THE RENAL ASSOCIATION
founded 1950

BTS
British Transplantation Society

Living Donor Kidney Transplantation

Third Edition

May 2011

United Kingdom Guidelines

UNITED KINGDOM GUIDELINES

FOR

LIVING DONOR KIDNEY TRANSPLANTATION

Compiled by a Joint Working Party of

The British Transplantation Society and

The Renal Association

Third Edition

May 2011

Posted on www.bts.org.uk & www.renal.org May 2011

CONTENTS

CHAPTER 1 INTRODUCTION AND OBJECTIVES

1.1 The Need for Guidelines

Living kidney donation has become an essential part of transplantation practice. Historically, this has been attributed to the shortage of deceased donor kidneys and the growing waiting list of potential recipients. However, kidney transplantation from a living donor has become the treatment of choice for many patients and their families, offering optimum patient and graft survival, and also the chance to avoid long periods on the transplant waiting list. This is particularly the case in pre-emptive transplantation, when the transplant occurs before the start of dialysis. Currently, pre-emptive transplantation averages 31% of the patients transplanted from living donors; a figure that most believe should increase over the next ten years (1).

Recently, living donation has offered patients who are more clinically complex, both immunologically and/or due to other co-morbidities, the opportunity to benefit from a transplant that they might otherwise not have received from the deceased donor waiting list. Nonetheless, the welfare of the donor remains paramount, and vigilance in donor care and management is essential to ensure that appropriate safeguards are in place to protect individuals and to inspire public confidence.

At the time of writing, living donors account for 1 in 2 organ donors and 1 in 3 kidney transplants performed in the UK are from living donors, this representing 38% of the total kidney transplant activity per annum. The latest national statistics show that in 2008-9 and 2009-10, there was an 11% increase in living donor kidney transplants performed year on year, to 927 and 1037 respectively (1). In part, these figures reflect a small but growing number of transplants from paired/pooled donation and non-directed altruistic donors, of which there were 32 and 16 transplants performed in 2009 and 2010 respectively. Over the last 10 years, there has been a 65% increase in overall living donor activity, from 372 donors in 2000-1 to 1061 in 2009-10, with all transplant centres now actively engaged in living donor kidney transplantation. This represents a significant change in practice and necessitates clear, contemporary, evidence-based guidance.

1.2 Scope of the Guidelines

This guidance relates only to living donor kidney transplantation and reflects a growing body of evidence, incorporating aspects of clinical practice that are relevant to both adult and paediatric settings. These include the ethical and medico-legal aspects of donor selection, medical and pre-operative donor evaluation, identification of high risk donors, the management of complications, and expected outcome. Scenarios that present an increased level of risk to the potential recipient, such as antibody incompatible transplantation, recurrent disease and transplantation in the context of other co-morbidities, are also included. In addition, guidance is provided on the most appropriate investigations to be considered to assist clinical decision-making, and the best surgical approaches when faced with different clinical scenarios.

1.3 Process of Writing and Methodology

The original 'UK Guidelines for Living Donor Kidney Transplantation' were commissioned by the British Transplantation Society (BTS) and the Renal Association (RA) as part of a wider initiative to develop 'Best Practice' guidance for clinicians involved in the area of transplantation. Initially published in 2000 (2) and revised in 2005 (3), the guidelines have achieved international repute. This third edition has continued the collaboration between BTS and RA, under the auspices of the BTS Standards Committee, and the document has been significantly updated in the light of new data and changing practice. It has been produced with wide representation from UK colleagues and professional bodies involved in both donor and recipient management.

A systematic review of the relevant literature and synthesis of the available evidence was undertaken by selected relevant clinical experts. This was followed by peer group appraisal and expert review. Draft proposals were amended by an editorial committee and the appropriate levels of evidence added to recommendations. Wider consultation with the transplant community was undertaken by 'face to face' consultation in the form of a BTS-sponsored consensus meeting at the BTS Living Donor Forum, and through subsequent e-mail commentary. The penultimate draft of the document was placed on the BTS and RA websites in March and April 2011 for an additional period of open consultation, to which patient and transplant groups were actively encouraged to contribute. The final document was posted in May 2011.

Where available, these guidelines are based on published evidence, and the evidence and recommendations have been graded for strength except where the published studies are descriptive. With a handful of exceptions, conference presentations have not been included and the publication cut off date for evidence was February 2011.

It is anticipated that these guidelines will next be revised in 2015.

1.4 Editorial Committee

Professor Derek Manas MD FCS (SA)
Professor of Transplantation
University of Newcastle upon Tyne and Newcastle NHS Trust
Co-Chair Editorial Group & BTS Living Donor Forum

Miss Lisa Burnapp RN MA
Consultant Nurse, Living Donor Kidney Transplantation, Guy's & St Thomas' NHS Foundation Trust, London
Lead Nurse - Living Donation, Organ Donation and Transplantation, NHS Blood and Transplant (NHSBT)
Co-Chair Editorial Group & BTS Living Donor Forum

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

Professor J Andrew Bradley FRCS F Med Sci (Cambridge)
Professor of Surgery, University of Cambridge
Clinical Director of Transplantation, Cambridge University Hospitals NHS Trust
Co-editor of previous Living Donor Guidelines, Chair of NHSBT Kidney Advisory Group

Dr Chris Dudley MD FRCP
Consultant Nephrologist & Clinical Director of Renal and Transplant
Southmead Hospital, Bristol
Secretary of BTS, RA Representative

1.5 Contributing Authors

Dr Peter Andrews MD FRCP, Consultant Nephrologist & Clinical Lead for Transplantation, SW Thames Renal & Transplantation Unit, St Helier Hospital, Surrey

Dr Kesh Baboolal MD FRCP, Director of Acute University Hospital Services, Cardiff and Vale University Health Board, University Hospital of Wales

Dr Richard Baker PhD FRCP, Consultant Nephrologist, St. James's University Hospital, Leeds

Dr Simon Ball PhD FRCP, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham

Prof J Andrew Bradley FRCS F Med Sci (Cambridge), Professor of Surgery, University of Cambridge and Clinical Director of Transplantation, Cambridge University Hospitals NHS Trust

Miss Lisa Burnapp RN MA, Consultant Nurse, Living Donor Kidney Transplantation, Guy's & St Thomas' NHS Foundation Trust, London; & Lead Nurse, Living Donation, NHS Blood and Transplant

Dr Jamie Cavenagh MD FRCP FRCPath, Consultant Haematologist, Barts and the London NHS Trust

Dr Brian Clapp PhD MRCP, Consultant Cardiologist, Guy's & St Thomas' NHS Foundation Trust, London

Dr Antonia Cronin MRCP MA (Medical Law and Ethics), Consultant Nephrologist, Guy's & St Thomas' NHS Foundation Trust and King's College London

Dr Susan Fuggle DPhil FRCPath, Consultant Clinical Scientist, Oxford Transplant Centre

Dr Colin Geddes FRCP (Glas), Consultant Nephrologist and Honorary Senior Lecturer, Greater Glasgow, Clyde and Forth Valley Renal Service

Mr Paul Gibbs FRCS, Consultant Surgeon, Wessex Regional Renal and Transplant Unit, Portsmouth

Mr David Glass, Lead Clinical Health Psychologist, Guy's & St Thomas' NHS Foundation Trust, London

Ms Kay Hamilton RN, Living Donor Co-ordinator, Southmead Hospital, Bristol

Ms Sian Hedges, Central Policy Unit, Home Office, UK

Dr Robert Higgins MD FRCP, Consultant Nephrologist, University Hospitals Coventry and Warwickshire

Dr Rachel Hilton PhD FRCP, Consultant Nephrologist, Guy's & St Thomas' NHS Foundation Trust, London

Mrs Rachel Johnson MSc, Head of Organ Donation and Transplantation Studies, NHS Blood and Transplant

Mr Paul Lear MS FRCS, Divisional Director of Surgery and Consultant Surgeon, Dorset County Hospital Foundation Trust, North Bristol NHS Trust

Dr Robert Lewis MD FRCP, Consultant Nephrologist, Wessex Regional Renal and Transplant Unit, Portsmouth

Mr Nizam Mamode MD FRCS, Consultant Surgeon, Guy's & St Thomas' NHS Foundation Trust, London

Prof Derek Manas MD FCS (SA), Professor of Transplantation, University of Newcastle upon Tyne and Newcastle NHS Trust

Ms Ann Marsden RN, Live Donor Transplant Co-ordinator, Cardiff Transplant Unit

Miss Lorna Marson MD FRCS, Senior Lecturer in Transplant Surgery, Royal Infirmary of Edinburgh

Dr Adam Mclean DPhil FRCP, Consultant Nephrologist & Transplant Physician, West London Renal & Transplant Centre

Ms Jen McDermott BSc Hons MA, Lead Living Donor Co-ordinator, Imperial College Healthcare NHS Trust

Mrs Sue Moore RN, Living Donor Co-ordinator, Queen Elizabeth Hospital, Birmingham

Dr Pramod Nagaraja MRCP, SpR in Nephrology and Transplantation, University Hospital of Wales

Dr Chas Newstead FRCP MD, Consultant Renal Physician, St James's University Hospital, Leeds

Mr Jonathan Olsburgh MBBS FRCS (Urol), Consultant in Urology & Transplant Surgery, Guy's & St Thomas' NHS Foundation Trust, London

Dr Michael Picton PhD FRCP, Consultant Nephrologist, Manchester Royal Infirmary

Mr David Rix MD FRCS, Consultant Urologist, Freeman Hospital, Newcastle

Dr Richard Sandford PhD FRCP, Honorary Consultant in Medical Genetics, University of Cambridge

Dr John Scoble MD FRCP, Associate Medical Director, Guy's & St Thomas' NHS Foundation Trust, London

Prof Neil Sheerin PhD MRCP, Professor of Nephrology, Newcastle University

Dr John Sayer MRCP PhD, Senior Lecturer in Nephrology, Newcastle

Dr Richard Smith PhD MRCP, Consultant and Senior Lecturer, University of Bristol

Ms Linda Stowe, Central Policy Unit, Home Office, UK

Dr Craig Taylor PhD FRCPath, Director of Histocompatibility and Immunogenetics, Cambridge University Hospital NHS Foundation Trust

Dr Paul Telfer FRCP FRCPath, Consultant Haematologist, Barts and the London NHS Trust

Dr Raj Thuraisingham MD FRCP, Honorary Senior Lecturer and Consultant Nephrologist, Barts and the London NHS Trust

Dr E Jane Tizard FRCP FRCPCH, Consultant Paediatric Nephrologist, Bristol Royal Hospital for Children

Dr Nicholas Torpey PhD FRCP, Consultant Nephrologist, Addenbrooke's Hospital, Cambridge

Dr Robert Vaughan PhD FRCPath, Director of Clinical Transplantation Laboratory, King's College, London

Mr Peter Veitch FRCS, Consultant Transplant Surgeon, Royal Free Hospital, London

1.6 Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All practitioners 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 and Renal Association 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.

1.7 Grading of Recommendations

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

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

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 (5).

References

1. NHS Blood and Transplant. Transplant Activity in the UK, Activity Report 2009-2010. http://www.organdonation.nhs.uk/ukt/statistics/transplant_activity_report/transplant_activity_report.jsp
2. British Transplantation Society / Renal Association. United Kingdom Guidelines for Living Donor Kidney Transplantation, January 2000.

3. British Transplantation Society / Renal Association. United Kingdom Guidelines for Living Donor Kidney Transplantation, Second Edition, April 2005. http://www.bts.org.uk/transplantation/standards-and-guidelines/
4. 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.
5. 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-S157.

CHAPTER 2 LEGAL FRAMEWORK

Statements of Recommendation

- ***All kidney 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 countries of 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 both 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.***

In September 2006, new legislation came into effect in England, Wales and Northern Ireland. The Human Tissue Act 2004 (1) is now the primary legislation regulating transplantation in those countries. The 2004 Act repeals and replaces earlier legislation, including the Human Tissue Act 1961 (2), the Anatomy Act 1984 (3), and the Human Organ Transplants Act 1989 (4).

The 2004 Act does not apply in Scotland (save for section 45 prohibiting the possession of bodily material with the intentions of analysing DNA within it without consent). Separate legislation, the Human Tissue (Scotland) Act 2006 (5), has been developed and now applies in Scotland.

2.1 The Human Tissue Act 2004

The 2004 Act provides the legal framework governing the removal, storage and use of human organs and other tissues (excluding gametes and embryos) and 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 kidney 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).

2.2 The Human Tissue Authority (HTA)

A regulatory body, the Human Tissue Authority (HTA), was established under the 2004 Act to oversee and control the working of the Act (10). At the present time, activities involving human tissue are regulated by the HTA (11). The HTA regulates the removal, storage, use and disposal of human bodies, organs, and tissue from the living and deceased (excluding gametes and embryos) (12).

In a recent review of the Department of Health's (DH) arm's length bodies sector, it was proposed that the functions of HTA would be transferred by the end of the current Parliament. In the meantime the DH will examine the practicalities (and legal implications) of how to divide the HTA's functions between a new 'research regulator', the Care Quality Commission (13) and the Health and Social Care Information Centre (14). The Department of Health has indicated that there is currently no intention to make any changes to the Human Tissue Act 2004.

Living donor kidney transplants do not, at present, require a licence, but certain kinds of transplant activities require special approval from the HTA. The HTA is responsible for approving organ donation for kidney transplantation from living people. The HTA approves all transplants involving living people following an independent assessment process. All donors and recipients see a local Independent Assessor (IA) who is trained and accredited by the HTA and acts on behalf of the Authority to ensure the best interests of the donor. 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 (15).

2.3 Consent for the Removal of Organs from Living Donors

Consent for the removal of organs from living donors, for the purposes of transplantation, is one of the matters that must be considered by the HTA in its statutory approval process (Regulation 11). Clinicians are also required to consider consent under the common law on consent for those under 16 years of age and, where necessary, the Mental Capacity Act 2005 (16).

2.4 Types of Living Kidney Donation Permitted by the Legislation

The Human Tissue Act 2004 (1) and the Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants) Regulations 2006 (17) expressly allow the following types of living donation for kidney transplantation:

1. Directed donation. A form of donation where a healthy person donates an organ (kidney) to a specific recipient. These include:
   (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. Altruistic non-directed donation. A form of living donation whereby a kidney 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. Although not described in the initial Act, an amendment has been made to facilitate the development of altruistic donor chains to further optimise organ allocation.

2.5 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 Regulations 9–14 of the Regulations (19). It is an offence to remove or use a kidney 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 kidney transplantation must be approved by the HTA before donation can take place. Before the HTA can approve such cases, the Regulations require that 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.

At the present time, in cases of directed genetically or emotionally related donation, the HTA requires evidence of relationship to be provided, so that it can be satisfied the relationship between donor and recipient is as stated. The Regulations require that the decision on whether a transplant proceeds must be made by an HTA panel of at least three Authority members in all cases of paired and pooled donation; all cases of altruistic non-directed living donation (to include altruistic donor chains); if the organ donor is a child; and if the organ donor is an adult who lacks capacity (Regulation 12).

2.6 Prohibition of Commercial Dealings in Human Material

Section 32 of the Human Tissue Act 2004 prohibits commercial dealings in human material, including kidneys 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 a kidney;
2. look for a person willing to supply a kidney for reward;

3. offer to supply a kidney for reward;
4. initiate or negotiate any arrangement involving the giving of a reward for the supply of, or for an offer to supply, a kidney 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, an advertisement inviting people to supply, or offer to supply, a kidney for reward, or indicate that the advertiser is willing to initiate or negotiate any such arrangements. This covers all and any types of advertising.

The following terms apply:

- 'Transplantable material' is defined in Part 3, Regulations 9 and 10 of the Regulations and includes living donor kidneys for transplants (17);
- 'Relevant Material' is material, other than gametes, which consists of or includes human cells;
- 'Advertisement' is defined in section 32(11) and includes any form of advertising, whether to the public generally, to any section of the public, or individually to selected persons, for reward;
- 'Reward' is defined in section 32(11) and means any description of financial or other material advantage.

2.7 Reimbursement of Expenses

The Human Tissue Act 2004 (20) 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 Chapter 9).

2.8 Exceptional Circumstances

2.8.1 Children

The Human Tissue Act 2004 defines a child as a person under 18 years old (21). 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'* (22). 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. The HTA would always require that parental consent is obtained and that an advance ruling be sought from the High Court before considering statutory approval for the donation (23,24).

Children should only be considered as living organ donors in exceptionally rare circumstances. Living donation by a child under 18 years of age can only go ahead under the 2004 Act with the approval of an HTA panel, and court approval should also be obtained.

2.8.2 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 (Mental Capacity Act Code of Practice paragraph 8.20). Following court approval, donation may then only proceed if the case is approved by an HTA panel.

2.9 The Human Tissue (Scotland) Act 2006

The purpose of the 2006 Act (5) is to make provision in relation to 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 has now been incorporated into the 2006 Act. While provisions of the Human Tissue Scotland Act are based on 'authorisation' (25) rather than 'appropriate consent' as in the Human Tissue Act 2004 (7), these are essentially both expressions of the same principle.

In the specific context of living organ donation, the 2006 Act replicates the approach in the 2004 Act in stipulating 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 outlines specific circumstances in which the removal of organs may take place: in which the donor gives their consent, without coercion and there is no reward given. Restrictions on transplants involving living donors are set out in section 17 of the 2006 Act (26). These provisions are supplemented by the

Human Organ and Tissue Live Transplants (Scotland) Regulations 2006 (the Scottish Live Transplants Regulations) (27). Prohibitions of commercial dealings in parts of a human body for transplantation are set out in section 20 of the 2006 Act (28).

Although not governed by the 2006 Act, under arrangements made between the Scottish Executive and the HTA, potential living donors are scrutinised by the HTA to ensure that there is no evidence of coercion or financial reward, as in other parts of the United Kingdom. Other areas that are discussed in the 2006 Act are the introduction of paired exchange renal transplant programmes and the legalisation of altruistic donation, in response to the acknowledgement of the Scottish Executive of the benefits of increased numbers of living donor transplants.

Exceptional Circumstances

Under Scottish legislation children are defined as persons who have not yet reached the age of 16 years (29). The principle of competency of children under 16 years to consent to procedures is incorporated into Age of Legal Capacity Act (Scotland) 1991 (29), 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 (30).

The Human Tissue (Scotland) Act 2006 prohibits the donation of non-regenerative tissue such kidneys by minors (under 16 years of age) and adults lacking capacity (31).

The Scottish Government has issued detailed guidance on the 2006 Act and its implications for NHS Scotland (32).

2.10 The EU Organ Donation Directive

Published on 7th July 2010, the EU Organ Donor Directive (ODD) aims to bring all EU countries up to the same standards of quality and safety with regard to human organs intended for transplantation (27). It is the first time a formal regulatory framework has been developed for the donation and transplant of organs in the EU. The aim is to

standardise the systems and processes used by member states. It will also help facilitate the more effective exchange of organs between member states. The ultimate goal is to ensure common high quality and safe standards for the donation, procurement, transportation, traceability and follow-up of donated organs for transplant across the EU.

The Human Tissue Authority has been named as the Competent Authority for England and Wales for the EU Organ Donation Directive (ODD) and will take the lead on developing the first formal regulatory framework for the donation and transplant of organs and its implementation into legislation by August 2012. The Scottish and Welsh Assemblies have also asked the HTA to be their Competent Authority for the ODD.

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. www.opsi.gov.uk/acts/acts1989/ukpga_19890031_en_1
5. The Human Tissue (Scotland) Act 2006. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_1
6. The Human Tissue Act 2004. Scheduled purposes requiring general consent are outlined in Part 1 of Schedule 1 of the 2004 Act. http://www.opsi.gov.uk/acts/acts2004/40030--e.htm#sch1
7. Appropriate Consent requirements are set out in section 3 of the 2004 Act.
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. Gametes and embryos at the present time are regulated by the Human Fertilisation and Embryology Authority (HFEA).
13. The Care Quality Commission. www.cqc.org.uk
14. The Information Centre for Health and Social Care. www.ic.nhs.uk
15. Guidance for Transplant Teams and Independent Assessors. http://www.hta.gov.uk/_db/_documents/IA_Guidance_FINAL.pdf
16. Mental Capacity Act 2005. www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1

17. Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants) Regulations 2006. www.opsi.gov.uk/si/si2006/20061659.htm
18. Human Tissue Act 2004 Part 2, sections 33 and 34. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb6
19. Human Tissue Act 2004 Part 2, section 32. http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb5-l1g32
20. Human Tissue Act 2004 Part 2. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_4#pt2-pb6
21. Human Tissue Act 2004 Part 3, section 54. www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_5#pt3-pb2-l1g54
22. The Human Tissue (Scotland) Act 2006, sections 6-10. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_2#pt1-pb2-l1g6
23. The Human Tissue (Scotland) Act 2006, section 17. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_3#pt1-pb3
24. 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
25. The Human Tissue (Scotland) Act 2006, section 20. www.opsi.gov.uk/legislation/scotland/acts2006/asp_20060004_en_3#pt1-pb5-l1g20
26. Adults with Incapacity (Scotland) Act 2000. www.opsi.gov.uk/legislation/scotland/acts2000/asp_20000004_en_1
27. Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:

CHAPTER 3 ETHICS

Statement of Recommendation

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

3.1 Ethics

Since its inception more than 50 years ago, living donor kidney transplantation has raised a wide range of complex ethical issues. With continued expansion of living donor programmes, it is essential that all health professionals involved in living donor transplantation are fully aware of the general principles that underpin good ethical practice. A detailed description of the theoretical and philosophical background to the subject is beyond the scope of these guidelines, but there are several helpful reviews in the academic literature (1-6). Here we provide a summary of the key ethical principles in living donor kidney transplantation and guidance on how they are applied in clinical practice.

3.2 Key Ethical Principles in Living Donor Kidney Transplantation

Altruism: The basis of organ donation in the UK has, from the start, been presented as one of altruism understood as a selfless gift to others without expectation of remuneration (7). Altruistic giving may be to strangers, or may take place within the context of family or other relationships. A strong emphasis on altruism reinforces the philosophy of voluntary and unpaid donation, and solidarity between donor and recipient. Some have expressed concern that the traditional altruistic model can often be subject to hidden coercive pressures, as when patients on a transplant list might ‘expect’ a suitable relative to donate an organ to help them (8).

Autonomy: The principle of autonomy recognises the rights of individuals to self determination. Autonomy is widely understood as underpinning our entitlement to control our own bodies, because they are 'ours'. Respect for autonomy is shown primarily through the importance placed on consent: valid consent must be given before a living donor nephrectomy may take place. Concerns about coercion and 'undue inducement' undermining valid consent similarly reflect the importance attached to ensuring that decisions about living donation are freely and autonomously made by the person (the donor) concerned.

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

Dignity: Dignity is an elusive term. It is often associated with concerns that putting a price on any part of a human body would 'commodify' it in such a way that is incompatible with its unique status. The concept of the inherent dignity, or special status, of the human body is usually traced back to the work of philosopher Immanuel Kant. According to Kant, dignity and price are in essence mutually incompatible: the maintenance of human dignity requires human beings to be beyond negotiable price. Putting a price on a human being, or on part of their body, would be to give it a relative value, while human beings are of 'incomparable ethical worth' (9). If this view of human dignity is accepted, then any form of financial payment, or 'commodification' of bodies or body parts would constitute a violation of human dignity, even if the person concerned did not personally feel in any way degraded. Such a view is strongly challenged by some who argue that 'degradation very much depends on one's own perception of what is degrading' (10).

Non-Maleficence: The ethical principle of 'doing no harm'. This principle is based on the Hippocratic Oath maxim 'abstain from doing harm'.

Reciprocity: The principle of reciprocity refers to providing benefits or services to another as part of a mutual exchange. Reciprocity underpins paired living donor kidney transplantation in which one donor/recipient 'pair' enters into a reciprocal arrangement with another. Pooled donations work on the same basis with three or more sets of donors/recipients.

3.3 The Recipient Perspective

The benefits of living donation to the recipient are detailed in the introduction and in Chapter 11 of these guidelines. They can be summarised as:

a) A better outcome than transplantation from deceased donors – regardless of the degree of genetic relationship or HLA mismatching between donor and recipient;

b) The avoidance of prolonged dialysis while waiting for a kidney from a deceased donor to become available. Time on dialysis is increasingly recognised as a risk factor for poorer outcomes after transplantation;

c) An option to facilitate pre-emptive (pre-dialysis) transplantation;

d) The opportunity to minimise disruption to school, work and social life by having a planned procedure.

None of these benefits justify living donation unless the interests of the donor are given primacy. The welfare of the potential living donor should always take precedence over the needs of the potential transplant recipient.

3.4 The Donor Perspective

Living kidney donation involves a detailed process of investigation, major surgery, and a life thereafter with a single kidney. A living donor kidney transplant has a number of benefits both for the donor and from a societal perspective. However, these good effects notwithstanding, a living donor nephrectomy entails risk and this includes a small risk of death (see Chapter 6). Removal of a kidney will inevitably cause physical harm, to a lesser or greater extent, to the donor. As a result it may seem difficult to justify, particularly when the risk of harm is considered together with the well known maxim ‘first, do no harm’. Demonstrating that living organ donation is, or may be, harmful provides a powerful argument against it. However, this does not take account of other morally relevant reasons, in particular individual autonomy, which may have contributed to an individual’s decision, and motivation, to donate. Further, although living kidney donors gain no physical benefit from the transplant procedure, they often gain psychological benefit

knowing that their gift has provided an opportunity to dramatically improve the quality of life of a relative, partner, close friend, or (in the case of paired and altruistic donation) stranger. Some might even argue 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 the basis upon which the legitimacy of living kidney donation can be supported. A living donor nephrectomy is morally acceptable when carried out with 'informed consent, freely given' (see Chapter 4: Informing the Potential Donor). Establishing 'informed consent freely given' may be more difficult in practice than it sounds.

While all living donor programmes would 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 at an early stage that they wish to donate and then to be impervious to or oblivious of any suggestion that they should make a more informed decision in the light of further counselling (11). The consent may be real, but whether it is truly informed may be questionable.

With regard to the term 'freely given' – who can truly know that, other than the donor himself? While it may be possible to identify the donor who has clearly come under pressure or coercion, from either the recipient or from other family members, it seems almost inevitable that more subtle pressures exist in many situations that the donor does not reveal and that health care professionals do not detect. These may make it difficult or impossible for a potential donor not to proceed through the process.

It is important to recognise that there will be as many variations of 'informed consent, freely given' as there are donor-recipient pairs. In very many situations the motives and autonomy of the donor will be beyond question. However, it may on occasion 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 recommended – allowing for, in effect, a donor advocate. A similar role may be played by a living donor coordinator, or more formally by an independent third party, the Independent Assessor (see Chapters 2 and 4). It is essential that this separation of responsibility remains standard and is applied to all potential living donors.

3.5 The Transplant Team Perspective

A major role of the transplant team is to inform the potential donor of the risks associated with living kidney donation. There may be circumstances in which the transplant team has concerns about the medical suitability of a potential donor and consider that proceeding with donation and transplantation is inappropriate.

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 the team find acceptable or appropriate, they are under no obligation to proceed. In such circumstances, referral for a second opinion would be appropriate.

3.6 Confidentiality

Both the donor and recipient have a right to a confidential relationship with their respective clinicians. Clinical teams have a duty to respect that right. Highlighting this aspect of living donor kidney transplantation is of particular importance 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 as a matter of course 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, and breach of confidentiality. (See Chapter 4: Informing the Potential Donor)

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 kidney transplant. Examples would include HLA mismatching/ crossmatching results, CMV/EBV status (for post transplant prophylaxis or monitoring) 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. renal vasculature, renal function) 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 his or her genetic relationship with the potential recipient may become available during the living donor transplantation work-up process. There may be occasions when this information, quite unexpectedly, identifies that a genetic relationship has been misattributed. The potential personal, social and cultural implications of this for both donor and recipient may be devastating and the effects of receiving such information should not be underestimated. Donors and recipients may or may not wish to be informed. (See Chapter 4: Informing the Potential Donor). 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 Chapter 4).

3.7 Expanding the Living Donor Pool

In the UK, as elsewhere, the landscape of living donor kidney transplantation has evolved considerably over the last ten years. In particular, the number of genetically unrelated and antibody incompatible donations have increased. Key developments in the UK have included:

1. Paired and pooled donation (see Chapter 8);
2. Altruistic, non-directed donation (see Chapter 8);
3. The use of an altruistic donation to catalyze a cascade of transplants (see Chapter 8);
4. High risk antibody incompatible donor-recipient pairs (see Chapter 7).

There are specific considerations that are unique to these areas of living donor kidney transplantation. They are discussed separately in the relevant chapters highlighted.

3.8 The Child or Young Person as a Living Donor

The moral arguments for not subjecting young people, under the age of 18 years, to the rigours of living kidney donation are compelling and minors should rarely, if ever, be considered as potential living donors. There are genuine concerns about autonomy and the validity of consent from minors in this situation. (See Chapter 2: Legal Framework).

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 (12). This view is highly controversial and has been challenged (13,14). 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’ (15).

3.9 The British Transplantation Society (BTS) Ethics Committee

The BTS Ethics Committee is a subcommittee of the BTS Council. Healthcare professionals responsible for living donor kidney 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. Price D. Human tissue in transplantation and research: A model legal and ethical donation framework. Cambridge University Press, 2009.
2. Price D. Legal and ethical aspects of organ transplantation. Cambridge University Press, 2000.
3. Plant WD, Akyol MA, Rudge CJ. The ethical dimension to organ transplantation in transplantation surgery (2nd edn). Ed Forsythe JLR. WB Saunders London, 2002.
4. Ross LF, Glannon W, Josephson MA. Should all living donors be treated equally? Transplantation 2002; 74: 418-21.
5. Kahn J, Matas AJ. What's special about the ethics of living donors? Transplantation 2002; 74: 421-2.
6. Truog RD. The ethics of organ donation by living donors. N Engl J Med 2005; 353: 444-6.
7. Titmuss RM. The gift relationship: from human blood to social policy. London: Allen and Unwin, 1970.
8. Scheper-Hughes N. The tyranny of the gift: sacrificial violence in living donor transplants. Am J Transplant 2007; 7: 507-11.
9. Cohen CB. Selling bits and pieces of humans to make babies: the gift of the Magi revisited. J Med Philos 1999: 24; 288-306.
10. Daar AS. Paid organ donation – the grey basket concept. J Med Ethics 1988; 24: 365-8.
11. Russell S, Jacob RG. Living related organ donation: the donor's dilemma. Patient Educ Couns 1993; 21: 89-99.
12. WHO guiding principles on human cell, tissue and organ transplantation. Transplantation 2010; 90: 229-33.
13. Curran WJ. Kidney transplantation in identical twin minors – justification is done in Connecticut. New N Engl J Med. 1972; 287: 26-7.
14. Hollenberg NK. Altruism and coercion: should children serve as kidney donors. N Engl J Med. 1977; 296: 390-1.
15. Medical ethics today: its practice and philosophy. London: BMJ Books, 1998.

CHAPTER 4 INFORMING THE POTENTIAL DONOR

Statements of Recommendation

- ***The living donor must be offered the best possible environment for making a voluntary and informed choice about donation. In line with current best practice, 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 to disclosure under these circumstances may jeopardise the transplant proceeding. (Not graded)***

- ***Independent assessment of the donor and recipient is required by primary legislation (Human Tissue Act 2004). In order to achieve the best outcome for donor, recipient and transplant, the boundaries of confidentiality must be specified and discussed at the outset. Separate clinical teams for donor and recipient are considered best practice but 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)***

- ***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 in the evaluation to ensure that appropriate support and/or intervention is initiated. Access to specialist psychiatric/psychological services must be available for donors/recipients requiring referral. (B2)***

4.1 Informing the Potential 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 the respect by the medical practitioner 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 Chapter 3: Ethics).

4.2 Informed Consent for Living Kidney Donation

The need for informed consent and its significance in terms of the validity of the consent process should be explained to the potential donor. Ideally, both verbal and written information about living kidney donation should be provided. The risk of death associated with living donor nephrectomy and the risks of short and long-term complications must be fully explained (see Chapter 6).

Although the surgical risks associated with nephrectomy are unchanged for the potential living donor regardless of the identity of the recipient, the likelihood of transplantation being successful may be material to the donor's decision to donate or not. If it is established that information regarding the likelihood of success would materially affect an individual's decision to donate, providing such information necessarily becomes an integral part of the consent process. In this event the prospective living donor is entitled to, and should be given, a realistic estimate of the likelihood of a successful transplant outcome. Similarly, if there are factors that increase the risk of recipient mortality or morbidity and/or graft survival, these must be discussed openly with the donor (e.g. pre-emptive transplantation vs time on dialysis, recurrent disease, positive viral serology, age, immunological complexity).

Providing the donor with such information will only be possible if the potential recipient agrees to such information being shared. If the recipient is unwilling for this information to be shared, it is imperative that he or she understands that the decision not to do so directly impinges on the ability of a donor to give valid consent, and that as a direct consequence it may not be possible to progress to surgery.

Where there is insufficient evidence available to give comprehensive information regarding the likelihood of successful transplantation, this must also be shared so that both donor and recipient have realistic expectations about possible outcomes (see Chapter 11). These discussions with donor and recipient should be performed at an early stage of assessment, in separate consultations so each has the opportunity to speak openly and freely with health professionals and so that expectations can 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. As above, the potential donor must be seen separately, in the absence of the prospective recipient and their family, on at least one occasion during the donor assessment process and be reassured that their views concerning kidney donation, as well as their medical and social history will be treated in strict confidence (see Chapter 3: Ethics).

A balanced view must be provided of the advantages and disadvantages of living donor transplantation. The option for the potential donor to withdraw at any stage in the donation process, without having to provide an explanation for his or her decision must be made clear from the outset, and he or she must be allowed adequate time to reflect on the decision to donate. If after discussion, the donor decides not to proceed, the decision must be respected and this should not be regarded as a failure but as a natural result of the informing process (2). If additional emotional support is required, this may be adequately addressed within the transplant hub, the referring centre, or in the primary care setting, and does not necessarily require referral to a mental health professional. However, provision must be made to ensure access to specialist psychological/ psychiatric services are available if referral is necessary (see section 4.4).

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 adequately provided for in this situation.

The decision regarding whether or not to proceed with living kidney donation can be stressful for both donor and recipient, and their respective family and friends. If several family members are contemplating donation, the decision making process as to whom should be considered as the preferred potential donor may be complex. The healthcare team can assist by identifying and addressing the relevant issues at an early stage so that all parties can make a choice that is as fully informed as possible.

4.3 Donor Identity

The significance of donor identity in the context of informed consent is the subject of much debate. Information regarding a donor's identity and their genetic relationship with the potential recipient of their donation may become available during the living donor

transplant work-up. There may be occasions when this information, quite unexpectedly, identifies that a genetic relationship has been misattributed. For example, 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 at an early stage in the assessment process. To date, there has been 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).

The above should not be confused 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). This does not mean that the Independent Assessor is responsible for establishing that claimed genetic relationships are real; it is the responsibility of the clinical teams to establish such genetic relationships and to provide any relevant information to the Independent Assessor, in confidence, as part of the assessment process.

The principle of seeking donor consent prior to HLA testing is attractive as a risk management strategy with regard to the above, 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 kidney 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, it should be possible to uphold the underlying principle of valid consent in this situation by appropriate discussion to ensure that the individuals concerned understand the 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 are important to help minimise the assumptions being made about the information that donors and recipients wish to know in the event of an issue arising.

4.4 Patient Advocacy

It has always been considered best practice for the potential donor to be given an opportunity to meet separately with a party who is independent of the transplant team, and this is now reflected in the legislative framework in the United Kingdom. In order to comply with the Regulations and Codes of Practice of the HTA, every donor-recipient pair must be assessed by an appropriately trained and accredited third party (the Independent Assessor) (7).

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. Separation of the donor and recipient clinical teams is also considered to represent best practice, but it is recognised that this may not always be possible. It is important for the potential donor to understand that he or she is not the only possible source of a transplant. In particular, when a potential recipient is considered unsuitable for inclusion on the deceased donor waiting list but a planned living donor transplant is considered an acceptable risk, the donor must not feel under any ‘obligation’ to donate. 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 (8). 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 (MDMs) 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 within 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 kidney. This is especially important in the case of young adults (9).

While the outcome of living donor kidney transplantation is superior to that of deceased donor kidney transplantation, particularly in the pre-emptive scenario (see Chapter 11), some recipients may choose to remain on the national deceased donor transplant waiting list for other reasons such as family, work and lifestyle considerations. If a potential recipient has a living kidney donor who is healthy and keen to proceed to donation, it is usually appropriate to recommend that the potential recipient is suspended from the deceased donor transplant waiting list until living donation proceeds or the potential donor is deemed unsuitable. The decision whether to remain on the waiting list should be a joint decision between the donor and recipient so that both are aware of the risks and benefits. Ultimately, all decisions of this nature are made on a case-by-case basis. However, at later stages of transplant work-up, it is usually inappropriate for a patient to remain on the deceased donor waiting list once the donor has been fully assessed and deemed suitable to proceed, unless there are extremely strong competing arguments.

4.5 Independent Translators

There is a rich cultural and ethnic diversity within the United Kingdom and a high proportion of donors for whom English is not their first language. Novel presentations of both verbal and written information, even when translated, often do not help individual donors to acquire the depth and breadth of knowledge they need in order to be an informed kidney donor. This may mean that they are vulnerable to coercion. Independent translators are a requirement under the HTA Codes of Practice (10) to ensure that the interests of the potential donor are protected and, as a matter of best practice, they should always be used where there are difficulties in communicating freely with both parties. The translator should be unknown to both the donor and recipient and should be competent to

discuss the implications and associated risks of donor nephrectomy and the post operative recovery process. The translator should have sufficient knowledge and skill to accurately translate complex discussions and to understand the nature and subtlety of the conversation in order for the donor to make the right decision. In the absence of face-to-face translation, 'language line' (telephone translation) can be helpful.

4.6 Psychological Issues

Psychological problems are infrequent after donation and most donors experience increased self-esteem, whilst donor and recipient relationships are enhanced. The majority of donors express no regrets after donation (11). However, it is essential to identify pre-existing or potential mental health issues that might arise for the prospective donor, to ensure that these are appropriately addressed. An opportunity to explore any concerns in confidence should be offered as an integral part of the assessment process, including aspects related to the donor assessment process, family relationships and decision-making. The purpose of such an assessment is to identify the level of support or intervention that may be required so that appropriate arrangements can be made, including referral to a mental health professional if necessary. A full psychological or psychiatric assessment should be sought if there is concern about the suitability of a donor on mental health grounds; for example, if there is evidence of previous or current mental illness, active substance abuse, dependence on prescribed medication, self-harming behaviour, or significantly dysfunctional family relationships, particularly between recipient and donor. Such an assessment is valuable in establishing when it is unsuitable to proceed to donation on these grounds (12).

Support may be provided by a variety of healthcare professionals who have the necessary knowledge and skills to deal with a range of psychological and social needs. Most transplant centres have designated personnel (usually a transplant co-coordinator or nurse specialist) who play a key role in organising the assessment and surgery for donor and/or recipient. Such individuals generally become closely acquainted with the patients and their families and may be best placed to provide the necessary support, even in the context of adverse events prior to or following transplantation. Other centres have dedicated social workers, counsellors, psychologists and psychiatrists, or access to such colleagues, to whom patients can be referred for specialist intervention and additional support. The development of peer support/patient befriending programmes, in which

patients who have experienced living donor transplantation offer support and guidance to donors and recipients who are considering this option, has also become an established and effective part of clinical practice in some centres, providing a complementary approach to that of healthcare professionals (13).

Current HTA policy requires all non-directed altruistic donors to undergo a mandatory mental health assessment (14). This is because the circumstances are unique, due to the lack of proximity with the recipient. Not all genetically and/or emotionally related donors and recipients will require referral to a mental health professional but a clear, stratified framework for psychological care must be in place to ensure that needs are accurately identified and appropriately met and that there is access to a range of specialist services for patients who may need to be referred. A 'tiered approach' to delivering support and psychological services is an appropriate model in the context of living kidney donation (15).

There is some evidence to suggest that, by merely presenting the option of living donation, the potential donor is immediately placed under an unwarranted moral burden and may feel in a 'no win' situation (16). While this may be true for some people and it may not be possible for the donor to avoid these pressures completely, a supportive environment which encourages discussion can relieve the strain and facilitate decision-making.

Sibling decision-making has been reported as one of the most complex areas (15). Motivational factors such as altruism, manipulation of familial relationships, coercion and covert pressure are reported (see Chapter 3). Donor advocacy is essential in these situations to ensure that donors feel supported to make the right decision for them (see section 4.4).

Psychological problems have been reported after donation, of which both donor and recipient should be made aware (17). These usually focus around the gift exchange elements of donation: recipients suffer psychological distress from feelings of indebtedness, which they can never repay; and donors exhibit proprietary interest in the health, work, and private life of the recipient that can damage relationships. Such issues should be raised prior to surgery to pre-empt difficulties that might arise at a later date. In terms of psychological care, the impact of living donor transplantation for donor and

recipient should be considered within the context of the wider family network to ensure effective support and intervention.

4.6.1 Death

Death is a rare complication of transplant surgery, but can occur (see Chapters 6 &11). Studies show that there is a need for immediate bereavement support to help with the feelings of guilt, loss, anger and depression expressed by both the survivor and members of the family. Bereavement support in these cases should be provided by qualified, independent counsellors and should continue in the community for as long as required.

4.6.2 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 from this disappointment without psychological morbidity (10). Support must be accessible to all patients and their families, up to and including referral to a mental health professional.

Living donor kidney transplantation is increasingly considered the treatment of choice for recipients with increased baseline comorbidity. An increased risk of post-operative co-morbidity, transplant failure and death is likely and the appropriate management of expectations is an essential part of the pre-transplant preparation for all parties concerned.

4.7 The Responsibility of the Donor Surgeon

The surgeon performing living donor nephrectomy 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 Chapter 6 of this document are specifically addressed.

References

1. General Medical Council. Consent: patients and doctors making decisions, 2008. http://www.gmc-uk.org/static/documents/content/Consent_2008.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. Absence of presumed genetic relationship, recommendation by letter, 21/06/2010 (n/a on website 13/08/10).
6. 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
7. 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
8. 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.
9. Franklin P, Crombie A. Live related renal transplantation: psychological, social and cultural issues. Transplantation 2003; 76: 1247-52.
10. 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
11. Fehrman-Ekholm I, Brink B, Ericsson C, Elinder CG, Dunér F, Lundgren G. Kidney donors don't regret: follow-up of 370 donors in Stockholm since 1964. Transplantation 2000; 69: 2067-71.
12. Potts SG. Triggers to Psychiatric Referral in Renal Transplant Assessment. http://renux.dmed.ed.ac.uk/edren/Handbookbits/TPHdbkbits/appendices/TPhdbkappendix3.pdf. Accessed 3rd May 2011.

13. Guy's & St Thomas' NHS Foundation Trust & King's College Hospital Foundation Trust Kidney Disease Modernisation Initiative. No white coat between us: developing peer support services for kidney patients, 2008. http://www.gsttcharity.org.uk/pdfs/whitecoat.pdf
14. Human Tissue Authority. Guidance for transplant teams and Independent Assessors, 2009, para 51. http://www.hta.gov.uk/_db/_documents/Guidance_for_transplant_teams_and__Independent_Assessors.pdf
15. British Renal Society. The Renal Team: A multi-professional renal workforce plan for adults and children with renal disease. Recommendation of the National Renal Workforce Planning Group, 2002. www.britishrenal.org/workfpg/wfp_renal_book.pdf
16. Russell S, Jacob R. Living-related organ donation: the donor's dilemma. Patient Educ Couns 1993; 21: 89-99.
17. Fox RC, Swazey JP. Spare parts. Oxford University Press, 1992.

CHAPTER 5 DONOR EVALUATION

5.1 INTRODUCTION

The primary goals of the donor evaluation process are to ensure the suitability of the donor and to minimise the risk of donation. This involves the identification of contraindications to donation and the presence of unreasonable medical risks. In order to avoid important omissions, the evaluation of potential donors should be carried out according to an agreed, evidence-based protocol with which the donor assessment team is fully conversant. Investigations should be undertaken in a logical sequence so that the potential donor is protected from unnecessary, particularly invasive, procedures until the appropriate time in the course of the assessment. Although some donors may require additional assessment, there is good agreement regarding the routine screening tests that should be performed (1-4).

It is important to respect the confidentiality of the donor and to maintain a clear separation of the interest of the donor and recipient (sections 3.6 and 4.2). This is best achieved by ensuring that the donor and recipient are assessed by separate physicians during the process of the transplant work up.

Throughout the evaluation, it is important to maintain good communication with the GP caring for the potential donor and to ensure the donor's GP informs the donor assessment team of any undisclosed medical or other issues that might influence the decision to donate.

The stage during the donor evaluation at which to remove a recipient from the national transplant waiting list will vary according to individual circumstances and should be decided after discussion with individual donor and recipient pairs. However, consideration must be given to the benefit afforded to the recipient from a living donor kidney in comparison with a deceased donor transplant, as well as to the optimal management of the national transplant waiting list.

The evaluation of potential living donors is an expensive and labour intensive process. A large proportion of individuals who volunteer as donors will be found to be unsuitable for a variety of clinical and non-clinical reasons during the evaluation process (5). Emphasis should be placed on the earliest possible triage of unsuitable donors to maximise benefit

and to minimise risk for all parties concerned. Strategies should also be in place to offer appropriate counselling and follow-up for those potential donors who are found to be unsuitable.

References

1. Bay WH, Hebert LA. The living donor in kidney transplantation. Ann Intern Med 1987; 106: 719-27.
2. Riehle RA Jr, Steckler R, Naslund EB, Riggio R, Cheigh J, Stubenbord W. Selection criteria for the evaluation of living related renal donors. J Urol 1990; 144: 845-8.
3. Bia MJ, Ramos EL, Danovitch GM, et al. Evaluation of living renal donors. The current practice of US transplant centers. Transplantation 1995; 60: 322-7.
4. Davis CL. Evaluation of the Living Kidney Donor: Current Perspectives. Am J Kid Dis 2004; 43: 508-30.
5. Calder FR, Chang RW. Panning for gold: screening for potential live kidney donors. Nephrol Dial Transplant 2004; 19: 1276–80.

5.2 DONOR EVALUATION: SUMMARY

Best Practice

- ***The suitability of the potential recipient for transplantation should be established prior to the evaluation of a prospective donor. If additional assessment is required, this should be performed as soon as possible to avoid unnecessary delay. (Not graded)***

- ***Donor assessment should be planned to reflect the wishes of the donor as far as possible and to minimise inconvenience to him/her. Flexibility in terms of timescales, planning consultations, attending for investigations and date of surgery is helpful. (Not graded)***

- ***The assessment process should be achieved in a focused, coherent fashion. Good communication between all parties is important and may be achieved most effectively by a designated co-ordinator. The results of investigations should be relayed accurately, appropriately and efficiently to the potential donor. Emphasis should be placed on identifying unsuitable donors at the earliest possible stage of assessment. (Not graded)***

- ***A policy should be established for managing prospective donors who are found to be unsuitable and provision should be made for appropriate follow-up and support. (Not graded)***

- ***The organisational details for evaluating a prospective donor will vary between centres, reflecting available resources and personnel. Evaluation should be undertaken according to an agreed protocol and emphasis should be placed upon the appropriateness and progression of assessment rather than the specific manner in which it is conducted. Table 5.2.1 shows a suggested model for donor evaluation[1]. (Not graded)***

- ***To facilitate pre-emptive transplantation, donor evaluation should start sufficiently early to allow time for more than one donor to be assessed if necessary. Information should be provided at an early stage and***

discussion with potential donors and recipients should be started when the recipient eGFR is approximately 20 ml/min. Thereafter, recipient and donor assessment should be tailored according to the rate of decline in recipient renal function, taking into account disease specific considerations and individual circumstances. (B2)

[1] NHS 18 week commissioning pathway. Accessed at: www.18weeks.nhs.uk/Content.aspx?path=/achieve-and-sustain/Specialty-focussed-areas/Renal/living-donor-transplantation

Table 5.2.1 Donor Evaluation: Summary and Organisational Chart

Early education & discussion with all potential transplant recipients +/- potential donors about optimal options for transplantation.

RATIONALE: **To promote planned, pre-emptive LD transplantation as the treatment of choice for suitable transplant recipients.**

↓

Within 2 weeks of referral **(2)**

Establish recipient fit for transplantation & initiate appropriate pre-transplant assessment as per local protocol.

RATIONALE: **To optimise management of recipient & donor(s) expectations**
To avoid unnecessary investigative assessment/inconvenience for the prospective donor if transplantation cannot proceed.
To ensure that the recipient can give valid consent.

↓

Within 2-4 weeks of referral **(4)***

Potential donor(s) identified.
ABO compatibility +/- HLA sensitisation (if indicated) confirmed. Primary contra-indications identified from donor(s) previous medical history. Routine blood & urinalysis tests performed.

RATIONALE: **To initiate early triage of unsuitable donors.**
To identify potential incompatibility issues (ABO/HLA).

↓

Within 2-4 weeks of referral **(4)***

LD Co-ordinator facilitates initial discussion with potential donor(s), +/- recipient & other family members as appropriate. If more than one potential donor, the most appropriate should be identified, taking into account possible social, psychological and medical risk factors.

RATIONALE: **To minimise evaluation of multiple donors & maximise best use of local resources.**
To ensure that the donor can give valid consent for donation.

↓

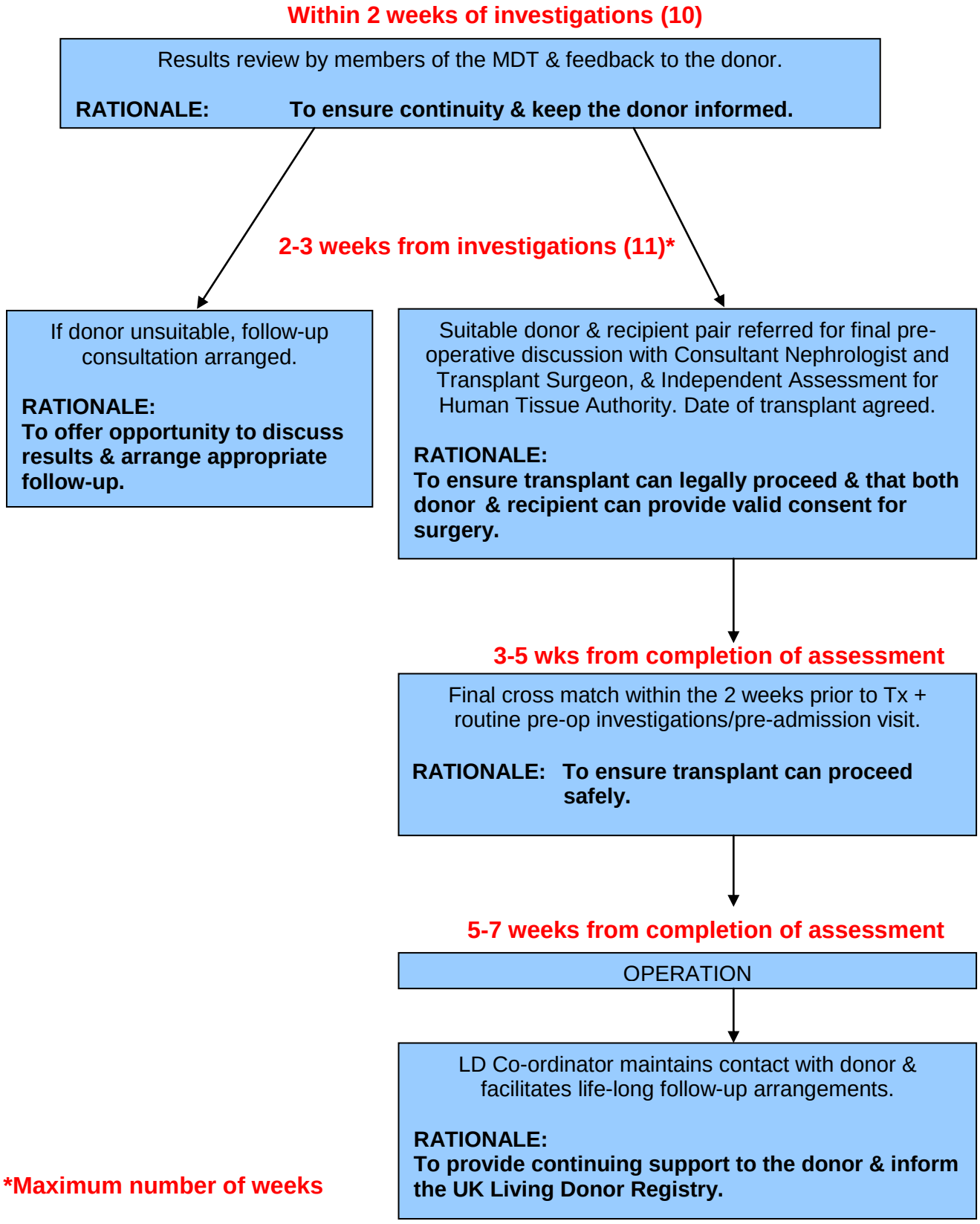
Within a further 4 weeks **(8)**

Donor evaluation is planned in conjunction with the prospective donor, in a timely & appropriate manner, to an agreed protocol & in accordance with the availability of local resources. Emphasis should be placed upon a coherent, consultant led service with a logical progression of assessment using 'gold standard' investigative procedures, multi-disciplinary input & excellent communication between all parties. A designated LD co-ordinator is considered optimal.

RATIONALE: **To provide a clinically effective service based upon the best evidence available & national best practice guidelines.**

↓

Table 5.2.1 Donor Evaluation: Summary and Organisational Chart (Continued)



***Maximum number of weeks**

5.3 ABO BLOOD GROUPING AND CROSSMATCH TESTING

Statements of Recommendation

- ***Where an ABO compatible donor-recipient pair is available, this is the preferred option. (A1)***

- ***Where low antibody titre ABO incompatibility is present, transplantation is not precluded, but should be performed in a unit with the relevant experience and appropriate support. (A1)***

ABO blood grouping is an important early screening test as it allows the early identification of individuals who cannot donate because of blood group incompatibility (1). It may be undertaken by the GP, nephrologist, specialist nurse, or at a transplant assessment clinic.

If blood group compatibility is established, initial HLA typing +/- crossmatch testing should be performed in accordance with the recommendations in Chapter 7.

If the donor and recipient are not blood group compatible, the usual next step would be to enquire whether there are other potential donors. One specific exemption would be in the case of a blood group A2 donor wishing to donate to a blood group O recipient, where a low titre of anti-A2 antibody may not preclude transplantation. Similarly, where low titres of anti-A and/or anti-B antibody are present in other incompatible blood group combinations, living donation may still be possible, but specialist assessment is required. ABO and HLA-incompatible transplantation are considered in Chapter 7 and in more detail in separate guidelines (British Transplantation Society Guidelines for Antibody Incompatible Transplantation, http://bts.demo.eibs.co.uk/transplantation/standards-and-guidelines/).

Reference

1. Alexandre GPJ, Latinne D, Carlier M, et al. ABO-incompatibility and organ transplantation. Transplant Rev 1991; 5: 230-41.

5.4 MEDICAL ASSESSMENT

It is important to manage the expectations of the donor from the outset and to emphasise the difference between a healthy individual and one who is suitable to donate. For example, a donor may be precluded from donation on the grounds of having a single kidney or short renal vessels, neither of which may be detrimental to his/her own health. The assessment may reveal previously undiagnosed disease, and potential donors must be warned of this possibility. In addition, the existence of a previously unrecognised condition may prejudice future attempts to obtain life insurance or specialist employment. Conversely, screening may benefit the potential donor in that early detection of a health problem can occur, which might otherwise have gone undiagnosed.

A full medical history must be taken and the areas listed in Tables 5.4.1 should be specifically addressed and followed up where appropriate. The history should also aim to identify any risk of latent or current infection in the donor that could be transmitted to the recipient by a kidney allograft (see Table 5.4.2 and section 5.14). Importantly, all female potential donors of childbearing age must be counselled regarding the need to take contraceptive precautions when considering organ donation, and the possible implications of kidney donation upon future pregnancy (see also section 10.3 Pregnancy following Kidney Donation). 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; although neither are an absolute contraindication to donation.

A thorough clinical examination must be performed, taking particular account of the cardiovascular and respiratory systems and including the assessments listed in Table 5.4.3.

In most units, donor assessment will be arranged by a specialist transplant nurse, supported by a clinician. The clinician should undertake the medical examination of the potential donor and, as previously noted, should not be exposed to a potential conflict of interest by also having direct care of the transplant recipient (1). Table 5.4.4 details the routine screening investigations that should be performed on the potential donor.

Reference

1. The Council of the Transplantation Society. Commercialisation in transplantation: the problems and some guidelines for practice. Lancet 1985; 2: 715-6.

Table 5.4.1

Points of particular importance in the medical history of a potential kidney donor

Haematuria/proteinuria/urinary tract infection
History of peripheral oedema
Gout
Nephrolithiasis
Hypertension
Diabetes mellitus, including family history
Ischaemic heart disease/peripheral vascular disease/other atherosclerosis
Cardiovascular risk factors
Thromboembolic disease
Sickle cell and other haemoglobinopathies
Weight change
Change in bowel habit
Previous jaundice
Previous malignancy
Systemic disease which may involve the kidney
Chronic infection such as tuberculosis
Family history of a renal condition that may affect the donor
Smoking
Current or prior alcohol or drug dependence
Psychiatric history
Obstetric history
Residence abroad
Previous medical assessment e.g. for life insurance
Previous anaesthetic problem
History of back or neck pain and trauma
Results of national screening programme tests e.g. cervical smear, mammography, colorectal screening

Table 5.4.2

History with respect to transmissible infection

Previous illnesses

Jaundice or hepatitis

Malaria

Previous blood transfusion

Tuberculosis / atypical mycobacterium

Family history of tuberculosis

Family history of Creutzfeldt-Jakob disease (CJD), previous treatment with natural growth hormone, or undiagnosed degenerative neurological disorder

Specific geographical risk factors: e.g. fungi and parasites, tuberculosis, hepatitis, malaria, worms

Increased risk of HIV, HTLV1 and HTLV2 infection

History of intravenous drug use

History of infectious hepatitis or syphilis

Tattoo or skin piercing within last 6 months

Sexual partner of drug addict

Sexual partner of an HIV positive individual

Female sexual partner of man who has had sex with another man

Sexual partner of an indigenous African within the last year

Payment for, or been paid for sex within the last year

Male homosexual

Haemophiliac or sexual partner of haemophiliac

Table 5.4.3

Points of particular importance when undertaking clinical examination of a potential kidney donor

Body mass index

Abdominal fat distribution

Blood pressure measurement

Urinalysis

Examination of the cardiovascular and respiratory systems

Examination for abdominal masses or herniae

Examination for scars or previous surgery

Examination for lymphadenopathy

Examination / history of regular self-examination of the breasts

Examination / history of regular self-examination of the testes

Table 5.4.4

Routine screening investigations for the potential donor

Urine

Dipstick for protein, blood and glucose (at least twice)

Microscopy, culture and sensitivity (at least twice)

Measurement of protein excretion rate (ACR or PCR)

Blood

Haemoglobin and blood count

Coagulation screen (PT and APTT)

Thrombophilia screen (where indicated)

Sickle cell trait (where indicated)

Haemoglobinopathy screen (where indicated)

G6PD deficiency (where indicated)

Creatinine, urea and electrolytes

Isotopic or other reference test for measurement of GFR

Liver function tests

Bone profile (calcium, phosphate, albumin and alkaline phosphatase)

Urate

Fasting plasma glucose

Glucose tolerance test (if family history of diabetes or fasting plasma glucose >5.6 mmol/l)

Fasting lipid screen (if indicated)

Thyroid function tests (if strong family history)

Pregnancy test (if indicated)

Virology and infection screen (see section 5.14 for details)

Hepatitis B and C

HIV

HTLV1 and 2 (if appropriate)

Cytomegalovirus

Epstein-Barr virus

Toxoplasma

Syphilis

Varicella zoster virus (where recipient seronegative)

HHV8 (where indicated)

Malaria (where indicated)

Trypanosoma cruzi (where indicated)

Schistosomiasis (where indicated)

Cardiorespiratory system (see section 5.10)

Chest X-ray

ECG

ECHO (where indicated)

Cardiovascular stress test (as routine or where indicated)

5.5 ASSESSMENT OF RENAL FUNCTION

Statements of Recommendation

- ***GFR should be measured using measured using a reference GFR procedure e.g. ^{51}Cr EDTA. A prospective donor should not be considered for donation if the corrected GFR is predicted to fall below a satisfactory level of kidney function within the lifetime of the donor. A predicted GFR of at least 37.5 ml/min/1.73m^2 at the age of 80 is recommended as a minimum standard. There is a lack of evidence to guide acceptable levels of kidney function for donors over 60 years of age. (B1)***

- ***A living kidney donor with normal renal function prior to donation is at no greater risk than an individual in the general population of developing end stage renal disease after unilateral nephrectomy. Measurement of eGFR in living donors has not been validated to predict the risk of long-term kidney disease and should not be used in this context. (B1)***

The first principle underlying the assessment of kidney function in the potential living donor is to ensure that the donor will have sufficient kidney function after donation such that they will remain in good health in the future. Alongside the need to ensure adequate residual kidney function in the donor, accurate measurement of renal function is important to secure sufficient graft function in the recipient following transplantation.

There are now long term data to inform this process. A measurement of kidney function was performed on a selected group from 2,949 (out of a total of 3,404) patients who had donated over a 40 year period (1). The original requirement to qualify for donation was a GFR of greater than 80 ml/min/1.73m^2. The majority of individuals (85.5%) had a clearance of greater than 60 ml/min/1.73m^2 on follow-up, and none were below 30 ml/min/1.73m^2. In a small representative sample of donors, the rate of decline of renal function was 0.6 +/- 3.8 ml/min/1.73m^2 per year, this being measured on average 12 years after donation with two samples three years apart. There are some caveats in the interpretation of these data, including the fact that the population was predominantly Caucasian. However, they strongly support the view that a measured GFR over 80 ml/min/1.73m^2 provides sufficient kidney function not to cause ill health in the future.

These data do not address the changes in kidney function that occur with age. Data from cross-sectional studies show that there is a wide range of 'normal' renal function and that this declines in a predictable manner beyond 40 years of age. When evaluated according to the British Nuclear Medicine Society Guidelines (2), the mean GFR in young adults of both sexes is 103 ml/min/1.73m^2 with a decline of 0.9 ml/min/1.73m^2 per year after the age of 40 (3). A review of the change in kidney function with age in living donors suggests between 0.4-0.8 ml/min/1.73m^2 per year with increasing age (4). It is important to note that the individuals in this study were being assessed as potential living donors and as such were in good health. Overall, for the purposes of calculation, the use of an estimated rate of change of 0.9 ml/min/1.73m^2 per year is at the cautious end of the values reported.

Following donation there is a compensatory increase in function in the remaining kidney. Across a broad age range (19-61 years), the remnant kidney increases its filtration to provide a GFR of approximately 75% of the combined value that both kidneys had before donation (5). Special consideration may be needed when assessing kidney function in older donors as the degree of recovery of post-nephrectomy GFR may be less than that for younger people, and there is not a significant body of evidence available for patients over the age of 60.

Any guideline for donor GFR must be based upon the premise that an individual in his or her lifetime will not develop clinically significant renal impairment as a result of unilateral nephrectomy. On this basis, the potential kidney donor must have sufficient kidney function prior to donation to have an effective GFR at the age of 80 years, independent of the age at which he or she donated. Table 5.5.1 gives the values for GFR and age that will leave a GFR of 37.5 ml/min/1.73m^2 at the age of 80, given the reduction in GFR due to donation and a cautious estimate of the rate of annual decline, as above. This threshold is shown plotted as the red line in Figure 5.5.1. This correlates closely with previous guidance based on smaller studies, which has supported practice to date (6). The graph has been adjusted from the previous BTS Guideline to use a baseline age unrestricted GFR of 80 ml/min/1.73m^2. The calculation for decline from this point is based on a rate of loss of kidney function at 0.9 ml/min/1.73 m^2 per year.

Table 5.5.1 Acceptable GFR by donor age prior to donation

Donor age (years)	Acceptable corrected GFR prior to donation (ml/min/1.73m^2)
Up to 46	80
50	77
60	68
70	59
80	50

Figure 5.5.1 Acceptable GFR by donor age prior to donation

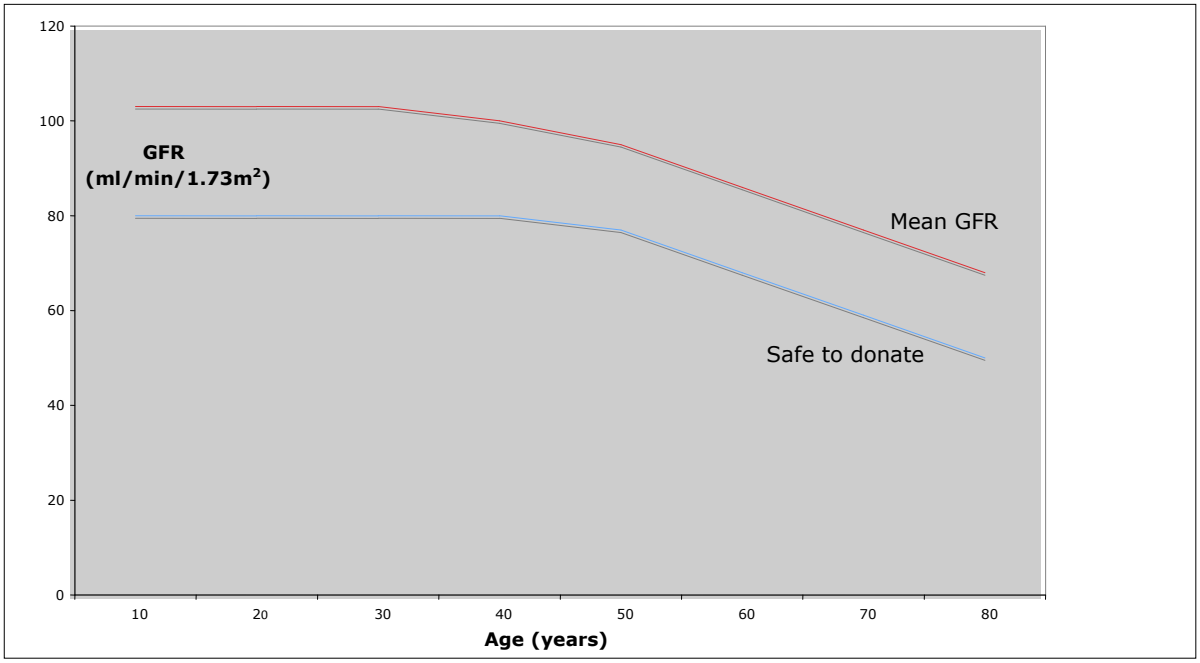


Figure 5.5.1 Diagram showing the variation with age of mean GFR. The red (upper) line reference plot is based on an analysis of data for 428 living renal transplant donors who had ^{51}Cr-ETDA GFR measurements performed according to the method described in the British Nuclear Medicine Society GFR guidelines (2). The blue (lower) line shows the safety limit of 80 ml/min/1.73m^2 (1) for adults up the age of 46 years and declining to 50 ml/min/1.73m^2 at age 80. For transplant donors with pre-operative GFR values above the blue line, the GFR of the remaining kidney will still be greater than 37.5ml/min/1.73 m^2 at age 80.

The most accurate assessment of glomerular filtration rate (GFR) is achieved using radioisotopes such as ^{51}Cr-EDTA or the use of iohexol clearance techniques, and these are recommended in all potential donors. Alternative methods based upon serum creatinine concentration are not sufficiently accurate in this context and measured creatinine clearance, using timed urine collections, is susceptible to considerable inaccuracy.

Divided Renal Function

Divided renal function can be measured by combining a ^{51}Cr-EDTA GFR measurement with a ^{99m}Tc-DMSA scan of the kidneys (7). This information is advisable before nephrectomy if there is considerable disparity in the size of the kidneys or anatomical abnormality is noted, but is otherwise not indicated. When renal function is normal but there is a significant (>10%) difference in function between the two kidneys, the kidney with lower function should normally be used for transplantation.

End Stage Kidney Disease Post Nephrectomy

End stage kidney disease following donation may be a consequence of issues unrelated to the individual possessing a single kidney. A large cohort of kidney donors followed up in Minnesota demonstrated that the cause for end stage disease in 11 individuals out of the cohort of 3,404 was variable but that some were related to subsequent medical conditions. The overall rate of end stage kidney disease was 180 per million persons per year, as compared to the control adjusted rate of 268 per million per year (1).

The issue of eGFR use in living donors has been considered (8). It is important to note that the original use of eGFR was to identify the risk of developing end stage kidney disease in population studies, and that it has not been formally validated in living donors. However, the data discussed above show that the risk of end stage kidney disease is not increased in the donor population (1), and these and other observations suggest that the eGFR overestimates the decline in kidney function when compared to formal assessment (8).

References

1. Ibrahim HN, Foley R, Tan LP, et al. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-69.

2. Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS. Guidelines for the measurement of glomerular filtration rate using plasma sampling. Nucl Med Commun 2004; 25: 759-69.
3. Grewal GS, Blake GM. Reference data for ^{51}Cr-EDTA measurements of GFR derived from live kidney donors. Nucl Med Commun 2005; 26: 61-5.
4. Poggio E, Braun WE, Davis C. The Science of Stewardship: due diligence for kidney donors and kidney function in living donation – evaluation, determinants and implications for outcomes. Clin J Am Soc Nephrol 2009; 4: 1677-84.
5. Velosa JA, Griffin MD, Larson TS, et al. Can a transplanted living donor kidney function equivalently to its native partner? Am J Transplant 2002; 2: 252-9.
6. United Kingdom Guidelines for Living Donor Kidney Transplantation. British Transplantation Society and The Renal Association 2nd Edn April 2005. www.bts.org.uk/transplantation/standards-and-guidelines/
7. Farmer CKT, Cook GJR, Blake GM, Reidy J, Scoble JE. Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis. Nephrol Dial Transplant 1999; 14: 2880-4.
8. Tan JC, Busque S, Blouch K, Derby G, Efron B, Myers BD. Imprecision of creatinine-based GFR estimates in uninephric kidney donors. Clin J Am Soc Nephrol 2010; 5: 497-502.

5.6 DONOR AGE

Statements of Recommendation

- ***Old age alone is not an absolute contraindication to donation but the medical work-up of older donors must be particularly rigorous to ensure they are suitable. (A1)***

- ***Both donor and recipient should be made aware that the older donor may be at greater risk of peri-operative complications and that the function and possibly the long-term survival of the graft may be compromised. This is particularly evident with donors >60 years of age. (B1)***

The young and the old raise different issues with respect to consideration as potential living kidney donors (1). The ethical barriers to the use of minors and young people as living donors are addressed in Chapter 3. For older donors the increased risk of post-operative complications as a consequence of increased age and the potential for poorer graft function and long term transplant outcome, as a consequence of reduced donor GFR, must both be considered.

5.6.1 Donor Complication Rates Related to Age

Early reports produced no consensus with Johnson et al reporting no increase in the incidence of post-operative complications when older donors were used, although donor age ≥50 years was associated with a longer post-operative stay (2). In contrast, Fauchald reported a higher incidence of post-operative cardiac complications and pneumonia in donors over the age of 60 years (3). Considering 80,347 living kidney donors in the US between 1st April 1994 and 31st March 2009, Segev et al demonstrated poorer 12 year survival for donors aged >50 years as compared to donors <40 years of age, with donors >60 years having worse survival than those aged 50-59 years (4). However, the long-term risk of death was no higher for older living donors than for age- and comorbidity-matched NHANES III participants, the poorer survival therefore not being clearly attributable to kidney donation.

Given the lower complication rates and faster recovery, laparoscopic nephrectomy may have particular benefit for the older donor. Hsu et al (5) reported good outcomes following laparoscopic nephrectomy in six donors of mean age 69.5 years (range 65-74), and Jacobs has argued that age should not preclude laparoscopic donation on review of the outcome of a series of 738 consecutive laparoscopic living donor nephrectomies performed in Maryland (6). In keeping with this, some centres report higher laparoscopic nephrectomy rates in donors >50 years (7).

When considering older donors the medical evaluation, especially that of the cardiovascular system, needs to be particularly rigorous. Many centres consider stress cardiac testing to be mandatory when evaluating older potential donors, particularly men over the age of 55 years (section 5.10). Cardiopulmonary exercise testing, and in particular definition of anaerobic threshold, has been validated as a predictor of post-operative complications, particularly in elderly patients. If available, it may be of particular use in the assessment of elderly donors (8).

5.6.2 Graft Outcome from Older Donors

The second concern regarding the older donor is the suggestion that kidneys obtained from older living donors have a worse outcome after transplantation (3). Renal function declines progressively with age and kidneys from older living donors have reduced function (9). Early studies suggested that both short-term and medium-term (5 year) graft survival rates were similar for kidneys from older (over 55 years) and younger donors (10,11). Kerr et al demonstrated that in the absence of rejection, graft survival at 10 years was equivalent for donors over and under 55 years (12). However, a subsequent report of this cohort, when 2,540 living donor kidney transplants had been performed in this centre, documented worse outcome when the donor was >55 years of age (13). In a further study, 5 year graft survival after living donor transplantation was 76% for kidneys from donors over 60 years (n=241) and 79% for kidneys from donors aged less than 60 years (n=518). However, serum creatinine levels remained significantly lower in the recipients of kidneys from younger donors and beyond 5 years their graft survival was significantly better (14).

An extensive study recently demonstrated poorer outcomes for kidneys from donors >59 years of age in 3,142 transplants performed in the UK between 2000 and 2007 (15). This is in keeping with a Scandinavian study demonstrating no effect of donor age on

transplant outcome when all donors aged >50 years were considered, but poorer outcomes in the subgroup with donor age >65 years (16). Donor GFR has been demonstrated to be an important determinant of transplanted kidney function (17) and it has been suggested that donor function rather than age may be the most important determinant of outcome, although not all studies have confirmed this (16).

Older donors are more likely than younger donors to be excluded from donating on the basis of problems discovered during the medical evaluation. However, each case should be considered on individual merit and if the older donor is judged fit after rigorous medical evaluation, and if the renal function of the donor is normal after correction for age and gender, there is no compelling evidence for excluding donation on the basis of chronological age alone (2,18,19).

References

1. Jones J, Payne WD, Matas AJ. The living donor risks, benefits, and related concerns. Transplant Rev 1993; 7: 115-28.
2. Johnson EM, Remucal MJ, Gillingham KJ, Dahms RA, Najarian JS, Matas AJ. Complications and risks of living donor nephrectomy. Transplantation 1997; 64: 1124-8.
3. Fauchald P, Sodal G, Albrechtsen D, Leivestad T, Berg KJ, Flatmark A. The use of elderly living donors in renal transplantation. Transpl Int 1991; 51-3.
4. Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010; 303: 959-66.
5. Hsu THS, Su L-M, Ratner LE, Kavoussi LR. Laparoscopic donor nephrectomy in the elderly patient. Urology 2002; 60: 398-401.
6. Jacobs SC, Cho E, Foster C, Liao P, Bartlett ST. Laparoscopic donor nephrectomy: the University of Maryland 6-year experience. J Urol 2004; 171: 47-51.
7. Johnson SR, Khwaja K, Pavlakis M, Monaco AP, Hanto DW. Older living donors provide excellent quality kidneys: a single center experience (older living donors). Clin Transplant 2005; 19: 600-6.
8. Hall A, Older P. Clinical review: How to identify high-risk surgical patients. Crit Care 2004, 8: 369-72.

9. Sumrani N, Daskalakis P, Miles AM, Hong JH, Sommer BG. The influence of donor age on function of renal allografts from live related donors. Clin Nephrol 1993; 39: 260-4.
10. Kim YS, Kim SI, Suh JS, Park K. Use of elderly living related donors in renal transplantation. Trans Proc 1992; 24: 1325-6.
11. Shmueli D, Nakache R, Lustig S, et al. Renal transplant from live donors over 65 years old. Trans Proc 1994; 26: 2139-40.
12. Kerr SR, Gillingham KJ, Johnson EM, Matas A. Living donors >55 years. To use or not to use? Transplantation 1999; 67: 999-1004.
13. Matas AJ, Payne WD, Sutherland DER, et al. 2,500 living donor kidney transplants: A single-center experience. Ann Surg 2001; 234: 149-64.
14. Kahematsu A, Tanabe K, Ishikawa N, et al. Impact of donor age on long-term graft survival in living donor kidney transplantation. Trans Proc 1998; 30: 3118-9.
15. Fuggle SV, Allen JE, Johnson RJ, et al. Kidney Advisory Group of NHS Blood and Transplant. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. Transplantation 2010; 89: 694-701.
16. Oien CM, Reisæter AV, Leivestad T, Dekker FW, Line PD, Os I. Living donor kidney transplantation: The effects of donor age and gender on short- and long-term outcomes. Transplantation 2007; 83: 600–6.
17. Hawley CM, Kearsley J, Campbell SB, et al. Estimated donor glomerular filtration rate is the most important donor characteristic predicting graft function in recipients of kidneys from live donors. Transpl Int 2007; 20: 64-72.
18. Kumar A, Kumar RZ, Srinadh ES, et al. Should elderly donors be accepted in live related renal transplant programs? Clin Transplant 1994; 8: 523-6.
19. Lezaic V, Djukanov L, Blagojevic-Lazik R, et al. Living related kidney donors over 60 years old. Transpl Int 1996; 9: 109-14.

5.7 DONOR OBESITY

Statements of Recommendation

- ***Otherwise healthy overweight patients (BMI 25-30 kg/m^2) may safely proceed to kidney donation. (B1)***

- ***Moderately obese patients (BMI 30-35 kg/m^2) should undergo careful pre-operative evaluation to exclude cardiovascular, respiratory and kidney disease. (C1)***

- ***Moderately obese patients (BMI 30-35 kg/m^2) should be counselled carefully about the increased risk of peri-operative complications, based on extrapolation of outcome data from very obese donors (BMI > 35 kg/m^2). (B1)***

- ***Moderately obese patients (BMI 30-35 kg/m^2) should be counselled carefully about the long-term risk of kidney disease. They should be advised to lose weight prior to donation and to maintain their ideal weight following donation. (B1)***

- ***Data on the safety of kidney donation in the very obese (BMI > 35 kg/m^2) are limited and such patients should be discouraged from donating. (C1)***

In 2008 almost a quarter of adults in England were classified as obese (BMI > 30 kg/m^2) (1). In the general population, obesity is associated with increased morbidity and mortality. For a BMI of 30-35 kg/m^2, the median life expectancy is reduced by 2-4 years and for a BMI of 40-45 kg/m^2, it is reduced by 8-10 years, which is comparable with the effects of smoking (2). In comparison with individuals of normal weight, overweight and obese individuals are at increased risk of hypertension, hypercholesterolemia, insulin resistance and diabetes mellitus, heart disease, stroke, sleep apnoea and certain cancers (3).

Obesity is generally considered a relative contra-indication to living kidney donation because of the increased risk of surgical complications and because of the adverse impact of obesity on renal function in the longer term. The presence of obesity in kidney donors is associated in some studies with an increase in peri-operative complications,

although these are mostly relatively minor in nature. In a single centre retrospective study of 553 consecutive hand-assisted laparoscopic living kidney donations, those with a high BMI (≥ 35 kg/m^2) had longer operative times (mean increase 19 minutes), more minor peri-operative complications (mostly wound complications), but the same low rate of major surgical complications (conversion to open nephrectomy or re-operation) and a similar length of stay (2.3 vs 2.4 days) as low BMI (< 25 kg/m^2) donors (4). In a recent retrospective cross-sectional analysis of 6,320 cases, obesity was identified in only 2% of donors but was an independent predictor of donor risk; 28.3% of obese patients had complications compared with 18.2% of non-obese patients (5). In another retrospective analysis of 3,074 living kidney donors from 28 US centres during 2004 and 2005, 2.4% of donors were obese and obesity was associated with an increase in peri-operative complications (odds ratio 1.92), but no peri-operative mortality (6). A systematic review and meta-analysis of ten studies, including that by Heimbach et al (4), examined 484 obese living donors with a mean BMI of 34.5 kg/m^2 at donation (range 32–39 kg/m^2) and reported no deaths. It found statistically significant (but clinically insignificant) differences in operative time, blood loss and hospital stay between obese and non-obese donors (7). According to a recent cohort study of all (80,347) living donors during a 15-year period in the US, 22.6% were obese (BMI ≥ 30 kg/m^2) but obesity was not associated with a statistically significant difference in surgical mortality (8). Overall, these data suggest that laparoscopic donor nephrectomy is generally safe in otherwise healthy obese kidney donors and does not result in a high rate of major peri-operative complications.

The principle concern for the obese living donor is the possibility that donation may have an adverse effect on long term kidney function. Obesity associated co-morbidities, such as hypertension, diabetes, and the metabolic syndrome, may compromise kidney function. In addition, data suggest that obesity is independently associated with a higher risk of developing end stage kidney disease (9). Focal glomerulosclerosis and obesity-related glomerulopathy (glomerular enlargement and mesangial expansion) with associated proteinuria have been described in patients with severe obesity (10), and this may be reversible with weight loss. Obesity is also a risk factor for renal insufficiency after unilateral nephrectomy. At 10 years post-nephrectomy, 60% of patients whose BMI was > 30 kg/m^2 at the time of nephrectomy developed proteinuria (> 3 g/day) and 30% developed renal insufficiency (creatinine clearance < 70 ml/min) (11). These data suggest that nephrectomy in obese patients increases the risk of developing proteinuria and/or renal insufficiency.

Individual risk for developing obesity increases with time, both in the general population and in living kidney donors. Weight gain post-donation is a common observation, particularly in those who are overweight prior to donation (12). At mean follow-up of 12 years post-donation, a higher BMI was associated with both hypertension and a GFR that was lower than 60 ml/min/1.73m^2 (13). In a recent retrospective analysis, kidney function in 98 obese (BMI > 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients who donated a kidney 5 to 40 years previously was similar, though both donor groups had reduced kidney function compared with BMI-matched two-kidney control subjects (14). Obesity was associated with a higher risk of hypertension and dyslipidaemia in both donors and control subjects. In a study of 39 African American living kidney donors 4 to 10 years post-donation, 8 subjects whose BMI was > 35 kg/m^2 were found to have a significantly greater fall in eGFR (MDRD) than those with BMI < 35 kg/m^2 (40 and 28 ml/min/1.73m^2 respectively) (15). However, in a different retrospective cohort study using OPTN data from 5,304 donors among whom 40% were overweight (BMI > 25 kg/m^2), 18% were obese (BMI > 30 kg/m^2) and 5% were very obese (BMI > 35 kg/m^2), the decline in eGFR from baseline and percentage change in creatinine at 6 months did not differ significantly across the three groups (16). In a very recent study of 36 obese living kidney donors 7 years post-donation, 47% had an eGFR below 60 ml/min/1.73m^2, 42% were hypertensive and 19% had microalbuminuria (17). There was no control group in this study.

These findings support the current practice of using otherwise healthy overweight (BMI 25-30 kg/m^2) and moderately obese (BMI 30-35 kg/m^2) donors, although there are few studies that address long-term health outcomes for the very obese (BMI > 35 kg/m^2). Pre-donation counselling should include a careful discussion of the uncertain long-term risks of donation in obese individuals along with advice about weight maintenance following donation.

References

1. Statistics on obesity, physical activity and diet: England, 2010. NHS Health and Social Care Information Centre, February 2010. www.ic.nhs.uk/pubs/opad10
2. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; 373: 1083-96.

3. Nguyen NT, Magno CP, Lane KT, Hinojosa MW, Lane JS. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the national health and nutrition examination survey, 1999 to 2004. J Am Coll Surg 2008; 207: 928-34.
4. Heimbach JK, Taler SJ, Prieto M, et al. Obesity in living kidney donors: clinical characteristics and outcomes in the era of laparoscopic donor nephrectomy. Am J Transplant 2005; 5: 1057-64.
5. Friedman AL, Cheung K, Roman SA, Sosa JA. Early clinical and economic outcomes of patients undergoing living donor nephrectomy in the United States. Arch Surg 2010; 145: 356-62.
6. Patel S, Cassuto J, Orloff M, et al. Minimizing morbidity of organ donation: analysis of factors for perioperative complications after living-donor nephrectomy in the United States. Transplantation 2008; 85: 561-5.
7. Young A, Storsley L, Garg AX, et al. Health outcomes for living kidney donors with isolated medical abnormalities: a systematic review. Am J Transplant 2008; 8: 1878-90.
8. Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010; 303: 959-66.
9. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006; 144: 21-8.
10. Kambham N, Marcowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity related glomerulopathy; an emerging epidemic. Kidney Int 2001; 59: 1498-509.
11. Praga M, Hernandez E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int 2000; 58: 2111-8.
12. Torres VE, Offord KP, Anderson CF, et al. Blood pressure determinants in living-related renal allograft donors and their recipients. Kidney Int 1987; 31: 1383-90.
13. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-69.
14. Tavakol MM, Vincenti FG, Assadi H, Frederick MJ, Tomlanovich SJ, Roberts JP, Posselt AM. Long-term renal function and cardiovascular disease risk in obese kidney donors. Clin J Am Soc Nephrol 2009; 4: 1230-8.
15. Nogueira JM, Weir MR, Jacobs S, et al. A study of renal outcomes in African American living kidney donors. Transplantation 2009; 88: 1371-6.

16. Reese PP, Feldman HI, Asch DA, Thomasson A, Shults J, Bloom RD. Short-term outcomes for obese live kidney donors and their recipients. Transplantation 2009; 88: 662-71.
17. Nogueira JM, Weir MR, Jacobs S, et al. A study of renal outcomes in obese living kidney donors. Transplantation 2010; 90: 993-9.

5.8 HYPERTENSION IN THE DONOR

Statements of Recommendation

- ***Potential donors with blood pressure <140/90 mmHg should be considered as normotensive and therefore suitable for nephrectomy on the basis of blood pressure. (B1)***

- ***Potential donors with 'high normal' blood pressure (>130/85 mmHg) should be warned about the greater future risk of developing hypertension and associated cardiovascular events and the need for monitoring (which should be recommended irrespective of nephrectomy). Additional assessment (24 hour blood pressure monitoring) should be considered but is not required. (B1)***

- ***The definition and treatment of hypertension in prospective donors should follow the British Hypertension Society guidelines. (B1)***

- ***Office blood pressure measurements are sufficient for the assessment of the majority of potential donors. Ambulatory blood pressure monitoring should be considered for potential donors who have hypertension (blood pressure greater than 140/90 mmHg or who are taking pharmacological treatment for hypertension) and if this is normal (see below) donor nephrectomy is not precluded. (B1)***

- ***Living kidney donors should be encouraged to minimise the risk of hypertension and its consequences by lifestyle measures including smoking cessation, frequent exercise and, where appropriate, weight loss. (B1)***

- ***Prospective donors should be warned about the potential risks of hypertension, particularly if in a high risk group. Blood pressure measurement should be part of annual donor monitoring. (B1)***

- ***The presence of mild-moderate hypertension that is controlled with 1-2 antihypertensive agents is not a contraindication to kidney donation providing significant end organ damage has been excluded. (B1)***

- ***Evidence of hypertensive end organ damage, poorly controlled hypertension, or hypertension that requires more than two drugs to achieve adequate control are relative contraindications to donor nephrectomy. (C2)***

- ***Donors who develop hypertension should be managed according to British Hypertension Society guidelines and are at similar risk of developing complications as other patients with hypertension. (B1)***

Hypertension is one of the commonest reasons for declaring a potential kidney donor medically unsuitable (1). There are two concerns with hypertension in the potential donor. The first is that the hypertension presents a risk for peri-operative morbidity and mortality. The second is that pre-existing hypertension in the donor will be worsened by unilateral nephrectomy and this will be associated with an unacceptable increase in long-term cardiovascular risk. This guideline concentrates on the second of these concerns.

The paucity of high quality evidence in this field and the fact that the relationship between pre-donation blood pressure and subsequent hypertension is likely to be continuous mean it is not possible to give a precise pre-operative blood pressure level below which donation is safe and above which donation should not be considered. As with other aspects of living donation, the consideration of potential risk also must take account of the age of the donor in that the older donor will have a higher absolute annual risk, but this will be spread over a shorter remaining life-span. Each case needs to be considered individually, bearing in mind that many potential donors may be willing to accept a higher risk of developing hypertension than their transplant professionals (2).

5.8.1 Definition of Hypertension in the Donor

There is a general consensus from the Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure (3), British Hypertension Society (4) and European Society of Hypertension (5) that, in the absence of other cardiovascular risk factors or end organ damage, adults with a blood pressure above 140/90 mmHg should be considered hypertensive. All guidelines agree that a blood pressure above 140/90 mmHg requires further assessment and/or treatment. British guidelines recommend treatment of all

patients with blood pressure above 160/100 mmHg and those with end organ damage or high cardiovascular risk (≥ 20% in 10 years) if the blood pressure is above 140/90 mmHg.

Although blood pressure increases with age (6), guidelines for the diagnosis and treatment of hypertension are applied to all age groups. As increasing numbers of older donors are being considered, it is likely more potential donors with a blood pressure above 140/90 mmHg will be assessed. This level of blood pressure should not preclude further evaluation.

In addition, it is evident that the risk of cardiovascular mortality increases with blood pressure values that are still within the normal range. The Joint National Committee reports that cardiovascular risk doubles for every 20/10 mmHg rise in blood pressure above 115/75 mmHg. This has in part led to the classification of blood pressure above 130/85 mmHg as 'high normal' (4) and recognition of a need to monitor these patients because of the future risk of developing hypertension. There is no evidence that 'high normal' blood pressure is a contra-indication to donor nephrectomy but these donors should be informed of the high lifetime risk of developing hypertension irrespective of nephrectomy, and therefore the need for follow-up.

5.8.2 Method of Blood Pressure Measurement

Most of the large population based studies of cardiovascular risk have relied upon office blood pressure measurements. There is no evidence to suggest that office blood pressure measurements will be a less accurate predictor of cardiovascular risk in potential donors undergoing nephrectomy and therefore this method should be used for the standard measurement of blood pressure. Some individuals will exhibit a stress response (white coat hypertension) that may lead to an incorrect diagnosis of hypertension (7). In this situation, 24-hour ambulatory blood pressure monitoring (ABPM) may be useful. The British and European guidelines define hypertension using ABPM as a 24-hour mean blood pressure >125/80 mmHg (4,5) and the American guidelines as awake blood pressure >135/85 mmHg and asleep >120/75 mmHg (3). In a study of 238 potential donors, 36.7% were classified as hypertensive based on office measurements. However, this proportion decreased to 11% when ABPM was used for assessment (hypertension defined as awake blood pressure >135/85 mmHg). This discrepancy was most marked in

older donors (8). These data would support the use of ABPM in the assessment of potential donors with hypertension based on office measurements.

ABPM can predict both hypertensive end organ damage and cardiovascular risk, perhaps more accurately than office blood pressure (9,10). Ozdemir et al suggested that ABPM was more sensitive at identifying hypertension in potential donors than office blood pressure measurements (11). However, there is little evidence to support the routine use of ABPM to assess potential donors who are normotensive on initial office blood pressure measurements.

5.8.3 Risk of Developing Hypertension Post Donation

There are no conclusive data that unilateral nephrectomy increases the risk of developing hypertension and in a recent survey only 50% of transplant professionals believed that hypertension develops after nephrectomy (12). There are no good prospective controlled studies to assess the risk of hypertension after donation. Several small studies have failed to show an increased risk, possibly because they were underpowered. Nevertheless, overall cardiovascular risk should be considered in all potential donors and measures taken to reduce risk irrespective of baseline blood pressure.

The reported incidence of hypertension after unilateral nephrectomy varies significantly from 9-75% (13-16). Several larger studies with varying duration of follow-up suggest that approximately one third of donors will develop hypertension (17-19). Although this rate is high, these studies do not quote the incidence of hypertension in control populations and therefore it is not possible to determine whether there is any excess risk attributable to unilateral nephrectomy. Even if controlled data were available, it would not account for the element of screening involved in living donor selection.

A large database study from the US which involved 3,698 donors concluded that the rate of hypertension in donors was similar to the general population (18). In contrast, a similar study from Ontario suggested that donors were more frequently diagnosed with hypertension (16.3% vs 11.9%) (20). Several small studies have suggested an increase in the incidence of hypertension after unilateral nephrectomy when compared to a control population (16,21,22). However, larger studies have failed to reproduce this finding

(18,23,24). In addition, no difference was found when the incidence of hypertension was compared in kidney donors and their siblings (25).

Two meta-analyses have considered the effect of unilateral nephrectomy on hypertension. The first in 1995 reported a small increase in both systolic and diastolic pressures post nephrectomy (2.4 and 3.1 mmHg respectively) but no increase in the incidence of hypertension compared to controls (26). A more recent meta-analysis performed in 2006 suggested that blood pressure may rise by 5 mmHg in the first 5-10 years post donation (27).

It is clear that the risk of developing hypertension after kidney donation is influenced by pre-donation characteristics including pre-donation blood pressure, body mass index and age (18,19). Higher risk groups should be warned of the higher risk of developing hypertension and the need for monitoring, although it is unclear whether this risk is greater than in an appropriately matched 'two kidney' control group (28).

There are few data on the long-term outcome of nephrectomy in ethnic groups, which may be at greater risk of developing complicated hypertension. In a small study of African American donors, the incidence of hypertension was 41% at a mean follow-up of 7.1 years after donation, although this rate was not compared to an age and sex matched control population (29). A larger retrospective study of US donors with a mean 7.7 year follow-up showed that black and Hispanic donors had an increased risk of hypertension as compared with white donors (adjusted hazard ratio 1.52) (30).

5.8.4 Pre-existing Hypertension in the Donor

There is relatively little information on the influence of nephrectomy in patients with pre-existing hypertension. However, it is generally accepted that the presence of hypertensive end organ damage (left ventricular hypertrophy on echocardiography), uncontrolled hypertension, or hypertension that requires polytherapy to achieve adequate control are contraindications to donor nephrectomy. Since it is unlikely that donor nephrectomy will be performed in these circumstances, evidence to support this practice will not be generated in the living donor setting.

Evidence is also sparse for potential donors who present with less severe hypertension and it is difficult to draw definite conclusions from the available literature (reviewed by Young et al) (31). This is a common scenario and will be become increasingly common as older donors are considered. In a series by Textor et al (published only in abstract), 58 patients with hypertension controlled on 1 or 2 agents underwent nephrectomy (32). There were no increased risks to the donor identified (renal function, proteinuria and hypertension). In a smaller series of patients reported by the same group, 24 patients with hypertension (>140/90 mmHg) underwent donor nephrectomy. Pre-existing hypertension did not have an adverse effect on outcome with no evidence of higher blood pressure or renal injury after nephrectomy (33). These reports suggest that potential donors with mild or moderate hypertension should be considered suitable for nephrectomy, particularly if the blood pressure is controlled with non-pharmacological methods and 1 or 2 antihypertensive agents.

Potential donors with hypertension should have this confirmed by either repeated office measures or ABPM. If confirmed, non-pharmacological interventions should be recommended and drug treatment initiated if required. If adequate blood pressure control is achieved or if the long-term cardiovascular risk is deemed acceptable by both patient and assessor, the donor can proceed to nephrectomy.

The target blood pressure in a potential donor should be the same as the general population. A large population study suggested that the greatest reduction in cardiovascular risk was achieved with the diastolic blood pressure below 85 mmHg (34) and therefore the British Hypertension Society recommends an optimal treatment target of <140/85 mmHg (4).

5.8.5 Management of Hypertension following Donor Nephrectomy

Hypertension will develop in at least 30% of patients following unilateral nephrectomy. Several studies have reported longitudinal data on patients after unilateral nephrectomy including renal function, albuminuria and blood pressure. The data are conflicting with some reports suggesting that hypertension after nephrectomy is associated with the development of renal complications (23), but this has not been confirmed by others (14,35). An association would be predicted because of the known relationship between

hypertension and renal disease. However, there is no evidence to suggest that this effect is amplified by unilateral nephrectomy.

References

1. Fehrman-Ekholm I, Gabel H, Magnusson G. Reasons for not accepting living kidney donors. Transplantation 1996; 61:1264-5.
2. Young A, Karpinski M, Treleaven D, et al. Differences in tolerance for health risk to the living donor among potential donors, recipients, and transplant professionals. Kidney Int 2008; 73: 1159-66.
3. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.
4. Williams B, Poulter NR, Brown MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ 2004; 328: 634-40.
5. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21: 1011-53.
6. Miall WE, Chinn S. Blood pressure and ageing; results of a 15-17 year follow-up study in South Wales. Clin Sci Mol Med 1973; 45 Suppl 1: S23-33.
7. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA 1988; 259: 225-8.
8. Textor SC, Taler SJ, Larson TS, et al. Blood pressure evaluation among older living kidney donors. J Am Soc Nephrol 2003; 14: 2159-67.
9. Verdecchia P. Prognostic value of ambulatory blood pressure: current evidence and clinical implications. Hypertension 2000; 35: 844-51.
10. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA 1999; 282: 539-46.
11. Ozdemir N, Guz G, Muderrisoglu H, et al. Ambulatory blood pressure monitoring in potential renal transplant donors. Transplant Proc 1999; 31: 3369-70.
12. Housawi AA, Young A, Boudville N, et al. Transplant professionals vary in the long-term medical risks they communicate to potential living kidney donors: an international survey. Nephrol Dial Transplant 2007; 22: 3040-5.

13. Anderson CF, Velosa JA, Frohnert PP, et al. The risks of unilateral nephrectomy: status of kidney donors 10 to 20 years postoperatively. Mayo Clin Proc 1985; 60: 367-74.
14. Eberhard OK, Kliem V, Offner G, et al. Assessment of long-term risks for living related kidney donors by 24-h blood pressure monitoring and testing for microalbuminuria. Clin Transplant 1997; 11: 415-9.
15. Miller IJ, Suthanthiran M, Riggio RR, et al. Impact of renal donation. Long-term clinical and biochemical follow-up of living donors in a single center. Am J Med 1985; 79: 201-8.
16. Saran R, Marshall SM, Madsen R, Keavey P, Tapson JS. Long-term follow-up of kidney donors: a longitudinal study. Nephrol Dial Transplant 1997; 12: 1615-21.
17. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tyden G, Groth CG. Kidney donors live longer. Transplantation 1997; 64: 976-8.
18. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-69.
19. Torres VE, Offord KP, Anderson CF, et al. Blood pressure determinants in living-related renal allograft donors and their recipients. Kidney Int 1987; 31: 1383-90.
20. Garg AX, Prasad GV, Thiessen-Philbrook HR, et al. Cardiovascular disease and hypertension risk in living kidney donors: an analysis of health administrative data in Ontario, Canada. Transplantation 2008; 86: 399-406.
21. Watnick TJ, Jenkins RR, Rackoff P, Baumgarten A, Bia MJ. Microalbuminuria and hypertension in long-term renal donors. Transplantation 1988; 45: 59-65.
22. Hakim RM, Goldszer RC, Brenner BM. Hypertension and proteinuria: long-term sequelae of uninephrectomy in humans. Kidney Int 1984; 25: 930-6.
23. Fehrman-Ekholm I, Duner F, Brink B, Tyden G, Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation 2001; 72: 444-9.
24. Goldfarb DA, Matin SF, Braun WE, et al. Renal outcome 25 years after donor nephrectomy. J Urol 2001; 166: 2043-7.
25. Williams SL, Oler J, Jorkasky DK. Long-term renal function in kidney donors: a comparison of donors and their siblings. Ann Intern Med 1986; 105: 1-8.
26. Kasiske BL, Ma JZ, Louis TA, Swan SK. Long-term effects of reduced renal mass in humans. Kidney Int 1995; 48: 814-9.
27. Boudville N, Prasad GV, Knoll, G, et al. Meta-analysis: risk for hypertension in living kidney donors. Ann Intern Med 2006; 145: 185-96.

28. Tavakol MM, Vincenti FG, Assadi H, et al. Long-term renal function and cardiovascular disease risk in obese kidney donors. Clin J Am Soc Nephrol 2009; 4: 1230-8.
29. Nogueira JM, Weir MR, Jacobs S, et al. A study of renal outcomes in African American living kidney donors. Transplantation 2009; 88: 1371-6.
30. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med 2010; 363: 724-32.
31. Young A, Storsley L, Garg AX, et al. Health outcomes for living kidney donors with isolated medical abnormalities: a systematic review. Am J Transplant 2008; 8: 1878-90.
32. Textor SC, Taler SJ, Pierto M, et al. Hypertensive living renal donors have lower blood pressures and urinary microalbumin one year after nephrectomy. Am J Transplant 2003; 3 (Abstract).
33. Textor SC. Atherosclerotic renal artery stenosis: how big is the problem, and what happens if nothing is done? J Hypertens Suppl 2005; 23: S5-13.
34. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351: 1755-62.
35. Praga M, Hernandez E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int 2000; 58: 2111-8.

5.9 DIABETES MELLITUS

Statements of Recommendation

- ***All potential living kidney donors must have a fasting plasma glucose level checked. A level between 5.6–6.9 mmol/l is indicative of an impaired fasting glucose state and an oral glucose tolerance test (OGTT) must be undertaken. (B1)***

- ***Prospective donors with an increased risk of Type 2 diabetes because of family history, ethnicity or obesity should also undergo an OGTT. (B1)***

- ***If OGTT reveals a persistent impaired fasting glucose and/or an impaired glucose tolerance, then the risks of developing diabetes after donation must be carefully considered. (B1)***

- ***Consideration of patients with diabetes as potential kidney donors requires very 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 kidney donation after a thorough assessment of the lifetime risk of cardiovascular and progressive renal disease in the presence of a single kidney. (Not graded)***

5.9.1 Diagnosis of Diabetes Mellitus

All prospective donors should have a fasting plasma glucose measurement to exclude diabetes mellitus. The WHO and American Diabetes Association recommend repeat testing of fasting glucose on a different day before placing someone in a glucose intolerant category (6). A fasting venous plasma glucose of >7.0 mmol/l indicates diabetes mellitus (6). Fasting plasma glucose values of between 5.6 and 6.9 mmol/l indicate impaired fasting glucose. A glucose value in this range together with a family history of Type 2 diabetes (sibling or parental) is associated with a 30% 5-year risk of diabetes and donation is usually contraindicated (7).

In the context of living donation, impaired fasting glucose is an indication for a standard 2-hour oral glucose tolerance test (OGTT). A 2-hour glucose value of >11.1 mmol/l indicates diabetes (6). A 2-hour value between 7.8 and 11.0 mmol/l indicates impaired glucose tolerance. Caucasians in this latter category have a 10% 5-year risk of diabetes (7). The risk is higher for certain ethnic groups, notably individuals from Southern Asia and the Caribbean (8).

Traditional guidance has suggested that individuals with diabetes should not donate kidneys. However, in an observational study of 444 donors from a single Japanese centre that has cautiously accepted subjects with an abnormal OGTT, including those with diabetes, no difference was found in the rate of immediate post-operative complications or survival at 20 years between the glucose tolerant and intolerant groups. Through self reporting of status at follow-up, no major diabetic complications were observed in the glucose intolerant group (21). Further studies are required in this area. Consideration of a diabetic as a donor requires thorough evaluation of the risks and benefits of donation and transplantation, for both donor and recipient. Specifically, a careful search should be made for any evidence of target organ damage and cardiovascular risk factors such as obesity, hypertension and hyperlipidaemia. Testing for glycosuria and measurement of random blood glucose levels has low sensitivity for the diagnosis of diabetes (9). After exclusion of pre-existing diabetes, the clinical risk factors for diabetes and diabetic nephropathy should be evaluated and discussed with the potential donor (3,4).

5.9.2 Risk of Type 1 Diabetes

Type 1 diabetes presents predominantly in childhood and early adulthood and 50% of cases have presented by the age of 20 years (10). The incidence of Type 1 diabetes in adults is less than 1 in 10,000 (10). First degree relatives of an individual with Type 1 diabetes have a 15-fold increased risk of developing the disease. Moreover, the relatives of Type 1 diabetics with diabetic nephropathy appear to be at increased risk of nephropathy should they subsequently develop diabetes (11). However, because Type 1 diabetes is relatively uncommon and most cases have presented before the age at which living donation is under consideration, there is little need for concern even when there is a family history of Type 1 diabetes. Sometimes it may be difficult to determine from the history whether an affected family member had Type 1 or Type 2 diabetes. As a working definition, Type 1 diabetes is characterised by onset below the age of 30 years and a requirement for insulin treatment from the time of diagnosis.

5.9.3 Risk of Type 2 Diabetes

Type 2 diabetes is predominantly a disease of later life and in 50% of cases Type 2 diabetes is clinically unrecognised (12). The crude prevalence of undiagnosed disease in the Caucasian population is 2.3% (13). Individuals who have a family history (first degree relative) of Type 2 diabetes are at higher risk of developing the disease (relative risk 3.0). Because the prevalence of Type 2 diabetes is much higher than for Type 1, the absolute risk of developing the disease is high (lifetime risk 38%) (14). The combination of family history and obesity (BMI >30 kg/m^2) places an individual at very high risk of diabetes in later life (15). Individuals from South East Asia and the Caribbean are at increased risk of Type 2 diabetes, independently of age and obesity. Individuals at high risk of Type 2 diabetes because of a positive family history and/or obesity should undergo an OGTT and should only be considered further as donors if this is normal. For individuals with a normal OGTT, the risk of developing Type 2 diabetes within 5 years is around 1% overall and is modulated by ethnicity and obesity. In a large survey of living kidney donors in the United States, Ibrahim et al found that the self reported prevalence of diabetes was 5.2% in the 2,929 patients who responded. The eGFR and the rate of decline of eGFR were not significantly different between diabetic and matched non-diabetic donors (22).

If there is a history of transient gestational diabetes, the lifetime risk of Type 2 diabetes is very high (16,17) and kidney donation is relatively contraindicated. An important consideration for a potential kidney donor is the risk of developing nephropathy should they subsequently develop Type 2 diabetes. There is a sharp increase in the incidence of Type 2 diabetes after the age of 50 and the median age at diagnosis is around 60 years. Less than 1% of Europeans with Type 2 diabetes develop ESRD but the incidence is higher in other ethnic groups (18). However, there is a 50% cumulative incidence of proteinuria after Type 2 diabetes has been present for 20 years (19) which may reasonably become an issue for kidney donors who have an above average life expectancy and may expect to live to their 80s (20). A prudent approach should be adopted when assessing potential donors who are at increased risk of Type 2 diabetes.

References

1. Barnes DJ, Pinto JR, Viberti GC. The patient with diabetes mellitus. In: Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG. Oxford Textbook of Clinical Nephrology. Oxford University Press 1998; 723-75.

2. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. N Engl J Med 1984; 310: 356-60.
3. Simmons D, Searle M. Risk of diabetic nephropathy in potential living related kidney donors. BMJ 1998; 316: 846-8.
4. Kasiske BL, Ravenscraft M, Ramos EL, Gaston RS, Bia MJ, Danovitch GM. The evaluation of living renal transplant donors: Clinical practice guidelines. JASN 1996; 7: 2288-313.
5. Peters A, Kerner W. Perioperative management of the diabetic patient. Exp Clin Endocrinol Diabetes 1995; 103: 213-8.
6. Alberti NJ, Zimmet PZ, for the WHO consultation. Definition, diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine 1998; 15: 539- 53.
7. Wareham NJ, Byrne CD, Williams R, Day NE, Hales CN. Fasting proinsulin concentrations predict the development of type 2 diabetes. Diabetes Care 1999; 22: 262-70.
8. Yudkin JS, Alberti KG, McLarty DG, Swai AB. Impaired glucose tolerance. Is it a risk factor for diabetes or a diagnostic ragbag? BMJ 1990; 301: 397-402.
9. Engelgau MM, Thompson TJ, Aubert RE, Herman WH. Screening for NIDDM in non pregnant adults. Diabetes Care 1995; 18: 1606-18
10. Green A, Gale G. The aetiology and pathogenesis of IDDM – an epidemiological perspective. In: Williams R, Papoz L, Fuller J, eds. Diabetes in Europe. London: John Libbey & Company Ltd, 1994; 11-20.
11. Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease: Evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med 1989; 320: 1161-5.
12. Harris MI. Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 1993; 16: 642-57.
13. Williams DRR, Wareham NJ, Brown DC, et al. Glucose intolerance in the community; the Isle of Ely Diabetes Project. Diabetic Med 1995; 12: 30-5.
14. Pierce M, Keen H, Bradley C. Risk of diabetes in offspring of parents with non-insulin-dependent diabetes. Diabetic Medicine 1995; 12: 6-13.
15. Morris RD, Rimm DL, Hartz AJ, Karlhoff RK, Rimm AA. Obesity and heredity in the etiology of non-insulin-dependent diabetes mellitus in 32,662 adult white women. Am J Epidemiol 1989; 130: 112-21.

16. O'Sullivan B. Subsequent morbidity among gestational diabetic women. In: Sutherland HW, Stowers JM, eds. Carbohydrate metabolism in pregnancy and the newborn. Edinburgh: Churchill Livingstone, 1984; 174-80.
17. Oats JN, Beischer NA, Grant PT. The emergence of diabetes and impaired glucose tolerance in women who had gestational diabetes. In: Weiss PA, Coustan DR, eds. Gestational diabetes. New York: Springer-Verlag, 1988; 199-210.
18. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT. The kidney in maturity onset diabetes mellitus: a clinical study of 510 patients. Kidney Int 1998; 35: 681-7.
19. Borch-Johnsen K. Renal disease in diabetes. In: Williams R, Papoz L, Fuller J, eds. Diabetes in Europe. London: John Libbey & Company Ltd, 1994; 56-60.
20. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tyden G, Groth C-G. Kidney donors live longer. Transplantation 1997; 64: 976-8.
21. Okamoto M, Suzuki T, Fujiki M, et al. The consequences for live kidney donors with preexisting glucose intolerance without diabetic complication: analysis at a single Japanese center. Transplantation 2010; 89: 1391-5.
22. Ibrahim HN, Kukla A, Cordner G, Bailey R, Gillingham K, Matas AJ. Diabetes after kidney donation. Am J Transplant 2010; 10: 331-7.

5.10 CARDIOVASCULAR EVALUATION

Statements of Recommendation

- ***A low threshold should be set for screening potential living donors for cardiovascular disease, and for their exclusion from donation. (B1)***
- ***Potential donors with an exercise capacity of <4 METS or >10% estimated risk of significant coronary atherosclerosis should undergo formal cardiological assessment. (B1)***
- ***Potential donors with exercise capacity >10 METS are at very low cardiac risk. (B1)***
- ***Screening of higher risk donors should be performed by CT calcium scoring and/or functional assessments such as dynamic stress tests. (B2)***

Cardiovascular assessment prior to non-cardiac surgery is a complex subject with conflicting advice from the available clinical evidence. When assessing individuals for potential living kidney donation, it needs to be remembered that the retrieval operation is a cardiovascular stress and that subclinical cardiac disease may impact upon the safety of the procedure. Although coronary artery disease is the most commonly encountered issue, consideration should also be given to valvular and cardiac muscle disease. In addition to providing an assessment of the cardiovascular risk of undergoing surgery, the pre-operative screening allows an opportunity to address the cardiovascular risk factors of an individual, consider the long term effects of kidney donation, and act to reduce the progression of cardiac disease.

5.10.1 Role of Screening Electrocardiogram

Electrocardiography complements the clinical assessment and may indicate the presence of pre-existing ischaemic heart disease or cardiomyopathy. The latter is important as cardiomyopathies, particularly hypertrophic cardiomyopathy (incidence 1:500), are the most common cause of sudden cardiac death in apparently healthy young people (1). Particular attention needs to be given to the presence of pathological Q waves (>25% R wave height), left bundle branch block, voltage criteria for left ventricular hypertrophy, pathological T wave changes, and atrial arrhythmias. Any abnormality should trigger

formal assessment which is likely to include echocardiography and a cardiac opinion. A normal electrocardiogram, whilst reassuring, does not exclude coronary disease.

5.10.2 Screening Patients with Established Overt Cardiac Disease

Every attempt should be made to ensure that individuals presenting as potential living kidney donors are not exposed to additional significant or unavoidable risk by taking part in such a program. As such the threshold for refusal on health grounds will be relatively low and the presence of overt cardiac disease is likely to exclude most individuals as potential donors. The specific issues surrounding hypertension and diabetes are dealt with elsewhere (sections 5.8 and 5.9). In terms of cardiac disease, a detailed history and examination needs to be carefully focused to uncover existing problems. It is important that further assessment is sought for those individuals excluded due to symptoms or signs of existing disease. Usually this will be performed by a cardiologist so that current best practice is followed in their management.

5.10.3 Screening for Occult Cardiac Disease

Although there are challenges with overt disease, it is significantly more difficult to produce clear guidance for ostensibly asymptomatic individuals. As the positive predictive value of any test is dependent upon the risk within the population being studied there is a significant danger that screening low risk individuals will produce an excessive number of false positive results. This will expose potential living kidney donors to unnecessary anxiety and result in the recommendation of further investigations which may be invasive or use ionising radiation. In addition, further testing will lead to an additional economic burden upon the healthcare system.

In considering this subject, evidence has been sought from existing guidance on the investigation of patients with non-cardiac chest pain and in the management of individuals undergoing non-cardiac surgery who are suspected of having underlying cardiac disease. As such, this does not fully apply to the population of potential living kidney donors; however, this is offset when it is remembered that the lack of clinical benefit from kidney donation means that stricter than usual criteria need to be applied to define risk.

In defining a low risk group who do not need further investigation there are two areas which need to be considered. Firstly, the overall risk of having underlying cardiac disease; secondly, the exercise capacity of the individual.

In order to determine the risk of vascular disease for individuals, a number of established cardiovascular risk factors need to be assessed: in particular, the age of the donor; the smoking history; the presence of hypercholesterolaemia; the presence of diabetes; and the presence of hypertension. Although a family history of cardiovascular disease has not been always been used as a risk factor, it would seem reasonable that a confirmed diagnosis of coronary artery disease in a first degree relative under the age of 55 years would also elevate the donor into the 'high risk' group. Using these factors, the probability of significant angiographically evident coronary disease can be estimated in a population of similar individuals (2). Modifying the stratification used in the recent NICE guidance on chest pain to look at asymptomatic people, these subjects may be grouped according to risk as shown in Table 5.10.1.

Table 5.10.1 Percentage of people estimated to have coronary disease presenting with non- cardiac chest pain according to age, sex and risk.

	Male		Female	
Age (years)	Low Risk**	High Risk*	Low Risk**	High Risk*
35	3	35	1	19
45	9	47	2	22
55	23	59	4	25
65	49	69	9	29

*High risk = presence of diabetes, smoking or cholesterol >6.47 mmol/l

**Low risk = none of above

[Modified from Diamond and Forrester (2)]

There is no clear guidance on what cut-off should be used to determine the need for further investigation. However, a threshold of ten percent or greater has been used by other guidance to indicate that investigations are required to exclude a possible cardiac pathology and this would seem reasonable to also apply to living donation (3). As a result, all potential donors with any of these cardiac risk factors and all men over the age of 55 years would require formal testing to exclude occult ischaemia. Although this is likely to over-estimate the actual cardiac risk, it is appropriate in this setting to have a low threshold for investigation as already discussed.

In all other individuals, the presence of a functional capacity in excess of 4 METS (metabolic equivalents, where the resting oxygen consumption of a 70 kg, 40-year-old man is 3.5 ml/kg/min is 1 MET) has been shown to predict a very low peri-operative risk and longer term rate of cardiovascular events (4-8). Activities that require more than 4 METS include moderate cycling, climbing hills, ice skating, roller blading, skiing, singles tennis, and jogging. Functional capacity can be assessed formally with a treadmill or using the Duke Activity Status Index which can be determined by a short questionnaire (Figure 5.10.1) (9). Following calculation of the Activity Status, this can be used to calculate the peak oxygen consumption (ml/min = (0.43 x index) + 9.6) and therefore METS of activity. Provided a functional capacity of greater that 4 METS can be reliably established in subjects without cardiovascular risk factors, as discussed above, there will be little incremental screening benefit from formal stress testing (10).

In situations of uncertainty about functional capacity and in those with a pre-test population probability over 10%, there is debate as to the best way to assess cardiac risk. The conventional approach has been to perform a stress test. The choice of stress test is likely to reflect the practice of the screening unit; however, the positive predictive value of each option needs to be considered and becomes particularly relevant in the presence of an abnormal resting electrocardiogram and in pre-menopausal women. Evidence from exercise treadmill testing and other techniques indicate that completing the equivalent of 10 METS without ECG changes or symptoms indicates a low, <1% per annum, risk of events (3,11). Recent reviews have suggested that exercise treadmill tests have poor discriminatory value when compared with other techniques such as stress echocardiography or myocardial perfusion scanning (3,11). These non-invasive imaging techniques have similar sensitivity and specificity and a test which does not involve ionising radiation (i.e. stress echo) is usually preferred. Abnormal results should trigger a

Figure 5.10.1 Duke Activity Status Index

Item	Activity	Yes	No
1	Can you take care of yourself (eating, dressing, bathing or using the toilet)?	2.75	0
2	Can you walk indoors around your house?	1.75	0
3	Can you walk a block (hundred yards) or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.50	0
5	Can you run a short distance	8.00	0
6	Can you do light work around the house like dusting or washing dishes	2.70	0
7	Can you do moderate work around the house like vacuuming, sweeping floors or carrying groceries?	3.50	0
8	Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	8.00	0
9	Can you do garden work like raking leaves, weeding or pushing a power mower?	4.50	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities like golf, bowling, dancing, doubles tennis or throwing a baseball or football?	6.00	0
12	Can you participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	7.50	0

Duke Activity Status Index is the sum of the results (range 0 to 58.2) and can be used to calculate maximum oxygen uptake in ml/min [(0.43 x index) + 9.6] (12).

formal cardiology review both in order to clarify their clinical validity and also to allow for treatment of any uncovered cardiovascular disease.

An alternative approach is to screen patients at increased cardiac risk using CT coronary calcium scoring. The radiation exposure of a CT calcium score is one sixth that of an abdominal CT scan and a scan takes only 5 minutes, making this an attractive option in many centres for the assessment of patients at low cardiac risk. Using this technique in an asymptomatic individual, a coronary calcium score of zero effectively excludes significant coronary atherosclerosis and obviates the need for further structural or functional assessments (3). Higher scores will of course require careful interpretation and further assessment in concert with local cardiological expertise. The technique has recently been recommended by NICE as the most appropriate screening technique in patients presenting to a rapid access chest pain clinic in whom the clinical suspicion of significant coronary atherosclerosis is low (3). In many centres, an elevated coronary calcium score of 1-400 can for convenience be followed by a CT coronary angiogram at the same examination, with higher scores usually indicating a need for formal angiography.

5.10.4 Screening for Non-coronary Pathology

A combination of clinical assessment and 12 lead surface ECG has a reasonable sensitivity for the detection of non-coronary cardiac pathology. There is an extensive literature on the pre-participation screening of athletes and in this group of young individuals there is little incremental benefit of routine echocardiography. However, in an older cohort this may not be true. Currently there is no consensus regarding the definition of a relatively “high risk” cohort and it is therefore difficult to justify a policy of routine echocardiogram screening for living kidney donors who have no abnormalities clinically or on an electrocardiogram.

5.10.5 Conclusion

Due to the nature of the procedure, a low threshold needs to be set for formal investigation and for the exclusion of individuals for living kidney donation. As well as determining suitability, the process should act as an opportunity to identify and correct recognised cardiovascular risk factors. The choice of stress test will be influenced by local service provision, although clinicians should consider the relatively increased predictive

value of structural techniques over electrocardiography alone. CT coronary calcium scoring may be an alternative way of stratifying coronary risk.

References

1. 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; 276: 199-204.
2. 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.
3. NICE Guidance 2010. Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. London: National Clinical Guideline Centre for Acute and Chronic Conditions. Accessed 16th February 2011 at: http://guidance.nice.org.uk/CG/Wave14/25
4. Nelson CL, Herndon JE, Mark DB, et al. Relation of clinical and angiographic factors to functional capacity as measured by the Duke Activity Status Index. Am J Cardiol. 1991; 68: 973–5.
5. Myers J, Do D, Herbert W, Ribisi P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. Am J Cardiol 1994; 73: 591-6.
6. Bartels C, Bechtel JF, Hossmann V, Horsch S. Cardiac risk stratification for high-risk vascular surgery. Circulation 1997; 95: 2473-5.
7. 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.
8. 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.
9. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989; 64: 651-4.
10. 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.
11. Weiner DA, Ryan TJ, McCabe CH, et al. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. J Am Coll Cardiol 1984; 3: 772-9.

5.11 PROTEINURIA

Statements of Recommendation

- ***Urine protein excretion should be quantified in all potential living donors. (B1)***

- ***A urine albumin/creatinine ratio (ACR) performed on a spot urine sample voided after waking is the recommended screening test, although both urine protein/creatinine ratio (PCR) and 24-hour urine protein collection are acceptable alternatives. (A1)***

- ***Significant proteinuria is an ACR >30 mg/mmol, PCR >50 mg/mmol or 24-hour total protein >300 mg/day, and usually contraindicates donation. (B1)***

- ***The significance of microalbuminuria (ACR 3.5-30 mg/mmol) and of 24-hour urine protein of 150-300 mg (PCR 15-30) has not been fully evaluated in living kidney donors. However, since both the risk of CKD and cardiovascular morbidity increase progressively with increasing albuminuria, such donors require careful evaluation and counselling about the risks of donation. (C2)***

Proteinuria is a well established important risk factor for both chronic kidney disease (1) and cardiovascular morbidity and mortality (2). In particular, proteinuria predicts both progression of CKD and cardiovascular events in patients with established CKD, established cardiovascular disease and, in patients with diabetes, co-morbidities that clearly preclude living kidney donation (2,3). Proteinuria also predicts the development of CKD and cardiovascular disease in those without medical co-morbidities, and for this reason is considered an absolute contraindication to living kidney donation.

Several large cohort studies from the general population have identified proteinuria as a risk factor for CKD and cardiovascular disease (4,5), even in those patients with an eGFR >60 ml/min/1.73m^2. In a study of nearly 1 million people from Alberta in Canada the risk of developing end-stage renal disease (ESRD) in those with a baseline eGFR >60 ml/min was 0.03/1,000 patient years if there was no proteinuria, 0.05 with ‘mild proteinuria’

(urinalysis trace or 1+, ACR 3.5-35 mg/mmol), but 1.0 in those patients with 'heavy proteinuria' (urinalysis >1+, or ACR >35 mg/mmol) (5). A study of 40,854 individuals from the Netherlands gave similar results, with a linear relationship between albuminuria and subsequent ESRD (6). In this study, urine albumin concentrations of <20 mg/l and 20-100 mg/l (roughly equivalent to an ACR of 3.5-20 mg/mmol, or 'low level' microalbuminuria) were associated with a low risk of ESRD (0.06 and 0.15% at 9 years follow-up) compared to those with 100-200 mg/l or >200 mg/l of albuminuria (2.45 and 5.67% respectively).

There are few studies examining either the renal or cardiovascular outcome for living kidney donors who have donated despite proteinuria. In many donors there is a modest increase in urine protein excretion after nephrectomy, the majority of whom have no evidence of accelerated GFR loss over time (7-10). In one study, 5 donors with low grade proteinuria (mean 210 mg in a 24-hour urine collection) were more likely to have significant proteinuria 20 years or more after donation (>800 mg/24 hours), although without significant loss of kidney function (11). A review of 1,519 living kidney donors in Japan identified 8 who developed ESRD (12). Of these, only 2 had pre-donation proteinuria, both of whom developed cardiovascular disease, hypertension and ESRD 6 and 16 years after donation.

Methods of Testing for Proteinuria

For many years, assessment of proteinuria was based on an accurately timed 24-hour urine collection, with <150mg protein/24 hours considered normal and >300 mg/24 hours pathological. However the urine albumin /creatinine ratio (ACR) or protein /creatinine ratio (PCR) in a spot urine sample are now the preferred methods as both correlate well with 24-hour urinary protein excretion and overcome inaccuracies related to incomplete urine collection. Recent studies, including those described above, have used ACR, which is a better screening test, and there is now consensus that ACR is an appropriate and sufficient test for proteinuria (13-15). A normal ACR of <2.5 mg/mmol in men and <3.5 mg/mmol in women equates to <150 mg protein over 24 hours. An ACR of between 2.5 and 30 mg/mmol defines microalbuminuria (urine albumin excretion of between 30 and 300 mg/day, roughly equating to a 24-hour protein excretion of 150-500 mg), and >30 mg/mmol defines macroalbuminura. Dipstick analysis alone is inadequate to detect low level but clinically significant albuminuria. Table 5.11.1 provides a summary of the comparative values detected using these screening methods.

Table 5.11.1 Expressions of urinary protein concentration and their approximate equivalents and clinical correlates

	Dipstick reading	Protein:creatinine ratio (mg/mmol)	Total protein (mg/24h)	Albumin:creatinine ratio (mg/mmol)	Albumin excretion (mg/24h)
Normal	Negative	<15	<150	<2.5 (males) <3.5 (females)	<30
Micro-albuminuria	Negative	<15	<150	2.5 - 35 (males) 3.5 - 35 (females)	30 – 300
'Trace' protein	Trace	15-50	150-500		

Assessment of Proteinuria in Living Donors

There is uncertainty over the definition of significant proteinuria in a potential kidney donor. A recent US survey reported that although many US centres use a 24-hour urine collection for protein, some rely on a spot urine PCR, but almost one-half of centres now use urine ACR as a screen (16). The most common exclusion criterion for kidney donors in the US is 300 mg/day proteinuria, but almost as many centres now use 150 mg/day as a cut-off, unless the proteinuria is postural. Recently, the Amsterdam Forum concluded by consensus that a 24-hour urinary protein excretion of >300 mg is a contraindication to donation (17). However, it is not clear what is to be done with patients with proteinuria below 300 mg/day but above the upper limit of normal for the testing laboratory.

This issue was recently addressed in a single centre prospective study of 39 potential kidney donors who had simultaneous measurements of both urinary total protein and albumin (18). Although 13/39 had elevated 24-hour urinary total protein values, none had elevated urinary albumin excretion, suggesting a low risk of subsequent CKD or cardiovascular morbidity. Similarly, orthostatic proteinuria should not be considered as a contraindication to donation. Orthostatic proteinuria appears benign (19), but confident diagnosis requires performing an ACR on a spot urine sample voided immediately after waking.

References

1. Halbesma N, Kuiken DS, Brantsma AH, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol 2006; 17: 2582-90.
2. Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. PREVEND Study Group. Extended prognostic value of urinary albumin excretion for cardiovascular events. J Am Soc Nephrol 2008; 19: 1785-91.
3. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Medicine 2008; 5: 1486-95.
4. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003; 63: 1468-74.
5. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria and adverse outcomes. JAMA 2010; 303: 423-9.
6. Van de Velde M, Halbesma N, de Charro FT, et al. Screening for albuminuria identifies individuals at increased renal risk. J Am Soc Nephrol 2009; 20: 852-62.
7. Fehrman-Ekholm I, Dunér F, Brink B, Tydén G, Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. Transplantation. 2001; 72: 444-9.
8. Garg AX, Muirhead N, Knoll G, et al. Donor Nephrectomy Outcomes Research (DONOR) Network. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis and meta-regression. Kidney Int 2006; 80: 1801-10.
9. Gossmann J, Wilhelm A, Kachel HG, et al. Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. Am J Transplant 2005; 5: 2417-24.
10. Ibrahim HN, Foley R, Tan L, Rogers et al. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-69.
11. Goldfarb DA, Matin SF, Braun WE, Schreiber MJ, Mastroianni B, Papajcik D. Renal outcome 25 years after donor nephrectomy. J Urol 2001; 166: 2043-7.
12. Kido R, Shibagaki Y, Iwadoh K, et al. How do living kidney donors develop end-stage renal disease? Am J Transplant 2009; 9: 2514-9.
13. K/DOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007; 49(2 Suppl 2): S12.

14. National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September 2008.
15. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? Ann Clin Biochem 2009; 46: 205-17.
16. Mandelbrot DA, Pavlakis M, Danovitch GM, et al. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant 2007; 7: 2333-43.
17. Delmonico F. Council of the Transplantation Society. A report of the Amsterdam Forum on the care of the live kidney donor: data and medical guidelines. Transplantation 2005; 79(6 Suppl): S53-66.
18. Leischner MP, Naratadam GO, Hou SH, Singh AK, Leehey DJ. Evaluation of proteinuria in healthy living kidney donor candidates. Transplant.Proc 2006; 38: 2796-7.
19. Springberg PD, Garrett LE Jr, Thompson AL Jr, Collins NF, Lordon RE, Robinson RR. Fixed and reproducible orthostatic proteinuria: results of a 20-year follow-up study. Ann Intern Med 1982; 97: 516-9.

5.12 NON-VISIBLE HAEMATURIA

Statements of Recommendation

- ***All potential living donors should have reagent strip (dipstick) urinalysis performed on at least 2 separate occasions. (B1)***

- ***Two or more positive tests, including trace positive, should be considered as persistent non-visible haematuria (PNVH). (B1)***

- ***If PNVH is present, perform urine culture and renal imaging to exclude common urologic causes including infection, nephrolithiasis and urothelial carcinoma. (A1)***

- ***If no cause is found, perform cystoscopy in patients age >40 years to exclude bladder pathology. (B1)***

- ***If no cause is found and the donor still wishes to donate, then a kidney biopsy should be considered, and is recommended if haematuria is >1+ on dipstick testing. (B2)***

- ***Glomerular pathology precludes donation, with the possible exception of thin basement membrane disease. (B1)***

Non-visible haematuria is the preferred term (replacing microscopic haematuria) for blood identified in a urine sample either by microscopy or by reagent strip analysis. Non-visible haematuria is a common finding in the general population, may indicate either urological or renal parenchymal disease, and must be carefully evaluated in prospective living kidney donors.

Non-visible haematuria is present in 1-21% of the general population, the prevalence increasing with age (1-4). Most patients are asymptomatic with no urologic symptoms, no proteinuria and normal renal function. Subsequent urine testing is often normal. Such **transient haematuria** is generally considered insignificant, although with little supporting evidence from longitudinal studies. In one report including 432 patients with normal

urological investigation and followed for 5.8 +/- 4.4 years, haematuria disappeared in 44%, none of whom developed proteinuria or renal impairment (5). In a smaller study of 49 patients investigated for non-visible haematuria, those in whom haematuria disappeared all had a normal kidney biopsy (6).

Persistent asymptomatic non-visible haematuria (PANVH) is present in about 25% of those with an initial positive test (1-7) and, in two single centre reports, 2.7% and 8.3% of potential living kidney donors in the US and Japan respectively (8,9). Malignant disease of the urinary tract, present in 3-5% of patients overall (10,11), is rare under the age of 40 but diagnosed in up to 10% of those aged >60. In patients with normal urological investigations, kidney biopsy is frequently abnormal. In a UK-based study 77 of 165 patients, 46% were found to have glomerular pathology, most commonly IgA nephropathy, mesangial proliferative glomerulonephritis without IgA deposition, or thin basement membrane nephropathy (12). Similar pathology has been demonstrated in a Dutch study where 29 out of 49 biopsies were abnormal (6), a Korean study in which only 10 out of 156 biopsies were normal (13), and in a US study of potential living donors with PANVH in which 8 out of 10 biopsies were abnormal (8).

Longitudinal studies have confirmed the importance of PANVH. In the Dutch study of 49 patients, those with a normal biopsy developed neither proteinuria nor worsening renal function during 11 years of follow-up. In contrast, proteinuria (10 patients), hypertension (14) and worsening kidney function (4) were found in the 29 patients with an abnormal biopsy (6). In a Japanese study of 242 living donors, 8.3% had PANVH prior to donation and 15.3% following donation. None were investigated with a kidney biopsy, but the presence of haematuria predicted the development of proteinuria during a median follow-up of 2.3 years (9). In a similar study including patients from the Japanese general population, 10% of those with PANVH developed proteinuria over a median follow-up of 5.8 years (5).

The above supports current practice that persistent asymptomatic non-visible haematuria should be investigated in potential living kidney donors, both to exclude urological disease and to identify glomerular pathology that would preclude donation. However, there remain uncertainties: in particular, the relevance of low levels of haematuria (‘trace’ positive), and the importance of thin basement membrane nephropathy (TBMN) merit further discussion.

'Trace' microscopic haematuria

Non-visible haematuria is routinely detected using semi-quantitative reagent strips. A reagent strip 'trace positive' result corresponds to 1-5 red cells/μl (15). Urine microscopy is not required to confirm the presence of haematuria, and indeed often produces false negative results, although the detection of dysmorphic red cells and red cell casts may be useful to identify glomerular haematuria.

One difficulty is that existing studies rarely, if ever, distinguish between the degrees of non-visible haematuria recorded on dipstick testing. As the incidence of significant disease following the investigation of trace positive haematuria is no different to that of control populations, recent primary care and Urology guidelines in the UK have recommended that trace non-visible haematuria be considered a normal variant (14). However, glomerular pathology has been reliably identified in potential living donors using thresholds of even 1 or 3 red cells/μl (8,9). No studies have directly addressed the threshold below which investigation of the potential donor is unnecessary, and a balance must be struck between the risk of missing significant renal disease in a potential donor, against the inconvenience and risk of biopsy. High degrees of non-visible haematuria mandate biopsy prior to donation, but trace haematuria is at present a relative indication.

If, after counselling, the prospective donor with non-visible haematuria remains committed to donation and a kidney biopsy is performed, histological evaluation must include immunofluorescence or immunohistochemistry, and electron microscopy.

Considerable evidence also suggests that cystoscopy is of limited value in the investigation of non-visible haematuria below the age of 40 years, especially in women, and this is reflected in current UK guidelines (14). Risk factors for uro-epithelial cancer should be assessed including donor age, smoking history, exposure to aniline dye, analgesics or cyclophosphamide, and pelvic irradiation. In younger asymptomatic patients, it is reasonable to discuss the risk/benefit ratio of cystoscopy with the prospective donor. Above the age of 40 years, however, the increased incidence of urological disease mandates a full urological assessment, including cystoscopy.

Thin basement membrane nephropathy

Thin basement membrane nephropathy (TBMN) is an autosomal dominant disorder often associated with mutations in either the *COL4A3 or COL4A4* genes (encoding the α3 and α4 chains of type 4 collagen). Individuals in whom both alleles of either gene are

abnormal may have autosomal recessive Alport syndrome, and TBMN can be regarded as the carrier state for this condition. TBMN is present in 10-50% of patients biopsied for PANVH (6,8,12,13) and although often considered a benign diagnosis may carry some risk of progression. Both proteinuria (10-20% of patients) and renal impairment (5%) have been described (16-18), often associated with additional pathological abnormalities including FSGS (18) or IgA nephropathy (19,20) (both of which would preclude donation). Many individuals with TBMN but otherwise normal investigations have undoubtedly donated kidneys, either knowingly (8) or unknowingly (9), and although adverse outcomes have not been reported these donors must be made aware of uncertainty over long-term safety. Referral to a clinical geneticist for molecular testing may be warranted, especially when donating to a family member with unexplained kidney failure or where there is a family history of sensori-neural deafness or haematuria (see also section 5.17 Familial Renal Disease). Referral to a geneticist is mandatory in potential donors of Cypriot origin, where associations of TBMN and FSGS leading to significant rates of renal failure have been noted (21).

TBMN must be distinguished from the carrier state of **X-linked Alport syndrome** (XLAS), which is associated with a 5-20% risk of progressive renal impairment (22) and generally considered to prohibit donation. A recent study describing six XLAS carriers who donated kidneys to their affected children supports this view (23). A decline in kidney function of between 25 and 60% was observed in four of the six donors over 2–14 years of follow-up, although in no case was creatinine clearance <40 ml/min. Four of the six developed microalbuminuria or proteinuria, and four developed hypertension. Some have argued that, if no other donor can be found, women with XLAS who are over the age of 45, have normal kidney function, no proteinuria and no hearing deficiency (both risk factors for progression to end-stage kidney disease) might be considered as donors after appropriate counselling (24). Involvement of a clinical geneticist would be mandatory in the screening of such a potential donor.

References

1. Topham PS, Jethwa A, Watkins M, Rees Y, Feehally J. The value of urine screening in a young adult population. Fam Pract 2004; 21: 18-21.
2. Mohr DN, Offord KP, Owen RA, Melton LJ. Asymptomatic microhematuria and urologic disease: a population based study. JAMA 1986; 256: 224-9.

3. Messing EM, Young TB, Hunt VB. Home screening for haematuria: results of a multiclinic study. J Urol 1992; 148: 289-92.
4. Froom P, Ribak J, Benbassat J. Significance of microhematuria in young adults. BMJ 1984; 288: 20-2.
5. Yamagata K, Kobayashi M, Koyama A. A long-term follow up study of asymptomatic haematuria and/or proteinuria in adults. Clin Nephrol 1996; 45: 281-8.
6. Nieuwhof C, Doorenbos C, Grave W. A prospective study of the natural history of idiopathic non-proteinuric haematuria. Kidney Int 1996; 49: 222-5.
7. Jaffe JS, Ginsberg PC, Gill R, Harkaway RC. A new diagnostic algorithm for the evaluation of microscopic haematuria. Urology 2001; 57: 889-94.
8. Koushik R, Garvey C, Manivel C, Matas AJ, Kasiske B. Persistent, asymptomatic microscopic hematuria in prospective kidney donors. Transplantation 2005; 80: 1425-9.
9. Kido R, Shibagaki Y, Iwadoh K, et al. Persistent glomerular haematuria in living kidney donors confers a risk of progressive kidney disease in donors after heminephrectomy. Am J Transplant 2010; 10: 1597-604.
10. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with haematuria to evaluate current diagnostic practice. J Urol 2000; 163: 524-7.
11. Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int 2006; 97: 301-5.
12. Topham PS, Harper SJ, Furness PN, Harris KPG, Walls J, Feehally J. Glomerular disease as a cause of isolated microscopic haematuria. Q J Med 1994; 87: 329-35.
13. Kim BS, Kim YK, Shin YS, et al. Natural history and renal pathology in patients with isolated microscopic haematuria. Korean J Intern Med 2009; 24: 356-61.
14. Kelly JD, Fawcett DP and Goldberg LC. Assessment and management of non-visible haematuria in primary care. BMJ 2009; 338: 227-32.
15. Freni SC, Heederik GJ, Hol C. Centrifugation techniques and reagent strips in the assessment of microhematuria. J Clin Pathol 1977; 30: 336-40.
16. Savige J, Rana K, Tonna S, Buzza M, Dagher H, Wang YY. Thin basement membrane nephropathy. Kidney Int 2003; 64: 1169-78.
17. Auwardt R, Savige J, Wilson D. A comparison of the clinical and laboratory features of thin basement membrane disease (TBMD) and IgA glomerulonephritis (IgA GN). Clin Nephrol 1999; 52: 1-4.

18. van Passen P, van Breda Vriesman PJ, van Rie H, Tervaert JW. Signs and symptoms of thin basement membrane nephropathy: a prospective regional study on primary glomerular disease – The Limburg Renal Registry. Kidney Int 2004; 66: 909-13.
19. Cosio FG, Falkenhein ME, Sedmark DD. Association of thin glomerular basement membrane with other glomerulopathies. Kidney Int 1996; 46: 471-4.
20. Berthoux FC, Laurent B, Alamartine E, Diab N. A new subgroup of primary IgA nephritis with thin glomerular basement membrane (GBM): Syndrome or association. Nephrol Dial Transplant 1996; 11: 558-61.
21. Voskarides K, Damianou L, Neocleous V, et al. COL4A3/COL4A4 mutations producing focal segmental glomerulosclerosis and renal failure in thin basement membrane nephropathy. J Am Soc Nephrol 2007; 18: 3004-16.
22. Kashtan CE. Alport syndrome and the X chromosome: implications of a diagnosis of Alport syndrome in females. Nephrol Dial Transplant 2007; 22: 1499-505.
23. Gross O, Weber M, Fries JW, Muller GA. Living donor kidney transplantation from relatives with mild urinary abnormalities in Alport syndrome: Long-term risk, benefit and outcome. Nephrol Dial Transplant 2009; 24: 1626-30.
24. Kashtan CE. Women with Alport syndrome: risks and rewards of kidney donation. Nephrol Dial Transplant 2009; 24: 1369-70.

5.13 PYURIA

Statement of Recommendation

- ***Prospective donors found to have pyuria should only be considered for donation if it can be demonstrated that the pyuria is due to a reversible cause, such as an uncomplicated urinary tract infection. (C1)***

Pyuria may be defined as the presence of at least 10 leukocytes/mm^3 of uncentrifuged urine (1), which occurs in less than 1% of asymptomatic, non-bacteriuric patients but in greater than 96% of symptomatic men and women with significant bacteriuria.

Pyuria can occur in the absence of apparent bacterial infection, particularly in patients who have already taken antimicrobials, or where there is infection with atypical organisms such as Chlamydia trachomatis, Ureaplasma urealyticum, or tuberculosis. Most symptomatic women with pyuria but without significant bacteriuria have urinary infection, either with bacterial uropathogens present in colony counts less than 10^5/ml or with Chlamydia (1). Other causes of sterile pyuria include contamination from genital secretions, acute or chronic interstitial nephritis, nephrolithiasis and uroepithelial tumour.

The cause of the pyuria must be established before a potential donor proceeds for further assessment.

Reference

1. Stamm WE. Measurement of pyuria and its relation to bacteriuria. Am J Med 1983; 75: 53-8.

5.14 INFECTION IN THE PROSPECTIVE DONOR

Statements of Recommendation

- ***Infection screening in the prospective donor prior to donation is important to identify potential risks for the donor from previous or current infection and to assess the risks of transmission of infection to the recipient. (B1)***

- ***Active HBV and HCV infection in the donor are usually contraindications to living donor kidney transplantation; however, donors with no evidence of active viral replication may be considered under some circumstances. (B1)***

- ***The CMV status of donor and recipient should be determined before transplantation. When the donor is CMV positive and the recipient is CMV negative, the donor and recipient should be counselled about the risk of post-transplant CMV. (B1)***

- ***The EBV status of donor and recipient should be determined before transplantation. When the donor is EBV positive and the recipient is EBV negative, the donor and recipient should be counselled about the risk of developing PTLD. (B1)***

- ***The presence of HIV or human T lymphotrophic virus (HTLV) infection is an absolute contraindication to living donation. (B1)***

The risk of transmission of infections between donor and recipient must be kept to a minimum. The same principles that apply to deceased donors and blood donors should be applied to the screening of living donors in this respect (1,2). Identification of current or previous infection in the prospective donor is an important aspect of donor evaluation. The presence of active infection usually precludes donation. Apart from the implications for the potential donor, a number of infections may be transmitted by organ transplantation. Those that are of established clinical significance are listed in Table 5.14.1.

Table 5.14.1 Infections of established clinical significance in transplantation

Viral

Cytomegalovirus (CMV or HHV 5)

Epstein-Barr virus (EBV or HHV4)

Hepatitis B virus (HBV)

Hepatitis C virus (HCV)

Herpes simplex virus (HSV or HHV1 and HHV2)

Human immunodeficiency virus (HIV-1 and HIV-2)

Human T lymphotrophic virus (HTLV)

Kaposi's Sarcoma virus (KSKV or HHV8)

Varicella-zoster virus (VZV or HHV3)

Bacterial

Atypical mycobacterial infections

Bacterial meningitis

Mycobacterium tuberculosis

Syphilis

Fungal and parasitic

Leishmania

Malaria

Schistosomiasis

Toxoplasmosis

Trypanosoma

Prion-associated

Creutzfeldt-Jakob disease (CJD)

Variant Creutzfeldt-Jakob disease (vCJD)

5.14.1 Evaluation of the Prospective Donor

A detailed clinical history is important and should include a psychosocial and sexual history to define at-risk behaviour (see Table 5.4.2 in section 5.4). Prospective donors who have been resident in geographical areas outside the UK where there is a high prevalence of infection may require additional evaluation. During routine physical examination of the donor, examination of the chest and reticuloendothelial system may reveal evidence of infection. The routine screening investigations already outlined in Table 5.4.4 in section 5.4 include those ordinarily required to exclude infection in the prospective donor. Particular attention should be paid to the possibility of past tuberculosis when examining the chest X-ray. A mid-stream urine should be cultured and examined by microscopy on at least two occasions. If sterile pyuria is detected the cause must be identified. The presence of eosinophilia may indicate chronic parasite infection.

The serological tests that should be performed on the prospective donor and recipient are listed in Table 5.14.2. Infections can be transmitted by both blood transfusion and organ donation during the incubation period of the offending organism and before a serological response has been mounted. Serology should not, therefore, be regarded as a substitute for a detailed psychosexual and medical history. Routine testing for viral infection may, if a positive result is obtained, raise complex ethical problems.

It is important that there is full discussion with the prospective donor before testing for viral infection, particularly for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). A strategy for dealing with a positive result should be formulated before testing.

5.14.2 Viral Infections in the Prospective Donor

HIV and HTLV

The presence of HIV or human T lymphotrophic virus (HTLV) infection is an absolute contraindication to living donation. HTLV serology is not routinely tested but should be performed if the prospective donor comes from an endemic area e.g. Africa, the Caribbean and Japan. Kidney donation should not be undertaken if significant doubt remains about the possibility of HIV infection in the donor.

Table 5.14.2 Serological testing of donor and recipient

Donor screening	Recipient screening
HIV 1 & 2	HIV 1 & 2
CMV	CMV
VZV	
EBV	EBV
HCV	HCV
HBV	HBV
Syphilis	
Toxoplasmosis	
*HHV8	*HHV8
*HTLV	*HTLV
*Schistosomiasis	*Schistosomiasis
*Strongyloides stercoralis	*Strongyloides stercoralis
*Malaria (blood film)	*Malaria (blood film)
*Trypanosoma cruzi	*Trypanosoma cruzi

*Where clinically indicated e.g. specific endemic (geographical) risks

HCV

Active HCV in the donor is often a contraindication to living donation, not only because of the risk of transmitting HCV to the recipient but also because of the risk of glomerular disease in the donor (3,4). The risk of HCV transmission from an HCV RNA positive donor approaches 100% if transplanted into a naïve recipient (5). All potential donors should have HCV antibody testing performed and, if positive, HCV RNA should be checked. If the donor is consistently RNA negative, then transplantation may be considered, even into a naïve recipient. The risks entailed, however, must be carefully explained to both donor and recipient. In these exceptional circumstances, the likely life expectancy of the recipient has to be considered.

Advances in anti-viral agents and vaccination may influence such decisions in the future.

HBV

Most transplant units would not consider potential donors with evidence of active HBV viral replication. All prospective donors should have both HB surface antigen and HB core antibody IgG checked. HBV DNA testing should be performed in prospective donors from HBV endemic areas who are hepatitis core antibody positive, those with possible mutant HBV, and those with abnormal liver tests or a past history of liver disease of unknown aetiology. HB core antibody IgM is not indicated unless the donor is e antigen positive and acute infection is being queried.

There are a substantial number of reports of kidneys transplanted from HB surface antigen negative/DNA negative, HB core antibody-positive cadaver donors in which there have been a low risk of HBV seroconversion and no excess risk of graft failure or short-term morbidity (6-9). In the context of living donation, donors who are HBcAb positive with negative HBsAg and undetectable DNA in blood may be considered as donors, providing the recipient has been effectively immunised against HBV. In addition, the use of HBV immunoglobulin and anti-viral drugs may be considered. Advice from a virologist and hepatologist should be sought under these circumstances and the donor and recipient need to be fully informed.

CMV

CMV infection is the most commonly encountered clinically significant viral infection after kidney transplantation and may cause significant morbidity and mortality, particularly if the recipient is heavily immunosuppressed (10). It also increases the risk of chronic graft

dysfunction as well as post-transplant lymphoproliferative disorder (PTLD) and opportunistic infection.

CMV disease may result from reactivation of latent infection or because of primary infection transmitted by a kidney from a CMV positive donor. For CMV and other viral infections, primary infection is generally more severe than reactivation and the recipients most at risk are those who are CMV seronegative and receive a kidney graft from a CMV seropositive donor. 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 kidney transplantation. Either CMV prophylaxis or pre-emptive therapy with close monitoring of viral loads should be offered (11). The donor and recipient should be informed about the increased risk of CMV disease before the transplant is performed.

EBV

Primary EBV infection is most likely to occur in EBV negative paediatric recipients who receive a kidney 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. Consideration should be given in this situation to the prophylactic use of antiviral agents (aciclovir or valganciclovir) in order to minimise the viral load after transplantation. This strategy may protect renal transplant recipients from PTLD (12), but was not found to be of benefit in paediatric liver transplant recipients (13). When the donor is EBV positive and the recipient is EBV negative, clinical vigilance is required following transplantation to detect PTLD as early as possible. The use of quantitative PCR to monitor the recipient viral load after transplantation is contentious.

VZV

It is important to know whether the potential recipient is VZV seropositive as a primary VZV infection may be rapidly fatal in an immunocompromised host (14,15). Vaccination is available for recipients who are VZV antibody negative.

HHV8

HHV8 may be transmitted by organ transplantation and is associated with an increased risk of Kaposi's sarcoma (16). However, there is no evidence to support screening of potential organ donors.

5.14.3 Bacterial Infections in the Prospective Donor

The main risk of bacterial infection is from Mycobacterium tuberculosis (and atypical mycobacteria). Donors should be screened for mycobacterial infection. Screening should include a careful history, including ethnic origin and country of upbringing. Chest X-ray is important, but the value of skin testing is questionable. If a specific bacterial microbiological diagnosis has been made in the donor, then a course of appropriate antibiotic is likely to be effective in preventing transmission (Table 5.14.3). A history of urinary tract infection in a potential donor, particularly if there is a family history of reflux nephropathy, or in a male, requires detailed imaging of the kidneys (e.g. DMSA for cortical scarring).

Transmission of syphilis has been reported in the UK to two recipients from a deceased donor with a past history of treated disease (18). Recipients of living donor transplants from donors considered to carry a risk of syphilis transmission should be given prophylactic treatment (2.5 MU benzathine penicillin im single dose, or doxycycline 100 mg po for 14 days, or 1 g azithromycin po single dose) in line with British Association for Sexual Health and HIV guidelines (19). Discussion and liaison with specialist GU medicine advice would be advisable.

5.14.4 Fungal and Parasitic Infections in the Prospective Donor

A living donor is unlikely to transmit a fungal infection if otherwise in good health. Nevertheless, this remains a theoretical possibility and should be considered in patients from areas where fungal infections are endemic. Toxoplasmosis and malaria can be transmitted by a renal transplant (14). In most of the reported cases, transmission has been from living unrelated donor transplantation taking place in the developing world.

Other infections are either transmitted rarely (occasional case report) or are only of theoretical risk. Table 5.14.3 summarises the use of prophylactic antimicrobial agents for different types of donor infection.

Table 5.14.3 Use of prophylactic antimicrobial agents

1	HBV positive donor		Vaccinate recipient Prophylactic lamivudine
2	CMV (donor +ve, recipient -ve)		Prophylactic antiviral drugs (usually valganciclovir)
3	EBV (donor +ve, recipient -ve)		Consider prophylactic aciclovir or valganciclovir
4	Toxoplasmosis		Sulphonamide, clindamycin, clarithromycin, azithromycin or pyrimethamine (covered also by co-trimoxazole)
5	Mycobacterial infections		Prophylactic isoniazid
6	Bacteria	Low virulence	7 days of appropriate antibiotic
		High virulence	14 days of appropriate antibiotic
7	Syphilis		Benzathine benzylpenicillin

5.14.5 Prion-Associated Diseases in the Prospective Donor

CJD and vCJD

There is no screening test currently available for CJD or vCJD. Four individuals in the UK have been shown to have acquired CJD prions from blood or blood products in the UK, two of whom went on to develop clinical CJD (19). No cases of transmission by living donor kidney transplantation have been reported. National guidance for blood and tissue donors states that prion-associated disease in the prospective donor is an absolute contra-indication to donation (2). Individuals who may be at increased risk of developing such a disease are also precluded from donating and a detailed personal and family history must be taken from the donor to identify potential risk factors. Healthy living donors may not have been exposed to many of these, but relevant history would include recipients of human pituitary-derived (growth) hormones, dura mater, corneal and scleral grafts and a positive family history (two or more blood relatives) of prion-associated disease, subject to genetic counselling. The current guidelines imply that prospective donors who have received blood or blood products anywhere in the world after 1980 should be viewed as at increased risk (and are, in fact, excluded from blood donation). This is not reflected in current UK practice, and is probably impractical (2).

References

1. Standards for solid organ transplantation in the United Kingdom. British Transplantation Society 2003; ISBN 0 9542221-2-1.
2. UK Blood Transfusion & Tissue Guidelines. Donor selection guidelines. www.transfusionguidelines.org.uk
3. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 1992; 328: 465-70.
4. Stehman-Breen C, Willson R, Alpers CE, Gretch D, Johnson RJ. Hepatitis C virus-associated glomerulonephritis. Curr Opin Nephrol Hypertens 1995; 4: 287-94.
5. Pereira BJ, Milford EL, Kirkman RL, et al. Prevalence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. N Engl J Med 1992; 327: 910-5.
6. Satterthwaite R, Ozgu I, Shidban H, et al. Risks of transplanting kidneys from hepatitis B surface antigen-negative, hepatitis B core antibody-positive donors. Transplantation 1997; 64: 432-5.

7. Madayag RM, Johnson LB, Bartlett ST, et al. Use of renal allografts from donors positive for hepatitis B core antibody confers minimal risk for subsequent development of clinical hepatitis B virus disease. Transplantation 1997; 64: 1781-6.
8. De Feo TM, Grossi P, Poli F, et al. Kidney transplantation from anti-HBc+ donors: results from a retrospective Italian study. Transplantation 2006; 81: 76-80.
9. Ouseph R, Eng M, Ravindra K, Brock GN, Buell JF, Marvin MR. Review of the use of hepatitis B core antibody-positive kidney donors. Transplant Rev 2010; 24: 167-71.
10. Van Son WJ, The TH. Cytomegalovirus infection after organ transplantation: an update with special emphasis on renal transplantation. Transpl Int 1989; 2: 147-64.
11. Guidelines for the prevention and management of cytomegalovirus disease after solid organ transplantation. British Transplantation Society, 2002. ISBN: 0954222105.
12. Darenkov IA, Marcarelli MA, Basadonna GP, et al. Reduced incidence of Epstein-Barr virus associated post transplant lymphoproliferative disorder using preemptive antiviral therapy. Transplantation 1997; 64: 848-52.
13. Green M, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for the prevention of cytomegalovirus and Epstein-Barr virus disease after liver transplantation in children. Clin Infect Dis 1997; 25: 1344-9.
14. Parnham AP, Flexman JP, Saker BM, Thatcher GN. Primary varicella in adult renal transplant recipients: a report of three cases plus a review of the literature. Clin Transplant 1995; 9: 115-8.
15. Rothwell WS, Gloor JM, Morgenstern BZ, Milliner DS. Disseminated varicellla infection in pediatric renal transplant recipients treated with mycophenolate mofetil. Transplantation 1999; 68: 158-61.
16. Regamey N, Tamm M, Wernli M, et al. Transmission of human herpesvirus 8 infection from renal transplant donors to recipients. N Engl J Med 1998; 19: 1358-63.
17. Joint UKBTS / NIBSC Professional Advisory Committee Position Statement: Creutzfeldt-Jakob Disease. 11th March 2010. www.transfusionguidelines.org.uk/index.aspx?Publication=DL&Section=12&pageid=794
18. Cortes NJ, Afzali B, MacLean D, et al. Transmission of syphilis by solid organ transplantation. Am J Transplant 2006; 6: 2497-9.
19. Kingston M, French P, Goh B, et al. UK National Guidelines on the Management of Syphilis 2008. Syphilis Guidelines Revision Group 2008, Clinical Effectiveness Group Int J STD AIDS. 2008; 19: 729-40.

5.15 NEPHROLITHIASIS

Statement of Recommendation

- ***In the absence of a significant metabolic abnormality, potential donors with a limited history of previous small calcium stones, or a small renal calculus on imaging, may still be considered as potential kidney donors. Full counselling of donor and recipient is required along with access to appropriate long term donor follow-up. (C2)***

- ***Potential donors with metabolic abnormalities detected on screening should be discussed with a specialist in renal stone disease. (C2)***

5.15.1 Incidence, Natural History and Management of Renal Stones

In the UK, symptomatic renal stones are common with a prevalence of around 3-5%. The use of CT to evaluate potential kidney donors has led to increased detection of asymptomatic small kidney stones, which are present in 5% of potential kidney donors undergoing a non-contrast CT scan.

The lifetime risk of recurrent kidney stones is an important consideration in evaluating suitability for kidney donation. There are few data on the lifetime risk specific to the kidney donor population. However, people who present with a symptomatic (calcium oxalate) kidney stone have a 50% chance of developing a further stone within 5 years (1). Stone recurrence rates also are related to the number of previous stone episodes and the time interval to stone recurrence.

Most renal stones (75%) are composed predominantly of calcium oxalate. In symptomatic patients who undergo metabolic evaluation (who may be a selected group), a metabolic abnormality (e.g. hypercalciuria, hyperoxaluria, or hypocitraturia) may be detected in over 50% (2,3). The remaining 25% of stones are composed of uric acid, cystine, pure calcium phosphate, or struvite (magnesium ammonium phosphate, also called infection stones) (2,4). Uric acid stones are often associated with a history of gout, ileostomy diarrhoea or with the metabolic syndrome, in all of which the urine is highly acidic. Cystine stones are always associated with cystinuria. Calcium phosphate stones may occur with

hypercalciuria and are the predominant stone type formed by patients with a low urinary citrate and distal renal tubular acidosis. Infection stones are commonly associated with an anatomical abnormality.

Most asymptomatic stones found in potential donors are small (<5 mm). Small stones usually pass spontaneously but can occasionally cause ureteric obstruction leading to acute renal failure in patients with a single kidney. Small kidney stones can now be treated using less invasive treatment modalities e.g. extra-corporeal shock wave lithotripsy (ESWL) and flexible ureterorendoscopy. However, for the general population, the evidence that treating small asymptomatic stones is superior to simply observing them is mixed. Lower pole stones are more likely to progress than upper or middle pole stones, and progression is more likely if an asymptomatic stone is $\geq$4 mm at the time of detection (5).

In transplant recipients, the long term risks associated with a small stone in the donor kidney appear low (6,7).

Extensive or staghorn calculi can commonly lead to chronic renal damage (2) and are usually associated with infection or a significant metabolic abnormality

5.15.2 Assessment of Potential Donors

Imaging

The use of CT for renal vascular imaging has increased the detection rate of asymptomatic kidney stones. Where CT is not used routinely for vascular imaging and a stone is suspected from USS or MRI, a non contrast CT KUB is advisable to determine the number, size and location of suspected stones.

If a probable stone is identified on imaging, a urological and radiological review should be undertaken. The number, size, position and density of the potential stones should be considered; as should the presence of any underlying structural renal abnormality. A CT IVU may be useful in these circumstances. A DMSA scan is useful if renal scarring is suspected and will give an estimate of split renal function.

Biochemical Assessment

A full metabolic screen should be carried out prior to donation on potential donors with a history of stone disease or radiological evidence of a current stone. This screen should include 24-hour urine collections for calcium, oxalate, citrate and urate, and early morning pH assessment. This will require at least two separate urine collections as calcium, oxalate and citrate analyses require an acidified collection, whereas electrolytes, urate and pH are measured in a plain urine collection. Creatinine should be measured on each collection as an internal marker of completeness. A pH measurement on an early morning urine sample is useful, together with a qualitative cystine screen for cystinuria (8), followed, if positive, by a 24-hour collection for cystine concentration. A metabolic screen (urine and plasma biochemistry) may also be indicated in potential donors with a significant family history of stone disease or with significant risk factors for the development of stones e.g. inflammatory bowel disease.

In patients with previous calculus disease, where a stone has been retrieved, biochemical stone analysis is also of value.

5.15.3 Proceeding to Donation

If a significant and uncorrectable metabolic abnormality is identified then kidney donation is contra-indicated (9). However, donation may be considered in potential donors with minor or correctable metabolic abnormalities e.g. isolated hypocitraturia or isolated hypercalciuria, particularly if the history of calculus disease is very limited.

A history of a previous infection-related (struvite) or cystine renal stone is generally considered a contra-indication to donation.

A history of a previous uric acid stone would usually be considered a contra-indication to donation. However, donation may be considered where factors that have previously put the patient at risk of uric acid stone formation e.g. diet or medication, have been successfully modified, urine pH has been raised to >6.5 (preferably using pH meter rather than dipstick testing), and 24-hr urate levels have been demonstrated to have fallen within the normal range. In such cases, careful counselling of the donor is mandatory prior to surgery, and it is recommended that advice is obtained from a clinician with a specific interest in this field.

In potential donors who have a history of previous stones but no metabolic abnormality, proceeding with donation should be considered providing the bulk and frequency of the previous stones has been low.

Potential donors found to have small stone(s) on imaging, or cases where there is uncertainty as to whether there is a true calculus or parenchymal calcification, may be suitable to donate. In all cases, the results of the metabolic screen, donor age, and history of previous stone formation should be considered, and donation should only take place after full counselling of the donor and recipient. Both need to be aware of the limited data regarding long term outcomes in these circumstances (10). The smaller the stone bulk and the older the potential donor, the lower is the threshold for proceeding with donation.

It is recognised that the natural history of small asymptomatic stones detected during a donor work-up may be very different to stones presenting with clinical features or described in the existing urological literature. A recent study of 1,957 potential kidney donors evaluated at the Mayo Clinic from 2000 to 2008 reported that 3% had past symptomatic stones, while 11% had radiographic stones detected on screening (11). In this study, asymptomatic stone formers were not characterised by older age, male gender, hypertension, obesity, metabolic syndrome, abnormal kidney function, hyperuricaemia, hypercalcaemia or hypophosphataemia. One conclusion is that asymptomatic stone formers may lack the co-morbidities found in patients with symptomatic stone disease and that different pathophysiological mechanisms may be involved in asymptomatic stone formation versus symptomatic stone passage.

Perhaps reflecting the above, there is a lack of evidence to guide decision making and a lack of unanimity between the current recommendations regarding age and stone size cut-offs (12-14). On balance, it is likely that the risks of recurrent stone formation are currently over-emphasised in asymptomatic potential kidney donors. However, in the absence of a reliable evidence base, a degree of caution is warranted.

If donation proceeds, it is preferable to remove the kidney containing the suspected calculus. If the stone is very small it may be left in situ at the time of transplantation. However, it is relatively straight forward, with urological input and modern flexible ureterorendoscopes, to inspect the collecting system and remove any confirmed stones, *ex vivo*, prior to implanting the donor kidney (15).

Leaving the donor with a single kidney containing a possible small stone is undesirable, but may be considered in exceptional circumstances, e.g. strong anatomical reasons to remove the contralateral kidney. Full counselling of the donor is required in this situation and appropriate close long-term follow-up of the donor is necessary.

5.15.4 Follow-up

All management decisions need to take into consideration the potential follow-up requirements, with particular reference to donors from overseas.

Donors who have a past history of stones and those who have donated a stone-bearing kidney should be counselled about symptoms of renal/ureteric colic and anuria and information should be provided regarding the availability of local urological expertise. Donors should also be advised to maintain a high fluid intake for life (at least 2.5 litres of fluid per day) and also (where appropriate) to continue any medication prescribed to reduce the risk of future stone formation. Regular follow-up imaging e.g. annual renal ultrasound is advisable, and regular re-assessment of the metabolic profile should be considered.

Potential donors deemed unsuitable to donate because of stone disease should be referred to a local urologist for further management.

References

1. Coe FL, Keck J, Norton ER. The natural history of calcium urolithiasis. JAMA 1977; 238: 1519-23.
2. Johri N, Cooper B, Robertson W, Choong S, Rickards D, Unwin R. An Update and Practical Guide to Renal Stone Management. Nephron Clin Pract 2010; 116: c159–c171.
3. Spivacow FR, Negri AL, Del Valle EE, Calvino I, Zanchetta JR. Clinical and metabolic risk factor evaluation in young adults with kidney stones. Int Urol Nephrol 2010; 42: 471-5.

4. Sayer JA. The genetics of nephrolithiasis. Nephron Exp Nephrol 2008; 110: e37-43.
5. Burgher A, Beman M, Holtzman JL, Monga M. Progression of nephrolithiasis: long-term outcomes with observation of asymptomatic calculi.J Endourol 2004; 18: 534-9.
6. Martin G, Lipke MC, Sharfuddin A, Govani M, Sundaram P. Asymptomatic unilateral urolithiasis in living donor transplant kidneys. Urology 2007; 70: 2-5
7. Ho KLV, Chow G. Prevalence and early outcome of donor graft lithiasis in living renal transplants at the Mayo Clinic. J Urol 2005; 173: S439 abstract 1622.
8. Singh SK, Agarwal MM, Sharma S. Medical therapy for calculus disease. BJU Int 2011; 107: 356-68.
9. Kasiske BL, Ravenscraft M, Ramos EL, Gaston RS, Bia MJ, Danovitch GM. The evaluation of living renal transplant donors: clinical practice guidelines: Ad Hoc Clinical Practice Guidelines Subcommittee of the Patient Care and Education Committee of the American Society of Transplant Physicians. J Am Soc Nephrol 1996; 7: 2288-313.
10. Strang AM, Lockhart ME, Amling CL, Kolettis PN, Burns JR. Living renal donor allograft lithiasis: A review of stone related morbidity in donors and recipients. J Urol 2008; 179: 832-6.
11. Lorenz EC, Lieske JC, Vrtiska TJ, et al. Clinical characteristics of potential kidney donors with asymptomatic kidney stones. Nephrol Dial Transplant 2011 Feb 1. [Epub ahead of print].
12. Kälble T, Alcaraz A, Budde K, et al. European Urology Association Guidelines. Renal transplantation 2009. www.uroweb.org/gls/pdf/Renal%20Transplantation%202010.pdf
13. Delmonico F. A report of the Amsterdam Forum on the care of the live kidney donor: data and medical guidelines: Council of the Transplantation Society. Transplantation 2005; 79(S6): S53-66.
14. Rydberg J, Kopecky KK, Tann M, et al. Evaluation of prospective renal donors for laparoscopic nephrectomy with multisection CT: the marriage of minimally invasive imaging with minimally invasive surgery. Radiographics 2001; 21: S223-36.
15. Rashid MG, Konnak JW, Wolf JS, et al. Ex vivo ureteroscopic treatment of calculi in donor kidneys at renal transplantation. J Urol 2004; 171: 58-60.

5.16 HAEMATOLOGICAL DISEASE

Statements of Recommendation

- ***Donor anaemia needs to be investigated and treated prior to donation. (A1)***

- ***Haemoglobin electrophoresis should be carried out in patients with non-Northern European heritage or if indicated by the full blood count. (A1)***

- ***Careful consideration needs to be given to the use of potential donors with haemoglobinopathies. (B1)***

- ***Advice should be sought from a Consultant Haematologist for haematological conditions not covered in this guideline. (Not graded)***

Haematological abnormalities can place both the donor and recipient at risk in living donor kidney transplantation. Any prior history of anaemia or venous thromboembolism (VTE) should be obtained from the donor, as should any family history of haemoglobinopathy. All donors should have a full blood count and clotting screen as part of their assessment. Attention should be paid to the haemoglobin concentration, total and differential white count, and the mean corpuscular volume (MCV and MCH). Abnormalities of these parameters will require further investigation. In addition, haemoglobin electrophoresis needs to be carried out in potential donors of non-northern European heritage or where indicated by the MCV to screen for haemoglobinopathies. If there is a history of VTE, a thrombophilia screen should also be undertaken in the donor.

5.16.1 Red cell disorders

Anaemia

Anaemia (WHO classification Hb < 13 g/dL for men and < 12 g/dL for women) should be fully investigated and treated prior to organ donation.

Sickle cell disease and sickle cell trait

Sickle cell disease is an absolute contraindication to living kidney donation, with as many as 5-20% of patients developing CKD in their lifetime (1). In addition, the risks of general anaesthetic are much greater in this population.

The situation is more complex in potential donors with sickle call trait (SCT). There is a high incidence of urine concentrating abnormalities in such patients. In addition, visible and non-visible haematuria are well described, often as a result of papillary necrosis. There is some epidemiological evidence that SCT is associated with a higher risk of progression to end stage renal disease, this being true for Hb AS as well as Hb AC (2). In addition, the peri-operative risks may be higher in patients with SCT, including complications such as venous thromboembolism (3). Individuals with SCT are also at increased risk of renal medullary carcinoma. There are few data on the safety of kidney donation in individuals with SCT. A survey of US Transplant centres found that 37% would or might exclude patients on the basis of having SCT (4). On balance, SCT should not be an absolute contraindication to kidney donation, but donors wishing to proceed need to be counselled about the possible risks with input from a haematologist with an interest in sickle cell disease. Careful screening for the presence of existing renal involvement is required, with particular attention to a history of macroscopic haematuria.

Thalassaemia

Patients with thalassaemia can be categorised into those with thalassaemia major, thalassaemia intermedia (including Haemoglobin H disease, a form of alpha thalassaemia) and thalassaemia trait (thalassaemia carriers). Only the latter can be considered for living kidney donation as individuals with thalassaemia major or intermedia require transfusions and often suffer with iron overload and associated medical sequelae. There have been a few reports of minor tubular dysfunction in some patients with thalassaemia trait but there is no other reported association with renal disease (5).

Haemoglobin C & Haemoglobin E

These haemoglobinopathies may be encountered when screening donors of non-northern European heritage. Neither should pose a problem with kidney 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 accepted as living kidney donors. There is also some evidence that individuals with Hb AC may at increased risk of developing CKD (2).

Red cell membrane disorders

These include hereditary spherocytosis and hereditary eliptocytosis, inherited haemolytic anaemias of variable severity. Some of these patients undergo splenectomy to ameliorate anaemia. Renal function is not significantly impaired in these conditions and organ donation is acceptable in mild forms of the conditions where treatment has not been required. Advice from the treating haematologist should be sought.

5.16.2 White cell disorders

Monoclonal gammopathy of uncertain significance (MGUS)

MGUS is a plasma cell proliferative disorder that is characterised by a plasma cell content of <10% in the bone marrow, a monoclonal band of ≤30 g/l on protein electrophoresis, and the absence of end organ damage in the form of hypercalcaemia, renal insufficiency, anaemia or bone lesions (6). MGUS occurs in 2% of the population over the age of 50 years. There is a small year on year risk of transformation to myeloma or AL amyloid (1-2% per year) (7). However, MGUS *per se* does not cause end organ disease and as such individuals with this condition could with caution be considered as living kidney donors. However, such a decision has to be taken with great care and following discussion with the donor and their haematologist. Potential donors with MGUS need to be aware of the potential risk of progression to malignant B cell disorders which may adversely affect their remaining kidney; and also that they will have a lower GFR following donation, which may limit their treatment options should their MGUS transform into a malignant condition.

Myelodysplasia

Myelodysplastic syndromes (MDS) are a range of conditions resulting from abnormal clonal proliferation of bone marrow derived stem cells. As such there is a theoretical possibility of carry-over in a donor kidney to the recipient. In addition to the risk of transformation into acute myeloid leukaemia, patients with MDS are also at increased risk of premature death, especially as a result of cardiac disease (8). The presence of MDS should be considered a strong contraindication to donation.

References

1. Shaw C, Sharp CC. Could sickle cell trait be a predisposing risk factor for CKD? Nephrol Dial Transplant 2010; 25: 2403-5.
2. Derebail VK, Nachman PH, Key NS, et al. High prevalence of sickle cell trait in African Americans with ESRD. J Am Soc Nephrol 2010; 21: 413-7.
3. Austin H, Key NS, Benson JM, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. Blood 2007; 110: 908-12.
4. Reese PP, Hoo AC, Magee CC. Screening for sickle trait among potential live kidney donors: policies and practices in US transplant centers. Transpl Int 2008; 21: 328-31.
5. Cetin T, Oktenli C, Ozgurtas T, et al. Renal tubular dysfunction in beta-thalassemia minor. Am J Kidney Dis 2003; 42: 1164-8.
6. Berenson JR, Anderson KC, Audell RA, et al. Monoclonal gammopathy of undetermined significance: a consensus statement. J Haematol 2010; 150: 28-38.
7. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. New Engl J Med 2002; 346: 564-9.
8. Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. J Clin Oncol 2010; 28: 2847-52.

5.17 FAMILIAL RENAL DISEASE

Statements of Recommendation

- ***All potential transplant recipients should have a detailed family history recorded. Other family members with known kidney disease should have their diagnosis confirmed if possible. This may aid diagnosis for the recipient, clarify mode of inheritance and identify at risk relatives. (A1)***

- ***When the cause of kidney failure in the recipient is due to an inherited condition, reasonable steps should be taken to exclude genetic disease in the potential donor. (A1)***

- ***Many inherited kidney diseases are rare so involvement of clinical genetics services should be considered at an early stage to assess likely risks to family members. (B1)***

When renal failure in the recipient is due to an inherited renal disease or where there is a family history of renal disease, it is important to thoroughly investigate genetically related potential donors to assess their risk of developing renal disease (1). The diagnosis of many familial renal diseases still relies on a high index of suspicion coupled with biochemical, radiological and histological investigations. It may also be revealed only through a detailed pedigree which must be obtained for all individuals with renal disease.

A significant proportion of patients with ESRD (end stage renal disease) will have a family history of renal disease and so confirmation of all diagnoses within the family is essential to identify whether there is a clinically significant genetic predisposition to renal disease that is relevant to potential donors (2). Information on constructing a pedigree can be obtained via the National Genetics Education and Development Centre (www.geneticseducation.nhs.uk). However, in most cases the family history is due to polygenic influences such as diabetes, glomerular disease and hypertension for which no additional genetic testing or screening is required above that recommended for routine donor evaluation (2). A negative family history does not exclude a primary renal genetic disease. With the exception of autosomal dominant polycystic kidney disease (ADPKD), most other familial renal diseases are rare. Where the diagnosis is a known genetic

disease or the family history is suggestive of a monogenic (Mendelian) disease, the pedigree will aid in the identification of the mode of inheritance (typically autosomal dominant, autosomal recessive or X-linked) and the identification of at-risk relatives. This information is important to clarify the lifetime risk to a genetically related potential donor of developing significant renal disease.

The genetic basis of many familial renal diseases has been elucidated, providing the opportunity to use molecular investigations for diagnostic testing in the recipient and predictive testing in the potential living related donor (3). Genetic testing may also aid the prediction of the likelihood of disease recurrence in the transplanted kidney e.g. in atypical haemolytic uraemic syndrome. The UK Genetic Testing Network (www.ukgtn.nhs.uk) provides information on all tests currently available through the NHS and links to other sources of information such as GeneReviews (www.ncbi.nlm.nih.gov/sites/GeneTests) and OMIM (www.ncbi.nlm.nih.gov/omim). As genetic testing may be offered to individuals and families, involvement of clinical genetics services or specialist renal genetics services should be considered at an early stage to support the donor assessment team. This will be of value in identifying risks to family members and for the type and use of genetic testing for diagnostic and exclusion purposes. Details of all UK genetics centres can be found on the British Society of Human Genetics website (www.geneticseducation.nhs.uk). It should also be noted that molecular testing can take in excess of 3 months, although guidelines recommend <8 weeks for a full screen when the familial mutation is not known. This should be considered when planning donor evaluation and screening.

In autosomal dominant (AD) diseases, first-degree relatives are at 50% risk of carrying the familial mutation although variable penetrance and expression, common in many genetic diseases, may suggest some at-risk family members are unaffected or that the recipient represents a *de novo* mutation. At risk relatives must be carefully evaluated for specific disease manifestations and consideration given to genetic testing to definitively clarify risk and therefore suitability as a potential donor.

In autosomal recessive (AR) disease, unless there is a family history of consanguinity, only siblings have a significant risk of developing disease (25%). Parents will be obligate gene carriers and second degree relatives will be at 50% risk of also being gene carriers. For most AR diseases, carrier status will have no important clinical sequelae and individuals may be considered as potential donors. One exception is AR Alport syndrome (see section 5.12 Non-Visible Haematuria). In this disease, which accounts for ~15% of

Alport syndrome cases, carriers may manifest non-visible haematuria as a consequence of thin basement membrane disease due to mutation of the *COL4A3* or *COL4A4* genes. It remains unclear what the risk of progression to proteinuria and renal impairment is for carriers, although this has been described (4,5). Molecular testing can be used to confirm the diagnosis in the affected individual and carrier status in parents and other relatives. This will also have benefit in distinguishing AR from X-linked Alport syndrome. It is currently unclear whether mutation carriers who do not have non-visible haematuria on repeat testing can be donors. Despite this uncertainty, carriers with no renal abnormality by age 45 might be considered as donors in a similar manner to X-linked Alport syndrome.

X-linked (XL) conditions should be considered in pedigrees where there are isolated or several affected males. In X-linked conditions such as XL Alport syndrome and Dent's Disease, female carriers may manifest a phenotype as severe as males, or very minor abnormalities with a low likelihood of progression. In XL Alport syndrome, female carriers may develop ESRD (see section 5.12, Non-Visible Haematuria). The majority, >95%, will develop non-visible haematuria by adulthood but have a life-time risk of progressive renal disease of 5-20%. Gene testing for both conditions is available and is important for diagnostic confirmation and the carrier testing of other female family members. Therefore careful evaluation of renal function, possibly including renal biopsy, may be indicated in X-linked diseases to provide accurate risks for potential female donors who have been shown to be carriers.

In all familial renal diseases, if the familial mutation has been identified, a genetically related potential donor can be offered predictive genetic testing. This should only be offered by experienced individuals, usually via a regional clinical genetics service, because of the potential impact of identifying clinical or genetic status to an otherwise clinically asymptomatic individual. Anyone found to carry the familial mutation would normally be excluded as a potential donor if this predicts development of disease. They should also be referred for appropriate follow-up.

Genetic testing is currently available for diseases where a mutation has a high probability of predicting development of disease. This is largely confined to Mendelian diseases as discussed above. However, genetic determinants of complex diseases have also been identified. These tend to have a much smaller predictive value of developing disease and are relevant to populations and not families. A particular example is the association of *MYH9* variants with the development of FSGS in African Americans. Whilst mutations in

MYH9 can cause autosomal dominant diseases characterised by sensori-neural deafness, platelet abnormalities and renal disease e.g. Epstein Disease, other unidentified variants in the *MYH9* gene are associated with a lifetime risk of FSGS and hypertension associated ESRF of 0.8% and 2.25% respectively (6). Currently there are no prospective data on which to base recommendations for screening for what are also common variants in the normal population.

Disease status in an at-risk potential donor may also be determined by clinical assessment without genetic testing. This requires the use of appropriate screening tests and is straightforward for diseases such as ADPKD where robust criteria for the use of ultrasound screening have been produced. For some diseases such as UMOD associated nephropathy (OMIM 162000), the only abnormality may be a reduction in fractional excretion of urate (FE_{ur}), or in Dent's Disease the carrier status may only be revealed by measuring low molecular weight proteinuria.

Conditions in which renal dysfunction may be inherited and transplantation indicated for renal replacement therapy include the following:

Autosomal dominant:	ADPKD; Renal cysts and diabetes; Von Hippel Lindau disease; Familial haemolytic uraemic syndrome; Familial FSGS; Tuberose sclerosis complex; UMOD associated nephropathy; Nail patella syndrome.
Autosomal recessive:	ARPKD; Alport syndrome; Familial nephrotic syndrome.
X-linked:	Alport syndrome; Fabry disease; Dent's disease.
Polygenic:	VUR; FSGS.

In the majority of these conditions, the presence of disease in the potential donor precludes transplantation.

The most common inherited renal disease is ADPKD, which affects over 1:1000 individuals and is responsible for ~6% of UK patients receiving renal replacement therapy. The diagnosis of ADPKD in someone at 50% risk of being affected is based on the following recently revised ultrasound criteria (7):

- Three or more unilateral or bilateral cysts in individuals aged 15-39 years
- At least two cysts in each kidney for individuals aged 40 to 59 years
- At least four cysts in each kidney for individuals aged > 60 years

A negative renal ultrasound beyond the age of 40 years excludes disease. Between the ages of 20-40 years, a negative ultrasound should be followed by a CT or MRI scan. However, diagnostic criteria for CT and MRI have not been produced. Recent analysis of the UNOS database indicates better graft survival from genetically unrelated donors in ADPKD. As genetic testing for ADPKD has recently become available via the UKGTN, this may permit more accurate disease exclusion for donors when combined with radiological screening. Indeed, many units would not use a kidney from a relation under 30 years of a patient with ADPKD who had even just one renal cyst without mutation screening. Genetic testing may therefore be helpful where equivocal imaging studies do not allow formal exclusion of the diagnosis. Guidelines for the use of genetic testing for living related donors have been published and advice is also available via the UKGTN (8).

Vesico-ureteric reflux on the other hand is a condition where the genetic basis is unclear but where family studies show a high sibling recurrence risk and significant risk of inheritance (9). It affects around 1-2% of infants and is one of the most common reasons for transplantation in young adults. A careful search for evidence of reflux or its consequences should be undertaken in relatives being considered as donors. A history of childhood enuresis or urinary infections is common in affected individuals. Nuclear medicine scanning can detect renal scars and this can be used to look for indirect evidence of reflux in potential donors. Genetic testing is currently unavailable.

Sources of Information

The following websites may be consulted for up-to-date guidance regarding genetic disease and testing:

UK Genetic Testing Network (www.ukgtn.nhs.uk)
OMIM (www.ncbi.nlm.nih.gov/omim)
GeneReviews (www.ncbi.nlm.nih.gov/sites/GeneTests)
United Network for Organ Sharing (www.unos.org)
British Society of Human Genetics (www.bshg.org.uk)
National Genetics Education and Development Centre (www.geneticseducation.nhs.uk)

References

1. Kasiske BL, Ravenscraft M, Ramos EL, Gaston RS, Bia MJ, Danovitch GM. The evaluation of living renal transplant donors: clinical practice guidelines. Ad Hoc Clinical Practice Guidelines Subcommittee of the Patient Care and Education Committee of the American Society of Transplant Physicians. J Am Soc Nephrol 1996; 7: 2288-313.
2. Freedman BI, Volkova NV, Satko SG, et al. Population-based screening for family history of end-stage renal disease among incident dialysis patients. Am J Nephrol 2005; 25: 529-35.
3. Hildebrandt F. Genetic kidney diseases. Lancet 2010; 375:1287-95.
4. Marcocci E, Uliana V, Bruttini M, et al. Autosomal dominant Alport syndrome: molecular analysis of the COL4A4 gene and clinical outcome. Nephrol Dial Transplant 2009; 24: 1464-71.
5. Pierides A, Voskarides K, Athanasiou Y, et al. Clinico-pathological correlations in 127 patients in 11 large pedigrees, segregating one of three heterozygous mutations in the COL4A3/COL4A4 genes associated with familial haematuria and significant late progression to proteinuria and chronic kidney disease from focal segmental glomerulosclerosis. Nephrol Dial Transplant 2009; 24: 2721-9.
6. Kopp et al. 2010. Semin Nephrol 2010; 30: 409-417.
7. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; 20: 205-12.
8. Huang E, Samaniego-Picota M, McCune T, et al. DNA testing for live kidney donors at risk for autosomal dominant polycystic kidney disease. Transplantation 2009; 87: 133-7.
9. Cordell HJ, Darlay R, Charoen P, et al. Whole-genome linkage and association scan in primary, nonsyndromic vesicoureteric reflux. J Am Soc Nephrol 2010; 21: 113-23.

5.18 DONOR MALIGNANCY

Statements of Recommendation

- ***Careful history taking, clinical examination and investigation of potential donors are essential to exclude occult malignancy prior to kidney donation, particularly in older (age >50 years) donors. Active malignant disease is a contraindication to living donation, but donors with certain types of successfully treated low-grade tumour may be considered after careful evaluation and discussion. (B1)***

- ***Bilateral angiomyolipomata preclude living kidney donation. Kidneys containing lesions of 4 cm or larger should only be transplanted if ex vivo excision of the tumour is straightforward. Kidneys with lesions of 1 cm or smaller may be transplanted and followed with serial ultrasound imaging. Lesions between 1 cm and 4 cm in diameter need to be assessed on a case-by-case basis and the lack of evidence shared with the donor and recipient pair. (C1)***

The accidental transmission of malignant disease from donor (deceased or living) to recipient by kidney transplantation is well described and was relatively common before stringent donor criteria were enforced (1-6). In a US registry review of 154 cadaveric donors with known cancer, transmission occurred in 43% of recipients (70/154 donors to 103 recipients) (1). 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 this risk, care must be taken during evaluation of the potential living donor to ensure that a past medical history of malignant disease is recorded and that symptoms consistent with undiagnosed malignancy are identified.

During clinical examination, the possibility of occult malignancy should be borne in mind and care taken to exclude the presence of potentially malignant skin lesions, abdominal masses, breast lumps, testicular swelling and lymphadenopathy. Screening procedures applicable to the general population should have been carried out e.g. cervical screening, mammography, faecal occult blood for colorectal malignancy. A chest X-ray and imaging

of the renal tract should be carried out, and urine analysis to look for haematuria. Other tests such as PSA, tumour markers or screening for aortic aneurysm are not necessary unless indicated on the basis of history, clinical examination or routine investigation. It should be remembered that the risk of malignancy increases with age and that this effect is particularly marked over the age of 50; at least 75% of cancer cases are diagnosed in those over 65 years old (7).

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 cadaveric donors reveals that certain tumours seem to be particularly high risk e.g. renal cell, lung, breast, prostate and colonic carcinomas as well as lymphoma, glioblastoma multiforme and metastatic melanoma (6,8). It would seem prudent to exclude any potential donor with a history of these cancers. In contrast, other registry data have documented no evidence of tumour transmission, especially when most tumours were non-melanoma skin cancers or low-grade malignancies (9,10). Advice from the Amsterdam Forum for Living Donation in 2005 (11) is shown in Table 5.18.1.

The biology of the tumour should be considered and there is universal agreement that tumours with a propensity to late recurrence, e.g. breast cancer, malignant melanoma and sarcomas are an absolute contraindication to organ donation, irrespective of the tumour free interval. For other types of malignancy, it has been suggested that consideration for donation may be appropriate if there is no evidence of tumour recurrence after ten years (12). Factors such as the natural history of the disease, the grade, stage and site of the tumour and the disease-free interval must all be taken into account when assessing the risk of transmission.

If a donor with previously treated malignant disease is to be considered, it is important that the consent process includes a detailed discussion of risk with both the donor and the recipient. It should be made clear that transmission of malignant disease cannot be completely excluded (11). It is also important to bear in mind the possibility that should a potential donor develop recurrent malignancy, the presence of a solitary kidney may in certain situations be a major disadvantage, either because it may be affected directly by recurrent disease or indirectly by the additional treatment (e.g. chemotherapy) required.

Table 5.18.1 Previous cancer and fitness for living donation

Recommendation	Type of Cancer
Absolute contraindication	Melanoma Testicular cancer Renal cell carcinoma* Choriocarcinoma Haematological malignancy Lung carcinoma Breast cancer Monoclonal gammopathy**
Possible donation	Treated cancer with high probability of cure after 5-10 years (favourable classification and staging) e.g. colon cancer (Dukes A >5 years ago), non-melanoma skin cancer, carcinoma-in-situ of the cervix or vulva

* In some centres, donation may be considered where there is a small (<4 cm) subcapsular renal cell carcinoma with complete bench excision at the time of donor surgery and no distant spread.
** See also section 5.16.2 for a 2011 UK perspective

Angiomyolipomata

Angiomyolipomata of the kidney in a potential donor deserve particular comment. They are rare, benign neoplasms composed of mature adipose tissue, smooth muscle and thick walled blood vessels. With modern imaging techniques their diagnosis as well as their discrimination from the uncommon subtype of epitheloid angiomyolipoma, which may not have a benign phenotype, can usually be made without recourse to biopsy (13). The largest single series observing the natural history of isolated angiomyolipomata (not as part of tuberous sclerosis complex) comprises 29 patients followed for approximately four years (14). Four patients had bilateral tumours. A large proportion (40%) presented with symptoms: pain, a mass, haemorrhage or haematuria. This group would be predicted to have a more adverse outcome compared to incidental lesions discovered as part of living donor work up. The initial mean tumour size was 4.5 cm and 21% of tumours had grown at an average follow-up of 4 years (range 1 to 14 years). Overall, the proportion of

tumours that grew was double if the tumours were more than 4 cm in diameter at presentation.

For living donors, bilateral disease (whether proven angiomyolipomata or small renal cell carcinomas) would preclude donation. In unilateral disease, only the affected kidney should be considered for donation. If the tumour is 4 cm or larger, donation should only be contemplated if excision of the tumour is possible, because of the risk of subsequent symptoms. This approach has been published as case reports describing either *in*- or *ex vivo* (15-19) excision of angiomyolipoma of varying sizes from living donors with a successful outcome.

If the tumour is small, for example 1 cm or less, and its position makes removal particularly difficult, then donation followed by bi-annual ultrasound surveillance is reasonable and has also been published as a case report (20). For tumours between 1 cm and <4 cm in diameter, there is little evidence available and management will depend, in large part, on the position of the tumour.

References

1. Penn I. Transmission of cancer from organ donors. Ann Transplant 1997; 2: 7-12.
2. Wilson RE, Hager EB, Hampers CL, Corson JM, Merrill JP, Murray JE. Immunologic rejection of human cancer transplanted with a renal allograft. N Engl J Med 1968; 278: 479-83.
3. Matter B, Zukoski CF, Killen DA, Ginn E. Transplanted carcinoma in an immunosuppressed patient. Transplantation 1970; 9: 71-4.
4. Martin DC, Rubini M, Rosen VJ. Cadaveric renal homotransplantation with inadvertent transplantation of carcinoma. JAMA 1965; 192: 752-4.
5. Birkeland SA, Storm HH. Risk for tumor and other disease transmission by transplantation: a population-based study of unrecognized malignancies and other diseases in organ donors. Transplantation 2002; 74: 1409-13.
6. Buell JF, Beebe TM, Trofe J, et al. Donor transmitted malignancies. Ann Transplant 2004; 9: 53-6.
7. Cancer in the UK: July 2010. 2010. Accessed 11th August 2010, at http://info.cancerresearchuk.org/cancerstats/incidence/

8. Ison MG, Hager J, Blumberg E, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant 2009; 9: 1929-35.
9. Feng S, Buell JF, Cherikh WS, et al. Organ donors with positive viral serology or malignancy: risk of disease transmission by transplantation. Transplantation 2002; 74: 1657-63.
10. Kauffman HM, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. Transplantation 2000; 70: 1747-51.
11. Delmonico F. A report of the Amsterdam Forum on the care of the live kidney gonor: data and medical guidelines. Transplantation 2005; 79: S53-66.
12. Penn I. Donor transmitted disease: cancer. Transplant Proc 1991; 23: 2629-31.
13. Halpenny D, Snow A, McNeill G, Torreggiani WC. The radiological diagnosis and treatment of renal angiomyolipoma - current status. Clin Radiol 2010; 65: 99-108.
14. Steiner MS, Goldman SM, Fishman EK, Marshall FF. The natural history of renal angiomyolipomata. J Urol 1993; 150: 1782-6.
15. Chen A, Scherr D, Eid JF. Renal transplantation after in vivo excision of an angiomyolipoma from a living unrelated kidney donor. J Urol 2000; 163: 1859.
16. Bissada NK, Bissada SA, Fitts C, Rajagopalan PR, Nelson R. Renal transplantation from living related donor after excision of angiomylopoma of the donor kidney. J Urol 1993; 150: 174-5.
17. Johannes JR, Doria C, Lallas CD. In vivo partial nephrectomy of angiomyolipoma with concurrent transplantation. Can J Urol 2008; 15: 4184-7.
18. Hetet JF, Rigaud J, Blancho G, Renaudin K, Bouchot O, Karam G. Renal transplantation after excision of an angiomyolipoma on living donor kidney. Prog Urol 2004; 14: 205-6.
19. Sener A, Uberoi V, Bartlett ST, Kramer AC, Phelan MW. Living-donor renal transplantation of grafts with incidental renal masses after ex-vivo partial nephrectomy. BJU Int 2009; 104:1655-60.
20. Fritsche L, Budde K, Rogalla P, Turk I, Neumayer H-H, Loening SA. Successful living related kidney transplantation despite renal angiomyolipoma in situ. J Urol 1999; 162: 480-1.

CHAPTER 6 SURGERY: TECHNICAL ASPECTS, DONOR RISK AND PERI-OPERATIVE CARE

Statements of Recommendation

- ***Initial evaluation of renal anatomy in potential donors should include a renal ultrasound. Kidneys which differ significantly in size should be submitted to a split function isotope scan, and the kidney with poorer function should be selected for nephrectomy irrespective of vascular anatomy. (C2)***

- ***CT evaluation is at least as good as catheter angiography (CA) and digital subtraction angiography (DSA) in depicting the detailed vascular anatomy of donor kidneys. Sixteen slice CT machines may be superior to CA and DSA. MRI may be slightly inferior to CT evaluation. Both CT and MRI provide additional information about the renal parenchyma and urinary drainage of the kidneys. Both are less expensive than CA or DSA. (B1)***

- ***Multiple renal arteries or kidneys with anatomical anomalies are not absolute contraindications to donation. Decisions should be made on an individual basis as part of a multi-disciplinary meeting. (C2)***

- ***All living donors should receive adequate thromboprophylaxis. Intra-operative mechanical compression and post-operative compression stockings, along with low molecular weight heparin, are recommended. (A2)***

- ***All donor surgery should be performed or directly supervised by a consultant surgeon with appropriate training in the technique. (Not graded)***

- ***Pre-operative hydration with an overnight infusion and/or a fluid bolus during surgery may be beneficial for laparoscopic donor nephrectomy. (B2)***

- ***Laparoscopic donor surgery is the preferred technique for living donor nephrectomy, offering a quicker recovery, shorter hospital stay and less pain. Mini-incision surgery is preferable to standard open surgery. (B1)***

6.1 Introduction

Living donor nephrectomy is a major surgical operation. This section covers the pre-operative care and preparation, including the anatomical assessment of the donor, the nephrectomy, and the early post-operative care of the donor. Responsibility for the donor lies ultimately with the surgeon performing the donor nephrectomy but optimal peri-operative care depends on an effective multidisciplinary approach that includes key contributions from medical, nursing, anaesthetic, theatre and ward staff. The importance of effective communication between different team members cannot be over emphasised. Transplant units should have in place a written protocol detailing the peri-operative preparation and post-operative care of kidney donors. This should be reviewed annually and updated where necessary. The consent of the donor to undergo nephrectomy is made on the understanding that the operation will be performed by an experienced and competent surgeon and that all possible steps will be undertaken to reduce the incidence of peri-operative complications. Transplant units should regularly audit outcomes from living donor nephrectomy.

The risks associated with donor nephrectomy can be divided into pre-operative assessment, peri-operative risks and the long-term risks of life with a single kidney. The majority of donor nephrectomies in the UK are now performed laparoscopically, but this section will consider both the laparoscopic and open operation (including mini-incision), since all are still performed.

6.2 Assessment of Renal Anatomy

The use of kidneys with anatomical anomalies is now considered only a relative contraindication to donation by most experienced transplant centres. Relevant anatomical anomalies may include renal cysts, pelvi-ureteric junction obstruction, solitary stones <1 cm, duplex ureteric system, and multiple arteries and veins. Despite initial caution in the use of kidneys with multiple vessels, retrospective reports have suggested that kidneys with multiple renal artery or vein anomalies, such as circumaortic or retroaortic renal veins, do not carry an increased risk of complications in experienced hands (1).

6.2.1 Initial Evaluation

The imaging of kidneys prior to donor nephrectomy can be performed using several modalities including ultrasound (US), catheter angiography (CA), digital subtraction angiography (DSA), computed tomography (CT), and magnetic resonance angiography (MRA). All imaging modalities have both strengths and weaknesses. The preferred modality is one that can best assess the renal parenchyma, the urinary drainage system and the presence or absence of variant renal arteries, and which best anticipates complications during the transplant procedure.

Renal anatomy should be assessed during the donor evaluation to confirm the presence of two kidneys of normal size, and to exclude abnormalities such as hydronephrosis, pelvi-ureteric obstruction, renal cysts and nephrolithiasis. The simplest non-invasive investigation in this regard is an abdominal ultrasound. Although an IVU is considered to be useful by some, this involves submitting the donor to radiation and equivalent imaging can be performed as part of a subsequent evaluation by CT or MRI (see below). A difference in size of 2 cm or more between the kidneys indicates that a split function isotope scan should be considered (a difference in function of more than 10% between the kidneys may be considered significant). Usually the kidney with significantly lower function is selected for nephrectomy, irrespective of vascular anatomy.

Multiple renal cysts may indicate polycystic kidney disease, although 11% of individuals over the age of 50 will have one or more simple renal cysts. Family history is important, and in those with a family history of polycystic kidney disease under the age of 40 years, the presence of two or more cysts (unilateral or bilateral) indicates autosomal dominant polycystic disease (APKD) (2). It should be noted that a negative scan in this age group is associated with a 4% false negative rate, and even the presence of a single cyst is of sufficient concern that advice should be sought regarding genetic testing (section 5.17). For those aged 40 to 59 years, the absence of at least two cysts in each kidney gives a 100% negative predictive value for APKD, whilst for those older up to four cysts are acceptable in each kidney. It is, however, important to be aware that polycystic disease can arise from spontaneous mutations, and that a family history may not always be evident. Kidneys with large simple cysts (>2 cm) are likely to be suitable for donation but should undergo review in a multidisciplinary meeting including a radiologist, and may require further cross-sectional imaging.

6.2.2 Vascular Anatomy

Approximately 25% of potential donors will have multiple arteries to one kidney and around 7% will have multiple vessels to both kidneys (3). A donor kidney with a single renal artery should, whenever possible, be chosen for transplantation; similarly, single renal veins are usually preferred. If both kidneys have single vessels, the left kidney is usually selected for donation because the longer renal vein on this side facilitates implantation.

Multiple renal arteries are associated with an increased incidence of complications in the recipient but do not adversely influence patient or graft survival (1). It may be acceptable to use a kidney with multiple renal arteries and/or veins for transplantation, provided that the surgeon responsible has the necessary experience in reconstructing the vasculature of the kidney. Decisions should be made on an individual basis (4). Imaging is often helpful to identify early arterial bifurcation and short renal arteries prior to the donor nephrectomy, and to anticipate the need for additional vascular reconstruction.

6.2.3 Final Evaluation

Prior to donor nephrectomy, all donors should undergo a detailed evaluation of vascular and ureteric anatomy by CT or MR scanning. Since these investigations have a small but defined risk for donors and are relatively costly, they are usually performed as the final investigation during the process of donor evaluation. Definition of arterial anatomy is important to select the most appropriate kidney for donation. CT has been shown to have a high (98%) correlation with operative findings (5,6). MR angiography may also be used, although the sensitivity at detecting accessory arteries may be lower (7,8). Both modalities can be used to assess venous anatomy, although variations in venous drainage such as duplex or retro-aortic renal veins or large lumbar veins are not normally considered as contraindications to donation on that side. Similarly, assessment of ureteric anatomy and exclusion of nephrolithiasis can be performed with either modality, and a duplex ureter is not normally considered to be a contraindication to donation.

Although several case series have been published comparing the use of CT angiography with MR angiography in the preoperative assessment of living kidney donors, there appears to be little difference in accurately characterising the renal vasculature prior to donation (9). It is important to recognise that local preference and facilities may affect the preferred imaging modality, and this is perfectly acceptable in light of published evidence and local expertise.

Nephrolithiasis is considered separately (see section 5.15).

6.3 Peri-operative Mortality

In the USA, good data from retrospective studies show that the peri-operative mortality is approximately 1 in 3,000 after open living donor nephrectomy (10-13). More recently, a large study of over 80,000 donors in the US considered all donors reported using the national mandatory reporting system and showed the 90 day mortality to be 3.1 in 10,000 donations (95% CI 2.0-4.6), despite increasing age and obesity in the donor population (14). Mortality was higher in men than in women (5.1 vs. 1.7 per 10,000 donors), in black vs white and Hispanic individuals (7.6 vs. 2.6 and 2.0 per 10,000 donors), and in donors with hypertension vs. those without hypertension (36.7 vs. 1.3 per 10,000 donors). However, the long-term risk of death was no higher for living donors than for age- and comorbidity-matched NHANES III patients, both overall and stratified by age, sex, and race.

In the UK, a study published in 2007 of 2,509 donors showed no peri-operative deaths based on complete Registry data including 601 laparoscopic cases (15). Prior to 1998, two known peri-operative donor deaths had been reported in the UK (16). One was due to myocardial infarction and one to pulmonary embolus. Since the inception of the UK Transplant Living Donor Registry in 2000, three further deaths have been reported, from 3 to 18 months post nephrectomy, from a cohort of 958 donors (0.3%). Two were due to myocardial infarction/ischaemic heart disease (at 3 and 14 months) in donors who were 60 and 53 years old respectively. A third death was due to cancer of the uterus (at 14 months) in a 67 year-old donor. Although occurring relatively soon after surgery, it is not clinically plausible that these events were directly related to the process of donation.

The most common causes of death after living donation are pulmonary emboli, hepatitis and cardiac events (myocardial infarction and arrhythmia) (11,17,18). It has been pointed out that these death rates are comparable with the annual risk of dying in a road traffic accident in the USA (0.02%) (13).

6.4 Peri-operative Morbidity

Many studies of morbidity after donor nephrectomy do not give definitive estimates of the morbidity rate as non-standard, differing classifications are used, and large series are often from single centres of excellence. Notwithstanding these problems, the reported peri-operative complication rates for living donor nephrectomy have been summarised for a large number of single centre studies (13). The mean overall complication rate was 32% and the major peri-operative complication rate was 4.4%. The estimated 'major complication' rate in a survey by Bay and Hebert (12) was 1.8%, whereas the American Society of Transplant Physicians (ASTP) survey (10) reported that 22 out of 9,692 (0.23%) kidney donors experienced 'potentially life-threatening or permanently debilitating' complications.

In the UK, analysis of Registry data with mandatory reporting has shown the major morbidity rate after laparoscopic donor nephrectomy to be 4.5%, and 5.1% for open nephrectomy (no significant difference) (15). The rate of any morbidity was 10.3% for laparoscopic surgery and 15.7% for open surgery (p=0.001). In a review of 10,828 living donor nephrectomies performed in the USA between January 1999 and June 2001, reoperation rates were 0.4% for open donors and 1% and 0.9% for hand-assisted and non-hand-assisted laparoscopic surgery respectively (p=0.001) (19). Complications not requiring reoperation were 0.3%, 1% and 0.8% respectively (p=0.02). However, this study was based on a retrospective survey of transplant centres with a 73% response rate.

Randomised controlled trials (see section 6.8.3) comparing open, mini-incision (MODN) and laparoscopic donor nephrectomy (LDN) have not allowed an adequate comparison of the rates of complications between these techniques. The only trial of MODN versus (totally) laparoscopic donor nephrectomy (TLDN) was a small study with 50 patients in each group. This found the incidence of intra-operative complications to be 12% during TLDN and 6% in MODN (p=0.49), with postoperative complications at 6% in each group (20). Blood loss was less after TLDN (100 v 240 ml, p<0.001). Although a meta-analysis (21) suggested that complication rates were less after MODN when compared with open surgery and equivalent between MODN and LDN, this only included the single randomised trial mentioned above. Table 6.4.1 gives complication rates reported in these trials.

Table 6.4.1 Complication rates following donor nephrectomy (20)

Complication	**Open nephrectomy (5,660) %**	**Laparoscopic hand assisted (2,239) %**	**Full laparoscopic nephrectomy (2,929) %**
Re-operation	0.4	1.0	0.9
Complications not needing re-operation	0.3	1	0.8
Bleeding	0.15	0.18	0.45
Bowel obstruction	0.05	0.27	0.1
Bowel injury	-	0.1	0.14
Hernia	0.18	0.5	0.03
DVT/pulmonary embolus	0.02	0.09	0.1
Pneumothorax	0.09	0.05	-
Prolonged ileus	-	0.05	0.06
Rhabdomyolysis	-	0.09	0.13
Readmission rate	0.6		1.6

Of the four trials comparing open surgery and LDN, one did not report complications (22), one found no difference in complication rates (23), one study of 122 patients found an 8% major complication rate after TLDN compared with none after open surgery (24), and one study of 84 patients found a complication rate of 0.3 per donor after TLDN compared with 0.6 per donor after open surgery (p=0.03) (25). A meta-analysis which included these trials concluded that there was no difference in post-operative complication rates between laparoscopic and open surgery (26). However, there is no trial comparing complication rates after hand-assisted laparoscopic donor nephrectomy with open surgery.

Specific complications that require special mention include wound related problems such as sepsis, hernia and chronic pain; the impact of conversion from laparoscopic to open surgery (1-3%); blood loss and the requirement for blood and blood products (which donors may find unacceptable e.g. Jehovah's Witnesses); and finally the cosmetic consequences, especially of open surgery.

Irrespective of the type of incision, wound pain is a major source of anxiety for the donor. The incidence of prolonged wound pain following laparoscopic surgery is difficult to determine but a figure of 3.2% should be regarded as realistic (19). A small number of patients may require referral to a pain clinic. A recent UK centre report of 123 donors undergoing open nephrectomy reported that 12% of donors experienced chronic disabling pain and 14% neuropathic pain (26).

6.5 Long Term Mortality

Counselling prospective living kidney donors about the potential of long-term risk to health is an essential part of the pre-operative management of the prospective donor. Recent data have shown that long term survival after donor nephrectomy is at least equal to a matched cohort. A large study of over 80,000 donors reported through the mandatory reporting system in the US, with only 24 donors excluded from follow-up, showed that survival was no worse than that of a cohort of over 9,000 controls matched for age and co-morbidity, over a period of 6 years (14). Similarly, a study of 3,698 donors showed no difference in survival at up to 40 years after donation when compared with a group of age, sex and ethnicity matched controls (27).

The best quality information on late mortality following donor nephrectomy comes from Sweden (28). A single unit in Stockholm performed 459 living donor nephrectomies over a 20 year period from 1964 onwards. All 430 donors still living in Sweden were traced and actual survival was compared to national mortality rates. The cause of death in the kidney donors was similar to that seen in the general population: most deaths were due to cardiovascular disease and cancer. Actuarial survival at 20 years was 85% compared to an expected survival rate of 66%. This result suggests that the donor work up in Stockholm ensured that only healthy individuals proceeded to donation and encouraged the authors to select as a title for their publication 'Kidney donors live longer'.

6.6 Pre-operative Care and Preparation

6.6.1 General Considerations

Living donor surgery must be carried out by a team with adequate expertise, in an environment where donors are regularly cared for. A senior anaesthetist with experience of managing such patients should be present. It is recommended that a transplant unit should undertake at least 20-30 living donor operations per annum, to ensure that adequate expertise is maintained, and should regularly audit its results. Each donor surgeon should maintain up to date surgical experience, and should also audit his or her individual results.

6.6.2 DVT Prophylaxis

Deep venous thrombosis and pulmonary embolism remain major causes of morbidity and mortality after major surgery, and living kidney donors are no exception to this. They should be classified as 'medium risk' patients, even if undergoing laparoscopic surgery and the NICE approved thromboprophylaxis policy should be followed (29). This entails applying the DH risk assessment tool to all donors on admission and grading the 'relative risk' of venous thromboembolism (VTE), which includes the potential risk of bleeding and which will help to inform the best form of prophylaxis. Factors such as age >60 years, dehydration, known thrombophilia, obesity (BMI >30 kg/m^2), personal history or first-degree relative with a history of VTE, use of HRT, use of oestrogen-containing contraceptive therapy, and varicose veins with phlebitis must all be taken into account. Details are available at http://guidance.nice.org.uk/CG92.

The relative risk of VTE with laparoscopic versus open procedures has not yet been investigated in depth. Based on the pathophysiology of VTE, factors that may heighten the risk with laparoscopy are the duration of the procedure (>90 minutes), patient positioning, and the effect of the pneumoperitoneum. Conversely, shorter hospital stays and more rapid post operative mobilisation should decrease the risk (30). Typically this will mean the use of mechanical compression during surgery and both TED stockings and LMWH following surgery until discharge (31).

Early mobilisation (on the first postoperative day) is recommended. Donors with a personal history of DVT or PE who undergo surgery are at high risk of developing further venous thromboembolism (30% within 5 years) and should be screened to exclude significant thrombophilia, as should any potential donors with a family history (first or second degree relative) of VTE. In such cases, donation may not be precluded but advice should be sought from a haematologist (32). Any donors deemed high risk should have prolonged prophylaxis following discharge for at least 7 to 14 days. New oral anti-thrombotic agents should be considered in the future, such as dabigatran etexilate.

6.6.3 Prophylactic Antibiotics

There is no evidence for the use of prophylactic antibiotics in donor surgery, although some centres do use a single dose at induction. Local practice should be followed and further research is required in order to make a definitive recommendation.

6.6.4 Consent and Site Marking

Standard practice for major surgery is to seek written consent prior to admission, and reconfirm this on admission for surgery. The site should be marked and confirmed with the patient before leaving the ward for theatre. The appropriate imaging must be available in theatre and standard safety checks, usually involving the WHO checklist (33), should be performed prior to the start of surgery.

6.6.5 Blood Transfusion

Blood is rarely needed during donor nephrectomy, but when it is the case it may be needed urgently. All donors should be ‘group and saved’ and surgery should only take place where adequate facilities for provision of urgent blood products are available. All donors should be counselled about the potential risk of bleeding and the use of blood and blood products, especially donors with specific religious affiliation such as Jehovah’s

Witnesses. Where blood transfusion is refused or contraindicated, the use of a cell saver may be indicated.

6.7 Donor Nephrectomy

6.7.1 General Considerations

A Consultant surgeon should perform or supervise living donor surgery. Donor and recipient operations may be carried out sequentially or using parallel lists; the latter is preferred where complex, high risk recipient surgery is undertaken, to ensure that the recipient operation can continue before kidney extraction is performed. Whichever method is employed, dedicated elective lists must be available.

In the majority of UK centres, the donor and recipient operations are undertaken synchronously in parallel operating theatres staffed by two full teams of theatre personnel. This minimises cold ischaemic time and ensures that the kidney is removed from the donor only after it has been confirmed that there are no unforeseen problems with the recipient that might prevent implantation. Sequential donor and recipient operations are also acceptable and have been shown to give equivalent outcomes in several uncontrolled and one controlled series (34).

6.7.2 Peri-operative Fluids

There is some evidence that aggressive peri-operative fluid management is beneficial in laparoscopic donor nephrectomy (35). In this small randomised trial of 24 patients, pre-operative hydration prevented the intra-operative reduction in stroke volume and creatinine clearance seen in the control group. Ideally, hydration should involve an overnight infusion of fluid and a bolus during surgery. Some units use intravenous mannitol or loop diuretics during surgery but there is limited human evidence for this. A useful approach is to use trans-oesophageal Doppler guidance to titrate intravenous fluid replacement, and this is used by some transplant centres in the UK (36,37).

6.7.3 Type of Surgery

Donor nephrectomy may be performed using a standard open technique, a mini-incision (MODN), or laparoscopically, using a hand-assisted (HLDN) or ‘totally laparoscopic’ (TLDN) approach. The minimally invasive techniques (TLDN, HLDN) have now been widely adopted as the standard surgical approach by many transplant units in the UK and

worldwide. Laparoscopic operations may be performed trans- or retro-peritoneally. There is one randomised trial of MODN versus laparoscopic donor nephrectomy (20), and one meta-analysis (21). There are four randomised trials of laparoscopic versus open surgery (22,23,25,38) and one meta-analysis (39). Laparoscopic surgery has been shown to result in a quicker recovery, shorter hospital stay (by 1.6 days, $p<0.001$) and less pain and a quicker return to work (by 2.4 weeks, $p<0.001$) than standard open surgery, with comparable complication rates (39). Operative time may, however, be longer after laparoscopic surgery. Mini-incision surgery results in a quicker recovery compared with open surgery, but more pain than laparoscopic surgery (21). One small study compared HLDN with TLDN and found no difference in outcomes (38). An ongoing trial (the HARP study) will compare retroperitoneal HLDN with transperitoneal TLDN (40).

6.7.4 Preferred Kidney and Vasculature

The left kidney is usually preferred, assuming both kidneys have equal numbers of arteries, due to the greater length of the left renal vein. One randomised trial comparing right and left laparoscopic donor nephrectomy showed no difference in complication rates but a shorter operating time for right nephrectomy (41). Great care must be taken when selecting which kidney to remove. Surgery on a kidney with a short artery risks encroaching on the bifurcation of the renal artery and may result in two arteries to implant which is technically more challenging; while efforts to secure a single vessel in the donor may result in avulsion of the artery from the aorta with associated risks to the donor.

It is recommended that the side of donor nephrectomy is selected and documented at a multi-disciplinary meeting which includes a review of the vascular imaging, and that the potential donor is informed of any increased risk associated with this decision. Numerous reports exist showing safe and successful laparoscopic surgery in the presence of multiple arteries and veins, as well as in obese patients. Although there are increased anaesthetic and peri-operative risks in patients with these conditions, they do not constitute absolute contraindications to laparoscopic surgery.

6.7.5 Training for Laparoscopic Surgery

Laparoscopic donor nephrectomy is a complex operation with potentially high risks. It should only be undertaken by those who have been appropriately trained in the technique, and should not be performed on an occasional basis. Difficult cases may require help from an experienced mentor.

6.7.6 Pain Relief

Early post-operative pain is the most frequent complaint after living donor surgery. The laparoscopic technique does not require the use of an epidural, but PCA and a 'pain ladder' approach may be useful. Early mobilisation, ideally the day after surgery, is preferred, and in this regard newer pump devices which provide continuous analgesia for mobile patients may be useful.

References

1. Hsu TH, Su LM, Ratner LE, Trock BJ, Kavoussi LR. Impact of renal artery multiplicity on outcomes of renal donors and recipients in laparoscopic donor nephrectomy. Urology 2003; 61: 323-7.
2. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; 20: 205-12.
3. Weinstein SH, Navarre RJ, Loening SA, Corry RJ. Experiences with live donor nephrectomy. J Urol 1980; 124: 321-3.
4. Kälble T, Lucan M, Nicita G, Sells R, Burgos Revilla FJ, Wiesel M. EAU guidelines on renal transplantation. Eur Urol 2005; 47: 156-66.
5. Rajamahanty S, Simon R, Edye M, Butt K, Eshghi M. Accuracy of three-dimensional CT angiography for preoperative vascular evaluation of laparoscopic living renal donors. Endourol 2005; 19: 339-41.
6. Lewis GR, Mulcahy K, Brook NR, Veitch PS, Nicholson ML. A prospective study of the predictive power of spiral computed tomographic angiography for defining renal vascular anatomy before live-donor nephrectomy. BJU Int 2004; 94: 1077-81.
7. Kim JC, Kim CD, Jang MH, et al. Can magnetic resonance angiogram be a reliable alternative for donor evaluation for laparoscopic nephrectomy? Clin Transplant 2007; 21: 126-35.
8. Israel GM, Lee VS, Edye M, et al. Comprehensive MR imaging in the preoperative evaluation of living donor candidates for laparoscopic nephrectomy: initial experience. Radiology 2002; 225: 427-32.
9. Gluecker TM, Mayr M, Schwarz J, et al. Comparison of CT angiography with MR angiography in the preoperative assessment of living kidney donors. Transplantation 2008; 88; 1249-56.
10. Bia MJ, Ramos EL, Danovitch GM, et al. Evaluation of living renal donors. The current practice of US transplant centers. Transplantation 1995; 60: 322-7.

11. Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992; 340: 807-10.
12. Bay WH, Hebert LA. The living donor in kidney transplantation. Ann Intern Med 1987; 106: 719-27.
13. Kasiske BL, Ravenscraft M, Ramos EL, Gaston RS, Bla MJ, Danovitch GM. The evaluation of living renal transplant donors: clinical practice guidelines. J Am Soc Nephrol 1996; 7: 2288-313.
14. Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA. 2010; 303: 959-66.
15. Hadjianastassiou VG, Johnson RJ, Rudge CJ, Mamode N. 2509 living donor nephrectomies, morbidity and mortality, including the UK introduction of laparoscopic donor surgery. Am J Transplant. 2007; 7: 2532-7.
16. Bakran A. Postal survey of living donor kidney transplant units. Presented at the Symposium “Meeting the challenges of live donation”. Royal College of Physicians, 21 April 1998.
17. Bennett AH, Harrison JH. Experience with living familial renal donors. Surg Gynecol Obstet 1974; 139: 894-8.
18. Uehling DT, Malek GH, Wear JB. Complications of donor nephrectomy. J Urol 1974; 111: 745-6.
19. Matas AJ, Bartlett ST, Leichtman AB, Delmonico FL. Morbidity and mortality after living kidney donation, 1999-2001: survey of United States transplant centers. Am J Transplant. 2003; 3: 830-4.
20. Kok NF, Lind MY, Hansson BM, et al. Comparison of laparoscopic and mini incision open donor nephrectomy: single blind, randomised controlled clinical trial. BMJ 2006; 333: 221.
21. Antcliffe D, Nanidis TG, Darzi AW, Tekkis PP, Papalois VE. A meta-analysis of mini-open versus standard open and laparoscopic living donor nephrectomy. Transpl Int 2009; 22: 463-74.
22. Wolf JS Jr, Merion RM, Leichtman AB, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. Transplantation 2001; 72: 284-90.
23. Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. BJU Int 2005; 95: 851-5.

24. Øyen O, Andersen M, Mathisen L, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. Transplantation 2005; 79: 1236-40.
25. Nicholson ML, Kaushik M, Lewis GR. Randomized clinical trial of laparoscopic versus open donor nephrectomy. Br J Surg 2010; 97: 21-8.
26. Owen M, Lorgelly P, Serpell M. Chronic pain following donor nephrectomy – a study of incidence, nature and impact of chronic post nephrectomy pain. Eur J Pain 2010; 14: 732-4.
27. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-69.
28. Fehrman-Ekholm I, Elinder C-G, Stenbeck M, Tyden G, Groth CG. Kidney donors live longer. Transplantation 1997; 64: 976-8.
29. NICE Guidance on VTE. www.nice.org.uk/guidance/CG92
30. Kakkar AK. Prevention of venous thromboembolism in general surgery. In: Colman RW, Clowes AW, George JN, Goldhaber SZ, Marder VJ, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006: 1361-7.
31. Roderick P, Ferris G, Wilson K, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health Technol Assess 2005; 9: iii-iv, ix-x, 1-78.
32. British Society for Haematology (BSCH) Guidelines, Investigation and Management of Heritable Thrombophilia, 2001. www.bcshguidelines.com/guidelinesMENU.asp
33. Editorial. WHO's patient-safety checklist for surgery. Lancet 2008: 372; 1148-9.
34. Baverstock RJ, Manson AD, Liu L, Gourlay WA. A prospective comparison of simultaneous and sequential live-donor renal transplantation. Transplantation 2002; 74: 1194-7.
35. Mertens zur Borg IR, Di Biase M, Verbrugge S, Ijzermans JN, Gommers D. Comparison of three perioperative fluid regimes for laparoscopic donor nephrectomy: A prospective randomized dose-finding study. Surg Endosc 2008; 22: 146-50.
36. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 2008; 63: 44-51.
37. Walsh SR, Tang T, Bass S, Gaunt ME. Doppler-guided intra-operative fluid management during major abdominal surgery: systematic review and meta-analysis. Int J Clin Pract 2008; 62: 466-470.

38. Andersen MH, Mathisen L, Oyen O, et al. Postoperative pain and convalescence in living kidney donors - laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant 2006; 6: 1438-43.
39. Nanidis TG, Antcliffe D, Kokkinos C. Laparoscopic versus open live donor nephrectomy in renal transplantation: a meta-analysis. Ann Surg 2008; 247: 58-70.19.
40. Dols LF, Kok NF, Terkivatan T, et al. Hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy: HARP-trial. BMC Surg 2010; 10: 11.
41. Minnee RC, Bemelman WA, Maartense S, Bemelman FJ, Gouma DJ, Idu MM. Left or right kidney in hand-assisted donor nephrectomy? A randomized controlled trial. Transplantation 2008; 85: 203-8.

CHAPTER 7 HISTOCOMPATIBILITY TESTING FOR LIVING DONOR KIDNEY TRANSPLANTATION

Statements of Recommendation

- ***Initial assessment of donor and recipient histocompatibility status should be undertaken at an early stage in living donor kidney transplant workup to avoid unnecessary and invasive clinical investigations. (B2)***

- ***Screening of potential living donor kidney transplant recipients for clinically relevant antibodies is important for ensuring optimal donor selection and graft survival. (A1)***

- ***Antibody screening is especially important when potential living donor recipients reduce or withdraw immunosuppression. (B2)***

- ***Post-transplant antibody monitoring should be undertaken according to the BSHI/BTS guidelines. (B1)***

- ***Transplant units and histocompatibility laboratories should agree an evidence-based protocol to define crossmatch results which constitute a veto to transplantation. (B2)***

- ***A pre-transplant serum sample collected within 14 days of the planned date for transplantation must be tested in a sensitive crossmatch and if the crossmatch test is positive transplantation should not usually be performed, unless the antibody is shown to be indicative of acceptable immunological risk. (A1)***

- ***Changes in immunosuppression during the transplant work-up should be notified to the histocompatibility laboratory and additional antibody screening and donor-recipient crossmatch tests undertaken as required. (B1)***

- ***HLA matching should be considered of benefit when there is an option of selecting between living donors, particularly in reducing the possibility of subsequent sensitisation. This is important for younger recipients where repeat transplantation may be required. However, it is recognised that other donor factors will be taken into account. (B1)***

- ***The histocompatibility laboratory should issue an interpretive report stating the donor and recipient HLA mismatch, recipient sensitisation status and crossmatch results, and define the associated immunological risk for all living donor-recipient pairs. (A1)***

Policies defining histocompatibility requirements for living donor kidney transplantation should be jointly established between the clinical transplant team and the consultant histocompatibility scientist in each centre. There are three components to the histocompatibility assessment: determination of donor-recipient HLA mismatch status; identification of alloantibodies in patient serum that could be potentially harmful to a transplanted organ; and confirmation of antibody compatibility by performing a donor-recipient crossmatch. The results of these investigations provide a risk assessment, which together with clinical information provide guidance on the suitability of a particular living kidney donor-recipient pair for transplantation. These guidelines are applicable to ABO blood group compatible, HLA antibody compatible transplants and are to be read in conjunction with the BSHI/BTS 'Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation' (1). The BTS has separate guidelines for ABO Blood Group and HLA Antibody Incompatible (HLAi) Transplantation (2).

Initial assessment of donor and recipient histocompatibility status should be undertaken at an early stage in the donor workup to avoid unnecessary and invasive clinical investigations. Histocompatibility assessments and interpretation of test results should only be undertaken in an appropriately accredited laboratory (e.g. Clinical Pathology Accreditation (CPA)/European Federation for Immunogenetics (EFI)) by scientists with specialist training in Histocompatibility & Immunogenetics, as demonstrated by FRCPath or equivalent level qualification and experience. The onus is on the referring centre to provide appropriate information and donor and recipient samples necessary to fulfil these guidelines.

7.1 Assessment of Donor-Recipient HLA Mismatch Status

In the absence of preconditioning protocols, the choice of a living donor is restricted by the requirement for ABO blood group compatibility. HLA typing of the recipient and all potential living donors should be performed using DNA-based methods to at least two digit (low) resolution for HLA-A, -B, -C, -DR and -DQ and the donor-recipient mismatch determined. The level of donor and recipient HLA compatibility is usually expressed as an HLA-A, -B and -DR mismatch grade determined from the number of donor HLA specificities at each locus that are absent in the recipient. A donor and recipient with no HLA-A, -B, -DR incompatibilities is denoted '000', whereas a fully mismatched combination is denoted '222'. In the case of transplants between siblings there is a 1 in 4 chance of inheriting the same two HLA bearing parental haplotypes, a 1 in 2 chance of sharing one parental haplotype and a 1 in 4 chance of sharing no parental haplotypes. Thus in the case of genetically related donors, ABO blood group and HLA typing results can indicate the familial relationship and therefore informed consent must be obtained by the referring centre from both the recipient and all genetically related potential donors before these tests are undertaken (see section 4.3).

Selection of the most suitable donor for a particular recipient is complex and the HLA mismatch grade will be considered together with other factors such as donor and recipient age and alternative options for transplantation both now and in the future (section 7.4 and Chapter 11).

7.2 Identification and Characterisation of Alloantibodies

Pre-transplant antibody screening

The presence of pre-transplant HLA specific antibodies that are reactive against mismatched donor HLA is potentially harmful to a transplanted kidney and therefore a policy for the detection of such antibodies must be rigorously implemented. Immunological sensitisation can arise through exposure of the potential recipient to allogeneic tissue bearing foreign HLA, such as transfusion of blood products, pregnancy (including miscarriage and terminated pregnancy), and previous transplants. HLA specific alloantibodies can also arise naturally through crossreactivity with pathogens, when they are termed idiopathic antibodies.

It is essential for the laboratory to have accurate information about the timing and nature of all potential allosensitisation events, throughout the patient's lifetime. Recent and past potential allosensitisation events, including recent infections, must be documented by the referring clinical team and reported to the histocompatibility laboratory. Recipient serum samples must be obtained for HLA specific antibody screening at least every three months, and additional samples collected at 14 and 28 days after transfusion of any blood products. Potential recipients who are receiving immunosuppression while being assessed for living kidney transplantation are at high risk of de-novo sensitisation, particularly if immunosuppression is changed, reduced or withdrawn. It is the responsibility of the clinical team to notify the histocompatibility laboratory of such changes and additional serum samples should be obtained for HLA specific antibody screening at four weeks after any change in immunosuppression.

Recipient sera must be tested for HLA specific alloantibodies according to the BSHI/BTS guidelines (1) and HLA specificities to which the patient is sensitised should be identified as unacceptable mismatches. In cases where HLA-DP specific antibodies are detected in recipient serum, donor-recipient HLA-DP status and potential HLA-DP specific antibody incompatibility should be determined. Recipients that have donor HLA specific antibodies (unacceptable mismatches) identified in recent and/or past (historic) serum samples should be referred for formal immunological risk assessment by the clinical team and, where appropriate, may be considered for HLAi transplantation. These discussions should take place at the earliest opportunity, to avoid delay and unnecessary clinical investigation.

In many cases, the living donor kidney transplant workup may be prolonged and it is not uncommon for a year or more to elapse between the initial histocompatibility assessment and the planned operation. During this period, the antibody compatibility status of the potential recipient and donor(s) must be monitored and any changes in the patient's antibody profile should be reported to the transplant team. The recipient must have contemporary antibody screening results available using samples obtained within three months of the transplant operation. Any potential alloantibody priming events that occur within one month of the latest antibody screening sample, or after the sample collection date could change the donor-recipient antibody compatibility status and will obviate all previous results.

Post-transplant antibody screening

Monitoring of HLA specific antibodies in recipient serum after the transplant operation can provide helpful prognostic information for the diagnosis of antibody-mediated rejection and to guide post-transplant rejection treatment, antibody reduction therapy and choice of maintenance immunosuppressive therapy. Post-transplant antibody monitoring should be undertaken according to the BSHI/BTS guidelines (1).

7.3 Pre-transplant Donor-Recipient Crossmatch Test

A prospective pre-transplant donor-recipient crossmatch test is performed to confirm the presence or absence of donor HLA specific alloantibodies. The results can only be interpreted in conjunction with knowledge of pre-transplant alloantibody priming events, donor-recipient HLA mismatches and pre-transplant antibody screening results. In the case of donor-recipient combinations where donor HLA specific antibodies are present in recipient serum, the crossmatch test can provide information about antibody levels and the associated immunological risk (3). Pre-formed donor HLA specific antibodies present in recipient serum can cause hyperacute and acute rejection and there should be close liaison between the histocompatibility laboratory and the clinical team.

Living kidney donor crossmatch tests should be carried out according to the BSHI/BTS Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies, and tested using lymphocytes isolated from donor peripheral blood (1). Because of the opportunity for planned living donor transplant work-up, a virtual crossmatch is not acceptable. Living donor crossmatch testing is usually carried out at the time of first referral. The final crossmatch must always be undertaken using a serum sample obtained within 14 days of the planned operation date. This time frame minimises the risk of a change in recipient antibody status, but any potential alloantibody priming event around the time of the final crossmatch will obviate the results.

The selection of recipient serum samples for crossmatch and choice of target cell type (i.e. donor peripheral blood lymphocytes, isolated donor T lymphocytes and/or B lymphocytes) and the technique used (complement dependant lymphocytotoxicity [CDC] and/or flow cytometric [FC] crossmatch) will depend on previous alloantibody priming events and pre-transplant antibody screening results, and should conform to the BSHI/BTS guidelines (1). It is recommended that allosensitised recipients with pre-formed

HLA class I and/or class II specific alloantibodies and recipients awaiting repeat transplantation should undergo donor T lymphocyte (for HLA class I sensitised patients) or T and B lymphocyte (for HLA class II sensitised patients) flow cytometric crossmatching as a minimum. Undertaking a CDC donor T and B lymphocyte crossmatch using untreated and dithiothreitol (DTT) treated recipient serum can provide further information for risk stratification (3). Result interpretation and acceptable immunological risk stratification should be undertaken according to local policy and BSHI/BTS guidelines. A positive donor lymphocyte crossmatch test performed using DTT treated sera by CDC carries a high immunological risk of hyperacute rejection and constitutes a veto to transplantation, unless an effective HLAi strategy is used to minimise the risk of graft failure.

Careful consideration must be given to the sensitisation status and crossmatch results for proposed transplants where recipient allosensitisation priming has previously occurred through exposure to the donor HLA, either directly (e.g. offspring donor to mother) or indirectly (shared donor HLA haplotype in spousal/partner donation to female recipient following pregnancy, or repeat transplants using a second related donor). The occurrence of an anamnestic immune activation of latent donor alloantigen specific lymphocytes and uncontrolled graft rejection has been observed following crossmatch negative male to female spousal transplantation and this risk may be pre-empted and minimised by using sensitive antibody screening methods, appropriate crossmatch techniques and tailored immunosuppression.

A further important consideration relates to patients undergoing living donor kidney transplant assessment following a previous failed or failing kidney transplant that remains in situ. Such patients often have immunosuppression reduced or withdrawn during the period of clinical workup, because of a desire to reduce unnecessary medication. This is frequently associated with the development of de-novo HLA specific antibodies to the allograft which cause a previously unexpected positive crossmatch and which then preclude future transplantation from an HLA mismatched living donor. Consideration must be given to the relative risk of maintaining recipient immunosuppression during the donor workup, the benefit of immunosuppressive drug reduction or withdrawal, and the risk of de-novo allosensitisation. A reduction or cessation of immunosuppression within one-month of the planned operation date is contraindicated and may delay or preclude transplantation. As a minimum, this would necessitate additional antibody screening and

donor-recipient crossmatch tests to be undertaken using a current serum sample obtained within 24 hours before the transplant operation.

7.4 Selection of Suitable Donor-Recipient Pairs

The presence of donor specific HLA antibodies or a positive crossmatch in a sensitised patient is a contraindication to transplantation unless desensitisation protocols are employed. In a sensitised patient, a well matched donor is more likely to be antibody compatible than a poorly matched donor. Transplants between siblings offer the best opportunity for a well matched graft because of familial inheritance of HLA genes. As described above, kidney transplants from offspring to mother or from a father to the mother of his children should be approached with caution, but where HLA sensitisation is excluded and a negative crossmatch achieved, transplant outcomes are equivalent to those for other non-HLA identical living donor transplants (4,5).

A widely cited publication of the experience of living unrelated spousal donor kidney transplantation in North America showed that graft survival rates for such transplants was equivalent to that of HLA mismatched living related donor kidney transplants (5). This equates with the current UK experience (see Chapter 11). The Collaborative Transplant Study (CTS) found a significant reduction in graft survival when living donor kidney transplants were mismatched at HLA-A, -B and -DR (4). CTS analysis of more than 5,000 living unrelated donor transplants performed between 1995 and 2002 showed a highly significant influence of HLA matching on graft survival (6), but survival of even the worst matched kidneys was better than seen in deceased donor transplantation. However, a more recent analysis of the UK Transplant registry of living donor kidney transplants performed between 2000 and 2007 did not show an influence of HLA matching on transplant outcome (7).

A key point is that when a poorly matched kidney transplant fails because of rejection, the recipient is at high risk of becoming highly sensitised (1), restricting options for repeat transplantation. This is particularly relevant for paediatric recipients and young adults who are likely to require re-transplantation within their lifetime and for whom avoiding sensitisation, particularly to common antigens, is important. Children are often registered on the transplant list with mismatched parental HLA specificities listed as unacceptable to avoid sensitisation against these prospective living donors. In contrast, in the context of

older spouse couples where a second transplant is unlikely, the risk of sensitisation is not a major concern.

7.5 Antibody Incompatible Living Donor Transplantation

Antibody incompatible transplantation (AiT) may be an option for some patients who have a potential living donor but where there is a specific immunological barrier to transplantation. Such transplantation falls into two categories: ABO incompatible transplantation, where transplantation occurs across an ABO blood group barrier (e.g. from a blood group B donor to a blood group O recipient); and HLA-incompatible transplantation, where the recipient has high titres of antibodies against one or more specific HLA antigens present in the donor.

Both forms of transplantation are becoming more common in the UK and will in future make major contributions to expansion of the living donor pool. Close liaison between clinicians and histocompatibility laboratories is obviously critical for such transplantation, which should be initially concentrated in units with particular expertise.

The BTS has published specific guidelines on antibody incompatible transplantation, which should be referred to (2). The following summary points are derived from these guidelines:

Recommendations (Not graded)

- *Antibody incompatible transplantation (AiT) should be considered as part of an ongoing structured programme, and should not be performed on an occasional basis.*

- *To initiate a programme, a unit should be able to demonstrate a demand of at least 5 cases a year and appropriate support from clinical transplant, plasmapheresis and histocompatibility teams. An AiT programme requires funding for additional staff and consumables, and all programmes should receive Commissioner support.*

- *There is insufficient evidence to make precise recommendations for treatment protocols, but units should have a written protocol based on best published practice. This should include recommendations on prevention, diagnosis and treatment of antibody mediated rejection.*

- *Protocols that follow the above can be regarded as established treatment and do not require Ethics Committee approval as research procedures. However, the standard of consent should include detailed written information which describes the risks of the procedure. The transplant donor should receive equivalent information to the recipient, so they are aware of the risks of the procedure to the recipient, whether it results in a transplant or not. Potential recipients and donors should be aware of their treatment choices, especially the option of exchange (pooled/paired) transplantation.*

- *Laboratories should be able to define antibodies to the standard defined in the BSHI/BTS document 'Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Solid Organ Transplantation'. Sensitive and rapid techniques for the measurement of donor-specific HLA antibody levels must be available.*

- *If ABOi transplantation is to be performed, blood group antibody titres need to be measured, with differentiation between A1 and A2 subgroups of recipient blood group A (when appropriate) and discrimination between IgG and IgM specific for ABO antibodies. In living donor transplantation, a 7 day per week service with same day turn-around time is required.*

- *AiT is able to provide successful transplantation for significant numbers of patients, potentially up to 20% of the total living donor transplant programme nationally.*

- *AiT should be supported because of the improvements in quality of life after transplantation compared to dialysis. Additionally, many patients receiving antibody incompatible transplants may have no other chance of a transplant. Transplantation is cost effective over time with a saving of about £15,000 per annum compared to dialysis when averaged over a 10 year period*

- *Every patient undergoing antibody incompatible transplantation should be audited on a local and national basis, with the national audit through the AiT Registry.*

- *The UK AiT Registry will define the optimal dataset to be collected, and will be able to report AiT activity against benchmark outcome data from international reports and the national dataset of renal transplantation.*

References

1. Guidelines for the detection and characterisation of clinically relevant antibodies in allotransplantation. British Society for Histocompatibility and Immunogenetics and British Transplantation Society, 2010. http://bts.demo.eibs.co.uk/transplantation/standards-and-guidelines/
2. Guidelines for Antibody Incompatible Transplantation. British Transplantation Society. http://bts.demo.eibs.co.uk/transplantation/standards-and-guidelines/
3. Taylor CJ, Kosmoliaptsis V, Summers DM, Bradley JA. Back to the future: application of contemporary technology to longstanding questions about the clinical relevance of human leukocyte antigen-specific alloantibodies in renal transplantation. Human Immunol 2009; 70: 563-8.
4. Opelz G. Impact of HLA compatibility on survival of kidney transplants from unrelated live donors. Transplantation 1997; 64: 1473-5.
5. Terasaki PI, Cecka JM, Gjertson DW, Cho YW. Spousal and other living donor transplants. In: Clinical Transplants 1997. Eds Cecka JM, Terasaki PI. UCLA Tissue Typing Laboratory, Los Angeles, USA. pp 269-84.
6. Collaborative Transplant Study Newsletter 2004; 2, May 1. www.ctstransplant.org
7. Fuggle SV, Allen JE, Johnson RJ, *et al*. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. Transplantation 2010; 89: 694-701.

CHAPTER 8 EXPANDING THE DONOR POOL

Statements of Recommendation

- ***All donor and recipient pairs who are incompatible by blood group and/or HLA type are entitled to a full appraisal of the available treatment options, tailored to their individual circumstances, so that they can make an informed decision about their choice of treatment. (C1)***

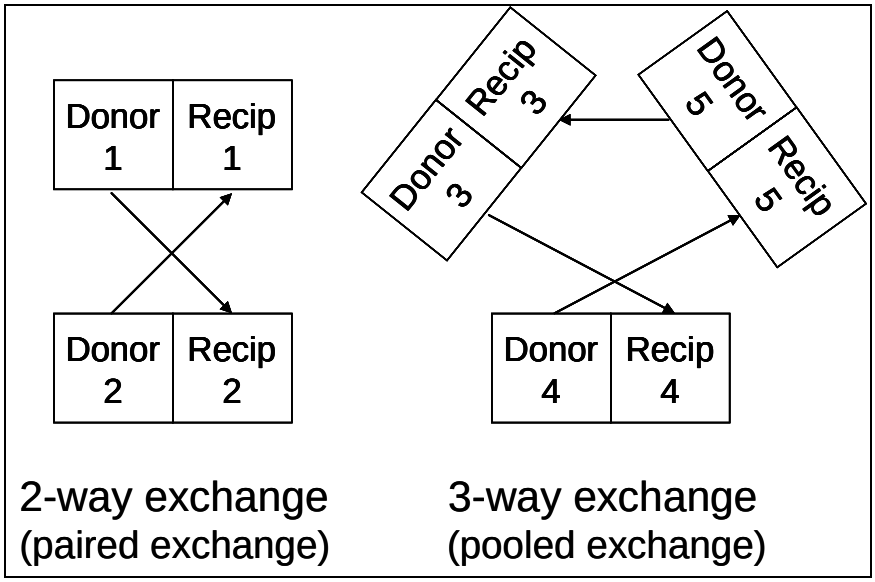
- ***Coherent organisational processes and clinical practices between transplant centres are essential to optimise the benefits of living donor kidney sharing schemes and to maximise the number of potential transplants that proceed. (B1)***

8.1 Paired/Pooled Living Donation

From September 2006, the Human Tissue Act enabled paired donation in the UK. A national scheme was established whereby incompatible donor-recipient pairs can exchange kidneys so that recipients can receive alternative compatible living donor organs. Exchanges are identified between two or three incompatible pairs (Figure 8.1). It is also possible to register compatible pairs into the scheme in order to achieve a more favourable HLA or age match for the recipient concerned.

The paired/pooled scheme presents some logistical challenges which need careful co-ordination and administration to ensure that the use of kidneys is optimised and maximum patient benefit is achieved.

Figure 8.1 Two and three-way exchanges



Registration in the scheme

Only donor/recipient pairs who have been fully evaluated and deemed suitable to proceed to donation/transplantation can be registered for the scheme and entered into the matching runs. In order to have the correct information available at the time of the run, NHSBT specifies deadlines for registration of potential pairs prior to each matching run. This is usually 3 weeks before the quarterly run with a further opportunity to suspend or activate pre-registered pairs (positively confirm registration) up to 7 days before the run. Deadline dates for registration and dates of matching runs are published in advance by NHSBT. As part of the registration process it is possible to attach a maximum acceptable donor age in addition to any HLA match requirements. These restrictions may seriously limit the chances of a match, however, and should only be applied where necessary. They must be specified at the time of registration and re-confirmed at activation prior to each matching run.

For each centre and/or referring hub there is a nominated contact from the living donor co-ordinator team who is responsible for ensuring that all eligible pairs are registered and their status appropriately updated at the specified time points. Key responsibilities for the nominated contact include:

- Close collaboration with the histocompatibility and immunogenetics (tissue typing) laboratory to ensure HLA antibody screening is up to date before each matching run.
- Close collaboration with clinical colleagues to ensure that donor & recipient assessment is up to date.
- Particular donor information that is relevant to the acceptance of a kidney by a recipient centre should be cited with the registration. These include the presence of complex donor vasculature, borderline GFR, stone disease in the kidney to be donated, and donor hepatitis B core antibody positivity.
- Contact with both donor and recipient individually to confirm their commitment to enter/remain in the scheme and to ensure that no issues have emerged since the last matching run which might preclude them. It is particularly important that donor/recipient pairs understand the implications and expectations of participation in the scheme and the impact of late withdrawal (after pairs have been matched) on other pairs should they decide not to proceed. This should not override their right to withdraw consent at any time, but is sensible to highlight in advance to minimise the risk of later ambivalence.
- Collation and confirmation of information to register/positively confirm the participation of relevant pairs in the scheme at the notified times. This includes specifying preferences for acceptable HLA and age match criteria, if relevant (see above).

Matching runs

There are currently four matching runs per year, at approximately quarterly intervals. At the time of a matching run, all potential matches within the pool are identified and evaluated according to a scoring system. Scoring is necessary to decide, in some cases, which of multiple possible transplants for a single recipient is optimal. Identification of possible matches takes into account any donor age or HLA restrictions specified at the time of registration. Scoring is based on a number of factors including the calculated level of sensitisation (to promote matches for sensitised patients where such are identified); the HLA mismatch level of the potential transplant (to promote good matching where possible); and the age difference between the two donors. The latter acts as a tie-breaker and ensures that, as far as possible, the exchange is fair in terms of expected outcome. It is inevitable that the scheme will evolve, however, and up-to-date matching arrangements can be found on the ODT website (www.organdonation.nhs.uk).

Experts in matching algorithms collaborate with NHSBT to ensure that the number of transplants and the scores of different possible alternatives are optimised over all possibilities involving both 2-way and 3-way exchanges. There are usually 100-160 pairs in any one matching run and typically 10-30 transplants may be identified.

When a matching run has taken place, the nominated scheme leads are notified electronically and a hard copy report is provided specifying the donor/recipient pairs that have been successfully matched. The nominated scheme leads in transplanting centres are then responsible for:

- Liaising with local nominated scheme leads in referring centres and/or notifying the donor/recipient pairs from their centre that they are in a potential match, but emphasising that this cannot be confirmed until the initial crossmatch has been performed between all pairs. Recipients should be reminded that they are automatically suspended from the deceased donor list at this time until confirmation of the initial crossmatch test. The initial crossmatch should be arranged as soon as possible after the matching run and within a maximum of 14 days. In the event of a positive crossmatch, the recipients from the matched group will be reinstated on the national deceased donor list unless an alternative match within the same group can proceed.
- Liaising with local leads and living donor co-ordinators in the other participating centres to arrange initial crossmatching, exchange of donor information, scheduling of surgery and pre-admission requirements, including Independent Assessment and HTA approval (see Chapter 3). Transport arrangements for essential samples and organs on the day of the transplant should be co-ordinated via NHSBT transport or an equivalent courier service to ensure door to door collection and delivery.
- Updating the Scheme Co-ordinator within NHSBT of the progress of the matched group, in particular the outcomes of crossmatch results and potential problems that may prevent surgery proceeding or delay the scheduled date of surgery.
- Liaising with the wider in-centre team to facilitate arrangements for admission, co-ordinating the start of synchronised lists on the day of surgery and ensuring colleagues are updated and informed throughout the process.

Special considerations

It is important to manage the expectations of donor/recipient pairs entering the paired/pooled scheme. The potential benefit from a compatible living donor transplant (or improved HLA- or age-matched transplant for compatible pairs) must be tempered by

specific information giving a realistic expectation of the likelihood of being matched, tailored to their particular circumstances (e.g. degree of sensitisation, blood group mismatch etc).

The greatest chance of success in identifying a possible transplant is for unsensitised incompatible pairs where the donor is blood group A and the recipient is group B, or vice-versa (about a third of such pairs registered for the scheme have achieved a paired donation transplant). HLA incompatible pairs where the donor is blood group O and the recipient is blood group A with only moderate levels of sensitisation also have a good chance of transplantation as there are many A donor, O recipient pairs in the scheme. In general for sensitised patients, 20-30% achieve a transplant where the calculated sensitisation is <95%, with <5% of patients achieving a paired donation transplant where sensitisation is $\geq$95%.

Even if a potential match is identified for a particular pair, the transplant may not proceed if the crossmatch test results are not acceptable. There have also been a number of other reasons why identified potential transplants have not proceeded (e.g. donor or recipient becoming unfit for transplant). Overall, about 1 in 5 registered patients successfully receive a paired donor transplant.

Donors and recipients need to be aware of how the scheme works, the registration requirements, and their responsibilities as participants within it. There are some key considerations:

- All donor/recipient pairs are entitled to an option appraisal of the treatment choices that are available to them. Practices vary between centres, but in HLA or high titre ABO blood group incompatible scenarios, it is often recommended to suggest two attempts in the paired scheme before considering alternative interventions. There should not be an expectation that the longer one stays in the scheme, the greater the chance of transplantation, as this is unlikely to be true.
- Multiple donors with different HLA types and blood groups can be assessed and registered for a single recipient, to increase the potential for matching.
- Registration in the paired scheme does not preclude listing for a deceased donor kidney.
- Recipients considering antibody removal treatment must be suspended from the paired scheme if such treatments are initiated using agents (e.g. Rituximab®) that could influence the interpretation of a crossmatch with a paired donor.

- Donor/recipient pairs must be made aware of the implications of late withdrawal on other matched pairs and should be encouraged to consider this carefully prior to registration in the scheme and at the time of each subsequent matching run (see above).

Transplants and outcomes

On the day of transplantation it is usual for the kidneys, rather than the patients, to travel between donor and recipient hospitals. This is not a requirement and other arrangements can be made if all parties agree. Donor operations start simultaneously at the induction of general anaesthesia for the donors, with contact either directly between the donor surgeons or indirectly via the living donor co-ordinators to ensure that both operations proceed and that the kidneys are dispatched to the recipient hospital at the expected time. Cold ischaemia times have averaged about five hours in the scheme. To streamline the transplant process and prevent delay at the time of implantation, the retrieved kidney should be appropriately prepared in the retrieval centre so that it is ready for implantation into the recipient on arrival.

One year transplant survival rates (not censored for patient death) are comparable for paired donation transplantation and other forms of living donor transplantation, but the longer term outcomes are not yet known.

Anonymity

The scheme relies upon anonymity between matched donor and recipient pairs to avoid disclosure of identity prior to donation/transplantation (1). This should be emphasised to donors and recipients, and all members of the transplant team need to be vigilant about the exchange of information and conscious of the confidentiality issues involved to avoid inadvertent disclosure. This is particularly challenging when two or more pairs are matched within the same centre and consideration needs to be given to the admission arrangements, proximity of operating theatres, and where donor/recipient pairs are cared for during their inpatient stay. Anonymity can be broken with the consent of all parties after the exchange transplant has been performed and it is recommended that this is facilitated through the respective living donor co-ordinators.

Future Developments

See the end of section 8.2 for information about developments to the National Living Donor Kidney Sharing Schemes, including altruistic donor chains.

8.2 Non-Directed Altruistic Donation

Non-directed altruistic donors (NDAD) have been able to donate kidneys following the implementation of the Human Tissue Act in 2006. Non-directed donors who fulfil all the assessment criteria and wish to proceed with donation are notified to NHSBT for the identification of a recipient.

Registering an altruistic donor offer

A donor is registered with NHSBT once he or she has been fully evaluated, including mandatory mental health assessment and HTA Approval, and is deemed suitable to proceed to donation. There are particular considerations about the lack of proximity between the donor and recipient which are unique to NDADs and which must be carefully explored during the assessment process, so that there are realistic expectations about feedback after transplantation. Registration is usually facilitated by the living donor co-ordinator in the referring centre or in the transplant centre where the donor assessment and/or donor surgery will be performed. Once an offer has been accepted in principle, the living donor co-ordinators in donor and recipient centres liaise to arrange the initial crossmatching, exchange of donor information, scheduling of surgery and pre-admission arrangements. Some principles of best practice have been established:

- Particular donor information that is relevant to the acceptance of a kidney by a recipient centre should be cited with the registration. These include the presence of complex donor vasculature, borderline GFR, stone disease in the kidney to be donated, and donor hepatitis B core antibody positivity.
- If the NDAD is donating directly to a recipient on the national transplant waiting list, the preferred timeframe for the donor surgery can be cited with donor registration, but specific dates should not be applied in order to provide flexibility between donor and recipient centres.
- Wherever possible the donor's wishes should be accommodated regarding the timing of surgery and a date for surgery should be negotiated between the donor and recipient centre within 6 weeks of the offer being made.
- If a preferred timeframe is cited and the recipient centre cannot accommodate the offer and an alternative date cannot be negotiated, the offer should be passed to another centre before the potential recipient is informed about the kidney offer.

Allocation process

Upon receipt of the registration form, NHSBT will enter the details into the national database, run the matching process and notify the donor's transplant coordinator of the outcome within three working days.

National allocation arrangements have been agreed for these kidneys, in which the NHSBT Duty Office offers the kidney to the most suitable recipient on the deceased donor transplant waiting list using the allocation scheme for deceased donor kidneys. Offers are made through the living donor co-ordinator team in the recipient transplanting centre. The allocation scheme prioritises patients with a 000 HLA-A, B, DR mismatch with the donor, giving first priority to paediatric patients (<18 years) and then to highly sensitised patients. Seventy-five percent of kidneys are offered to less well matched patients, however, and this is done according to a number of factors, of which the most important are the waiting time on the list and the age/HLA match combined. Full details can be found on the ODT website (www.organdonation.nhs.uk).

The allocation of kidneys from NDADs will be subject to different arrangements in future in order to optimise the use of available organs for transplantation through altruistic donor chains (see end of section), but the basic principles will remain consistent.

Receiving an altruistic donor offer

After an offer of a kidney from a NDAD has been made through the Duty Office, the living donor co-ordinators are responsible for liaising with appropriate colleagues to facilitate the transplant process according to local arrangements.

Key considerations:

- The timing of donor/recipient surgery is subject to negotiation between the participating centres but consideration should be given to the preferences of the donor and the expectations of both donor and recipient if it is envisaged that a timely date cannot be accommodated.
- Prior to accepting an offer in principle and **before** informing the potential recipient, any rate-limiting steps must be identified as a priority (e.g. recipient clinical issues, centre logistics, suitability of offer for particular recipient). Once the recipient has been informed about the offer, expectations have been raised and it is difficult to retract if it is not appropriate to proceed. The donor will also be subjected to delay if the decision to accept is prolonged.

- Initial crossmatching between donor and recipient should be facilitated within 14 days of the offer being made unless exceptional circumstances apply.
- Transport arrangements for essential samples (crossmatching) and organs on the day of transplant should be co-ordinated via NHSBT transport or an equivalent courier service to ensure door to door collection and delivery. Costs should be met by the recipient centre.
- The Duty Office within ODT should be kept informed of the progress of the potential transplant, and in particular the outcomes of crossmatch results, potential problems or delays that may prevent surgery proceeding, and the scheduled date of surgery.
- If the donor and recipient are within the same centre, the recipient and donor co-ordinators should liaise with the wider in-centre team regarding arrangements for admission, in-patient stay, and surgery and ensuring colleagues are informed about the anonymity requirements.
- To streamline the transplant process and prevent delay at the time of implantation, the retrieved kidney should be appropriately prepared in the retrieval centre so that it is ready for implantation into the recipient on arrival.

Anonymity

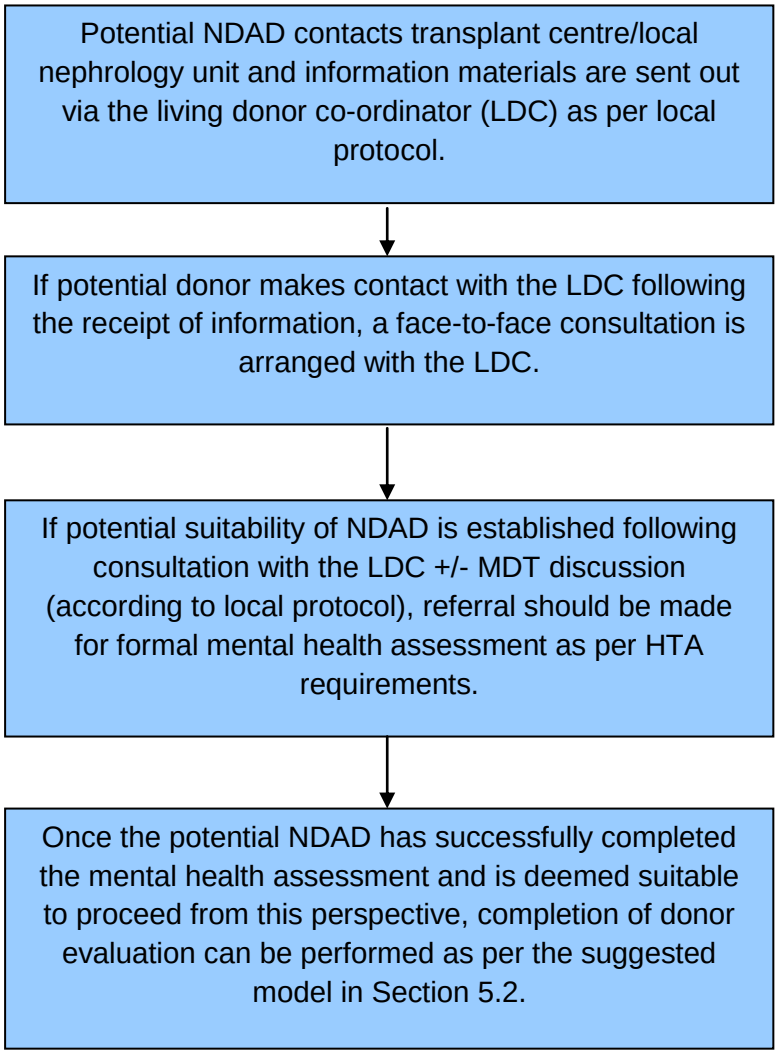
Anonymity between the donor and recipient prior to surgery is required (1). The donor and recipient and all members of the transplant team need to be vigilant about the exchange of information and conscious of the confidentiality issues involved to avoid inadvertent disclosure, particularly when a donor is matched to a recipient within the same centre. Although this is not as logistically challenging as the paired/pooled situation, similar consideration needs to be given to admission arrangements, proximity of operating theatres and where the donor and recipient are cared for during their in-patient stay. After the transplant has been performed, anonymity can be broken with the consent of both parties and it is recommended that this is facilitated through the respective living donor co-ordinators.

Special considerations

Experience to date suggests that there are particular considerations that should be taken into account in the assessment of NDADs in order to streamline the evaluation process and manage the expectations of the donor. The attrition rate from this programme, i.e. the number of donors who are unsuitable for donation or who exit the programme, is higher than for most other aspects of living donation and this can lead to disappointment for the potential donor and additional work for the clinical team. It is recommended that the

mandatory mental health assessment is performed at an early stage of the evaluation process, as this reduces the risk of donor withdrawal and helps to support the potential donor in the decision-making process. A suggested model for NDAD evaluation is shown in Figure 8.2.

Figure 8.2 Suggested model for assessment of NDADs



The ‘stand alone’ NDAD scheme differs from the paired/pooled scheme in that there is no specific requirement for the recipient to be automatically suspended from the deceased donor list when an offer of a kidney has been made, or even when the initial crossmatch has been performed.

It is clearly in the best interests of the recipient to receive a kidney from a living donor and so consideration should be given to the relative risk of removing the potential recipient from the national waiting list whilst finalising the arrangements for transplantation and at which time point this should happen. There is also the potential disruption to the donor if the recipient is offered a kidney from an alternative donor during this period, as the option of proceeding with a different recipient may be refused. As a minimum standard, discussion must be initiated with the recipient about suspension from the national list at the time of the offer, and again following the outcome of initial crossmatching. The recipient transplant centre is then responsible for activating that decision with ODT.

If a kidney is offered to a recipient and the date of surgery is subsequently postponed, a decision has to be made about re-offering the kidney, depending upon the reason for the delay. Without betraying confidential information, this decision should involve the donor as he or she may be willing to reschedule for the same recipient if it is a problem that is likely to resolve (e.g. PD peritonitis). If it is a more permanent issue, clinical or otherwise, it may be advisable to re-offer the kidney with the donor’s agreement.

Future allocation arrangements

Changes to the National Living Donor Kidney Sharing Schemes will be introduced in late 2011. Allocation arrangements for NDAD kidneys will be enhanced to allow NDADs to benefit more than one recipient by allocation of their kidney through the paired/pooled donation programme. The agreement is that unless a high priority patient is identified on the deceased donor transplant list (000 mismatched child or 000 mismatched, highly sensitised adult), the kidney will be allocated instead to a patient in the paired/pooled donation programme who is compatible with the donor. In turn, the donor registered with the ‘paired’ recipient would then donate to a patient on the deceased donor waiting list through the national allocation scheme. This is called an altruistic donor chain. Longer chains involving two or more paired donation couples are also anticipated. When this programme is implemented, full details will be available on the ODT website (www.organdonation.nhs.uk).

Donor reimbursement for paired/pooled and altruistic donors

Special considerations for donors within these groups have been identified and are addressed in Chapter 9.

8.3 Antibody Incompatible Donation

Antibody incompatible transplantation (AiT) may be an option for some patients who have a potential living donor but where there is a specific immunological barrier to transplantation. Such transplantation falls into two categories: ABO incompatible transplantation, where transplantation occurs across an ABO blood group barrier (e.g. from a blood group B donor to a blood group O recipient); and HLA-incompatible transplantation, where the recipient has high titres of antibodies against one or more specific HLA antigens present in the donor.

Both forms of transplantation are becoming more common in the UK and will in future make major contributions to expansion of the living donor pool.

The BTS has published specific guidelines on antibody incompatible transplantation, which should be referred to. These are also summarised in section 7.5.

Sources of Information

NHS Blood and Transplant. www.nhsbt.org.uk or www.organdonation.nhs.uk
Human Tissue Authority. www.hta.gov.uk
British Transplantation Society, Standards & Guidelines.
http://bts.demo.eibs.co.uk/transplantation/standards-and-guidelines/

Reference

1. Human Tissue Authority, Code of Practice 2, Donation of Solid Organs for Transplantation, July 2009. http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code2donationoforgans.cfm

CHAPTER 9 LOGISTICAL CONSIDERATIONS

Statements of Recommendation

- ***The reimbursement of legitimate expenses incurred by a living donor as a direct result of the preparation for an act of donation is supported by the Department of Health. Prospective agreement for reimbursement from local recipient commissioners is currently recommended as the most effective mechanism for achieving reimbursement but a national scheme is being developed which will replace this guidance in the near future and this guidance will be updated accordingly. (B1)***

- ***Donors from overseas present unique logistical challenges. In order for the process to be clinically effective and to comply with UK Border Agency and Department of Health requirements, there is an agreed entry clearance (visa) application process and duration of stay in the UK (6 months) for the donor which must be honoured in all but exceptional, unforeseen circumstances. (B1)***

9.1 Reimbursement of Living Donor Expenses

The reimbursement of reasonably incurred expenses to a living donor, including loss of earnings which are directly attributable to the organ donation, is supported by the HTA and the Department of Health (DH) (1,2) Reimbursement does not contravene the current UK legislation under the Human Tissue Act (3) (see Chapter 2: Legal Framework) which forbids payment for supplying a human organ, provided that the donor does not gain any financial advantage as a result.

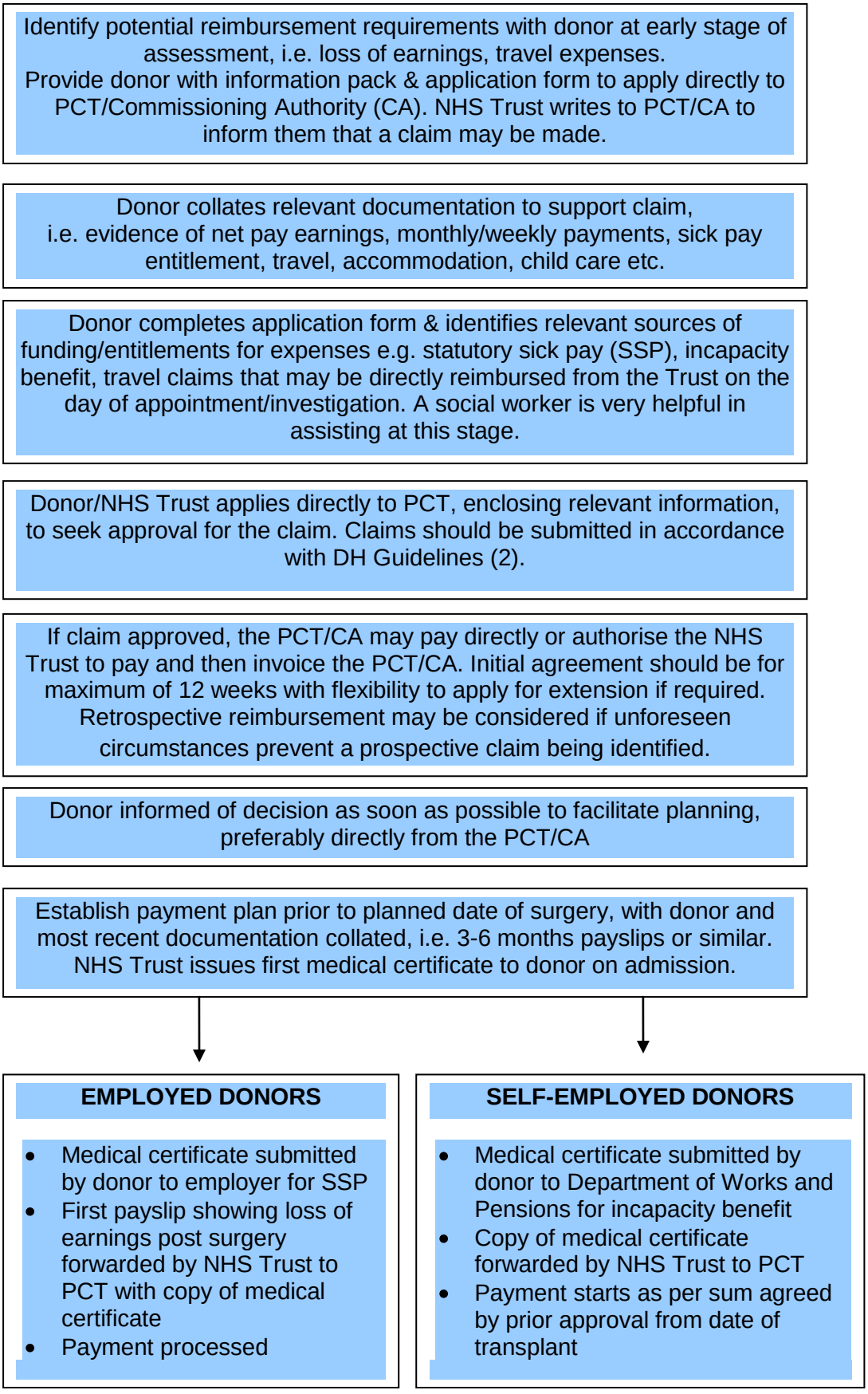
The NHS is not legally obliged to make such payments, but the DH recognises that the most cost effective treatment for end stage kidney disease is transplantation and that the costs incurred as a direct result of performing a living donor transplant are justified. The DH expects that suitable arrangements will be made as part of local commissioning agreements between the recipient's Commissioning Consortium or Authority (e.g. Scotland/Channel Islands) and the NHS Trust in which the transplant is performed.

Whilst some regions are well organised, there is no universal consensus about how such arrangements are implemented and there is considerable variability at local level. Despite the lack of standardisation, progress has been made in agreeing some key principles that underpin the application and approval processes to prevent delay in settling claims:

- Individual claims should be settled in a timely fashion to prevent unnecessary financial hardship to the donor as a consequence of the donation
- Claims will be settled by the recipient Commissioning Consortium/Authority on a case by case basis according to agreed criteria
- Early identification of potential claims during the donor assessment period is essential to facilitate prior approval and timely settlement
- Early notification to relevant Commissioning Consortium/Authority of claim must be made and, whenever possible, prior to the date of donation to facilitate timely settlement. However, provision should be available for considering claims retrospectively if, for genuine reasons, it has not been possible to highlight a prospective claim to the Commissioning Consortium/Authority
- Donor expectations about the nature and size of claims that will be approved must be appropriately managed
- Donors must be provided with appropriate and specific information about criteria for application, approval processes and timeframes at an early stage of the assessment process
- Alternative sources of reimbursement, e.g. statutory sick pay, must be declared when a donor applies for reimbursement

The current system still lacks consistency and is often time-consuming to administer. The development of a centrally administered, national scheme for England is under development and it is envisaged that the implementation of such a scheme will help to streamline processes across the UK and facilitate best practice between England and the existing schemes within the devolved administrations. A suggested model for best practice in effective claims management is outlined in Figure 9.1.

Figure 9.1 Best Practice Model for Reimbursement of Living Donor Expenses



9.2 Paired/Pooled and Non-Directed Altruistic Donors

In cases of paired/pooled donation and non-directed altruistic donation, living donor kidneys are shared and exchanged across the UK between different transplant centres, which may be subject to different mechanisms of donor reimbursement. In both scenarios, there is limited time to obtain prior approval for donor reimbursement from the recipient's Commissioning Consortium/Authority because dates for surgery are set as soon as possible following a paired/pooled matching run and/or non-directed altruistic donor offer.

It is recommended that in cases of paired/pooled donation, an application to the local recipient Commissioning Consortium/Authority is made by the local donor at the time of registration into the scheme in the same way as for a direct living donation (as above). This would facilitate prior approval of anticipated expenses and timely reimbursement when the transplant proceeds. Reciprocity between each donor/recipient pair means that the costs to the local Commissioning Consortium/Authority are likely to be equitable.

In cases of non-directed altruistic donation, there is no direct reciprocity between the donor and recipient transplant centres unless the kidney is allocated by chance to a local recipient through the national allocation scheme. However, any recipient in the UK may be a potential beneficiary of such a kidney and, as non-directed altruistic donor activity continues to increase, it is important to have clarity about the mechanism for donor reimbursement. Local resolution with Commissioning Consortia/Authorities is problematic because of the time constraints previously highlighted for prospective application. The preferred option would be for recipient Commissioning Consortia/Authorities to undertake to reimburse donors in this situation without prior approval, provided that the claim meets the agreed financial criteria for settlement. With changes to the National Living Donor Kidney Sharing Schemes due to be implemented towards the end of 2011, the same principles will apply in the altruistic donor chain scenario if local reimbursement arrangements are still in place.

9.3 Donors from Overseas

Donors from overseas present unique logistical challenges. Representatives from the UK Border Agency (UKBA), the HTA and the transplant community have worked together to overcome commonly encountered issues around overseas donors who wish to travel to

the United Kingdom to donate. This joint collaboration has facilitated a full discussion around the perceived definition of provision of funding to overseas donors. It has also enabled a review of existing processes for the potential overseas donor‘s application for entry clearance (visa) to travel to the UK to donate to UK recipients. The following issues have been considered:

- The DH Guidance emphasises the importance of avoiding donor reimbursement from the recipient or his/her family, which could be seen as an inducement to donate.
- The DH Guidance emphasising that the recipient is ordinarily resident in the UK and not subject to the National Health Service (Charges to Overseas Visitors) Regulations 1989, as amended, or their equivalent regulations in the devolved administrations.
- The Immigration Rules require the UK Border Agency to ensure that any person applying for entry to the UK in this category provides sufficient evidence to demonstrate that:
    - They are genuinely seeking entry for a specified purpose within the UK and that the intention at the time of entry is that the stay will not exceed six months. However, subsequent unforeseen circumstances may result in the migrant applying for an extension.
    - They will maintain and accommodate themselves adequately out of the resources available to them (self-financing), without recourse to public funds or taking employment, or will be maintained and adequately accommodated by friends or family.
    - They can meet the cost of the return or onward journey.

The following process has been agreed to facilitate the entry clearance application process from a potential donor who is resident overseas and wishes to donate to a recipient who is resident in the UK and is eligible for NHS treatment:

- The Human Tissue Authority (HTA) has confirmed that if a donor is supported by their family and/or the recipient to fund travel and living expenses, this is deemed acceptable provided that the requirements of the Independent Assessor are subsequently met. A claim for reimbursement may also be made by the donor to reclaim legitimate expenses (as above) if the donation proceeds. Commissioners have been advised of this requirement and that applications for reimbursement of

donor expenses will be made retrospectively (i.e. post-donation) in the majority of cases, enabling an accurate assessment of legitimate expenses to be made once the donor has been assessed and surgery has proceeded as planned.

- The UK Border Agency has confirmed that entry clearance applications including applications for visas should be dealt with as a specific group (on a case by case basis) and considered against the requirements for one immigration category for six months duration. In most cases the applications will be made direct to the British Embassy or High Commission, and then referred back to the UK. There is no guarantee that entry clearance will be granted by the UK Border Agency.
- All applications for entry clearance will need to be accompanied by appropriate supporting information. A template letter has been provided which has been approved by the UK Border Agency and includes the minimum requirement for supporting information. This is annexed at the end of this chapter. It is strongly recommended that this template letter is used in all cases, as the format immediately identifies the nature of the application to Entry Clearance Personnel in local Embassies/High Commissions, and the manner in which it should be processed. Of note, the Channel Islands and the Isle of Man have separate immigration arrangements from the UK and additional supporting information may be required when applying for entry clearance for a donor whose recipient is resident in these islands. Direct liaison with these Authorities is advised in advance of the application to avoid delay in issuing entry clearance. The letter should be addressed to the potential donor, copied to the potential recipient and sent from the transplanting centre detailing:

    - The purpose of the application. This needs to be clearly visible at the top of the letter to ensure that it is appropriately identified in local Embassies/High Commissions for processing through the UK Border Agency in the UK.
    - The claimed relationship between donor and recipient, specifying demographic details for both donor and recipient.
    - Confirmation of any donor evaluation (i.e. medical assessments/tests/ investigations) that have already been undertaken to support the potential suitability of the donor.
    - The reason for the choice of donor (i.e. no suitable donors in the UK).
    - The treatment plan for the donor and the estimated duration of the stay in the UK required (i.e. 6 months). It should be made explicit to the donor that there is ‘no right to stay’ in the UK beyond the time that is clinically

necessary and that there is an expectation that he/she will return to the country of origin after a suitable period of convalescence post donation.

- The prospective start date for the entry clearance and subsequent start of donor evaluation on arrival in the UK.
- If the donor evaluation reveals that treatment for a medical condition is required before donation can be considered, the donor must be informed that he or she will be expected to return to the country of origin for such treatment. Similarly, any late surgical or medical complication arising post-nephrectomy once the donor has returned to his/her country of origin must be treated locally and there is no recourse to the NHS to provide such treatment.
- The DH position on entitlement to NHS treatment/donor reimbursement. This should detail any costs which are known at the outset and are likely to be reimbursed during the process (e.g. confirming the cost for the return flight home is going to be reimbursed helps demonstrate that the donor has the means to return back to country of origin).
- The relative cost-effectiveness of living donor transplantation within the UK health economy.
- Confirmation that the recipient is ordinarily resident in the UK and not subject to the National Health Service (Charges to Overseas Visitors) Regulations 1989, as amended, or their equivalent regulations in the devolved administrations.
- Contact details for further information from the transplanting centre.

- Following the UK Border Agency's full consideration of the evidence provided, successful applicants will normally be issued entry clearance for 6 months, starting on the day entry clearance is issued unless stipulated otherwise. For planning purposes, a prospective date for start of the entry clearance can be specified in the supporting information so that delays in the start of donor evaluation are minimised once the donor arrives in the UK. This date should be requested sufficiently far ahead to allow sufficient time (minimum of 4 weeks and maximum 12 weeks at time of application) for the donor to receive the supporting information, present the application to the local Embassy/High Commission and for the application to be processed. The 6 month visa is issued to facilitate the donation process, (i.e. required clinical evaluation, surgery, recovery of the donor post-nephrectomy) and is the maximum stay that is permitted for a visa issued on these grounds.

- Costs incurred can subsequently be reclaimed by the donor once the donation has gone ahead as part of the reimbursement process (see above).
- Where there are extenuating circumstances, of a medical nature, an extension of stay can be applied for, but there is a fee for such applications and there is no guarantee that the extension will be granted. It is important to manage the clinical pathways for both donor and recipient effectively to minimise delay and to facilitate transplantation in a timely manner; this includes scheduling the complete process (including sufficient time for convalescing) within the six months granted.
- Healthcare professionals must take responsibility to manage the expectations of both donor and recipient from the outset about the requirement for the donor to return to his/her country of origin following recovery from surgery and appropriate convalescence.

Representatives from UK Border Agency are keen to be informed about cases where entry applications are refused or issued for under 6 months, or where there have been difficulties encountered in the application process, so that they can continue to monitor and review individual cases. Please direct any specific queries about visa applications and/or general queries about this guidance to Lisa Burnapp (lisa.burnapp@nhsbt.nhs.uk). Lisa has agreed to provide liaison between living donor co-ordinators (LDCs) and UK Border Agency personnel for initial enquiries, and the latter will then deal directly with the relevant LDC as required.

References

1. Saving Lives, Valuing Donors: A Transplant Framework for England. Department of Health, July 2003. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006700
2. Reimbursement of Living Donor Expenses by the NHS. Department of Health, July 2009. http://www.dh.gov.uk/en/Healthcare/Longtermconditions/Vascular/Renal/RenalInformation/DH_4069293
3. Human Tissue Act 2004, Human Tissue Act (Scotland) 2006. http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1

Annex Chapter 9

Template Letter for Potential Overseas Donors

Trust Headed Paper

[include contact details for living donor co-ordinator]

[Name and address (overseas) of potential donor]

Hospital No/ID (if available)

NHS No (if available)

Date of Birth

Dear [Donor's name]

RE: PROPOSED LIVING KIDNEY DONATION FOR UK RECIPIENT:

(NAME, HOSPITAL ID, DOB, ADDRESS IN UK)

We understand that you wish to be considered as living kidney donor for your [relationship donor to recipient].

Thank you for providing us with some preliminary medical information, which indicates your suitability for proceeding to the next stage of the donation process. To ensure a thorough assessment of your medical suitability to donate a kidney and so that you have an opportunity to discuss this in detail, you will need to travel to the United Kingdom (UK) to attend ['X'] Hospital, [Name of City/Town] for further tests and consultations. **As you know, we have provisionally organised for you to attend for these appointments starting [Day, Date]** and so you should request a visa to start as close to this date as possible and then arrange your travel accordingly (see below). Please read this letter carefully before proceeding any further.

Next Steps:

1. Your application to travel to the UK

To travel to, enter and stay in the UK for 6 months you will need to satisfy UK immigration requirements. You will need to make an application to your local British Diplomatic Mission for a UK Visitor's Visa (entry clearance), specifying your intention to donate an organ for your relative. Your relative, the potential recipient of your kidney, must ordinarily be resident

in the UK and entitled to kidney transplant treatment on the National Health Service (NHS). Your relative must check this information with the hospital in the UK before you submit an application, otherwise it will not be valid.

You will find all the information you require to apply for your visa on the UK Border Agency Visa Services website: http://www.ukvisas.gov.uk/en/ or at your local British Diplomatic Mission. To avoid unnecessary delays in processing your application, which will be referred to the UK for a decision by your local British Diplomatic Mission, you should ensure you read the information carefully before completing your application to make sure you provide all the necessary information needed to satisfy the requirements set out in the guidance and here in this letter. This should avoid any unnecessary delays or uncertainty about travel dates. As your visa application will be considered in the UK, you should allow at least 4 weeks (maximum 12 weeks) from the time of application. If successful, your visa will then be issued for **6 months,** starting on the date you have agreed with us and as stated on the visa application form.

2. Your medical testing and donation in the UK

We need to plan your further medical assessment and surgery carefully and in advance, in order to ensure we complete the kidney donation process within 6 months. Once you have completed the assessments in the UK, we will be able to confirm whether or not you are a suitable donor and, if you still wish to donate, we will schedule a date for the living donor transplant operation for you and your recipient as soon as possible. You will need to recover in the UK after the surgery for up to 4 weeks before you travel back to your own country. You must arrange to stay with your family throughout your stay in the UK, or make independent accommodation arrangements before your arrival in the UK (you will have to provide evidence of this in your visa application to travel to the UK). It is particularly important to make sure that you can stay with your family when you are discharged from hospital so that you are not living alone while you recover from your surgery.

3. Your checklist to proceeding

To help us plan everything as smoothly as possible for you with the minimum of delay, you can help us by doing the following:

1. Ensure you have discussed with the hospital when you wish to travel to the UK **before submitting your application**. This is essential in order to allow enough time for the hospital to arrange your tests in advance, to start as soon as possible after your arrival in the UK and to provide you with enough time to recover and convalesce after your operation. Prior to this discussion you should consider the date that you think you will be able to make travel plans and UK reception arrangements (staying with your family). You will need to allow at least 4 weeks (but no more than 12 weeks) between the date you intend to submit your visa application to the British Diplomatic Mission and the date you wish to travel. Once this information has been discussed and agreed with the hospital you will have a date and all the relevant information for your visa application.

2. Follow the guidance on the website when applying for your visa to ensure that you have met the UK Border Agency requirements in full **before** you submit your application.

3. Attach this letter to your visa application, and submit it together with all your other documents for your visa application to your local British Diplomatic Mission for consideration by an Entry Clearance Officer. If your application is approved, your visa will be issued to start on the specified date, previously agreed with the hospital. Please keep a copy of all these documents for yourself for future reference.

4. **It is your responsibility to advise the hospital directly if there is any delay in submitting your visa application to your local British Diplomatic Mission overseas or in approving it so that we know when to expect you and to adjust dates accordingly.**

Costs

It is important that you know which costs and expenses are covered during your visit. The cost of your medical treatment specifically for the purposes of donating a kidney (donor assessment, +/- donor surgery and out-patient appointments) will be covered by the NHS whilst you are in the UK, but this is not available to you once you have returned to your own country at the end of the 6 month period. Whilst you are in the UK, any treatment outside of the donor process, including dentistry, is not covered by the NHS and, if you do not have medical insurance, you will be expected to pay for this yourself or return to [Country of residence for donor] for treatment. You are, therefore, advised to obtain medical insurance before you travel. You are entitled to apply for reimbursement for travel and living expenses specifically in connection with process of donation from the NHS once you have donated your kidney and you are advised to keep a record of expenses that you incur. If you are unable to proceed with the donation as planned following assessment in the UK, you will not be entitled to claim these expenses.

Please ensure that you and your family have read this letter and fully understand the information before proceeding with a visa application. I will be co-ordinating your donor assessment at the hospital. Please contact me directly or via your recipient if you are not clear about any aspect of this letter. My contact details are at the top of this letter.

Yours sincerely

Living Donor Co-ordinator/member of Transplant/Referring Team

Cc: [potential recipient]

CHAPTER 10 DONOR FOLLOW-UP

Statements of Recommendation

- ***Life-long follow-up is recommended after donor nephrectomy. For donors who are resident in the UK, this should 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 on long term morbidity and mortality. Donors from overseas who travel to the UK to donate are not entitled to follow-up in the UK but should be given advice about appropriate follow-up before returning to their country of origin (C1)***

- ***Arrangements must be put in place to ensure that the unsuitable donor, who is unable to proceed to donation, is appropriately followed-up and referred for further investigation and management. (B1)***

- ***NHSBT has given a formal undertaking that any living kidney donor who develops renal failure in the peri-operative period as a consequence of donation will receive priority for a deceased donor kidney transplant. (Not graded)***

10.1 Arrangements for Follow-up

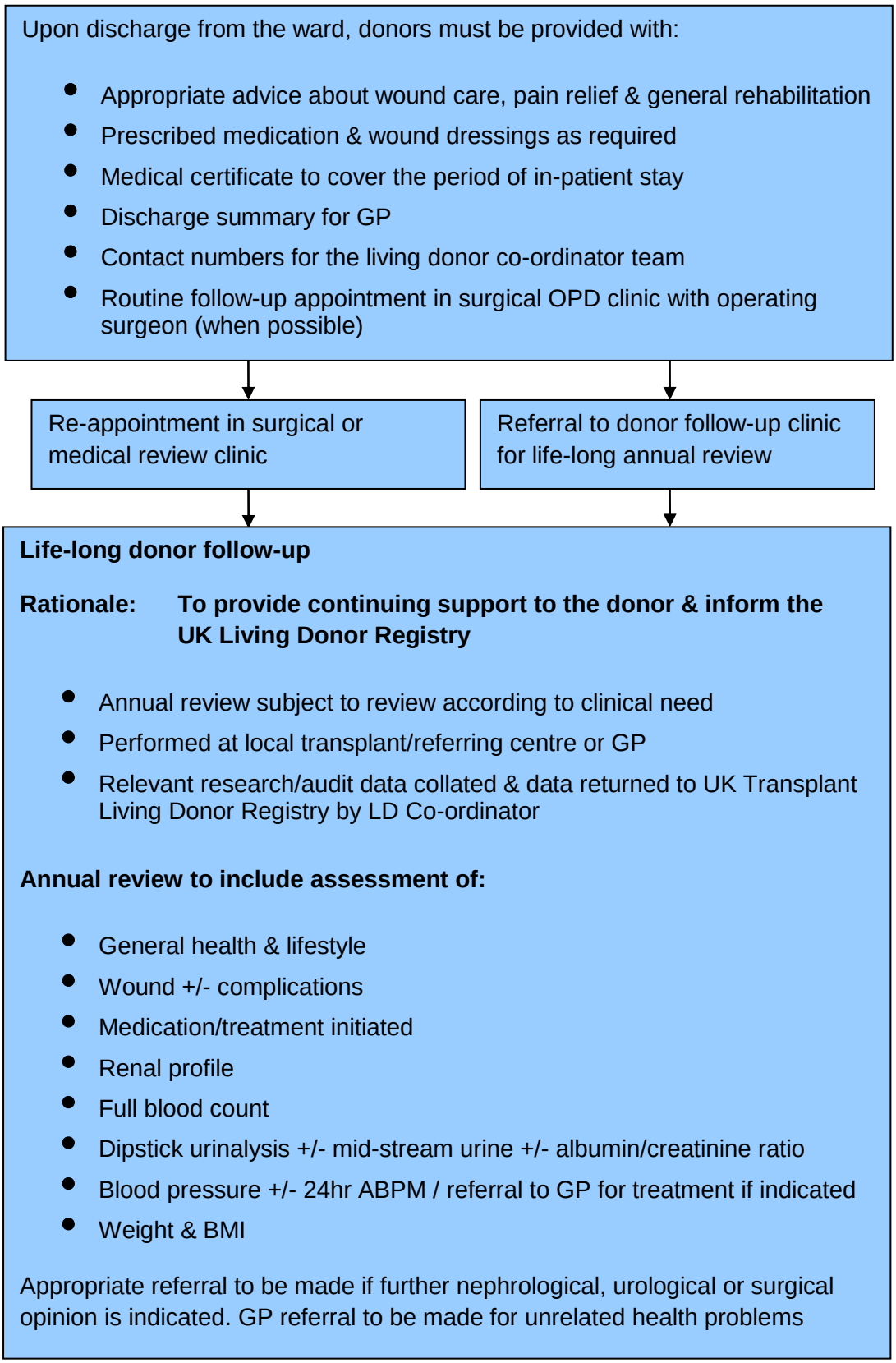
Early follow-up of the donor is recommended within the first few weeks after surgery to ensure that he or she is making progress following the operation and is appropriately supported. This should include monitoring of kidney function as well as the early detection of problems such as infection and wound healing. By the end of three months it is anticipated that the donor will have made a full recovery and have returned to normal activities. Some centres offer a further review at this stage as an opportunity to ensure that this has happened as well as offering ongoing support and advice for continued optimal health.

Long term follow-up, on an annual basis, provides a forum for review of kidney function, urinalysis and blood pressure as well as general health status. Existing guidelines based upon a consensus of professional opinion recommend that the transplant centre has a responsibility to encourage and facilitate the long term follow-up of the donor after donation, particularly for individuals with pre-existing or acquired conditions that potentially place them at greater risk (1-3). These include hypertension, obesity, diabetes and proteinuria (see Figure 10.1 for a suggested model for donor follow-up). This follow-up can be provided by the transplant centre, the referring nephrology unit or the donor's General Practitioner. Whilst not all donors wish to return for regular review, anecdotally many welcome the opportunity and appreciate the continuing support and interest in their welfare.

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 Chapter 4). Practice with respect to long term follow-up still varies between centres and is subject to local arrangement. The principle of long-term surveillance and monitoring of the donor is considered to be best practice and is encouraged in the UK by the National Living Donor Registry, which was established in 2000 and is held by NHS Blood & Transplant (5). All UK centres are expected to submit data to the Registry on all donors at specified time points both pre-and post donation in order to optimise the value of the Registry Data in informing living donor practice. In developing models of care for donor follow-up, timing of annual review in accordance with the month of donation, offering flexible clinic times and local follow-up arrangements should be considered in order to offer choice to the donor and facilitate the timely collation of Registry Data for willing participants. Annual review telephone clinics may be less suitable for long-term donor follow-up due to the infrequency of the interaction with a healthcare professional. Anecdotal feedback from previous donors when offered this option in a single centre was not favourable on the basis that the annual face-to-face consultation is of intrinsic value to the follow-up experience.

Figure 10.1

Model Referral Pathway for Follow-up Post Living Donor Nephrectomy



For donors who travel from overseas to donate, there are implications for long-term follow-up arrangements and access to data once they return to their country of origin, particularly 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 put in place and it is rarely possible to collect accurate data on overseas donors for the UK Living Donor Registry.

10.2 The Unsuitable Donor

An area that is easily overlooked is the care and follow-up of patients who start the donor assessment process but who do not subsequently donate. If this is the result of concerns about the potential donor's health, it is essential that appropriate arrangements are made for any necessary further investigation and management. A donor who is unsuitable for other reasons (for example a positive crossmatch) may need emotional support as they could conceive themselves to have "failed" the recipient – and blame themselves inappropriately for any subsequent adverse outcome for the recipient (see Chapter 4).

10.3 Pregnancy following Kidney Donation

Many centres consider women of childbearing age as potential living donors. Pregnancy has a number of well documented effects on the kidney raising the possibility that these may have an adverse effect in an individual with a solitary kidney. The information in this area is relatively limited. A study of 39 pregnancies in 23 women with 32 viable births revealed no significant problems and in particular no significant hypertension or proteinuria (5). Another study of 23 viable births in 14 kidney donors reported no significant problem (3). Two recent reports based upon retrospective Norwegian Registry Data and a large single centre survey in Minnesota, USA have raised concern about the potential for increased maternal complications after donation. Both studies are limited and interpretation is therefore difficult (6). Nevertheless, the presence of a solitary kidney does not appear to pose a significant risk during the course of a normal pregnancy and outcomes for pregnant kidney donors are considered comparable to those in the general population. Anecdotally, this opinion has been corroborated by expert obstetric opinion in the field when seeking advice on how to advise potential kidney donors.

Within the UK, there is an opportunity to report births post-donation to the Living Donor Registry as 'a significant medical event' at each annual review (4). This should be encouraged in order to improve the evidence base. Close follow-up is advisable in donors during pregnancy and periodic assessment should be undertaken of serum creatinine and creatinine clearance in addition to urine culture and blood pressure.

10.4 Renal Failure following Living Kidney Donation

Renal failure after living kidney donation is rare, but there have been occasions (at least one in the UK) where peri-operative complications have resulted in a living kidney donor developing chronic dialysis-dependent renal insufficiency following surgery. In this rare situation, NHSBT has given a formal undertaking that any living kidney donor who develops renal failure as an acute consequence of donation will receive priority for a deceased donor kidney for transplantation.

References

1. Buszta C, Steinmuller DR, Novick AC, et al. Pregnancy after donor nephrectomy. Transplantation 1985; 40: 651-4.
2. The Ethics Committee of the Transplantation Society. The Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor. Transplantation 2004; 78: 491-2.
3. A Report of the Amsterdam Forum on the care of the Live Kidney Donor; Data and Medical Guidelines. Transplantation 2005; 79; S53-S66.
4. Living Donor Registry. www.nhsbt.org.uk
5. Jones JW, Acton RD, Elick B, Granger DK, Matas AJ. Pregnancy following kidney donation. Transplant Proc 1993; 25: 3082.
6. Josephson, MA. Pregnancy after kidney donation: more questions than answers. Nature Reviews, Nephrology 2009; 5: 495-7.

11.0 RECIPIENT OUTCOME AFTER LIVING DONOR KIDNEY TRANSPLANTATION IN ADULTS

Statements of Recommendation

- ***Graft and patient survival after living donor kidney transplantation should be consistent with the national average. (A1)***

- ***Transplant centres should regularly audit secondary outcomes after living donor kidney transplantation and should reappraise practice if their results are not comparable with other units. (B1)***

- ***Where a recipient is considered to be at high risk, transplantation should only proceed if, in the view of the team of professionals involved, there is an expectation that the patient is likely to survive with a functioning transplant for more than 2 years. (C2)***

- ***Patients at higher risk (see definition in text) may be considered for transplantation when the professional team regard the risk to the specific recipient to be acceptable. An agreement between the clinical team and the donor-recipient pair should be documented in the clinical records, including a prediction of the chance of success and the risk of failure for this specific transplant. A copy of this document should also be given to the donor and recipient. The transplant should be undertaken within 3 months of this agreement and it should be pre-emptive where possible.***

Clinical audit is integral to transplant practice. Outcome after living donor transplantation can be measured by recipient and graft survival and should be sent to National Health Service Blood and Transplant (NHSBT). Data should also be collected by each unit for the following secondary outcome measures, which are currently not reported centrally but which give important audit measures for success:

- incidence of delayed graft function (which is uncommon (<5%) in living donor transplants);

- incidence of acute rejection;
- incidence of post-operative infection;
- renal function one year post transplantation.

Data from the UK transplant registry (held by NHSBT) have recently been analysed for living donor kidney transplants undertaken in the UK between 2000 and 2007 (1). Table 1 shows the patient and death-censored graft survival.

Table 11.1 Patient and death-censored graft survival at 1 and 5 years after living kidney donation (2000-7) (1)

	Related donors (n=2,227)		Unrelated donors (n=917)	
	% survival	95% CI	% survival	95% CI
Graft survival				
1 yr	95	94-96	96	94-97
5 yr	89	87-91	93	90-95
Patient survival				
1 yr	99	98-99	97	96-98
5 yr	97	95-98	93	90-95

Higher donor age, the presence of recipient diabetes and grafts from adult offspring were associated with poorer patient survival in the first three years after transplantation (Tables 11.2 and 11.3). The relative risk of death in recipients with diabetes compared to those without diabetes was 8.8 after 3 years.

Poorer graft survival at 3 months was independently associated with donor age older than 59 years (relative risk of graft failure compared to 18-34 year old donors 2.95) and female recipients (relative risk of graft failure compared to males 1.88). Poorer graft survival at 3 years was associated with recipient diabetes (relative risk of graft failure compared to non-diabetes 2.96). The age of the recipient did not significantly affect outcome.

The degree of HLA A, B and DR mismatch had no effect on graft survival in the 2000-7 cohort. This finding is different from that seen in data from the same source for transplants undertaken between 1993-2002, where five-year graft survival was significantly lower in grafts with 2 and 3 HLA mismatches compared to those with zero or 1 HLA mismatch (2). Databases from other countries have also reported a relationship between HLA matching an outcome (3).

Table 11.2 Risk-adjusted relationship between donor age and recipient survival after first living transplant (2000-7) *p<0.01, **p<0.001 (1)

		Recipient survival			
		0-3 yrs		>3 yrs	
Donor age (y)	n	Relative risk of death	95% CI	Relative risk of death	95% CI
18-34	484	1.00	-	1.00	-
35-49	1349	7.93**	2.35-26.75	0.54	0.11-2.60
50-59	896	8.63*	2.12-35.16	0.39	0.06-2.47
60+	413	15.14**	3.54-64.68	0.37	0.04-3.66

Table 11.3 Risk-adjusted effect of donor to recipient relationship on recipient survival after first living transplant (2000-7) *p<0.01 (1)

		Recipient survival			
		0-3 yrs		>3 yrs	
Donor-recipient relationship	n	Relative risk of death	95% CI	Relative risk of death	95% CI
sibling	1032	1.00	-	1.00	-
parent	919	0.15*	0.04-0.52	1.28	0.16-10.07
Son/daughter	176	3.51*	1.29-9.53	0.56	0.04-8.33
Other related	98	0.73	0.16-3.25	1.15	0.10-12.98
Spouse/partner	737	1.32	0.64-2.74	1.24	0.36-4.30
Other unrelated	180	0.21	0.03-1.64	0.63	0.06-6.63

The High Risk Recipient

For the purpose of this guideline, a high-risk recipient is defined as a potential recipient of a kidney transplant who is at a significantly higher risk of death, complications or graft failure because of pre-existing co-morbidity or immunological status. There is currently no robust, clinically applicable scoring system upon which to base this assessment of risk.

Statistically, this equates to an expected outcome that is outside the 95% confidence interval for graft and patient survival in the UK. It is recognised that this cannot be predicted with any certainty and will depend entirely on the clinical judgement of the professionals involved.

A key issue is that, whilst these patients may expect a relatively poorer outcome from transplantation compared with individuals considered to be at lower risk, their outcome may be better than it would be if they remained on dialysis. Pre-existing cardiovascular disease, pulmonary disease, obesity and diabetes all affect survival of patients with a transplant or on dialysis. Whilst the survival of patients with diabetes on the transplant waiting list is increased if they receive a graft rather than remain on dialysis, the relevance of this to high-risk recipients is uncertain. There are insufficient data to give clear guidance on this issue to individual high-risk recipients. Accordingly, risk assessment in each case must, by default, be based on multidisciplinary expert opinion. Notwithstanding this, it is important that certain limits are set, not least to ensure appropriate use of resources.

In cases considered to be higher risk, living donation has certain advantages over deceased donor transplant, including:

- daylight operating time;
- availability of greater numbers of senior staff from multidisciplinary team (e.g. cardiology, chest physiotherapy);
- known quality of the organ to be transplanted;
- predicted day of surgery allowing optimisation of recipient factors (e.g. reversal of anticoagulation);
- pre-transplant immunosuppression or immunomodulation.

Since the outcome of deceased donor transplantation is affected by long cold ischemic time and delayed graft function (both of which are avoided with a living transplant), there

may be circumstances where living transplant provides the best option for some high risk patients, provided there is a clear understanding of risk by both donor and recipient.
An agreement must be reached by the clinical team and the donor-recipient pair which includes a realistic prediction of success and recognition of the risks of failure (death of the recipient or failure of the graft). Although such an agreement is applicable to living donation in general, it is particularly important for the high risk recipient where expectations will not usually accord with registry data. Although there is a paucity of information on the balance of risks and benefits in high-risk recipients, the clinical team should do their best to describe the best and worst case scenarios. The timing and content of these discussions should be documented in the medical notes.

The assessment should include the following elements:

- The option of living donor transplantation should be discussed with all patients, unless it is considered unlikely that the patient would survive with a functioning graft for more than 2 years.
- The multi-professional clinical team should establish what the recipient wants and expects from the transplant in terms of quality and extension of life.
- Consideration of living donor transplantation should be started early enough for the procedure to be performed pre-emptively (i.e. before dialysis becomes essential), which should be considered the preferred option.
- The trigger for initiation of discussion should normally be an eGFR of ~20 ml/min, but this may vary depending on the rate of decline of renal function.
- The risks and benefits of living donor transplantation should be described but so should other management options including maximal conservative care, dialysis and transplantation from a deceased donor.
- The details of the final understanding must be compliant with the NHS consent process. It should be recorded and signed by both the recipient and the donor in addition to the consultant transplant surgeon taking responsibility for the recipient operation. Copies of the agreement, which should be filed in the notes, should be given to both the donor and the recipient alongside the consent form. This agreement would serve as part 1 of the consent for transplantation surgery in the two-part consent process.

- If an agreement cannot be achieved within a particular transplant centre e.g. because of differences in opinion on the degree of risk, the option of referral to another transplant centre for a second opinion should be discussed with the potential recipient and donor.

Outcomes

Recipient outcome following living donor transplantation is subject to comparative national audit. It is important that the decision to transplant high-risk recipients is not influenced by undue concern about outcome data. In view of demographic differences between units and the likelihood of variations in the definition of "high-risk", it is not possible to set national standards for transplant outcome in this group.

The outcome data for a transplant programme may be skewed if a unit is prepared to undertake more high risk transplants. It is recommended that each unit should maintain detailed records of relevant clinical features for each high-risk recipient. This may be valuable for future audit. Co-morbidity reports sent to the Renal Registry provide a minimum data set, but more detailed assessment of risk using an in-house scoring system is recommended.

References

1. Fuggle SV, Allen JE, Johnson RJ, et al. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. Transplantation 2010; 89: 694-701.
2. United Kingdom guidelines for living donor kidney transplantation 2nd Edition. British Transplant Society 2005. Accessed 16th February 2011 at: http://www.bts.org.uk/transplantation/standards-and-guidelines/
3. Opelz G. Impact of HLA compatibility on survival of kidney transplants from unrelated live donors. Transplantation 1997; 64: 1473-5.

CHAPTER 12 RECURRENT RENAL DISEASE

Summary Statements of Recommendation

- ***A wide range of diseases that cause renal failure may recur in the transplanted kidney. This is important to consider when determining the optimal treatment strategy for a recipient and when counselling both donor and recipient on the relative risks and benefits of living donor transplantation. The risks of recurrence, the consequences for transplant function and the time-course of any deterioration must all be considered. A discussion of the effects of immunosuppression and transplant failure on morbidity and mortality may also be appropriate. (B1)***

- ***The risks of recurrent disease are high in atypical HUS, FSGS and MCGN. In these diseases, the presence of specific adverse clinical features may indicate living donor transplantation should be avoided, even where a donor is available. This will require careful assessment and deliberation with all interested parties. (B2)***

- ***In patients with risks related to underlying activity such as SLE or systemic vasculitis, adequate disease control and an appropriate period of quiescence are important to ensure optimal outcomes. (B1)***

- ***Recommendations for individual diseases follow in the subsequent text.***

Many native kidney diseases can recur following transplantation and may result in allograft failure. They include systemic disorders of metabolism and glomerulonephritis (1,2). The reduction in acute rejection associated with modern immunosuppression means that recurrent disease is now an important determinant of graft outcome (3). The likelihood and consequences of recurrence are therefore important when assessing and counselling living donor-recipient pairs.

In many diseases, the published literature on recurrent disease post-transplantation consists largely of case series. These give only a limited quantification of risk as they are

confounded by ascertainment bias since there is an interaction between the indication for biopsy and the consequences of disease recurrence (2). Large registry studies provide a better estimation of risk; however, they too require careful interpretation because disease rates will be influenced by diagnostic practice and convention in the contributing centres (4-7). This is particularly important when considering heterogeneous disease processes such as FSGS (2).

These issues are considered in the following discussion of individual diseases. However, this is an evolving field and it may be necessary to review source data or seek specialist advice to estimate risk and decide upon optimal treatment for individual cases. For example, previous reports of an association between living kidney donation and the recurrence of glomerulonephritis, particularly in zero mismatched donor-recipient pairs, have either been unconfirmed (6) or not so clear-cut as to definitely preclude transplantation (8). In other diseases such as atypical haemolytic uremic syndrome (HUS), a different risk, that of unrecognised genetic susceptibility to disease in the donor as well as in the recipient, has significantly changed practice (9).

12.1 Diabetic Nephropathy

Histological recurrence of diabetic nephropathy is relatively common following renal transplantation (10). However, the time required for this to cause kidney failure is long and it does not contraindicate living donor transplantation. This treatment option offers significant benefits with respect to patient and graft outcomes (11-13).

Recommendation

- ***Type 1 and type 2 diabetes are not contraindications to living donor transplantation, irrespective of whether they are the underlying cause of renal failure. Both the donor and recipient should be counselled regarding the increased risks associated with surgery.***

12.2 Primary Focal Segmental Glomerulosclerosis

The recurrence of focal segmental glomerulosclerosis (FSGS) following renal transplantation is a significant problem. It is estimated to recur in 20 to 50% of cases (1,2). The wide range in the reported frequency of recurrence is likely to reflect heterogeneity in the underlying diagnoses associated with FSGS. The histological description of FSGS

with proteinuria and renal failure occurs frequently as a non-specific finding in many forms of kidney disease. This secondary FSGS may complicate the interpretation of undifferentiated reports of recurrence in transplantation.

Primary FSGS, characterised by the nephrotic syndrome, is associated with a high risk of disease recurrence in the transplant, particularly if there is:

- end stage renal failure at a young age, particularly during adolescence (5,14-16)
- rapid progression to end stage renal failure (17)
- recurrent disease in a previous transplant (5,15,18)

In these situations the rate of graft loss secondary to recurrent disease may be significantly above 50%.

Even primary FSGS presenting with the nephrotic syndrome seems not to be a single disease entity, and this may explain differences in the rate of recurrence in different groups. For example, there is evidence that recurrent disease is more common in whites than blacks (19). Also, familial forms of FSGS, which can have a rapid course of deterioration and present at a young age, represent a relatively low risk for recurrence in a transplant (20-23).

Recurrent primary FSGS generally occurs in the first 6 months following transplantation and this is an important consideration if transplant recipients are not to be incorrectly labelled as having recurrent disease.

The report by Cibrik and colleagues that the outcome of transplantation for FSGS is best in zero mismatched living donation is reassuring (6), although it should be remembered that a wide range of different presentations are likely to have been included in a registry report such as this.

Recommendation

- ***Living donor kidney transplantation is a reasonable option in patients with primary FSGS. However, both donor and recipient need to be specifically counselled about the risk of recurrent disease, which may occur early and result in rapid graft loss. Transplantation in an individual with unequivocal evidence of graft loss secondary to recurrent disease has a high risk of subsequent failure such that some centres consider this a contraindication to repeat transplantation (24). In this context, living donor transplantation***

should be considered only in special circumstances and after careful discussion between the multi-professional team, the donor and the recipient (15,18). The risk of recurrence is low when the previous graft did not fail due to recurrent disease.

12.3 IgA Nephropathy

IgA nephropathy frequently recurs in transplanted kidneys on histological grounds but is of less clinical significance. It may be associated with transient, but more commonly slowly progressive transplant dysfunction. The prevalence of graft loss due to recurrent IgA disease was 2.8% in the report of Briganti and colleagues, which gave an estimated 10-year incidence of graft loss of 9.7% (7).

Recommendation

- ***The risk of recurrent disease does not contraindicate living donor transplantation in IgA nephropathy. Both the donor and recipient should be counselled regarding the risks of recurrent disease.***

12.4 Membranous Nephropathy

The recurrence rate of idiopathic membranous nephropathy has been reported as 29% in the first 3 years post-transplantation with a corresponding graft survival of 52% at 5 years and 38% at 10 years (25,26). In the report of Briganti and colleagues, recurrent disease was responsible for 12.5% of the 40.1% of failed transplants at 10 years in patients with membranous nephropathy (7).

Recurrent disease may relate to the persistence of antibody to PLA2 but this remains to be proven (27). Living donation seems not to be a risk factor for recurrent disease.

Recommendation

- ***This risk of recurrent disease does not contraindicate living donor transplantation in membranous nephropathy. Both the donor and recipient should be counselled regarding the risks of recurrent disease.***

12.5 Amyloidosis

In patients with amyloidosis, the underlying cause, disease activity, response to treatment and extra-renal involvement will inform the strategy for renal transplantation. Initial assessment will usually involve the National Amyloidosis Centre in London. Living donor kidney transplantation is a reasonable treatment option in some circumstances, when adequate control of the underlying disease can be achieved (28,29). The donor and recipient will need to be counselled regarding the additional risks arising from recurrent renal disease and the additional mortality associated with the underlying disease and its treatment.

Recommendation

- ***Patients with amyloidosis should be discussed with the National Amyloidosis Centre before progressing to living donor transplantation. Patients with AA amyloidosis should have effective disease control before surgery.***

12.6 Systemic Lupus Erythematosus

The rate of recurrence of lupus nephritis within a transplant is said to be low. The risk of recurrence is higher in young black females and is associated with a high rate of graft loss (30), although this is not always directly attributable to disease activity. The treatment of active lupus should be optimised prior to transplantation, although it is recognised that serological markers of disease, native renal histology and duration of dialysis are not significant predictors of recurrent disease. The presence of anti-phospholipid antibodies is a risk factor for thrombotic complications following transplantation. Where these are present, this should be discussed with the donor and recipient prior to transplantation and increased peri-operative anti-thrombotic prophylaxis considered.

Recommendation

- ***The overall risks associated with recurrent disease are small in SLE and living donor transplantation is safe in quiescent disease. Both the donor and recipient should be counselled regarding the risks of recurrent disease. (B2)***

12.7 ANCA Associated Systemic Vasculitis

The risk of recurrent disease in ANCA associated systemic vasculitis (AASV) is small when patients are transplanted in remission: reportedly 1% per year of patient follow-up. The consequences of recurrence may, however, be significant, with increased mortality and graft loss (31).

There is an increased risk associated with kidney transplantation less than 1 year following the induction of remission, because of increased recipient mortality. Living donor transplantation should therefore usually take place only after 1 year of disease quiescence, although this should be balanced against the potential risks of staying on dialysis (31). Although the detection of ANCA is a risk factor for disease recurrence, a persistently positive ANCA is a common finding and is not a contraindication to transplantation if unaccompanied by clinical disease.

Recommendation

- ***The overall risks associated with recurrent disease are small and the outcomes of transplantation good, therefore AASV does not contraindicate living donor transplantation if the aforementioned criteria are met. Both the donor and recipient should be counselled regarding the risks of recurrent disease.***

12.8 Goodpasture's Disease

Recurrent renal disease is rare following a diagnosis of Goodpasture's disease provided the recipient no longer produces anti-glomerular basement membrane antibodies. Transplantation should be delayed for at least 6 months following the disappearance of anti-GBM antibodies and for 12 months following presentation (31-33).

Recommendation

- ***The overall risks associated with recurrent disease are small and the outcomes of transplantation good, therefore Goodpasture's disease does not contraindicate living donor transplantation if the aforementioned criteria are met. Both the donor and recipient should be counselled regarding the risks of recurrent disease.***

12.9 Alport Syndrome

De novo anti-GBM disease is reported in approximately 5% of patients with Alport syndrome and despite treatment may result in transplant failure (34).

When a patient has already lost one transplant due to post-transplant anti-GBM disease, repeat transplantation is difficult because there is a high risk of recurrence. The decision to proceed should be considered only after careful discussion between the multi-professional team, the donor and recipient.

Recommendation

- ***The overall risks associated with Alport syndrome are small and the outcomes of transplantation good, therefore Alport syndrome does not contraindicate living donor transplantation. Both the donor and recipient should be counselled regarding the risks of de novo anti-GBM disease. (B2)***

12.10 Mesangiocapillary Glomerulonephritis

Type I mesangiocapillary glomerulonephritis (MCGN) has been reported to recur in between 33% and 48% of renal allograft recipients after four years. The mean graft survival following recurrence is 40 months (8) and the risk of recurrence in a subsequent graft may be as high as 80% (35). The risk of graft loss in patients with recurrent type 1 MCGN is therefore around 15% at 5 years, and represents a significant cause of transplant failure (7,8). The risk of recurrence may be higher in living donor transplantation (8,35).

Type II MCGN is the most likely primary glomerulonephritis to recur after renal transplantation and does so in virtually all cases. The outcome after transplantation is variable, however; in 75 patients reported by the North American Pediatric Renal Transplant Cooperative Study, the 5 year graft survival was 65.9% and 34.1% in living and deceased donor transplantation respectively (36). Poor outcome has been associated with heavy pre-transplant proteinuria and increased glomerular proliferation (37).

Recommendation

- ***Type I and II MCGN do not contraindicate living donor transplantation. However, the risk of recurrent disease and subsequent graft loss is sufficiently high that it should be undertaken only following careful discussion between the multi-professional team, the donor and the recipient.***

12.11 Haemolytic Uraemic Syndrome

The subject of transplantation in HUS is discussed in detail in 'Clinical Practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom' (9).

HUS may be associated with infection, most commonly with diarrhoea caused by verocytotoxin producing coliforms. It may also occur in association with disorders of complement regulation, most commonly of genetic origin. Rarely, it may occur in other settings including HIV infection, malignancy, pregnancy, connective tissue disease and with certain medications.

Patients presenting with atypical HUS or wishing to be considered for transplantation should be assessed in accordance with the aforementioned guidelines (9). The rate of recurrence is high following transplantation in patients known to have a factor H or I mutation and renal transplantation alone is therefore not recommended.

Patients carrying an MCP mutation but no additional mutation in factor H, factor I, factor B and C3 or an anti-factor H autoantibody have a low risk of recurrence after transplantation (9). Living unrelated transplantation may be considered in such cases after appropriate counselling of donor and recipient. Living related renal transplantation should normally be avoided in atypical HUS because there is a risk of disease occurring in the donor, even in the absence of a currently recognised mutation. In exceptional circumstances, living related donation may be considered after all known mutations have been excluded in the donor and the risks of HUS in the donor have been discussed carefully.

In patients in whom the underlying cause has unequivocally been attributed to Shiga-toxin, the recurrence rate is low and living donor transplantation may be considered (39).

Recommendations

- ***In patients in whom the underlying cause has <u>unequivocally</u> been attributed to Shiga-toxin, the recurrence rate of HUS is low and living donor transplantation may be considered (38).***
- ***Living related renal transplantation should be avoided in atypical HUS unless all known mutations have been excluded in the donor.***
- ***Living unrelated renal transplantation may be considered in some settings after careful assessment.***

12.12 Primary Hyperoxaluria

Primary hyperoxaluria is a rare condition that requires careful assessment and specialist advice to optimise management. Living donor kidney transplantation is a treatment option in certain circumstances, whereas in others combined liver and kidney transplantation is preferred.

Primary hyperoxaluria type 1 is generally treated with combined liver and kidney transplantation (39,40) or early liver transplantation alone (41). However, some groups in North America have advocated early living donor kidney transplantation, particularly if there is evidence of pyridoxine responsiveness (42).

Primary hyperoxaluria type 2 has been treated successfully with kidney transplantation alone. This is ideally pre-emptive, therefore living donor transplantation is a reasonable treatment option (43)

Recommendation

- ***In appropriately selected cases, living donor kidney transplantation is a reasonable treatment option in primary hyperoxaluria. Both the donor and recipient should be counselled regarding the risks of recurrent disease.***

12.13 Cystinosis

The outcome of living donor transplantation in cystinosis is primarily determined by extra-renal complications, which can be mitigated by long-term treatment with cysteamine (44).

Recommendation

- ***Cystinosis is not a contra-indication to living donor transplantation. However, both donor and recipient should be counselled regarding the long term extra-renal complications related to disease progression.***

References

1. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. Am J Transplant 2006; 6: 2535-42.
2. Golgert WA, Appel GB, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol 2008; 3: 800-7.
3. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. Am J Transplant 2009; 9: 527-35.
4. Hariharan S, Adams MB, Brennan DC, et al. Recurrent and de novo glomerular disease after renal transplantation: a report from Renal Allograft Disease Registry (RADR). Transplantation 1999; 68: 635-41.
5. Briggs JD, Jones E. Recurrence of glomerulonephritis following renal transplantation. Scientific Advisory Board of the ERA-EDTA Registry. European Renal Association-European Dialysis and Transplant Association. Nephrol Dial Transplant 1999; 14: 564-5.
6. Cibrik DM, Kaplan B, Campbell DA, Meier-Kriesche HU. Renal allograft survival in transplant recipients with focal segmental glomerulosclerosis. Am J Transplant 2003; 3: 64-7.
7. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 2002; 347: 103-9.
8. Lorenz EC, Sethi S, Leung N, Dispenzieri A, Fervenza FC, Cosio FG. Recurrent membranoproliferative glomerulonephritis after kidney transplantation. Kidney Int 2010; 77: 721-8.
9. Taylor CM, Machin S, Wigmore SJ, Goodship TH. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol 2010; 148: 37-47.
10. Hariharan S, Smith RD, Viero R, First MR. Diabetic nephropathy after renal transplantation. Clinical and pathologic features. Transplantation 1996; 62: 632-5.

11. Young BY, Gill J, Huang E, et al. Living donor kidney versus simultaneous pancreas-kidney transplant in type I diabetics: an analysis of the OPTN/UNOS database. Clin J Am Soc Nephrol 2009; 4: 845-52.
12. Poommipanit N, Sampaio MS, Cho Y, et al. Pancreas after living donor kidney versus simultaneous pancreas-kidney transplant: an analysis of the organ procurement transplant network/united network of organ sharing database. Transplantation 2010; 89: 1496-503.
13. Reese PP, Israni AK. Best option for transplant candidates with type 1 diabetes and a live kidney donor: a bird in the hand is worth two in the bush. Clin J Am Soc Nephrol 2009; 4: 700-2.
14. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis posttransplantation in 42 allografts in children - a single-center experience. Transplantation 1991; 51: 401-5.
15. Moroni G, Gallelli B, Quaglini S, Banfi G, Montagnino G, Messa P. Long-term outcome of renal transplantation in adults with focal segmental glomerulosclerosis. Transpl Int 2010; 23: 208-16.
16. Baum MA, Ho M, Stablein D, Alexander SR. Outcome of renal transplantation in adolescents with focal segmental glomerulosclerosis. Pediatr Transplant 2002; 6: 488-92.
17. Schachter M, Monahan M, Radhakrishnan J, et al. Risk of recurrent focal glomerulosclerosis (RFSGS) in the renal allograft. J Am Soc Nephrol 2007; 18: 683A.
18. Stephanian E, Matas AJ, Mauer SM, et al. Recurrence of disease in patients retransplanted for focal segmental glomerulosclerosis. Transplantation 1992; 53: 755-7.
19. Abbott KC, Sawyers ES, Oliver JD 3rd, et al. Graft loss due to recurrent focal segmental glomerulosclerosis in renal transplant recipients in the United States. Am J Kidney Dis 2001; 37: 366-73.
20. Weber S, Gribouval O, Esquivel EL, et al. NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephrotic syndrome and low post-transplant recurrence. Kidney Int 2004; 66: 571-9.
21. Kuusniemi AM, Qvist E, Sun Y, et al. Plasma exchange and retransplantation in recurrent nephrosis of patients with congenital nephrotic syndrome of the Finnish type (NPHS1). Transplantation 2007; 83: 1316-23.
22. Ghiggeri GM, Aucella F, Caridi G, et al. Posttransplant recurrence of proteinuria in a case of focal segmental glomerulosclerosis associated with WT1 mutation. Am J Transplant 2006; 6: 2208-11.

23. Becker-Cohen R, Bruschi M, Rinat C, et al. Recurrent nephrotic syndrome in homozygous truncating NPHS2 mutation is not due to anti-podocin antibodies. Am J Transplant 2007; 7: 256-60.
24. Ghiggeri GM, Carraro M, Vincenti F. Recurrent focal glomerulosclerosis in the era of genetics of podocyte proteins: theory and therapy. Nephrol Dial Transplant 2004; 19: 1036-40.
25. Cosyns JP, Couchoud C, Pouteil-Noble C, Squifflet JP, Pirson Y. Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. Clin Nephrol 1998; 50: 144-53.
26. Moroni G, Gallelli B, Quaglini S, et al. Long-term outcome of renal transplantation in patients with idiopathic membranous glomerulonephritis (MN). Nephrol Dial Transplant 2010; 25: 3408-15.
27. Stahl R, Hoxha E, Fechner K. PLA2R Autoantibodies and recurrent membranous nephropathy after transplantation. N Engl J Med 2010; 363: 496-8.
28. Lachmann HJ, Gillmore JD. Renal amyloidosis. Br J Hosp Med 2010; 71: 83-6.
29. Leung N, Griffin MD, Dispenzieri A, et al. Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. Am J Transplant 2005; 5: 1660-70.
30. Contreras G, Mattiazzi A, Guerra G, et al. Recurrence of lupus nephritis after kidney transplantation. J Am Soc Nephrol 2010; 21: 1200-7.
31. Little MA, Hassan B, Jacques S, et al. Renal transplantation in systemic vasculitis: when is it safe? Nephrol Dial Transplant 2009; 24: 3219-25.
32. Netzer KO, Merkel F, Weber M. Goodpasture syndrome and end-stage renal failure - to transplant or not to transplant? Nephrol Dial Transplant 1998; 13: 1346-8.
33. Kluth DC, Rees AJ. Anti-glomerular basement membrane disease. J Am Soc Nephrol 1999; 10: 2446-53.
34. Browne G, Brown PA, Tomson CR, et al. Retransplantation in Alport post-transplant anti-GBM disease. Kidney Int 2004; 65: 675-81.
35. Andresdottir MB, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Recurrence of type I membranoproliferative glomerulonephritis after renal transplantation: analysis of the incidence, risk factors, and impact on graft survival. Transplantation 1997; 63: 1628-33.
36. Braun MC, Stablein DM, Hamiwka LA, Bell L, Bartosh SM, Strife CF. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience. J Am Soc Nephrol 2005; 16: 2225-33.

37. Little MA, Dupont P, Campbell E, Dorman A, Walshe JJ. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. Kidney Int 2006; 69: 504-11.
38. Bassani CE, Ferraris J, Gianantonio CA, Ruiz S, Ramirez J. Renal transplantation in patients with classical haemolytic-uraemic syndrome. Pediatr Nephrol 1991; 5: 607-11.
39. Hoppe B, Latta K, von Schnakenburg C, Kemper MJ. Primary hyperoxaluria - the German experience. Am J Nephrol 2005; 25: 276-81.
40. Brinkert F, Ganschow R, Helmke K, et al. Transplantation procedures in children with primary hyperoxaluria type 1: outcome and longitudinal growth. Transplantation 2009; 87: 1415-21.
41. Kemper MJ. The role of preemptive liver transplantation in primary hyperoxaluria type 1. Urol Res 2005; 33: 376-9.
42. Scheinman JI. Liver transplantation in oxalosis prior to advanced chronic kidney disease. Pediatr Nephrol 2010; 25: 2217-22.
43. Kemper MJ, Conrad S, Muller-Wiefel DE. Primary hyperoxaluria type 2. Eur J Pediatr 1997; 156: 509-12.
44. Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. Ann Intern Med 2007; 147: 242-50.
45. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: results from the Scientific Registry of Transplant Recipients. Am J Kidney Dis 2007; 49: 294-300.

CHAPTER 13 LIVING DONOR KIDNEY TRANSPLANTATION IN CHILDREN

Statements of Recommendation

- ***Every effort should be made to minimise HLA mismatches (especially with common antigens) to reduce the risk of future sensitisation. (Not graded)***

- ***All children should be seen by or discussed with a local paediatric urologist to assess the need for complete urological investigation prior to living donor transplantation. (Not graded)***

- ***In general, children who are ≥ 10 kg in weight are suitable to receive a kidney from an adult living donor. (Not graded)***

When transplanting children from living donors, there are some specific issues that require consideration. The purpose of this section is to highlight some of the key areas that warrant special mention, primarily in the context of donor selection, recipient considerations, the transplant operation and peri-operative management.

Donor Selection

Parents are the usual source of a living kidney donor for children but any suitable adult may be considered, including unrelated donors. The following issues require particular consideration in children:

HLA mismatching As children are likely to require re-transplantation during their lifetime, every effort should be made to minimise HLA mismatches (especially with common antigens) to reduce the risk of future sensitisation (see Chapter 7). One parent may fortuitously be better than a one haplotype match, or may mismatch on less common antigens and therefore be the optimum donor.

ABO incompatible transplantation This should be considered when an ABO compatible transplant is not available (including after consideration of a paired exchange). However, it should only be performed in centres with appropriate support for the additional treatment required.

EBV mismatch Children have a much higher chance than adults of being EBV naïve at the time of transplantation, while most adults are EBV positive. When available, the use of an EBV negative kidney donor could therefore reduce the risk of post transplant lymphoproliferative disease. This should be discussed with parents where relevant.

Social aspects Choosing a donor must include assessment of the psychosocial aspects of the family. In some transplant units, parent donors are cared for in a different hospital from the recipient and clear plans for supporting the donor, the recipient and other children during the post operative period should be clarified.

Recipient Considerations

In comparison with adults, glomerular disease accounts for a higher proportion of children with established renal failure. This group includes a number of conditions that may recur after the transplant. Specific advice for these conditions is detailed in Chapter 12. In children, the most common of these is primary focal segmental glomerulosclerosis. Pre-transplant genetic studies may identify those at least risk of transplant recurrence and therefore those in whom living related donation may be considered at an early opportunity.

Obstructive uropathy is another significant cause of renal failure in children, accounting for 16.2% of cases (1). All children should be seen by or discussed with a local paediatric urologist and some will need complete urological investigation (including flow studies and video urodynamics) prior to living donor transplantation. The most appropriate timing of any urinary tract reconstructive surgery should be discussed between the transplant surgeon and paediatric urologist.

In children, particularly those requiring dialysis in infancy, there is a risk of thrombosis of major intra-abdominal vessels and this requires careful evaluation prior to surgery.

Surgery

In general, children who are ≥10 kg in weight (and occasionally even less) are suitable to receive a kidney from an adult living donor. In small children, the kidney is usually placed in the right side of the abdomen. The intra-peritoneal approach allows access to the mid aorta and vena cava for attachment of the renal vessels. Some surgeons prefer the extra-peritoneal approach to the great vessels. This decision is usually dictated by the size of the recipient but there are other factors that may influence this, including the presence of a thrombosed inferior vena cava (IVC) or other anatomical abnormalities.

In small children, standard abdominal closure following transplantation onto the iliac vessels (or onto the aorta and IVC in those closer to the minimum weight) may compromise graft perfusion. On table Duplex scanning is valuable in assessing organ perfusion after wound closure (2). In the presence of high intra-abdominal compartment pressure compromising renal perfusion, delayed closure or a porcine dermal collagen graft inserted as a patch closure of the abdominal muscle reduces the graft compression and does not lead to herniation (3).

The implantation of an adult kidney into a paediatric recipient requires close cooperation between the surgical and anaesthetic teams. Meticulous attention needs to be paid to the child's intravascular volume status. When the aortic and inferior vena cava clamps are released, the transplanted organ and lower extremities fill with blood, potentially resulting in severe hypovolaemia unless adequate volume loading has taken place. Washout of the organ preservation fluid into the child's circulation may reduce core temperature and produce severe hyperkalaemia. Careful monitoring and replacement of on-going fluid loss is required, remembering that the urine output from the adult kidney may be significant. The surgical/anaesthetic team should note a target blood pressure for adequate renal perfusion during the surgical procedure which should guide the post-operative management. However, a peri- and post-operative blood pressure of at least 100 mmHg systolic should be aimed for.

In the early post-operative phase, particular attention should be paid to fluid and electrolyte balance because of the large volumes of urine that can be passed. Urine output and insensible losses are replaced initially with 2.5% glucose/0.45% saline, volume for volume on an hourly basis. Plasma electrolytes and blood sugar are checked at 4-6 hourly intervals for the first 12 to 24 hours and replacement fluids should be adjusted according to these results. Central venous pressure (CVP) monitoring is mandatory and the CVP should be maintained at 6-10 mmHg in the spontaneously breathing patient, with intravenous normal saline or by the administration of an alternative colloid to correct hypovolaemia.

In young children (<5 years), elective ventilation may be considered for the first 24-48 hours after transplantation to allow optimal control of fluids and blood pressure over this critical period.

Where intra-peritoneal surgery has taken place, a post-operative ileus may develop and the child may not be able to start feeds for a number of days. In such situations careful consideration should be given to administering immunosuppressive agents via the intravenous route where it is possible and safe to do so. The risk of vascular thrombosis is greater in this group than in larger/adult recipients and the use of anti-platelet therapy may be appropriate.

It may be necessary to carry out the donor and recipient procedures in separate hospitals and, provided that the kidney is transported safely and efficiently between the two centres to minimise cold ischaemic time, there is no impact on the incidence of primary graft function. Consideration should be given to the geographical separation of the donor and recipient during the post-operative period and the emotional impact that this may have on the donor, recipient and carers. Provision should be made e.g. via webcam technology or similar, to facilitate contact between the donor, child and their carers at this time.

References

1. Lewis M et al. Demography of renal replacement therapy in children. The UK Renal Registry 12th Annual Report 2009; 279-88. Accessed 16th February 2011 at: http://www.renalreg.com/Reports/2009.html
2. Wiebe S, Kellenberger CJ, Khoury A, Miller SF. Early Doppler changes in a renal transplant patient secondary to abdominal compartment syndrome. Pediatr Radiol 2004; 34: 432-4.
3. Pentlow A, Smart NJ, Richards SK, Inward CD, Morgan JD. The use of porcine dermal collagen implants in assisting abdominal wall closure of pediatric renal transplant recipients with donor size discrepancy. Pediatr Transplant 2008; 12: 20-3.