant Institute
University of Pennsylvania Health Systems Perelman School of Medicine
Philadelphia, PA
USA

Neil Halliday, MB BS, BSc
Speciality Registrar
Institute for Liver and Digestive Health
University College London
The Sheila Sherlock Liver Centre
Royal Free Hospital
London
UK

Emma L. Hathorn, MD
Fellow
Queen Elizabeth Hospital
Birmingham
UK

Jessica Hause
Fellow
Gastroenterology & Hepatology Faculty
University of Wisconsin
Madison, WI
USA

Peter C. Hayes, MD, PhD
Professor of Hepatology and Consultant Physician
Scottish Liver Transplant Unit
Royal Infirmary of Edinburgh
Edinburgh
UK

Julie K. Heimbach, MD
Professor of Surgery
Consultant and Chair
Division of Transplantation Surgery, Department of Surgery
Mayo Clinic
Rochester, MN
USA

Jose Ignacio Herrero, MD
Consultant, Liver Unit
Clinica Universidad de Navarra
Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd)
Instituto de Investigación Sanitaria de Navarra (IdiSNA)
Pamplona
Spain

Moira B. Hilscher, MD
Consultant Gastroenterologist
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, MN
USA

Gideon M. Hirschfield, MRCP, PhD
Lily and Terry Horner Chair in Autoimmune Liver Disease Research
Toronto Centre for Liver Disease, Toronto General Hospital
University Health Network
Toronto
Canada

Paul Horn, MSc, MD
Research Fellow
Centre for Liver and Gastrointestinal Research
Birmingham
UK

Stefan G. Hübscher, MC, ChB, FRCPath
Leith Professor and Professor of Hepatic Pathology
Institute of Immunology and Immunotherapy
University of Birmingham
Consultant Histopathologist
Queen Elizabeth Hospital
Birmingham
UK

Manhal Izzy, MD
Assistant Professor of Medicine
Department of Gastroenterology and Hepatology
Vanderbilt University Medical Center
Nashville, TN
USA

Rajiv Jalan, MD, FRCP
Professor of Hepatology and Head, Liver Failure Group
UCL Institute for Liver and Digestive Health
UCL Medical School, Royal
Free Hospital London
UK

Nick D. Jones, BSc, DPhil
Senior Lecturer
Institute of Immunology and Immunotherapy
University of Birmingham
Birmingham
UK

Rowena Jones, MD
Liver Unit, Queen Elizabeth Hospital
Birmingham
UK

Jeffrey Kahn, MD
Assistant Professor of Clinical Medicine
Division of Gastrointestinal and Liver Diseases
University of Southern California
Los Angeles, CA
USA

Patrick S. Kamath, MD
Consultant, Division of Gastroenterology and Hepatology
Department of Internal Medicine
Mayo Clinic
Rochester, MN
USA

Amardeep Khanna, MRCP
Specialist Registrar
Liver Unit
Queen Elizabeth Hospital
Birmingham
UK

Jennifer C. Lai, MD
Gastroenterologist
Division of Gastroenterology and Hepatology
Department of Medicine
University of California–San Francisco
San Francisco, CA
USA

John R. Lake, MD, BCh, BAO
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
University of Minnesota
Minneapolis, MN
USA

Joanna A. Leithead, MBChB, MRCP
Consultant Hepatologist
Addenbrookes Hospital
Cambridge
UK

Josh Levitsky, MD, MS
Professor of Medicine (Gastroenterology and Hepatology), Medical Education and Surgery (Organ Transplantation)
Northwestern Memorial Hospital
Chicago, IL, USA

Nicholas Lim, MD
Professor of Surgery and Medicine
Executive Medical Director for Solid Organ Transplantation
University of Minnesota Medical Center
Minneapolis, MN
USA

Ken Liu, MD
Senior Clinical Lecturer
Centenary Institute of Cancer Medicine and Cell Biology;
AW Morrow Gastroenterology and Liver Centre;
Australian National Liver Transplant Unit
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Michael Ronan Lucey, MD
Professor of Medicine
Chief, Division of Gastroenterology and Hepatology
University of Wisconsin School of Medicine and Public Health
Madison, WI
USA

Gerry MacQuillan, PhD, FRACP, FRCP
Consultant Transplant Hepatologist/Gastroenterologist
WA Liver Transplantation Service
Hepatology Department and Liver Transplant Service
Sir Charles Gairdner Hospital
Nedlands, WA
Australia

Avik Majumdar, MD
Senior Clinical Lecturer
AW Morrow Gastroenterology and Liver Centre;
Australian National Liver Transplant Unit
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Tommaso Maria Manzia, MD, PhD, FEBS
Professor in Liver and Kidney Transplantation
Transplant and Hepatobiliary Unit
Department of Surgery
University of Rome Tor Vergata
Rome
Italy

Paul Martin, MD, FRCP, FRCPI
Chief, Division of Digestive and Liver Diseases
Professor of Medicine
University of Miami Miller School of Medicine
Miami, FL
USA

Geoffrey W. McCaughan, MD
Professor of Medicine
Faculty and Program Head, Liver Injury and Cancer Program
Centenary Institute of Cancer Medicine and Cell Biology
Director, AW Morrow Gastroenterology and Liver Centre
Co-Director, Australian National Liver Transplant Unit
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Jessica Mellinger, MD, MSc
Assistant Professor
Department of Medicine
University of Michigan
Taubman Center
Ann Arbor, MI
USA

K.V. Narayanan Menon, MD
Staff Hepatologist/Medical Director of Liver Transplantation
Cleveland Clinic
Cleveland, OH
USA

Hynek Mergental, MD
Consultant Liver Transplant and Multi-Organ Retrieval Surgeon
Queen Elizabeth Hospital
Birmingham
UK

Magdalena Meszaros, MD
Fellow
Hepatology and Liver Transplantation Unit, CHU Saint Eloi
Montpellier University
Montpellier
France

Lucy Meunier, MD
Chief of Clinic
Hepatology and Liver Transplantation Unit, CHU Saint Eloi
Montpellier University
Montpellier
France

Charles Miller, MD
Enterprise Director of Transplantation
Cleveland Clinic
Cleveland, OH
USA

Tim Mitchell, FRACP
Fellow
Hepatology Department and Liver Transplant Service
Sir Charles Gairdner Hospital
Nedlands, WA
Australia

Paolo Muiesan, MD, FRCS, FEBS
Consultant Surgeon
Liver Unit
Queen Elizabeth Hospital and Birmingham Childrens' Hospital
Birmingham
UK

David J. Mutimer, MD, FRACP
Consultant Physician
University of Birmingham
Birmingham
UK

Amit Nair, MD, FRCS
Assistant Professor of Surgery
Division of Transplantation/Hepatobiliary Surgery
University of Rochester
Rochester, NY, USA

James Neuberger, DM, FRCP
Honorary Consultant Physician
Queen Elizabeth Hospital
Birmingham
UK

Philip N. Newsome, PhD, FRCPE
Professor of Experimental Hepatology and Hon Consultant Hepatologist
Institute of Immunology and Immunotherapy
Director of the Centre for Liver and Gastrointestinal Research
Director of the Midlands & Wales Advanced Therapy Treatment Centre
Deputy Director of the NIHR Birmingham Biomedical Research Centre
University of Birmingham
Birmingham
UK

John O'Grady, MD, FRCPI
Consultant Hepatologist
Liver Unit
King's College Hospital
London
UK

Kim M. Olthoff, MD
Surgical Director, Liver Transplant Program
The Children's Hospital of Philadelphia
Donald Guthrie Professor of Surgery and Chief, Division of Transplant Surgery
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA
USA

Fernanda Q. Onofrio, MD
Hepatology Fellow
Toronto Centre for Liver Disease, Toronto General Hospital

University Health Network
Toronto
Canada

Esteban Otero, PhD
Liver Transplantation Unit
University Hospital
Santiago de Compostela, Spain

Georges-Philippe Pageaux, MD, PhD
Professor
Hepatology and Liver Transplantation Unit, CHU Saint Eloi
Montpellier University
Montpellier
France

Alessandro Parente, MD
Surgical Fellow
Liver Unit
Queen Elizabeth Hospital
Birmingham
UK

Parita Patel, MD
Gastroenterology and Hepatology Fellow
Division of Gastroenterology and Hepatology
University of Chicago
Chicago, IL
USA

Giovanni Perricone, MD
Consultant in Hepatology and Gastroenterology
Liver Failure Group, UCL Institute for Liver and Digestive Health
UCL Medical School, Royal Free Hospital
London, UK
Hepatology and Gastroenterology Unit
Azienda Socio-Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda
Milan
Italy

Rutger J. Ploeg, MD, PhD, FRCS, FEBS (Hon)
Professor of Transplant Biology
Nuffield Department of Surgical Sciences, University of Oxford
Consultant Transplant Surgeon
Oxford University Hospitals NHS
Foundation Trust
Oxford, UK
Professor of Transplant Surgery and Research
University of Groningen
Groningen, Netherlands
Leiden University
Leiden, Netherlands

Cristiano Quintini, MD
Director of Liver Transplantation
Cleveland Clinic
Cleveland, OH
USA

Mina Rakoski, MD
Gastroenterologist
Division of Gastroenterology and Hepatology
Loma Linda University Health
Loma Linda, CA
USA

Ashwin Rammohan, MCh, FRCS
Director, Academics and Research
Consultant, Abdominal Trauma, HPB Surgery and Liver Transplantation
Institute of Liver Disease & Transplantation
Dr. Rela Institute & Medical Centre
Chennai
India

Elizabeth B. Rand, MD
Medical Director, Liver Transplant Program
The Children's Hospital of Philadelphia
Philadelphia, PA
USA

Mohamed Rela, MS, FRCS, DSc
Chairman and Director
Institute of Liver Disease & Transplantation, Dr. Rela Institute & Medical Centre
Chennai
India
Institute of Liver Studies
King's College Hospital
London
UK

John P. Rice, MD
Section Chief of Hepatology
Division of Gastroenterology and Hepatology
Department of Medicine
Medical Director, Liver and Pancreas Center
UW Health Digestive Health Center
University of Wisconsin
Madison, WI
USA

Bruno Roche, PH, MD
Practicien hospitalier
Centre Hépato-Biliaire
AP-HP, Hôpital Paul-Brousse
Villejuif
France

Didier Samuel, MD, PhD
Professor of Hepatology and Gastroenterology
Université Paris-Sud
Medical Director, Liver Transplant Program
Head of Liver and Intensive Care Units
Centre Hépato-Biliaire
AP-HP, Hôpital Paul-Brousse
Villejuif
France

Marianne Samyn, MD
Consultant Paediatric Hepatologist
Clinical Lead for Liver Transition
Service
Paediatric Liver, GI and Nutrition Centre
King's College Hospital NHS Foundation Trust
London
UK

Salvatore Stefano Sciarrone, MD
Digestive Specialist
Multivisceral Transplant Unit
Department of Surgery, Oncology and
Gastroenterology
Padua University Hospital
Padua
Italy

Nazia Selzner, MD, PhD
Assistant Professor of Medicine
University of Toronto
Medical Director, Live Donor Transplant
Multi-organ Transplant Program, Toronto General
Hospital
University Health Network
Toronto
Canada

Amanda Smith, BParm(Hons), MRPharmS, DipClinPharm
Lead Pharmacist
Liver and Solid Organ Transplantation
Queen Elizabeth Hospital
Birmingham
UK

Erin Spengler, MD
Assistant Professor (CHS)
Gastroenterology & Hepatology Faculty
University of Wisconsin
Madison, WI
USA

Simone I. Strasser, MD
Associate Professor
AW Morrow Gastroenterology and Liver Centre;
Australian National Liver Transplant Unit
Royal Prince Alfred Hospital
University of Sydney
Camperdown
Australia

Shareef Syed, MD, ChB, MRCS
Transplant Surgeon
Division of Transplantation, Department of Surgery
University of California–San Francisco
San Francisco, CA
USA

Santiago Tome, PhD
Liver Transplantation Unit
University Hospital
Santiago de Compostela, Spain

Puneeta Tandon, MD
Assistant Professor, Department of Medicine
Division of Gastroenterology (Liver Unit)
University of Alberta
Edmonton, Alberta
Canada

Norah A. Terrault, MD, MPH
Professor Emeritus, Medicine
Division of Gastrointestinal and Liver Diseases
University of Southern California
Los Angeles, CA
USA

Fiona Thompson, DM
Consultant Physician
Liver Unit
Queen Elizabeth Hospital
Birmingham
UK

Douglas Thorburn, MD, FRCP
Consultant Hepatologist
Clinical Director for Liver
Transplantation, HPB & Hepatology
Royal Free Hospital
Professor of Hepatology
Institute for Liver & Digestive Health
University College London
Royal Free London NHS Foundation Trust
Royal Free Hospital
London
UK

Giuseppe Tisone, MD
Professor of Medicine and Director
of Transplant Centre
Transplant and Hepatobiliary Unit
Department of Surgery
University of Rome Tor Vergata
Rome, Italy

Navneet Tiwari, MD
Senior Clinical Fellow
Queen Elizabeth Hospital
Birmingham
UK

Luca Toti, MD, PhD
Consultant Surgeon
Transplant and Hepatobiliary Unit Department
of Surgery
University of Rome Tor Vergata
Rome, Italy

Palak J. Trivedi, PhD, MRCP
Consultant Physician and Clinical Scientist
Honorary Consultant Hepatologist
Liver Unit
University Hospitals Birmingham
Birmingham
UK;
Clinician Scientist
NIHR Birmingham BRC
Institute of Immunology and Immunotherapy
University of Birmingham
Birmingham
UK

Hector Vilca-Melendez, MD
Consultant Surgeon
Liver Unit
King's College Hospital
London
UK

Michael L. Volk, MD
Medical Director of Liver Transplantation
Chief of Gastroenterology and Hepatology
Associate Professor of Medicine
Loma Linda University Health
Loma Linda, CA
USA

Christopher J.E. Watson, MA, MD BChir, FRCS
Professor of Transplantation and Hon
Consultant Surgeon
University of Cambridge and Cambridge University
Hospitals NHS Foundation Trust
Addenbrooke's Hospital
Cambridge
UK

Kymberly D. Watt, MD
Medical Director, Liver Transplant Program
Consultant in Gastroenterology and Hepatology
Mayo Clinic and Foundation
Rochester, MN
USA

Kerry Webb, MSc
Nurse Consultant
Birmingham and Solihull Mental Health Trust
Birmingham
UK;
Liver Unit, Queen Elizabeth Hospital
Birmingham
UK

Robert M. Weinrieb, MD, FACLP
Professor of Psychiatry
Chief Psychiatric Consultant, Penn Transplant Institute
Program Director, Penn/VA Consultation-Liaison Psychiatry Fellowship
University of Pennsylvania Health Systems Perelman School of Medicine
Philadelphia, PA
USA

Maureen Whitsett, MD
Gastroenterology Fellow
NYU Langone Health
New York
USA

Felicity R. Williams, BSc
NIHR Clinical Research Fellow
Biomedical Research Centre, Institute of Inflammation and Ageing
University of Birmingham
Birmingham
UK

Michael J. Williams, PhD
Consultant Hepatologist
Scottish Liver Transplant Unit
Royal Infirmary of Edinburgh
Edinburgh
UK

Foreword to the Second Edition

Without doubt, liver transplantation is one of the greatest success stories in medicine and I never cease to be amazed when I see in follow-up patients who I remember as having terminal illness, 20–30 years after transplantation, living happily in good health and on minimum immunosuppression.

Many more people are going to have this opportunity with the greater number of donor organs that advances in machine preservation are making possible. Donor livers that would not have been considered because of fatty change or ischemic damage can be restored with a period of preservation to a healthy functioning state. The move to an "opt-out" plan of deemed consent in England in May will also significantly increase the number of consents to donation, as has been proven by the experience in Wales. The scenario of patients suitable for transplant being on the waiting list for months and with a mortality of about 20% should become a matter of the past.

But there are important ongoing issues that need to be addressed, for instance the impairment of cognitive ability and educational attainment that has been demonstrated in children after transplantation for biliary atresia or autoimmune hepatitis, detracting from the otherwise remarkable survival figures. Also in the pediatric area are the difficulties that can occur in the transition period to adult life.

The biggest challenge, though, is the emergence of non-alcoholic fatty liver disease (NAFLD) taking over as the leading cause for liver transplantation, supplanting viral hepatitis cases now that there are effective drugs, particularly against hepatitis B and C. Cardiovascular and metabolic complications of obesity can add up to a considerable co-morbidity affecting NAFLD patients coming to transplantation, in both immediate and long-term outcomes. The long timeframe of NAFLD disease causes difficulties in assessing prognosis and need for transplantation. There can also be problems in the diagnosis of primary hepatocellular carcinoma (HCC) in patients who are likely to be obese. The steadily rising prevalence of HCC poses additional challenges to transplant programs with the burgeoning number of effective medical agents as well as ablative techniques used in conjunction with transplantation, making close collaboration between Hepatology and Oncology even more necessary.

Finally, the unmet need for transplantation in instances of severe liver failure consequent on decompensated cirrhosis or on acute alcohol hepatitis will need to be addressed, and here there have been reports of successful transplantation even at the stage of multiorgan failure. Even at 50 years since transplantation got underway, there are unsolved issues to be solved and new challenges – in other words, much to do, but with continuing great outcomes for the patients.

Professor Roger Williams, CBE
Director, Institute of Hepatology London
Professor of Hepatology, King's College London
(Roger Williams sadly died on 25 July 2020; see https://bts.org.uk/passing-of-prof-roger-williams/)

Foreword to the First Edition

Liver transplantation in humans has come a very long way in a short period of time. My first studies of liver transplantation in animals began in 1958 when I showed that such a procedure was technically possible. I identified three key challenges: the need to preserve the liver between retrieval and implantation, the need to preserve the recipient in hemodynamic stability, and the need to prevent rejection.

The first human liver transplant was performed in 1963 and identified a number of issues that needed resolution, so the program was put on hold, but restarted with the first successful transplant in 1967. The program, initially in Denver and subsequently in Pittsburgh, grew rapidly and was followed by the successful program in Cambridge, UK, in 1968, led by Sir Roy Calne and Roger Williams. Those early pioneering days were exciting but stressful, physically and emotionally. Outcomes improved slowly but surely. In 1983, the procedure came of age when liver transplantation was recognized by the NIH as an effective treatment. Other programs developed around the world and liver transplantation is now routine, with many recipients surviving 20 and more years with an excellent quality of life.

The progression from a high-risk and resource-intensive procedure, where blood use of less than 100 units was considered a success and outcomes were measured in 1-year survival, to a low-risk, routine, and usually blood-free procedure has been achieved as a result of the dedication, hard work, enthusiasm, imagination, and sheer persistence of a large number of people: surgeons, physicians, scientists, intensivists, microbiologists, and many others have all made huge contributions to the success of the procedure. The contribution of both donors and recipients must also be acknowledged for, without their support, these advances could never have occurred.

Yet many challenges remain. Despite advances in medical care, the need for liver transplantation is increasing and the availability of donor livers inadequate. Liver preservation is still a concern: new perfusion fluids and machine perfusion may mitigate some of the problems. While immunosuppression has improved enormously, with the introduction initially of ciclosporin and tacrolimus and, more recently, mycophenolate, sirolimus, and biologic agents, most recipients require long-term treatment, with its associated side effects; tolerance remains an elusive goal. Selection and allocation policies are attracting, quite appropriately, public scrutiny. Regulation is increasing: indeed, it is doubtful whether liver transplantation could have developed as quickly as it did under the current risk-averse climate.

Liver transplantation is expanding and outcomes are better than ever, so more clinicians will be touched by the procedure, whether for referral or for follow-up. It is hoped that this volume will provide a useful and practical guide to the successful management of these patients.

Thomas E. Starzl, MD, PhD
Professor of Surgery
University of Pittsburgh School of Medicine
Pennsylvania, PA, USA

Preface

Welcome to the second edition of *Liver Transplantation*. Since the first edition, there have been many changes in the management of patients with liver disease, both before and after transplantation, and this new edition reflects this.

As with the first edition, the aim of the volume is to provide a concise, practical, and authoritative guide for junior medical staff and other health professionals working in liver transplant units, for healthcare professionals looking after those patients with liver disease who are or may become liver transplant candidates, and for patients following liver transplantation.

We have expanded both the number and the reach of authors, with a consequent increase in chapters. We have sought to represent the breadth of liver transplant medicine across Europe and North America, while recognizing also the role of liver transplantation in the rest of the world. We appreciate that this means some duplication and occasional divergence of views. We have intentionally retained these so that each chapter is entire in and of itself and the reader understands where there is uncertainty.

We are very grateful to the authors who have written and revised their contributions during the height of the Covid-19 pandemic. We are grateful to those at Wiley-Blackwell, especially Jennifer Seward, Pri Gibbons, Bhavya Boopathi and Sally Osborn, for their help and patience and, most importantly, to our partners and children who have been patient with us during the preparation of this second edition.

Finally, we would like to acknowledge the work of Professor Roger Williams, who died in July 2020 and who contributed so much to hepatology worldwide; he was one of the first to recognize the importance of liver transplantation and helped ensure that it rapidly transitioned from an experimental, high-risk procedure to a routine operation that has benefited so many people. We are delighted and honored to include his Foreword to this second edition.

James Neuberger
James Ferguson
Philip N. Newsome
Michael Ronan Lucey

Abbreviations

6MWD/6MWT	6-minute walk distance/time
AA	amino acids
AASLD	American Association for the Study of Liver Diseases
ABC	adenosine triphosphate-binding cassette
ABOi LT	ABO-incompatible liver transplant
ABP	arterial blood pressure
ACE	angiotensin-converting enzyme
ACLF	acute-on-chronic liver failure
ACP	advance care planning
ACR	albumin creatinine ratio/acute cellular rejection
AD	acute decompensation
ADH	antidiuretic hormone
ADL	activity of daily living
ADV	adefovir
AH	alcoholic hepatitis
AICD	activation-induced cell death
AIH	autoimmune hepatitis
AILD	autoimmune liver disease
AKI	acute kidney injury
ALD	alcohol-related liver disease
ALDLT	adult living donor liver transplantation
ALF	acute liver failure
ALP	alkaline phosphatase
ALPPS	associating liver partition and portal vein ligation for staged hepatectomy
ALT	alanine aminotransferase
AMA	American Medical Association/antimitochondrial antibody
AMR	antibody-mediated rejection
ANA	antinuclear antibody
APA	American Psychiatric Association
APAP	N-acetyl-para-aminophenol (acetaminophen)
APC	antigen-presenting cell

APOLT	auxiliary partial orthoptic liver transplantation
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
ASMA	anti-smooth muscle antibody
AST	aspartate transaminase
AT	anaerobic threshold
ATG	anti-thymocyte globulin
ATP	adenosine triphosphate
AUC	area under the curve
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorder Identification Test
AZA	azathioprine
BCAA	branched chain amino acid
BCC	basal cell carcinoma
BCG	Bacille Calmette–Guerin
Bcl6	B-cell lymphoma 6
BCLC	Barcelona Clinic Liver Cancer
BD	twice daily
BEC	biliary epithelial cell
BIA	bioelectric impedance analysis
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BSEP	bile salt export pump
CA	cancer antigen/carbohydrate antigen
CAD	coronary artery disease
CAM	cell adhesion molecule
CANONIC	CLIF Acute-oN-ChrONic LIver Failure in Cirrhosis
CBC	complete blood count
CBD	common bile duct
CBT	cognitive behavioral therapy
CCA	cholangiocarcinoma
CCM	cirrhotic cardiomyopathy
CCR	CC chemokine receptor
cccDNA	covalently closed circular DNA
CDC	complement detection cytotoxicity
CDR	crude death rate
CHA	common hepatic artery
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CIA	common iliac artery
CIT	cold ischemia time
CKD	chronic kidney disease
CKD-EPI	CKD-Epidemiology Collaboration
CLEVER-1	common lymphatic endothelial and vascular endothelial receptor-1
CLIF-SOFA	Chronic Liver Failure-Sequential Organ Failure Assessment

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