Living Donor Liver Transplantation

July 2015

Compiled by a joint working party of the British Transplantation Society and the British Association for Studies of the Liver

NHS Evidence accredited provider
NHS Evidence - provider by NICE
www.evidence.nhs.uk

United Kingdom Guidelines

CONTENTS

1 INTRODUCTION

1.1 The Need for Guidelines

Transplantation offers patients with end-stage organ failure a cost-effective treatment that improves quality of life and increases life expectancy.

In most Western countries, deceased donor liver transplantation (DDLT) remains the standard of care for patients with end stage liver disease. Split liver transplantation and subsequently living donor liver transplantation (LDLT) were first pioneered in children in the late 1980s due to a lack of appropriately sized donors and the high mortality rate among children awaiting liver transplantation. As experience with liver resection techniques grew and success with paediatric living donor transplantation became apparent, LDLT was introduced for adults in the early 1990s, with the first successful adult LDLT being performed in Japan.

LDLT has now become an important part of many liver transplantation programs around the world. While adult-to-adult LDLT remains the transplant procedure of choice in most Asian countries due to the lack of deceased donors in these areas, LDLT is less commonly undertaken in Western countries because of the greater availability of deceased donors (1). This is especially true for the UK following a recent increase in the deceased donor pool (especially DCD grafts). LDLT now accounts for 7% of liver transplants performed per year in the UK, the majority of which are performed in three centres.

Obvious advantages of LDLT over DDLT include the ability to provide transplantation before the recipient becomes too ill, knowledge of the donor history, the avoidance of the physiologic derangement induced by brain death in the donor, and reduced cold ischaemic time. These advantages are balanced by the risk to the donor, the additional technical complexity of receiving a partial graft, and the need for careful medical and surgical judgment in choosing the appropriate donor and recipient. While the risk-benefit ratio may favour LDLT in some parts of the world, the most appropriate role for LDLT in the UK is still to be defined.

This is the first national guideline in this rapidly evolving field. It aims to review the current evidence relating to the evaluation process of both recipient and donor candidates, address the moral and ethical issues surrounding this procedure, outline

the technical aspects of the procedure, including the middle hepatic vein controversy and the ‘small for size syndrome’, review donor and recipient outcomes and complications including donor mortality, and examine evidence relating to the advantages and disadvantages of LDLT.

1.2 Process of Writing and Methodology

This document has been written under the auspices of the BTS Standards Committee. The guidance has been produced in line with the BTS Clinical Practice Guideline and the recommendations of NHS Evidence (2). It has been produced with wide representation from UK clinicians and professional bodies involved in liver transplantation including the British Association for the Study of the Liver (BASL).

A systematic review of the relevant literature and synthesis of the available evidence was undertaken by selected clinical experts. This was followed by peer group appraisal and expert review. Draft proposals were collated by the editors and draft guidelines were presented to the UK transplant community for wider discussion at a BTS consensus meeting in London in November 2013. This was attended by transplant surgeons and physicians, intensivists, Clinical Leads in Organ Donation (CL-ODs), Specialist Nurses in Organ Donation (SN-ODs), and representatives of NHS Blood and Transplant (NHSBT). Following revision of the text, appropriate levels of evidence were added to the recommendations by editorial and author consensus. The draft of the document was placed on the BTS website in April 2015 for a period of open consultation, to which patient and transplant groups were actively encouraged to contribute. It was also externally reviewed by Professor David Grant, Professor of Transplantation at Toronto General Hospital, Canada. The final document was posted in July 2015.

Where available, these guidelines are based upon published evidence. With the exception of descriptive studies, the evidence and recommendations have been graded for strength. A small number of conference presentations have been included where relevant. Data relating to UK transplantation and outcomes were kindly provided by NHSBT. With minor exceptions where relevant results became available, the publication ‘cut off’ date for evidence was June 2014.

It is anticipated that these guidelines will next be revised in 2020.

1.3 Editorial Committee

Professor Derek Manas MD FCS (SA) FRCS
Professor of Transplantation & Director of the Institute of Transplantation, University of Newcastle-upon-Tyne and Newcastle NHS Trust
Co-Chair Living Liver Donor Editorial Committee

Ms Lisa Burnapp RN MA
Consultant Nurse, Living Donor Kidney Transplantation, Guys & St Thomas NHS Foundation Trust, London; Lead Nurse - Living Donation, Organ Donation and Transplantation, NHSBT
Co-Chair Living Liver Donor Editorial Committee

Dr Peter A Andrews MD FRCP
Reader in Renal Medicine & Clinical Lead for Transplantation, SW Thames Renal & Transplantation Unit, St Helier Hospital, Surrey
Chair BTS Standards Committee

1.4 Contributors and Collaborators

Dr Varuna Aluvihare, Consultant Hepatologist and Transplant Physician, King's College Hospital, London

Dr Peter Andrews, Consultant Nephrologist and Transplant Physician, St Helier Hospital, Surrey

Ms Lisa Burnapp, Consultant Nurse, Guy's & St Thomas' NHS Foundation Trust and Lead Nurse Living Donation, Organ Donation and Transplantation, NHSBT

Dr John Devlin, Consultant Hepatologist, King's College Hospital, London

Prof Nigel Heaton, Consultant in Hepatobiliary and Transplant Surgery, King's College Hospital, London

Dr Michael Heneghan, Consultant Hepatologist and Transplant Physician, King's College Hospital, London

Ms Jacqui Hennessy, Living Donor Liver Co-ordinator, King's College Hospital, London

Mr John Isaac, Consultant in Hepatobiliary and Transplant Surgery, Queen Elizabeth Hospital, Birmingham

Ms Julie Jeffery, Living Donor Liver Co-ordinator, St James' Hospital, Leeds

Dr Rebecca Jones, Consultant Hepatologist, St James' Hospital, Leeds

Prof Massimo Malagó, Consultant in Hepatobiliary and Transplant Surgery, Royal Free Hospital, London

Prof Derek Manas, Consultant in Hepatobiliary and Transplant Surgery, Freeman Hospital, Newcastle

Dr Patrick McKiernan, Consultant Paediatric Hepatologist, Birmingham Children's Hospital, Birmingham

Dr Stephen Potts, Consultant Liaison Psychiatrist, Edinburgh Royal Infirmary, Edinburgh

Mr Raj Prasad, Consultant in Hepatobiliary and Transplant Surgery, St James' Hospital, Leeds

Dr Phaedra Tachtatzis, Consultant Hepatologist, St James' Hospital, Leeds

Prof Steven White, Consultant in Hepatobiliary and Transplant Surgery, Freeman Hospital, Newcastle

1.5 Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in this aspect of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine.

These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool. It follows that the guidelines should be interpreted in the spirit rather than to the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient. The guidelines are not designed to be prescriptive, nor to define a standard of care.

The British Transplantation Society cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept any responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

1.6 Declarations of Interest

Editors, authors and contributors have worked to the standards detailed in the BTS Clinical Practice Guideline accessible at:

http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx (5).

1.7 Grading of Recommendations

In these guidelines, the GRADE system has been used to rate the strength of evidence and the strength of recommendations. This approach is consistent with that adopted by KDIGO in guidance relating to renal transplantation, and also with guidelines from the European Best Practice Committee, and from the Renal Association (3,4).

For each recommendation the quality of evidence has been graded as:

A (high)

B (moderate)

C (low)

D (very low)

For each recommendation, the strength of recommendation has been indicated as one of:

Level 1 (we recommend)

Level 2 (we suggest)

Not graded (where there is not enough evidence to allow formal grading)

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of the evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice and is similar to the approach adopted by KDIGO (4).

1.8 Definitions and Abbreviations

The following definitions and abbreviations are used in this document:

ALF	Acute liver failure
BASL	British Association for the Study of the Liver
BMI	Body mass index
BTS	British Transplantation Society
CILW	Calculated ideal liver weight
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CT	Computed tomography
DAT	Donor advocacy team
DBD	Donation after brain death
DCD	Donation after circulatory death
DDLT	Deceased donor liver transplantation
EBV	Epstein Barr virus
EU	European Union
EUODD	European Organ Donation Directive
GFR	Glomerular filtration rate
GBWR	Graft to body weight ratio
GW/RW	Graft weight to recipient weight
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HTA	Human Tissue Authority
HTLV	Human T lymphotrophic virus
IA	Independent Assessor
KDIGO	Kidney Disease: Improving Global Outcomes
LAG	Liver Advisory Group
LD	Living donor
LLD	Living liver donation
LLG	Left lobe graft
LDLT	Living donor liver transplantation
LHA	Left hepatic artery
LPV	Left portal vein
LT	Liver transplantation

MELD	Model for end-stage liver disease
MDT	Multidisciplinary team
MHV	Middle hepatic vein
MRI	Magnetic resonance imaging
NHSBT	NHS Blood and Transplant
OPTN	Organ Procurement and Transplant Network
PTLD	Post-transplant lymphoproliferative disorder
PV	Portal vein
RHA	Right hepatic artery
RLG	Right lobe graft
RLV/BWR	Remnant liver volume to body weight ratio
RLV/TLV	Remnant liver volume to total liver volume ratio
SCT	Sickle cell trait
SFSG	Small for size graft
SFSS	Small for size syndrome
SMA	Superior mesenteric artery
UCSF	University of California, San Francisco
UNOS	United Network for Organ Sharing
VTE	Venous thromboembolism

References

1. Porret PM, Olthoff KM. Clinical Liver Disease 2013; 2: 160-4.
2. Andrews PA. BTS Clinical Practice Guideline 2011. Accessed at: http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx
3. Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 70: 2058-65.
4. Kidney Disease Improving Global Outcomes (KDIGO) Transplant Work Group: KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9(S3): S1-157.

2 EXECUTIVE SUMMARY OF RECOMMENDATIONS

Legal Framework

- All transplants performed from living donors must comply with the requirements of the primary legislation (Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006) which regulate transplantation and organ donation across the United Kingdom. (Not graded)
- Consent for the removal of organs from living donors, for the purposes of transplantation, must comply with the requirements of the Human Tissue Act 2004, the common law for those under 16 years of age, and the Mental Capacity Act 2005 in England and Wales. Consent in Scotland must comply with the Human Tissue (Scotland) Act 2006 and the Adults with Incapacity (Scotland) Act 2000. (Not graded)

Ethics

- All health professionals involved in living donor liver transplantation must acknowledge the wide range of complex moral issues in this field and ensure that good ethical practice consistently underpins clinical practice. The BTS has an Ethics Committee to provide additional support and advice if required. (Not graded)
- Regardless of potential recipient benefit, the safety and welfare of the potential living donor must always take precedence over the needs of the potential transplant recipient. (Not graded)
- Independence is recommended between the clinicians responsible for the assessment and preparation of the donor and the recipient. In living liver donation, the donor advocacy team provides an essential safeguard for the potential donor, in addition to the Independent Assessor for the Human Tissue Authority. (Not Graded)

Indications for Living Donor Transplantation in Adults and Children

- Living donor liver transplantation (LDLT) must only be performed in specialist centres working with a multi-disciplinary transplant team. (1A)
- Decision making must be multi-disciplinary and meet the national standards for transplant services in the UK. (1A)
- The UK standard for transplant benefit, an overall graft and patient survival of >50% at five years, is the recommended standard for both deceased donor

liver transplantation (DDLT) and LDLT. As liver transplant units are currently achieving >75% survival at five years for all paediatric transplants, an overall five year patient survival of 70% is expected for paediatric LDLT recipients. (1B)

- All elective transplant listed patients are entitled to routine discussion about the option of LDLT, although centre experience should limit recipient selection for the first 20 cases. (1B)
- The same recipient factors that influence survival in DDLT must be considered for LDLT in both adults and children. The presentation of a potential living donor must not influence the decision. (Not graded)
- Adult and paediatric recipients with acute liver failure, whose risk of peri- or post-operative mortality is at the lower end of the clinical spectrum, can be considered for LDLT. (2B)
- Consideration of recipients for LDLT who do not meet indications as agreed through the NHSBT Liver Advisory Group (LAG), are subject to the national appeals process until such time as LAG have been able to consider such indications. (1A)
- The same selection contraindications apply for LDLT as for DDLT. LDLT recipient selection in patients with alcohol or substance misuse must follow UK NHSBT guidance. (1A)
- Recipients must be advised and supported to stop smoking pre-operatively and consideration given to not proceeding in the presence of ongoing smoking. (2B)
- Complete portal mesenteric vein thrombosis is an anatomical contraindication to LDLT. (1B)
- Patients with hepatitis C virus cirrhosis who meet current UK minimal listing criteria can be considered for LDLT. (1A)
- Potential recipients with hepatocellular carcinoma (HCC) who fall outside current UK guidelines (by tumour size and/or number) but who are within University of California San Francisco criteria and who also meet UK Alpha-fetoprotein guidance of <1000 ng/mL, can be considered for LDLT. (1B)
- In potential recipients with HCC, a three month interval scan must confirm good tumour biology before LDLT proceeds. Bridging therapies must be used during this interval. (2B)
- There is a lack of evidence about the long-term outcomes for recipients of liver transplants in some diseases e.g. alcoholism, cholangiocarcinoma, solitary

colorectal tumours. In these cases, experienced centres may wish to consider adult recipients for LDLT, with appropriate protocols, patient information and phased introduction. (Not graded)

- In diseases where long term outcomes are unclear due to lack of evidence or reproducibility of results, LDLT may offer an opportunity for ethically approved research studies within the UK, but LDLT should only be performed under that condition. (Not graded)
- ABO incompatible LDLT can be considered for paediatric recipients <3 years of age and for suitable adult recipients with appropriate protocols in experienced centres. (1B)

Informing the Donor and Donor Advocacy

- The living donor must be offered the best possible environment for making a voluntary and informed choice about donation. (Not graded)
- Potential donors should be provided with centre-specific complications rates. (Not graded)
- Relevant information about the recipient should be shared with the donor, provided that the recipient has given consent. The recipient must be informed that lack of permission for disclosure may jeopardise the transplant proceeding. In order to achieve the best outcome for donor, recipient and transplant, the boundaries of confidentiality must be discussed and specified at the outset. (Not graded)
- Independent assessment of the donor and recipient is a statutory requirement of the primary legislation (Human Tissue Act 2004). (A1)
- Separate clinical teams for donor and recipient are considered best practice and a donor advocacy team should be assigned to every potential living liver donor. Healthcare professionals must work together to ensure effective communication and co-ordination of the transplant process without compromising the independence of either donor or recipient. (Not graded)
- The donor must be informed that he/she may not be suitable to donate and/or can withdraw from the process at any time. In either case, appropriate support must be provided by the transplant team. (Not graded)
- Support for the prospective donor, recipient and family is an integral part of the donation/transplantation process. Psychological needs must be identified at an early stage to ensure that appropriate support and/or intervention is provided.

Access to specialist psychiatric/psychological services must be available for donors/recipients requiring referral. (B2)

Psychological Aspects

- All potential donors must undergo assessment by a mental health professional, preferably a member of the Donor Advocate Team. (B1)
- Mental health assessments can be undertaken by any suitably qualified mental health clinician. Centres with access to more than one type of clinician should direct referrals accordingly. Assessment by more than one professional may be appropriate in some cases. (D2)
- The purpose of mental health assessment is to:
    a) Identify potential donors who should be excluded from donation due to mental disorder or inappropriate motivation. (B1)
    b) Identify those who are more vulnerable to psychiatric risk and may need additional support after donation. (B1)
    c) Confirm capacity to consent. (B1)
    d) Explore motivation, particularly for altruistic donors. (B1)
- Mental health professionals undertaking these assessments should be familiar with the general issues that might arise in living donor transplantation, as well as organ-specific concerns. (Not graded)
- Clear referral routes to specialist mental health services must be identified for donors who later develop mental health problems. (C2)
- As part of the mental health assessment, it may be necessary to interview the donor's next of kin (other than the recipient). (B1)
- Particular consideration must be given to the mental health assessment and support for donors who donate to recipients in urgent need of a transplant. (Not graded)

Donor Evaluation

- Before starting donor evaluation:
    a) Establish recipient suitability. (A1)
    b) Provide information about alternative treatment options and potential outcomes. (A1)
    c) Ensure donor confidentiality is assured (Not graded)
- Identify unsuitable donors at the earliest possible stage of assessment. Initial donor triage can be performed using a standardised questionnaire by telephone

interview or online. (Not graded)

- Plan assessment around the donors' commitments and constraints wherever possible. The organisational details for evaluating a prospective donor will vary between centres, reflecting available resources and personnel. Evaluation must be undertaken according to an agreed protocol. (Not graded)
- Relay the outcome of investigations accurately, appropriately and efficiently to the potential donor. A designated senior coordinator facilitates optimal communication. (Not graded)
- Establish a policy for managing donors who are found to be unsuitable and provide appropriate follow-up and support. (Not graded)
- The pace of donor assessment may be tailored to the rate of decline of liver function, but this must not compromise donor safety nor the provision of adequate time for the donor. (A1)
- The timing of transplantation is optimised if donor evaluation is initiated early, allowing time for consideration of more than one donor where necessary. The pace of donor assessment must be tailored according to the rate of decline of recipient liver function, taking into account specific clinical and donor circumstances. (C1)

Donor Age

- There is no specific age beyond which donation is contraindicated, but the medical work-up of older donors must be especially rigorous. (Not graded)
- Both donor and recipient must be made aware that the older donor may be at greater risk of peri-operative complications. (Not graded)

Donor Obesity

- Any donor with body mass index (BMI) >30 kg/m^2 needs a liver biopsy because of the increased risk of donor hepatic steatosis and the possibility of steatohepatitis. (A1)
- Moderately obese donors (BMI 30-35 kg/m^2) should be counselled about the increased risk of peri-operative complications and long-term health risks. They should be advised to lose weight prior to donation and to maintain their ideal weight following donation. (B1)
- Donor BMI >35 kg/m^2 should be considered a contraindication to donation because of the high risk of post-operative complications. (B1)

Donor Hypertension

- Donors with well-controlled hypertension and no major end organ damage can be considered for living liver donation. (B1)

Donor Diabetes Mellitus

- In the absence of evidence of target organ damage and having ensured that other cardiovascular risk factors such as obesity, hypertension or hyperlipidaemia are optimally managed, potential donors with both type 1 and type 2 diabetes can be considered for living liver donation. (Not graded).

Donor Cardiovascular Evaluation

- All potential donors should be screened for cardiovascular disease and there should be a low threshold for their exclusion if significant risk factors are found. (B1)
- Potential donors with reduced exercise capacity or >5% estimated risk of significant coronary atherosclerosis should undergo formal cardiovascular assessment. (A2)
- Cardiopulmonary exercise testing should be available at all centres. (Not graded)

Donor Haematological Disease

- Patients with a personal or family history of bleeding or thrombosis should be screened for haematological abnormalities using evidence-based protocols. (A1)

Liver Integrity

- The donor must undergo comprehensive laboratory assessment. (A1)
- Imaging must assess fatty infiltration in addition to the biliary and vascular anatomy. (A1)
- Liver biopsy is indicated in the presence of biochemical, serological or imaging evidence of liver disease. (A1)
- The possibility of genetic liver disease in the donor requires specialist evaluation. (A1)
- When the cause of liver failure in the recipient is due to an inherited condition, reasonable steps must be taken to exclude genetic disease in the potential donor if he/she is a blood relative. (B1)

- Inherited liver disorders are rare, so a specialist paediatric hepatologist or clinical genetic service must assess likely risks to family members. (B2)
- The discovery of a potential familial or genetic risk must be conveyed to the donor, with advice on sharing this information with appropriate family members. (B2)

Donor-Recipient Transmissible Disease: Infection

- Infection screening is important to identify potential risk for the donor from previous or current infection and to assess potential risk of transmission to the recipient. (A1)
- Active hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are contraindications to donation. HBV core antibody positive patients and HCV antibody positive/HCV RNA negative patients can be considered as liver donors in exceptional circumstances. (A1)
- Cytomegalovirus or Epstein Barr Virus positivity is not a contraindication to donation but counselling must be provided re the risk of primary infection and lymphoproliferative disorder. (B1)
- Human immune deficiency virus or human T lymphotrophic virus infection is an absolute contraindication to donation. (A1)

Donor-Recipient Transmissible Disease: Malignancy

- Careful history taking, clinical examination and investigation of potential donors are essential to exclude occult malignancy, particularly in older (age >45 years) donors. (A1)
- Active malignant disease is a contraindication to living donation, but donors with certain types of successfully treated low-grade tumours may be considered after careful evaluation and discussion. (A1)
- Axial imaging of the abdomen by CT or MR examination is mandatory, with specific liver review for secondary malignant disease. (A1)

Donor Surgery

- Computerised tomography (CT) or magnetic resonance imaging (MRI) of the donor liver with intravascular contrast must be performed. (A1)
- 3D reconstructions, using either in house or propriety software, are recommended to create detailed 3D models of liver anatomy for volumetric analysis and determination of vascular/biliary anatomy. (B1)

- Conventional arteriography and hepatic venography must only be used in exceptional circumstances when conventional enhanced CT fails to give adequate imaging information. (B1)
- Magnetic resonance cholangiopancreatography (MRCP) is the gold standard for biliary anatomy. Endoscopic retrograde cholangiopancreatography (ERCP) must not be used to assess biliary anatomy. CT cholangiography or intra-operative cholangiography are suitable alternatives. (B1)
- Steatosis assessment:
  - Ultrasound can be used as a screening tool. MRI provides a better assessment in grading steatosis than CT and is the preferred option. (A1)
  - With CT, the liver-to-spleen attenuation ratio (difference between hepatic and splenic attenuation) and blood-free hepatic parenchymal attenuation must be used. The maximum amount of steatosis is not well defined but acceptable limits range from 10–30%. (B1)
- For volume calculation, the percentage of steatosis must be subtracted from the estimated liver mass for the graft. (C2)
- Liver biopsy is reserved for the potential donor with unexplained abnormalities in liver function tests, BMI approaching 30 kg/m^2, or aspartate aminotransferase (AST) > alanine transaminase (ALT). (B2)
- For donors who are initially rejected due to steatosis, a low calorie ‘defatting diet’ and reassessment with new volumetry can be considered. (B1)
- For calculation of donor graft volume, software-assisted image post processing is recommended as it provides the most accurate method of assessment. (A1)
- In calculating the standard liver volume of the recipient, published formulae with error rates of <10% must be used. (1B)
- In adults, the choice of donor graft is aimed at reducing donor risks by achieving a large remnant volume, i.e. a small resection. A left graft should usually be considered first. (B1)
- A graft weight/standard liver volume of 40% is the acceptable lower limit. If <40%, outflow and inflow modulation techniques must be used. (B1)
- Using small for size grafts (graft weight to recipient weight (GW/RW) ratio <0.8) can result in good outcomes but caution is advised in decompensated patients. (B1)
- It is widely accepted that the absolute minimum donor remnant volume is 30%. (A1)

- To avoid congestion in segment 5/8 for a right lobe graft, a “with middle hepatic vein graft” or venous reconstruction of the anterior segment with an interposition vein graft is mandatory if the volume of the graft is borderline for the recipient and the portal pressures are elevated. (B1)
- The left graft can be procured with the left and the middle hepatic vein, particularly when the GW/RW ratio is low and extra liver volume is required to meet the metabolic demands of the recipient. (A2)
- Although good outcomes have been reported from small series using laparoscopic or laparoscopy-assisted donor hepatectomy for the left lateral and left lobe, open donor hepatectomy is recommended in the interests of donor safety. (B1)
- If the operating surgeon encounters an unexpected finding that, in his/her opinion, jeopardises the safety of the donor, donation must not proceed. (B1)
- If a graft is explanted and cannot be used, a policy to utilise the organ must be in place. The donor must be informed in advance about this possibility and pre-operative consent should be obtained to use the graft for another recipient. (B1)
- For the purposes of consent, information about all aspects of morbidity and mortality associated with living liver donation must be provided. For new programmes, international statistics on morbidity and mortality must be used and the centre must make it known to the donor that it is an ‘emerging’ programme. For established programmes (>20 cases per year), centre-specific activity and morbidity and mortality data must be provided during the donor consent process. (B1)
- A two stage consent process is best practice to ensure that the donor can give valid consent based upon the information provided. (B1)
- The donor may choose to withdraw consent at any time prior to donation and the reasons must remain confidential. (B1)

<u>Recipient Surgery: Technical Aspects, Risk and Perioperative Care for Adults and Children</u>

- Standardisation of surgical techniques is limited. (Not graded)
- Techniques for left lateral segment paediatric living donor liver transplantation are the same as for deceased donor liver transplantation. (2A)
- Specific attention in recipient assessment is given to the anatomy of the vasculature and biliary tree to enable planning of surgery. Issues to be

addressed include the proximity of cancer to vascular structures, portal vein thrombosis, and a detailed vascular anatomy of inflow and outflow structures in recipients considered for re-transplantation. (1B)

- Predicting graft size must rely on preoperative volumetry with the understanding that predicted values often overestimate the size of the graft by a margin of 10 to 20%. (1B)
- University of Wisconsin (UW) and Histidine-tryptophan-ketoglutarate (HTK) solutions are equally effective for perfusion of the graft. (1A)
- In recipient surgery, hilar dissection differs significantly from deceased donor liver transplantation. Every attempt should be made to preserve as long a length of the hilar structures as possible and to avoid de-vascularising the extra-hepatic common duct. (1B)
- Optimising venous outflow is essential to improve graft function. In grafts that are considered small for size (GW/RW ratio <0.8), aim to bring the portal pressure to <20 and preferably 15 mmHg, especially in patients with high MELD. (1B)
- The hepatic arterial, portal venous and venous outflow must be assessed with Doppler ultrasound prior to abdominal closure. (2A)
- Management of early venous outflow problems can be challenging, especially with venous reconstructions from segment 5 and 8 veins. Interventional radiology is superior to surgical intervention in management of these venous outflow problems. (1B)

<u>Outcomes</u>

- As for deceased donor liver transplantation, only recipients with >50% five year survival can be considered for living donor living transplantation. (2A)
- Adult-to-adult LDLT is associated with a significant learning curve within the first 20 cases. All emerging centres must have access to mentoring over this period. (1B)
- 21% is an acceptable overall complication rate for donors following left hepatic lobectomy. (1B)
- There is a 40% risk of complications in the first year following right living donor lobectomy. (1B)
- Reporting of donor death and morbidity is mandatory via the NHSBT incident reporting process. (2A)

- In the event of donor death:
  a) Root Cause Analysis must be performed to identify possible causes and the centre LDLT programme suspended pending the outcome of the investigation. (2B)
  b) A documented national disaster and media communication plan agreed by all centres performing LDLT must be followed. (2B)
- Recipient outcome and graft survival at 12 months following LDLT must be at least equivalent to that from DDLT. (1B)
- It is accepted that the frequency of biliary complications in LDLT recipients is 25% to 35%, which is higher than in DDLT. (1B)

Expanding the Donor Pool

- Left lobe liver grafts can only be considered in low risk recipients. (2B)
- Left lobe liver grafts can be used if the graft size is at least 40% of the recipient's standard liver volume and achieves a GW/RW ratio of >0.8. (2C)
- If the GW/RW ratio is <0.8 or the graft size is less than 35%, a right lobe graft must be considered. If this is not possible, graft inflow modulation should be considered. (2B)
- Dual living donor living transplants have only been performed in highly specialised, high volume centres. (Not graded)
- Dual transplants are indicated when the donor's left lobe is too small to meet the metabolic demands in the larger recipient, e.g. GW/RW ratio <0.8, or the graft volume to standard liver volume (GV/SLV) is <40%. (C2)
- Dual transplants can also be used when a potential right lobe graft makes up >70% of the donor's total liver volume meaning the remnant left lobe volume (<30%) would put the donor at risk of small for size syndrome after donation. (C2)
- Altruistic living donation of part of a liver can be considered in low risk individuals. (C2)
- If a potential liver donor has previously donated another organ, the transplant centre should ask the patient for permission to contact he original transplant team to ensure that there are no concerns re mental or physical suitability for donation. (Not graded)
- The donor assessment must comply with Human Tissue Authority (HTA) requirements and include a review by an Independent Assessor. (A1)

- Mental health assessment by a mental health expert is compulsory and best performed at an early stage in the donor assessment. (C1)
- ABO blood group incompatible (ABOi) living donor liver transplants must only be performed in centres with considerable experience of both LDLT and ABOi kidney transplantation and using an established protocol. (B1)
- ABOi LDLTs should only be considered when all other options have been excluded e.g. deceased donor liver transplantation or living donor ABO compatible liver transplantation. (B1)
- There is insufficient evidence and limited experience to make precise recommendations for ABOi treatment protocols. (Not graded)

Donor Follow Up

- Life-long follow-up is recommended after donor hepatectomy. For donors who are resident in the UK, this can be offered locally or at the transplant centre according to the wishes of the donor, but such arrangements must facilitate the collection of data for submission to the UK Living Donor Registry. Donors from overseas who travel to the UK to donate (privately or to a NHS entitled recipient) are not entitled to NHS follow-up but must be given advice about appropriate follow-up before returning to their country of origin. (C1)
- Potential donors who are unable to proceed to donation must be appropriately followed up and referred for further investigation and management as required. (B1)

Logistical Considerations

- Wherever possible, the aim must be to ensure that the financial impact on the living donor is cost neutral by the reimbursement of legitimate expenses incurred as a direct result of the preparation for and/or act of donation. There is a clear UK policy for claiming such expenses, which must be followed so that claims may be settled in full and in a timely manner (B1)
- Donors from overseas present unique logistical challenges. To ensure the process is clinically effective and to comply with Visa and Immigration requirements, there is an agreed visa application process and duration of stay in the UK (six months) for the donor which must be honoured except in exceptional or unforeseen circumstances. (B1)

3 LEGAL FRAMEWORK

Statements of Recommendation

- ***All transplants performed from living donors must comply with the requirements of the primary legislation (Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006) which regulate transplantation and organ donation across the United Kingdom. (Not graded)***

- ***Consent for the removal of organs from living donors, for the purposes of transplantation, must comply with the requirements of the Human Tissue Act 2004, the common law for those under 16 years of age, and the Mental Capacity Act 2005 in England and Wales. Consent in Scotland must comply with the Human Tissue (Scotland) Act 2006 and the Adults with Incapacity (Scotland) Act 2000. (Not graded)***

The Human Tissue Act 2004 (1) is the primary legislation regulating transplantation in England, Wales and Northern Ireland. This repeals and replaces all earlier relevant legislation (2,3,4). Separate legislation, the Human Tissue (Scotland) Act 2006 (5), applies in Scotland.

3.1 The Human Tissue Act 2004

The Human Tissue Act (2004) sets out the licensing and legal framework for the storage and use of human organs and tissue (excluding gametes and embryos) from the living and for the removal, storage and use of human organs and tissue from the deceased. It permits authorised activities to be carried out for certain scheduled purposes. The Act covers seven scheduled purposes requiring general consent, one of which is transplantation, and this incorporates living donor transplantation (6).

Authorised activities, including transplantation, are only lawful if done with ‘appropriate consent’ (7). Unauthorised dealings may result in offences which carry penalties (8). Codes of practice establish guidelines for practice, particularly with regard to the meaning and extent of ‘appropriate consent’ (9).

3.2 The Human Tissue Authority (HTA)

The Human Tissue Authority (HTA) was established as the regulatory body under the 2004 Act (10). The HTA regulates the removal, storage, use and disposal of human bodies, organs and tissue from the deceased and the storage of human organs and tissue (excluding gametes and embryos) from the living (11,12). The HTA is responsible for assessing all applications for organ donation from living people, including lobe of liver transplantation. This involves an independent assessment process. All donors and recipients see an Independent Assessor (IA) who is trained and accredited by the HTA and acts on behalf of the Authority to ensure that the donor has given valid consent and that reward is not a motivating factor in the donation. If the HTA is satisfied on these matters then approval for the living donation will be given. Clear guidance about the roles and responsibilities of the transplant team and Independent Assessors in the context of living donation is published and regularly updated by the HTA (13).

3.3 European Organ Donation Directive

The European Organ Donation Directive (EUODD) came into effect in August 2012 (14). The EUODD was implemented to standardise systems and processes across all member states to improve the quality and safety of human organs intended for transplantation. It is the first pan-European regulatory framework governing the donation and transplantation of organs from the living and deceased and includes common standards for the procurement, transportation, traceability, characterisation and follow-up of donated organs across the EU.

The HTA is the Competent Authority for the UK under the EUODD. Every donating and/or transplanting hospital is licensed by the HTA to perform specified activities related to the donation and/or implantation of a donated organ (15).

3.4 Consent for the Removal of Organs from Living Donors

Seeking consent for the removal of organs from living donors, for the purposes of transplantation, is the responsibility of the treating clinician. Part of the HTA's statutory assessment process is to ensure that valid consent has been given by the donor (16).

The common law and Mental Capacity Act 2005 also applies for minors and those who lack capacity to give valid consent (17).

3.5 Types of Living Donation Permitted by the Legislation

In September 2012, the HTA published a revised legal framework which specifies the types of relationships that are permitted between the living donor and recipient under the Human Tissue Acts (13).

1. Directed donation

   Also known as 'specified donation' in EU member states, a form of donation where a healthy person donates an organ or part of an organ to a specific recipient. This includes:

   (i) Genetically related donation: where the potential donor is a blood relative of the potential recipient;

   (ii) Emotionally related donation: where the potential donor has a relationship with the potential recipient; for example, spouse, partner, or close friend;

   (iii) Paired donation: where a relative, friend or partner is fit and able to donate an organ but is incompatible with the potential recipient and they are matched with another donor and recipient in a similar situation, so that both people in need of a transplant receive a compatible organ;

   (iv) Pooled donation: a form of paired donation whereby the pair are matched with other donors and recipients from a pool of pairs in similar situations, and more than two donors and two recipients are involved in the swap, so that more than two people in need of a transplant receive a compatible organ.

2. Non-directed altruistic donation

   Also known as 'unspecified donation' in EU member states, a form of living donation whereby an organ or part of an organ is donated by a healthy person who does not have a relationship with the recipient and who is not informed whom the recipient will be.

3. Directed altruistic donation

   A form of living donation whereby an organ or part of an organ is donated by a healthy person and contact between the donor and recipient has been made

because the recipient requires a transplant. Within the HTA framework, these donors are categorised as follows:

(i) Genetic relationship and no established emotional relationship (e.g. donors who have not seen their relative for many years; relative with whom there has been no contact previously)

(ii) No pre-existing relationship between donor and recipient prior to the identification of the recipient's need for a transplant (i.e. contact through social networking or media campaigns)

3.6 Requirements for Transplants Involving a Living Donor

Restrictions on living donor transplants and requirements for information about transplant operations are set out in Part 2, sections 33 and 34 of the Human Tissue Act 2004 respectively (18) and sections 9-14 of the Regulations (16). It is an offence to remove or use an organ from the body of a living person for transplantation unless the requirements of the 2004 Act and the Regulations are met.

The Regulations require that all living donations for organ transplantation must be approved by the HTA before donation can take place and, prior to giving approval, the Authority must be satisfied that:

1. No reward has been, or is to be, given;
2. Consent to removal for the purpose of transplantation has been given (or removal for that purpose is otherwise lawful);
3. An Independent Assessor (IA) has conducted separate interviews with the donor (and if different from the donor, the person giving consent) and the recipient (or the person acting on behalf of the recipient) and submitted a report of their assessment to the HTA.

In cases of directed genetically or emotionally related donation, the HTA requires that evidence of relationship is provided to confirm that the relationship between donor and recipient is as stated. At the time of writing, the decision on whether a transplant proceeds must be made by an HTA panel of at least three members in all cases where there is perceived to be a higher regulatory risk. These include:

- paired and pooled donation
- non-directed altruistic living donation

- directed altruistic donation cases where the donor is travelling from overseas
- certain directed donation cases where the donor has an economic dependence on the recipient
- if the organ donor is a child
- if the organ donor is an adult who lacks capacity

In emergency cases of living donor liver transplantation, e.g. rapid decline in recipient condition, the HTA provides an out-of-hours emergency telephone approval service via the executive.

The HTA also requires the living donor to specify how they wish their donated organ or part organ to be used should it not be possible to transplant it into the intended recipient. The donor is asked to explicitly consent to one of a range of options which include implantation into another recipient, re-implantation back into the donor, or disposal of the organ. Typically, this consent is taken during discussion with the surgeon and the donor's wishes are recorded prior to the independent assessment for the HTA.

3.7 Prohibition of Commercial Dealings in Human Material

Section 32 of the Human Tissue Act 2004 prohibits commercial dealings in human material, including organs for transplantation (19). Unless designated by the HTA to carry out such activity, a person is committing an offence if they:

1. Give, offer or receive any type of reward for the supply or offer of supply of an organ or part of an organ;
2. Look for a person willing to supply an organ or part of an organ for reward;
3. Offer to supply an organ or part of an organ for reward;
4. Initiate or negotiate any arrangement involving the giving of a reward for the supply of, or for an offer to supply, an organ or part of an organ for transplantation;
5. Take part in the management or control of any type of group whose activities consist of or include the initiation or negotiation of such arrangements;
6. Cause to be published or distributed, or knowingly publish or distribute, any type of advertisement inviting people to supply, or offer to supply, an organ or

part of an organ for reward, or indicate that the advertiser is willing to initiate or negotiate any such arrangements.

The following terms apply:

- 'Transplantable material' is defined in Part 3, sections 9 and 10 of the regulations and includes living donor liver lobes for transplantation (20);
- 'Relevant Material' is material, other than gametes, which consists of or includes human cells;
- 'Advertisement' includes any form of advertising for reward, whether to the public generally, to any section of the public, or individually to selected persons;
- 'Reward' means any description of financial or other material advantage.

In July 2014, the UK also adopted the Council of Europe Convention against Trafficking in Human Organs (21). This is the first legal document that provides an internationally agreed upon definition of trafficking in human organs, identifying the activities that ratifying States must criminalize in their national laws. It also includes provisions to deter these practices and to protect victims.

3.8 Reimbursement of Expenses

The Human Tissue Act 2004 (22) allows donors to receive reimbursement of expenses, such as travel costs and loss of earnings, which are reasonably attributable to and directly result from donation (see section 14.1).

3.9 Exceptional Circumstances

3.9.1 Children

The Human Tissue Act 2004 defines a child as a person under 18 years old (22). In England and Wales the legal position regarding consent by minors (under the age of 18 years) to medical treatment is determined in case law by '*Gillick'* (23). It could be argued that organ donation is not, *prima facie,* in the best interests of the minor as a potential donor, nor is it therapeutic treatment. However, if the young person is *'Gillick* competent' (understands fully what is proposed and is capable of making a choice in his/her best interests) in principle, he or she may be able to consent to donation.

However, children should only be considered as living organ donors in exceptionally rare circumstances. As a minimum, good practice demands that parental consent is always obtained and, even if there is parental consent to donation, that an advanced ruling be sought from the High Court before proceeding. The use of a living organ from a child can only proceed with court approval followed by approval from an HTA panel (22).

3.9.2 Adults without Mental Capacity

The removal of an organ or part organ from an adult who lacks the capacity to consent to such a procedure requires court approval (16). Following court approval donation may then only proceed if the case is approved by an HTA panel.

3.10 The Human Tissue (Scotland) Act 2006

The purpose of the 2006 Act (5) is to make provision for activities involving human tissue in the context of transplantation, research and education, its removal, retention and use following post mortem examinations, and for the purposes of the Anatomy Act (1984), which is incorporated into the 2006 Act. Provisions of the Human Tissue Scotland Act are based on ‘authorisation’ (24) rather than ‘appropriate consent’ as in the Human Tissue Act 2004 (6), but the principles in each Act are essentially the same.

In living organ donation, the 2006 Act replicates the 2004 Act and stipulates that the removal and use of organs, parts of organs or tissue from the body of a living person for use in transplantation constitutes an offence unless certain conditions are satisfied. The 2006 Act specifies that the donor must give consent, without coercion or reward, for the removal of organs to take place. Restrictions on transplants involving living donors are set out in section 17 of the 2006 Act (25). These provisions are supplemented by the Human Organ and Tissue Live Transplants (Scotland) Regulations 2006 (the Scottish Live Transplants Regulations) (26) Prohibitions of commercial dealings in parts of a human body for transplantation are set out in section 20 of the 2006 Act (27).

Although not governed by the 2006 Act, under arrangements made between the Scottish Executive and the HTA, potential living donors are assessed by the HTA to ensure that there is no evidence of coercion or financial reward, as in other parts of the United Kingdom. The 2006 Act also includes provision for paired exchange kidney transplant programmes and altruistic donation.

Exceptional Circumstances

Under Scottish legislation children are defined as persons who have not yet reached the age of 16 years. The principle of competency of children under 16 years to consent to procedures is incorporated into Age of Legal Capacity Act (Scotland) 1991 (28) which states that 'A person under the age of 16 years shall have legal capacity to consent on his own behalf to any surgical, medical or dental procedure or treatment where, in the opinion of a qualified medical practitioner attending him, he is capable of understanding the nature and possible consequences of the procedure or treatment'. The Children (Scotland) Act 1995 endorsed this principle. The Adults with Incapacity (Scotland) Act 2000 governs adults without capacity to make their own decisions in Scotland (29).

The Human Tissue (Scotland) Act 2006 prohibits the donation of non-regenerative tissue such as kidneys and liver lobes by minors (under 16 years of age) and adults lacking capacity (30).

References

1. Human Tissue Act 2004. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1
2. The Human Tissue Act 1961.
3. The Anatomy Act 1984.
4. Human Organ Transplant Act 1989.
5. The Human Tissue (Scotland) Act 2006. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_1
6. The Human Tissue Act 2004. Part 1 of Schedule 1 of the 2004 Act. http://www.opsi.gov.uk/acts/acts2004/40030--e.htm#sch1
7. Human Tissue Act, section 3.
8. Human Tissue Act 2004, section 5.
9. Human Tissue Act 2004, section 26.
10. Human Tissue Act 2004, Part 2, sections 13-15.
11. The Human Tissue Authority. www.hta.gov.uk
12. The Human Fertilisation and Embryology Authority www.hfea.gov.uk.
13. Guidance for Transplant Teams and Independent Assessors. http://www.hta.gov.uk/_db/_documents/Guidance_to_Transplant_Teams_and_Independent_Assessors_201209105840.pdf

14. Directive 2010 /45/EU of the European Parliament and of the Council of 7 July 2010. http://www.hta.gov.uk/_db/_documents/EUODD_Directive_August_2011.pdf
15. Organ Donation Directive - The Human Tissue Authority. http://www.hta.gov.uk/organdonationdirective.cfm
16. Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants). Regulations 2006. www.opsi.gov.uk/si/si2006/20061659.htm
17. Mental Capacity Act 2005. www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1
18. Human Tissue Act 2004 Part 2, section 33-34. http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb5-l1g32
19. Human Tissue Act 2004 Part 32. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb6
20. Human Tissue Act 2004 Part 3, section 54. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_5#pt3-pb2-l1g54
21. http://www.declarationofistanbul.org/resources/recommended-reading/the-council-of-europe-convention-against-trafficking-in-human-organs.
22. Human Tissue Act 2004 Part 2. http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb5-
23. Gillick v West Norfolk & Wisbech Area Health Authority and Department of Health & Social Security (1985).
24. The Human Tissue (Scotland) Act 2006, sections 6-10. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_2#pt1-pb2-l1g6
25. The Human Tissue (Scotland) Act 2006, section 17. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_3#pt1-pb3
26. Human Organ and Tissue Live Transplants (Scotland) Regulations 2006 (the Scottish Live Transplants Regulations). www.oqps.gov.uk/legislation/ssi/ssi2006/ssi_20060390_en_1
27. The Human Tissue (Scotland) Act 2006, section 20. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_3#pt1-pb5-l1g20
28. Age of Legal Capacity Act (Scotland) 1991. http://www.legislation.gov.uk/ukpga/1991/50/contents
29. Adults with Incapacity (Scotland) Act 2000. www.opsi.gov.uk/legislation/scotland/acts2000/asp_20000004_en_1
30. The Human Tissue (Scotland) Act 2006. http://www.legislation.gov.uk//asp/2006/4

4 ETHICS

Statements of Recommendation

- ***All health professionals involved in living donor liver transplantation must acknowledge the wide range of complex moral issues in this field and ensure that good ethical practice consistently underpins clinical practice. The BTS has an Ethics Committee to provide additional support and advice if required. (Not graded)***

- ***Regardless of potential recipient benefit, the safety and welfare of the potential living donor must always take precedence over the needs of the potential transplant recipient. (Not graded)***

- ***Independence is recommended between the clinicians responsible for the assessment and preparation of the donor and the recipient. In living liver donation, the donor advocacy team provides an essential safeguard for the potential donor, in addition to the Independent Assessor for the Human Tissue Authority. (Not Graded)***

4.1 Ethics

Living donor transplantation has become a well-established practice in the UK, contributing more than a third of all organ transplants. Living donor transplantation trebled from 2000-10, mostly in living donor kidney transplantation. At the time of writing, 3% of living donors donate a lobe of liver, this representing a small but growing trend in the UK (1). By its nature, living donor organ transplantation raises a wide range of complex ethical issues. As transplant programmes continue to expand, all health professionals involved in living donor transplantation must be familiar with the general principles that underpin and are applicable to good ethical practice (2-7).

4.2 Key Ethical Principles in Living Donor Transplantation

Altruism has been the basis of organ donation in the UK from the outset and is understood as a selfless gift to others without expectation of remuneration (8). Altruistic giving may be to strangers or take place within the context of family or other relationships. Altruism reinforces the philosophy of voluntary and unpaid donation and solidarity between donor and recipient. There are some concerns that altruism may be compromised by hidden coercive pressures; for example, the expectation that a family member will donate an organ to help another family member in need of a transplant (9). These pressures may be exacerbated by a sense of urgency to transplant a recipient whose clinical condition is rapidly deteriorating, which can be the case in the context of living donor liver transplantation.

Autonomy is the right of an individual to self-determination. Autonomy underpins our entitlement to control our own body, because it is 'ours'. Valid consent must be given by the living donor before an organ can be removed; a primary aim is that such decisions are freely and autonomously made to offset concerns about coercion and 'undue inducement' that undermine valid consent.

Beneficence refers to actions that promote the wellbeing of others. In medicine this means taking actions that serve the best interests of patients.

Dignity is often associated with the Kantian concept of the inherent dignity, or special status, of the human body. According to Kant, dignity and price are mutually incompatible: the maintenance of human dignity requires human beings to be beyond negotiable price (10). If this view is accepted, any form of financial payment or 'commodification' of bodies or body parts constitutes a violation of human dignity, even if the person concerned does not personally feel in any way degraded. This view is strongly challenged by some who argue that 'degradation very much depends on one's own perception of what is degrading' (11).

Non-maleficence is the principle of 'doing no harm' and it is based on the Hippocratic Oath maxim 'abstain from doing harm'.

Reciprocity refers to providing benefits or services to another as part of a mutual exchange. For example, reciprocity underpins paired/pooled living donor kidney transplantation in which donor/recipient 'pairs' enter into a reciprocal arrangement with each other, and also domino donation in which an organ or part of an organ from a living donor may be donated for the benefit of another as part of a therapeutic procedure for the donor.

4.3 The Recipient Perspective

The rationale for living donor liver transplantation and the risk versus benefit to the recipient are detailed elsewhere in these guidelines. A deceased donor liver transplant would almost always be the preferred option, particularly for an adult recipient. However, in the absence of a suitable alternative, a living donor liver transplant may offer a life-saving or life-enhancing choice for some patients who would otherwise die or become ineligible for transplantation whilst waiting. For some children, e.g. with primary hyperoxaluria, living donation offers a unique opportunity to minimise disruption to growth, development and school, by planning sequential living donor liver and kidney transplant procedures from one or two family members over the period of a few weeks or months.

Regardless of recipient benefit, living donation can only be justified if the interests of the donor are given primacy. The safety and welfare of the potential living donor must always take precedence over the needs of the potential transplant recipient.

4.4 The Donor Perspective

Donating a lobe of liver involves a detailed process of investigation, major surgery, and a significant period of recovery. Whilst there are documented overall benefits for the individual donor and wider society, living donor liver surgery entails risk, which includes a small risk of death (see section 11.2). In addition, removal of a lobe of liver will inevitably cause physical harm, to a lesser or greater extent, to the donor. This conflicts with the concept of non-maleficence and the maxim ‘first, do no harm’ and is often invoked as a powerful argument against it. However, this does not take into account of other moral considerations such as individual autonomy, which may contribute to an individual’s decision and motivation to donate. Further, although there is no physical benefit from the act of donating an organ or part of an organ for transplantation, donors often gain psychological benefit knowing that their gift has provided an opportunity to dramatically improve the quality of life of a relative, friend or stranger (12). It could be argued that a potential living donor may be psychologically harmed if his/her donation, for whatever reason, does not take place.

The principle of autonomy provides a legitimate basis for supporting living donation. Living donor surgery is morally acceptable when carried out with ‘informed consent,

freely given' (see section 6.2) but establishing 'informed consent freely given' can be problematic. While all living donor programmes expect potential donors to be given an appropriate, detailed description of the risks of donation, it is much less clear that all such donors will listen. There is a well-described tendency for some people to decide that they wish to donate at an early stage and then to be impervious to or oblivious of any suggestion that they should make a more informed decision following counselling (13). The consent may be real, but whether it is truly informed may be questionable.

The only person who can know that consent is 'freely given' is the living donor. While it may be possible to identify the donor who has come under overt pressure or coercion, from either the recipient or from other family members, more subtle pressures may not be revealed and/or remain undetected by health care professionals. These may make it difficult or impossible for a potential donor not to proceed through the assessment process.

It is important to recognise that the concept of 'Informed consent, freely given' will vary according to the donor-recipient pair involved. In most situations, the motives and autonomy of the donor will be beyond question but, in others, it can be more difficult to establish that consent is both informed and freely given. For this reason, independence between the clinicians responsible for the donor and the recipient is strongly recommended. In living liver donation, the donor advocacy team provides an essential safeguard for the potential donor in addition to the Independent Assessor for the Human Tissue Authority (see sections 6.3 and 6.4).

4.5 The Transplant Team Perspective

A major role of the transplant team is to inform the potential donor of the risks associated with living liver donation. In circumstances where the transplant team has concerns about the medical suitability of a potential donor and feels that proceeding with donation is inappropriate, the team is under no obligation to proceed.

In this situation, it is important to recognise that members of the transplant team have individual rights as well as professional responsibilities. If a fully informed potential living donor wishes to proceed with a course of action that involves risks that goes beyond that which individuals or the team find acceptable or appropriate, they are

under no obligation to proceed. Referral for a second opinion may be appropriate in such circumstances.

The transplant team also has an obligation to utilise organs that are made available for transplantation in ways that benefit the whole patient pool most. An area of controversy in living liver donation is the possibility that the transplanted liver lobe may fail in the recipient at or shortly after transplantation. This creates an urgent need for the recipient to receive a deceased donor graft, thereby prioritising him/her on the deceased donor list in competition with equally urgent potential recipients. This is particularly problematic if the recipient of the living donor graft is transplanted for a less urgent reason/condition (e.g. hepatocellular carcinoma) or if the recipient is an overseas donor who is then rendered dependent on a further transplant within the UK.

4.6 Confidentiality

Both the donor and recipient have a right to a confidential relationship with their respective clinicians and clinical teams have a duty to respect that right. This is particularly relevant to living donor transplantation because the uniqueness of the donor-recipient scenario creates a novel proximity between all parties involved.

It is important that boundaries are made explicit from the outset and that there are realistic expectations on both sides about what information can be shared between all parties and what is confidential to each individual. It may be assumed that both parties have an equal right to information about one another, but information should only be shared if express consent is given by either donor or recipient. It is advisable to have this discussion at an early stage and to ensure that the wishes of both donor and recipient are known to each other and to their respective clinical teams to avoid any possible misunderstanding or breach of confidentiality (see section 6.1).

The same principles should be applied to keeping and maintaining clinical records for recipients and donors. A separate clinical record should be maintained for each party. There are no grounds for amalgamating complete recipient and donor records or for maintaining joint clinical documentation. Nor should it be routine practice to file copies of results or correspondence relating to the potential donor in the potential recipient's notes, or vice versa.

It may be necessary to share information that is directly relevant to the management or performance of the transplant. Examples would include ABO blood group and recipient diagnosis (for consideration of recurrent/hereditary disease that might impact on graft or patient survival). It is accepted that essential information will be shared between clinical teams in the best interests of both parties when it has a direct bearing on the outcome of the transplant or donation (e.g. liver anatomy, function and size) and is material to the decision making process. Access to such information should be made available via the transplant centre for the purposes of long-term follow-up.

Information regarding a donor's identity and their genetic relationship with the potential recipient may become available during the living donor transplantation work-up. There may be occasions when this information, quite unexpectedly, identifies that a genetic relationship may have been misattributed. The potential personal, social and cultural implications of this for may be devastating both donor and recipient and the effects of receiving such information should not be underestimated. Donors and recipients may or may not wish to be informed (see section 6.3). Particular care is required to ensure that material is not inadvertently shared or filed in such circumstances.

If a potential donor wishes to withdraw from the transplant process at any time, the primary responsibility of the donor assessment team is to support him/her to do so. The team should not feel under pressure to provide a 'medical reason' for withdrawal in order to offer the recipient a plausible explanation as to why the donor is 'unsuitable' (see section 6.2).

4.7 Expanding the Living Donor Pool

The options for living donor transplantation in the UK have expanded rapidly over the years in line with technological advances, changes in the legal framework, and development of clinical practice. In living liver donation, this includes dual living liver grafts, use of left lobe grafts in adult recipients, non-directed altruistic (unspecified) donation and development of antibody incompatible transplantation for ABO blood group incompatible pairs. There are unique ethical considerations in each of these areas, which are discussed section 12.

4.8 The Child or Young Person as a Living Donor

Minors (under the age of 18 years) should rarely, if ever, be considered as potential living donors because of concerns about autonomy and the validity of consent from young people in this situation (see section 3).

In living donor kidney transplantation, some regard the use of an identical twin as an acceptable child donor, on the basis that the outcome for the recipient twin is exceptional and because the relationship between identical twins is so close that restoring the health of the recipient confers major psychological benefit for the donor (14). This view is highly controversial and has been challenged (15,16). The British Medical Association has previously expressed the view that 'it is not appropriate for live, non-autonomous donors (minors) to donate non-regenerative tissue or organs' (17). Although it could be argued that this may not be a relevant exclusion in living liver donation *per se*, the most compelling argument for not using a child donor in this context is the ability to fully understand the risks and, hence, validity of consent.

4.9 The British Transplantation Society (BTS) Ethics Committee

The BTS Ethics Committee is a subcommittee of the BTS Council. Healthcare professionals responsible for living donor organ transplantation are encouraged to contact the Chairman of the BTS ethics subcommittee (via ethics@bts.org.uk) if they would like help or advice relating to ethical aspects of a particular living donor recipient pair.

References

1. NHS Blood and Transplant, Annual Activity Report, 2012/13. www.odt.nhs.uk
2. Price D. Human tissue in transplantation and research: A model legal and ethical donation framework. Cambridge University Press, 2009.
3. Price D. Legal and ethical aspects of organ transplantation. Cambridge University Press, 2000.
4. Plant WD, Akyol MA, Rudge CJ. The ethical dimension to organ transplantation in transplantation surgery (2nd edn). Ed Forsythe JLR. WB Saunders London, 2002.

5. Ross LF, Glannon W, Josephson MA. Should all living donors be treated equally? Transplantation 2002; 74: 418-21.
6. Kahn J, Matas AJ. What's special about the ethics of living donors? Transplantation 2002; 74: 421-2.
7. Truog RD. The ethics of organ donation by living donors. N Engl J Med 2005; 353: 444-6.
8. Titmuss RM. The gift relationship: from human blood to social policy. London: Allen and Unwin, 1970.
9. Scheper-Hughes N. The tyranny of the gift: sacrificial violence in living donor transplants. Am J Transplant 2007; 7: 507-11.
10. Cohen CB. Selling bits and pieces of humans to make babies: the gift of the Magi revisited. J Med Philos 1999: 24; 288-306.
11. Daar AS. Paid organ donation - the grey basket concept. J Med Ethics 1988; 24: 365-8.
12. Clarke A, Michell A, Abraham C. Understanding donation experiences of unspecified (altruistic) kidney donors. Br J Health Psychol 2013; 19: 393-408.
13. Russell S, Jacob RG. Living related organ donation: the donor's dilemma. Patient Educ Couns 1993; 21: 89-99.
14. WHO guiding principles on human cell, tissue and organ transplantation. Transplantation 2010; 90: 229-33.
15. Curran WJ. Kidney transplantation in identical twin minors – justification is done in Connecticut. N Engl J Med 1972; 287: 26-7.
16. Hollenburg NK. Altruism and coercion: should children serve as kidney donors? N Engl J Med 1977; 296: 390-1.
17. Medical ethics today: its practice and philosophy. London: BMJ Books, 1998.

5 INDICATIONS FOR LIVING DONOR LIVER TRANSPLANTATION IN ADULTS AND CHILDREN

Statements of Recommendation

- ***Living donor liver transplantation (LDLT) must only be performed in specialist centres working with a multi-disciplinary transplant team. (1A)***

- ***Decision making must be multi-disciplinary and meet the national standards for transplant services in the UK. (1A)***

- ***The UK standard for transplant benefit, an overall graft and patient survival of >50% at five years, is the recommended standard for both deceased donor liver transplantation (DDLT) and LDLT. As liver transplant units are currently achieving >75% survival at five years for all paediatric transplants, an overall five year patient survival of 70% is expected for paediatric LDLT recipients. (1B)***

- ***All elective transplant listed patients are entitled to routine discussion about the option of LDLT, although centre experience should limit recipient selection for the first 20 cases. (1B)***

- ***The same recipient factors that influence survival in DDLT must be considered for LDLT in both adults and children. The presentation of a potential living donor must not influence the decision. (Not graded)***

- ***Adult and paediatric recipients with acute liver failure, whose risk of peri- or post-operative mortality is at the lower end of the clinical spectrum, can be considered for LDLT. (2B)***

- ***Consideration of recipients for LDLT who do not meet indications as agreed through the NHSBT Liver Advisory Group (LAG), are subject to the national appeals process until such time as LAG have been able to consider such indications. This includes patients with hepatocellular carcinoma. (1A)***

The same selection contraindications apply for LDLT as for DDLT. LDLT recipient selection in patients with alcohol or substance misuse must follow UK NHSBT guidance. (1A)

- ***Portal vein thrombosis poses technical challenges in LDLT and is a relative anatomical contraindication to transplantation. Centre experience should be taken into consideration in such recipients. (1B)***

- ***Recipients must be advised and supported to stop smoking pre-operatively and consideration given to not proceeding in the presence of ongoing smoking. (2B)***

- ***Patients with hepatitis C virus cirrhosis who meet current UK minimal listing criteria can be considered for LDLT. (1A)***

- ***Potential recipients with hepatocellular carcinoma (HCC) who fall outside current UK guidelines (by tumour size and/or number) but who are within University of California San Francisco criteria and who also meet UK Alpha-fetoprotein guidance of <1000 ng/ml, can be considered for LDLT. (1B)***

- ***In potential recipients with HCC, a three month interval scan must confirm good tumour biology before LDLT proceeds. Bridging therapies may be considered during this interval. (2B)***

- ***There is a lack of evidence about the long-term outcomes for recipients of liver transplants in some diseases e.g. acute alcoholic hepatitis, cholangiocarcinoma, solitary colorectal liver metastases. In these cases, experienced centres may wish to consider adult recipients for LDLT, with appropriate protocols, patient information and phased introduction. (Not graded)***

- ***In diseases where long term outcomes are unclear due to lack of evidence or reproducibility of results, LDLT may offer an opportunity for ethically approved research studies within the UK, but LDLT should only be performed under that condition. (Not graded)***

- ***ABO incompatible (ABOi) LDLT can be considered for paediatric recipients <3 years of age and for suitable adult recipients with appropriate protocols and clinical governance review processes in experienced centres. ABOi LDLT is not recommended for acute liver failure. (1B)***

5.1 Indications for Living Donor Liver Transplantation (LDLT) in Adults

LDLT must only be performed in specialist centres on patients selected using UK Transplant Liver Advisory Group (LAG) standards and in the context of a multidisciplinary team. All centres undertaking LDLT must contribute to national audit of donor and recipient outcomes (1-4).

Recipient selection for LDLT must balance the benefit of transplantation to the recipient with the relative risk to the donor, without compromising the quality or outcomes of the UK liver transplant programme. The UK standard for selecting recipients for transplantation is an expected overall graft and patient survival of >50% at five years. Currently, all units are showing five year survival in excess of this. Between 1994 and 2012, the overall 90-day mortality in UK centres for all first adult transplants was 9.2% with five year mortality being 25.3%. Super-urgent transplants carry a higher short-term mortality of 20% at 90 days but a similar five year survival, whereas elective transplants carry a lower (<8%) 90-day mortality. Five year mortality is currently around 20% for elective first adult transplants (2).

Recipient factors influencing short-term mortality are well documented and include:

- renal impairment
- high cardiovascular risk
- malnutrition
- active uncontrolled sepsis
- inpatient status
- frailty

Recipient factors influencing five year survival include:

- cardiovascular risk
- smoking

- age
- hepatitis C (may change in significance with the advent of new anti-viral agents).

These factors are as applicable to LDLT as they are for DDLT and the presentation of a potential living donor must not influence the decision to transplant. Decision making must be multi-disciplinary and meet the national standards for transplant services in the UK.

The UK has a defined set of indications for liver transplantation (LT). These include minimal listing criteria for chronic liver disease and variant syndromes for complications of cirrhosis and portal hypertension. The variant syndromes include refractory ascites, port-systemic encephalopathy, and disease complications not associated with liver failure such as recurrent cholangitis and intractable pruritus. These indications are evidence-based and agreed by consensus through the UK Liver Advisory Group (LAG). Recipients meeting these criteria can be considered for LDLT as well as DDLT (4-6).

LAG has recommended previously that the indications for LDLT are identical to those for super-urgent and elective liver transplantation from deceased organs (7). Other guidance exists from the UK and USA to assist appropriate recipient selection for transplantation (6,8). There is also guidance from the UK re the appropriate selection of potential recipients with metabolic fatty liver disease, where cardiovascular disease risk may adversely affect outcomes (9). There are also accepted contraindications such as AIDS or poorly controlled HIV disease (BHIVA guidelines), extra-hepatic malignancy or past history of (variable) and advanced cardiopulmonary disease (10).

Existing UK guidance for patients with alcohol or substance misuse histories can be applied to recipient selection for LDLT (11). However, a stronger stance on smoking cessation is recommended. There is an increased incidence of vascular complications in recipients of LDLTs and the American Association for the Study of Liver diseases (AASLD) guidance suggests that LT recipients who smoke are at increased risk of hepatic artery thrombosis (8). It is well recognised that the risk of post-transplant malignancy is increased in smokers. Given the overall risk to the living liver donor (LLD), smoking cessation is recommended to optimise pre-transplant recipient conditioning (12-14).

Portal vein thrombosis extending beyond the portal vein has been considered to be an anatomical contraindication to LDLT. Thrombosis within the portal vein poses technical challenges, but this view that this is prohibits LDLT has been challenged by high volume centres and it therefore cannot be considered an absolute contraindication to LDLT (15,16).

LDLT in the UK may be most advantageous for patients with conditions where access to DDLT is limited due to lack of liver failure or other prioritisation systems (e.g. restricted organ resources (17). The concept of double equipoise can be considered in this context, as in others; the risk and benefits for both donors and recipients must be taken into account, including the increased recipient complication rate compared to DDLT (18). Examples include:

- HCC within current UK criteria in Child A patients
- genetic conditions
- quality of life indications
- ABO blood group incompatibility

There appears to be a recipient survival benefit across all Model for End Stage Liver Disease (MELD) ranges for patients without hepatocellular carcinoma (HCC) (19). Like other reports, the A2ALL Consortium reported recipient outcomes of 81% 1 year graft survival in which centre experience was a significant factor for better outcome (see section 11.3) (20).

5.1.1 Acute Liver Failure (ALF)

Experience in acute liver failure (ALF) is relatively limited. The A2ALL report of outcomes in 385 living donations reported only 4% recipients within this category (20). A more detailed report of 1201 potential LDLT recipients included only 1% who were wait-listed for ALF. Ten of 14 patients underwent LDLT and survival rates compared with three undergoing DDLT were similar, with donor-related morbidity that was also reported as similar (21). The Toronto group recently published a series of seven LDLT recipients transplanted for ALF compared to 26 patients undergoing DDLT, also with similar outcomes (22).

These numbers are very small and limited conclusions can be drawn. However, they do record a progression of opinion with increased experience. Most centres remain unable to offer LDLT in the emergency setting due to limited time and resources (23).

A much larger study from Japan of over 200 LDLT recipients included recipients with acute, subacute and late onset liver failure. Factors influencing outcome were recipient age (>40 years) for both short and long term mortality, ABO incompatibility for short term mortality, and donor age for long term mortality. ABO incompatibility in this setting gave long-term survival rates of only around 50%, with most of the mortality being early (24).

5.1.2 Hepatitis C Virus (HCV)

It is controversial whether recipients with HCV require special consideration when it comes to LDLT. Pre- and post-transplant treatment of HCV is a rapidly changing field so the long term outcomes which have historically only just reached 50% at five years may change. Reported recipient factors influencing worse outcomes with LDLT included HCC, which during this time was subject to changes in MELD exception points in the US allocation systems (25,26).

5.1.3 Hepatocellular Carcinoma (HCC)

The Milan criteria are well established and have formed the benchmark for liver transplantation for HCC since 1996 (27). Many clinicians in the liver transplant community have considered the criteria too restrictive and the issues have been well reviewed, including the place of LDLT, elsewhere (28-32). There is sufficient evidence from the University of California, San Francisco (UCSF) group to consider expanding criteria for transplanting HCC in DDLTs to UCSF criteria and using controlled downstaging procedures (33-35). Studies in both DDLT and LDLT show comparable outcomes to Milan criteria.

The Metroticket (or Up-to-7) criteria remain explant based criteria, although they could be helpful for transplantation decisions in salvage situations (36). Multiple studies report good outcomes and low donor morbidity/mortality with LDLT for HCC. A concern exists, e.g. from the US programme, that outcomes may not be as good as DDLT, which could relate to inadvertent selection of patients with poor tumour biology (37). There is also some concern about whether the regenerative growth post-LDLT might offer favourable conditions for tumour recurrence (38). However, a more recent meta-analysis did not show significant differences in outcome between DDLT and LDLT for HCC (39). There are no randomised controlled trials in this area, so meta-analysis cannot control for how patients were selected into the retrospective studies.

In view of concerns of pre-selecting less favourable tumour biology, it seems reasonable to use surrogate markers such as alpha-fetoprotein (AFP), as in current UK transplant criteria for HCC, and a test of time by interval scan. Local or distant extra-hepatic disease remains a contra-indication to transplantation.

Potential recipients with HCC who fall outside current UK guidelines (by tumour size and/or number) but who are within University of California San Francisco criteria and who also meet UK Alpha-fetoprotein guidance of <1000 ng/ml, can be considered for LDLT. Extending criteria beyond “Milan” may be justified in developing the living donor liver transplant strategy in the UK. Approval for such an approach will be required through the NHSBT liver advisory group.

5.1.4 ABO Blood Group Incompatibility

There are higher risks for recipients with ABO blood group incompatible grafts, although these risks differ between major (rejection plus haemolysis) and minor (haemolysis) incompatibility and degree and subtype of antibody titre. There is increasing experience of such transplants with LDLT and the results are encouraging, especially in very young paediatric recipients (<3 years of age) (40). LDLT offers a theoretical advantage in an elective transplant setting because recipients can be prepared with pre-immunosuppression and plasmapheresis (41-45). This area is worth exploring in the context of clear protocols in centres who have reached critical levels of experience, starting with minor incompatibility and progressing to low antibody titre major incompatibility. ABO incompatible LDLT is currently not recommended in the emergency setting (24).

5.1.5 Controversial Indications for LDLT

There are areas where recipients are currently excluded from LDLT because there is no proven benefit of transplantation, although a supportive literature exists. These may provide areas for future research and include LT for acute alcoholic hepatitis and liver malignancy other than HCC.

a) Acute alcoholic hepatitis

LDLT may offer an opportunity for a well governed programme for recipients with alcohol related liver disease, who:

- are drinking at time of presentation
- cannot achieve six months abstinence due to illness severity

- have favourable addiction specialist/psychiatrist reports

This may include patients aged <30 years with end-stage alcohol related liver disease (ARLD) or acute alcoholic hepatitis. As previously described, factors such as co-morbid psychiatric illness, social instability, drug co-dependency and non-acceptance of alcohol dependency are all associated with recidivism and must be absent (46). Acceptance of acute alcoholic hepatitis as an indication for DDLT is controversial, although more information from a multi-centre Spanish study (not yet open) may be available in the future.

The evidence for benefit, or the acceptance of this indication for transplantation is not sufficiently strong to recommend that acute alcoholic hepatitis can be considered for LDLT outside a clinical trial setting.

b) Malignancy other than HCC

The evidence for transplant benefit is not sufficiently strong to recommend that the following conditions can be considered for LDLT outside a clinical trial setting:

- cholangiocarcinoma
- neuroendocrine tumours (47)
- colorectal metastases (48)

In summary, in diseases where long-term outcomes are unclear due to lack of evidence or reproducibility of results, LDLT may offer an opportunity for ethically approved research studies within the UK and must only be performed under these conditions.

In these controversial examples, patients with living donors could be advantaged over patients without living donors, or there could be perceived pressure on family members to undergo donation. There is scope for the wider UK transplant community, including patient groups, to debate the practical and moral issues that arise and to agree whether it is appropriate to have different criteria for transplantation depending on whether or not a living donation is available, and whether to use the additional NHS resource of a donor operation in such circumstances.

5.2 Indications for Living Donor Liver Transplantation (LDLT) in Children

As for adult LDLT, LDLT in children must only be performed in specialist centres on patients selected using UK Transplant Liver Advisory Group (LAG) standards and in the context of a multidisciplinary team.

Likewise, recipient selection for LDLT must balance the benefit of transplantation to the recipient with the relative risk to the donor, without compromising the quality or outcomes of the UK liver transplant programme. Between 1994 and 2012, the overall 90-day mortality in UK centres for first paediatric transplants was 8.1% with one year mortality of 10.5%. Super-urgent transplants carry a higher short-term mortality of 19.1 % at 90 days, and 23.8% at one year, whereas elective transplants carry a lower 5.3% 90-day mortality risk. Recipients of LDLT are expected to meet the same survival probability as for DDLT (see section 11.3) (49).

Recipient factors influencing short-term mortality in children include:

- age
- active uncontrolled sepsis
- inpatient status
- frailty

Recipient factors influencing 5 year survival include:

- age (< 3 months)
- nutritional status
- congenital heart disease.

These factors are as applicable to LDLT as they are for DDLT and the presentation of a potential living donor must not influence the decision to transplant. Decision making must be multi-disciplinary and meet the national standards for transplant services in the UK.

The UK has a defined set of indications for LT in children:

1. Acute liver failure

2. Chronic liver disease

- life expectancy: anticipated length of life <18 months (because of liver disease)
- unacceptable quality of life (because of liver disease)
- growth failure or impairment due to liver disease
- reversible neuro-developmental impairment due to liver disease
- likelihood of irreversible end organ damage (may be renal, respiratory or cardiovascular depending on underlying disorder)

These indications are agreed through consensus by the UK LAG. Recipients meeting these criteria can be considered for LDLT as well as DDLT and the indications for LDLT are identical to those for both super-urgent and elective DDLT. Consideration of recipients for LDLT who do not meet indications as agreed through LAG are subject to the national appeals process until LAG have been able to consider such indications.

There are a number of conditions where the impact of LDLT is not identical to DDLT:

5.2.1 Hepatoblastoma

The outcome of transplantation for unresectable hepatoblastoma is excellent. The availability of LDLT and the ability to schedule transplantation allows accurate coordination of preoperative chemotherapy and, in selected cases, may allow more aggressive surgical resection than would be feasible without the known availability of a suitable donor.

5.2.2 Metabolic Liver Disease

The ability to schedule transplantation ensures that the recipient can be maintained in an optimal metabolic and nutritional status in the immediate preoperative period. This is particularly important in disorders prone to sudden decompensation such as organic acidaemias and urea cycle disorders.

As most metabolic disorders are autosomal recessive, many parents will be obligate heterozygotes but unaffected (50). In the majority of cases this will have no significant impact but there are some conditions where it is a factor to consider:

a) Maple syrup urine disease

Transplantation results in a functional, but partial correction of the defect. Therefore, at present, heterozygous parents should not be considered as potential donors (51).

b) Alpha -1-antitrypsin deficiency

There is a theoretical possibility that the heterozygous state may interfere with hepatic regeneration but successful cases have been reported (52).

c) Atypical haemolytic uremic syndrome (HUS)

Atypical HUS occurs due to mutations in genes encoding complement regulatory proteins. Although causative mutations are recognised, not all of the genes and factors involved in disease expression are known; hence, it is not always possible to completely exclude disease risk in close relatives (53).

d) Ornithine transcarbamylase deficiency

This is inherited in an X-linked fashion. As a result, the mother may be affected and hence unsuitable as a living donor.

e) Homozygous hypercholesterolaemia

This is an autosomal dominant condition and parents are usually affected, albeit more mildly. Families must be counselled that transplantation from a heterozygous parent will result in improvement but, not abolishment of the metabolic defect and that lifelong lipid lowering treatment will probably still be necessary.

f) Alagille's syndrome.

The inheritance is autosomal dominant in a proportion of cases; hence, one parent may be affected, which can be subclinical (54).

5.2.3 Acute Liver Failure (ALF)

Experience of LDLT in ALF is also relatively limited in children and, as expected, outcomes are not as good as for chronic liver disease. A Japanese series of 600 LDLT in paediatric recipients included 6.2% transplanted for fulminant liver failure (55). A case series of 13 paediatric recipients transplanted by LDLT for ALF showed five year survival around 55% (56). Short-term recipient complication rates were high. All deaths in the first postoperative month were attributed to the poor clinical status of the patients before the transplant and, although donation was never regretted, the presence of a living donor must not detract from ensuring appropriateness of transplantation by the clinical team. It is recommended that paediatric recipients with ALF whose risk of peri- or post-operative mortality is at the lower end of the clinical spectrum can be considered for LDLT. The donor assessment must be subject to all the rigour of a less time-sensitive assessment and performed by members of the usual LDLT multi-disciplinary team.

References

1. National Institute for Health and Clinical Excellence. Living donor liver transplantation. Interventional procedure guidance 194.2011. http://www.nice.org.uk/guidance/IPG194/Guidance/pdf
2. Royal College of Surgeons annual liver transplant audit 1994-2012. http://www.rcseng.ac.uk/surgeons/research/surgical-research/docs/liver-transplant-audit-report-2012
3. National Liver Transplant Standards 2005. http://www.specialisedservices.nhs.uk/library/25/National_Liver_Transplant_Standards.pdf
4. Liver transplantation: selection criteria and recipient registration policy Pol 195/4 http://www.odt.nhs.uk/pdf/liver_selection_policy_2015/pdf
5. Neuberger J, Gimson A, Davies M, et al. Liver Advisory Group, NHSBT. Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut 2008; 57: 252-7.
6. Devlin J, O'Grady J. Indications for referral and assessment in adult liver transplantation: a clinical guideline. British Society of Gastroenterology. Gut 1999; 45 (Suppl 6): V11-122.
7. National Standards for Live Donor Liver Transplantation LAG (11)34 http://www.odt.nhs.uk/pdf/advisory_group_papers/LAG/national_standards_for_live_donor_liver_transplants_april_2006/pdf
8. Murray KF, Carithers RL Jr. AASLD Practice Guidelines: Evaluation of the patient for liver Transplantation. Hepatology 2005; 41: 1407-32.
9. Newsome PN, Allison ME, Andrews PA, et al. Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. Gut 2012; 61: 484-500.
10. O'Grady J, Taylor C. Guidelines for liver transplantation in patients with HIV infection. 2005. www.bhiva.org/documents/Guidelines/Liver%20Transplantation/Transplant-guide.pdf).
11. NHSBT Liver Advisory Group: Recommendations for liver transplant assessment in the context of alcohol-related liver disease; NHSBT Liver Advisory Group: Recommendations for liver transplant assessment in the context of illicit drug use, Updated in: NHSBT Liver Transplantation: selection criteria and recipient registration 2013 http://www.odt.nhs.uk/pdf/liver_selection_policy.pdf).

12. Pungpanong S, Manzarbeita C, Ortiz J, et al. Cigarette smoking is associated with an increased risk of vascular complications after liver transplantation. Liver Transpl 2002; 8: 582-7.
13. Herrero JI, Lorenzo M, Quiroga J, et al. De novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. Liver Transpl 2005; 11: 89-97.
14. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Liver Transplantation. Liver Transpl 2013; 19: 3-26.
15. Song GW, Lee SG. Living donor transplantation. Curr Opin Organ Transplant 2104; 19: 217-22.
16. Kim SJ, Kim DG, Park JH, et al. Clinical analysis of living donor liver transplantation in patients with portal vein thrombosis. Clin Transplant 2011; 25: 111-8.
17. Florman S, Miller CM. Live donor liver transplantation. Liver Trans 2006; 12: 499-510.
18. Freise CE, Gillespie BW, Koffron AJ, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL retrospective cohort study. Am J Transplant 2008; 8: 2569-79.
19. Berg CL, Merion RM, Shearon TH, et al. Liver transplant recipient survival benefit with living donation in the MELD allocation era. Hepatology 2011; 54: 1313-21.
20. Olthoff KM, Merion RM, Ghobrial RM, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL consortium. Ann Surg 2005; 242: 314-25.
21. Campsen J, Blei AT, Emond JC, et al. Outcomes of living donor liver transplantation for acute liver failure: the adult-to-adult living donor liver transplantation cohort study. Liver Transpl 2008; 14: 1273-80.
22. Goldaracena N, Spetzler VN, Marquez M, et al. Live donor liver transplantation: a valid alternative for critically ill patients suffering from acute liver failure. Am J Transplant 2015. doi: 10.1111/ajt.13203. [Epub ahead of print] .
23. Shah SA, Levy GA, Adcock LD, et al. Adult to adult living donor liver transplantation. Can J Gastroenterol 2006; 20: 339-43.
24. Yamashiki N, Sugawara Y, Tamura S, et al. Outcomes after living donor liver transplantation for acute liver failure in Japan: results of a nationwide survery. Liver Transpl 2012; 18: 1069-77.
25. Brown RS. Live donors in liver transplantation. Gastroenterol 2008; 134: 1802-13.

26. Terrault NA, Schiffman ML, Lok ASF, et al. Outcomes in hepatitis C virus-infected recipients of living donor vs deceased donor liver transplantation. Liver Transpl 2007; 13: 122-9.
27. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Eng J Med 1996; 334: 693-9.
28. Khorsandi SE, Heaton N. Contemporary strategies in the management of hepatocellular carcinoma. HPB Surgery 2012; 2012:154056. doi: 10.1155/2012/154056.
29. Kakodkar R, Soin AS. Liver transplantation for HCC: a review. Indian J Surg 2012; 74: 100-17.
30. Mazzaferro V, Chun YS, Poon RTP, et al. Liver transplantation for hepatocellular carcinoma. Ann Surg Oncol 2007; 15: 1001-7.
31. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded. Ann Surg 2007; 246: 502-11.
32. Yao F, Ferrell L, Bass N, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl 2002; 8: 765-74.
33. Yao F, Breitenstien S, Broelsch CE, et al. Does a patient qualify for liver transplantation after the down-staging of hepatocellular carcinoma? Liver Transpl 2011; 17: S109-16.
34. Yao F, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 2005; 11: 1505-14.
35. Yao FY, Kerian RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention to treat analysis. Hepatology 2008; 48: 819-27.
36. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective exploratory analysis. Lancet Oncol 2009; 10: 35-43.
37. Fisher RA, Kulik LM, Freis CE, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 2007; 7: 1601-8.
38. Marcos A, Fisher RA, Ham JM, et al. Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. Transplantation 2000; 69: 1375-9.

39. Liang W, Wu L, Ling X, et al. Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma: a meta-analysis. Liver Transpl 2012; 18: 1226-36.
40. Gelas T, McKiernan PJ, Kelly DA, et al. ABO incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. Pediatr Transplant 2011; 15: 706-11.
41. Wu J, Ye S, Xu X, et al. Recipient outcomes after ABO-incompatible liver transplantation: a systematic review and meta-analysis. PLoS One 2011; 6: e16521.
42. Kluger MD, Guarrera JV, Olsen SK, et al. Safety of blood group A2-to-O liver transplantation: an analysis of the United Network of Organ Sharing database. Transplantation 2012; 94: 526-31.
43. Goralczyk AD, Obed A, Schnitzbauer A, et al. Adult living donor liver transplantation with ABO-incompatible grafts: a German single center experience. J Transpl 2009; Article ID 759581. doi:10.1155/2009/759581.
44. Egawa H, Teramukai S, Haga H, et al. Impact of rituximab densensitization on blood-type-incompatible adult living donor liver transplantation: A Japanese multicentre study. Am J Transplant 2014; 14: 102-14.
45. Kim JM, Kwon CH, Joh JW, et al. ABO-incompatible living donor liver transplantation is suitable in patients without ABO-matched donor. J Hepatol 2014 ; 59: 1215-22.
46. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011; 365: 1790-800.
47. Le Treut YP, Gregoire E, Klempnauer J, et al. Liver transplantation for neuroendocrine tumours in Europe - results and trends in patient selection. Ann Surg 2013; 257: 807-15.
48. Hagness M, Foss A, Line P-D, et al. Liver transplantation for non-resectable liver metastases from colorectal cancer. Ann Surg 2013; 257: 800-06.
49. Protocols and guidelines for children undergoing deceased donor liver transplantation in the UK. Liver Advisory Group; NHSBT 2010.
50. Morioka D, Takada Y, Kasahara M, et al. Living donor liver transplantation for noncirrhotic inheritable metabolic liver diseases: impact of the use of heterozygous donors. Transplantation 2005; 80: 623-8.
51. Strauss KA, Mazariegos GV, Sindhi R, et al. Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant 2006; 6: 557-64.

52. Tannuri AC, Gibelli NE, Ricardi LR, et al. Living related donor liver transplantation in children. Transplant Proc 2011; 43: 161-4.
53. Saland JM, Ruggenenti P, Remuzzi G. Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. J Am Soc Nephrol 2009; 20: 940-9.
54. Kasahara M, Kiuchi T, Inomata Y, et al. Living-related liver transplantation for Alagille syndrome. Transplantation 2003; 75: 2147-50.
55. Ueda M, Oike F, Ogura Y, et al. Long-term outcomes of 600 living donor liver transplants for pediatric patients at a single center. Liver Transpl 2006; 12: 1326-36.
56. Shouval DS, Mor E, Avitzur Y, et al. Living-related donor liver transplantation for children with fulminant hepatic failure in Israel. J Pediatr Gastroenterol Nutr 2009; 48: 451-5.

6 INFORMING THE DONOR AND DONOR ADVOCACY

Statements of Recommendation

- ***The living donor must be offered the best possible environment for making a voluntary and informed choice about donation. (Not graded)***

- ***Potential donors should be provided with centre-specific complications rates. (Not graded)***

- ***Relevant information about the recipient should be shared with the donor, provided that the recipient has given consent. The recipient must be informed that lack of permission for disclosure may jeopardise the transplant proceeding. In order to achieve the best outcome for donor, recipient and transplant, the boundaries of confidentiality must be discussed and specified at the outset. (Not graded)***

- ***Independent assessment of the donor and recipient is a statutory requirement of primary legislation (Human Tissue Act 2004). (A1)***

- ***Separate clinical teams for donor and recipient are considered best practice and a donor advocacy team should be assigned to every potential living liver donor. Healthcare professionals must work together to ensure effective communication and co-ordination of the transplant process without compromising the independence of either donor or recipient. (Not graded)***

- ***The donor must be informed that he/she may not be suitable to donate and/or can withdraw from the process at any time. In either case, appropriate support must be provided by the transplant team. (Not graded)***

- ***Support for the prospective donor, recipient and family is an integral part of the donation/transplantation process. Psychological needs must be identified at an early stage to ensure that appropriate support and/or intervention is provided. Access to specialist psychiatric/psychological services must be available for donors/recipients requiring referral. (B2)***

6.1 Informing the Donor

The General Medical Council (GMC) is explicit about the responsibility of registered doctors when seeking informed consent (1). Central to the validity of the process is respect for the right of the individual to exercise autonomy and the provision of information in the form that allows them to make an informed decision (see section 4).

6.2 Informed Consent for Living Liver Donation

The need for informed and valid consent should be explained to the potential donor. Ideally, both verbal and written information about living liver donation should be provided. The risk of death and the short and long-term complications associated with donation must be fully explained. The surgical risk associated with living liver donation will vary with respect to the lobe or segment that is being removed and the volume of the remnant liver (see sections 9 and 11).

The prospective living donor must be given a realistic estimate of the likelihood of a successful transplant outcome. This must include a summary of centre-specific complication rates and an explanation if these are significantly different from the national and international norms. If there are factors that increase the risk of recipient mortality or morbidity and/or graft survival (e.g. positive serology, recurrent hepatitis C, alcoholic liver disease, hepatocellular carcinoma), these must be discussed openly with the donor.

Providing this information for the donor is only possible if the potential recipient agrees to such information being shared. If the recipient is unwilling to permit sharing of appropriate information, the recipient must be informed that this may affect the ability of a donor to give valid consent and it may not therefore be possible to progress with surgery.

Where there is insufficient evidence to give reliable information regarding the likelihood of successful transplantation, this uncertainty must be shared so that both donor and recipient have realistic expectations about possible outcomes. Such discussion will include consideration of the part of the liver to be donated and any implications thereof. Discussion should occur at an early stage of assessment, in separate consultations, so

both donor and recipient have the opportunity to speak openly and freely and so that expectations may be appropriately managed.

Consent must be freely given and the clinician responsible for obtaining consent must be satisfied that the prospective donor has the ability to make a competent and cogent decision. On at least one occasion during the donor assessment process, the potential donor must be seen separately, in the absence of the prospective recipient and their family, by a designated independent medical consultant who is unconnected to the recipient's transplant team and whose primary responsibility is the welfare of the donor. The donor must be reassured that his/her views concerning donation, as well as medical and social history, will be treated in strict confidence. As well as a designated consultant, every donor must be assigned a multi-professional donor advocacy team (DAT) comprising of experienced healthcare professionals. This team is responsible for ensuring that the interests of the donor are upheld throughout the assessment and preparation for donation and that consent for donation is free and voluntary (see section 6.4).

It must be made clear that the potential donor has the option to withdraw at any stage in the donation process, without having to provide an explanation for his or her decision. Adequate time to reflect on the decision to donate must be provided, based upon a balanced view of the advantages and disadvantages of living donor transplantation. If after discussion, the donor decides not to proceed, the decision must be respected and not regarded as a failure but as a natural result of the informing process (2). Best practice includes referral to specialist psychological/psychiatric services to safeguard the mental health of the donor and provide access to appropriate support as required throughout the assessment and donation process (see section 7). If the prospective donor is unable to donate for a clinical reason, this can cause distress for both donor and recipient and may be associated with negative feelings of failure, anger at self and guilt, which can trigger depression. The need for emotional support must be anticipated and appropriate facilities provided.

The decision regarding whether or not to proceed with living liver donation can be stressful for both donor and recipient and their respective family and friends. In living liver donation, time is often constrained by the recipient's clinical condition and decisions may need to be made quickly. If several family members are contemplating donation, the decision re the preferred potential donor may be complex. The healthcare

team can assist by identifying and addressing the relevant issues as early and as quickly as possible so that all parties can make an informed choice.

6.3 Donor Identity

As part of donor work up, detailed studies are performed of donor and recipient tissue type and ABO blood group. There may be occasions when this information, unexpectedly, identifies that a presumed genetic relationship has been misattributed. Most cases of misattributed paternity have come to light when HLA typing has inadvertently disclosed the lack of genetic relationship between a father and a child. There is no consistency in how such cases are handled by healthcare professionals in terms of disclosure to both parties (3,4). While cases of misattributed paternity are most common, others may be identified; for instance, sibling pairs and children born to young teenage mothers who have been raised in the belief that another relative in the family is their mother.

The Human Tissue Authority (HTA) has issued guidance that encourages transplant teams to take responsibility for informing the donor of this possibility (i.e. that HLA typing may identify cases of misattributed genetic identity) and to seek consent for or against disclosure of donor identity in the event that the HLA typing does not support the claimed genetic relationship (5).

This guidance fits well with the role of the Independent Assessor who, under the HTA Current Codes of Practice has a responsibility, with appropriate evidence, to confirm the claimed relationship between donor and recipient (6). The principle of seeking consent prior to testing is attractive as a risk management strategy, particularly where there may be social and/or cultural considerations, but it must also extend to the recipient as both parties are inextricably linked in the context of living donation. There is potential for conflict within the relationship and within the wider family if the donor and recipient make different decisions about disclosure with the result that one is party to information that the other is not. However, valid consent can be achieved by appropriate discussion to ensure that the individuals concerned understand the potential implications of testing and the advantages and disadvantages of agreeing to consent for disclosure.

This is a difficult and controversial area because the relevance of genetic identity may be questioned in the context of a loving relationship where the perceived identity of the donor has never been at issue. There are also implications for the wider family and the impact on family dynamics. There is no 'one size fits all' answer to this issue, and each case will need to be judged on its merits. However, prior discussion and consent is important to help minimise the assumptions being made about what the donors and recipients wish to know in the event of an issue arising. This approach has been embedded in best practice guidelines for living donor kidney transplantation since 2011 (6) and is applicable to living liver transplantation. In the case of an unconscious recipient, consent would have to be postponed until after transplantation and then obtained prior to disclosure of any information to either the donor or recipient.

6.4 Donor Advocacy

In order to comply with the codes of practice of the HTA, and meet the demands of best practice, every donor-recipient pair must be assessed by an appropriately trained and accredited third party (the Independent Assessor) (8).

It is essential that an informed health professional who is not directly involved with the care of the recipient acts as the donor advocate in addressing any outstanding questions, anxieties or difficult issues, and assists the donor in making a truly autonomous decision. In addition to the independent assessor, a multi-professional donor advocacy team (DAT), comprising an independent medical consultant physician, experienced specialist transplant nurse/practitioner/co-ordinator in living liver donation, psychiatrist and social worker, is assigned to every donor.

The donor advocate team interacts with the transplant team but is essentially independent. The role of the members of the DAT is to:

1. Evaluate, protect and support the donor's well being
2. Ensure the donor is fully, appropriately and objectively informed to proceed with the consent
3. Ensure the donor assessment process has followed the Living Donor Assessment Pathway

All members of the team will meet the potential donor and produce a report back to the Living Donor Assessment team.

The DAT physician will have some experience in the field of liver disease and will be familiar with transplantation but should not have been directly involved in the liver transplant unit. They will have access to the candidate's notes, imaging and unit protocol.

The DAT clinical psychiatrist and social worker act independently to review the donor's psychosocial situation and support mechanisms. They support and may interview the donor's partner or significant other. The psychiatrist also assesses the donor's understanding of the process of assessment and tries to ensure that the potential donor(s) have not been coerced into surgery; and also discusses reactions to potential graft failure and expectations of gratitude and ownership. If the need for on-going psychological management is identified, this will be arranged through the donor's GP.

The DAT specialist transplant nurse/practitioner must also evaluate the donor. This can be the LDLT coordinator, who has an instrumental role during the assessment and is able to guide the donor throughout the entire process. There should be no conflict of interest since this person is by definition independent from the recipient's work up. During these meetings, the process of assessment will be further discussed, including what occurs on the day of surgery, to give the potential donor as much information as possible so that an informed decision about participation can be reached.

When each member has met with the donor, the DAT must agree that the donor is medically and psychologically suitable to donate. The DAT must be certain that donor is acting entirely voluntarily, is not under any (unreasonable) pressure or inducement to donate and fully understands the process. The team must be independent of influence by the recipient's medical team and therefore able to stop the donation proceeding. Every member of the team will produce a report and send it to the Living Donor Assessment Team. After all members of the DAT have assessed and reviewed the patient, the DAT must be in a position to agree, unanimously, that the donation can proceed. If there is not complete consensus, the donation cannot proceed.

This process ensures separation of the donor and recipient clinical teams and represents best practice in the assessment and preparation of the living liver donor. It is important for the potential donor to understand that he or she is not the only possible source of a transplant. When a donor does not wish to donate but is concerned that refusal may result in family conflict, the donor advocate should assist with discussions to limit damage to family relationships (9). If at all possible, it is preferable to encourage

open and honest discussion between the donor and recipient from the outset. Pre-emptive discussion is helpful in ensuring that both parties are fully informed about how information will be handled by their respective healthcare teams and to minimise the risk of future conflict. Multi-disciplinary meetings are essential to ensure appropriate information is shared and to facilitate the parallel management of both donor and recipient pathways. This is particularly pertinent when donor and recipient clinical teams are working independently of one another.

Not all recipients wish to accept living donation, but there is a tendency on the part of healthcare professionals and/or family members to assume that they will. Provided that their decision is an informed choice, it should be respected. In such cases, they may need support and guidance to refuse the offer without causing the potential donor distress or relationship conflict. Where potential recipients have formed good relationships with the transplant team, sufficient support may be available but an independent third party offers a different dimension and an environment in which there is potentially less pressure and more opportunity for free expression concerning acceptance of the organ. This is especially important in the case of young adults (10). In the case of the patient who lacks capacity or is unconscious, as in patients with acute hepatic or fulminant failure, reasonable enquiry should be made to establish if the patient had executed power of attorney; alternatively, views about the patient's preferences should be sourced from the highest ranking family members. However, often in these circumstances the highest ranking family member may be the potential donor, so the best interest of the patient must be considered by the medical team caring for the patient.

Living donor liver transplantation can be used to expand the donor pool and to extend the benefits of transplantation to suitable recipients. Most recipients remain on the deceased donor transplant list even if they have a living donor who is healthy and keen to proceed to donation. The decision whether to remain on the deceased donor waiting list should be a joint decision between the donor and recipient in the context of informed discussion with their clinical teams so that both are aware of the risks and benefits. Ultimately, all decisions of this nature are made on an individual basis. In some cases, it may be appropriate to suspend a patient from the deceased donor list once the donor has been fully assessed and deemed suitable to proceed, unless there are strong competing arguments.

6.5 Independent Translators

The United Kingdom is culturally and ethnically diverse and a high proportion of donors do not use English as their first language. Novel presentations of both verbal and written information, even when translated, may not help individual donors to acquire the depth and breadth of knowledge they need in order to be an informed living donor and may leave them vulnerable to coercion. Independent translators are a requirement under the HTA Codes of Practice (11) to ensure that the interests of the potential donor are protected and must always be used during key consultations (i.e. with physician, surgeon and DAT) when there are difficulties in communicating freely with both parties. The translator must be unknown to both the donor and recipient and competent to discuss the implications and associated risks of donor surgery and the post-operative recovery process. The translator needs sufficient knowledge and skill to accurately translate complex discussions and to understand the nature and subtlety of the conversation so that the donor can make the right decision. In the absence of face-to-face translation, ‘language line’ (telephone translation) can be helpful.

6.6 The Responsibility of the Donor Surgeon

The surgeon performing living liver donation surgery has a particular responsibility under his/her duty of care to ensure that the donor fully understands the potential risks and long-term effects of the operation (1). It is recommended that a combination of verbal and written information is given to the potential donor and that the areas detailed in this section are specifically addressed.

6.7 Death

Every centre performing living donor liver transplantation should have a contingency plan for donor death which will define a process to support patients and their families; to maximise patient safety and confidentiality, yet maintain transparency; and to inform stakeholders.

6.8 Transplant Failure

Early graft failure will result in feelings of profound loss for many donors and recipients. Emotional support is essential at this time**,** but studies show that with appropriate help the majority of donors and recipients recover without psychological morbidity (10). Support must be available for all patients and their families, up to and including referral to a mental health professional (see section 7).

References

1. General Medical Council. Consent: patients and doctors making decisions together, 2008. http://www.gmcuk.org/static/documents/content/GMC_Consent_0513_Revised.pdf
2. Bratton LB, Griffin LW. A kidney donor's dilemma: the sibling who can donate - but doesn't. Soc Work Health Care 1994; 20: 75-96.
3. Ross LF. Good ethics requires good science: why transplant programs should NOT disclose misattributed parentage. Am J Transplant 2010; 10: 742-6.
4. Sokol DK. Truth-telling in the doctor-patient relationship: a case analysis. Clinical Ethics 2006; 1: 1-5.
5. Human Tissue Authority. https://www.hta.gov.uk/policies/hta-position-statement-absence-presumed-genetic-relationship.
6. BTS/RA United Kingdom Guidelines for Living Donor Kidney Transplantation, 3rd Edition, May 2011. http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx
7. Human Tissue Authority. Code of Practice 2, Donation of solid organs for transplantation, living organ donation, revised Sept 2009; 34, para iii. http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code2donationoforgans.cfm
8. Human Tissue Authority. Code of Practice 2, Donation of solid organs for transplantation, living organ donation, revised Sept 2009; 60-4. http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code2donationoforgans.cfm
9. Jacobs C, Johnson E, Anderson K, Gillingham K, Matas A. Kidney transplants from living donors: how donation affects family dynamics. Adv Renal Replace Ther 1998; 5: 89-97.

10. Franklin P, Crombie A. Live related renal transplantation: psychological, social and cultural issues. Transplantation 2003; 76: 1247-52.
11. Human Tissue Authority. Code of Practice 1, Consent, general provisions, revised Sept 2009; 60-1. http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice.cfm/663-Consent-requirements---Part-1--General-provisions.html

7 PSYCHOLOGICAL ASPECTS

Statements of Recommendation

- ***All potential donors must undergo assessment by a mental health professional, preferably a member of the Donor Advocate Team. (B1)***

- ***Mental health assessments can be undertaken by any suitably qualified mental health clinician. Centres with access to more than one type of clinician should direct referrals accordingly. Assessment by more than one professional may be appropriate in some cases. (D2)***

- ***The purpose of mental health assessment is to:***
  - ***a) Identify potential donors who should be excluded from donation due to mental disorder or inappropriate motivation. (B1)***
  - ***b) Identify those who are more vulnerable to psychiatric risk and may need additional support after donation. (B1)***
  - ***c) Confirm capacity to consent. (B1)***
  - ***d) Explore motivation, particularly for altruistic donors. (B1)***

- ***Mental health professionals undertaking these assessments should be familiar with the general issues that might arise in living donor transplantation, as well as organ-specific concerns. (Not graded)***

- ***Clear referral routes to specialist mental health services must be identified for donors who later develop mental health problems. (C2)***

- ***As part of the mental health assessment, it may be necessary to interview the donor's next of kin (other than the recipient). (B1)***

- ***Particular consideration must be given to the mental health assessment and support for donors who donate to recipients in urgent need of a transplant. (Not graded)***

7.1 General Considerations

Various types of mental disorder are known to be prevalent in potential living organ donors. The evidence is best for the commonest type of donation, i.e. kidney donation (1). Prevalence rates may be higher among non-directed or altruistic donors (2).

UK practice for the mental health assessment of potential living kidney donors has evolved over time, and still varies widely between units, in terms of the proportion of potential donors referred for assessment, the professional affiliation of the assessing mental health clinician, and the remit and methods of assessment. For altruistic kidney donors, the Code of Practice for the Human Tissue Acts (see section 3) introduced a mandatory requirement for mental health assessment but said little about the form it should take, the questions it should seek to answer, or by whom it should be conducted (3). In 2012, the mandatory requirement was withdrawn but it remains the recommended clinical standard, endorsed by NHS Blood and Transplant (NHSBT) and British Transplantation Society (BTS).

Extrapolating from living donor kidney transplantation to living liver donor transplantation needs to take into account that:

- Living donor liver transplantation is much less common than living donor kidney transplantation and is concentrated in fewer transplant units. Therefore, there are fewer mental health clinicians familiar with the specific issues that need to be addressed in donor assessments.
- The short term medical and surgical risks for donors and recipients are significantly greater than in kidney transplantation. These need to be considered alongside the psychiatric risks of proceeding (or declining to proceed) with donation; this balance is different from living kidney donation.
- With no dialysis equivalent for patients with liver disease, the stakes and often the time pressures are greater for decisions about liver donation and transplantation in comparison with kidney donation and transplantation.
- The medical diagnoses and indications for liver transplantation are often stigmatised and may be viewed as self-induced through e.g. alcohol, drug abuse or obesity. This may impact more on the donor's decision to donate than it would with a kidney transplant recipient. A living organ donor to a recipient with alcoholic liver disease may also be adversely affected if the recipient relapses into alcohol misuse after transplant.

Since it became legally permissible in the UK in 2006, altruistic non-directed kidney donation has increased in frequency and in 2012-13 contributed 10% of all living donor kidney transplants (5). The first altruistic living liver donation in the UK was performed in 2012 to a paediatric recipient, but activity remains very low (see section 12.3). Experience in assessing such cases is necessarily limited.

Based upon these factors, the New York State Department of Health recommended in 2002 that all transplant units undertaking living donor liver transplantation should establish Donor Advocate Teams, to include a mental health clinician (4). These recommendations have since been adopted by UK centres undertaking liver transplantation using living donors (see section 6.4). The most important recommendation is that all potential donors should undergo mental health assessment at an early stage.

7.2 Purpose of Mental Health Assessment

Mental health assessments have several overlapping purposes, some specifically psychiatric (i.e. related to the subset with mental disorder), others psychological (applying to all donors). The overall purpose is to:

- Identify those whose wish to donate arises from mental disorder and who should, therefore, be excluded from donation. Few *direct* (family and friend) kidney donors are excluded on mental health grounds but anecdotal evidence suggests that 20-30% of non-directed altruistic donors do not proceed for these reasons (6). Potential living liver donors have also been excluded on mental health grounds (6).
- Identify otherwise suitable donors who may be more vulnerable to risks of mental health complications after surgery and could have additional support needs in the peri-operative and post-operative period.
- Clarify for all donors the appropriate route to access specialist mental health services in the event of mental health problems arising after donation.
- Confirm the donor's capacity (i.e. his/her ability to understand, remember and weigh up the information presented, then make and convey their decision).
- Explore motivation. This is particularly important in cases of altruistic donation or when subtle degrees of coercion or pressure are suspected. Significant concerns about motivation may result in a donor being excluded from donation.

7.3 Assessing Clinicians

There is wide variation in access to mental health specialists within transplant centres and how services are funded and organised. In the UK, most centres and referring units will have access to either a psychiatrist or psychologist but few will have direct access to more than one type of mental health clinician. It is important that services, however they are provided in individual centres, are broadly consistent.

Any mental health clinician working in this field must be able to assess mental disorder (including substance misuse and personality disorder), motivation and capacity. Given the different emphases in training and clinical practice, it is preferable, where possible, for psychiatrists and nurse specialists to assess mental disorder and psychologists and/or counsellors to assess motivation.

It is most important that the assessing mental health clinician is familiar with transplantation procedures, timescales, risks and outcomes. In the context of living liver donation, it is best practice to refer potential donors to clinicians who are already familiar with the organ-specific issues rather than assuming a level of knowledge through living kidney donation alone.

7.4 Standardisation of Assessments

There is no agreement within the UK, or elsewhere, about standardisation of mental health assessments in living donation, and practice varies between centres. There is currently no evidence to guide consensus or recommendations in most areas. However, there is broad agreement amongst mental health professionals that there is need for a separate interview with a donor's relative (other than the recipient).

Possible coercion and/or pressure should be considered when assessing motivation in the mental health assessment. This is also a requirement of the Independent Assessment for the Human Tissue Authority (see section 6.3). This may be best assessed by interviewing others as well as the donor, such as the donor's next of kin (4). Where the next of kin is the potential recipient, the interviewee should be the next nearest relative or a close friend, as nominated by the potential donor.

References

1. De MA, Jacobs CL, Jowsey SG, et al. Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. Am J Transplant 2007; 7: 1047-54.
2. Kranenburg L, Zuidema W, Erdman R, Weimar W, Passchier J, Busschbach J. The psychological evaluation of Good Samaritan donors: a systematic review. Psycholol Med 2008; 38: 177-85.
3. Potts SG. Assessing altruistic donation. Br J Renal Med 2009; 14: 26-9.
4. Novello AC. Quality improvement in living liver donation. Accessed March 16 2015. http://www.health.ny.gov/professionals/patients/donation/organ/liver/ 2015.
5. UK ODR Annual Activity Report 2015, section 5 (Kidney Activity) accessed at http://www.odt.nhs.uk/uk-transplant-registry/annual-activity-report/
6. Nadkarni A, Schartau P, Burnapp L, Santhouse A. Assessing potential nondirected altruistic kidney donors: a case note audit. Br J Renal Med Summer 2012; 17: 19-23.

8 DONOR EVALUATION

8.1 INTRODUCTION

Statements of Recommendation

- ***Before starting donor evaluation:***
  - ***d) Establish recipient suitability. (A1)***
  - ***e) Provide information about alternative treatment options and potential outcomes. (A1)***
  - ***f) Ensure donor confidentiality is assured (Not graded)***

- ***Identify unsuitable donors at the earliest possible stage of assessment. Initial donor triage can be performed using a standardised questionnaire by telephone interview or online. (Not graded)***

- ***Plan assessment around the donors' commitments and constraints wherever possible. The organisational details for evaluating a prospective donor will vary between centres, reflecting available resources and personnel. Evaluation must be undertaken according to an agreed protocol. (Not graded)***

- ***Relay the outcome of investigations accurately, appropriately and efficiently to the potential donor. A designated senior coordinator facilitates optimal communication. (Not graded)***

- ***Establish a policy for managing donors who are found to be unsuitable and provide appropriate follow-up and support. (Not graded)***

- ***The pace of donor assessment may be tailored to the rate of decline of liver function, but this must not compromise donor safety nor the provision of adequate time for the donor. (A1)***

- ***The timing of transplantation is optimised if donor evaluation is initiated early, allowing time for consideration of more than one donor where necessary. The pace of donor assessment must be tailored according to the rate of decline of recipient liver function, taking into account specific clinical and donor circumstances. (C1)***

Evaluation of potential candidates for donor hepatectomy in living donor liver transplantation (LDLT) is a rigorous multi-step, multi-disciplinary process that reflects the unique clinical circumstance where a healthy individual derives no inherent benefit from a major surgical procedure. Careful assessment must be undertaken to establish both donor and recipient risks, such as donor comorbidity and potential disease transmission.

The evaluation process aims to provide a systematic physical and psychosocial assessment of risk, the provision of informed consent, and the confirmation of autonomous motivation. This requires an experienced clinical team and a clear separation of donor and recipient clinical interests throughout. Independent Assessment for the HTA ensures the legal and ethical obligations are fulfilled (see sections 3 and 4).

The following provides a framework for donor evaluation, recognising that each donor presents unique circumstances in which adjustments to the protocol may be required.

8.1.1 Pre-Assessment

Before starting the formal donor assessment, the following preliminary steps are recommended:

- Establish the provisional suitability of the potential recipient for transplantation. This manages expectations for both the donor and recipient and avoids unnecessary anxiety, healthcare costs, inconvenience, and the risks of the evaluation process.
- Discuss alternatives to living donation with the prospective donor and explain that evaluation can be stopped at any point, as directed by them, without any sanction.
- Manage the expectations of the potential donor with respect to outcome of the assessment. Investigation may reveal previously undiagnosed disease that could prejudice future life, health insurance or specialist employment. Similarly, HLA analysis may reveal unexpected parentage (see section 6.3). An outline of the investigation protocol must be provided with specific mention of possible allergic reactions to intravenous contrast administered at abdominal imaging and the risks attached to a liver biopsy. Conversely, it should be explained that

screening may benefit the potential donor through early disease or genetic detection.

- Uphold patient confidentiality. Volunteering for living organ donation often involves detailed family discussion. However, donor confidentiality remains paramount and the reasons for declining a donor should not be volunteered to the recipient or other family members without explicit consent. A generic statement about the suitability of a donor with reference to the stringent assessment criteria can be helpful in providing an explanation. The donor should be informed of this ethical principle before assessment (see section 6).
- Ensure the donor understands the difference between a healthy individual and one who is suitable to donate (e.g. an anatomical variant within an otherwise normal liver or non-phenotypic genetic carriage may disqualify donation).

8.1.2 Triage

If the prospective donor wishes to proceed after the pre-assessment phase of education and counselling, a triage review is performed.

Enquiries about living donation originate predominantly from recipient family members, of whom a significant number will be unsuitable to be considered as donors. Emphasis is placed on the earliest possible identification of these inappropriate donors, given the intensive labour and cost resources of assessment.

It is recommended that an initial telephone interview, followed up by a standardised triage questionnaire is completed by a senior transplant coordinator / specialist nurse. This initial evaluation will identify lifestyle issues, body mass index (BMI), previous abdominal surgery, medical and psychiatric co-morbidity, and risk factors for liver disease. Some centres use a National Screening Medical Health Tool for this triage. Potential contraindications to proceeding with assessment can be discussed within the multi-disciplinary team at an early stage.

ABO blood grouping is an important early screening test to identify unsuitable donors due to blood group incompatibility. It may be undertaken by a general practitioner (GP), specialist nurse, or at a specialist clinic. If the donor and recipient are not compatible, this provides an early opportunity to enquire about other potential donors.

Access to appropriate counselling and clinical follow-up for unsuitable donors is recommended. This can be facilitated by liaison with community and primary care and through communication with the GP.

8.1.3 Systematic Assessment

Following successful completion of the triage review, a systematic donor evaluation process is undertaken.

In most units, donor assessment at this stage will be arranged by a senior transplant coordinator / specialist nurse supported by a clinician. The clinician, normally a physician / hepatologist, undertakes the medical examination of the potential donor. To avoid conflict of interest, the donor clinician should not have direct responsibility for the care of the transplant recipient.

In addition to the specialist transplant nurse and hepatologist, the core multidisciplinary team (MDT) includes colleagues from anaesthesia, intensive care, psychiatry and social work. A senior surgeon will take responsibility for both donor and recipient surgical safety. All these members will review the candidate individually. Some centres add a separate clinician as donor advocate. In the UK, the Independent Assessor fulfils the legal requirements for the HTA (see section 3). Additional support from radiology, cardiology, haematology and infectious disease colleagues may be necessary.

Objectives of the comprehensive assessment are well defined. Requirements include:

- determining the general medical health of the donor
- establishing the integrity of the donor liver function and potential graft quality
- assessing the risk of donor-derived transmission of disease to the recipient
- establishing the suitability of vascular and biliary anatomy
- psychosocial evaluation, including the capacity to give valid consent and the motivation for donation (see section 7).
- balancing the donor risk in relation to predicted recipient outcome (see section 11). This is judged from the health professionals' perspective rather than that of the potential donor, who is likely to be less risk averse. Stricter pre-operative criteria are, therefore, applied.

To appropriately address these potential risks and complications, members of the MDT must tailor their clinical history, examination and investigations accordingly. Best practice includes a standardised questionnaire and a pre-determined investigation order set (e.g. via an electronic patient record system) to consistently capture complete information. It is important to emphasise that the pace of the donor work up must be driven by donor safety and the provision of adequate time for informed consent, even when the potential recipient is very sick.

An MDT approach to assessment is essential to pool expertise and elicit essential information and history taking from different perspectives.

Clinical and family assessment must include the following:

***Cardiovascular*:** hypertension, diabetes mellitus, cardiovascular disease
***Haematological*:** thrombophilia, G6PD deficiency, haemoglobinopathy
***Obstetric/gynaecological*:** pregnancy complications (including cholestasis, venous thrombosis), hormonal therapy
***Hepatology*:** autoimmunity, high-risk adult behaviour for viral disease
***Transmissible disease*:** outcomes of national cancer screening programmes, malignancy, overseas residence (geographical risk factors), family history of Creutzfeldt-Jakob disease, treatment with natural growth hormone
***Anaesthesia*:** allergy, intubation history
Psychiatry: substance misuse, morbidity (see section 11 for full assessment)
***Lifestyle*:** tobacco exposure, alcohol intake, exercise capacity (Dukes Activity Index) (1)

8.1.4 Investigations

Laboratory - general screening:

- Full blood count, coagulation screen (PT and APTT), thrombophilia screen (lupus anticoagulant, anticardiolipin antibodies, activated protein C resistance / factor V Leiden, prothrombin II G-20210-A and MTHFR genotyping, protein C, S and antithrombin III levels, sickle cell and haemoglobinopathy screen, G6PD deficiency
- Creatinine, urea and electrolytes, liver enzymes, bone profile, fasting plasma glucose and lipid profile, thyroid function
- Pregnancy test (if indicated)

- Virology and infection screen (HIV, HTLV1 and 2 (if appropriate), cytomegalovirus, Epstein-Barr virus, toxoplasma, syphilis, malaria, trypanosoma cruzi, schistosomiasis (in donors originating from endemic geographical areas)

Cardiovascular system:

- Chest X-ray and ECG; echocardiogram, coronary vessel calcium score and cardiovascular stress test (where indicated), lung function tests in smokers and asthmatics

Liver specific:

- Chronic liver disease screen (autoantibodies, immunoglobulins, ferritin, alpha-1 antitrypsin levels and phenotypic studies if indicated, hepatitis serology, copper studies, angiotensin-converting enzyme, genetic studies in either donor or recipient cholestasis syndromes)
- Ultrasound of the abdomen with elastography (Fibroscan or equivalent), computerised tomography (CT) scan of the abdomen and liver, non-invasive biliary imaging (MRCP)
- Liver volumetrics in whole right or left lateral segment donation
- Biopsy of the liver in selected individuals

8.2 DONOR AGE

Statements of Recommendation

- ***There is no specific age beyond which donation is contraindicated, but the medical work-up of older donors must be especially rigorous. (Not graded)***

- ***Both donor and recipient must be made aware that the older donor may be at greater risk of peri-operative complications. (Not graded)***

When assessing general risk factors for surgery in living organ donation (e.g. age, diabetes and hypertension), data on the outcome of liver surgery are less comprehensive than for living donor nephrectomy, and data relating to open liver surgery are not directly comparable. United States (US) registry data on living liver donation are an important source of information.

8.2.1 General Risk Factors Related to Age and Gender

There is a lack of evidence about the impact of increasing age on donor complication rates but it is likely that older age increases the risk of complications through impaired hepatic regenerative capacity (2). Morbidity and mortality is disproportionately higher in older patients after hepatectomy, both in disease-generated and living-donor procedures. The medical evaluation, particularly of the cardiovascular system, needs to be especially rigorous in older donors.

Formal testing to exclude occult ischaemia is recommended in donors of 45 years or over. Cardiopulmonary exercise testing (CPET), particularly the definition of anaerobic threshold has been validated as a predictor of post-operative complications, particularly in older patients (see section 8.6: Cardiovascular Evaluation) (3).

Defining an upper age limit for liver donation is not feasible as other individual donor factors and the volume of the proposed liver resection required must be taken into account.

In UK practice, most LDLT is performed from adults to children (normally from a biological parent). There are specific considerations when assessing young mothers/female donors for donation:

- Pregnancy is a contraindication to donation
- Early counselling should be offered about non-pharmacological or progesterone-only contraception. Combined oestrogen and progestogen preparations should be avoided and/or stopped due to an increased risk of thrombosis. Early stopping allows for the latent period for pharmacological ‘wash-out’
- Where several potential living donors are available, it may be preferable to consider an alternative donor before assessing a woman who may still wish to bear children or who has young dependents

8.3 DONOR OBESITY

Statements of Recommendation

- ***Any donor with body mass index (BMI) >30 kg/m2 needs a liver biopsy because of the increased risk of donor hepatic steatosis and the possibility of steatohepatitis. (A1)***

- ***Moderately obese donors (BMI 30-35 kg/m^2) should be counselled about the increased risk of peri-operative complications and long-term health risks. They should be advised to lose weight prior to donation and to maintain their ideal weight following donation. (B1)***

- ***Donor BMI >35 kg/m^2 should be considered a contraindication to donation because of the high risk of post-operative complications. (B1)***

Obesity is associated with increased morbidity and mortality and is a relative contra-indication to living organ donation because of the increased risk of surgical complications (4,5). Peri-operative wound and urinary infection, venous thrombosis and cardiorespiratory events are more frequent. A systematic review and meta-analysis of ten studies examining the influence of obesity in living kidney donors found an upward trend in complications related to increasing BMI.

The frequent co-existence of obesity with the metabolic syndrome and fatty liver disease adds to complexity and risk. All overweight potential donors need careful evaluation of the liver parenchyma for macrosteatosis by imaging-based methodology, and potentially liver biopsy (see section 8.8). This is crucial as hepatic steatosis is a recognised risk factor for poor graft function; a recent systematic review showed an increased risk of poor graft outcome in livers with moderate-severe steatosis (6).

Increasing BMI is associated with specific complications following donor hepatectomy, including bile leakage and incisional hernia. The Pittsburgh group identified BMI ≥30 kg/m^2 and macrovesicular steatosis as significant risk factors for the development of high Clavien grade post-operative complications. Most units would consider a recipient BMI >35 kg/m^2 to be a strong contraindication to donation.

8.4 HYPERTENSION

Statement of Recommendation

- ***Donors with well-controlled hypertension and no major end organ damage can be considered for living liver donation. (B1)***

Office-blood pressure measurements are sufficient for the assessment of the majority of potential living liver donors. Mild to moderate hypertension that is controlled with one or two antihypertensive agents is not a contraindication to donation providing significant end organ damage has been excluded.

8.5 DIABETES MELLITUS

Statement of Recommendation

- ***In the absence of evidence of target organ damage and having ensured that other cardiovascular risk factors such as obesity, hypertension or hyperlipidaemia are optimally managed, potential donors with both type 1 and type 2 diabetes can be considered for living liver donation. (Not graded).***

Consideration of patients with diabetes requires careful evaluation of the risks and benefits. In the absence of evidence of target organ damage and having ensured that other cardiovascular risk factors such as obesity, hypertension or hyperlipidaemia are optimally managed, diabetics can be considered for liver donation. Cardiovascular stress testing should be routinely performed in the majority of this patient group (see section 8.6: Cardiovascular Evaluation).

8.6 CARDIOVASCULAR EVALUATION

Statements of Recommendation

- **All potential donors should be screened for cardiovascular disease and there should be a low threshold for their exclusion if significant risk factors are found. (B1)**

- **Potential donors with reduced exercise capacity or >5% estimated risk of significant coronary atherosclerosis should undergo formal cardiovascular assessment. (A2)**

- **Cardiopulmonary exercise testing should be available at all centres. (Not graded)**

Cardiovascular assessment of the donor attempts to detect subclinical cardiac disease in ostensibly asymptomatic individuals that may impact upon the safety of surgery.

Electrocardiography (12 lead, surface ECG) may indicate the presence of pre-existing ischaemic heart disease or cardiomyopathy. Cardiomyopathy, particularly hypertrophic cardiomyopathy (incidence 1:500), is the most common cause of sudden cardiac death in apparently healthy young people who would otherwise be ideal donors (7). Any abnormality should trigger formal assessment. The presence of overt cardiac disease will exclude most individuals as potential donors.

The presence of established cardiovascular risk factors (e.g. age, tobacco exposure, hypercholesterolaemia, diabetes, hypertension and family history) can be used to estimate the probability of coronary disease. A threshold of 10% or greater is cited in other guidance, including the UK Guidelines for Living Donor Kidney Transplantation which conclude that identification of more than one risk factor and all men over the age of 55 years require formal testing to exclude occult ischaemia (8,9). In view of the relative risk associated with donor hepatectomy in comparison with donor nephrectomy, a lower age threshold of 45 years (which approximates to a 3-5% risk of coronary disease) is recommended. Coronary vessel calcium scoring appears to be the best discriminant investigation for coronary artery disease.

In all other individuals (age <45 years and no cardiovascular risk factors), the presence of a functional capacity in excess of 4 metabolic equivalents (METS) has been shown to predict a very low peri-operative risk or later frequency of cardiovascular events. Functional capacity can be assessed formally with a treadmill or more simply using the Duke Activity Status Index (a short questionnaire). Following calculation of the Activity Status, a simple calculation of the peak oxygen and METS is performed. This algorithm can be incorporated into the screening questionnaire. If a functional capacity of greater than 4 METS can be reliably established, there appears to be little incremental screening benefit from stress testing (1,10-15).

Where there is uncertainty about functional capacity or identification of other risk factors, cardiology review is recommended. Investigation protocols are influenced by local service provision and access to the different modalities for assessment. The combined cardiopulmonary exercise test (CPET) is reliable, safe, repeatable and non-invasive. It quantifies the functional capacity to respond to increased metabolic demands and generates a patient-specific measure of risk. This test should be available to all LDLT programmes.

8.7 HAEMATOLOGICAL DISEASE

Statement of Recommendation

- **Patients with a personal or family history of bleeding or thrombosis should be screened for haematological abnormalities using evidence-based protocols. (A1)**

Venous thromboembolism (VTE) is a well-documented complication of hepatectomy and has been reported after living donation, contributing to at least two peri-operative deaths. VTE risk increases with the extent of hepatectomy, outweighs bleeding risk, and is associated with increased mortality. The individual risk of thrombosis following surgery can be more accurately defined by characterising underlying genetic profiles and performing a thorough thrombophilia screen. An extensive panel of investigations (acquired and genetic risk factors) is recommended (see section 8.1), with specialist haematology interpretation and advice. Prophylactic anticoagulation will be suitable for most low-risk candidates but will be absolutely contraindicated for certain profiles.

8.7.1 Red Cell Disorders

Sickle Cell Disease and Sickle Cell Trait

Sickle cell disease is an absolute contraindication to living donation due to the risk of anaesthesia triggering a crisis and the potential of sickle cell hepatopathy. Sickle cell trait (SCT) is not an absolute contraindication to donation but the peri-operative risks may be higher, including complications such as VTE. Donors with SCT wishing to proceed must be counselled about the possible risks. Input from a haematologist with an interest in sickle cell disease is recommended.

Thalassaemia

Patients with thalassaemia (major, intermedia and haemoglobin H disease) are not suitable for living liver donation as their requirement for blood transfusions causes iron overload and associated liver damage. Thalassaemia trait individuals can be considered.

Haemoglobin C & Haemoglobin E

These haemoglobinopathies may be seen in donors of non-northern European heritage. Neither should pose a problem to liver donation except where Hb C is combined with sickle haemoglobin i.e. Hb SC. Such patients behave like patients with sickle cell disease and therefore should not be considered.

Red cell membrane disorders

These disorders, including hereditary spherocytosis, hereditary elliptocytosis and inherited haemolytic anaemias may be acceptable in mild forms.

8.7.2 White Cell Disorders

Chronic white cell disorders are invariably contraindications to living liver donation. Expert haematological review of donors presenting with these disorders is required.

8.7.3 Platelet Disorders

There is no clear consensus regarding the appropriateness of organ donation from living donors with a history of treated idiopathic thrombocytopenia (ITP), but the

increased risk to the recipient appears low. However, case reports of transplantation-mediated alloimmune thrombocytopenia associated with the transfer of donor anti-platelet alloantibodies do indicate a potential for harm, and careful risk assessment and counselling is indicated (16).

8.8 LIVER INTEGRITY

Statements of Recommendation

- ***The donor must undergo comprehensive laboratory assessment. A1)***
- ***Imaging must assess fatty infiltration in addition to the biliary and vascular anatomy. (A1)***
- ***Liver biopsy is indicated in the presence of biochemical, serological or imaging evidence of liver disease. (A1)***
- **The possibility of genetic liver disease in the donor requires specialist evaluation. *(A2)***
- ***When the cause of liver failure in the recipient is due to an inherited condition, reasonable steps must be taken to exclude genetic disease in the potential donor if he/she is a blood relative. (B1)***
- ***Inherited liver disorders are rare, so a specialist paediatric hepatologist or clinical genetic service must assess likely risks to family members. (B2)***
- ***The discovery of a potential familial or genetic risk must be conveyed to the donor, with advice on sharing this information with appropriate family members. (B2)***

Confirmation that the proposed donor liver has suffered no significant previous injury is a fundamental element of assessment. It must be established that the residual liver will provide adequate physiological reserve for the donor after the partial hepatectomy and

additionally, that the donated lobe/segment will function satisfactorily for the recipient. The topics that need to be covered in the clinical history and laboratory screening tests for chronic liver disease have been listed previously.

Detailed structural review of the liver architecture and vasculature is required. Imaging of the liver is performed to investigate for signs of chronic disease, the presence of portal hypertension, and fatty liver disease. The latter is a common finding and the level of steatosis influences donor and recipient outcomes after liver transplantation (see sections 9.3 and 11). Among living liver donors, a residual liver with a fat content of less than 5% shows better regeneration than one with macrosteatosis between 5–30%. As the level of steatosis increases from mild to moderate (30%) to severe (60%), the risk of graft dysfunction and renal failure in the recipient increases (6). Early mortality and the frequency of severe ischemia-reperfusion injury also increase significantly. For these reasons, imaging is performed to allow an estimation of fat quantification.

Ultrasonography is a sensitive modality for screening for chronic liver disease but, although it can be used as a qualitative screening tool for the presence of fat, it is not sufficiently accurate for quantification. An unenhanced CT liver protocol allows comparatively accurate quantification and is recommended as the next image-based technique. Hepatic attenuation measurements and calculation of the hepatic attenuation index require expert radiology expertise. T1-weighted MR imaging (Dixon calculations) may be preferred by local radiologists. Although ^{1}H MR spectroscopy also allows accurate quantification, it is not routinely available in UK practice.

The sensitivity and specificity of these imaging modalities are technique and operator dependent and vary based on the degree of steatosis present. Increasing degrees of steatosis also increase the sensitivity of the imaging modalities. In one study, the presence of >33% fat on liver biopsy was optimal for the accuracy of estimation of steatosis. However, no imaging modalities are able to reliably quantify the amount of steatosis or distinguish between simple steatosis and steatohepatitis (17).

Where estimates of fat infiltration exceed 10-20% or whenever there is serological evidence of a liver disorder, careful consideration of liver biopsy is needed. The threshold for this invasive procedure, with its attendant risk of bleeding, has to be weighed against the valuable information that histological review often provides. In fatty liver disease, histopathological review not only grades the severity of steatosis but it allows differentiation between steatosis and steatohepatitis. It not only helps confirm

the diagnosis of non-alcohol-related fatty liver disease or non-alcohol-related steatohepatitis, but it may detect clinically unsuspected processes that coexist with or mimic fatty liver disease. Steatohepatitis is associated with less favourable outcomes following hepatectomy.

Data from the Fibroscan technique (or its equivalent) are controversial in detecting steatosis and evaluating fibrosis in asymptomatic healthy individuals and, as yet, cannot replace the traditional algorithm of ultrasound and biopsy. Expert hepatology review should be available to interpret and respond to the findings.

8.8.1 Alpha-1 Antitrypsin Deficiency

Alpha 1-antitrypsin deficiency is inherited as an autosomal recessive disorder. To date more than 100 alleles have been identified, only some of which are associated with liver disease. The most prevalent carrier phenotypes are PiMS and PiMZ, and deficiency phenotypes are PiSS, PiSZ and PiZZ.

If the liver screen of the potential donor reveals a low alpha-1 antitrypsin level, phenotyping and genotyping are recommended. Further action will be dependent on those results:

- If the phenotype is PiZZ, this is the most commonly associated phenotype with liver cirrhosis (one third of PiZZ adults will develop chronic liver disease) and further assessment of the donor is not recommended.

- If the phenotype is heterozygous for the Z or S phenotypes, then the risk of developing chronic liver disease is less clear. While the PiMZ phenotype may confer an increased risk for chronic liver disease, neither the PiMS nor PiSS phenotypes are directly correlated with liver disease. Such phenotypes therefore should not be disregarded but assessed further with a liver biopsy to look for evidence of underlying liver disease, especially if there are other co-factors for liver disease (18-19).

8.8.2 Hereditary Haemochromatosis Carriers

If the liver screen shows an elevated serum ferritin, then assessment of transferrin saturation is recommended. If this is elevated, then HFE-genotyping is recommended.

- If the genotype is consistent with HFE-related hereditary haemochromatosis, further assessment of the donor is not recommended.
- If the genotype is heterozygous for C282Y or H63D or a compound heterozygote C282Y/H63D, then liver biopsy is recommended to assess for the degree of siderosis and evidence of chronic liver disease (18-23).

8.8.3 Other Genetic Liver Disease

If the cause of chronic liver disease is due to other genetic causes such as Wilson's disease or other rare autosomal recessive conditions such as urea cycle disorders and the potential donor is a relative of the recipient, genetic testing is recommended for the specific condition. Liver biopsy is then recommended if there is concern about the potential for liver disease in the donor (19).

Data on the outcome of liver grafts from heterozygotic carriers for progressive familial intrahepatic cholestasis (PFIC) are encouraging (19,24,25).

8.9 DONOR-RECIPIENT TRANSMISSIBLE DISEASE

8.9.1 Infection

Statements of Recommendation

- ***Infection screening is important to identify potential risk for the donor from previous or current infection and to assess potential risk of transmission to the recipient. (A1)***

- ***Active hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are contraindications to donation. HBV core antibody positive patients and***

HCV antibody positive/HCV RNA negative patients can be considered as liver donors in exceptional circumstances. (A1)

- ***Cytomegalovirus or Epstein Barr Virus positivity is not a contraindication to donation but counselling must be provided re the risk of primary infection and lymphoproliferative disorder. (A1)***

- ***Human immune deficiency virus or human T lymphotrophic virus infection is an absolute contraindication to donation. (A1)***

Identification of current or previous infection in the prospective donor is an important component of donor evaluation. A number of infections may be transmitted at the time of organ transplantation.

Infections can be transmitted by organ donation during the incubation period of the offending organism and before a serological response has been mounted. Serology is therefore not a substitute for a detailed psychosexual and medical history. Routine testing for viral infection may, if positive, raise complex ethical problems.

Human Immune Deficiency Virus (HIV) or Human T Lymphotrophic Virus (HTLV)

The presence of human immune deficiency virus (HIV) or human T lymphotrophic virus (HTLV) infection is an absolute contraindication to living donation. HIV and HTLV serology must be performed in the prospective donor (26).

Hepatitis C Virus

Active hepatitis C virus (HCV) in the donor is a contraindication to living donation. The risk of HCV transmission from an HCV RNA positive donor approaches 100% if transplanted into a virus-naive recipient. All potential donors must have HCV antibody testing performed and, if positive, HCV RNA must be checked. If the antibody-positive donor is consistently RNA negative, then transplantation may be considered, even into a naive recipient. The risks must be carefully explained to both donor and recipient.

Hepatitis B Virus

Most transplant units would not consider potential donors with evidence of active hepatitis B virus (HBV) replication. All prospective donors must have both surface antigen (HBsAg) and total core antibody (HBV total core Ab) estimated. HBV DNA

testing must be performed in prospective donors from endemic areas who are core antibody positive, those with possible mutant HBV, and those with abnormal liver tests or a past history of liver disease of unknown aetiology. Testing for HBV IgM core antibody is not required unless the donor is HBeAg positive and acute infection is queried.

Several studies of both liver and kidneys transplanted from HBsAg and HBV DNA negative but core antibody-positive deceased donors report a low risk of seroconversion and no excess risk of graft failure or short-term morbidity. In the context of living donation, donors with this virological profile may be considered providing the recipient has either been effectively immunised against HBV or will be administered maintenance antiviral therapy. Advice from a hepatologist must be sought under these circumstances and the donor and recipient kept fully informed (27).

Cytomegalovirus (CMV) Infection

CMV infection is the most common clinically significant viral infection after liver transplantation and may cause significant morbidity and mortality. It also increases the risk of chronic graft dysfunction and post-transplant lymphoproliferative disorder (PTLD) and opportunistic infection.

CMV disease may result from reactivation of latent infection or because of primary infection transmitted by liver or blood product transfusion from a CMV positive donor. Primary infection is generally more severe. Matching CMV seronegative recipients with CMV seronegative donors is an effective strategy for reducing the risk of CMV infection but is rarely practicable in the context of living donor transplantation. Either CMV prophylaxis or pre-emptive therapy with close monitoring of viral loads must be offered. Education of donor and recipient regarding this viral illness is recommended.

Epstein-Barr virus (EBV) infection

Primary EBV infection is most likely to occur in EBV-negative paediatric recipients who receive a liver from an EBV-positive donor. EBV infection increases the risk of PTLD several-fold and this risk is increased further if the recipient is given anti-lymphocyte antibody immunosuppressive therapy. Vigilance is required to detect PTLD as early as possible. Consideration must be given to the prophylactic use of antiviral agents in order to minimise viral load after transplantation, although the benefit of this approach is unclear (28).

Miscellaneous Infection

HHV8 may be transmitted by organ transplantation and is associated with an increased risk of Kaposi sarcoma (29,30). However, there is no evidence to support the screening of potential organ donors.

There must be active screening for *Mycobacterium tuberculosis* and atypical mycobacteria. A careful history and a chest X-ray is a satisfactory initial triage.

Transmission of syphilis has been reported in the UK to two recipients from a deceased organ donor with a past history of treated disease. If there is concern re potential transmission, discussion with specialist in genitourinary medicine is recommended.

Toxoplasmosis and malaria have been transmitted by living donor kidney transplantation in the developing world.

No screening test is currently available for the prion-associated diseases (CJD or vCJD). To date, transmission by living donor kidney or liver has not been reported. Relevant history would include recipients of human pituitary-derived (growth) hormones, dura mater, corneal and scleral grafts or a positive family history of prion-associated disease.

8.10 MALIGNANCY

Statements of Recommendation

- ***Careful history taking, clinical examination and investigation of potential donors are essential to exclude occult malignancy, particularly in older (age >45 years) donors. (A1)***

- ***Active malignant disease is a contraindication to living donation, but donors with certain types of successfully treated low-grade tumours may be considered after careful evaluation and discussion. (A1)***

- ***Axial imaging of the abdomen by CT or MR examination is mandatory, with specific liver review for secondary malignant disease. (A1)***

Two types of donor-derived malignancy are possible: inadvertent transfer of tumour tissue (tumour transmission); and *de novo* malignancy arising after transplantation in donor-derived tissue. To minimise these risks, any past medical history of malignant disease is recorded and symptoms consistent with undiagnosed malignancy identified. During clinical examination, the possibility of occult malignancy must be considered and care taken to exclude the presence of potentially malignant skin lesions, abdominal masses, breast lumps, testicular swelling or lymphadenopathy.

Screening procedures applicable to the general population (age and gender dependent) must have been performed e.g. cervical screening, mammography, faecal occult blood for colorectal malignancy (31-33).

The lower age limit for donors generally accepted for liver, compared with kidney transplantation reduces the risk of cancer transmission. In contrast, the tendency of primary tumours to metastasise to the liver increases this risk, and accordingly axial imaging of the abdomen by CT or MR examination is recommended, with specific liver review to exclude secondary malignant disease.

If the potential donor gives a history of treated malignant disease, there are no reliable data from which to accurately predict the risk of tumour transmission to the recipient. The situation is further complicated by wide variations in the natural history of different primary tumours. Registry data relating to tumour transmission from deceased donors reveal that certain tumours are particularly high risk, e.g. renal cell, lung, breast, prostate and colonic carcinomas as well as lymphoma, glioblastoma multiforme and metastatic melanoma. Some of these tumours also have a known potential for very late recurrence. A donor with a history of any these cancers is excluded from donation.

For other rarer tumours, advice is available from the Amsterdam Forum for Living Donation (2005) and the Israel Penn International Transplant Tumor Registry.

8.11 PSYCHOSOCIAL EVALUATION

Assessment of the donor's psychosocial situation and support mechanisms is an essential part of donor evaluation. Both a psychiatrist and a social worker act

independently to review the donor (see sections 7 and 8.11).

8.12 IMMUNOLOGICAL ASSESSMENT

Studies regarding the role of HLA compatibility in LDLT have produced inconsistent results, with many focusing solely on paediatric data. Many of the early studies were limited by small sample size and a lack of specific subgroup analysis. In adult LDLT, HLA matching appears to be associated with a lower incidence of rejection, but data on graft survival are limited (34,35).

An early analysis of the Organ Procurement and Transplantation Network (OPTN) database suggested a higher graft failure rate in patients who underwent LDLT from donors with a close HLA match (36). An updated paper investigated the association between five year graft survival and total, locus-specific and haplotype matching in 631 recipients with autoimmune (fulminant autoimmune hepatitis, cirrhosis secondary to autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) or non-autoimmune liver disease (37). This study showed no detrimental impact of close HLA matching on graft survival in LDLT recipients. A close HLA match did not reduce graft survival in recipients with underlying autoimmune liver disease, compared with other recipients. Nor, using the degree of relatedness between the recipient and donor as a surrogate for close HLA match, was there any difference in graft survival in related vs. unrelated donor-recipient pairs.

Several investigators have proposed that transplanting a graft with a closely matched HLA phenotype could be associated with graft injury by enhancing immune-mediated mechanisms involved in the recurrence of hepatitis B, C, and autoimmune liver diseases, or by predisposing to CMV hepatitis. These observations have not been confirmed, but remain an area of particular interest in LDLT where there is a usually a higher degree of HLA matching (38).

References

1. Hltaky MA, Boineau RE, Higginbottom MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am

J Cardiol 1989; 64: 651-4.
2. Akamatsu N, Sugawara Y, Tamura S, et al. Impact of live donor age (>or=50) on liver transplantation. Transplant Proc 2007; 39: 3189-93.
3. Older P, Hall A. Clinical review: how to identify high-risk surgical patients. Crit Care 2004; 8: 369-72.
4. Moss J, Lapointe-Rudow D, Renz JF, et al. Select utilization of obese donors in living donor liver transplantation: implications for the donor pool. Am J Transplant 2005; 5: 2974-81.
5. Brandhagen D, Fidler J, Rosen C. Evaluation of the donor liver for living donor liver transplantation. Liver Trans 2003; 9: S16-28.
6. Chu MJ, Dare AJ, Phillips AR, Bartlett AS. Donor hepatic steatosis and outcome after liver transplantation: a systematic review. J Gastrointest Surg 2015 April 28 [Epub ahead of print].
7. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA 1996; 278: 199-204.
8. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979; 300: 1350-8.
9. UK guidelines for living donor kidney transplantation (3rd edition) 2011. http://www.bts.org.uk/BTS/Guidelines_Standards/Current/BTS/Guidelines_Standards/Current_Guidelines.aspx?hkey=e285ca32-5920-4613-ac08-fa9fd90915b5
10. Nelson CL, Herndon JE, Mark DB, Pryor DB, Califf RM, Hlatky MA. Relation of clinical and angiographic factors to functional capacity as measured by the Duke Activity Status Index. Am J Cardiol 1991; 68: 973-5.
11. Myers J, Do D, Herbert W, Ribisl P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. Am J Cardiol 1994; 73: 591-6.
12. Bartels C, Bechtel JF, Hossmann V, Horsch S. Cardiac risk stratification for high-risk vascular surgery. Circulation 1997; 95: 2473-5.
13. Reilly DF, McNeely MJ, Doerner D, et al. Self-reported exercise tolerance and the risk of serious perioperative complications. Arch Intern Med 1999; 159: 2185-92.
14. Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. Chest 1999; 116: 355-62.
15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100: 1043-9.

16. Diaz GC, Prowda J, Lo IJ, et al. Transplantation-mediated alloimmune thrombocytopenia: guidelines for utilization of thrombocytopenic donors. Liver Transpl 2008; 14: 1803-9.
17. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745-50.
18. Pungpapong S, Krishna M, Abraham SC, Keaveny AP, Dickson RC, Nakhleh RE. Clinicopathologic findings and outcomes of liver transplantation using grafts from donors with unrecognized and unusual diseases. Liver Transpl 2006; 12: 310-5.
19. Schielke A, Conti F, Gourmard C, Perdigao F, Calmus Y, Scatton O. Liver transplantation using grafts with rare metabolic disorders. Dig Liver Dis 2015; 47: 261-70.
20. Crawford DH, Fletcher LM, Hubscher SG, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: implications for pathogenesis. Hepatology 2004; 39: 1655-62.
21. Dwyer JP, Sarwar S, Egan B, Nolan N, Hegarty J. Hepatic iron overload following liver transplantation of a C282y homozygous allograft: a case report and literature review. Liver Int 2011; 31: 1589-92.
22. Wigg AJ, Harley H, Casey G. Heterozygous recipient and donor HFE mutations associated with a hereditary haemochromatosis phenotype after liver transplantation. Gut 2003; 52: 433-5.
23. Koskinas, Portmann B, Lombard M, Smith T, Williams R. Persistent iron overload 4 years after inadvertent transplantation of a haemochromatotic liver in a patient with primary biliary cirrhosis. J Hepatol 1992; 16: 351-4.
24. Shimizu H, Migita O, Kosaki R, et al. Living-related liver transplantation for siblings with progressive familial intrahepatic cholestasis 2, with novel genetic findings. Am J Transplant 2011; 11: 394-8.
25. Hori T, Egawa H, Takada Y, et al. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. Clin Transplant 2011; 25: 776-85.
26. Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO). Guidance on the microbiological safety of human organs, tissues and cells used in transplantation.
https://www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation
27. Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. Am J Transplant 2015; 15; 1162-72.

28. Holmes RD, Orban-Eller K, Karrer FR, Rowe DT, Narkewicz MR, Sokol RJ. Response of elevated Epstein-Barr virus DNA levels to therapeutic changes in pediatric liver transplant patients: 56-month follow up and outcome. Transplantation 2002; 74: 367-72.
29. Kemény L, Kiss M, Gyulai R, et al. Human herpesvirus 8 in classic Kaposi sarcoma. Acta Microbiol Immunol Hung 1996; 43: 391-5.
30. Brambilla L, Boneschi V, Corbellino M, Parravicini C. HHV8 cell-associated viraemia and clinical presentation of Mediterranean Kaposi's sarcoma. Lancet 1996; 347: 1338.
31. Chen YS, Cheng YF, De Villa VH, et al Evaluation of living liver donors. Transplantation 2003; 75: S16-9.
32. Sharma A, Ashworth A, Behnke M, Cotterell A, Posner M, Fisher RA. Donor selection for adult-to-adult living donor liver transplantation: well begun is half done. Transplantation 2013; 95: 501-6.
33. Trotter JF, Wisniewski KA, Terrault NA, et al. Outcomes of donor evaluation in adult-to-adult living donor liver transplantation. Hepatology 2007; 46: 1476-84.
34. Suehiro T, Shimada M, Kishikawa K, et al. Influence of HLA compatibility and lymphocyte cross-matching on acute cellular rejection following living donor adult liver transplantation. Liver Int 2005; 25: 1182-8.
35. Markus BH, Duquesnoy RJ, Gordon RD, et al. Histocompatibility and liver transplant outcome: does HLA exert a dualistic effect? Transplantation 1988; 46: 372-7.
36. Navarro V, Herrine S, Katopes C, Colombe B, Spain CV. The effect of HLA class I (A and B) and class II (DR) compatibility on liver transplantation outcomes: an analysis of the OPTN database. Liver Transpl 2006; 12: 652-8.
37. Jakab SS, Navarro VJ, Colombe BW, Daskalakis C, Herrine SK, Rossi S. Human Leukocyte Antigen and adult living-donor liver transplantation outcomes: an analysis of the Organ Procurement and Transplantation Network Database. Liver Transpl 2007; 13: 1405-13.
38. Donaldson P, Underhill J, Doherty D, et al. Influence of human leucocytes antigen matching on liver allograft survival and rejection: ‘the dualistic effect’. Hepatology 1993; 17: 1008-15.

9 DONOR SURGERY

Statements of Recommendation

- ***Computerised tomography (CT) or magnetic resonance imaging (MRI) of the donor liver with intravascular contrast must be performed. (A1)***

- ***3D reconstructions, using either in house or propriety software, are recommended to create detailed 3D models of liver anatomy for volumetric analysis and determination of vascular/biliary anatomy. (B1)***

- ***Conventional arteriography and hepatic venography must only be used in exceptional circumstances when conventional enhanced CT fails to give adequate imaging information. (B1)***

- ***Magnetic resonance cholangiopancreatography (MRCP) is the gold standard for biliary anatomy. Endoscopic retrograde cholangio-pancreatography (ERCP) must not be used to assess biliary anatomy. CT cholangiography or intra-operative cholangiography are suitable alternatives. (B1)***

- ***Steatosis assessment:***
  - ***Ultrasound can be used as a screening tool. MRI provides a better assessment in grading steatosis than CT and is the preferred option. (A1)***
  - ***With CT, the liver-to-spleen attenuation ratio (difference between hepatic and splenic attenuation) and blood-free hepatic parenchymal attenuation must be used. The maximum amount of steatosis is not well defined but acceptable limits range from 10–30%. (B1)***

- ***For volume calculation, the percentage of steatosis must be subtracted from the estimated liver mass for the graft. (C2)***

- ***Liver biopsy is reserved for the potential donor with unexplained abnormalities in liver function tests, body mass index (BMI) approaching***

30 kg/m^2, or aspartate aminotransferase (AST) > alanine transaminase (ALT). (B2)

- ***For donors who are initially rejected due to steatosis, a low calorie 'defatting diet' and reassessment with new volumetry can be considered. (B1)***

- ***For calculation of donor graft volume, software-assisted image post processing is recommended as it provides the most accurate method of assessment. (A1)***

- ***In calculating the standard liver volume of the recipient, published formulae with error rates of <10% must be used. (1B)***

- ***In adults, the choice of donor graft is aimed at reducing donor risks by achieving a large remnant volume, i.e. a small resection. A left graft should usually be considered first. (B1)***

- ***A graft weight/standard liver volume of 40% is the acceptable lower limit. If <40%, outflow and inflow modulation techniques must be used. (B1)***

- ***Using small for size (SFS) grafts (graft weight to recipient weight (GW/RW) ratio <0.8) can result in good outcomes but caution is advised in decompensated patients. (B1)***

- ***It is widely accepted that the absolute minimum donor remnant volume is 30%. (A1)***

- ***To avoid congestion in segment 5/8 for a right lobe graft, a "with middle hepatic vein (MHV) graft" or venous reconstruction of the anterior segment with an interposition vein graft is mandatory if the volume of the graft is borderline for the recipient and the portal pressures are elevated. (B1)***

- **The left graft can be procured with the left and the middle hepatic vein, particularly when the GW/RW ratio is low and extra liver volume is required to meet the metabolic demands of the recipient. (A2)**

- ***Although good outcomes have been reported from small series using laparoscopic or laparoscopy-assisted donor hepatectomy for the left lateral and left lobe, open donor hepatectomy is recommended in the interests of donor safety. (B1)***

- ***If the operating surgeon encounters an unexpected finding that, in his/her opinion, jeopardises the safety of the donor, donation must not proceed. (B1)***

- ***If a graft is explanted and cannot be used, a policy to utilise the organ must be in place.*** **The donor must be informed in advance about this possibility and pre-operative consent should be obtained to use the graft for another recipient.** ***(B1)***

- ***For the purposes of consent, information about all aspects of morbidity and mortality associated with living liver donation (LLD) must be provided. For new programmes, international statistics on morbidity and mortality must be used and the centre must make it known to the donor that it is an 'emerging' programme. For established programmes (>20 cases per year), centre-specific activity and morbidity and mortality data must be provided during the donor consent process. (B1)***

- ***A two stage consent process is best practice to ensure that the donor can give valid consent based upon the information provided. (B1)***

- ***The donor may choose to withdraw consent at any time prior to donation and the reasons must remain confidential. (B1)***

9.1 Donor Pre-operative Assessment and Preparation

The assessment and preparation of potential donors has two phases, detailed in section 8: Donor Evaluation.

After completion of the donor evaluation, a letter confirming the outcome must be sent to the referring clinician and the referring MDT informed.

9.2 Technical evaluation

9.2.1 Anatomy

Computed tomography (CT) or magnetic resonance imaging (MRI) of the donor liver with intravascular contrast is required.

3-D reconstructions are usually not needed for left lateral segment grafts. When considering right lobe or left lobe grafts, 3D reconstructions are recommended to create detailed models of liver anatomy, both for volumetric analysis and vascular/biliary anatomy. This provides detailed imaging for discussion of the suitability of right and left lobe donation in terms of vascular abnormalities and planning for venous reconstruction of veins of the cut surface. Conventional arteriography and hepatic venography are only used in exceptional circumstances when conventional enhanced CT fails to give adequate imaging information.

Magnetic resonance cholangiopancreatography (MRCP) is the gold standard for the assessment of biliary anatomy. CT cholangiography or intra-operative cholangiography may also be used, but endoscopic retrograde cholangiopancreatography (ERCP) is not suitable for this purpose.

9.2.2 Steatosis (see also 9.3.3)

CT: When using CT for steatosis evaluation, the liver-to-spleen attenuation ratio (the difference between the hepatic and splenic attenuation) and the blood-free hepatic parenchymal attenuation must be assessed.

Unenhanced CT provides high performance in the qualitative diagnosis of macrovesicular steatosis of 30% or greater and is helpful in avoiding unnecessary liver biopsy in those donor candidates with an unacceptable degree of macrovesicular steatosis. Current imaging may miss mild or moderate steatosis and some centres advocate a low threshold for liver biopsy, while performing selective biopsy if imaging raises doubts about the graft quality (1). With careful CT - calculating mean hepatic attenuation in multiple regions-of-interest (ROI), measurements on five sections (five ROI per section), and deriving a liver attenuation index (LAI) - it is possible to accurately grade steatosis as 0-5%, 5-30% and >30% in 90% of cases. Routine biopsy reveals non-specific hepatitis and subtle hepatic necrosis in 15% of cases judged as suitable donors (2).

MRI: There is growing evidence for the superiority of MRI over CT or US in grading steatosis. However, the choice of investigation can be left to individual centres. Studies have demonstrated that (in contrast to US and CT), T1-weighted MR imaging and point-resolved proton (hydrogen 1[(1)H]) MR spectroscopy; (1)H MR spectroscopy strongly correlate with histopathological steatosis assessment and is able to demonstrate differences across steatosis grades. T1-weighted dual-echo MR imaging and (1)H MR spectroscopy has the best diagnostic accuracy in depicting hepatic steatosis (3).

Fibroscan: Transient elastography has limited value for detecting steatosis in asymptomatic healthy individuals and does not correlate well with fibrosis in potential liver donors (4). Fibroscan readings may give additional information to CT and MRI evaluation and inform the decision to perform a liver biopsy.

With an acceptable CT and/or MRI in relation to steatosis, it is recommended that liver biopsy is reserved for potential donors with unexplained abnormalities in liver function tests, BMI approaching 30 kg/m^2, AST>ALT, or a Fibroscan Cap reading >200. A liver biopsy will differentiate between steatosis that may temporarily exclude the donor and steatohepatitis that will permanently exclude the donor.

9.3 Graft Selection

9.3.1 Graft Selection and Match to Recipient: Graft Size and Remnant Volume

The best results are achieved by balancing donor safety with optimal recipient outcome. In adults, the choice of donor graft aims to reduce risks to the donor by achieving as large a remnant volume as possible and, hence, a small resection; a left graft should usually be considered first. The graft of choice for transplantation into an adult recipient necessitates sufficient volume and function in order to meet the metabolic demands of the recipient and avoid small for size syndrome (SFSS). If the graft to body weight ratio (GBWR) is prohibitively low, then a right graft is considered to avoid SFSS in the recipient. In children, infants in particular, a left lateral graft is the usual choice. Conversely, a large for size (LFS) graft is a more frequent problem in these patients.

SFSS is a clinical picture characterised by:

- primary prolonged hyperbilirubinaemia
- ascites
- encephalopathy
- coagulopathy
- signs of liver failure

SFSS is often associated with kidney failure, sepsis, graft loss or death (5). It can lead to graft failure ranging from primary non-function to severe graft dysfunction (primary poor function or delayed graft function). Associated risk factors are low GBWR or graft volume. SFSS was first defined by the group at the University of Kyoto and since widely confirmed and validated. Low graft volume was identified to be a primary independent variable but recipient factors such as condition and metabolic demand also play a role. The syndrome has been further characterised and objective criteria have been proposed (6).

One of the potential problems with right lobe LDLT is congestion in the graft anterior segment due to deprivation of middle hepatic vein (MHV) tributaries. To overcome this constraint, several technical modifications have been reported. To avoid the development of a congestion area altogether, some centres prefer to use a “with MHV graft”. This is an extended right lobe graft with the MHV (7), either alone or reconstructed with a large common outflow tract (8). In contrast, additional venous reconstruction of the anterior segment with an interposition vein graft has been adopted by Lee et al (9). This can either be performed as routine, or based on visual evidence of congestion after reperfusion, or on volume estimates of the congested area on pre-operative imaging (10). Algorithms for the safe retrieval of the MHV have been proposed (11).

When calculating the volume of the donor remnant, it is advisable to use the native phase to minimise the risk of overestimation of graft volume, resulting in SFSS (12). It is widely accepted that the absolute minimum remnant volume is 30% (13).

The left lateral segment is almost always used in paediatric LDLT, except in the rare instance of auxiliary transplantation. Paediatric transplantation creates the unique scenario of graft size to recipient size mismatch, with resultant LFS necessitating reduction of the graft. GW/RW >4 is used as the guideline by most paediatric transplant

centres, although factors such as the antero-posterior diameter of the graft and the space available in the recipient's abdomen help to determine whether a left lateral segment graft should be reduced.

For calculation of donor graft volume, it has been shown that software-assisted image post-processing (SAIP) provides the most accurate method of assessment (14). Formulae are used for calculating the standard liver volume of the recipient, of which sixteen have been published. Recent studies show that the formulae of Yoshizumi, Yuan, Johnson, Noda and Puvathumkadavil correlate best with SAIP (15).

9.3.2 Points of Anatomy

a) Right Lobe Graft

Ideally, conventional anatomy in the potential donor is preferred to proceed with donation. As the experience of the centre increases, non-conventional anatomy may be accepted.

I. ***The hepatic arterial supply:*** favorable anatomical variations include a single pedicle with or without aberrant arterial supply (left hepatic artery (HA) from left gastric artery or right HA from superior mesenteric artery). Double pedicles with or without aberrant arterial supply will be considered on a case-by-case basis (more frequent in left lateral segment donation). Anatomical variations, including three or more arterial pedicles normally exclude donation.

II. ***The portal venous anatomy:*** preferably, normal to the proposed liver lobe but a trifurcation may be considered.

III. ***The hepatic venous drainage:*** ideally, conventional from the proposed donor liver lobe but reconstruction of venous drainage is a useful procedure to avoid congestion in the graft (see below). Accessory/inferior right hepatic veins >4 mm draining directly into the inferior vena cava (IVC) are not a technical contraindication as reconstruction is usually performed.

IV. ***The biliary drainage:*** conventional in only 57% of the cases for right lobes. Biliary anatomy must be reviewed on a case-by-case basis. Two separate ducts in right lobes are not a contraindication to living donation and transplantation. However, prospective donors with very complex biliary anatomy, with a greater

risk of developing a significant biliary complication, are precluded from donation.

b) Left Lobe Graft

A left lobe graft can include segments 2, 3 and 4 or it can be extended to segments 1, 2, 3 and 4. The rationale for inclusion of segment 1 (S1) in the graft is dictated by a low GW/RW in case the volume of the standard left lobe does not meet the GW/RW criteria and to avoid biliary complications in both donors and/or recipients. The anatomy of the left lobe is less variable than that of the right lobe. The portal vein (PV) is longer than in right lobe grafts; variations of the posterior right PV originating from the left are not contraindications to left graft retrieval. The length of the PV is variable depending on the inclusion of S1 in the graft. Small branches of S1 PV can be divided if the PV is too short, without compromising S1.

I. ***The left hepatic artery:*** the left graft is usually supplied by a single left HA but the presence of dual arteries is not a contraindication to left hepatectomy. The strategy and technique of reconstruction is guided by the size of the arteries, presence of arterial backflow and, more precisely, by the measurement of high arterial stump pressure in the smaller calibre artery. Whenever possible, it is advisable to reconstruct both arteries to avoid, in particular, biliary complications (16).

II. ***The left hepatic veins:*** the left graft is usually retrieved with the left and the middle hepatic vein (MHV), particularly when the GW/RW is low or the metabolic demand of the recipient is high. The left and MHV show a relative lack of diversity compared to the right hepatic vein. A situation of hemiliver right dominance of the MHV (MHV draining large volume of the right lobe remnant, mostly S8 and S5) is usually well tolerated by donors, since the remnant volume is more than sufficient. In extreme case of right hemiliver dominance, it may be necessary to tailor preservation of segment 8 (S8) (17). A plasty of the outflow tract of left and MHV or segmental veins is often required on the back table.

c) Left Lateral Graft

Anatomical variations in left lateral segments leading to rejection of the donor's suitability to donate are quite rare.

I. ***The hepatic arteries:*** the presence of two arteries is acceptable in experienced centres which are prepared to do microsurgical arterial anastomosis. More than two arteries is considered a relative contraindication. Very often the presence of a good backflow allows for only a single arterial anastomosis (18).

II. ***The hepatic veins:*** drainage from segments 2 (S2) and 3 (S3) occurs in 14% of patients as two separate veins draining into the IVC which may need venoplasty on the bench or two separate anastomoses. Rare anomalies such as S3 drainage into segment 4 (S4) or MHV must be recognised and surgical techniques modified accordingly.

III. ***The portal vein (PV):*** PV trifurcation, which has an incidence of 6-10%, is not a contraindication to donation but must be recognised during the evaluation to assist surgical planning. It is particularly important to recognise the association between PV anomalies and bile duct anomalies, especially with the right posterior duct joining the left duct. Variations in biliary anatomy are associated with a trifurcated PV in the right lobe of the donor liver (19).

9.3.3 Steatosis (see also 9.2.2)

Steatosis is a risk for both donor and recipient. For the donor, a fatty liver has a negative influence on liver regeneration. There is also evidence showing worse liver biochemistry post hepatectomy in the 'fatty livers' (20,21) but as the selection process has been rigorous it is not possible to recommend a cut off for donation.

If steatosis is severe, the donor is precluded without biopsy. The percent of fatty change acceptable for donation varies between centres, ranging from 10% to 60%. From the recipient point of view, higher levels of fat could be used despite a smaller graft size because of the shortened cold ischaemic time, but the risk to the donor is unacceptable.

The degree of fatty change needs to be considered with the remnant liver volume. For example, a 30% remnant would be unacceptable if there was more than 10% fat (4). The exact cut off value for acceptable steatosis in LDLT is not yet well defined but acceptable limits range from 10-30%. As steatosis reduces functional hepatic mass, some centres subtract the percentage of steatosis from the estimated liver mass before

calculating the final mass of the allograft and remnant liver. However, it is not known if this assumption is correct.

Left Lateral Lobe: steatosis is less of a problem with left lateral lobe donation for both donor and recipient. The risk to remnant functional mass in the donor is not as significant because of the good remnant volume and, in the recipient, the GW/RW ratio is usually >2 so it does not pose a problem. However, when using a small graft (GW/RW <1) with steatosis of >20%, there may be a significant effect on function. *(NB: Left lateral grafts with steatosis up to 50% have been used but this is not recommended).*

In patients initially rejected as donors due to steatosis, a low calorie 'defatting diet' and reassessment can be considered (22).

Once the technical evaluation is complete, the feasibility of a procedure and potential graft details will be discussed and reviewed by a multi-disciplinary team (MDT). This discussion must include the donor advocate team and members of the recipient team.

9.4 Donor Pre-operative Preparation

9.4.1 Donor Consent

Current data suggest that donating a right lobe of liver is associated with a 0.5-1% mortality and 40-60% morbidity. Left lobe donation carries a lower risk: mortality 0.1%, and morbidity 15-30% (23) (see section 11).

As these risks are not insignificant for the potential donor, valid and informed donor consent is paramount. For the purposes of consent, information about all aspects of morbidity and mortality associated with living liver donation (LLD) must be provided. For new programmes, international statistics on morbidity and mortality must be used and the centre must make it known to the donor that it is an 'emerging' programme. For established programmes (>20/year), centre-specific activity and morbidity and mortality data must be provided during the donor consent process. A two-stage consent process is best practice and ensures appropriate and fully informed consent is given (24). The donor may choose to withdraw consent at any time prior to donation, in which case the reasons must remain confidential.

9.4.2 Clinical Aspects

Once the decision has been made to proceed and a date for surgery is confirmed the donor is asked to:

- stop smoking
- stop oral contraceptives four weeks before surgery
- avoid acetylsalicylic acid/anti-inflammatory tablets
- consider proton pump inhibition therapy during the evaluation process (selected donors)
- attend a pre-anaesthetic clinic to discuss pain relief and the potential risks of anaesthesia

9.5 Donor Intra-Operative Management

9.5.1 Anaesthetic Aspects

- general anaesthetic
- epidural or transversus abdominal plane (TAP) block
- consideration of continuous wound infusion catheter
- central venous line
- arterial line
- antibiotic prophylaxis
- venous thromboembolism (VTE) prophylaxis: subcutaneous heparin, anti-embolism stockings and/or pulse flotation leggings
- warm air convection blanket heating to lower body
- cell saver use

9.5.2 Procedure Specific

a) Left lobe hepatectomy

- A left lobe graft typically is retrieved including the MHV. The caudate lobe (left side of S1) can be included if added volume is needed
- Laparotomy: predominantly upper midline xipho-umbilical incision
- Effective retraction for adequate exposure
- Division of falciform and left triangular ligaments
- After intraoperative ultrasound is performed, hilar dissection to the left of the hepato-duodenal ligament only

- Dissection of left hepatic artery (LHA), with identification of the right hepatic artery (RHA) bifurcation. Once this has been achieved, no further dissection to the right is required
- Preserve the right gastric artery if possible
- The left portal vein (LPV) is isolated

b) Segment (S) 2, 3, 4 graft

- The PV branches to the caudate lobe are suture ligated with 5-0 or 6-0 Prolene
- Dissection along Arantius groove, division of the ligamentun venosum of Arantius
- The common trunk of the left and MHVs are encircled with umbilical tape, to be used later for the hanging manoeuvre

c) S1 preservation for S 1, 2, 3, 4 graft

- The PV branches to the caudate lobe are preserved if possible; however, according to the required length of the left portal vein, they can be selectively suture ligated with 5-0 or 6-0 Prolene
- The caudate lobe is mobilised from the vena cava dividing all caudate veins except the main S1 vein that is later harvested with a large patch. This vein is usually re-implanted to the vena cava in the recipient to allow optimal graft function
- The common trunk of the left and MHVs are encircled with umbilical tape, to be used later for the hanging manoeuvre
- Cholecystectomy
- Cannulation of the cystic duct and cholangiogram or exploration of the bile duct with a fine metal probe
- The left bile duct is divided at this point or later during the parenchymal phase, always sharply with knife *en bloc* with the Glissonian sheath
- Ultrasound is repeated to identify the S8 and S5 hepatic veins and to confirm the plane of resection already demonstrated with a left Pringle manoeuvre. The line of liver partition is either from the line of Cantlie/MHV right border to the Arantius groove in S 2, 3, 4 grafts, or to the division of caudate process/lobe just to the left of the portal bifurcation in S 1, 2, 3, 4 grafts

- Parenchymal division follows with technique of choice, although Cavitron Ultrasonic Surgical Aspirator (CUSA®) dissection is mostly used
- The vessels are divided sequentially: HA sutured with 6-0 Prolene, PV sutured with 5-0 Prolene and common trunk of MHV and LHV with 4-0 Prolene
- The graft is immediately cooled and perfused at the prepared bench table; then it is weighed dry
- Control of cut section for haemo-biliostasis
- 20-24 Fr drains are placed along the cut section
- Closure of the abdomen in layers

d) Right lobe hepatectomy

- Laparotomy: predominantly right sided Mercedes, or hockey-stick incisions; an upper midline incision is possible with adequate retractors
- Cholecystectomy
- Cannulation of the cystic duct; cholangiogram; final decision to proceed
- Mobilisation of the right lobe off the diaphragm
- Filleting of the IVC on the right side and identification of inferior/accessory RHV if >4 mm in diameter
- Nylon tapes or small drains (#6 Fr) passed behind the RHV and behind potential inferior/accessory RHVs for hanging manoeuvre
- Porta hepatis: identification of right branch of the PV superficial to the caudate lobe
- The caudate portal branches (usually 2-4) are sutured (6/0 Prolene) and divided to allow encircling of the right branch of the PV
- Dissection of the RHA high in the porta and of potential accessory/replaced artery from the superior mesenteric artery (SMA). This is facilitated by swinging the cystic duct cannula towards the left side
- Minimal dissection in front of the bile duct and probing of the bifurcation via the cystic duct (lacrimal probes, microsurgical set)
- Once the bile duct confluence is identified, a line is drawn into the capsule with the diathermy on the inferior surface to meet the line drawn on the demarcation created by temporarily clamping the RHA and RPV with bulldogs
- Though the Pringle manoeuvre should be avoided, it should be set up by nylon tape and tourniquet in case of excessive bleeding

- *Tanaka* sutures are applied at the edge of the line of dissection with Teflon to protect the parenchyma from tearing
- Encourage the anaesthetist to keep the central venous pressure <5 mmHg during parenchymal transection
- Parenchymal dissection with CUSA, with clipping of all smallest vessels and minimal argon use
- Intra-operative Doppler ultrasound scanning is utilised to identify the MHV to help draw the line of resection
- S 5 and 8 veins are also identified with ultrasound. Their depth from the capsule is noted and their level is marked with diathermy on the capsule. These are carefully dissected and clipped on the right side of the cut surface with a white plastic clip. The other side is clamped and sutured
- The direction of the dissection is cranial and after completing the dome, packs are removed from the hepatic fossa to allow the liver to open *like a book*
- Once the parenchymal dissection is extended caudally, guided by the hanging manoeuvre, the right Glissonian sheet is met surrounding the right hepatic duct
- The caudate lobe is pulled anteriorly with two sutures for parenchymal division
- The hanging tape/tube is rerouted beneath the right-sided vascular and biliary structures to hang the caudate lobe cranially to the above named structures and its transection is completed
- Two sutures are placed after probing the right duct via the cystic duct, and two radiopaque markers are placed to define the proposed line of section of the duct(s)
- A cholangiogram is performed again
- The right hepatic duct is transected and flushed with normal saline
- Sutures are applied to the duct's feeding vessels on the right and left sides and the plate cranial to the ducts is sutured to avoid bleeding and leaks from minor ducts
- Review of haemostasis. The operation can be paused for a few minutes prior to hepatectomy in the recipient. This time allows for measurement with magnetic probes of flow in the right portal vein and in the RHA and also to identify potential new bleeding points after changes in blood pressure due to fluid resuscitation

- Heparin (5000 IU) is given prior to clamping the RHA, RPV and RHV in the donor. Heparin will usually not be reversed unless bleeding is apparent, when protamine sulphate can be given prior to closure
- Two Prolene 5/0 stay sutures are applied at the cranial and caudal edges of the RHV (both for security in case of faulty Satinsky clamp and for orientation in the recipient)
- The accessory/inferior hepatic veins are clipped with a white plastic clip. The caval side is clamped and sutured
- The artery is clamped and cut on the right side and allowed to back bleed
- The portal vein is transected between clamps
- The right lobe is gently squeezed to allow minimal blood loss, the RHV is clamped with a Satinsky clamp on the IVC, then it is divided and bled out on the liver side to allow cell saving
- The right lobe is transferred to the bench
- Repeat cholangiogram via the cystic duct and methylene blue injection to identify potential cut surface leaks
- Use of Tachosil on the cut surface if indicated
- Routine use of # 24-28 abdominal drain positioned in the right hepatic fossa
- Closure

e) Left lateral segment hepatectomy

- Hilum dissection: the standard approach is to go to the right of the round ligament, identify the segment 2,3 artery followed by identifying the right margin of the left portal vein, encircling it at that level after ligating the caudate branches from the left portal vein
- Cholecystectomy and intraoperative cholangiography are not routinely performed during left lateral segment donation but may be considered in donors where there is a pre-operative or intra operative indication (24)
- If an accessory left hepatic artery is present, it is identified and dissected to the origin from the left gastric artery. S 4 branches from the PV are ligated
- Subsequently transection is done 1 cm to the right of the falciform ligament. Staying in this line has a huge impact on the biliary anatomy as this can result in a single S 2 and 3 duct in 90% of cases
- In the presence of double arteries, the accessory is divided to look for adequate back flow to aid the decision on reconstruction of one or two arteries in the recipient

- Completion and closure: drainage and closure is the standard of care with subsequent removal of the drain if non-bilious by day three to five
- Bile leaks are common after left lateral segment donor hepatectomies and are often considered to be from the "cut surface". Understanding the caudate lobe biliary drainage will very often pin point the leak to one of the two areas:
    - the divided end of the segment 4 duct
    - the divided ducts of the Caudate lobe that were draining into the left duct
- Closure of these will result in a much lower incidence of bile leaks in left lateral segment donors.

f) Open versus laparoscopic hepatectomy

Although laparoscopic or laparoscopically assisted donor hepatectomy have been reported for left lateral and left lobe donations (small series with safe and effective outcomes), open donor hepatectomy still remains the standard of care. Morbidity from the open incision can be reduced by using an upper midline incision wherever possible.

g) "No go" hepatectomy

With the intensive assessment and preparation of a potential donor, this should be a rare event. Lei et al (25) reported five abandoned procedures out of 290 cases. The reasons were:

- unexpected biliary anatomy
- unexpected steatosis
- error in estimation of the remnant volume

There should be no hesitation in abandoning the donation if, in the opinion of the operating surgeon, an unexpected finding jeopardises the safety of the donor.

h) Abandoned hepatectomy

The intended recipient may become too unwell or die during the hepatectomy, prior to implantation of the graft. This is a rare and devastating event. As a precaution, the bile duct division is done only after completion of the transection just prior to explantation, so the graft can be retained as *"hepar divisum"* with intact inflow and reducing the morbidity associated with bile duct reconstruction. If the graft is explanted, a policy to

utilise the organ as a deceased donor 'split' must be discussed and agreed during the consent process with both donor and recipient (26).

9.6 Donor Post-Operative Care

9.6.1 Immediate Post-Operative Care (High Dependency or Intensive Care Unit)

a) *Monitoring lines*

- continue as in theatre for the first 24 hours
- remove oesophageal temperature probe
- maintain nasogastric tube, urinary catheter and abdominal drains
- alternatively, follow an Enhanced Recovery Pathway (locally defined)

b) *Medicines*

- protein pump inhibitor prophylaxis
- low molecular weight heparin VTE prophylaxis
- antibiotic therapy (Augmentin or Ciprofloxacin if penicillin allergic)
- sedation/anxiolytics/analgesia. Sedation may be necessary because of the highly emotive aspects of the donor operation
    - Temazepam/Midazolam as required
    - epidural or equivalent analgesia
    - patient controlled analgesic pump (PCA) or infusional opiates if epidural not available/functioning
    - oral 30/500 Cocodamol prescribed regularly as two tablets four times a day. If this is insufficient, then oral Tramadol 100mg three times a day and rectal or oral Paracetamol.

c) Investigations

- repeat tests as indicated clinically
- baseline arterial blood gas (ABG) and full blood count (FBC) / coagulation on ICU
- creatinine, urea and electrolytes, liver function tests
- chest X-ray

d) Other

- oxygen therapy via face mask for six hours post-operatively (as for any major operation)

- if ventilation required post-operatively, maintain for as short as possible to regain normothermia and "normal" blood tests and stabilise analgesia
- anti-embolism stockings for prophylaxis
- remove swan sheath (rapid infusion line)

9.6.2 Ward Post-Operative care

If appropriate, the donor is transferred on the first postoperative day to the high dependency unit (HDU). Management there includes:

- maintain all intravascular lines; central venous line remains until intravenous infusions and medicines are not required
- remove nasogastric tube day 1 if no or minimal drainage
- start oral fluids day 1 (some centres give on day 0 if tolerated)
- maintain and remove abdominal drain (remove day 3-5, if no sign of bile leak and ultrasound normal)

a) Monitoring

- high dependency nursing for the first three days. Routine observations include heart rate, temperature, blood pressure, weight
- quick response plan for emergencies
- low threshold to contact the Consultant surgeon on call directly
- physical examination

b) Medicines (non-analgesic)

- Pantoprazole 40 mg OD iv until patient has established oral intake
- Lansoprazole 30 mg OD orally continued for 2-4 weeks postoperatively
- low molecular weight heparin, at 22.00 hr until discharge
- three post-operative doses of Augmentin 1.2 g TDS

c) Analgesia

- epidural analgesia or continuous wound catheter infusion for 48-72 hours
- PCA or intravenous/subcutaneous opiates if epidural not available/functioning
- oral Cocodamol 30/500 two tablets QDS starting on day one post operatively
- if this fails to control pain, change to Tramadol 100mg TDS orally and rectal or oral Paracetamol at 1g QDS
- alternatively, follow an Enhanced Recovery Protocol

d) Investigations

- daily FBC, prothrombin time (PT), partial thromboplastin time (PTT), creatinine, urea and electrolytes, LFTs
- chest X-ray as clinically indicated
- ultrasound on day one and as clinically indicated
- bacteriology from sputum and abdominal drain when removed
- CT before discharge (for right lobe donor)
- ultrasound before discharge (for left lateral segment donor)

e) Other

- anti-embolism stockings for prophylaxis until full mobilisation/discharge

9.6.3 Discharge

- planned for day 5 to 10 according to clinical picture
- analgesia as needed
- proton pump inhibitor for 4 weeks post-operatively
- VTE prophylaxis for 6 weeks post-operatively

9.6.4 Follow up

See section 13 for details.

References

1. Nadalin S, Malago M, Broelsch CE, et al. Preoperative donor liver biopsy for adult living donor liver transplantation. Liver Transpl 2005; 11: 980-6.
2. Limanond P, Raman SS, Lassman C, et al. Macrovesicular hepatic steatosis in living related liver donors: correlation between CT and histologic findings. Radiology 2004; 230: 276-80.
3. van Werven JR, Marsman HA, Nederveen AJ. Assessment of hepatic steatosis in patients undergoing liver resection: comparison of US, CT, T1-weighted dual-echo MR imaging, and point-resolved 1H MR spectroscopy. Radiology 2010; 256: 159-68.

4. Kim KM, Choi WB, Park SH, et al. Diagnosis of hepatic steatosis and fibrosis by transient elastography in asymptomatic healthy individuals: a prospective study of living related potential liver donors. J Gastroenterol 2007; 42: 382-8.
5. Emond JC, Renz JF, Ferrell LD, et al. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. Ann Surg 1996; 224: 544-52; discussion 552-4.
6. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am J Transplant 2005; 5: 2605-10.
7. Fan ST, Lo CM, Liu CL. Technical refinement in adult-to-adult living donor liver transplantation using right lobe graft. Ann Surg 2000; 231: 126-31.
8. Malago M, Testa G, Frilling A, et al. Right living donor liver transplantation: an option for adult patients: single institution experience with 74 patients. Ann Surg 2003; 238: 853-62.
9. Gyu Lee S, Min Park K, Hwang S, et al. Modified right liver graft from a living donor to prevent congestion. Transplantation 2002; 74: 54-9.
10. Asakuma M, Fujimoto Y, Bourquain H, et al. Graft selection algorithm based on congestion volume for adult living donor liver transplantation. Am J Transplant 2007; 7: 1788-96.
11. Radtke A, Sgourakis G, Sotiropoulos GC, et al. Donor/recipient algorithm for management of the middle hepatic vein in right graft live donor liver transplantation. Am J Surg 2010; 199: 708-15.
12. Radtke A, Sotiropoulos GC, Nadalin S, et al. Preoperative volume prediction in adult living donor liver transplantation: how much can we rely on it? Am J Transplant 2007; 7: 672-9.
13. Facciuto MI, Contreras-Saldivar A, Singh MK, et al. Right hepatectomy for living donation: role of remnant liver volume in predicting hepatic dysfunction and complications. Surgery 2013; 153: 619-26.
14. Tongyoo A, Pomfret EA, Pomposelli JJ. Accurate estimation of living donor right hemi-liver volume from portal vein diameter measurement and standard liver volume calculation. Am J Transplant 2012; 12: 1229-39.
15. Pomposelli JJ, Tongyoo A, Wald C, Pomfret EA. Variability of standard liver volume estimation versus software-assisted total liver volume measurement. Liver Transplant 2012; 18: 1083-92.
16. Uchiyama H, Harada N, Sanefuji K, et al. Dual hepatic artery reconstruction in living donor liver transplantation using a left hepatic graft with 2 hepatic arterial stumps. Surgery 2010; 147: 878-86.

17. Hwang S, Lee SG, Ha TY, et al. Feasibility assessment for tailoring preservation of segment VIII hepatic vein during left liver graft procurement. Hepatogastroenterology 2006; 53: 928-32.
18. Kim KM, Choi WB, Park SH. Diagnosis of hepatic steatosis and fibrosis by transient elastography in asymptomatic healthy individuals: a prospective study of living related potential liver donors. J Gastroenterol 2007; 42: 382-8.
19. Kasahara M, Egawa H, Tanaka K, et al. Variations in biliary anatomy associated with trifurcated portal vein in right-lobe living-donor liver transplantation. Transplantation 2005; 79: 626-7.
20. Nagai S, Fujimoto Y, Kamei H. Mild hepatic macrovesicular steatosis may be a risk factor for hyperbilirubinaemia in living liver donors following right hepatectomy. Br J Surg 2009; 96: 437-44.
21. Shin YH, Ko JS, Kim GS, et al. Impact of hepatic macrovesicular and microvesicular steatosis on the postoperative liver functions after right hepatectomy in living donors. Transplant Proc 2012; 44: 512-5.
22. Oshita A, Tashiro H, Amano H, et al. Safety and feasibility of diet-treated donors with steatotic livers at the initial consultation for living-donor liver transplantation. Transplantation 2012; 93: 1024-30.
23. Brandhagen D, Fidler J, Rosen C. Evaluation of the donor liver for living donor liver transplantation. Liver Transpl 2003; 9: S16-28.
24. Broelsch CE, Whitington CF, Emond JC, et al. Liver transplantation in children from living related donors. Surgical techniques and results. Ann Surg 1991; 214: 428-37; discussion 437-9.
25. Lei JY, Yan LN. Intraoperative "no go" donor hepatectomy in living donor liver transplantation. Transplant Proc 2013; 45: 2253-7.
26. Seigler J, Segler M, Cronin DC 2nd. Recipient death during a live donor liver transplantation: who gets the "orphan" graft? Transplantation 2004; 78: 1241-4.

Appendix 1: Small For Size Syndrome (SFSS)

SFS has been quantified and graded as GW/RW 0.8-1 and extra SFS GW/RW <0.8 (1). A small for size graft (SFSG) is defined with respect to the weight of the graft and the standard liver volume (SLV) of the recipient; a graft weight GW/SLV ratio is used for the definition. In general, a graft with a GW/SLV ratio of 50% can be managed as a full-size graft, and a graft with a GW/SLV ratio < 40% is defined as a SFS graft. (1)

In most centres a GW/SLV of 40% is the acceptable lower limit. This equates to a GR/RW of 0.8.

Liver donor liver transplantation using SFS grafts (GW/RW <0.8) has, however, resulted in positive outcomes. It is recognised that factors such as the quality of graft and recipient conditions can influence recipient results. Patients with advanced cirrhosis (MELD >25) and increased metabolic demand have shown poorer results (2,3); thus, caution is recommended in severely decompensated patients. Other groups with high volume living donor programs have also reported good results in recipients with high MELD (4).

With new techniques of outflow and inflow modulation, the GW/SLV requirement can be reduced to 35%, and grafts with a GW/SLV ratio as low as 30% have been used selectively. This is particularly true for left lobe grafts (5).

References for Appendix 1

1. Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999; 67: 321-7**.**
2. Kiuchi T, Tanaka K, Ito T, et al. Small-for-size graft in living donor liver transplantation: how far should we go? Liver Transpl 2003; 9: S29-35.
3. Ben-Haim M, Emre S, Fishbein TM, et al. Critical graft size in adult-to-adult living donor liver transplantation: impact of the recipient's disease. Liver Transpl 2001; 7: 948-53.
4. Selzner M, Kashfi A, Cattral MS, et al. Live donor liver transplantation in high MELD score recipients. Ann Surg 2010; 251: 153-7.
5. Ishizaki Y1, Kawasaki S, Sugo H, Yoshimoto J, Fujiwara N, Imamura H. Left lobe adult-to-adult living donor liver transplantation: should portal inflow modulation be added? Liver Transpl 2012; 18: 305-14.

10 RECIPIENT SURGERY: TECHNICAL ASPECTS, RISK AND PERIOPERATIVE CARE FOR ADULTS AND CHILDREN

Statements of Recommendation

- ***Standardisation of surgical techniques is limited. (Not graded)***

- ***Techniques for left lateral segment paediatric living donor liver transplantation (LDLT) are the same as for deceased donor liver transplantation (DDLT). (2A)***

- ***Specific attention in recipient assessment is given to the anatomy of the vasculature and biliary tree to enable planning of surgery. Issues to be addressed include the proximity of cancer to vascular structures, portal vein thrombosis, and a detailed vascular anatomy of inflow and outflow structures in recipients considered for re-transplantation. (1B)***

- ***Predicting graft size must rely on preoperative volumetry with the understanding that predicted values often overestimate the size of the graft by a margin of 10 to 20%. (1B)***

- ***University of Wisconsin (UW) and Histidine-tryptophan-ketoglutarate (HTK) solutions are equally effective for perfusion of the graft. (1A)***

- ***In recipient surgery, hilar dissection differs significantly from deceased donor liver transplantation. Every attempt should be made to preserve as long a length of the hilar structures as possible and to avoid de-vascularising the extra-hepatic common duct. (1B)***

- ***Optimising venous outflow is essential to improve graft function. In grafts that are considered small for size (GW/RW ratio <0.8), aim to bring the portal pressure to <20 and preferably 15 mm Hg, especially in patients with high MELD. (1B)***

- ***The hepatic arterial, portal venous and venous outflow must be assessed with Doppler ultrasound prior to abdominal closure. (2A)***

- ***Management of early venous outflow problems can be challenging, especially with venous reconstructions from segment 5 and 8 veins. Interventional radiology is superior to surgical intervention in management of these venous outflow problems. (1B)***

10.1 Introduction

Surgical techniques of the recipient surgery depend on:

a) The type of graft – left lateral segment, left liver (segments 2, 3 and 4), and right lobe
b) The anatomy of the recipient – with specific reference to the hepatic vein, hepatic artery and bile duct
c) Institutional and surgeon preference

Only a limited amount of standardisation is possible. This is due to the large number of variations reported, the learning curve (first 20 cases), the small number of transplants performed in most institutions, and the lack of randomised controlled trials.

Irrespective of the graft type, a degree of consensus has been achieved, related to:

- recognition and understanding of the concept of 'Small for Size Syndrome'
- optimisation of venous outflow - being essential for good graft function
- use of microvascular techniques for the hepatic arterial anastomosis
- use of 'duct to duct' reconstruction as the default option for the biliary anastomosis
- perioperative care involving careful surveillance for vascular complications including stenosis and occlusion

10.2 Assessment of the Recipient

The assessment of paediatric and adult recipients is the same irrespective of whether they are to undergo deceased donor (DD) or living donor (LD) transplantation. The indications for transplantation are identical.

Specific attention must be given to the anatomy of the vasculature and biliary tree to enable planning of the recipient surgery. Issues that need to be addressed include:

- proximity of any cancer to vascular structures (especially the IVC in patients with HCC)
- potential portal vein thrombosis
- detailed vascular anatomy of inflow and outflow structures in recipients considered for re-transplantation
- recipients with 'situs inversus', although rare, need special attention in terms of planning for graft size

10.3 Assessment of the Graft

10.3.1 Graft Weight / Recipient Weight Ratio (GW/RW ratio))

For adult recipients, provision of an adequately sized graft is a critical limiting factor. The inability to accurately determine the minimal amount of liver tissue that can safely be removed from a healthy donor and provide an adequate amount of liver for the recipient still remains a significant concern. Multiple formulae have been derived in an attempt to estimate adequate graft size, yet there is no agreed formulation resulting in minimal donor morbidity and excellent recipient survival.

Current methods to predict graft size rely on preoperative imaging and 'volumetry'. Graft size is generally reported as either graft weight to recipient body weight ratio (GW/RW) (1), or as a percentage of the calculated standard liver volume (SLV) (1,2). A linear correlation exists between the two, and both are considered an acceptable means of expressing the estimated graft volume (3). The predicted values often over-estimate the size of the graft by a margin of 10 to 20%. The graft weight is confirmed after explantation from the donor. Although grafts of 25% and 32% of calculated ideal liver weight (CILW) have been successfully used in adult recipients (1,2), the accepted safe margins are 40% to 50% of CILW (2,3) or 0.8% to 1% when calculated as GW/RW ratio (4).

10.4 Explant

Incision and exposure for recipient surgery is similar to DD liver transplantation. Depending on the shape of the costal margin, transverse, Mercedes or reversed L

incisions can be used to gain access to the upper abdomen. Veno-venous bypass is rarely needed.

10.4.1 The Hilar Dissection

The hilar dissection differs significantly from DD liver transplantation. Every attempt should be made to preserve as long a length of the hilar structures as possible and to avoid de-vascularising the extra hepatic common duct. Hilar dissection starts very close to the hilar plate (5,6).

10.4.2 Bile Ducts

The right and left ducts are divided separately. The ducts should not be ligated as this results in loss of length and possible ischaemia of the duct ends. The bleeding from cut ends of the ducts can be temporarily controlled with a small vascular clamp placed along the transected ducts or with fine sutures of 6.0 Prolene/PDS. The cystic duct is similarly preserved as an alternative option for reconstruction in the presence of more than one duct within the graft (7,8).

10.4.3 The Hepatic Arteries

The right hepatic artery is similarly dissected close to its entry into the liver. If possible the right anterior and posterior branches are preserved. Tying is avoided as this may create an intimal flap. The artery is controlled with a small vascular clamp such as Ackland or Yasargil on the proximal end with a clip applied distally before division. (Similar attention is applied to other arteries including both the left and middle hepatic arteries if present).

10.4.4 The Portal Vein

The portal vein and proximal part of its right and left branches are dissected. The PV is kept flowing until the time comes to clamp the venous outflow. Alternatively, a portacaval shunt can be performed at this stage depending on the surgeon and unit preference. The right branch of the PV is used to create a portacaval shunt. There is no clear evidence as to the superiority of routine portacaval shunt; however, it reduces portal pressure and avoid mesenteric venous congestion (6,9,11).

10.4.5 The Hepatic Veins

The liver is mobilised from the IVC in a standard fashion. Finally, the right hepatic vein and combined stump of the middle and left hepatic veins are clamped and divided. Where a portacaval shunt is not performed, the portal vein is clamped and divided

distal to the bifurcation. The stumps of the middle and left hepatic veins are sutured with 4.0 Prolene if venous reconstruction is not anticipated. Occasionally, cross clamping of the IVC is required if caudate lobe mobilisation is particularly difficult or if venous reconstruction of multiple outflow veins is anticipated. Placement of multiple clamps on isolated segments of IVC in an attempt to preserve IVC flow may interfere with graft placement and compromise venous outflow. The vascular clamp (Satinsky) is placed vertically on the IVC including the right hepatic vein. A sizable cuff of cava with anterior encroachment should be included. A cuff of the anterior caval wall is excised (10)

10.5 Preparing the Graft

10.5.1 Perfusion

The graft is perfused on the bench with UW solution/HTK through the portal vein. Prospective studies show both solutions to be equally effective, with HTK being less expensive (12). Recent data suggest that retrograde flushing of the hepatic artery can help to reduce post-transplant cholestasis. Care should be taken that the perfusate flows through all segments of the graft. Hepatic artery perfusion is avoided to prevent unnecessary manipulation of the intima and damage (13,14,15). Perfusion is continued until the return looks clear. Vascular and biliary anatomy need to be confirmed on the back bench. The hilar plate with small caudate ducts need suturing with fine sutures, either 6.0 Prolene or PDS.

10.5.2 Vascular Reconstruction

The most common bench vascular reconstruction involves venous drainage for right lobe grafts. Specific attention is required for all large (>5 mm) veins draining the right anterior sector (segments 5 and 8) and for the inferior right hepatic vein. The inferior right hepatic vein can be anastomosed directly to the side of the recipient IVC but occasionally needs to be extended to improve the length. The most common grafts used for reconstruction are cadaveric donor iliac vein, iliac artery and cryopreserved vessels. Synthetic grafts such as ringed polytetrafluoroethylene (PTFE) have also been used with similar patency rates as autologous grafts (10).

The exact reconstruction depends on the number of branches to be reconstructed. As the segment 5 and 8 branches are thin walled, attention needs to be paid to an adequate depth of suture bites, occasionally incorporating the surrounding liver

parenchyma to provide strength to the anastomosis. In grafts with a significant length of MHV retrieved with a right lobe graft, there are two options to reconstruct. If the MHV is long enough, side-to-side plasty with the RHV is an option, with suturing of the common orifice to the recipient RHV and IVC. An alternative is to join the MHV to the recipient MHV stump, either directly or via an interposition graft.

10.6 Recipient Surgery – Adult

10.6.1 Implantation

Implantation of the graft starts with outflow venous anastomosis.

a) Left Lobe Grafts

For left lobe grafts that include the left and middle hepatic veins, the standard anastomosis is usually to the common orifice of the left and middle hepatic veins of the recipient IVC. An alternative is to cross clamp the recipient IVC and to perform, a larger triangulated anastomosis by extending the venotomy in the recipient IVC. Left lobe grafts may be small for size and hence every attempt to improve venous outflow by a wide anastomosis will help postoperative graft function (17).

b) Right Lobe Grafts

For right lobe grafts without the MHV, the donor right hepatic vein is anastomosed to the enlarged recipient right hepatic vein origin, which is extended inferiorly if the orifice needs to be larger. In addition, anterior extension of the IVC orifice helps to maintain a wide anastomosis. It is important to avoid redundancy between the two veins, as this results in kinking after post hypertrophy rotation. Incorporating surrounding liver parenchyma in some of the suture bites may help to reduce the laxity and kinking. Inferior right hepatic vein reconstruction is performed at this stage when required. Implantation of the middle hepatic vein branches reconstructed onto a graft is usually performed at this stage, but often deferred to the post-reperfusion phase. The left or right portal vein of the graft is anastomosed to the main portal vein of the recipient with a growth factor. Occasionally, the right or left portal vein of the recipient is used for anastomosis with the corresponding vessel on the donor graft (16).

10.6.2 Modulating Portal Flow

In grafts that are considered small for size (<0.8 GW/RW ratio), portal vein pressure is measured at the end of the procedure using a transducer. If the pressure is greater

than 20 mmHg, splenic artery ligation should be performed. If the pressure remains persistently above 20 mmHg despite splenic artery ligation, an interposition portacaval shunt should be considered (11). The aim is to bring the portal pressure to less than 20 and preferably 15 mmHg, especially in patients with high MELD (18).

10.6.3 Hepatic Artery Anastomosis

Hepatic arterial anastomosis is performed under magnification (x 2.5 - 4.5) or an operating microscope with interrupted 8.0 or 9.0 Prolene sutures. Care must be taken in preparing the artery for anastomosis by dissecting adventitial tissue away near the edge of cut margins. The anastomosis is usually performed with interrupted sutures. There is good evidence that microvascular techniques improve the patency rates for hepatic arterial anastomosis, with thrombosis rates of less than 4% in most series (19).

10.6.4 Intra-operative Flow Assessment

The hepatic arterial, portal venous and venous outflow needs to be assessed with Doppler ultrasound prior to abdominal closure. The best indicator for widely patent hepatic veins is triphasic flow pattern on Doppler examination. Good portal venous flow should be confirmed by the absence of high velocity jet and turbulence. The hepatic artery waveform should demonstrate a good upstroke, with absence of parvus tardus intrahepatically and high velocity jet >2 m/sec extrahepatically.

10.6.5 Bile Duct Anastomosis

Bile duct anastomosis presents a significant challenge in living donor liver transplantation. Biliary complications occur in up to 30% of right lobe recipients. These include bile leaks and strictures. Bile leaks can occur from the anastomosis, cut surface, or from small caudate ducts left unrecognised or unsutured in the hilar plate. Biliary strictures are either anastomotic or non-anastomotic. Hepatic artery stenosis and thrombosis can result in graft loss and biliary complications such as bile leaks, bile lakes and non-anastomotic strictures. These complications should prompt assessment of hepatic arterial flow to the graft. Duct-to-duct anastomosis is the preferred option for a single duct as long as the recipient duct is suitable in terms of vascularity, length and diameter.

10.6.6 Multiple ducts

When multiple ducts are present, options include use of right and left ducts, cystic duct and common duct, duct and Roux-en-Y hepaticojejunostomy or hepaticojejunostomy alone. Factors that increase the complexity of operation with hepaticojejunostomy are

the additional enteric anastomosis, lack of access for endoscopic interventions and the small bowel being oedematous, and congestion by the end of operation making it difficult to use. Several centres describe better results with biliary anastomosis by modifying the donor surgery. The bile duct is left undissected within the hilar plate until the very end of parenchymal transection. Lobar ducts are divided sharply along with periductal hilar tissue thereby preserving the vascularity (20,21).

10.6.7 Suturing: Materials and Techniques

The preferred suture material is PDS and can vary from 5.0 to 7.0 depending on the size of anastomosis and thinness of the donor ducts. Few centres report the use of 6.0 or 7.0 Prolene for biliary anastomosis. Non-absorbable sutures can form a nidus for stones and reports have confirmed intraluminal Prolene acting as a foreign body predisposing to stones and sludge.

Proponents for interrupted suturing argue that it will result in better placement of sutures and that loosening of one knot will not jeopardise the whole anastomosis. Proponents of continuous anastomosis argue for the absence of intraluminal knots, less risk of enlarging suture holes from reduced traction, and a more watertight anastomosis. Another option is to use a continuous posterior suture line and interrupted sutures for the anterior wall.

10.6.8 The role of a T-Tube or Intraluminal Stent

No clear evidence exists as to the superiority of a stent. There is no evidence of superiority of one technique over another in the absence of randomised trials. More important determinants of biliary complications are the vascularity of cut edges, tension-free anastomoses, and accurate apposition (22).

10.7 Recipient Surgery – Child

10.7.1 Implantation

The technique of paediatric LDLT using a left lateral segment is similar to deceased donor split liver transplantation. The main principles in recipient hepatectomy surgery include:

- preserving the length of the inflow vessels
- dissecting the portal vein from bifurcation to confluence
- avoiding tying arteries to prevent intimal dissection
- mobilising the IVC to enable cross clamping
- completing the hepatectomy with caval preservation

The left hepatic vein to IVC anastomosis is a 120^{o} triangulated anastomosis to prevent rotation and kinking of the venous outflow. The portal vein anastomosis is one of the challenging aspects of recipient surgery because of the need to deal with hypoplastic portal veins in children with biliary atresia. Complications to be avoided include size discrepancy between the donor LPV and the recipient main portal vein and the risk of rotation or twisting of the portal vein following anastomosis

10.7.2 Suturing: Materials and Techniques

Both PDS and Prolene have been used for portal vein anastomosis. A growth factor is often applied. Artery-to-artery anastomosis is performed with interrupted 8.0 to 9.0 sutures under high magnification with loupes or an operating microscope.

Biliary reconstruction is almost always performed with hepaticojejunostomy. Either continuous or interrupted sutures are applied using 5.0 to 6.0 PDS. The graft is anchored in position with sutures to the falciform ligament and diaphragm (23).

10.8 Perioperative Care

Perioperative care is similar to DDLT with the main exception of active surveillance of the vascular anastomosis with daily Doppler ultrasound. Abnormalities found on Doppler ultrasound are confirmed by CT angiography. Direct angiography/venography may occasionally be required followed by and interventional radiology or by surgery. (25)

Daily monitoring of progress with blood counts, liver and renal function tests and clotting profiles is essential. Abnormal changes in liver function tests need initial assessment with ultrasound to check for vascular and biliary complications, followed by other investigations including CT, angiography and liver biopsy. Appropriate measurement of CNI trough levels is important, as in deceased donor liver transplantation (32).

10.9 Early Complications Requiring Re-Interventions

10.9.1 Hepatic Artery

Early hepatic artery stenosis and thrombosis are infrequent but important complications that need prompt assessment and management. Management options include surgical re-exploration, angioplasty +/- stenting, percutaneous thrombolysis and ultimately re-transplantation. With hepatic artery thrombosis, if the recipient has normal liver function, CT scan shows no evidence of ischaemia, and the previous day's ultrasound scan was normal, then the child or adult should undergo emergency re-exploration and revascularisation (24,25).

10.9.2 Portal Vein

Portal vein thrombosis as an early complication is usually secondary to post clamping kinking, twisting or persistent thrombus within the recipient PV. Urgent surgical revascularisation is indicated. Portal venous interventions are unusual but may be indicated for late portal vein stenosis. Radiological options include venoplasty and stenting. Percutaneous interventions are also indicated for closure of surgically created shunts in the management of small for size graft and for splenic artery embolisation in the management of Small for Size syndrome.

10.9.3 Bile Duct

Early biliary complications need to be managed with percutaneous drainage to avoid intra-abdominal collections and sepsis. Management options include endoscopic, percutaneous and surgical interventions, often in combination.

10.9.4 Venous Outflow Problems

Management of early venous outflow problems, especially with venous reconstructions from segment 5 and 8 veins, can be challenging. Interventional radiology is superior to surgical intervention in this situation (26).

10.10 Small for Size Grafts and Syndrome

Small for size grafts are unavoidable in LDLT for adults as the size of the donor grafts are invariably smaller than the standard liver volume of a recipient. Initial attempts by transplant units to procure larger grafts resulted in a compromise to donor safety. The

focus has now shifted to optimising the outcomes from small for size grafts while maintaining the safety of the donor.

Small for size grafts (SFSG) are defined as either a graft weight to recipient weight ratio (GW/RW ratio) of <0.8 or a graft/standard volume of <40%. Small for size syndrome (SFSS) is defined as prolonged cholestasis, ascites and coagulopathy in the first two weeks of the peri-operative period without an anatomical or immunological cause.

Various factors influence the development of SFSS in a SFSG. These include donor, recipient and technical issues.

The important donor factors are donor age, steatosis, and venous drainage of the graft.

Recipient factors include the severity of liver disease as suggested by MELD scores. There is some evidence that sick recipients with a MELD score of >20 need larger grafts and are more prone to the development of SFSS.

Intra-operative technical factors include the quality of venous outflow reconstruction. There is growing evidence from retrospective and prospective single centre studies that modulation of portal inflow in the face of an optimal outflow can alleviate the development of SFSS. However, there is no consensus on what critical hemodynamic factors need to be addressed in modulating the inflow. There is ongoing debate surrounding the importance of portal pressure and hyperperfusion in causing dysfunction and graft failure. Some recent evidence points towards damage of the sinusoidal endothelium from congestion and high pressure as the more likely cause than hyper-perfusion per se (4,27,28,29).

10.11 Large for Size Grafts and Reduction for Paediatric Transplantation

Transplantation of small children with left lateral grafts can pose an occasional challenge of a large for size graft that needs a reduction in size to enable successful implantation. This scenario is most likely to be needed in the transplantation of neonates and children less than 5 kg in weight. Various techniques have been described to reduce the size including mono-segmental, reduced and hyper-reduced grafts. Surgical techniques are similar for both deceased and living donor grafts (30).

10.12 Portal Flow Modulation

Various surgical and pharmacological techniques have been developed to modulate portal flow and pressure. Surgical techniques include splenic artery ligation, splenectomy, and portacaval shunts. Peri-operative pharmacological manipulations to reduce portal pressure include the use of Octreotide, beta blockade and Terlipressin. Most positive evidence for improving outcomes comes from using surgical techniques to reduce portal pressure. However, there are no clear guidelines as to the optimal portal pressure or portal flow. Most units adopt a sequential use of splenic artery ligation followed by portacaval shunt to reduce portal pressure to <15 mmHg. Both synthetic and autologous grafts have been used to create an interposition shunt between the portal vein and inferior vena cava (11,29,31).

References

1. Chui AK, Rao AR, Island ER, Lau WY. Critical graft size and functional recovery in living donor liver transplantation. Transplant Proc 2004; 36: 2277-8.
2. Hill MJ, Hughes M, Jie T, et al. Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? Liver Transpl 2009; 15: 1056-62.
3. Mokry T, Bellemann N, Müller D, et al. Accuracy of estimation of graft size for living-related liver transplantation: first results of a semi-automated interactive software for CT-volumetry. PLoS One 2014. doi: 10.1371/journal.pone.0110201.
4. Tucker ON, Heaton N. The 'small for size' liver syndrome. Curr Opin Crit Care 2005; 11: 150-5.
5. Ikegami T, Shirabe K, Morita K, et al. Minimal hilar dissection prevents biliary anastomotic stricture after living donor liver transplantation. Transplantation 2011; 92: 1147-51.
6. Kim SH, Kim YK. Improving outcomes of living-donor right hepatectomy. Br J Surg 2013; 100: 528-34.
7. Soejima Y, Fukuhara T, Morita K, et al. A simple hilar dissection technique preserving maximum blood supply to the bile duct in living donor liver transplantation. Transplantation 2008; 86: 1468-9.
8. Kim BW, Bae BK, Lee JM, et al. Duct-to-duct biliary reconstructions and complications in 100 living donor liver transplantations. Transplant Proc 2009; 41: 1749-55.
9. Lee SG. A complete treatment of adult living donor liver transplantation: a review of

surgical technique and current challenges to expand indication of patients. Am J Transplant 2015; 15: 17-38.

10. Ghazaly M, Badawy MT, Soliman El-D, El-Gendy M, Ibrahim T, Davidson BR. Venous outflow reconstruction in adult living donor liver transplant: outcome of a policy for right lobe grafts without the middle hepatic vein. HPB Surg 2013; 2013: 280857. doi: 10.1155/2013/280857.
11. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. Liver Transpl 2003; 9: S36-41.
12. Song GW, Lee SG. Living donor liver transplantation. Curr Opin Organ Transplant 2014; 19: 217-22.
13. Voigt MR, DeLario GT. Perspectives on abdominal organ preservation solutions: a comparative literature review. Prog Transplant 2013; 23: 383-91.
14. Moray G, Sevmis S, Karakayali FY, Gorur SK, Haberal M. Comparison of histidine-tryptophan-ketoglutarate and University of Wisconsin in living-donor liver transplantation. Transplant Proc 2006; 38: 3572-5.
15. Kaltenborn A, Gwiasda J, Amelung V, et al. Comparable outcome of liver transplantation with Histidine-Tryptophan-Ketoglutarate vs. University of Wisconsin preservation solution: a retrospective observational double-center trial. Gastroenterol 2014; 14: 169. doi: 10.1186/1471-230X-14-169.
16. Lee SG, Park KM, Hwang S, et al. Adult-to-adult living donor liver transplantation at the Asan Medical Center, Korea. Asian J Surg 2002; 25: 277-84.
17. Bathla L, Vargas LM, Langnas A. Left lobe liver transplants. Surg Clin North Am 2013; 93: 1325-42.
18. Sánchez-Cabús S, Fondevila C, Calatayud D, et al. Importance of the temporary portocaval shunt during adult living donor liver transplantation. Liver Transpl 2013; 19: 174-83.
19. Yang Y, Zhao JC, Yan LN, et al. Risk factors associated with early and late HAT after adult liver transplantation. World J Gastroenterol 2014; 20: 10545-52.
20. Soin AS, Kumaran V, Rastogi AN, et al. Evolution of a reliable biliary reconstructive technique in 400 consecutive living donor liver transplants. J Am Coll Surg 2010; 211: 24-32.
21. Lin TS, Chen CL, Concejero AM, et al. Technical details of microsurgical biliary reconstruction in living donor liver transplantation. Transplantation 2014; 97 Suppl 8:S34-6.
22. Haberal M, Karakayali H, Sevmis S, Emiroglu R, Moray G, Arslan G. Results of biliary reconstructions in liver transplantation at our center. Transplant Proc 2006; 38: 2957-60.

23. Karnsakul W, Intihar P, Konewko R, et al. Living donor liver transplantation in children: a single North American center experience over two decades. Pediatr Transplant 2012; 16: 486-95.
24. Rodrigues S, Martins A, Barroso E. Hepatic artery thrombosis in live liver donor transplantation: how to solve - a case report. Transplant Proc 2014; 46: 1892-3.
25. Lee H, Lim CW, Yoo SH, et al. The effect of Doppler ultrasound on early vascular interventions and clinical outcomes after liver transplantation. World J Surg 2014; 38: 3202-9.
26. Umehara M, Narumi S, Sugai M, et al. Hepatic venous outflow obstruction in living donor liver transplantation: balloon angioplasty or stent placement? Transplant Proc 2012; 44: 769-71.
27. Iwasaki J, Iida T, Mizumoto M, et al. Donor morbidity in right and left hemiliver living donor liver transplantation: the impact of graft selection and surgical innovation on donor safety. Transpl Int 2014; 27: 1205-13.
28. Chen PX, Yan LN, Wang WT. Outcome of patients undergoing right lobe living donor liver transplantation with small-for-size grafts. World J Gastroenterol 2014; 20: 282-9.
29. Julka KD, Chen CL, Vasavada B. Liver lobe graft size and outcomes in living-donor liver transplant with small-for-size grafts. Exp Clin Transplant 2014; 12: 343-50.
30. Kasahara M, Sakamoto S, Umeshita K, Uemoto S. Effect of graft size matching on pediatric living-donor liver transplantation in Japan. Exp Clin Transplant 2014; 12 Suppl 1: 1-4.
31. Kaido T, Ogawa K, Fujimoto Y, Ito T, et al. A new therapeutic strategy on portal flow modulation that increases donor safety with good recipient outcomes. Transplantation 2014; 97 Suppl 8: S30-2.
32. Reichman TW, Katchman H, Tanaka T, et al. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. Transpl Int 2013; 26: 780-7.

11 OUTCOMES

Statements of Recommendation

- ***As for deceased donor liver transplantation (DDLT), only recipients with >50% five year survival can be considered for living donor living transplantation (LDLT). (2A)***

- ***Adult-to-adult LDLT is associated with a significant learning curve within the first 20 cases. All emerging centres must have access to mentoring over this period. (1B)***

- ***21% is an acceptable overall complication rate for donors following left hepatic lobectomy. (1B)***

- ***There is a 40% risk of complications in the first year following right living donor lobectomy. (1B)***

- ***Reporting of donor death and morbidity is mandatory via the NHSBT incident reporting process. (2A)***

- ***In the event of donor death:***
  - ***a) Root Cause Analysis must be performed to identify possible causes and the centre LDLT programme suspended pending the outcome of the investigation. (2B)***
  - ***b) A documented national disaster and media communication plan agreed by all centres performing LDLT must be followed. (2B)***

- ***Recipient outcome and graft survival at 12 months following LDLT must be at least equivalent to that from DDLT. (1B)***

- ***It is accepted that the frequency of biliary complications in LDLT recipients is 25% to 35%, which is higher than in DDLT. (1B)***

11.1 Introduction

Due to the greater availability of deceased donors and the use of split liver grafts in Western countries, living donor liver transplantation (LDLT) continues to comprise a much lower percentage of transplants performed in comparison with Asian countries.

Between April 2012 and March 2013, there were 705 adult and 79 paediatric deceased donor liver transplants (DDLT) performed in the UK, of which 112 were split liver grafts. Over the same period, 33 LDLT were performed; 11 adult to adult right lobe grafts and 22 adult to child left lateral grafts; this accounted for 7% of the total number of liver transplants performed, the majority being performed by 2 centres (1). Similarly, in the United States (US), LDLT makes up approximately 2-9% of adult liver transplants; this has been consistent over the last decade, with a larger percentage in children.

Recipients who benefit from LDLT are those currently disadvantaged by the minimal listing UKELD/MELD based liver allocation system, where access to deceased donor organs is often limited at lower UKELD/MELD scores. Obvious advantages of LDLT over DDLT include:

- planned transplantation before the recipient becomes too ill
- knowledge of the donor history
- avoidance of the physiologic derangement induced by brain death in the donor
- reduced cold ischaemic time

These advantages are balanced by:

- risk to the donor
- additional technical complexity of receiving a partial graft with smaller vessels and bile ducts
- the need for careful medical and surgical judgment in choosing the appropriate donor and recipient (2)

While the risk-benefit ratio may be in favour of LDLT in most Asian countries, the most appropriate role for LDLT in the UK is still to be defined. In addition more work is required to identify the risk factors associated with graft failure and recipient mortality.

Current multicentre outcomes of adult LDLT in the US are available from the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) Cohort Study. This consortium has

reported detailed retrospective and long-term prospective data on both donor and recipient outcomes of adult LDLT in the US among nine experienced transplantation centres and provides definitive evidence for the use and safety of LDLT in the US.

Within the A2ALL consortium, one of the first observations about adult-to-adult LDLT was the significant learning curve: improved graft survival was found after the first 20 cases at each centre (2). Friese et al have also recently described a lower incidence of recipient and donor complications after a period of experience (3,4). Similar findings have been reported in large single-centre reports: patient and graft survival has improved significantly after the initial centre experience (5-7).

11.2 Donor Outcome: Mortality and Morbidity

Living liver donation (LLD) puts the donor at risk of both medical and surgical complications and death. The 'true' risk of death after a donor hepatectomy is unknown. However, current available data suggest that overall donor mortality after LLD in the US and Europe is approximately 0.2% (10). In the US, reporting of donor death is now mandated by the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN). Compiled data suggest that mortality is higher among donors of the right hepatic lobe versus the left hepatic lobe; however, this finding has not been reported consistently (2).

The reported causes of death include:

- pulmonary embolism
- pulmonary infection (due to uncommon pathogens)
- emphysematous gastritis
- liver failure due to congenital lipodystrophy and non-alcoholic steatohepatitis
- acute pancreatitis
- cerebral haemorrhage
- donor suicide

The exact number of donor deaths worldwide is still not available because no central reporting agency exists. Current estimates of donor death rates are derived from either survey data or single-centre reports (8,9). The overall reported donor mortality of 0.2% (with the estimation of 12 to 13 deaths in 6,000 LDLT worldwide) includes donation of

left lateral segments, left or right lobes, adult-to-child, and adult to-adult donation (10). Mortality from donation of the right lobe (0.23-0.5%) is higher than that of left lobe donation (0.05-0.21%) and probably due to the extent of resection.

Other causes of death have been attributed to inappropriate donor selection and poor aftercare, and some “near misses” have occurred due to technical problem such as injuries to the hepatic vasculature. Right lobe donation also has a greater incidence of complications and liver failure requiring rescue transplantation, although extremely rare, has been reported (11). Mortality from right lobe donation often results from multiple organ failure and sepsis.

In general, the potential risk for adult-to adult LDLT is greater than adult-to-children LDLT due to the extensive surgery and the smaller donor remnant. The key to donor safety is to ensure the presence of sufficient well-functioning remnant liver volume. A remnant liver volume to total liver volume (RLV/TLV) of <30% or a remnant to body weight ratio (RLV/BWR) of <0.6 can have adverse effects on post-operative liver function and complications after living donor hepatectomy. However, when the two parameters of RLV/TLV and RLV/BWR are combined, the cut-off point of remnant to body weight ratio of 0.6 has no significant effect on the post-operative course (12) (see section 8).

In studies that have included donors of either the right or left hepatic lobe, the overall complication rate has been approximately 21%. However, when only right hepatic lobe donors are considered, complication rates are higher and have ranged between 38% and 47%. In 2008, Ghobial et al reported that in a retrospective cohort of 396 LLD (387 right and 9 full left lobes), 38% developed at least one complication, the vast majority within the first year (4). In 2010, the Toronto group reported that in a retrospective single centre experience of 202 right lobe donors with a minimum follow-up of 12 months, 40% developed complications within the first year (13). Also in 2010, the Kyoto group updated their previously published experience of 500 right lobe donors and reported that 44% experienced at least one complication within the follow-up period of 36.5 months (14).

In the most recent publication from the A2ALL consortium, involving 740 LLD (707 right lobes) from nine centres over nearly 12 years, 39% developed at least one complication in the first year, an incidence strikingly similar to and confirming the experience of others. They also confirmed that increasing centre experience is not

associated with a reduction in donor complications. Therefore, 40% can be considered a fairly definitive assessment of the risk of complications in the first year following living donor right lobectomy, ranging from mostly minor complications to a few life-threatening complications (16). Approximately 50% of donor complications are minor, defined as grade 1 by the Clavien system, and Clavien grade 3 or 4 complications were very rare (1.1%). Of all donor complications reported by the A2ALL consortium, infections, pleural effusion, biliary leak, and incisional hernia were the most common (see Table 11.2.1) (15).

Table 11.2.1 Donor Complications Post Living Liver Donation

Complication	Frequency (%)
Biliary leak	8.1
Biliary stricture	0.6
Incisional hernia	6.6
Unplanned re-exploration	2.7
Bowel obstruction	1.6
DVT	0.8
PE	0.9
Liver failure	0
HAT/PVT	0.5
Infection	13.2
Psychological difficulties	5.6

HAT: hepatic artery thrombosis
PVT: Portal vein thrombosis

Most laboratory abnormalities that occur in donors after lobectomy resolve quickly. 20% of donors have persistently low platelet counts two to three years after donation, although the clinical significance is unknown. In addition, there is documented trauma in an estimated 1.2% of donors due to unforeseen problems arising in the recipient, leading to abandonment of the donor hepatectomy (11).

The most recent data are from a worldwide survey of programmes performing LDLT conducted by Yee et al (11). In addition to donor demographics, case volumes, information about graft types and operative morbidity and mortality, they collected data on near-miss events and aborted hepatectomies to determine the incidence of all

potentially life-threatening events. A survey instrument was sent to 148 programmes performing LDLT. Seventy-one programmes (48%) performing 11,553 donor hepatectomies and representing 21 countries, completed the survey. The average donor morbidity rate was 24%, with five donors (0.04%) requiring transplantation. The donor mortality rate was 0.2% (23/11,553), with the majority of deaths occurring within 60 days, and all but four deaths were related to the donation surgery. The incidence of near-miss events and aborted hepatectomy was 1.1% and 1.2%, respectively. Programme experience did not appear to affect the incidence of donor morbidity or mortality, which remained consistent, but near-miss events and aborted hepatectomy were more likely in low-volume programs (≤50 LDLT procedures). It seems that potentially life-threatening near-miss events and aborted hepatectomy are underappreciated complications and should be discussed as part of the informed consent process.

11.3 Recipient Outcome: Mortality and Morbidity

Given the potential risks to the living donor, only recipients with a reasonably favourable post-transplant outcome (50% five year survival) should be considered for LDLT. Before proceeding to donor assessment, the potential recipient must first be deemed suitable for both LDLT and DDLT and be medically as well as surgically 'fit'. All potential LDLT recipients must first be listed for DDLT to avoid LDLT being performed in futile situations (e.g. inoperable hepatocellular carcinoma). This also allows for the transplant recipient to be upgraded to super-urgent priority status and obtain a DDLT if life threatening post-LDLT complications occur, such as non-function or vascular complications.

Informed consent for LDLT requires patients to be provided with accurate information on the relative benefits and risks of this procedure compared with DDLT. The evidence for efficacy in adult-to-adult LDLT is based on a systematic review and a large case–control study (10). No significant differences in 12 month recipient survival were found in three comparative studies included in the review (80-100% in the living donor (LD) group and 75-90% in the deceased donor (DD) group). In 65 studies with no comparator arms, median survival for LDLT recipients was reported to be 85.2% (ranging from 43-100%) at variable follow-up of 1-36 months.

Graft survival was also reported in three comparative studies. At a follow-up of at least 12 months, graft survival was 75-89% in the living donor groups compared with 73-89% in the deceased donor groups. The rate of re-transplantation was given in 38 non-comparative studies, with a median rate of 9.3% (range 0-26.7%) (follow up was not reported). Similar recipient survival rates were reported in a case-control study of 2234 patients where 754 had undergone living-donor transplantation. Two-year recipient survival was 79% in the LD group and 80% in the DD group. However, two-year graft survival was significantly lower in the LD group (17). In another case series of 385 patients, 1-year graft survival was 81%. There were 72 graft failures in the first 12 months, 71% occurring in the first 3 months. Thirty-seven patients (9.6%) underwent re-transplantation (16).

Reichman et al (17) performed a matched cohort comparison of 145 LDLT matched with 145 DDLT, matching recipients for age, MELD, date of transplant, gender, primary diagnosis, and recipient surgeon. LDLT had a higher overall rate of perioperative surgical complications (p=0.009). Most of this difference was caused by a higher rate of biliary complications. However, the complications that occurred in the DDLT group tended to be more serious (p=0.037), and these complications were strongly associated with graft loss in multivariate analysis. The three and five year graft and patient survivals were similar. It was concluded that DDLT and LDLT have different complication profiles, but comparable hospital stays and survival rates.

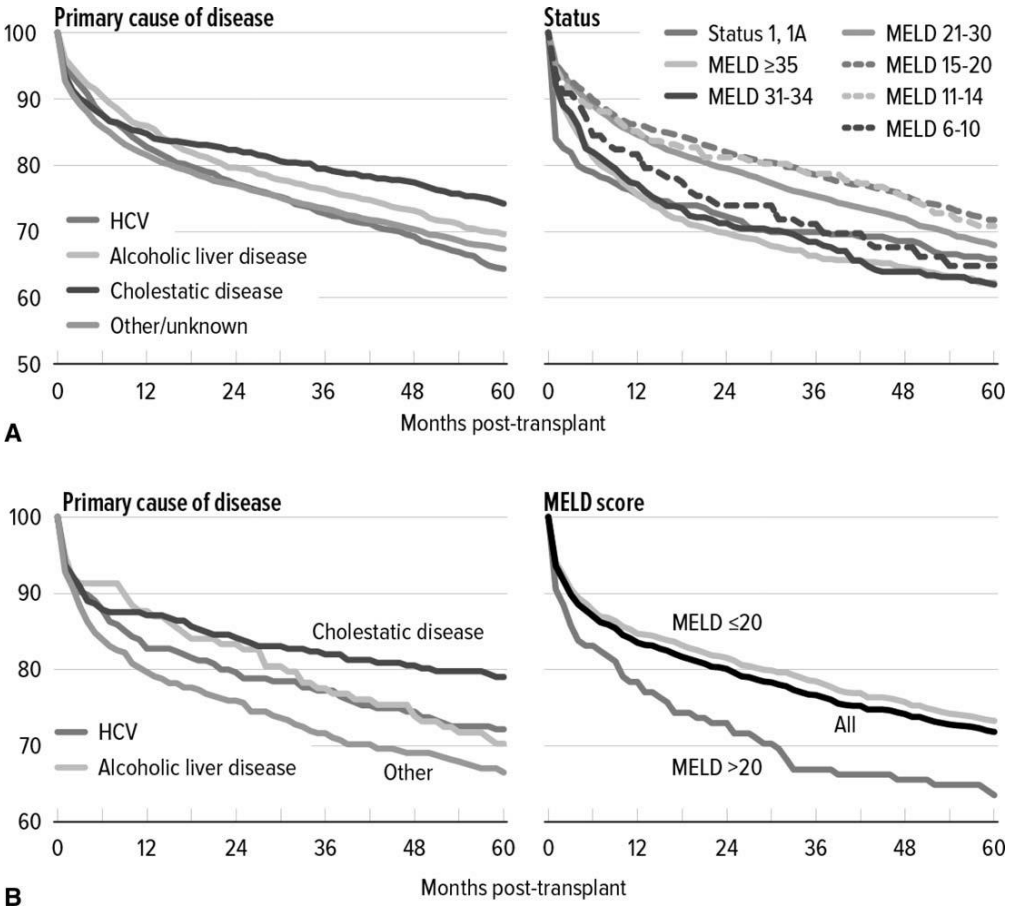
In areas of deceased donor organ shortage, LDLT offers an excellent alternative to DDLT because it facilitates access to a liver transplant without compromising short- or medium-term recipient outcomes. A2ALL has demonstrated the survival benefit of LDLT, primarily by minimising wait list death, and has shown that LDLT provides survival benefit for patients at most MELD scores (18,19). Specifically, overall mortality is significantly reduced among patients who undergo LDLT compared with patients who are waiting for DDLT (Fig. 11.3.1), due to early transplantation and the avoidance of death while on the waiting list. OPTN data for adults demonstrate comparable five year patient survival among DDLT recipients and LDLT recipients for MELD scores ≤20 (Fig 11.3.1), and the European Liver Transplant Registry reports 1-year and 5-year graft survival rates of 80% and 69% respectively (20).

Primary diagnosis is not a significant predictor of outcome when compared with DDLT. The presence of hepatocellular carcinoma appears to result in lower long-term survival, but this is probably due to a greater tumour burden (21).

DDLT is a better option for critically ill recipients who have a very high MELD score; however, LDLT has been performed successfully in candidates with higher MELD scores in certain high-volume centres in North America with comparable short- and long-term

outcomes to DDLT (22). Other data from A2ALL show no significant difference in the incidence or severity of acute cellular rejection between LDLT and DDLT recipients, and no difference in the progression of hepatitis C virus (Table 11.3.1) (23,24).

Figure 11.3.1 Survival Benefit of LDLT v DDLT



***Taken from: Clinical Liver Disease, Vol 2, No 4, August 2013*

Early data from the OPTN demonstrated a higher early graft failure rate and higher re-transplantation rate (25). However, as centre experience increased, complications dropped dramatically and outcomes improved. More recent data show a decrease in surgical complications associated with increased experience (3). Biliary complications

are more frequent in recipients of LDLT compared with DDLT because of the tenuous nature of the bile duct blood supply, small size, and frequent necessity for multiple duct anastomoses. The frequency of biliary complications is reported to be approximately 25-35%, often requiring endoscopic or surgical treatment (7,26).

Table 11.3.1 Recipient Complications LDLT v DDLT

Complication	LDLT (%)	DDLT (%)
Re-transplant	12	6.5
Complications leading to retransplant or death	15.9	9.3
Bile leak	27	10
Hepatic artery thrombosis	6.5	2.3
Portal vein thrombosis	2.9	0

The development of small-for-size syndrome (SFSS) contributes significantly to recipient morbidity and mortality. Although there is no agreed definition of SFSS, this syndrome is generally ascribed to patients who develop prolonged cholestasis, coagulopathy and ascites within the first week in the absence of technical or immunologic reasons for graft dysfunction, and has a reported incidence of 3% to 19% (27). Pre-operative calculation of recipient parenchymal requirements is important to avoid graft dysfunction, and avoidance of a GW/RW ratio of <0.8 is the most common parameter used. Recently, investigators have found that neither GW/RW ratio nor standard liver volume can reliably predict the development or outcome of SFSS (28,29). There is significant concern that the smaller graft mass provided by LDLT may be inadequate in patients who have a high physiologic demand, including patients undergoing super-urgent transplantation and those who have high MELD scores. However, the MELD score alone does not reliably identify recipients who are too ill for LDLT; rather, it is a multifactorial process that involves metabolic stress, parenchymal quality, magnitude of portal hypertension, vascular inflow and outflow, and avoidance of complications (22).

References

1. NHSBT UK ODR Annual Activity Report 2015, section 8 (Liver Activity) accessed at http://www.odt.nhs.uk/uk-transplant-registry/annual-activity-report/
2. Porrett PM, Olthoff KM. Current state of living donor liver transplantation. Clin Liver Dis 2013; 2: 156-9.
3. Freise CE, Gillespie BW, Koffron AJ, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL retrospective cohort study. Am J Transplant 2008; 8: 2569-79.
4. Ghobrial RM, Freise CE, Trotter JF, et al. Donor morbidity after living donation for liver transplantation. Gastroenterology 2008; 135: 468-76.
5. Lo CM, Fan ST, Liu CL, et al. Lessons learned from one hundred right lobe living donor liver transplants. Ann Surg 2004; 240: 151-8.
6. Pomposelli JJ, Verbesey J, Simpson MA, et al. Improved survival after live donor adult liver transplantation (LDALT) using right lobe grafts: program experience and lessons learned. Am J Transplant 2006; 6: 589-98.
7. Shah SA, Levy GA, Greig PD, et al. Reduced mortality with right-lobe living donor compared to deceased-donor liver transplantation when analyzed from the time of listing. Am J Transplant 2007; 7: 998-1002.
8. Ringe B, Strong R. The dilemma of living liver donor death: to report or not to report? Transplantation 2008; 85: 790-79.
9. Trotter JF, Adam R, Lo CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. Liver Transpl 2006; 12: 1485-8.
10. Middleton PF, Duffield M, Lynch SV, et al. Living donor liver transplantation – adult donor outcomes: a systematic review. Liver Transpl 2006; 12: 24-30.
11. Yee LC, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. Liver Transpl 2013; 19: 499–506.
12. Yaprak O, Guler N, Altaca G, et al. Ratio of remnant to total liver volume or remnant to body weight: which one is more predictive on donor outcomes? HPB 2012: 14: 476–482.
13. Adcock L, Macleod C, Dubay D, et al. Adult living liver donors have excellent long-term medical outcomes: The University of Toronto liver transplant experience. Am J Transplant 2010; 10: 364-71.
14. Iida T, Ogura Y, Oike F, et al. Surgery-related morbidity in living donors for liver transplantation. Transplantation 2010; 89: 1276-82.
15. Abecassis MM, Fisher RA, Olthoff KM, et al. Complications of living donor hepatic

lobectomy: a comprehensive report. Am J Transplant 2012; 12: 1208-17.
16. Thuluvath PJ, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. Liver Transpl 2004,10: 1263-8.
17. Reichman TW, Katchman H, Tanaka T, et al. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. Transplant Int 2013; 26: 780–7.
18. Berg CL, Gillespie BW, Merion RM, et al. Improvement in survival associated with adult-to-adult living donor liver transplantation. Gastroenterology 2007; 133: 1806-13.
19. Berg CL, Merion RM, Shearon TH, et al. Liver transplant recipient survival benefit with living donation in the model for endstage liver disease allocation era. Hepatology 2011; 54: 1313-21.
20. European Liver Transplant Registry. http://www.eltr.org/spip.php?article181
21. Kulik LM, Fisher RA, Rodrigo DR, et al. Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: results of the A2ALL cohort. Am J Transplant 2012; 12: 2997-3007.
22. Selzner M, Kashfi A, Cattral MS, et al. Live donor liver transplantation in high MELD score recipients. Ann Surg 2010; 251: 153-7.
23. Shaked A, Ghobrial RM, Merion RM, et al. Incidence and severity of acute cellular rejection in recipients undergoing adult living donor or deceased donor liver transplantation. Am J Transplant 2009; 9: 301-8.
24. Terrault NA, Shiffman ML, Lok AS, et al. Outcomes in hepatitis C virus-infected recipients of living donor vs. deceased donor liver transplantation. Liver Transpl 2007; 13: 122-9.
25. Abt PL, Mange KC, Olthoff KM, Markmann JF, Reddy KR, Shaked A. Allograft survival following adult-to-adult living donor liver transplantation. Am J Transplant 2004; 4: 1302-7.
26. Melcher ML, Pomposelli JJ, Verbesey JE, et al. Comparison of biliary complications in adult living-donor liver transplants performed at two busy transplant centers. Clin Transplant 2010; 24: E137-144.
27. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am J Transplant 2005; 5: 2605-10.
28. Hill MJ, Hughes M, Jie T, et al. Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? Liver Transpl 2009; 15: 1056-62.
29. Selzner M, Kashfi A, Cattral MS, et al. A graft to body weight ratio less than 0.8

does not exclude adult-to-adult right-lobe living donor liver transplantation. Liver Transpl 2009; 15: 1776-82.

12 EXPANDING THE DONOR POOL

Statements of Recommendation

- ***Left lobe liver grafts can only be considered in low risk recipients. (2B)***

- ***Left lobe liver grafts can be used if the graft size is at least 40% of the recipient's standard liver volume and achieves a graft recipient weight (GW/RW) ratio of >0.8. (2C)***

- ***If the GW/RW is <0.8 or the graft size is less than 35%, a right lobe graft must be considered. If this is not possible, graft inflow modulation should be considered. (2B)***

- ***Dual living donor living transplants have only been performed in highly specialised, high volume centres. (Not graded)***

- ***Dual transplants are indicated when the donor's left lobe is too small to meet the metabolic demands in the larger recipient, e.g. GW/RW <0.8, or the graft volume to standard liver volume (GV/SLV) is <40%. (C2)***

- ***Dual transplants can also be used when a potential right lobe graft makes up >70% of the donor's total liver volume meaning the remnant left lobe volume (<30%) would put the donor at risk of small for size syndrome (SFSS) after donation. (C2)***

- ***Altruistic living donation of part of a liver can be considered in low risk individuals. (C2)***

- ***If a potential liver donor has previously donated another organ, the transplant centre should ask the patient for permission to contact he original transplant team to ensure that there are no concerns re mental or physical suitability for donation. (Not graded)***

- ***The donor assessment must comply with Human Tissue Authority (HTA) requirements and include a review by an Independent Assessor. (A1)***

- ***Mental health assessment by a mental health expert is compulsory and best performed at an early stage in the donor assessment. (C1)***

- ***ABO blood group incompatible (ABOi) living donor liver transplants (LDLTs) must only be performed in centres with considerable experience of both LDLT and ABOi kidney transplantation and using an established protocol. (B1)***

- ***ABOi LDLTs should only be considered when all other options have been excluded e.g. deceased donor liver transplantation (DDLT) or living donor ABO compatible liver transplantation. (B1)***

- ***There is insufficient evidence and limited experience to make precise recommendations for ABOi treatment protocols. (Not graded)***

12.1 Left Lobe Grafts

Left lobe grafts (LLGs) were used for some of the first living donor liver transplants but were mostly abandoned because of concerns over the size of the graft when compared with a right lobe graft (RLG). A LLG comprises segments 1-4, with the caudate lobe adding about 8-12% weight to the graft. With concerns over morbidity and the mortality risk for adult to adult donation of right lobe grafts (RLG), there has been a shift to reducing the extent of resection and removing less liver from the donor and to reconsider LLGs in suitable situations. A LLG removes a significantly smaller percentage of liver tissue, which implies that donor risk will be less. UNOS data from the last 12 years indicate that LLGs now make up approximately 5% of all living donor grafts (1,2) (see also sections 9 and 10: Donor Surgery and Recipient Surgery).

One of the limitations of using a LLG is that it shifts the operative risk from the donor to the recipient as a smaller graft in a larger recipient increases the risk of small for size syndrome (SFSS) in the recipient. This makes balancing donor safety with acceptable recipient outcome much more difficult.

Recipient selection in the context of a LLG requires special attention to ensure that a graft weight to recipient weight ratio (GW/RW ratio) of >0.8 is achieved; lower values can adversely affect long-term survival. Alternatively, graft size should be at least 40%

of the recipient's standard liver volume (SLV), although 35% has been reported as sufficient in lower risk recipients (3).

To overcome the problem of a low GW/RW, some investigators advocate graft inflow modulation by either shunting, splenic artery ligation or embolisation and venous outflow modulation. Such approaches have generally been published in small case series and have not been subjected to controlled trials, but acceptable rates of survival have been reported (4-7).

12.2 Dual Living Donor Grafts

As described earlier, there has been a shift to reducing the extent of resection, removing less liver from the donor and considering smaller grafts in certain situations. The gold standard is to achieve a GV/SLV >40% of the recipient's standard liver volume or GW/RW ratio >0.8 (8).

If the donor is small and the recipient is large, then a LLG is unlikely to meet the recipient metabolic demand. However, using a larger RLG may then pose a risk to the donor. In 25% of patients, a RLG is more than 70% of the total liver volume and therefore the remnant left lobe would be <30% and pose a serious risk to the donor. To overcome this and taken together with the limitations of minimal deceased donor activity, Asian countries have used dual grafts (e.g. a left lobe graft with a left lateral segment) (9). Other combinations include two left lateral segments, a right lobe and a left lateral segment, and living donor combination with deceased donor split liver transplants (9,10). The major drawback is the potential for a 300% mortality (two donors and one recipient). Dual transplantation has only been described in high volume centres whose activity is predominantly from living donor liver transplantation (11). It is highly complex and technically demanding. There has been no experience in the UK to date.

12.3 Altruistic Living Liver Donation

There is limited world-wide experience of altruistic donation in LDLT but there have been two cases of left lateral lobe donation to a paediatric recipient within the UK since 2012 (12). In recent years there has been increasing interest and acceptance of

altruistic donation in living donor kidney transplantation (LDKT) (13). However, it is extremely important that potential donors understand the different risks associated with LDLT in comparison with LDKT.

Altruistic donation can be either non-directed (to an unknown recipient) or directed (towards a specific individual where there is no evidence of a genetic or pre-existing emotional relationship between the donor and recipient) (14,15).

The assessment of an altruistic donor for liver transplantation should be in accordance with British Transplantation Society (BTS) guidelines and a specific unit protocol. It is essential that all medical, surgical, psychiatric and psychological assessments are completed to ensure fitness to donate, competence to consent and appropriate motivation for donation (14,15).

Mental health assessment by a mental health professional (psychiatrist/psychologist) is required in all cases of altruistic donation and it is advisable that this is performed at an early stage in the evaluation (see section 7).

In the UK, all cases of altruistic donation, directed or non-directed, are approved by a panel of the Human Tissue Authority (HTA) following completion of donor evaluation and independent assessment (IA) (see section 3).

‘Serial’ Organ Donation from Non-Directed Altruistic Donors

Altruistic donors may come forward with an offer to donate a lobe of liver having already donated a kidney, or vice versa. In such circumstances, it is recommended that consent is obtained from the potential donor to allow contact with the centre where he/she has previously donated, in addition to the consent for disclosure that is requested to obtain medical information from the potential donor’s General Practitioner. The purpose of this is to ensure that any concerns about the mental or physical suitability of the donor, which may have arisen subsequent to the previous donation, can be addressed. Refusal to allow such communication would be a strong contraindication to proceeding with further assessment for subsequent donation.

12.4 ABO Blood Group Incompatible Living Donor Liver Transplantation

Experience of ABO blood group incompatible (ABOi) liver transplantation is limited in the UK, even for DDLT. In general, ABOi LDLT has only been performed in exceptional circumstances because of rapid graft loss due to antibody mediated rejection (AMR) (16). Grafts that survive have suffered from higher rates of biliary complications and infection.

With the lack of DDLT performed in the Far East, efforts to overcome the problems associated with ABOi transplantation have persisted, with five year graft survival in excess of 50% (17,18). A recent meta-analysis demonstrated higher graft survival rates at one, three and five years after blood group compatible LDLTs compared with ABOi LDLTs, although there was no difference in patient survival rates because of the use of re-transplantation (18). Outcomes from ABOi LDLT were also worse in older recipients. Various strategies have been developed to improve outcomes, including plasma exchange, intra-hepatic arterial or portal infusion (less commonly used now), and advanced immunosuppression, combined with Rituximab (since 2003). Splenectomy no longer appears to offer any immunological advantage (19).

ABO antigens are expressed on almost all body tissues and T-cell independent IgM and IgG antibodies are produced to A and/or B antigens not present in the recipient, which represent a major barrier in solid organ transplantation. In the UK, most recipients are either blood group 0 (44%) or A (45%). Blood group A occurs in several forms, A1 and A2 being the most frequent. A2 is less antigenic and expressed at lower levels than A1, meaning that experience of ABOi transplants is mostly with blood group A2 into an O recipient. Measuring ABO antibody (haemagglutinin titre) levels is difficult and inconsistent, therefore it is recommended that there is regular quality control in centres that perform this procedure, as recommended in the BTS guidelines for Antibody Incompatible Transplantation published in 2011 (16).

A high pre-operative antibody titre does not appear to have a significant effect on the frequency of antibody mediated rejection. In contrast, it is important to keep post-operative levels low as an antibody titre of >1 in 256 is a significant risk factor for antibody mediated rejection. Effective immunosuppression usually includes Rituximab administered at least seven days prior to transplantation and several sessions of plasma exchange to reduce antibody titres before transplantation, ideally to <1 in 64.

Triple therapy immunosuppression with Tacrolimus, Mycophenolate mofetil and steroid immunosuppression is required for at least one year after transplantation (20).

At present, it appears sensible to limit ABOi LDLT to centres with considerable experience of both LDLT and ABOi kidney transplantation, using an established protocol.

References

1. Saidi RF, Jabbour N, Li Y, Shah Sa, Bozorgzadeh A. Is left lobe adult to adult living donor liver transplantation ready for widespread use? The US experience (1998-2010). HPB (Oxford) 2012: 14; 455-60.
2. Soejima Y, Shirabe K, Taketomi A, et al. Left lobe living donor liver transplantation in adults. Am J Transplant 2012; 12: 1877-85.
3. Harada N, Shimada M, Yoshizumi T, Suehiro T, Soejima Y, Maehara Y. A simple and accurate formula to estimate left hepatic graft volume in living-donor adult liver transplantation. Transplantation 2004; 77: 1571-5.
4. Botha JF, Langnas AN, Campos D, et al. Left lobe adult-to-adult living donor liver transplantation: small grafts and hemiportocaval shunts in the prevention of small-for-size syndrome. Liver Transpl 2010; 16: 649-57.
5. Umeda Y, Yagi T, Sadamori H, et al. Effects of prophylactic splenic artery modulation on portal overperfusion and liver regeneration in a small-for-size graft. Transplantation 2008: 86; 673-80.
6. Ishizaki Y, Kawasaki S, Sugo H, Yoshimoto J, Fujiwara N, Imamura H. Left lobe adult-to-adult living donor liver transplantation: should portal inflow modulation be added? Liver Transpl 2012; 18: 305-14.
7. Troisi R, Cammu G, Militerno G, et al. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? Ann Surg 2003: 237; 429-36.
8. Hwang S, Lee SG, Sung KB, et al. Lessons learned from 1,000 living donor liver transplants in a single centre: how to make living donations safe. Liver Transpl 2006; 12: 920-7.
9. Lee SG, Hwang S, Park KM, et al. Seventeen adult-to-adult living donor liver transplantations using dual grafts. Transplant Proc 2001; 33: 3461-3.
10. Lee S, Hwang S, Park K, et al. An adult-to-adult living donor liver transplant using dual left lobe grafts. Surgery 2001: 129: 647-50.

11. Chen Z, Yan L, Li B, et al. Prevent small-for-size syndrome using dual grafts in living donor liver transplantation. J Surg Res 2009; 155: 261-7.
12. Wright L, Ross K, Abbey S, Levy G, Grant D. Living anonymous liver donation: case report and ethical justification. Am J Transplant 2007; 7: 1032-5.
13. Living Donor Kidney Transplantation 2020: A UK Strategy. NHS Blood and Transplant, June 2014. http://www.odt.nhs.uk/pdf/ldkt_2020_strategy.pdf
14. Jendrisak MD, Hong B, Shenoy S, et al. Altruistic living donors: evaluation for nondirected kidney or liver donation. Am J Transplant 2006: 6: 115-20.
15. Human Tissue Authority. Guidance to Transplant teams and Independent Assessors March 2015.
https://www.hta.gov.uk/policies/guidance-transplant-teams-and-independent-assessors
16. Guidelines for antibody incompatible transplantation. The British Transplant Society 2011.
http://www.bts.org.uk/BTS/Guidelines_Standards/Current/BTS/Guidelines_Standards/Current_Guidelines.aspx?hkey=e285ca32-5920-4613-ac08-fa9fd90915b5
17. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. Hepatology 2008; 47: 143-52.
18. Wu J, Ye S, Xu X, Xie H, Zhou L, Zheng S. Recipient outcomes after ABO-incompatible liver transplantation: a systematic review and meta-analysis. Plos One 2011; 6(1): e16521. doi: 10.1371/journal.pone.0016521.
19. Raut V, Mori A, Kaido T, et al. Splenectomy does not offer immunological benefits in ABO-incompatible liver transplantation with a preoperative rituximab. Transplantation 2012; 93: 99-105.
20. Soejima Y, Muto J, Matono R, et al. Strategic breakthrough in adult ABO-incompatible living donor liver transplantation: preliminary results of consecutive seven cases. Clin Transplant 2013; 27: 227-31.

13 DONOR FOLLOW-UP

Statements of Recommendation

- ***Life-long follow-up is recommended after donor hepatectomy. For donors who are resident in the UK, this can be offered locally or at the transplant centre according to the wishes of the donor, but such arrangements must facilitate the collection of data for submission to the UK Living Donor Registry. Donors from overseas who travel to the UK to donate (privately or to a NHS entitled recipient) are not entitled to NHS follow-up but must be given advice about appropriate follow-up before returning to their country of origin. (C1)***

- ***Potential donors who are unable to proceed to donation must be appropriately followed up and referred for further investigation and management as required. (B1)***

13.1 Arrangements for Follow-up

Early follow-up of the donor is recommended, within the first few weeks after surgery, to ensure that he or she is supported and is making appropriate progress following the operation. This includes the monitoring of liver function and the early detection of problems such as infection and poor wound healing.

Current practice in most centres includes a follow-up appointment four weeks after donation with three and six month follow up in primary care and annual review at the transplant centre for up to two years following donation. Additional reviews will be arranged if clinically indicated. By the end of three months, it is anticipated that the donor will have made a full recovery and returned to normal activities.

Long term annual follow up provides an opportunity for specific clinical review as well as a general health and wellbeing check, including psychosocial aspects. Since August 2012, there is a requirement under the European Organ Donation Directive (EUODD) to collect annual life-long follow-up data on all living organ donors (1). Local arrangements vary. However, best practice requires the offer of life-long follow-up for all donors, with submission of data to NHS Blood and Transplant at specified time

points for the UK Living Donor Registry (2). This follow-up can be provided by the transplant centre (in person or through virtual clinics) or in primary care. While not all donors wish to return for regular review, anecdotal experience from the living donor kidney programme suggests that many welcome the opportunity and appreciate the continuing support and interest in their welfare.

There are some logistical challenges in achieving life-long follow-up for all donors, particularly for non UK residents and/or those who are not NHS entitled. This is especially the case in countries where living donor transplantation is not an established practice or where individuals pay for healthcare. These donors should be provided with written advice about appropriate annual monitoring. However, it is difficult to ensure that robust arrangements are in place and it is rarely possible to collect accurate data on overseas donors for the UK Living Donor Registry.

In the event of an unsuccessful transplant, it is particularly important to provide adequate emotional as well as physical support for the donor, including access to counselling facilities (see section 7).

References

1. Directive 2010 /45/EU of the European Parliament and of the Council of 7 July 2010
   http://www.hta.gov.uk/_db/_documents/EUODD_Directive_August_2011.pdf
2. Living Donor Registry http://www.odt.nhs.uk/uk-transplant-registry/

14 LOGISTICAL CONSIDERATIONS

Statements of Recommendation

- ***Wherever possible, the aim must be to ensure that the financial impact on the living donor is cost neutral by the reimbursement of legitimate expenses incurred as a direct result of the preparation for and/or act of donation. There is a clear UK policy for claiming such expenses, which must be followed so that claims may be settled in full and in a timely manner (B1)***

- ***Donors from overseas present unique logistical challenges. To ensure the process is clinically effective and to comply with Visa and Immigration requirements, there is an agreed visa application process and duration of stay in the UK (six months) for the donor which must be honoured except in exceptional or unforeseen circumstances. (B1)***

14.1 Reimbursement of Living Donor Expenses

The reimbursement of legitimate expenses to a living donor, including loss of earnings which are directly attributable to the organ donation, is supported by the Health Departments in all four UK countries. Since 2013, UK policy on this issue has been more consistent and reimbursement is now part of national commissioning arrangements where these exist. NHS England has combined its separate kidney and liver policies to provide a single pathway. The policy has been developed in conjunction with both clinicians and commissioners, is compatible with the policies in each of the other UK countries, and sets out the framework and responsibilities of those involved in achieving a successful claim (1). Reimbursement does not contravene the current UK legislation under the Human Tissue Act (2) which forbids payment for supplying a human organ, provided that the donor does not gain any financial advantage as a result (see section 3.8).

The policy is underpinned by some key principles:

- Individual claims must be settled within a specified timeframe to prevent unnecessary financial hardship to the donor as a consequence of the donation

- Claims are settled by the recipient Commissioning Authority on a case-by-case basis according to agreed criteria
- Early identification of potential claims is essential during the donor assessment period to facilitate prior approval and timely settlement
- Whenever possible, claims must be submitted before the date of donation, with provision for considering claims retrospectively if there are genuine reasons why they have not been notified previously
- Donor expectations must be appropriately managed about the nature and size of claims that will be approved
- Donors must be provided with appropriate and specific information about the criteria for application at an early stage of the assessment process, in particular the need for supporting evidence, the approval processes, and the timeframes
- Alternative sources of reimbursement, e.g. statutory sick pay, must be declared when a donor applies for reimbursement

14.2 Donors who are Non UK Residents

Donors who are non UK residents present unique logistical challenges. Policies have been jointly developed to facilitate the entry of genuine donors into the UK for the purposes of donation to either an NHS entitled recipient or to a private patient. The current immigration routes provide a clear process for consideration of Entry Visa applications and define the supporting information that is required to support the donor application, including a letter from the recipient's transplant centre to clinically endorse the application (2). Appeals on compassionate grounds are considered on a case-by-case basis with the assistance of the Referred Case Unit at the Home Office in the UK. Non directed altruistic donors and directed altruistic donors that fall into category 2 within the HTA's revised legal framework (i.e. where donor and recipient have no pre-existing relationship, having met only for the purposes of living donor transplantation) are not eligible to apply for a UK Entry Visa (3) (see section 12.3)

Successful applicants will be issued with a six month visa under the visitor rules, during which time they must be assessed and prepared for donation, undergo donor hepatectomy and return to their country of origin following initial post-operative recovery. It is the responsibility of clinical teams to ensure that, pending unforeseen

circumstances, donors comply with the terms of the Entry Visa and that extensions to stay in the UK are only applied for in exceptional circumstances.

There are limitations to the current process for living liver donors (LLDs) who need to travel to the UK urgently to donate to a super-urgent recipient (e.g. in acute liver failure). Although this is rare, it is not accommodated by the existing routes of immigration and an appropriate solution is currently being explored.

14.3 Prisoners as Living Donors

In response to a small number of offers from prisoners to donate an organ altruistically, the British Transplantation Society (BTS) has collaborated with the relevant agencies to produce guidance for clinicians who receive requests to consider offers of organ donation from this source, for both family members and unknown recipients. The guidance provides a framework for management of such referrals, with particular emphasis on the logistical aspects that need to be addressed along the clinical pathway (4).

References

1. Policy for reimbursement of living organ donors, NHS England (revised and submitted for publication January 2015)
2. Visas and immigration, routes for living organ donors. November 2014. https://www.gov.uk/search?q=living+organ+donors
3. UK guidelines for directed altruistic donation. British Transplantation Society, 2014. http://www.bts.org.uk/Documents/Guidelines/Active/Guidelines
4. UK Guidelines for living organ donation from prisoners. British Transplantation Society, 2014. http://www.bts.org.uk/Documents/Guidelines/Active/Guidelines