THE RENAL ASSOCIATION
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BTS
British Transplantation Society

Guidelines for Living Donor Kidney Transplantation

Fourth Edition

March 2018

BTS/RA Living Donor Kidney Transplantation Guidelines 2018

United Kingdom Guidelines

CONTENTS

1 INTRODUCTION AND OBJECTIVES

1.1 Introduction

Kidney transplantation from a living donor, when available, is the treatment of choice for most patients with end stage renal disease, offering optimum patient and graft survival and reduced time on the national transplant waiting list. Living donor transplantation also offers a proportion of complex recipients the opportunity to benefit from a transplant that they might otherwise not have received from the deceased donor waiting list; or, through the UK Living Kidney Sharing Schemes (UKLKSS), a better quality or better matched kidney than might otherwise have been available.

For all these reasons, and the opportunity to expand the kidney donor pool, living kidney donation has been actively promoted in the UK over the last 20 years. At the time of writing, approximately 1 in 3 kidney transplants performed in the UK are from living donors. The latest national statistics show that there were 998 living kidney donor transplants in the UK in 2016-17 (1). Of 926 adult donor transplants, 484 were related, 442 were unrelated, 18 were HLA incompatible, 65 were ABO incompatible, 109 were paired/pooled, and 81 were altruistic donor transplants. 36% of the patients transplanted from living donors were transplanted pre-emptively, i.e. without a need for dialysis (1).

The expansion of the UKLKSS has represented a significant change in practice since the last edition of this guideline, not least by reducing the need for HLA- and ABO-incompatible transplantation. In parallel, increasing confidence in the safety of living kidney donation has permitted the expansion of the potential donor pool; to date, the oldest living kidney donor in the UK was aged 85.

Nonetheless, it must be recognised that living kidney donation carries some risk. 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. These guidelines are intended to act as a resource for the transplant community, and to underpin best practice in living donor kidney transplantation.

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. 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 transplantation. Initially published in 2000 (2) and revised in 2005 (3) and 2011 (4), the guidelines have achieved international repute. This fourth edition has used the framework of previous editions but 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 and in consultation with patient representatives.

In updating these guidelines, areas of interest were identified with input from clinicians and patient representatives. 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 the editorial committee and the appropriate levels of evidence added to recommendations. Wider consultation with the transplant community was undertaken by e-mail. The penultimate draft of the document was placed on the BTS website in January 2018 for a six week period of open consultation, to which professional groups, patients and other authorities were actively encouraged to contribute. The final document was posted in March 2018.

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 July 2017.

It is anticipated that these guidelines will next be revised in 2023.

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We also thank contributors to earlier editions of this guideline, some of whose work remains unchanged in this edition, but who have been previously acknowledged.

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. 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 the 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 third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained therein.

1.7 Declarations of Interest

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

http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx (7).

Declarations of interest are listed in an appendix to this document.

1.8 Grading of Recommendations

In these guidelines, the GRADE system has been used to rate the quality 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).

1.9 Abbreviations

The following abbreviations are used in this document:

ABPM	Ambulatory Blood Pressure Monitoring
ABOi	ABO Incompatible
ACR	Albumin: Creatinine ratio
ADPKD	Autosomal Dominant Polycystic Kidney Disease
AIT	Antibody Incompatible Transplantation
ADC	Altruistic Donor Chain
AML	Angiomyolipoma
BMI	Body Mass Index
BTS	British Transplantation Society
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CTS	Collaborative Transplant Study
DAD	Directed Altruistic Donor
DDD	Dense Deposit Disease
DSA	Donor-Specific antibody
DTT	Dithiothreitol
DVT	Deep Vein Thrombosis
EBV	Epstein-Barr Virus
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
EUODD	European Union Organ Donation Directive
ECD	Expanded Criterion Donor
ERAS	Enhanced Recovery After Surgery
FSGS	Focal Segmental Glomerulosclerosis
GMC	General Medical Council
GFR	Glomerular Filtration Rate

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
HLAi	HLA Antibody Incompatible
HTA	Human Tissue Authority
HTLV	Human T Lymphotrophic Virus
HUS	Haemolytic Uraemic Syndrome
IA	Independent Assessor
IFG	Impaired Fasting Glucose
KDIGO	Kidney Disease: Improving Global Outcomes
LD	Living Donor
LDC	Living Donor Co-ordinator
LDKMR	Living Donor Kidney Matching Run
LDKT	Living Donor Kidney Transplantation
MCGN	Mesangiocapillary Glomerulonephritis
MDT	Multi-Disciplinary Team
mGFR	Measured Glomerular Filtration Rate
METS	Metabolic Equivalents
MDS	Myelodysplastic Syndrome
MGUS	Monoclonal Gammopathy of Uncertain Significance
NDAD	Non-Directed Altruistic Donor
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NTNT	Non-Transfusion Dependent Thalassaemia
ODT	Directorate of Organ Donation and Transplantation
OGTT	Oral Glucose Tolerance Test
PANVH	Persistent Asymptomatic Non-Visible Haematuria
PCR	Protein: Creatinine Ratio
PNVH	Persistent Non-Visible Haematuria
PPD	Paired/Pooled Donation
RCC	Renal Cell Carcinoma
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs
SCD	Standard Criterion Donor
SCT	Sickle Cell Trait

TBMN	Thin Basement Membrane Nephropathy
UKLKSS	UK Living Kidney Sharing Schemes
VTE	Venous Thromboembolism

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2 LEGAL FRAMEWORK

Recommendations

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

- ***All transplant centres performing living organ donation must be licensed by the Human Tissue Authority in line with the requirements of the European Union Organ Donation Directive which sets out the minimum requirements for the Quality and Safety of Organs for Transplantation. (Not graded)***

- ***Consent for the removal of organs from living donors, for the purposes of transplantation, must comply with the requirements of the Human Tissue Act 2004, and the Mental Capacity Act 2005 in England and Wales, and the Mental Capacity Act 2016 in Northern Ireland. Consent in Scotland must comply with the Human Tissue (Scotland) Act 2006 and the Adults with Incapacity (Scotland) Act 2000. (Not graded)***

The Human Tissue Act 2004 is the primary legislation regulating transplantation in England, Wales and Northern Ireland (1). Separate legislation, the Human Tissue (Scotland) Act 2006, applies in Scotland (2).

2.1 The Human Tissue Act 2004

The Human Tissue Act (2004) sets out the licensing and legal framework for the storage and use of human organs and tissue (excluding gametes and embryos) from the living and for the removal, storage and use of human organs and tissue from the deceased. It permits authorised activities to be carried out for certain scheduled purposes. The Act covers seven scheduled purposes requiring general consent, one of which is transplantation, and this incorporates living donor transplantation (3).

Authorised activities, including transplantation, are only lawful if done with 'appropriate consent' (4). Unauthorised dealings may result in offences, which carry penalties (5). The Human Tissue Authority (HTA) issues Codes of practice applicable to those working in England, Wales and Northern Ireland, which establish guidelines for practice, particularly with regard to the meaning and extent of 'appropriate consent' (6,7).

2.2 The Human Tissue Authority (HTA)

The Human Tissue Authority (HTA) was established as the regulatory body under the Human Tissue Act 2004 (8). The HTA regulates the removal, storage, and use of human bodies, organs and tissue from the deceased and the storage and use of human organs and tissue (excluding gametes and embryos) from the living (9,10). The HTA is responsible for assessing all applications for organ donation from living people. This involves an independent assessment process. All donors and recipients see an Independent Assessor (IA) who is trained and accredited by the HTA and acts on behalf of the HTA to ensure that the donor has given valid consent, without duress or coercion, and that reward is not a factor in the donation. If the HTA is satisfied on these matters then approval for the living donation will be given. Clear guidance about the roles and responsibilities of the transplant team and Independent Assessors in the context of living donation is published and regularly updated by the HTA (11).

2.3 The European Union Organ Donation Directive

The European Union Organ Donation Directive (EUODD) came into effect in August 2012 (12). The EUODD was implemented to standardise systems and processes across all member states to improve the quality and safety of human organs intended for transplantation. It is the first pan-European regulatory framework governing the donation and transplantation of organs from the living and deceased and includes common standards for the procurement, transportation, traceability, characterisation and follow-up of living donors across the EU.

The HTA is the Competent Authority for the UK under the EUODD. Every transplanting hospital is licensed by the HTA to perform specified activities related to the donation and/or implantation of a donated organ (13).

2.4 Consent for the Removal of Organs from Living Donors

Seeking consent for the removal of organs from living donors, for the purposes of transplantation, is the responsibility of the treating clinician. Part of the HTA's statutory assessment process is to ensure that the donor has given valid consent (14). The common law, the Mental Capacity Act 2005, and the Mental Capacity Act (Northern Ireland) 2016 also apply for minors and those who lack capacity to give valid consent (15,16).

Following the UK Supreme Court judgment in *Montgomery v Lanarkshire Health Board* [2015] (17), the HTA revised its guidance on valid consent in living organ donation. The clinician responsible for the living donor is required to give the HTA explicit assurance that the person intending to donate understands both the generic and specific material risks of donation. This includes information about *generic risks* to which a) any reasonable person or all donors would attach significance, as well as b) information about *individual risks* to which the person consenting to donation is likely to attach significance (e.g. a clinical reason such as pre-existing hypertension or a non-clinical consideration such as a lifestyle or occupational hazard that is specific to the donor) (see also Chapter 4).

2.5 Types of Living Donation Permitted by the Legislation

In September 2012, the HTA published a revised legal framework, which specifies the types of relationships that are permitted between the living donor and recipient under the Human Tissue Acts (11,14).

1. <u>Directed donation</u>

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

recipient with whom they have a genetic or pre-existing emotional relationship. This includes:

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

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

2. Paired or pool donation

A form of living donation where donor-recipient pairs are involved in a linked 'exchange'. A healthy person, donor 'A', from one donor-recipient pair donates an organ to recipient 'B' in another pair, whose donor then donates to recipient A in a reciprocal arrangement. The donors are not genetically related or known to their respective recipients. 'Paired donations' involve two pairs in an exchange and 'pooled donations' include a series of paired donations, each of which is linked to another in the same series (see Chapter 8).

3. Non-directed altruistic donation

Also known as 'unspecified donation' in EU member states, a form of living donation whereby an organ or part of an organ is donated by a healthy person to an unknown recipient, i.e. someone they have never met and who is not known to them.

4. Directed altruistic donation

A form of living donation whereby an organ or part of an organ is donated by a healthy person and contact between the donor and recipient has been made because the recipient requires a transplant. Within the HTA framework, these donors are categorised as follows:

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

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

2.6 Requirements for Transplants Involving a Living Donor

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

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

1. No reward has been, or will 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. With the exception of non-directed altruistic donors (NDADs), a joint IA interview with donor and recipient is also required by the HTA.

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

- Paired and pooled donation
- Non-directed altruistic living donation
- Directed altruistic donation cases where the donor is non-resident in the UK
- Certain directed donation cases where the donor has an economic dependence on the recipient
- If the organ donor is a child
- If the organ donor is an adult who lacks capacity

The HTA provides an out-of-hours emergency telephone approval service via the executive but this is rarely required in the case of LDKT and must only be used in cases of directed donation where there is an urgent clinical need.

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

2.7 Prohibition of Commercial Dealings in Human Material

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

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

The following terms apply:

- 'Transplantable material' is defined in Part 3, sections 9 and 10 of the regulations and includes living donor liver lobes for transplantation (20);

- ‘Relevant Material’ is material, other than gametes, which consists of or includes human cells;
- ‘Advertisement’ includes any form of advertising for reward, whether to the public generally, to any section of the public, or individually to selected persons;
- ‘Reward’ means any description of financial or other material advantage.

In March 2015, the UK signed the Council of Europe Convention against Trafficking in Human Organs (21). This provides the first internationally agreed legal definition of trafficking in human organs, identifying the activities that ratifying States must criminalise in their national laws. It also includes provisions to deter these practices and to protect victims.

2.8 Reimbursement of Expenses

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

2.9 Exceptional Circumstances

2.9.1 Children

The Human Tissue Act 2004 defines a child as a person under 18 years old (22). In England and Wales the legal position regarding consent by minors (under the age of 18 years) to medical treatment is determined in case law by ‘*Gillick’* (23). It could be argued that organ donation is not, *prima facie,* in the best interests of the minor as a potential donor, nor is it therapeutic treatment. However, if the young person is *‘Gillick* competent’ (understands fully what is proposed and is capable of making a choice in his/her best interests) in principle, he or she may be able to consent to donation. However, children should only be considered as living organ donors in exceptionally rare circumstances. As a minimum, good practice demands that parental consent is always obtained and, even if there is parental consent to donation, that an advanced ruling be sought from the Court before proceeding. The use of a living organ from a child can only proceed with Court approval followed by

approval from an HTA panel (22). In Scotland, living donation of solid organs from children is not permitted under the Human Tissue (Scotland) Act 2006 (see 3.10)

2.9.2 Adults without Mental Capacity

In England, Wales and Northern Ireland, the removal of an organ or part organ from an adult who lacks the capacity to consent to such a procedure requires court approval (14). Following court approval donation may then only proceed if the case is approved by an HTA panel. In Scotland, living donation from adults without mental capacity is not permitted under the Human Tissue (Scotland) Act 2006 (see 3.10)

2.10 The Human Tissue (Scotland) Act 2006

The purpose of the 2006 Act (2) is to make provision for activities involving human tissue in the context of transplantation, research and education, its removal, retention and use following post-mortem examinations, and for the purposes of the Anatomy Act (1984), which is incorporated into the 2006 Act. Provisions of the Human Tissue (Scotland) Act are based on 'authorisation' (24) rather than 'appropriate consent' as in the Human Tissue Act 2004 (3), but the principles in each Act are essentially the same.

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

Under arrangements made between the Scottish Executive and the HTA, potential living donors are assessed by the HTA to ensure that there is no evidence of coercion or financial reward, as in other UK countries. The 2006 Act also permits kidney paired exchange programmes and altruistic donation.

Exceptional Circumstances

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

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

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3 ETHICS

Recommendations

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

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

- ***Independence is recommended between the clinicians responsible for the assessment and preparation of the donor and the recipient, in addition to the Independent Assessor for the Human Tissue Authority. (Not graded)***

3.1 Ethics

Living donor transplantation has become a well-established practice in the UK, contributing more than a third of all organ transplants, of which 97% are LDKT. (1). By its nature, living donor organ transplantation raises a wide range of complex ethical issues. As transplant programmes continue to expand, all health professionals involved in living donor transplantation must be familiar with the general principles that underpin and are applicable to good ethical practice (2-7).

3.2 Key Ethical Principles in Living Donor Transplantation

Altruism has been the basis of organ donation in the UK from the outset and is understood as a selfless gift to others without expectation of remuneration (8). Altruistic giving may be to strangers or take place within the context of family or other relationships. Altruism reinforces the philosophy of voluntary and unpaid donation

and solidarity between donor and recipient. There are some concerns that altruism may be compromised by hidden coercive pressures: for example, the expectation that a family member will donate an organ to help another family member in need of a transplant (9). These pressures may be exacerbated if there is a sense of urgency to transplant a recipient who, for example, is deteriorating rapidly.

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

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

Dignity is often associated with the Kantian concept of the inherent dignity or special status of the human body where dignity and price are mutually incompatible: the maintenance of human dignity requires human beings to be beyond negotiable price (10). Thus, any form of financial payment or 'commodification' of bodies or body parts violates human dignity, even if the person concerned does not feel in any way degraded. The opposing view is that degradation is dependent upon each person's own perception of what is degrading (11).

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

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

3.3 The Recipient Perspective

The rationale for LDKT and the risk versus benefit to the recipient are detailed elsewhere in these guidelines. In terms of outcome, a living donor kidney transplant would almost always be the preferred option, with better transplant and patient survival than for deceased donation. The added recipient benefits include the option for planned pre-emptive transplantation and more opportunities for a successful transplant through the UK living kidney sharing schemes (UKLKSS) and antibody

incompatible transplantation (AIT) programmes (see Chapter 8: Expanding the Donor Pool). For children, living donation offers a unique opportunity for early transplantation and to minimise disruption to growth, development and school.

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

3.4 The Donor Perspective

Donating a kidney involves a detailed process of investigation, major surgery, and a significant period of recovery. Whilst there are documented overall benefits for the individual donor and wider society, living donor surgery entails risk, which includes a small risk of death (see Chapter 6). In addition, removal of a kidney will inevitably cause physical harm to the donor and the potential life-long impact on health and well-being must be fully considered for every individual. This conflicts with the concept of non-maleficence and the maxim ‘first, do no harm’ and is often used as an argument against living organ donation. However, other moral considerations, such as individual autonomy, also contribute to an individual’s decision and motivation to donate and despite the lack of physical benefit for donors, they often describe a psychological gain in knowing that their gift has provided an opportunity to transform the life of a relative, friend or stranger (12). It could be argued that a potential living donor may be psychologically harmed if his/her donation, for whatever reason, does not take place.

The principle of autonomy provides a legitimate basis for supporting living donation. Living donor surgery is morally acceptable when carried out with ‘informed consent, freely given’ but establishing ‘informed consent freely given’ can be problematic. While all living donor programmes expect potential donors to be given an appropriate, detailed description of the risks of donation, it is much less clear that all such donors will listen. There is a well-described tendency for some people to decide that they wish to donate at an early stage and then to be impervious to or oblivious of any suggestion that they should make a more informed decision following counselling (13). The consent may be real, but whether it is truly informed may be questionable (see Chapter 4: Informing the Donor).

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

It is important to recognise that the concept of 'Informed consent, freely given' will vary according to the donor-recipient pair involved. In most situations, the motives and autonomy of the donor will be beyond question but, in others, it can be more difficult to establish that consent is both informed and voluntary. For this reason, a multi-disciplinary team (MDT) approach is recommended in the assessment and preparation of all donors and independence between the clinicians responsible for the donor and the recipient is strongly recommended. Once the clinical assessment is complete, the Independent Assessor for the Human Tissue Authority (see Chapter 2) provides an additional safeguard for the potential donor.

3.5 The Transplant Team Perspective

The collective transplant MDT is responsible for informing the potential donor of the risks associated with living kidney donation. When the MDT has concerns about the suitability of a potential donor and feels that proceeding with donation is inappropriate, the team is under no obligation to proceed.

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 go beyond that which individuals or the team find acceptable or appropriate, they are under no obligation to proceed. Referral for a second opinion may be appropriate in such circumstances (see section 5.2).

The transplant team has an obligation to utilise organs for transplantation to maximise benefit for the whole patient pool. An area of controversy in living kidney donation is when to remove patients from the national transplant list for a deceased donor kidney if they have a potential donor/s undergoing assessment. The risks to the individual recipient, the potential donor and the 'greater good' to the pool of

patients waiting for a kidney must be considered in coming to a decision. See Chapter 4 for further discussion and recommendations.

3.6 Expanding the Living Donor Pool

The options for living donor kidney transplantation in the UK have expanded rapidly over the years in line with technological advances, changes in the legal framework and development of clinical practice. There are unique ethical considerations associated with these developments, which are discussed in Chapter 8.

3.7 The Child or Young Person as a Living Donor

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

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

3.8 The British Transplantation Society (BTS) Ethics Committee

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

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4 SUPPORTING AND INFORMING THE POTENTIAL DONOR

Recommendations

- ***The living donor must be offered the best possible environment for making a voluntary and informed choice about donation. The transplant team must provide generic information that is relevant to all donors as well as specific information that is material to the person intending to donate. This includes information about the assessment process and the benefits and risks of donation to the individual donor. (B1)***

- ***Independent assessment of the donor and recipient is required by primary legislation (Human Tissue Act 2004). (Not graded)***

- ***To achieve the best outcome for donor, recipient and transplant, the boundaries of confidentiality must be specified and discussed at the outset. Relevant information about the recipient can only be shared with the donor if the recipient has given consent and vice versa. Both the recipient and donor must be informed that it is necessary and usual for all relevant clinical information to be shared across the transplant team in order to optimise the chance of a successful outcome for the transplant. (B1)***

- ***Ideally, the recipient will discuss relevant information with their donor, or allow it to be shared. If the recipient is not willing to disclose information, then the transplant team must decide whether it is possible to communicate the risks and benefits of donating adequately, without needing to disclose specific medical details. (Not graded)***

- ***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. 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. (B1)

- ***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. (B1)***

4.1 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 LDKT is of particular importance because the uniqueness of the donor-recipient scenario creates a novel proximity between all parties involved and can generate ethical challenges and uncertainty (1-3).

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 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 can only be shared if the respective party gives express consent. It is advisable to have this discussion at an early stage to avoid any possible misunderstanding or breach of confidentiality and to ensure that the wishes of both donor and recipient are known to each other and to their respective clinical teams.

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

It is necessary for clinical teams to share information that is directly relevant to the management or performance of the kidney transplant. Examples include HLA mismatching/cross matching 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 must 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 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. Both donor and recipient must be informed about the possibility of this before the work-up is started. It may be helpful to seek their views on disclosure of information that is not directly relevant to transplantation at that point. Particular care is required to ensure that material is not inadvertently shared in such circumstances (see section 4.4).

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.

4.2 Informing the Potential Donor

The General Medical Council (GMC) is explicit about the responsibility of registered doctors when seeking informed consent (4). 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).

4.3 Informed Consent for Living Kidney Donation

4.3.1 A Summary of Key Points to be Discussed with a Potential Donor

General points about process, consent and confidentiality:

1. For a living donor to give valid consent for donation, he/she must be properly informed about the generic risks (for all donors) and any specific, individual risks (for them) (see section 4.3.5 and Chapter 2).
2. Informed consent must be sought before progressing to each stage of the pathway.
3. Information must be given about what will be shared amongst the transplant team and the GP.
4. Information must be given about what will not be shared with the potential recipient, unless explicit consent is given to do so.
5. It should be explained that the tests might throw up unexpected findings that may or may not be relevant to donating a kidney. These findings might include:
    a. Information about the genetic relationship with the recipient.
    b. Medical or anatomical findings of uncertain significance that might require further assessment or referral to another specialty.
6. It should be emphasised that the donor can withdraw from the process at any time up until the time of surgery.

Specific points about process and possible outcomes:

1. Risks of donation (generic and specific).
2. Nature of surgical procedure and length of stay in hospital.
3. Potential graft loss in the recipient.
4. Requirement for HTA assessment.
5. Reimbursement of expenses.
6. Requirement for annual review.

4.3.2 Understanding what is Involved

The need for valid consent for kidney donation must be explained to the potential donor. An explanation of the concept of living kidney donation must be provided and a clear definition of the donor assessment pathway. There is a significant commitment involved in attending investigations and consultations and it is important that the donor understands what is expected of them.

Submitting to a number of medical tests can generate uncertainty and anxiety. Even when there are no concerns raised by the tests, the process may be stressful. There is also a chance that tests will uncover an 'incidental finding'. Although the finding of significant pathology in potential donors is low, one study of 1597 potential donors found that the incidence of proven malignancy discovered by CT scan was 0.1% (5). The same study reported that the proportion of people having CT scans that identified an 'incidentaloma' was 17% (5). In another study of 175 potential donors, CT scan revealed a 'potentially significant extra-renal finding' in 28% (6).

Information about the process of kidney donation must also include an explanation of proposed follow-up. Follow-up is recommended to ensure the safety of the donor's health and to facilitate data collection for monitoring outcomes via the National Transplant Registry maintained by NHS Blood and Transplant. It is important that potential donors are aware of the reasons and plans for follow-up after donation (see Chapter 10).

Ideally, both verbal and written information about living kidney donation must be provided.

4.3.3 Information about Likely Outcomes for the Kidney

Although the surgical risks associated with nephrectomy are independent of the identity of the recipient, the likelihood of the transplant being successful may be material to the donor's decision to donate or not. Providing information about the likelihood of success is an integral part of the consent process. The prospective living donor must be given a realistic estimate of the likelihood of successful transplant outcome. Factors that increase the risk of recipient mortality or morbidity and/or graft survival require open discussion with the donor (e.g. pre-emptive transplantation vs time on dialysis, recurrent disease, positive viral serology, age, immunological complexity).

It is only possible to provide the donor with specific information which is relevant to the outcome of the transplant if the potential recipient agrees to such information being shared. If the recipient is unwilling for this information to be shared, the transplant team must decide whether this impinges on the ability of the donor to give valid consent. There may be occasions where it is possible to communicate the risks and benefits of donating without needing to disclose specific medical details. There may, on the other hand, be occasions when the medical team feels that disclosure of a specific diagnosis is essential. The team must be able to articulate clearly why that is the case (7-9). It is then imperative that the recipient understands that reluctance to disclose information directly impinges on the ability of a donor to give valid consent, and that as a 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 fact must be shared so that both donor and recipient have realistic expectations about possible outcomes (see Chapter 11). These discussions with donor and recipient are best performed at an early stage of assessment in separate consultations so that each has the opportunity to speak openly and freely with health professionals and so that expectations can be appropriately managed.

4.3.4 Independence of Decision

Valid consent for surgery must be informed and 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 assured that their views concerning kidney donation, as well as their medical and social history will be treated in strict confidence. It is imperative that language barriers do not get in the way of this consultation (see section 4.6).

The potential donor must be provided with a balanced view of the advantages and disadvantages of living donor transplantation. It should be made clear from the outset that the potential donor may withdraw at any stage in the donation process without having to provide an explanation for his or her decision. He or she must be allowed adequate time to reflect on the decision to donate. If the donor decides not

to proceed, this decision must be respected and should not be regarded as a failure but as a natural result of the education process. If additional emotional support is required, this may be 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, access to specialist psychologist or psychiatrist must be available if necessary (see section 4.7).

If the prospective donor is unable to donate for a clinical reason, this can cause distress for both donor and recipient and may be associated with negative feelings of failure, anger or guilt, which could lead to depression or other negative psychological outcomes. The need for emotional support must be anticipated and adequately provided for in this situation (see section 4.7).

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 which donor should proceed be 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.

4.3.5 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 (4). 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. The risk of death associated with living donor nephrectomy and the risks of short and long-term complications must be fully explained. Following recent developments in case law (*Montgomery*), the clinician responsible for the living donor is required to give the HTA explicit assurance that the person intending to donate understands both the generic and specific material risks of donation. This includes information about *generic risks* to which any reasonable person or all donors would attach significance, as well as information about *individual risks* to which the person consenting to donation is likely to attach significance (10) (also see section 2.4).

4.4 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 have been handled by healthcare professionals in terms of disclosure to both parties (11-13). While cases of misattributed paternity are most common, other unexpected findings 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 previously 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 (14).

The above must 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 (15). 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 before HLA testing is attractive as a risk management strategy, particularly where there may be social and/or cultural considerations, but it must also extend to the recipient as both parties are inextricably linked in the context of living 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, appropriate discussion with the recipient

and donor/s involved allows the underlying principle of valid consent to be upheld provided that all parties 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 and each case will need to be judged on its own 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.

One study has estimated that misattributed paternity will be found in approximately 0.25% to 0.5% of all living kidney donations (12). Given the high likelihood that transplant centres will come across this issue from time to time, transplant teams should determine in advance how they will approach a finding of misattributed genetic identity.

4.5 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 reflected in the UK legislative framework. 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) (15) (see Chapter 2).

In addition to this, 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 be best practice, although it is recognised that this may not be possible at all stages of the donor pathway, particularly around the time of donation/transplantation.

Transplant teams must be aware that potential donors might be subject to significant pressure to donate, especially in cases where there is an expectation or sense of obligation. Such examples include when a potential recipient is unsuitable for inclusion on the deceased donor waiting list but the risk of a planned living donor transplant is considered acceptable, or if someone is the only potential donor. When a donor does not wish to donate but is concerned that refusal may result in family conflict, the donor advocate can assist with discussions to limit damage to family relationships (16).

If at all possible, it is preferable to encourage open and honest discussion between the donor and recipient from the outset. Pre-emptive discussion is helpful in ensuring that both parties are fully informed about how information will be handled by their respective healthcare teams and to minimise the risk of future conflict. Multi-disciplinary meetings are essential to ensure appropriate information is shared and to facilitate the parallel management of both donor and recipient pathways and underpin best practice. This is particularly pertinent when the 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, the recipient 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 (17).

While the outcome of LDKT, particularly pre-emptive transplantation, is superior to that of deceased donor kidney transplantation (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 or not must be made jointly between the donor and recipient, and in discussion with their clinical teams, so that the risks and benefits are clear. Ultimately, all decisions of this nature are made on a case-by-case basis. However, 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.

4.6 Independent Translators

There is a rich cultural and ethnic diversity within the UK 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 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 (18) to ensure that the interests of the potential donor are protected and, as a matter of best practice, they must be used where there are difficulties in communicating freely with both parties. The translator must be unknown to both the donor and recipient and competent to discuss the implications and associated risks of donor nephrectomy and the post-operative recovery process. The translator must 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, telephone translation can be helpful.

4.7 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 (19,20). 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 must 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 is recommended 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 (21). The EPAT tool provides a structured approach to initial psychosocial assessment, which can be performed by any member of the multi-disciplinary team and could help to identify potential areas of concern (22).

Psychological support for the donor 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-ordinator or nurse specialist) who play a key role in organising the assessment and surgery for donor and/or recipient. Such individuals often become closely acquainted with the donor and their families and may be best placed to provide the necessary support, even in the context of adverse events before 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 whereby 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 (23).

Although not mandated by the HTA, formal mental health assessment for all non-directed altruistic donors is recommended best practice (24) (see Chapter 8).

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 (25).

There is some evidence 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 (26). 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 that encourages discussion can relieve the strain and facilitate decision-making.

Sibling decision-making has been reported as one of the most complex areas (23). 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 4.5).

Donors and recipients need to be made aware that psychological problems have been reported after donation (27). 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. Discussion is recommended before 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 must be considered within the context of the wider family network to ensure effective support and intervention.

After donation, kidney donors generally consider that organ donation was a positive experience and regret about having donated is low (20,28). Although most donors report a better quality of life after donation compared to the general population, a small minority have experienced reduced quality of life, higher levels of fatigue and relationship changes (29). These appear to be associated with a pre-donation higher body mass index (BMI), smoking, and higher expectations regarding health consequences. Depression and fatigue after donation may be more prevalent in females (28). Potential donors must be made aware of these possible outcomes and must be followed up appropriately if they arise after donation.

4.8 Death and Transplant Failure

LDKT is increasingly considered the treatment of choice for recipients with higher 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.

Death is a rare complication of transplant surgery, but can occur (see Chapters 6 & 11). Bereavement support in these cases must be provided by qualified, independent counsellors and continue in the community for as long as required. Early graft failure is likely to result in feelings of profound loss for many donors and recipients. Emotional support must be accessible to all patients and their families, up to and including referral to a mental health professional.

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5 DONOR EVALUATION

5.1 INTRODUCTION

The primary goal of the donor evaluation process is to ensure the suitability of the donor and to minimise the risk of donation. This involves identifying contraindications to donation and potential clinical (physical and psychosocial) risks.

To ensure that the evaluation is comprehensive, potential donors must be assessed according to an agreed, evidence-based protocol which includes multi-disciplinary input and discussion. Investigations must be undertaken in a logical sequence so that the potential donor is protected from unnecessary, particularly invasive, procedures until the appropriate stage of assessment. There is good agreement about the recommended routine screening tests and supplementary investigations that may be required to assess the suitability of an individual donor (1). Use of evidence-based guidelines to ensure a consistent approach to the assessment and preparation of living donors has become increasingly important as the criteria for donor acceptance have extended and clarity about individual donor risk is paramount (1,2).

The same best practice principles apply to the assessment and preparation of all donors. Special consideration must be given to donors who are non-resident in the UK, and plan to donate to an NHS-entitled recipient, as well as to donor-recipient pairs who travel to the UK for the purposes of LDKT. These are discussed in more detail in Chapter 9.

The timing of donor assessment will vary according to individual clinical circumstances. In many cases, donor evaluation will only be undertaken once the suitability of the potential recipient for transplantation has been established. However, where the likelihood of recipient contraindications is low, it may be appropriate to start the donor work-up in parallel to the recipient assessment to maximise the chance of pre-emptive transplantation and avoid unnecessary delay.

It is important to respect the confidentiality of the donor and to maintain a clear separation of the interests of the donor and recipient (see Chapter 4). This is best

achieved by ensuring that separate physicians and/or clinical teams assess the donor and recipient before donation and transplantation.

Throughout the evaluation, good communication with the donor's GP is recommended to confirm past and present medical history and to reveal any undisclosed issues that might influence the decision to donate. It is recommended that non-UK resident donors who plan to donate to NHS-entitled recipients are registered as temporary patients at the recipient's GP practice for the duration of their stay in the UK. Written consent is recommended from the donor before disclosure of information or contact with his/her GP. If the donor has previously donated (e.g. a lobe of liver), consent to contact the previous donating centre is also recommended to confirm the outcome of the previous donation and any physical or psychosocial issues relevant to subsequent donation (3).

There are no absolute rules about when a recipient should be suspended from the active national deceased donor waiting list if they have a potential living donor under assessment, and the approach taken will vary according to individual circumstances. Plans are best made after discussion with the individual donor and recipient, but the recipient benefit from receiving a living donor compared with a deceased donor transplant must be made explicit. Another consideration is the optimal management of the national waiting list, although this must never take precedence over the potential recipient's or donor's best interests.

The evaluation of potential living donors is resource intensive and a proportion of those who volunteer as donors will not be suitable to proceed for a variety of clinical and non-clinical reasons. The earliest possible triage of unsuitable donors will help to maximise benefit, minimise risk and manage expectations for donors, recipients and their families. Strategies must also be in place to offer appropriate emotional support and clinical follow-up for potential donors who are found to be unsuitable.

The option of a second opinion must always be available to donors and recipients. A pathway to facilitate referral for a second opinion has been agreed by the LDKT 2020 strategy implementation group and is shown in Table 5.1.1.

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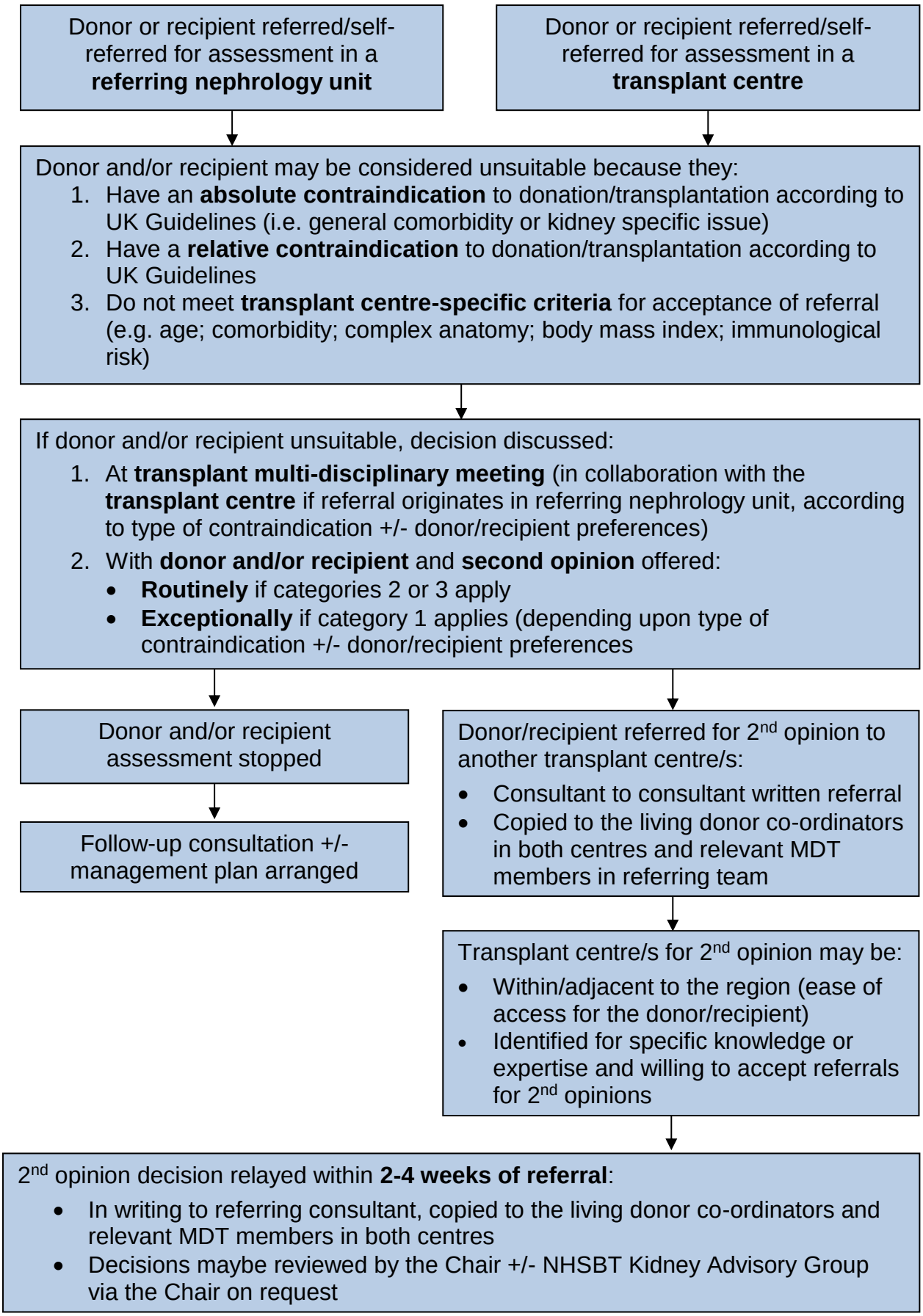
Table 5.1.1 Initiating a Second Opinion for a Living Donor or Recipient of a Living Donor Kidney Transplant



5.2 DONOR EVALUATION: SUMMARY

Recommendations

- ***In cases of directed donation (to a known recipient) the likely suitability of the potential recipient for transplantation must be established before starting donor assessment. If additional recipient assessment is required, unnecessary delay should be avoided. Non-invasive assessment of the donor may be undertaken in this phase. (Not graded)***

- ***As far as possible, donor assessment is planned to minimise inconvenience to him/her and to avoid unnecessary barriers to proceeding. Flexibility in terms of timescales, planning consultations, attending for investigations and date of surgery is helpful. (Not graded)***

- ***Donor assessment must be planned to ensure that it is focused, logical and coherent. Good communication with the donor and involvement of the wider multi-disciplinary team is essential and is achieved most effectively if a designated co-ordinator leads the organisation of the assessment process. The results of investigations must be relayed accurately and efficiently to the potential donor. Unsuitable donors must be identified at the earliest possible stage of assessment. (Not graded)***

- ***A policy must be in place to manage prospective donors who are found to be unsuitable to donate and appropriate follow-up and support must be made available. (Not graded)***

- ***The organisational aspects for donor evaluation will vary between centres, according to available resources and personnel, but the same principles apply for all donors. An agreed donor assessment protocol must be in place that is tailored to the needs of the individual. Table 5.2.1 shows a suggested best practice model with an audit standard for donor evaluation. (Not graded)***

- ***To facilitate pre-emptive transplantation, donor evaluation must start sufficiently early to allow time for more than one donor to be assessed if required. Information must be provided at an early stage and discussion with potential donors and recipients will usually be started when the recipient eGFR is approximately 20 mL/min or when the recipient is expected to require renal replacement therapy within 12-18 months. Recipient and donor assessment can then be tailored according to the rate of decline of recipient renal function, disease specific considerations and individual circumstances. (B2)***

- ***The evaluation of a potential donor should be undertaken within an 18 week pathway, assuming there are no logistical issues such as donor unavailability. There may, of course, be pauses if the recipient's transplant assessment is complicated or if the recipient's renal function remains satisfactory. A suggested timeline for donor work-up is presented in Table 5.2.1***

References

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Table 5.2.1 Donor Evaluation: Summary and Organisational Chart (directed donor-recipient pair)

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
To minimise time on dialysis for suitable recipients

↓

Establish recipient fit for transplantation & start appropriate pre-transplant assessment as per local protocol [see section 5.1]

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

↓

Weeks 0-2

Potential donor(s) identified.
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 resources
To ensure that the donor can give valid consent for donation

↓

Weeks 2-4

ABO compatibility +/- HLA sensitisation (if indicated) confirmed. Primary contra-indications identified from donor(s) past and present medical history*. Routine blood & urinalysis tests.

* Donor screening questionnaire (Appendix 5.2) with telephone or face to face triage

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

↓

Weeks 4-8

Donor evaluation is planned with the prospective donor, in a timely 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' investigations, multidisciplinary 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

Within 2 weeks of investigations (10)

Weeks 8-10

Results review by members of the MDT & feedback to the donor.

RATIONALE: To ensure continuity & keep the donor informed

Weeks 11

If donor unsuitable, follow-up arranged.

RATIONALE:

To offer opportunity to discuss results & arrange appropriate follow up

Suitable donor & recipient pair referred for final pre-operative discussion with Consultant Nephrologist and Transplant Surgeon, & Independent Assessment for Human Tissue Authority. Date of transplant or management plan via the UKLKSS agreed

RATIONALE: To ensure transplant can legally proceed & that both donor & recipient can provide valid consent for surgery

Final cross match within the 7-10 days before Tx + routine pre-op investigations/pre-admission visit*

RATIONALE: To ensure transplant can safely proceed*

* only applies to UKLKSS pairs once matched

Week 18

OPERATION/ready to list in UKLKSS

LD co-ordinator maintains contact with donor & facilitates life-long follow-up arrangements

RATIONALE: To provide continuing support to the donor & inform the UK Living Donor Registry

APPENDIX 5.2	**DONOR HEALTH QUESTIONNAIRE** **PLEASE ANSWER ALL QUESTIONS**
Name: Date of birth: Address: E mail: Telephone number:	Name of person requiring transplant (if known): Date of birth: Address: Relationship to you (if any):

Have you ever been in hospital? If yes, please give details	Yes	No
Have you had any operations? If yes, please give details	Yes	No
Do you attend your GP regularly? If yes, please give details	Yes	No
Are you on any regular medication? If yes, please give details	Yes	No
Do you take:		
The contraceptive pill	Yes	No
Hormone replacement therapy (HRT)	Yes	No
Aspirin	Yes	No
Do you have any allergies? If yes, please give details	Yes	No

What is your height? _____

What is your weight? _____

Have you been diagnosed with any of the following?

High blood pressure	Yes	No
Diabetes	Yes	No
Angina / heart disease	Yes	No
Stroke	Yes	No
Kidney stones	Yes	No
Cancer	Yes	No
Blood clot	Yes	No
Bleeding from the bowel	Yes	No
Depression or mental health issues	Yes	No

When was your last smear test (women only)? ----------
When was your last mammogram (women over 50)? ----------
Have you participated in the National Bowel Screening Programme (over 60 years only)? ----------

Do you smoke? Yes No

Have you ever injected recreational drugs? Yes No

How many units of alcohol do you drink on average per week? ----------

Have you travelled outside Europe/North America within the past 12 months? Yes No

Have any of your family members (close blood relatives) been diagnosed with?

Diabetes	Yes	No
Kidney failure	Yes	No
Cancer	Yes	No
Early onset heart disease/failure	Yes	No

Are you willing for us to contact your GP and review your medical records if necessary? Yes No

I have completed these questions to the best of my knowledge:

Signature: …….. Date:

Please provide the following details so that we can register you in our hospital system	
GP Details Name: Address: Telephone number:	Next of Kin Name: Relationship: Address: Telephone number:

For hospital use only	
Date received:	Date reviewed:
Comment/special instructions:	

5.3 ABO BLOOD GROUPING AND CROSSMATCH TESTING

Recommendations

- ***A compatible ABO blood group and human leucocyte antigen (HLA) transplant offers the best opportunity for success. (A1)***

- ***Where ABO or HLA incompatibility is present, alternative options for transplantation must be discussed with the donor and recipient, including paired/pooled donation and antibody incompatible transplantation. Antibody incompatible transplantation must only be performed in a transplant centre with the relevant experience and appropriate support. (A1) (see Chapters 7 and 8)***

ABO blood grouping is an important early screening test as it identifies if a (directed) donor is blood group compatible or incompatible with his/her intended recipient at an early stage. Alternatively, in non-directed donation, it provides information that will be used to allocate the kidney to a suitable recipient. ABO blood group testing may be undertaken by the GP, nephrologist, specialist nurse, or at a transplant assessment clinic.

Initial HLA typing +/- crossmatch testing is performed once the blood group status is established, in accordance with the recommendations in Chapter 7. For non-directed donors, HLA typing provides essential information for kidney allocation purposes, but crossmatching is only performed once a potential recipient has been identified in the UK Living Kidney Sharing Schemes (UKLKSS) or on the national transplant list (see Chapter 8).

If the directed donor is not blood group compatible with his/her recipient, an alternative donor may be sought or options for paired pooled donation and/or antibody incompatible transplantation can be considered. See Chapters 7 and 8.

5.4 MEDICAL ASSESSMENT

It is important to manage the expectations of the donor from the outset and to be clear about the difference between a healthy individual and a suitable donor. For example, an otherwise healthy person with one kidney or short renal vessels may be unsuitable to donate. The assessment may reveal previously undiagnosed disease, and potential donors must be warned of this possibility. A previously unrecognised condition may impact on future life insurance or specialist employment. Conversely, early detection of a health problem, which might otherwise have gone undiagnosed, may benefit the donor.

A full past and present medical history must be taken and the areas listed in Tables 5.4.1 must be addressed and followed up where required. The history aims 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), or any past or present condition that could impact on the safety of the donor at the time of surgery or in the long-term. These aspects are discussed in detail throughout Chapter 5. 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.

A psychosocial assessment is recommended for all donors with appropriate referral to a mental health professional as required (see Chapters 4 and 8). The EPAT tool provides a structured approach to initial psychosocial assessment which can be performed by any member of the multi-disciplinary team and which can help to identify potential areas of concern. A particular issue is the assessment of mental and physical health in the potential donor with a history of substance or drug abuse. Such potential donors should always receive formal psychiatric assessment. For non-directed donors, assessment by a mental health professional is recommended in all cases and a structured assessment process has been developed in the UK to assist this (appended to Chapter 8).

Donor assessment will usually be arranged by a specialist transplant/living donation nurse, supported by a clinician. The clinician will undertake the medical examination of the potential donor and, if possible, should not be directly involved in the care of the intended recipient. Table 5.4.4 details the routine screening investigations that are recommended for the potential donor.

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Table 5.4.1

Summary of Key Points of Importance in the Medical +/- Family History of a Potential Kidney Donor

Haematuria/proteinuria/urinary tract infection
Difficulty in passing urine, including urgency, frequency, dysuria
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 or current 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
Mental health 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, 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, Hepatitis B and C infection

Haemophiliac or sexual partner of haemophiliac

High risk sexual behaviour

History of infectious hepatitis or syphilis

History of intravenous drug use

Tattoo or skin piercing within last 6 months

Sexual partner of an individual with positive serology

Sexual partner of drug addict

Table 5.4.3

Points of Particular Importance when Undertaking Clinical Examination of a Potential Kidney Donor

Abdominal fat distribution
Blood pressure
Body mass index
Dipstick urinalysis
Evidence of self-harm
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
Examination of the cardiovascular and respiratory systems
Mental health

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)

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

Recommendations

Measurement of Renal Function

- ***Initial evaluation of donor candidates should be using estimated glomerular filtration rate (eGFR), expressed as mL/min/1.73m^2 computed from a creatinine assay standardised to the International Reference Standard. (B1)***

- ***GFR must subsequently be assessed by a reference measured method (mGFR) such as clearance of ^{51}Cr-EDTA, ^{125}iothalamate or Iohexol performed according to guidelines published by the British Society of Nuclear Medicine. (B1)***

- ***Differential kidney function, determined by ^{99m}TcDMSA scanning is recommended where there is >10% variation in kidney size or significant renal anatomical abnormality. (C1)***

Advisory GFR Thresholds for Donation

- ***Pre-donation mGFR should be such that the predicted post-donation GFR remains within the gender and age-specific normal range within the donor's lifetime. Recommended threshold levels are defined in Table 5.5.2. (B1)***

- ***The risk of end-stage renal disease (ESRD) after donation is no higher than that of the general population. However, there is a very small absolute increased lifetime risk of ESRD following donation for which the potential donor must be consented. (D2)***

- ***The decision to approve donor candidates whose renal function is below the advisory GFR threshold or who have additional risk factors for the development of ESRD should be individualised and based on the predicted lifetime incidence of ESRD. (D2)***

- ***The renal function requirements of the intended recipient, based upon the absolute GFR of the donor, are relevant to the decision to donate (in a directed donation) and to the acceptance of a kidney offer from a non-directed donor or within the UK Living Kidney Sharing Schemes. (Not Graded)***

Monitoring of Kidney Donor

- ***The donor must be offered lifelong annual assessment of renal function including serum creatinine, estimation of urine protein excretion and blood pressure measurement. (B1)***

5.5.1 Initial Assessment of Donor Renal Function

The initial assessment of renal function in potential living kidney donors is by measurement of serum creatinine. This is most commonly performed by an estimate of glomerular filtration rate ($eGFR_{cr}$) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and employing a creatinine assay with calibration traceable to standardised reference material. A correction factor must be applied to $eGFR_{cr}$ values estimated for people of African-Caribbean or African family origin (multiply $eGFR_{cr}$ by 1.159) (1).

Screening identifies potential living donors with evidence of existing CKD ($eGFR_{cr}$ <45 mL/min) who may be saved further investigation as potential kidney donors and who may require investigation in their own right. However, there is significant imprecision of $eGFR_{cr}$ around the normal range, making it unsuitable as a marker of renal function without confirmation (1).

More detailed assessment of potential donor function requires an accurate measurement of GFR using a reference standard measure such as clearance of inulin, ^{51}Cr-EDTA, ^{125}I-iothalamate or iohexol (1). This is used to inform potential donors of the long-term risks of donation and potential recipients of the anticipated level of kidney function being transplanted. ^{51}Cr-EDTA is the most widely available reference test. Recent data show a significant coefficient of variation of ^{51}Cr-EDTA measured GFR in potential living kidney donors across UK centres (2). The

technique must be performed strictly according to guidelines of the British Society of Nuclear Medicine (3).

Divided Renal Function

Divided renal function, measured by combining ^{51}Cr-EDTA and ^{99m}Tc-DMSA, can be helpful in decision-making where there is a size disparity between the two kidneys (>10%) in a potential donor, if renal function is close to the acceptable threshold for donation, or when there is anatomical abnormality or complexity. If suitable for transplantation, the kidney with lower function is usually donated. Some centres choose to perform split function testing routinely on all donors, although the evidence for doing so is limited (4).

5.5.2 What is a Safe Threshold Level of Kidney Function to Donate?

A safe threshold level of pre-donation kidney function is one that leaves sufficient function after donation to maintain the donor in normal health (or minimal absolute reduction of health) without affecting lifespan. This requires a definition of normal renal function and of the normal range of age-related change in renal function in healthy adults over time.

It is reasonable to assume that a threshold which leaves the donor with normal age-related kidney function after donation is safe. This assumption must be supported by long-term post-donation health outcomes of kidney donors. These outcomes include:

- Early post donation kidney function after compensation of the residual kidney
- Lifetime rate of decline in kidney function after donation
- Any increased risk of ESRD and long-term mortality, as well as any impact on other non-renal health outcomes when compared to a matched equally healthy comparator population

It is important to recognise the limitations of the current evidence base (5). Most series reporting long-term post-donation outcomes comprise mainly Caucasian donors who have been normotensive, non-diabetic and normo-albuminuric. The mean age at donation of the cohorts has been around 45 years and the lower

threshold for donation a GFR >80 mL/min/1.73m^2. The current practice of living donation includes donors outside these criteria.

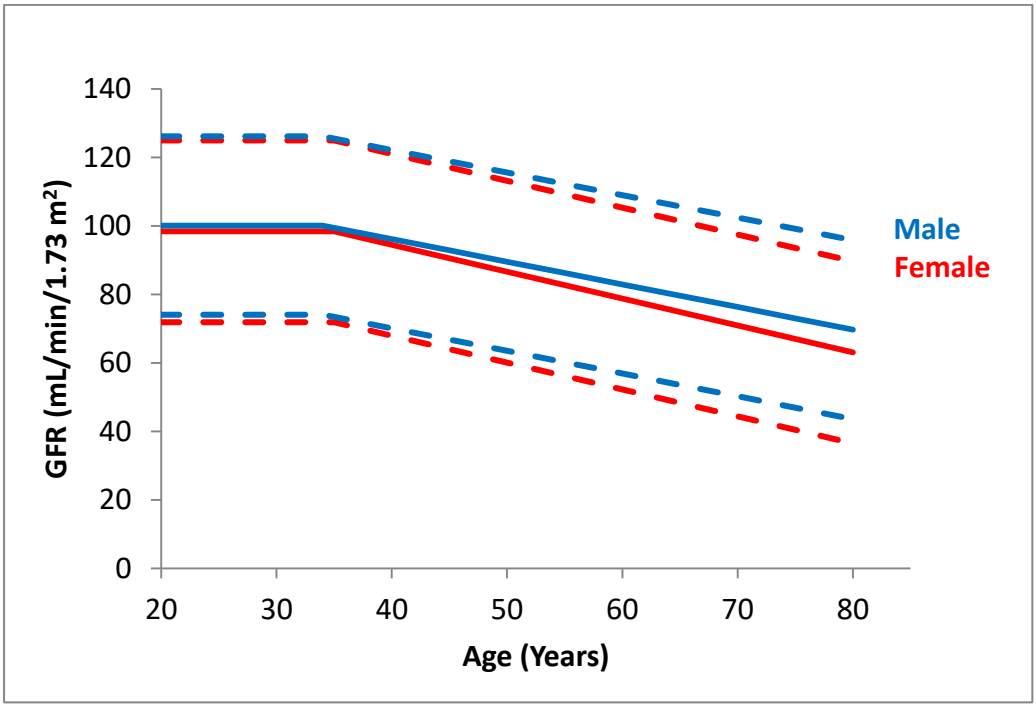
Normal Kidney Function & Change in Kidney Function with Aging

Recent data accurately define gender and age-specific mean and normal ranges for measured GFR in over 3000 healthy potential UK living kidney donors. Data on glomerular filtration rate measured by ^{51}Cr-EDTA clearance in donors at two large UK centres were amalgamated with patient level data from a recent study of GFR in over 1800 potential donors from 15 UK centres (6,7). This study conclusively indicates that renal function corrected for BSA is significantly higher for men than women after age 40 years. GFR in this normal population remains stable in both sexes until aged around 40 years and then declines each decade at a rate of 6.6 mL/min/1.73m^2 for men and 7.7 mL/min/1.73m^2 in women.

Table 5.5.1 Age and Gender-Specific GFR based on almost 3000 Healthy Potential UK living kidney donors

Age (years)	Measured GFR (mL/min/1.73m^2)	
	Male	Female
20-29	100 (74-126)	98 (72-125)
30-34	100 (74-126)	98 (72-125)
35	99 (73-126)	98 (72-125)
40	96 (70-122)	94 (68-121)
45	93 (67-119)	91 (64-117)
50	90 (63-116)	87 (60-113)
55	86 (60-112)	83 (56-109)
60	83 (57-109)	79 (52-105)
65	80 (54-106)	75 (48-101)
70	76 (50-102)	71 (44-97)
75	73 (47-99)	67 (40-94)
80	70 (44-96)	63 (36-90)

Figure 5.5.1 Mean and Lower Normal Values (-2SD) for GFR Determined in Almost 3000 Healthy UK Potential Living Kidney Donors (6)*



*** The mean fall in GFR each decade after 40years is 6.6 mL/min/1.73m^2 for men and 7.7 mL/min/1.73m^2 in women**

Early changes to Renal Function Following Living Kidney Donation

Following kidney donation there is a compensatory increase in function in the remaining kidney in male and female donors across a broad age range. By three months, remnant kidney clearance increases to a mean GFR of around 65-75% of pre-donation renal function. In 22 studies where it was described, the average decrement in GFR after donation was 26 mL/min/1.73m^2 (range 8-50) (7).

Long-Term Loss of GFR in Kidney Donors

The rate of decline in renal function following kidney donation appears to be no higher, and it is likely that it is lower, than in the healthy general population. It appears reasonable and cautious to employ the cross-sectional age-related decline in renal function in the normal population to predict renal function after donation in the long term. The recommended age-related GFR thresholds for donation in this

guideline ensure that predicted renal function will remain within the lower limit of normal GFR with aging.

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 in a single US centre (selection criteria for donation, GFR >80 mL/min/1.73m^2). Most donors (85.5%) had a clearance of >60 mL/min/1.73m^2 on follow-up, and none were <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/y, this being measured with two samples three years apart an average of 12 years after donation. A caveat is that the population was predominantly Caucasian (9). In a prospective study of GFR in 203 donors and healthy matched controls, residual renal function continued to improve in donors over three years post-donation, whereas controls had the expected age-related decline in function (10). Analysis of 9229 UK kidney donors selected according to previous (2011) UK Guidelines (1-10 year follow-up) demonstrates the expected fall in eGFR from baseline to 1 year post-donation (35%). Thereafter, renal function remained stable up to 5 and 10 years across all donor age ranges (20-70 years), albeit numbers by 10 years were small (11).

5.5.3 Is Donation Associated with an Increased Risk of End-Stage Renal Disease, Cardiovascular Disease or Death?

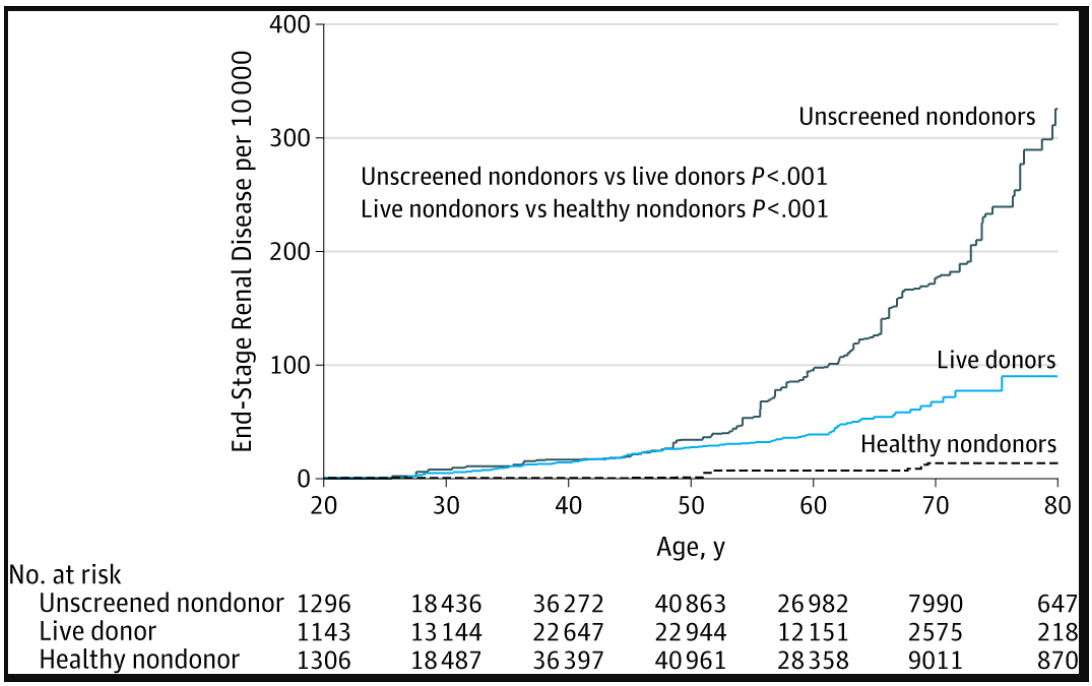
Decreased GFR in the general population is associated with an increased risk of adverse outcomes including ESRD, cardiovascular disease and death. This increase becomes apparent with a GFR between 60-75 mL/min/1.73m^2 as compared to GFR >90 mL/min/1.73m^2 and rises exponentially thereafter (1).

The incidence of ESRD in living kidney donors appears to be similar to or lower than that seen in the unselected general population despite a reduction in GFR (12). This is reassuring but not unexpected. Two recent studies compared the post-donation risks of ESRD with carefully matched healthy controls. Muzaale compared the outcome of 96,000 kidney donors in the USA over a maximum follow-up of 15 years (mean 9 years) with matched healthy controls. The donor population was 75% white, 25% obese and 22% had a pre-donation eGFR <80 mL/min. The estimated risk of ESRD 15 years post-donation was 31 per 10,000 compared to 4 per 10,000 in

matched controls. The increased risk was far greater in high risk donor populations such as African American donors, 75 per 10,000. The estimated lifetime risk of ESRD was 90 per 10,000 in donors, 326 per 10,000 in the general population, and 14 per 10,000 in matched healthy non-donor controls (13). A second study included 1,901 Norwegian donors compared with healthy matched controls and demonstrated a similar increased risk of ESRD after kidney donation (14).

Donors may be reassured that the absolute increase life time risk of GFR <30 mL/min/1.73m^2 or ESRD is very small (<1%) for the populations included in this study. The absolute risk for young donors over a lifetime, particularly with additional risk factors for ESRD is likely to be more significant.

Figure 5.5.2 Estimated Lifetime Risk of End-Stage Kidney Disease in Matched but Unscreened Non-Donors, Living Kidney Donors and Matched Healthy Controls (12)



5.5.4 Individualisation in Discussion of the Risks of ESRD

Physicians are faced with advising potential donors how to proceed when they have additional adverse factors associated with an increased lifetime risk ESRD. Factors and compounding risks include:

- Measured GFR just below the guideline threshold
- Ethnic groups at higher risk (African Caribbean or South Asian origin (by inference))
- Hypertension, obesity and/or (pre) diabetes

A recent US study is helpful in counselling these potential donors (14). Outcome data of almost 5 million participants from seven US cohorts followed for 4-16 years enabled 15 year and lifetime risk projections for the incidence of ESRD in non-donors. This was based on baseline clinical and demographic factors in people **who did not donate**. An online calculator allows estimation of the risk of ESRD using 10 clinical and demographic factors (www.transplantmodels.com/esrdrisk). Hypertension, obesity (BMI >30 kg/m^2), smoking status, eGFR 60-89 mL/min/1.73m^2 and abnormal urine albumin excretion independently increased the long-term risks of ESRD by 1.35, 1.16, 1.76, 1.63 and 2.94 fold respectively.

The actual risk of ESRD in almost 53,000 living donors was then compared with the risk of the matched population. The 15 year observed risk of ESRD for donors was 3.5 to 5.3 times greater than the expected risk, and was higher for blacks compared with Caucasians and in men compared with women. The risk of ESRD was greatest for younger patients of black ethnicity. The absolute increased lifetime risk of ESRD may be helpful in counselling potential donors with risk factors including those below threshold GFR as defined above. The data also support donation from some older donors who have additional risk factors such as hypertension but whose lifetime risk of ESRD is low.

Three retrospective observational studies compared mortality among living kidney donors in comparison with healthy non-donors (8-10). Two studies (one from the United States with a follow-up of up to 12 years and one from Canada with a median follow-up of 6.5 years) revealed a lower risk of death in donors compared to healthy non-donors whilst the third study suggested a possible small increase. Garg et al conducted a study of living kidney donors in the province of Ontario, Canada, who

donated between 1992 and 2009 (8). A total of 2028 donors and 20,280 matched non-donors were followed for a median of 6.5 years (maximum 17.7 years). The risk of death and cardiovascular events was lower and the risk of death-censored cardiovascular events was the same in the donors as compared with the healthy matched population. The quality of the evidence is considered poor. There is no clear evidence that donation reduces long-term survival (5) (see section 10.1).

5.5.5 Advisory Threshold Measured GFR Considered Safe for Donation

The age and gender-specific GFRs that are considered safe to donate are defined in Table 5.5.2. Long term outcome studies demonstrate a very small absolute increased risk of ESRD in large donor populations with mGFR in excess of 80 mL/min/1.73m^2 where the mean age at donation was around 40-50 years. However, these series contain only small numbers of young donors (13,14).

A threshold GFR >80 mL/min/1.73m^2 appears safe for donation in the 35 year and above age range.

Given the extended expected lifetime risk of over 60 years for a 20-year-old, recommendations for minimum GFR in younger donors are more conservative. Grams demonstrated an increased absolute lifetime risk in younger donors with GFR <90 mL/min/1.73m^2, particularly those with additional risk factors (15). A threshold for donation of >90 mL/min/1.73m^2 has therefore been set for those <30 years.

For those >45 years the threshold renal function is predicated on post-donation GFR (75% of pre-donation function) remaining above the lower limit of the age and gender-specific normal range described above (-2SD below mean). At all age and gender-specific GFR thresholds, predicted post-donation renal function in the long term is based cautiously on loss of GFR each decade after age 40 of 6.5 mL/min/1.73m^2 for men and 7.9 mL/min/1.73m^2 in women. As such, if the thresholds given in table 5.5.2 and Figures 5.5.3 and 5.5.4 below are adopted, renal function will be expected to remain within the normal range up to age 80.

Table 5.5.2 Advisory Threshold GFR Levels Considered Acceptable for Living Kidney Donation*

Age (years)	Threshold GFR (mL/min/1.73m^2)	
	Male	Female
20-29	90	90
30-34	80	80
35	80	80
40	80	80
45	80	80
50	80	80
55	80	75
60	76	70
65	71	64
70	67	59
75	63	54
80	58	49

***Where the potential donor GFR lies just below these thresholds or there are additional factors for the development of ESRD, the decision on suitability for donation should be based on a discussion of the lifetime risk of ESRD without donation. www.transplantmodels.com/esrdrisk**

Figure 5.5.3 Advisory Threshold GFR Considered Acceptable for Donation in Males

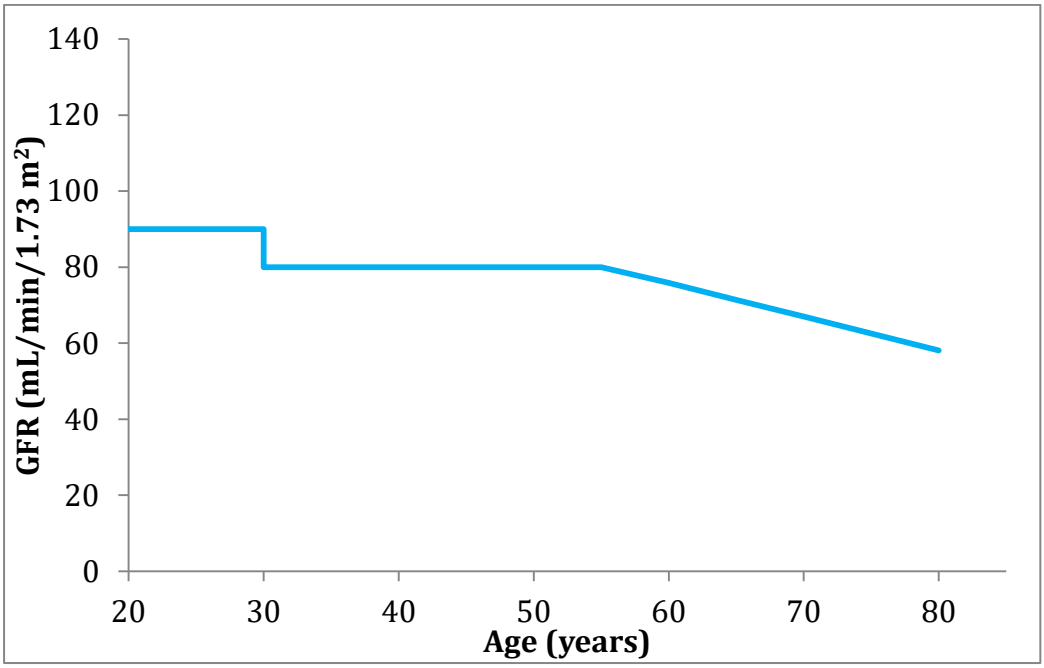
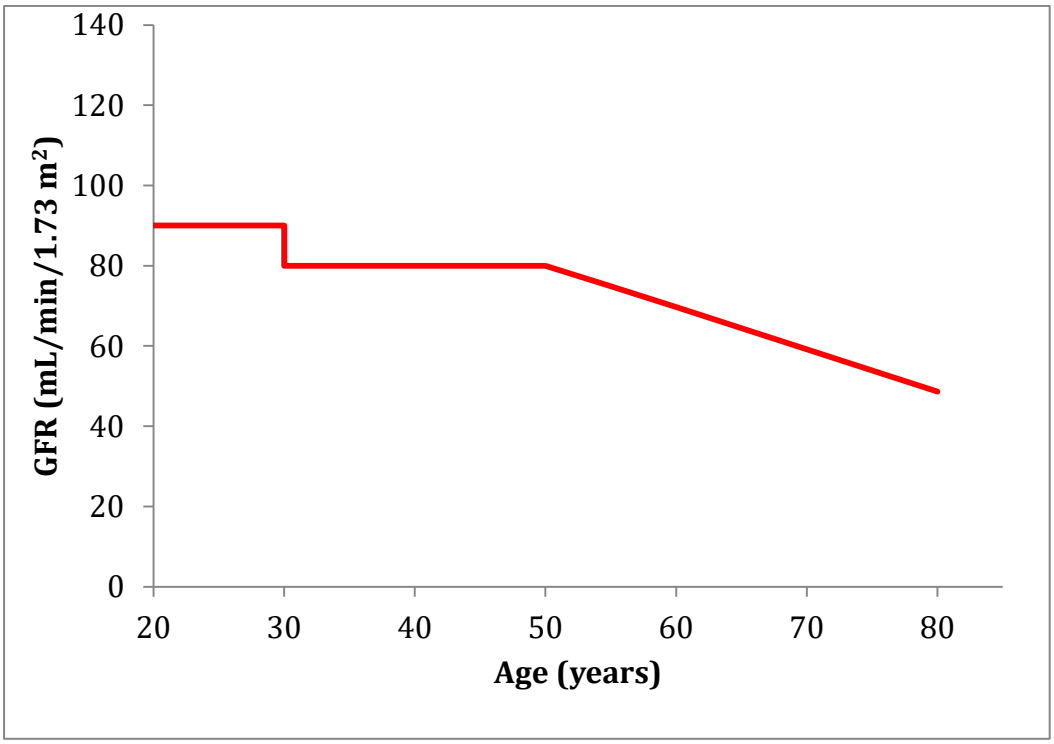


Figure 5.5.4 Advisory Threshold GFR Considered Acceptable for Donation in Females



5.5.6 Research Recommendation

Prospective monitoring of post-donation outcomes compared with matched healthy controls, particularly amongst ethnic minority donors, those with GFR lower than current BTS recommendations, and those with co-morbidities.

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5.6 DONOR AGE

Recommendations

- ***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 must 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.

5.6.1 The Young Donor

Most programmes do not consider donors aged <18 years and consider an age of 18-21 years as a relative contraindication to donation. Younger donors, even if without risk factors for kidney disease at the time of evaluation, may still develop diabetes, hypertension, obesity, immunologically mediated disease or other renal risk factors, and have more time for these risk factors to progress to CKD and ultimately ESRD. This is supported by OPTN data which show that most of the donors that have been placed on the transplant waiting list had donated between the ages of 18 and 34 years and developed ESRD >15 years after donation (2). Careful psychological assessment is recommended before donation.

5.6.2 The Older Donor

In the last five years there has been a significant increase in the number of living donations in the UK from the 60-69 and ≥70 year groups. Donors above 60 years of

age need careful consideration with respect to the increased risk of peri-operative complications, existing comorbidities and residual function post-donation, and also the long-term transplant outcome in the recipient associated with reduced donor GFR and potential donor vasculopathy.

5.6.3 Donor Complication Rates Related to Age

Much of the change in attitude towards accepting older donors is due to the wide and almost universal use of laparoscopic kidney donation in the UK and the resultant reduction in morbidity and improved recovery. Although peri-operative outcomes such as operative time, blood loss and length of stay are shown in some recent studies to be no different from younger donors in carefully selected donors above 60 years (3-5), caution should be exercised in the evaluation, operation and post-operative management of the older donor.

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 (6). 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. 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 (7). In keeping with this, some centres report higher laparoscopic nephrectomy rates in donors >50 years (8).

Pre-donation cardio-respiratory function should be carefully assessed in older donors. Most centres perform a stress echocardiogram and/or myocardial perfusion scan if indicated. Respiratory function tests may be indicated in smokers and those with airway disease. Cardiopulmonary exercise testing, and in particular the definition of the 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 (9).

Screening of serum PSA is mandatory in males above 55 years. Although a mildly elevated PSA may not preclude donation, a rising PSA over time may be of concern

and there should be a low threshold for formal urological review. In women, an up-to-date mammogram and relevant history should be reviewed. In all patients, there should be a careful review of bowel function, incorporating the results of up-to-date population screening tests such as tests for faecal occult blood. Social, family and psychological support for elderly donors should be provided, particularly in the case of altruistic donation.

5.6.4 Graft Outcome from Older Donors

Renal function declines progressively with age and kidneys from older living donors have reduced function (10). Matas et al reported the outcome of 2,540 living donor kidney transplants in their centre and documented worse outcome when the donor was >55 years of age (11). In one study, 5 year graft survival after living donor transplantation was 76% for kidneys from donors >60 years (n=241) and 79% for kidneys from donors aged <60 years (n=518). However, serum creatinine levels remained significantly lower in the recipients of kidneys from younger donors, and graft survival was significantly better beyond 5 years after transplantation (12).

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 (13). 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 (14).

More recently, using the UNOS data from 1994 to 2012, 250,827 kidney transplant recipients were categorised by donor status: standard criteria donor (SCD), expanded criteria donor (ECD), or living donor (LD); and by donor age: <60, 60-64, 65-69, ≥70 years. 92,646 of the transplants studied from living donors, with 4.5% of the recipients (4,186) transplanted with older LD kidneys. Transplant recipients with older LD kidneys had significantly lower graft and patient survival compared to younger LD recipients. Compared to SCD recipients, graft survival was decreased in recipients with living donors 70 years or older, but patient survival was similar. Older LD kidney recipients had better graft and patient survival than ECD recipients (15).

Overall, the use of older kidney donors appears to be an equivalent or beneficial alternative to awaiting deceased donor kidneys (15). Donor GFR has been demonstrated to be an important determinant of transplanted kidney function (16) 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 (14).

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 (17,18).

5.6.5 Long Term Risk for Older Donors

Older donors with potential risk factors for kidney disease, such as hypertension or diabetes, are less likely than younger donors to have enough time for such risk factors to lead to progressive kidney disease, or for any kidney disease that develops to affect life expectancy (19).

5.6.6 Summary

Most US transplant programs currently do not have an upper age limit for accepting donors and are more flexible in applying exclusion criteria for renal risk factors in older donors (20). UK practice also tends to this conclusion. Younger potential donors with borderline risk factors should be subjected to stringent exclusion criteria (21).

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5.7 DONOR OBESITY

Recommendations

- ***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) must undergo careful pre-operative evaluation to exclude cardiovascular, respiratory and kidney disease. (C2)***

- ***Moderately obese patients (BMI 30-35 kg/m^2) must be counselled 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) must be counselled about the long-term risk of kidney disease and be advised to lose weight before 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 donation should be discouraged. (C1)***

In 2013 over 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, heart disease, stroke, sleep apnoea and certain cancers (3).

Obesity is considered a relative contra-indication to living kidney donation because of the increased risk of surgical complications and 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, n=58) 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 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). A further meta-analysis in 2013 of nearly 6000 laparoscopic donor nephrectomies showed a significant increase in conversion to open surgery as the only morbidity risk that was significantly increased in the obese donor (absolute risk 2.7% versus 1.5%, odd ratio 1.69) (8). 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 (9). Similar findings were supported by US Registry Analysis of 14,964 living donors, of whom a moderate proportion were obese (10).

Overall, these data suggest that laparoscopic donor nephrectomy is an increasingly safe procedure in the otherwise healthy obese kidney donor and does not result in a high rate of major peri-operative complications.

The principal 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 future kidney function. In addition, data suggest that obesity is independently associated with a higher risk of developing end stage kidney disease (11). Focal glomerulosclerosis and obesity-related glomerulopathy (glomerular enlargement and mesangial expansion) with associated proteinuria have been described in patients with severe obesity (12) and 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) (13). 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 before donation (14). 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 (15). 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 (16). Obesity was associated with a higher risk of hypertension and dyslipidaemia in both donors and controls. 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 had a significantly greater fall in eGFR than those with BMI <35 kg/m^2 (40 and 28 mL/min/1.73m^2 respectively) (17). 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 (18). In a more 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 (19). There was no control group in this study.

These findings support the current practice of accepting 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.

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5.8 HYPERTENSION IN THE DONOR

Recommendations

- ***Blood pressure must be assessed on at least two separate occasions. Ambulatory blood pressure monitoring or home monitoring is recommended if blood pressure is high, high normal or variable, or the potential donor is on treatment for hypertension. (C2)***

- ***We suggest that a blood pressure <140/90 mmHg is usually acceptable for donation. (C1)***

- ***Prospective donors must be warned about the risk of developing donation-related hypertension, particularly if in a high-risk group. Blood pressure measurement is part of annual donor monitoring. (C1)***

- ***Potential donors with mild-moderate hypertension that is controlled to <140/90 mmHg (and/or 135/85 mmHg with ABPM or home monitoring) with one or two antihypertensive drugs and who have no evidence of end organ damage may be acceptable for donation. Acceptance will be based on an overall assessment of cardiovascular risk and local policy. (C1)***

- ***It is recommended that potential donors with hypertension are excluded from donation if: (C1)***
    - ***Blood pressure is not controlled to <140/90 mmHg on one or two antihypertensive drugs***
    - ***Evidence of end organ damage (retinopathy, left ventricular hypertrophy, proteinuria, previous cardiovascular disease)***
    - ***Unacceptable risk of future cardiovascular risk or lifetime incidence of ESRD***

- ***All living kidney donors must be encouraged to minimise the risk of hypertension and its consequences before and after donation by lifestyle measures including stopping smoking, reducing alcohol intake, frequent exercise and, where appropriate, weight loss. (C1)***

- ***It is recommended that donors who are diagnosed with hypertension during assessment or who develop hypertension following donation are managed according to British Hypertension Society guidelines. (B1)***

Hypertension is one of the commonest reasons for declaring a potential kidney donor medically unsuitable (1). Sub-clinical, hypertensive nephrosclerosis may be present at the time of donation. In addition, an increase in blood pressure after donation may increase future cardiovascular risk or predicted lifetime incidence of ESRD above an acceptable level. As with other aspects of living donation, 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 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.

In addition, it is evident that the risk of cardiovascular disease 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 recognition of the risk of 'high normal' blood pressure and the need to monitor this patient group (4). 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 are 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. 20-25% of the population will exhibit 'white coat' hypertension (6). In this situation, 24-hour ambulatory blood pressure monitoring (ABPM) or home readings may be useful. In addition 10-30% of the population may have a normal office blood pressure but demonstrate hypertension with ABPM or home readings (masked hypertension) (7).

The British Hypertension Society define hypertension when daytime ABPM or average home blood pressure is >135/85 mmHg (8). 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. This discrepancy was most marked in older donors (9). These data would support the use of ABPM in the assessment of potential donors with hypertension based on office measurements. Ozdemir et al suggested that ABPM was more sensitive at identifying hypertension in potential donors than office blood pressure measurements (10). 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

The reported incidence of hypertension after unilateral nephrectomy varies significantly from 9-75% (11-14). Several larger studies with varying duration of follow-up suggest that approximately one third of donors will develop hypertension (15-17). 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 screening during 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 that of 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%) (18). Several small studies have also suggested an increase in the incidence of hypertension after unilateral nephrectomy when compared to a control population (14,19,20). However, other studies have failed to reproduce this finding (16,21,22). In addition, no difference was found when the incidence of hypertension was compared in kidney donors and their siblings (23).

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 (24). A more recent meta-analysis performed in 2006 reported a weighted mean increase in blood pressure of 7 mmHg systolic and 5 mmHg diastolic (25).

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 (16,17). Data on the effect of race on donor outcomes are more limited. The available data suggest higher rates of hypertension in black donors after donation, paralleling the observed prevalence in the general population (26). However several large studies have suggested that hypertension is more prevalent in black donors that in matched non-donor controls (27,28). Similar changes in blood pressure were seen in Hispanic donors (27).

Higher risk groups should be warned of the higher risk of developing hypertension and the need for monitoring. Although there is no direct evidence to support a lower acceptable blood pressure threshold in younger potential donors, the advice given to such patients should take account of donor age in the assessment of long-term donor risk.

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, retinopathy, proteinuria) (29,30), uncontrolled hypertension, or hypertension that requires more than two drugs 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 scenario will 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 donor 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 started 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 may proceed to nephrectomy.

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 (21), but this has not been confirmed by others (12,34). Hypertension in this context should

be managed according to the standard guidelines of the British Hypertension Society (4).

5.8.6 Conclusion

All potential donors should be carefully assessed for the presence of hypertension which, if present, may exclude donation. However, donation may be possible in the presence of controlled hypertension with no evidence of end organ damage. All donors should be warned that blood pressure may rise after donation. Blood pressure should be monitored regularly after donation and lifestyle should be modified to minimise the risk of hypertension and future cardiovascular disease.

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5.9 DIABETES MELLITUS

Recommendations

- ***All potential living kidney donors must have a fasting plasma glucose level checked. (B1)***

- ***A fasting plasma glucose concentration between 6.1-6.9 mmol/L is indicative of an impaired fasting glucose state and an oral glucose tolerance test (OGTT) should be undertaken. (B1)***

- ***Prospective donors with an increased risk of type 2 diabetes because of family history, a history of gestational diabetes, 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 should be given to the use of a diabetes risk calculator to inform the discussion of potential kidney donation. (B2)***

- ***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 and the Oral Glucose Tolerance Test

All prospective donors should have a fasting plasma glucose measurement to exclude diabetes. A fasting venous plasma glucose of >7.0 mmol/L indicates

diabetes (6). Fasting plasma glucose values of between 6.1 and 6.9 mmol/L indicate impaired fasting glucose (IFG). 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 equal to or greater than 11.1 mmol/L indicates diabetes (6). A 2-hour value between 7.8 and 11.1 mmol/L indicates impaired glucose tolerance (IGT) (1).

Impaired fasting glucose

Impaired fasting glucose is not a distinct clinical entity but rather indicates a significantly increased risk for the development of diabetes and adverse health outcomes in the future. The overall prevalence of IFG is around 5%. The reproducibility of the test is not good: around 51-64% of patients with IGT will continue to have IGT if the test is repeated, around 30% will be reclassified as normal, and around 10% will be reclassified as having diabetes. Of Europeans with IFG, around 6.6% will at the same time fulfil the criteria for diabetes whilst 18.9% of South-Asians with IFG will have diabetes, as defined by the OGTT limits. An individual with IFG has an 4.7 fold increased annualised relative risk of developing diabetes and the annualised relative risk of adverse health outcomes is 1.19-1.28 times higher than someone with a normal fasting plasma glucose (1).

Impaired glucose tolerance

Impaired glucose tolerance was initially defined in terms of an increased future risk of diabetes, but it is now appreciated that it is also associated with an increased risk of premature mortality and increased cardiovascular risk. The overall prevalence of IGT is around 10%, is higher in ethnic minority groups, and increases with age. There is moderate reproducibility of the test result with 33-48% remaining unchanged on repeat testing, 39-46% reclassified as normal and 6-13% reclassified as in keeping with diabetes. If present, the annualised relative risk of a patient developing diabetes is 6 times higher compared to those with a normal test result and all-cause mortality is 1.48 times higher (1).

HbA1c

Diabetes may also be diagnosed based upon HbA1c criteria, a result >48 mmol/mol (6.5%) being sufficient to diagnose diabetes if confirmed by repeat testing (2). An HbA1c <48 mmol/mol (6.5%) may be used to predict the future likelihood of developing diabetes; for example, an HbA1c result of 42-48 mmol/mol (6.0-6.5%)

indicates a 5-year incidence risk of diabetes of 25-50%, 20 times higher than that associated with a HbA1c of 31 mmol/mol (5%). An OGTT should be strongly considered when the HbA1c is in this range. It is reasonable to consider HbA1c values between 39 and 46 mmol/mol (5.7% and 6.4%) as identifying individuals with pre-diabetes, and at increased risk of developing diabetes and cardiovascular disease in the future (3).

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 (4). The incidence of type 1 diabetes in adults is less than 1 in 10,000 (4). 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 (5). 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. It may sometimes 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 is clinically unrecognised (6). The crude prevalence of undiagnosed disease in the Caucasian population is 2.3% (7). 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). The prevalence of type 2 diabetes is much higher than for type 1 diabetes and the absolute risk of developing the disease is high (lifetime risk 38%) (8). The combination of a positive family history and obesity (BMI >30 kg/m^2) places an individual at very high risk of diabetes in later life (9). Individuals from South Asia and the Caribbean are at increased risk of type 2 diabetes, independent of age and

obesity. A history of gestational diabetes is an independent risk factor for later diabetes.

Individuals at high risk of type 2 diabetes because of a positive family history, gestational diabetes, and/or obesity should undergo an OGTT. For individuals with a normal OGTT, the risk of developing type 2 diabetes within 5 years is around 1% and is modulated by ethnicity and obesity.

5.9.4 Risk Calculators

The OGTT can be used either to diagnose diabetes or to predict the risk of developing diabetes in the future. More recently, risk calculators have been developed that use data for a particular individual to give an estimated risk for that individual for the development of diabetes over the subsequent 10 years. The use of such calculators has been advocated when making therapy decisions and when discussing those decisions with patients (QDiabetes®-2015 risk calculator: http://qdiabetes.org) (10). Such calculators may usefully be used in the assessment of kidney donors and discussion of the results may be part of the assessment process.

5.9.5 Impaired Fasting Glucose and Kidney Donation

In a small study, 45 donors with impaired fasting glucose were matched with 45 donors with a normal fasting glucose at the time of donation and followed for a median duration of 10.4 years. Those with IFG appeared to do well, when compared with donors with a normal fasting glucose. Urine albumin excretion and MDRD eGFR were similar in both groups. Almost 60% of the donors with IFG had a normal fasting glucose at follow-up, but significantly more had developed diabetes (15.6% vs 2.2%) (11).

5.9.6 Diabetes and Kidney Donation

Traditional guidance has suggested that individuals with diabetes should not donate a kidney. However, in an observational study of 444 donors from a single Japanese

centre that has accepted subjects with an abnormal OGTT, including a small number 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 (12).

Consideration of a diabetic as a potential donor requires a thorough evaluation of the risks and benefits of donation and transplantation, for both the donor and recipient. Specifically, a careful search should be made for any evidence of target organ damage and assessment of cardiovascular risk factors such as obesity, hypertension and hyperlipidaemia. The age of the donor, donor GFR, and the relationship to the potential recipient are critical factors. After exclusion of pre-existing diabetic nephropathy, possibly including renal biopsy, the potential risk of development of diabetic nephropathy should be discussed with the potential donor (13,14).

5.9.6 Risk of Diabetes Causing ESRD in Living Kidney Donors

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 (15). There is, however, a 50% cumulative incidence of proteinuria after type 2 diabetes has been present for 20 years (16) which may become an issue for kidney donors who have an above average life expectancy and who may expect to live into their 80s (17).

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 2,954 patients who responded. The vast majority of kidney donors where white, about 50% were genetically related to the recipient. The eGFR and the rate of decline of eGFR were not significantly different between diabetic and matched non-diabetic donors. In this study, 11 donors developed ESRD requiring dialysis or transplantation, of which none were due to diabetic kidney disease (18).

Similar reassurance comes from a review from the Organ Procurement and Transplantation Network and the Center for Medicare and Medicaid Services databases. These identified 126 cases of ESRD post-kidney donation from 56,458 living donors across the USA between 1987 and 2003. The median time to ESRD after donation was 10.4 years and glomerulonephritis was considered to be the cause in 33%, hypertension in 25%, and diabetes in 9% (19).

In conclusion, diabetic nephropathy in a kidney donor is not common during the follow-up periods reported in the published literature. It is, however, quite possible that this may not be the case with longer follow-up, particularly in younger donors and in minority ethnic groups (20).

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5.10 CARDIOVASCULAR EVALUATION

Recommendations

- ***There is no evidence to support the routine use of stress testing in the assessment of the potential donor at low cardiac risk. (C2)***

- ***Potential kidney donors with a history of cardiovascular disease, an exercise capacity of <4 metabolic equivalents (METS) or with risk factors for cardiovascular disease should undergo further evaluation before donation. (C2)***

- ***For higher risk potential donors, stress testing is recommended by whichever method is locally available or by CT calcium scoring . (C2)***

- ***Discussion with and/or review by cardiologists, anaesthetists and the transplant MDT is recommended as part of the clinical assessment of donors with higher cardiovascular and peri-operative risk. (D2)***

Cardiovascular assessment before donation has two purposes. First, it identifies prospective donors with higher than average risk of peri-operative complications who may be unsuitable for donation. Second, it provides an opportunity to assess the cardiovascular risk factors of a donor, to consider the long-term effects of kidney donation, and to 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 cardiology opinion. A normal electrocardiogram, whilst reassuring, does not exclude coronary artery disease.

5.10.2 Screening Patients with Established Overt Cardiac Disease

Every attempt should be made to ensure that potential living kidney donors are not exposed to significant or unavoidable risk. As such the threshold for refusal on health grounds must be relatively low and the presence of overt cardiac disease will 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 should 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. This will usually be involve referral to a cardiologist so that current best practice may be ensured.

5.10.3 Screening for Occult Cardiac Disease

Although there are challenges with the management of overt disease, it is even more difficult to produce clear guidance for 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 of low risk individuals will produce a large number of false positive results. This will expose potential living kidney donors to unnecessary anxiety and result in further investigation which may be invasive or use ionising radiation. Some potential donors who would have been at low risk of complications will withdraw, or be withdrawn from the donation process for no justifiable cause. Further testing will also lead to an additional economic burden upon the healthcare system.

There are various methods to estimate cardiovascular risk in people without known disease (for example QRISK 2 (2) and the Framingham Coronary Heart Disease Risk Score (3)). These risk calculators variably use factors such as age, smoking status, presence of hypertension or diabetes, family history and cholesterol to

predict the risk of a new cardiovascular event over a period of time, usually 10 years. Although this will identify higher risk potential donors, there is no evidence to support a specific risk threshold above which further investigation is required or donation should not occur. Each case should be considered individually. The most commonly used method to predict peri-operative cardiovascular risk, the Lee index, includes factors such as previous ischaemic heart disease, congestive cardiac failure and diabetes and is therefore not applicable to the low risk donor population (4).

Assessment of functional capacity, either by self-reporting of exercise capacity or measured by cardiopulmonary exercise testing, can predict peri-operative cardiovascular mortality and long-term outcomes (5,6). The ability to undertake activities that require more than 4 METS, for example moderate cycling and jogging, is associated with a low peri-operative risk. There are no data to support a level of functional status, reported or measured, that either requires further evaluation or excludes donation. However, a functional capacity of >4 METS and without the cardiovascular risk factors listed above would predict a low risk of peri-operative cardiovascular events.

If potential donors have a high predicted risk of cardiovascular disease and/or poor functional capacity, further evaluation should be undertaken. However, there are no data to inform the most appropriate method to detect or exclude coronary artery disease in an asymptomatic population. Whichever method of stress testing is used is likely to give false positive results in this population, and the negative predictive value will be unknown.

CT coronary calcium scoring can be used to assess risk of coronary atherosclerotic disease. 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 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 (7). It should be re-emphasised, however, that no evidence currently exists to support the hypothesis that donor candidates at low risk of cardiac events should undergo additional pre-operative cardiac evaluation before donation (8).

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 high performance athletes and in this group of young, fit people there is little incremental benefit from routine echocardiography. However, this may not be true in an older cohort. Currently there is no consensus regarding the definition of a “high risk” cohort and the role of routine echocardiography in potential living kidney donors who have no clinical or electrocardiographic abnormalities is unclear.

5.10.5 Conclusion

There is no evidence to support cardiac stress testing or invasive testing in potential donors at low cardiac risk. However, a low threshold should be set for formal cardiac investigation and for the exclusion of individuals at higher risk. As well as determining suitability for donation, the assessment process should provide an opportunity to identify and correct recognised cardiovascular risk factors. The choice of stress test will be influenced by local service provision. CT coronary calcium scoring may be an alternative way of stratifying coronary risk.

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5.11 PROTEINURIA

Recommendations

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

- ***A urine albumin/creatinine ratio (ACR) performed on a spot urine sample is the recommended screening test, although urine protein/creatinine ratio (PCR) is an acceptable alternative. (A1)***

- ***ACR >30 mg/mmol, PCR >50 mg/mmol, albumin excretion >300 mg/day or protein excretion >500 mg/day represent absolute contraindications to donation. (C2)***

- ***The significance of moderately increased albuminuria (ACR 3-30 mg/mmol) and proteinuria (PCR 15-50 mg/mmol or 24-hour urine protein 150-500 mg/day) has not been fully evaluated in living kidney donors. However, since the risk of CKD and cardiovascular morbidity increase progressively with increasing albuminuria or proteinuria such levels are a relative contraindication to donation. (C2)***

Proteinuria should be quantified in all potential living kidney donors. Increased urinary protein excretion is a marker of kidney damage, reflecting either increased glomerular permeability (albuminuria) or decreased tubular reabsorption (low molecular weight proteinuria). Proteinuria may also be a manifestation of conditions other than kidney disease such as lymphoproliferative disorder (overflow proteinuria) or lower urinary tract disease (post-renal proteinuria).

Proteinuria is an important risk factor for both chronic kidney disease (1,2) and cardiovascular morbidity and mortality (3). In particular, proteinuria predicts both the progression of CKD and cardiovascular events in patients with established CKD, established cardiovascular disease, and patients with diabetes (3,4). Proteinuria also predicts the development of CKD and cardiovascular disease in those without medical co-morbidities.

A recent meta-analysis based on data from nearly five million healthy people identified from seven general population cohorts in the US found that each 10-fold increase in urinary ACR was associated with three times the risk of ESRD over a median follow-up of 4 to 16 years, although this finding was not statistically significant (5). The projected risk of ESRD was higher among people with additional risk factors, including middle age, male gender, black ethnicity and smokers, than among those without additional risk factors.

5.11.1 Methods of Testing for Proteinuria

Historically, abnormal proteinuria has been defined as the excretion of more than 150 mg of total protein per day. However, early renal disease may be reflected by lesser degrees of proteinuria, and particularly by increased albuminuria. The normal rate of albumin excretion is <10 mg per day in healthy young adults and increases with age and with increased body weight. Persistent albumin excretion between 30 and 300 mg/day is termed moderately increased albuminuria (formerly known as "microalbuminuria") and in non-diabetic patients is associated with an increased risk of cardiovascular disease (3). An albumin excretion >300 mg/day is considered overt proteinuria or severely increased albuminuria (formerly known as "macroalbuminuria"), and is the level at which the standard urine dipstick becomes positive. It should be noted that the standard urine dipstick primarily detects albumin and is relatively insensitive to non-albumin proteins. Furthermore, the dipstick is insensitive to low levels of albumin excretion with a lower limit of detection of approximately 10-20 mg/dL. Thus patients with moderately increased albuminuria or low molecular weight proteinuria may be missed if this is the sole method of detection.

The gold standard for measurement of protein excretion is a 24-hour urine collection, but this is cumbersome for patients and often collected inaccurately. Hence 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. Both are supported by Kidney Disease: Improving Global Outcomes (KDIGO) (6) as appropriate methods to aid in the diagnosis of chronic kidney disease, but ACR is preferred by both KDIGO and the National Institute for Health and Care Excellence (NICE) as it has greater sensitivity than PCR for low levels of proteinuria (7). 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 (adapted from reference 5)

Albuminuria category	Dipstick reading	PCR (mg/mmol)	Total protein (mg/24h)	ACR (mg/mmol)	Albumin excretion (mg/24h)
Normal to mildly increased (A1)	Negative to trace	<15	<150	<3	<30
Moderately increased (A2)	Trace to +	15-50	150-500	3-30	30-300
Severely increased (A3)	+ or greater	>50	>500	>30	>300

5.11.2 Assessment of Proteinuria in Living Donors

There is uncertainty regarding the threshold of proteinuria that precludes kidney donation. In 2005 the Amsterdam Forum concluded by consensus that a 24-hour urinary protein excretion of >300 mg is a contraindication to donation (8). According to a 2007 survey among US transplant centres, the most common exclusion criterion for kidney donors was 300 mg/day proteinuria, but almost as many centres were using a protein excretion of 150 mg/day as a cut-off (9).

Albumin excretion >30 mg/day (ACR >3 mg/mmol) is associated with an increased risk for complications of CKD. A meta-analysis by the CKD Prognosis Consortium demonstrated associations of an ACR >3 mg/mmol or reagent strip +1 protein with a subsequent risk of all-cause and cardiovascular mortality, kidney failure, acute kidney injury, and CKD progression in the general population and in populations with increased risk for CVD (3,10,11). ACR is associated with an increased risk of mortality linearly on the log-log scale, without threshold effects. For this reason, although the significance of moderately increased albuminuria has not been fully evaluated in living kidney donors, raised albumin excretion would currently constitute at least a relative contraindication to donation, although other risk factors for ESRD may be taken into account. Severely increased proteinuria (ACR >30 mg/mmol, PCR >50 mg/mmol, albumin excretion >300 mg/day, or protein excretion >500 mg/day) constitute an absolute contraindication to donation.

Orthostatic proteinuria should not be considered as a contraindication to donation. Orthostatic proteinuria appears benign (12), but a confident diagnosis requires an ACR on a spot urine sample voided immediately after waking.

There are few studies examining either the renal or cardiovascular outcome for living kidney donors who have donated despite pre-existing low level 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 (13-16). In one study, five donors with low-grade proteinuria (mean 210 mg in a 24 hr urine collection) were more likely to have significant proteinuria 20 years or more after donation (>800 mg/day), although without significant loss of kidney function (17). A review of 1,519 living kidney donors in Japan identified eight who developed ESRD (18). Of these, only two had pre-donation proteinuria, both of whom developed cardiovascular disease, hypertension and ESRD 6 and 16 years after donation. A recent US study among 4,650 living donors found that by 7 years post-donation, after adjustment for age and sex, greater proportions of black compared with white donors had chronic kidney disease (12.6% vs 5.6%), proteinuria (5.7% vs 2.6%) or nephrotic syndrome (1.3% vs 0.1%), suggesting the need for more stringent risk stratification among black donors (19).

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5.12 NON-VISIBLE HAEMATURIA

Recommendations

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

- ***Two or more positive tests, including trace positive, is 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 is recommended if haematuria is 1+ or greater on dipstick testing. (B1)***

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

- ***For donors with persistent asymptomatic non-visible haematuria (PANVH) and a family history of haematuria or X-linked Alport syndrome, a renal biopsy (B1) and referral to a clinical geneticist are recommended. (B2)***

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.

5.12.1 Detection of Non-Visible 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, while >10 red cells/μl are conventionally considered to be significant in urological practice (1). In the UK urine microscopy is not recommended to confirm the presence of haematuria (2) 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. Potential living donors must have reagent strip urinalysis performed on at least two occasions not related to fever, menstruation or exercise. If two out of three consecutive tests are positive then the donor is considered to have persistent non-visible haematuria.

Non-visible haematuria is present in 1-21% of the general population, the prevalence increasing with age (3-7). 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 who were followed for 5.8 +/- 4.4 years, haematuria disappeared in 44%, none of whom developed proteinuria or renal impairment (8). In a smaller study of 49 patients investigated for non-visible haematuria, those in whom haematuria disappeared all had a normal kidney biopsy (9).

5.12.2 Persistent Asymptomatic Non-Visible Haematuria (PANVH)

PANVH is present in about 25% of those with an initial positive test (3-10) and, in two single centre reports, 2.7% and 8.3% of potential living kidney donors in the US and Japan respectively (11,12). Malignant disease of the urinary tract, present in 3-5% of patients overall (13,14), 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 of 165 patients, 77 (46%) were found to have glomerular pathology, most commonly IgA nephropathy, mesangial proliferative glomerulonephritis without IgA deposition, or thin basement membrane nephropathy (15). Similar pathology has been demonstrated in a Dutch study where

29 out of 49 biopsies were abnormal (9), a Korean study in which only 10 out of 156 biopsies were normal (16), a Japanese study in which all of 56 biopsies were abnormal (17), and in a US study of potential living donors with PANVH in which 8 out of 10 biopsies were abnormal (11).

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 (9). In a Japanese study of 242 living donors, 8.3% had PANVH before 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 (12). 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 (8).

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.

5.12.3 ‘Trace’ Microscopic Haematuria

A reagent strip ‘trace positive’ result corresponds to 1-5 red cells/µL (1). 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 (2) and Urology guidelines in the UK have recommended that trace non-visible haematuria be considered a normal variant (18). However, glomerular pathology has been reliably identified in potential living donors using thresholds of even 1 or 3 red cells/µl (11,12). 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 (1+ or greater) mandate biopsy before 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 (18). 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.

5.12.4 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 (9,11,15,16) 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 (19-21), often associated with additional pathological abnormalities including FSGS (21,25) or IgA nephropathy (22,23) (both of which would preclude donation). A recent study of Greek-Cypriot families with familial haematuria identified *COL4A3 or COL4A4* mutations in 16/57 families (28.1%), and in this population 10/87 (11.5%) heterozygous patients developed ESRD (24, 25).

Many individuals with TBMN but otherwise normal investigations have undoubtedly donated kidneys, either knowingly (11) or unknowingly (12), and although adverse

outcomes have not been reported these donors must be made aware of uncertainty over long-term safety. Recently published consensus guidelines recommend a renal biopsy (to exclude FSGS-like lesions associated with progression to ESRD) and referral to a clinical geneticist for genetic testing, especially when donating to a family member with unexplained kidney failure or where there is a family history of sensori-neural deafness or haematuria (26 - see also section 5.17 Familial Renal Disease). Referral to a geneticist is mandatory in potential donors of Cypriot origin.

TBMN must be distinguished from the carrier state of **X-linked Alport syndrome** (XLAS - caused by mutations in the *COL4A5* gene encoding the α5 chain of type 4 collagen), which is associated with a 5-20% risk of progressive renal impairment (27,28) and generally considered to prohibit donation (26). A recent study describing six XLAS carriers who donated kidneys to their affected children supports this view (29). 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 (26,30). Involvement of a clinical geneticist and renal biopsy would be mandatory in the screening of such a potential donor.

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5.13 PYURIA

Statement of Recommendation

- ***Prospective donors found to have pyuria can 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 is defined as the presence of 10 or more white cells/mm^3 in a urine specimen, three or more white cells per high-power field of unspun urine, a positive result on Gram's staining of an unspun urine specimen, or a urinary dipstick test that is positive for leukocyte esterase (1). Sterile pyuria is defined as the persistent presence of white cells in the urine in the absence of bacteria.

Sterile pyuria is relatively common, affecting 13.9% of women and 2.6% of men (2) and can occur in patients who have already taken antimicrobials, or where there is infection with atypical organisms. These include sexually transmitted infections such as gonorrhoea and chlamydia, genital herpes and herpes zoster, human papilloma virus and HIV infections; genitourinary tuberculosis; fungal infections such as candidiasis; and parasitic infections such as trichomoniasis and schistosomiasis. Other causes of sterile pyuria include inflammatory and autoimmune conditions such as systemic lupus erythmatosus, Kawasaki's disease and analgesic nephropathy, or urological conditions such as stones, foreign bodies and stents. For a more complete list of causes see reference 3.

The cause of the pyuria must be established before a potential donor proceeds for further assessment (3).

In a retrospective study of 86 living kidney donors whose procedures were over 1 year ago (mean 17.24 ± 5.04 months), pyuria was found in 7 (8.1%). The cause and longer-term outcome for these patients was not reported (4).

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5.14 INFECTION IN THE PROSPECTIVE DONOR

Recommendations

- ***Screening for infection in the prospective donor is essential 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 donation; however, donors with evidence of active viral replication may be considered under some circumstances. (B1)***

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

- ***Screening for HBV, HCV and HIV infection must be repeated within 30 days of donation. (Not graded)***

- ***All potential donors should be provided with dietary advice regarding avoidance of HEV infection, and screening should be undertaken for HEV viraemia by nucleic acid testing within 30 days of donation. (Not graded)***

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

- ***The EBV status of donor and recipient must be determined before transplantation. When the donor is EBV positive and the recipient is EBV negative, the donor and recipient must be counselled about the risk of developing Post Transplant Lymphoproliferative Disease. (B1)***

- ***Potential donors must be screened by history for travel or residence abroad to assess their potential risk for having acquired endemic***

infections and appropriate microbiological investigations instigated if indicated. (Not graded)

5.14.1 Introduction

Potential living donors undergo careful screening for infectious diseases. This allows both for identification and treatment, and minimisation of any risk associated with transmission between donor and recipient. In many cases, donation is possible following resolution of infection, although on specific occasions recipient monitoring and prophylaxis might be recommended following transplantation.

The same principles that apply to deceased donors and blood donors should be applied to the screening of living donors (1-3). Expert advice is provided on a national basis by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) (3). All risk assessments are regularly reviewed and amended if new relevant evidence becomes available.

Global travel and the increasing number of donors from all areas of the world has necessitated that consideration be given to geographically relevant infections, with which the transplant team may be unfamiliar (4). In these cases, the involvement of a Consultant with relevant expertise should be sought to guide appropriate assessment and investigations.

Identification of current or previous infection in the prospective donor is an important aspect of donor evaluation. The presence of any 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

Herpes group viruses

- Cytomegalovirus (CMV or HHV 5)
- Epstein-Barr virus (EBV or HHV4)
- Herpes simplex virus (HSV or HHV1 and HHV2)
- Varicella-zoster virus (VZV or HHV3)
- Kaposi Sarcoma virus (KSKV or HHV8)

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

Human T lymphotrophic virus (HTLV-1 and HTLV-2)

Hepatitis B virus (HBV)

Hepatitis C virus (HCV)

Hepatitis E virus (HEV)

West Nile Virus (WNV)

Bacterial

Atypical mycobacterial infections

Mycobacterium tuberculosis

Syphilis

Fungal and parasitic

Toxoplasmosis

Coccidiomycosis

Malaria

Schistosomiasis

Trypanosoma cruzi

Strongyloides

Prion-associated

Creutzfeldt-Jakob disease (CJD)

Variant Creutzfeldt-Jakob disease (vCJD)

5.14.2 Evaluation of the Prospective Donor

A detailed clinical history is important and must include a psychosocial and sexual history to define at-risk behaviour (see Table 5.4.2 in section 5.4). Prospective donors who were born or lived in geographical areas outside the UK where there is a high prevalence of certain infections may require additional evaluation (5). 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 are listed in Table 5.14.2. SaBTO recommendations state that a blood sample taken up to 30 days before organ donation is considered to meet the requirements for testing, as long as the donor's risk status has not changed in the time between the sample being taken and the donation. Infections can be transmitted by both blood transfusion and organ donation during the incubation period of the relevant organism and before a serological response has been mounted, and is discussed further below. Serology should not, therefore, be regarded as a substitute for a detailed psychosexual and medical history exploring potential risk factors.

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.

Table 5.14.2 Serological Testing of Donor

Routine tests for all donors

HbsAg and HBcAb

HCV IgG

HIV 1/2 Ab / HIV Ag combination assay (minimum 4th generation assay)

HTLV 1/2 Ab

Treponema pallidum Ab

CMV IgG

EBV IgG

Toxoplasma gondii IgG

Consider in selected cases

*Coccidiomycosis antibody

*Malaria blood film

*Schistosomiasis antibody, urine microscopy

*Trypanosoma cruzi antibody

*Strongyloides stercoralis antibody

*West Nile Virus antibody/RNA

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

5.14.3 Viral Infections in the Prospective Donor

Hepatitis B

All prospective living donors should be tested for both Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb). If the HBcAb is positive, the donor should be tested for the presence of HBV DNA and Hepatitis B surface antibody (HBsAb). If HBsAb is >100 iU/L and HBV DNA is not detected, the infectious risk of the donor is low.

There are a substantial number of reports of kidneys transplanted from HBsAg negative/DNA undetectable, HBcAb positive deceased 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 alone

(with negative HBsAg and undetectable DNA in blood) can therefore donate. The prospective recipient will ideally have been effectively immunised against HBV, although immunization can be repeated post-transplant if a suboptimal antibody response has been made. The addition of anti-viral drugs may be considered, especially in recipients with a low HBsAb response to vaccination. Under these circumstances, advice from specialists with appropriate expertise should be sought and the donor and recipient should be fully informed. Further discussion is available in the BTS Guidelines for Hepatitis B in Solid Organ Transplantation (10).

Most transplant units would not consider potential donors with evidence of active HBV viral replication. If it is necessary to consider a potential donor who is HBsAg positive (or in whom HBV DNA is detected), then advice should be sought from a specialist with appropriate expertise (10).

Hepatitis C

Active hepatitis C in the donor is a relative 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 (11,12). The risk of HCV transmission from an HCV RNA positive donor approaches 100% if transplanted into a naïve recipient (13). 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. However, the risks entailed must be carefully explained to both donor and recipient. In these exceptional circumstances, the likely life expectancy of the recipient and the risks of remaining on dialysis may be deciding factors.

Advances in anti-viral agents and vaccination may influence such decisions in the future. Effective anti-viral therapy resulting in sustained virological response for HCV has recently become available. As such, if donation from a HCV-infected donor was the only option for a life-preserving transplant then a risk/benefit analysis would be appropriate and advice from a specialist with appropriate expertise should be sought. The risks entailed must be carefully explained to both donor and recipient.

Hepatitis E

Hepatitis E is an RNA virus with enteric transmission and was previously considered an endemic infection in developing countries. However, an increasing number of infections have been reported in the UK and the virus is now considered endemic in Europe. HEV infections are usually relatively asymptomatic in healthy individuals, but can lead to chronic hepatitis and liver cirrhosis in infected solid organ transplant recipients (14,15).

BTS guidelines published in April 2017 recommend that all solid organ donors, including living donors, are screened for HEV in line with the UK Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) (16). It is recommended that potential living donors are provided with dietary advice regarding avoidance of HEV infection (from undercooked meat, particularly pork products) and that screening with a single sample HEV-Nucleic Acid Amplification Test (NAAT) be undertaken within 30 days of organ donation as part of routine assessment. If HEV viraemia is detected, donation should be deferred until laboratory testing confirms spontaneous resolution of HEV infection (plasma and stool HEV RNA not detected).

Human immunodeficiency virus (HIV) and Human T Lymphotrophic virus

The presence of HIV or HTLV infection is an absolute contraindication to living donation. HTLV is known to be endemic in Africa, the Caribbean and Japan but HTLV serology must be performed for all prospective donors, regardless of country of origin (3). Kidney donation should not be undertaken if significant doubt remains about the possibility of HTLV infection in the donor.

High risk donors and window period infection

Behavioural risk information obtained from potential living donors is generally more reliable than the collateral history obtained for deceased donors. If there is any doubt about the acquisition of a blood borne virus that might be transmitted to the recipient, consideration should be given to delaying the transplant to allow for the “window period” to have passed and repeat testing performed. The “window period” for a pathogen is the time between infection and detection by a specific testing method. NAAT shortens the window period for blood borne viruses relative to serology and therefore may decrease the risk of transmitting disease from a serologically negative

donor (17). The period of observation should be at the discretion of the transplant centre, based on an individual risk analysis and discussion with a specialist with appropriate virological expertise.

Cytomegalovirus (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 (18). 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 to all recipients except those who are CMV seronegative in receipt of a graft from a CMV seronegative donor (19). In all other combinations, the donor and recipient should be informed about the increased risk of CMV disease before the transplant is performed.

Epstein Barr virus (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 post-transplant lymphoproliferative disorder (PTLD) and this risk is increased further if the recipient is given lymphocyte depleting immunosuppressive therapy. When the donor is EBV positive and the recipient EBV negative, clinical vigilance is required following transplantation to detect PTLD as early as possible. However, PTLD can also occur in recipient EBV positive antibody patients, and occasionally in those who are negative.

Additional potentially significant viral infections (no routine screening)

Human Herpes Virus 8 (HHV8)

HHV8 may be transmitted by organ transplantation and is associated with an increased risk of Kaposi sarcoma (20). However, there is no evidence to support screening of potential organ donors.

West Nile Virus

West Nile Virus (WNV) was first reported in the USA in the New York area in 1999, and has since become endemic in widespread regions of the US. Since 2002, at least nine instances of donor-derived infection to solid organ transplant recipients have been reported following deceased donation. There is the potential for transmission from a living donor, although no cases have been reported to date. Interpretation of serological results is complex, and exclusion of infection at the time of donation requires nucleic acid testing. Expert advice should be sought if there are concerns when assessing a donor from an endemic area (21).

5.14.4 Bacterial Infections in the Prospective Donor

The risk of transmission of a bacterial infection from a healthy living donor is extremely small. If a specific bacterial microbiological diagnosis has been made, then a course of appropriate antibiotic is likely to be effective in preventing transmission.

Urine should be sent for culture from all potential donors. Asymptomatic bacteriuria is relatively common, especially in women. If the potential donor is male or there is a personal or family history of urinary tract infection, appropriate imaging of the kidneys to assess for cortical scarring should be performed.

The main risk of inadvertent transmission of a bacterial infection comes from mycobacteria (both *M. tuberculosis*, MTB, and atypical species). As of September 2012, 30 cases of potential or proven donor-derived tuberculosis had been described in solid organ transplant recipients (22). Four of these had been from living donors.

Up to 30% of the world's population is infected with MTB, although this proportion is much lower in the UK. After initial infection, most people do not develop active

tuberculosis, but the organism persists in the body - this is referred to as latent TB, and can be transmitted by transplantation.

Donors should initially be screened for mycobacterial infection on the basis of their history. Particular high risk factors include: country of birth and any previous prolonged periods (>3 months) spent in a country with high prevalence; previous close contact with individuals known to be infected; or working with high risk groups (prison inmates, the homeless, those with alcohol or other substance abuse). Screening should include a careful history, including ethnic origin and country of upbringing, and any previous exposure to TB. A chest X-ray may be suggestive of previous disease. Tuberculin skin testing or interferon gamma release assay may be considered for donors at risk of latent infection, although diagnostic tests for latent TB are limited in sensitivity (23). In cases of concern, discussion with a Consultant with appropriate expertise is recommended. The risk of transmission is minimal if the infection has been identified and fully treated, and is not a contraindication to subsequent donation.

Transmission of syphilis has been reported in the UK to two recipients from a deceased donor with a past history of treated disease (24). Donation may be considered after treatment, with informed consent and post-transplant monitoring of the recipient. If a recipient is considered to be at risk of syphilis transmission from the donor, prophylactic treatment should be given (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 (25). Involvement of a specialised clinic in genitourinary medicine is recommended.

5.14.5 Fungal and Parasitic Infections in the Prospective Donor

A living donor is unlikely to transmit a fungal infection if otherwise in good health. However, this possibility should be borne in mind when assessing donors from areas where fungal infections are endemic. *Toxoplasma gondii*, *Coccidioidomycosis, Strongyloides stercoralis*, *Trypanosoma cruzi* (the causative agent of Chagas disease) and malaria can be transmitted by a renal transplant (21). In most of the reported cases, transmission has been from living unrelated donor transplantation taking place abroad.

Coccidioidomycosis is a fungal infection caused by *Coccidioides* species endemic to the southwestern United States, where it presents a challenge for transplant recipients (26). In this area, up to 8% recipients may develop infection, usually in the first year following transplantation.

Infection with *Strongyloides stercoralis* results from skin penetration by larvae and thus may after walking in soil with faecal contamination. It typically occurs in rural agricultural regions with poor sanitation. Adult worms can live for up to 5 years, and autoinfection is an important source of prolonged infection even when the individual is no longer living in an endemic area. Symptomatic infection with Strongyloides is more common in the immunocompromised (27).

We suggest screening the following groups: those who were born or lived in tropical or subtropical countries where sanitation conditions are poor, those with unexplained eosinophilia and travel to an endemic area and those with a prior history of Strongyloides infection. Initial screening is by serology, which may indicate current or past infection. If positive, an opinion from a Consultant with appropriate expertise should be sought. Donation may proceed after treatment of the donor with an appropriate agent, such as ivermectin.

Trypanosoma cruzi

Endemic areas for *T. cruzi* include parts of Mexico and most of Central and South America, and transmission has been reported following living organ donation (28). Initial screening of donors from these areas is by serology. Donation may be considered after appropriate treatment.

Other infections are either transmitted rarely (occasional case report) or may be considered a possible risk but there have been no reports of donor derived infection.

5.14.6 Prion-Associated Diseases in the Prospective Donor

CJD and vCJD

There is no screening test currently available for CJD or vCJD. No cases of transmission by organ transplantation have been reported, although there has been transmission of vCJD infection via transfusion of red blood cells (4 cases) and from

the plasma used to produce factor VIII (one case) (3). Donor deferral issues concerning the potential for transmission of vCJD are complex, and are detailed in the UK blood transfusion and SaBTO guidelines (2,3). Donation is contraindicated from individuals with a personal or family history of CJD or vCJD (unless considered not at risk following genetic counselling). Circumstances requiring an individual assessment, taking into consideration the level of risk or exposure, expected benefit of transplantation and the availability of alternative donors include: history of blood transfusion since 1980; history of receipt of *dura mater* graft; and history of receipt of human pituitary derived growth hormone or gonadotrophin.

5.14.7 Summary

Provided a careful history is obtained and appropriate screening tests performed, the risk of transmission of infection from a healthy living donor is very small. Should there be any uncertainties concerning potential risk, the advice of a Consultant with appropriate expertise in infectious diseases, microbiology, virology or hepatology should be sought, to maintain the health and safety of both donor and recipient.

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5.15 NEPHROLITHIASIS

Recommendations

- ***In the absence of a significant metabolic abnormality, potential donors with a limited history of previous kidney stones, or small renal stone(s) 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)***

- ***In appropriate donors with unilateral kidney stone(s) the stone-bearing kidney can be considered for donation (if vascular anatomy and split kidney function permit) in order to leave the donor with a stone-free kidney after donation. (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 kidney stones, which are generally small (≤4 mm) and present in about 5% of potential kidney donors undergoing non-contrast CT scan.

The lifetime risk of recurrent kidney stones is an important consideration in evaluating the suitability for kidney donation. There are few data on the lifetime risk specific to the kidney donor population. However, data relating to risk of further stone episodes are available for people who present with a symptomatic kidney stone (overall 50% chance of developing a further stone within 5 years) and a risk prediction tool exists (1). Risk prediction tools do not yet exist for asymptomatic stone formers, but ≥1 stone at presentation confers an increased risk of metabolic risk factors and future stone episodes (1).

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, pure calcium phosphate, cysteine 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 acidic. 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. Cystine stones are always associated with cystinuria and people with these stones should not donate a kidney. Infection stones are commonly associated with an anatomical abnormality and people with these stones should not donate a kidney unless the anatomical abnormality is easily correctable.

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 be treated using less invasive treatment modalities e.g. flexible uretero-renoscopy. However, for the general population, the evidence that treating small asymptomatic stones is superior to simply observing them is mixed (6), with about 25% becoming symptomatic in 5 years and 3% developing painless silent obstruction (7). Upper or middle pole stones are more likely to become symptomatic and also to pass spontaneously.

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 symptomatic stone formers and that different mechanisms may be involved in asymptomatic versus symptomatic stone formation.

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

Large or staghorn stones can commonly lead to chronic renal damage (2) and are usually associated with infection or a significant metabolic abnormality and people with these stones should *not* be considered as donors.

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

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 and imaging screen should be carried out before 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 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. Urine creatinine should be measured on each collection as an internal

marker of completeness and the 24 hour urine volume should be noted. 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. Serum calcium (adjusted for albumin level) and urate should be measured. 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

There is an increasing literature of single centre units utilising donors with small unilateral kidney stones. 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, isolated hypercalciuria, isolated hyperuricosuria, particularly if the history of calculus disease is very limited. Donation may be considered where factors that have previously put the patient at risk of stone formation e.g. diet or medication, have been successfully modified, urine pH has been corrected to normal (preferably using a pH meter rather than dipstick testing), and 24 hr urine levels have demonstrated to a return to the normal range. In such cases, careful counselling of the donor is mandatory before surgery. It is recommended that advice is obtained from a clinician with a specific interest in this field. A history of a previous infection-related (struvite) or cystine renal stone is generally considered a contra-indication to donation.

In potential donors who have a history of previous stones but no metabolic abnormality, proceeding with donation should be considered providing the number, size and frequency of 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 risk associated with proceeding to donation.

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 ureterorenoscopes, to inspect the collecting system and remove any confirmed stones *ex vivo*, before implanting the donor kidney (15,16).

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.

People with bilateral kidney stones should in general not be considered as kidney donors. This situation both suggests an inherent metabolic or anatomical abnormality and would leave the individual with a single kidney containing a stone placing them at significant risk of a future stone event in a solitary kidney.

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 or biennial renal ultrasound may be 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.

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5.16 HAEMATOLOGICAL DISEASE

Recommendations

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

- ***A haemoglobinopathy screen must 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 from a consultant haematologist is recommended for haematological conditions not covered in this guideline. (Not graded)***

5.16.1 Introduction

Haematological abnormalities can be associated with increased risk to either or both of the donor and recipient in living donor kidney transplantation. A targeted history should be obtained from the donor, with specific enquiry about anaemia, venous thromboembolism (VTE), and 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 any of the above will require further investigation. In addition, haemoglobinopathy screening 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.

5.16.2 Red Cell Disorders

Anaemia

Anaemia (WHO classification Hb <130 g/L for men and <120 g/L for women) should be fully investigated and treated before 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 epidemiological evidence to suggest that SCT is associated with a higher risk of progression to end stage renal disease, a higher incidence of CKD and albuminuria, and a more rapid deterioration in renal function. This is equally true for Hb AS and Hb AC (2,3). What is not clear is whether those without albuminuria are at increased risk. In addition, the peri-operative risks may be higher in patients with SCT, including complications such as venous thromboembolism (4). 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 centers found that 37% would or might exclude patients on the basis of having SCT (5). On balance, SCT should not be an absolute contraindication to kidney donation, but donors wishing to proceed need to be counseled 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 transfusion dependent thalassaemia (TDT), non-transfusion dependent thalassaemia (NTDT) (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 even individuals with NTDT periodically require transfusion 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 (6).

Other haemoglobin variants

Other haemoglobinopathies may be encountered when screening donors of non-northern European heritage and in general should not pose a problem with kidney donation except where they form part of a compound heterozygote with Hb S (e.g. Hb SC, Hb ES, etc). 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 CC and Hb AC may at increased risk of developing CKD (3).

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 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 (7). 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) (8).

MGUS *per se* does not cause end organ disease and 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. Although the risk of disease transmission is considered negligible, the potential recipient should also be counselled re a potential increased risk associated with donation.

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 (9). The presence of MDS should be considered a strong contraindication to donation.

5.16.3 Clotting Disorders

Patients with a history of VTE can be classified into high, medium and low risk as per the AT9 Guidelines (10) whereby the risk of an event is >10%, 5-10% or <5% respectively. The risk of VTE in the low risk group (on warfarin) following a procedure is less than 0.2% irrespective of the use bridging anticoagulation peri-procedure. However, those receiving bridging anticoagulation are more likely to have bleeding complications. These data should inform discussion with potential donors in this category and may represent a relative contraindication to donation but, in general, the risks should be discussed with a haematologist.

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5.17 FAMILIAL RENAL DISEASE

Recommendations

- ***All potential transplant recipients must have a detailed family history recorded and confirmation where possible of the diagnosis in other family members with known kidney disease. This may aid diagnosis for the recipient, clarify any mode of inheritance and identify at risk relatives. (A1)***

- ***When the cause of kidney failure in the recipient is due to an inherited condition, appropriate tests - including genetic testing if available - are recommended to exclude genetic disease in the potential donor. (A1)***

- ***Many inherited kidney diseases are rare, so involvement of clinical and laboratory genetics services must be considered at an early stage to assess likely risks to family members and the appropriate use of molecular genetic testing. (B1)***

When renal failure in the recipient is due to an inherited renal disease, where there is a family history of renal disease, or where the primary disease is unknown, it is important to thoroughly investigate genetically related potential donors to assess their risk of developing renal disease (1,2). 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 who are being considered for transplantation. Genetic testing for a wide range of inherited renal diseases is now available through the NHS (see below) resulting in more families also having a genetic diagnosis.

A significant proportion of patients with ESRD will have a family history of renal disease. In such cases, confirmation of all diagnoses within the family is essential to identify whether there is a clinically significant genetic predisposition to renal disease that may be relevant to potential donation (3). Information on constructing a pedigree can be obtained via the National Genetics Education and Development

Centre (www.genomicseducation.hee.nhs.uk). However, in most cases the family history is due to polygenic influences such as diabetes, certain types of glomerulonephritis and hypertension for which no additional genetic testing or screening is required above that recommended for routine donor evaluation (3).

A negative family history does not exclude a primary renal genetic disease. With the exception of autosomal dominant polycystic kidney disease (ADPKD), most familial renal diseases are rare in the nephrology clinic. 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 (4). Genetic testing may also aid the prediction of the likelihood of disease recurrence in the transplanted kidney, e.g. in atypical haemolytic uraemic syndrome (aHUS) and steroid resistant nephrotic syndrome (SRNS). 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.bsgm.org.uk/information-education/genetics-centres/).

It should also be noted that molecular testing can take in excess of 3 months and, with the increasing use of gene panels containing many genes, the likelihood of identifying a genetic variant that requires further interpretation is increased. This should be considered when planning donor evaluation and screening. Bespoke genetic testing may also be available for some families through the use exome

testing or whole genome sequencing, even if the test is not currently listed on the UKGTN. Projects such as the 100,000 Genomes project may facilitate the latter and further necessitates interaction with genetic services at an early stage of donor/recipient evaluation www.genomicsengland.co.uk/the-100000-genomes-project/.

Autosomal Dominant Conditions

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.

Autosomal Recessive Conditions

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 (5). It remains unclear what the risk of progression to proteinuria and renal impairment is for carriers, but this has been described (6,7). 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 Conditions

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 Disease, female carriers may manifest a phenotype as severe as males, or very minor abnormalities with a low likelihood of disease 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, a genetically related potential donor can be offered predictive genetic testing if the familial mutation has been identified. 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. Any person found to carry the familial mutation would normally be excluded as a potential donor if this predicted development of disease, and 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 be associated with a much smaller predictive value of developing disease and are relevant to populations and not families. A particular example is the association of *APOL1 gene* variants which account for some of the excess risk of chronic and ESRD in persons of African ancestry, including FSGS. Currently there are no prospective data on which to base recommendations for *APOL1* genetic testing and screening for what are also common variants in the normal population (8,9).

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 and MRI screening have been produced (10). 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 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 (autosomal dominant tubulointerstitial disease); Nail patella syndrome
Autosomal recessive:	ARPKD; Alport syndrome; Familial nephrotic syndrome, renal ciliopathies including nephronophthisis
X-linked:	Alport syndrome; Fabry disease; Dent disease
Polygenic:	VUR; FSGS, IgA nephropathy

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

ADPKD

The most common inherited renal disease is ADPKD, which affects 1:1000-1:2000 individuals and is responsible for ~10% 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 (11):

- 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. Criteria for the diagnosis or exclusion of disease using CT or MRI have recently been published with a total of >10 cysts being sufficient for diagnosis and <10 cysts being sufficient to exclude disease (10). An analysis of the UNOS

database indicates better graft survival from genetically unrelated donors in ADPKD (12). As genetic testing for ADPKD is 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 relative 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 (2,13).

Reflux Nephropathy

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 (14). 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 tract infection 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)

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5.18 DONOR MALIGNANCY

Recommendations

- ***Careful history taking, clinical examination and investigation of potential donors are essential to exclude occult malignancy before kidney donation, particularly in older (age >50 years) donors. (B1)***

- ***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)***

- ***Donors with an incidental renal mass lesion must have this diagnosed and managed on its own merit (out with discussion of kidney donation) with appropriate referral to a Urology Specialist in line with the '2-week wait' pathway. (A1)***

- ***Contrast enhanced renal CT scan, ultrasound and / or MRI can usually distinguish between benign lesions such as angiomyolipoma (AML) or malignancy such as renal cell carcinoma (RCC). Review by a specialist uroradiologist is recommended. (C1)***

- ***Bilateral AML and AML >4 cm generally preclude living kidney donation although occasionally unilateral large (>4 cm) AML can be used if ex vivo excision of the AML appears to be straightforward.***

- ***An incidental, unilateral solitary AML <4 cm with typical characteristic CT criteria does not usually preclude donation.***

- ***A kidney with an AML <1 cm may be considered for donation or left in situ in the donor's remaining kidney.***

- ***Kidneys containing a single AML between 1 and 4 cm can be considered for donation depending on its position, consideration of whether ex vivo excision of the AML is straightforward, or whether it***

can be left in situ in the recipient and followed with serial ultrasound imaging. (C1)

- ***Donors with an incidental small (<4 cm) renal mass that appears on imaging to be a RCC must be seen in a specialist Urology clinic and be offered standard of care treatment options, including partial and radical nephrectomy. Renal function permitting, if the person wishes to consider radical nephrectomy, ex-vivo excision of the small renal mass with subsequent donation of the reconstructed kidney can be considered on an individual basis with specific caveats, full MDM discussion and appropriate informed consent from the donor and recipient. (D2)***

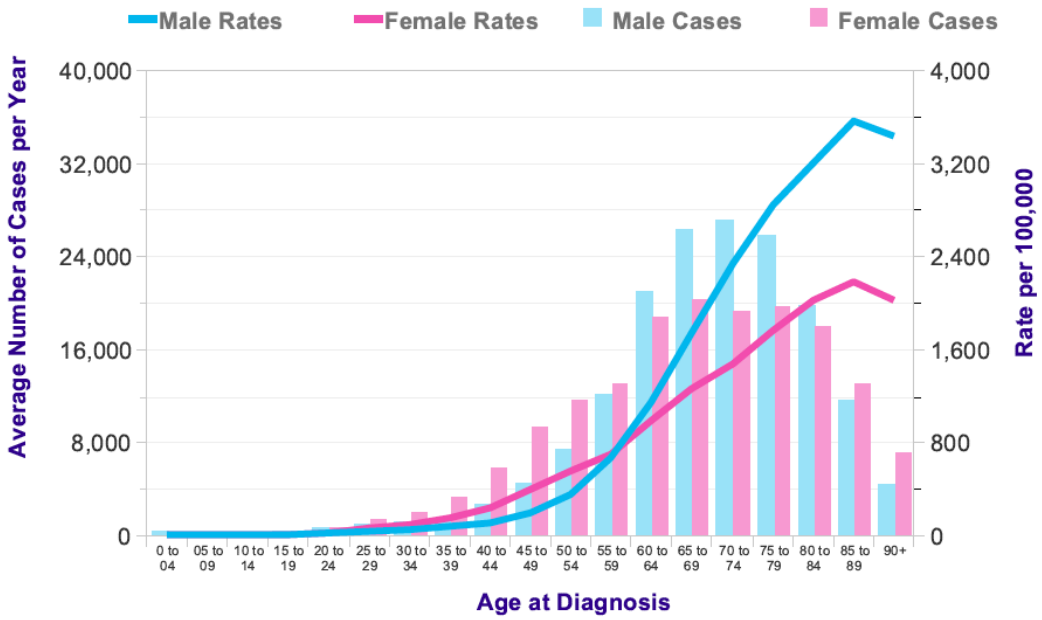
The accidental transmission of malignant disease from donor (deceased or living) to a recipient by kidney transplantation is well described and was relatively common before stringent donor criteria were enforced (1-7). Two types of donor-derived malignancies are possible: inadvertent transfer of tumour tissue (donor transmitted), and *de-novo* malignancy arising after transplantation in donor-derived tissue (donor derived). In a US registry review of 154 cadaveric donors with known cancer, transmission occurred in 45% of recipients (70/154 donors to 103 recipients), although these risks may be exaggerated as they come from a voluntary reporting registry (6). More recent reports from both sides of the Atlantic suggest that transmission is much less common but still occurs (8-11). 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.

It is worth stating that outcomes after transplantation should be compared to outcomes when remaining on dialysis, a condition with a high morbidity and mortality. This has led some to question whether previous tumours with low grade and slowly progressive biology should be considered in individual cases after discussion with the oncology MDT. Unfortunately, we do not know the biology of such tumours under the influence of immunosuppressive drugs. As an example it has been possible to transplant kidneys from unrelated donors with small renal cell carcinomas (<3 cm) with a very low risk of recurrence (12-14). Others have highlighted the low risk of renal transplantation from donors with successfully treated

low grade and localised prostate cancer (15). Registry data in the UK has demonstrated that donors in the UK with a past history of high risk cancer have donated organs with very low risk of transmission (16).

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 be up to date 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. Cross sectional imaging of the kidneys may reveal incidental adrenal masses. Evidence suggests that these are extremely unlikely to be malignant and if causing clinical concern can be removed at the same time as nephrectomy with minimal morbidity (17). 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 (18).

Figure 5.18.1 Age at First Diagnosis with cancer



If the potential donor has 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 indicate that certain tumours seem to be particularly high risk, e.g. lung, breast, and colonic carcinomas, as well as lymphoma and metastatic melanoma (2,8,10,11). There should be a low threshold to exclude any potential donor with a history of these cancers, although some potential donors with treated disease, no evidence of recurrence, long follow-up and favourable histology may be considered following careful oncology review. 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 (19,20). Advice adapted from the Amsterdam Forum for Living Donation in 2005 (21) is shown in Table 5.18.1.

The biology of the tumour should be considered and discussed with the relevant expert oncology team. There is universal agreement that tumours with a propensity to late recurrence, e.g. advanced breast cancer, lung cancer, malignant melanoma and sarcoma are an absolute contraindication to organ donation (22-24), 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 (5). 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. An attempt to grade tumours into categories of risk was published in 2011 by the Donor Transmission Advisory Committee (DTAC) in the United States (see Figure 5.18.2) (25,26).

Table 5.18.1 Previous Cancer and Fitness for Living Donation

Recommendation	Type of Cancer
Strong or absolute contraindication	• Malignant melanoma • Testicular cancer • Renal cell carcinoma >3 cm • Choriocarcinoma • Haematological malignancy • Lung cancer • Breast cancer • Sarcoma
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 • Localised low grade prostate cancer with curative treatment, minimum cancer-free period of 5 years • Renal cell carcinoma <3 cm • Breast cancer Stage I, hormone receptor-negative, curative surgery, minimum cancer-free period of 5 years • Ovarian cancer following curative surgery and minimum cancer-free period of 10 years • Small low grade thyroid cancers • Low grade CNS tumors (WHO Grade 1 & 2)

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 (21). It is also important to consider 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.

Figure 5.18.2 DTAC Risk Categorisation

Suggested risk categorizations for specific malignancy types from DTAC.

Risk category	Malignancies
Minimal risk (<0.1% transmission)	Basal cell carcinoma, skin
	Squamous cell carcinoma, skin without metastases
	Carcinoma in situ, skin (nonmelanoma)
	In situ cervical carcinoma
	In situ vocal cord carcinoma
	Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage) (nonrenal transplant only)
	Solitary papillary thyroid carcinoma, ≤0.5 cm
	Minimally invasive follicular carcinoma, thyroid, ≤1.0 cm
	(Resected) solitary renal cell carcinoma, ≤1.0 cm, well differentiated (Fuhrman 1–2)
Low risk (0.1–1% transmission)	(Resected) solitary renal cell carcinoma, >1.0 cm ≤ 2.5 cm, well differentiated (Fuhrman 1–2)
	Low grade CNS tumor (WHO grade I or II)
	Primary CNS mature teratoma
	Solitary papillary thyroid carcinoma, 0.5–2.0 cm
	Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm
	History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure
Intermediate risk (1–10% transmission)	Breast carcinoma (stage 0 i.e. carcinoma in situ)
	Colon carcinoma (stage 0 i.e. carcinoma in situ)
	(Resected) solitary renal cell carcinoma T1b (4–7 cm) well differentiated (Fuhrman 1–2) stage I
	History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90–99%
High risk (>10% transmission)	Malignant melanoma
	Breast carcinoma > stage 0 (active)
	Colon carcinoma > stage 0 (active)
	Choriocarcinoma
	CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation or extra-CNS metastasis
	CNS Tumor WHO grade III or IV
	Leukemia or lymphoma
	History of melanoma, leukemia or lymphoma, small cell lung/neuroendocrine carcinoma
	Any other history of treated non-CNS malignancy either (a) insufficient follow-up to predict behavior, (b) considered incurable or (c) with probability of cure <90%
	Metastatic carcinoma
	Sarcoma
	Lung cancer (stages I–IV)
	Renal cell carcinoma >7 cm or stage II–IV
	Small cell/neuroendocrine carcinoma, any site of origin
	Active cancer not listed elsewhere

5.18.1 Small Renal Mass, including Angiomyolipoma and Renal Cell Carcinoma

Classic angiomyolipoma (AML) is a triphasic, benign neoplasm composed of mature adipose tissue, smooth muscle and thick walled blood vessels (27) and can occur as an incidental finding in donor work-up. Diagnosis of an AML can usually be made

by imaging without recourse to biopsy; however, it is important to discriminate classic AML from the uncommon subtype of epitheloid AML, which may have a malignant phenotype. A specialist uroradiologist should review all cases.

Two large series (29 and 33 patients) observed the natural history of isolated AML (not as part of tuberous sclerosis complex) followed for approximately two to four years (28-30). Small (<4 cm) isolated AMLs, detected incidentally, showed a low risk of increase in size during long-term follow-up. 92% of renal AMLs showed no radiographic changes, serious complications or new renal or extra-renal lesions during follow-up. Such patients may be followed conservatively by ultrasonography every 2 years. AML more than 4 cm in diameter at presentation were more likely to have significant growth.

For living kidney donors, bilateral AML preclude donation. In unilateral disease, generally only the affected kidney should be considered for donation. However, if the AML is <1 cm, the affected kidney may be considered for donation, or in a male donor can be left *in situ* in the donor's remaining kidney. In contrast, it would not be appropriate to leave an AML in the single remaining kidney of a female of childbearing age due the risk of increase size and rupture during pregnancy (31). If an AML is 4 cm or larger, donation should only be contemplated if excision of the AML is possible, because of the risk of subsequent symptoms. This approach has been published as case reports describing either *in* or *ex vivo* excision of AML of varying sizes from living donors with a successful outcome (32-35).

If the AML is small, for example 1 cm or less, and its position makes removal particularly difficult, then implantation of the AML-bearing kidney followed by bi-annual ultrasound surveillance is reasonable (36).

Donors with an incidental renal mass that appears on imaging to be a renal cell carcinoma must be seen urgently in a specialist urology clinic. The incidental renal mass must be diagnosed and managed on its own merit, outwith discussion of kidney donation, and referred to the appropriate Urology Specialist in a time frame in keeping with the 2-week wait pathway. Contrast enhanced renal CT scan, ultrasound and / or MRI are usually able to characterise whether the renal mass might be a renal cell carcinoma (RCC). The imaging must be reviewed by a specialist uroradiologist.

Standard of care treatment options depend on the size and location of the renal mass and include partial nephrectomy and radical nephrectomy. Most people with an incidental small (<4 cm) renal mass will be counselled toward partial nephrectomy to preserve renal function, and occasionally minimally invasive techniques such as radio-frequency ablation or cryotherapy may be indicted.

Most potential kidney donors have excellent renal function and lack co-morbidity in order to be considered for donor nephrectomy. If the potential donor wishes to consider radical nephrectomy as opposed to partial nephrectomy, *ex vivo* excision of the small renal mass with subsequent donation of the reconstructed kidney can be considered on a case-by-case basis with specific caveats and after full MDM discussion; and with appropriate informed consent from the donor and recipient pair (37-41). Case series from 2005-15 totalling around 60 living donor / recipient pairs have recently been summarised in a systematic review (42). There are also two case reports from UK units: one involving the management of a small renal mass found at the time of donor nephrectomy; and the second in recipients who were at high immunological risk (43,44). A small survey of UK transplant recipients, nephrologists and transplant surgeons were supportive of this approach (45).

These approaches should permit transplantation without transmission of donor malignancy and minimise intervention in the donor, but do require careful case-by-case discussion. Specific issues requiring careful consideration are:

i) Consideration of percutaneous biopsy in the donor. Histopathological assessment of biopsy for SRM has become much more widely used and with improved sensitivity and specificity. It allows diagnosis of whether a SRM is a RCC, often the subtype of RCC (e.g. clear cell or papillary RCC) and exclusion of high nuclear grade (Fuhrman 4) RCC.

ii) What is the chance in the donor of bilateral non-synchronous RCC? This is rare but more likely if there is a family history of RCC or if there is a papillary RCC. Such patients are likely to be counselled against donation.

iii) A negative chest CT scan (not chest X-ray) is required for donation to be considered.

iv) Is the recipient appropriate to receive a kidney that will have *ex-vivo* excision and reconstruction of a potentially malignant SRM? This may not be appropriate due to age of recipient, immunological risk or surgical risks from reconstruction, e.g. bleeding if recipient requires anticoagulation.

v) Will frozen section pathology be needed at the time of *ex-vivo* excision of the SRM and reconstruction?

vi) What imaging follow-up will be arranged for both donor and recipient?

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

Recommendations

- ***Work-up for living kidney donation may include direct or indicative evaluation of split renal function with the kidney with poorer function selected for nephrectomy irrespective of vascular anatomy (see Chapter 5.5). (C2)***

- ***Work-up for living kidney donation must include detailed imaging confirming the vascular anatomy of both donor kidneys and information about the renal parenchyma and collecting systems. Either CTA or MRA can be used as current evidence indicates little difference in accuracy. (B1)***

- ***Multiple renal arteries or kidneys with anatomical anomalies are not absolute contraindications to donation. Decisions must be made on an individual basis as part of a multi-disciplinary team evaluation. (B2)***

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

- ***All living donor surgery must be performed or directly supervised by a Consultant surgeon with appropriate training in the technique. (C1)***

- ***Pre-operative hydration with an overnight infusion and/or a fluid bolus during surgery improves cardiovascular stability during laparoscopic donor nephrectomy. (B2)***
- ***Pre- and peri-operative intravenous fluid replacement with Hartmann's solution is preferred to 0.9% Saline. (B2)***

- ***Laparoscopic donor surgery (fully laparoscopic or hand-assisted) 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)

- ***Haem-o-lok clips are not to be used to secure the renal artery during donor nephrectomy following a report of an adverse event involving this technique*.(C2)**

- ***Patients undergoing living donor nephrectomy are likely to benefit from the management approaches widely used in "enhanced recovery after surgery" (ERAS) programmes. (D2)***

6.1 Introduction

Living donor nephrectomy is a major surgical operation. This Chapter 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 a written protocol detailing the peri-operative preparation and post-operative care of kidney donors. This should be reviewed regularly 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 vary in accordance with factors identified in the course of pre-operative assessment and can be divided into 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 from multiple centres have shown that kidneys with multiple renal artery or vein anomalies, such as circumaortic or retroaortic renal veins, have not been associated with an increased risk of complications in experienced hands (1,2).

6.2.1 Initial Evaluation

Renal imaging 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 vascular anatomy, and which best identifies anatomical factors predictive of 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 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 achieved as part of a subsequent evaluation by CT or MRI (see below).

The rationale for this initial imaging is to confirm equality or near equality of renal size and function between the two native kidneys, ensuring that the donor will retain adequate renal function after surgery. A difference in size of 2 cm or more between the kidneys indicates the possibility of a significant difference in GFR between the

two kidneys (a difference in function of more than 10% may be considered significant). In such cases, a split function isotope scan or equivalent split function measurement should be performed. Many units chose to perform such a study for all potential donors. Usually the kidney with significantly lower function is selected for nephrectomy, irrespective of vascular anatomy.

The interpretation of multiple cystic lesions in a potential living kidney donor requires careful assessment. 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. In such a situation, a detailed family history is crucial 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 (ADPKD) (3). 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 ADPKD, 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 (4). A donor kidney with a single renal artery should, whenever possible, be chosen for transplantation to minimise the risk of vascular complications in the recipient procedure; similarly, single renal veins are usually preferred. If both kidneys have single vessels, the left is usually selected as the longer renal vein on this side facilitates implantation.
Multiple renal arteries have been associated with an increased incidence of complications in the recipient in some studies but do not adversely influence patient or graft survival (1,2). It is acceptable to use a kidney with multiple renal arteries and/or veins for transplantation, provided that the surgeon responsible has the

necessary experience in implanting and where necessary, reconstructing, the vasculature of the kidney. Decisions should be made on a case-by-case basis supported by input from an MDT (5). 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 Anatomical and Vascular Evaluation

Prior to donor nephrectomy, all donors should undergo a detailed evaluation of vascular and ureteric anatomy by appropriate imaging, usually 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 (6-11). MR angiography may also be used, although the sensitivity at detecting accessory arteries may be lower (8,9,11). 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 characterising the renal vasculature before donation (10,11). 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.

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 (12-15). More recently, a large study of over 80,000 donors in the US - including significant numbers of laparoscopic donations - considered all donors reported using the national mandatory reporting system and showed the 90 day mortality to be a very similar 3.1 in 10,000 donations (95% CI 2.0-4.6), despite increasing age and obesity in the donor population (16). 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). The longer term risk of death is addressed below.

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 (17). Before 1998, two known peri-operative donor deaths had been reported in the UK. One was due to myocardial infarction and one to pulmonary embolus (17) with at least one further death occurring in 2011 also due to myocardial infarction.

Since the inception of the UK Transplant Living Donor Registry in 2000, a number of further deaths have been reported following living donor nephrectomy but beyond the perioperative period. Causes of death have included myocardial infarction/ischaemic heart disease and malignancy. Although occurring within the first year after surgery, case reviews have not considered it likely that these events have been 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) (13,19,21). 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%) (15); the corresponding risk for the UK is 0.33%. Such analogies should be used with caution. Although most potential donors are accepting of the risks associated with surgery, it must always be emphasised that there is a small but measurable risk which cannot be eliminated.

6.4 Peri-operative Morbidity

Until 2015, many studies of morbidity after donor nephrectomy had not provided definitive estimates of the rates of typical post-donation complications as non-standard, differing classifications were used, and most large published series were from single centres of excellence. In 2015, Lentine et al combined data from the United States Transplant Registry with records from a consortium of 97 hospitals performing living donor kidney transplantation. Data from 14,964 living donors performed from 2008-12 showed an overall incidence of 16.8% for any perioperative complication. Complications were formally graded using the Clavien-Dindo classification (22) with 8.8% of donors manifesting a Clavien 2 complication, 7.3% a Clavien 3 and 2.5% the most severe (life-threatening) Clavien 4. Complications included respiratory, cardiac, infections, hernia/wound complications, thrombosis, bleeding, and most commonly gastrointestinal.

This series included predominantly laparoscopic (including hand-assisted) donor surgeries but also 2.4% robotically performed nephrectomies and 3.7% open donor procedures. Only 1 complication (the most severe) was considered for each donor and multivariate analysis showed that obesity and African American ethnicity were associated with increased risk of complications, whilst higher annual centre volume was associated with lower rates of complications.

Earlier reported peri-operative complication rates for living donor nephrectomy had been summarised for a large number of single centre studies (15). The mean overall complication rate was estimated at 32% and the major peri-operative complication rate at 4.4%. The estimated 'major complication' rate in a survey by Bay and Hebert (14) was 1.8%, whereas the American Society of Transplant Physicians (ASTP) survey (12) 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) (17). 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)

(23). 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 comparing open mini-incision (MODN) and laparoscopic donor nephrectomy (LDN) have not thus far had sufficient statistical power to allow an adequate comparison of complication rates between these techniques. However, comparison of the latest reported complication rates in the USA with historical series suggests that complication rates in laparoscopic donor nephrectomy are not significantly higher than those observed with open surgery.

Specific complications that require special mention in pre-operative planning and counselling 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 (23). 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 (24).

6.5 Long-Term Mortality

The donor must be counselled about the life-long risks of donation in the context of their own health, age and ethnic background before giving consent for donation. (See Chapters 5.5 and 10).

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, and in an environment where donors are regularly cared for. A Consultant 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 year 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 (DVT) and pulmonary embolism (PE) 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 (25). 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 donor nephrectomy 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 (26). Typically this will mean the use of pneumatic mechanical compression during surgery and both TED stockings and LMWH from surgery until discharge (27).

Early mobilisation (on the first post-operative 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. A case series of 130 living donors who were prospectively screened identified laboratory evidence of thrombophilia in 6.9% of donors and were managed with intensified and prolonged prophylaxis. (28). In such cases, donation may not be precluded but advice should be sought from a haematologist (29). Any donors deemed high risk should have prolonged prophylaxis following discharge for at least 7 to 14 days.

6.6.3 Prophylactic Antibiotics

There is little published evidence to support the use of prophylactic antibiotics in donor surgery, although many centres have historically used a single dose of antibiotic at induction.

A randomised controlled trial has recently been reported in abstract form (30). 293 living kidney donors across five UK transplant centres were randomised 1:1 to either placebo or a single dose of intravenous co-amoxiclav at the time of surgery. The primary endpoint was the occurrence of any infection at 30 days following surgery. Antibiotic administration led to a significant reduction in postoperative infection (41.4% placebo v 26.6% antibiotic, p=0.006), with much of this related to a reduced incidence of surgical site infection (21.4% placebo v 11.9% antibiotic, p=0.023). Overall the administration of prophylactic antibiotics reduced the odds of developing postoperative infection by 50% (CI 31-82%). Following the full publication of this trial and given the limited downsides, the use of antibiotic prophylaxis is likely to become routine practice in laparoscopic living donor nephrectomy.

6.6.4 Consent and Site Marking

The law on informed consent has changed following a Supreme Court judgment. Doctors must now ensure that patients are aware of any “material risks” involved in a proposed treatment, and of reasonable alternatives, following the judgment in the case *Montgomery v Lanarkshire Health Board* (see Chapter 2).

The judgment describes this in terms of “materiality”: “A material risk is one that a reasonable person in the patient’s position is likely to attach significance to, or if the doctor is or should reasonably be aware that their patient would be likely to attach significance to it.” The key is to understand what matters - or is likely to matter - to

the individual patient.

The GMC guidance *'Good medical practice and Consent: patients and doctors making decisions together'* should be followed. Central to this is the principle that the relationship between a doctor and a patient should be a partnership based on openness, trust and communication (31).

Standard practice for major surgery is to seek written consent before admission, and to 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 (32), should be performed before 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 the 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

Living donor surgery is a unique sub-discipline of general surgery. Patients are selected for their fitness rather than the presence of a morbidity that requires surgical intervention. Donor surgery, other than the potentially significant psychological benefits of performing an act of altruism, can only lead to the potential for harm. Therefore, it is imperative, for the patient and the UK living donor transplant programme in its entirety, that careful consideration and effort goes into maximising each donor experience.

6.7.2 Type of Surgery

The vast majority of donor nephrectomy in the UK is carried out using minimally invasive techniques, either fully laparoscopic or hand assisted, using a trans- or retro-peritoneal approach to the kidney. A number of studies have attempted to demonstrate superiority of one technique over another, but the differences or advantages between the techniques are small and surgery should be performed using whichever technique the operating surgeon has been trained to perform safely (33).

A number of vascular stapling devices are available for surgeons to use. The choice of which device to use is down to surgeon preference.

Discussion at the BTS Chapter of Surgeons meeting, London 2014, reached consensus that Haem-o-lok clips were not to be used to secure the renal artery during donor nephrectomy following a report of an adverse event involving this technique.

6.7.3 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.

The decision on the side of donor nephrectomy should be documented and ideally made at a multi-disciplinary meeting which includes a review of the vascular imaging. The potential donor should be informed of any increased risk associated with this decision. When assessed in the context of a paired exchange programme, the donor and recipient surgeons should communicate directly to discuss which kidney is selected for nephrectomy.

6.7.4 Peri-operative Considerations

Multi-modal strategies to enhance recovery after Donor Nephrectomy

Since the 1990s, Henrik Kehlet, a surgeon working in Denmark, has advocated strategies to address and attenuate the surgical stress response (34,35). These Enhanced Recovery After Surgery (ERAS) Pathways are well established in several surgical sub-disciplines, notably colorectal surgery, and have been demonstrated to

reduce post-operative morbidity, mortality and the length of post-operative hospital stay (36-38). The role of Enhanced Recovery pathways has yet to be established in donor nephrectomy; however, the enhanced recovery principles eschewed by other surgeons performing major intra-abdominal surgery are readily transferrable to donor nephrectomy. As such, several units in the UK are now adopting these strategies.

6.7.5 Pre-operative Psychological Preparation

A very simple and key intervention of an Enhanced Recovery pathway is that of pre-operative preparation. A number of stages in the donor assessment pathway allow for expectation management, and repeated education at each of these steps aids with information retention.

Information given to the potential donor should be detailed and should concentrate on each step of their pre- and post-operative journey. Emphasis should be placed on what is expected of the patient so that they may aid their own recovery, and the reasons for each recommendation. The pre-operative consent process should be performed by the operating surgeon and not be rushed.

6.7.6 Peri-operative Fasting and Insulin Resistance

Guidelines surrounding peri-operative fasting in non-emergency surgical cases (in patients with no history of gastric emptying disorders) recommend fasting for six hours for solids (including milk in tea or coffee) and two hours for clear liquids (40,41).

Overnight fasting has been demonstrated to increase insulin resistance associated with the surgical stress response, presumably as an adaptation to increase the bioavailability of glucose for consumption during the ‘fight or flight’ response. Insulin resistance is related to increased peri-operative morbidity and length of hospital stay for patients undergoing cardiac and major gastro-intestinal surgery.

Reversing the ‘fasting’ state of the patient by administration of an oral carbohydrate drink pre-operatively can increase insulin sensitivity by 50%, a state which continues into the post-operative period. A recent Cochrane analysis of randomised controlled trials looking at pre-operative carbohydrate loading prior to major abdominal surgery suggests that there is a more rapid recovery with administration of a carbohydrate

drink rather than traditional fasting regimens (42). There have been no studies to date looking at the effect of insulin resistance in donor nephrectomy; however, extrapolating the results achieved from gastrointestinal surgery, it would seem reasonable to consider pre-operative carbohydrate loading in patients undergoing donor nephrectomy. Nutricia Pre-op has been designed and validated for this purpose. The pre-operative dosing regimen is 4 x 200 mL cartons between 9 pm and midnight before the operation with a further 2 x 200 mL 2 hours pre-operatively. In addition, allowing clear fluids up to 2 hours pre-operatively improves patient comfort by reducing thirst and allows black tea or coffee to be consumed by habitual caffeine drinkers who may be susceptible to withdrawal headache.

Post-operative fasting should be avoided and early and unrestricted resumption of fluid and solid food is recommended in the immediate post-operative period.

6.7.7 Peri-operative fluid requirements

The surgical stress response initiates a well-documented cascade of hormonal pathways leading to a diminished ability of the patient to excrete sodium and water.

Traditional pre-operative intravenous fluid regimens using 0.9% Saline have been demonstrated to lead to significant fluid retention and weight gain, the development of hyperchloraemic acidosis, renal oedema, reduced renal blood flow and reduced renal cortical perfusion, even in healthy volunteers (43). The use of 0.9% Normal Saline has been demonstrated to lead to inferior surgical outcomes in gastrointestinal and orthopaedic surgery with increased rates of pulmonary complications, post-operative Ileus, anastomotic dehiscence and delayed post-operative recovery. Peri-operative complications in gastrointestinal surgery increase when the post-operative weight gain exceeds 2.5 kg, reflecting a net fluid gain of 2,500 mL of fluid (44,45). A number of units within the UK follow aggressive pre-operative intravenous fluid regimens for living donors, with or without the addition of diuretic agents. Evidence from one randomised control trial (46) and one series has demonstrated improved cardiovascular stability and reduced sub-clincal renal injury respectively when such pre-operative hydration strategies are applied (47). Other units within the UK perform donor nephrectomy restricting intravenous fluid therapy to Hartmann’s solution given intra-operatively only, aiming for a ‘near 0 fluid balance.’

Whilst there are no comparative studies to inform on best practice, outcomes for donor and recipients from units in the UK are satisfactory. However, with mounting evidence to suggest that 0.9% Normal Saline is detrimental to patient outcome, and may indeed contribute to renal dysfunction, the use of this solution in donors cannot be recommended. Hartmann's solution is the recommended intravenous fluid of choice.

6.7.8 Post-operative Analgesia

Adequate analgesia is paramount to achieving excellent outcomes. However, balancing the level of analgesia with the unwanted side effects of analgesic agents requires thought, observation and an individual, tailored approach to each patient.

Epidural Anaesthesia

Epidural anaesthesia can achieve excellent post-operative analgesia as well as significantly attenuate the surgical stress response. In early Enhanced Recovery protocols, epidural anaesthesia was the preferred method of choice to minimise the use of opiates in the peri-operative period. However, the side effects (hypotension, headache, potential for infection, urinary retention, reduced mobility) are well documented and other opiate sparing strategies have now superseded epidural use. There is now little place for epidural use within the domain of donor nephrectomy, especially when performed laparoscopically (48,49).

In-Dwelling Nerve Catheters

The anatomical basis of the nerve supply to the abdominal wall has been well described. Blockade of the nerve supply to the wound with local anaesthesia is therefore a very straightforward and attractive option as an 'opiate sparing' technique.

Indwelling nerve catheters have been in use for around 15 years and can provide safe and effective analgesia to a variety of surgical wounds in the thorax and abdomen as well as upper and lower limbs. Their use as a potential 'opiate sparing' strategy within Enhanced Recovery programs is gaining popularity. Their use in donor nephrectomy surgery is novel but they have been shown to reduce opiate requirements in hand assisted laparoscopic donor nephrectomy (using an upper abdominal transverse extraction scar) and in fully laparoscopic donor nephrectomy (using a Pfannenstiel incision to extract the donor kidney) (50-55).

The On-Q pain buster device has a well-documented safety record. Correct anatomical placement of the catheter is paramount to achieving success and there is a short learning curve to achieve expertise of use. A bolus of 30 mL 0.25% levobupivacaine is introduced on the operating table followed by a continuous infusion of 0.125% levobupivacaine at 6-10 mL/hr. The infusion can be administered via an elastomeric pump or a battery run infusion pump (52).

Opiates

Opiates are an effective analgesic and remain a common treatment of post-operative pain control worldwide. However, the short term side effects of this class of medication are significant. Drowsiness, nausea, vomiting, pruritis and lack of appetite all work against the principles of Enhanced Recovery surgery aiming for early mobilisation and return to oral intake. More recently, multimodal strategies have been attempting to introduce 'opiate sparing' regimens to ameliorate the early unwanted side effects of these drugs (55).

Despite these drawbacks, many units in the UK use intravenous patient controlled opiate administration strategies to good effect. Opiates also have an effective role for breakthrough pain when opiate sparing strategies have not been effective.

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7 HISTOCOMPATIBILITY TESTING FOR LIVING DONOR KIDNEY TRANSPLANTATION

Recommendations

- ***Initial assessment of donor and recipient histocompatibility status must be undertaken at an early stage in living donor kidney transplant work-up to avoid unnecessary and invasive clinical investigation. (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 transplant recipients undergo reduction or withdrawal of immunosuppression. (B2)***

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

- ***Transplant units and histocompatibility laboratories must agree an evidence-based protocol to define antibody screening and crossmatch results that constitute a high immunological risk to transplantation. (B2)***

- ***When possible, the HLA type(s) of partners/offspring of female recipients who have had previous pregnancies should be determined to aid immunological risk assessment for repeat paternal HLA mismatches in women with low level DSA. (B1)***

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

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

- ***HLA matching may be preferred when there is an option of selecting between living donors, particularly to reduce 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)***

- ***For patients with an ABO/HLA incompatible and/or a poorly HLA matched living donor, consideration should be given to entry into the UK living kidney sharing scheme (UKLKSS) to identify a more suitable donor. (B2)***

- ***The histocompatibility laboratory must 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 the 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 an immunological 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 work-up 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. United Kingdom Accreditation Service (UKAS) / 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 accurate 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. In addition, for patients known to have HLA-DP specific alloantibodies, donor and recipient HLA-DP typing should be performed. 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 ‘0.0.0’, whereas a fully mismatched combination is denoted ‘2.2.2’. 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.

In the case of genetically related donors, ABO blood group and HLA typing results can indicate the nature of the familial relationship. Informed consent must therefore 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, sensitisation status and alternative options for transplantation, both now and in the future (see also 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 transplantation. HLA-specific alloantibodies can also arise naturally through cross-reactivity with pathogens, when they are termed idiopathic antibodies.

Particular attention should be paid to low-level donor HLA-specific antibodies (normally classified as low immunological risk) in patients previously exposed to that same HLA specificity through previous transplantation or, in female patients, pregnancy. In these cases there is the risk of an anamnestic response that is often refractory to baseline induction immunosuppression.

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 listed for repeat transplantation who are receiving immunosuppression while under assessment for living kidney transplantation are at high risk of *de novo* sensitisation, particularly if the baseline immunosuppression is changed, reduced or withdrawn. For patients with a failing/failed transplant,

consideration should be given to the potential benefits of immunosuppression reduction/withdrawal and the risks of developing *de novo* HLA-specific allosensitisation that could severely restrict future options for transplantation. 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. 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 have a formal immunological risk assessment based on donor HLA type, antibody levels, priming source and duration in consultation with 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 investigation.

In many cases, the living donor kidney transplant work-up 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 help 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 dependent 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 and acute humoral 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 work-up, 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 work-up, the benefit of immunosuppressive drug reduction or withdrawal, and the risk of *de novo* allosensitisation. A reduction or stopping 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 the 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.

For patients with an ABO/HLA incompatible and/or a poorly HLA matched, living donor, consideration should be given to entry into the UK living kidney sharing scheme (UKLKSS) to identify a more suitable donor (8).

7.5 Antibody Incompatible Living Donor Transplantation

Antibody incompatible transplantation (AIT) may be an option for some patients who have a potential living donor 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 established in the UK and contribute to the expansion of the living donor pool. (see section 8.3). Close liaison between clinicians and histocompatibility laboratories is obviously critical for such transplantation, which should be 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 only be undertaken after prior consideration of entry of the donor-recipient pair into the UK Living Kidney Sharing Schemes (UKLKSS) (see Chapter 8).***

- ***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 five 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 ABO antibodies. In living donor transplantation, a 7 day per week service with same day turn-around time is required.***

- ***AIT results in an improved quality of life when 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 AIT 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.***

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8 EXPANDING THE DONOR POOL

Recommendations

- ***Coherent organisational and clinical practices are essential between transplant centres to optimise the UK Living Kidney Sharing Schemes (UKLKSS) and to maximise the number of potential transplants that proceed. (B1)***

- ***To maximise transplant opportunities within the UKLKSS, donors and recipients must only be included in a matching run if:***
    - ***Their clinical assessment and histocompatibility screening are complete and up to date. (B1)***
    - ***If matched, they are available to attend for crossmatch testing and proceed to surgery within the designated timeframes. (B1)***
    - ***Relevant complex donor considerations identified in the 'pre-run' and donor HLA and age preferences have been discussed and agreed with the recipient. (B1)***
    - ***They understand their roles and responsibilities with respect to other donors and recipient pairs in the schemes with whom they may be matched. (B1)***

- ***The default for all non-directed altruistic kidney donors (NDADs) is to donate into an altruistic donor chain (ADC) within the UKLKSS provided that there is no higher priority patient on the national transplant list. (B1)***

- ***All altruistic donors (non-directed and directed) must undergo formal mental health assessment with a mental health professional before donation. (C1)***

- ***Living kidney donors who are antibody incompatible with their recipient must have all the options and risks explained to them, including donation into the UKLKSS and antibody removal. (C1)***

- ***As a minimum, donors must be made aware that a compatible transplant has the best chance of success and direct antibody incompatible transplant is associated with higher short- and long-term risk, if that is what is proposed. (C1)***

The UK Living Kidney Sharing Schemes (UKLKSS) were established after the introduction of the Human Tissue Acts in September 2006 (see Chapter 2), and the first transplants were performed in 2007. The UKLKSS enables kidneys donated from living donors to be shared across the UK to maximise the number of transplant opportunities and include:

- Paired/pooled donation
- Altruistic donor chains

8.1 Paired/Pooled Living Donation

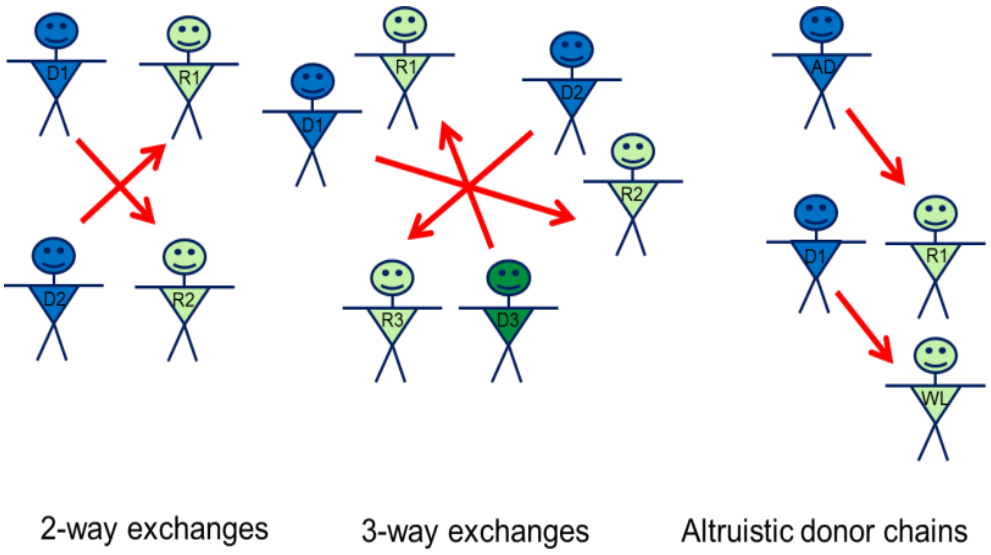
Paired/pooled donation (PPD) allows the exchange of kidneys between donor-recipient pairs so that recipients who are Human Leucocyte Antigen (HLA) or ABO blood group incompatible with their donors can receive a compatible transplant. Compatible donor-recipient pairs may also enter the scheme to achieve a better HLA- or age-matched transplant, or to optimise other relevant factors such as a discrepancy in BMI. The entry of such donor-recipient pairs increases the transplant opportunities for all recipients who are waiting within the UKLKSS. Exchanges are identified between two (paired) or three (pooled) pairs (Figure 8.1).

The paired/pooled scheme requires careful co-ordination and administration to ensure that the use of kidneys is optimised and maximum patient benefit is achieved.

Registration in the Scheme

Only donor-recipient pairs who have been fully evaluated and are suitable to proceed to donation/transplantation can be registered into the paired/pooled scheme and entered into the quarterly living donor kidney matching runs (LDKMR). Results of clinical investigations and up-to-date histocompatibility and

Figure 8.1 Exchange Options within the UKLKSS



immunogenetics (H&I) testing must be available before donor-recipient pairs are confirmed for inclusion in each matching run. At a minimum, relevant clinical investigations for registered donors and recipients must be repeated annually, or more frequently as clinically indicated, if they remain unmatched in the scheme.

The deadline for registration of potential pairs with NHS Blood and Transplant (NHSBT) is usually three weeks before the quarterly matching run with the opportunity to suspend or activate pre-registered pairs (positively confirm inclusion) up to seven days before the run. Deadline dates for registration and dates of LDKMR are published in advance by NHSBT. Recipients must be registered with maximum acceptable donor age and any specific HLA match requirements. However, these limitations can reduce the chances of a match and must be discussed with the recipient. Recipients can also be registered with 'extended criteria' for acceptable HLA and ABO blood group mismatches to increase the options for transplantation (e.g. a low risk ABOi transplant in preference to a higher risk HLAi transplant). Such preferences must be agreed before registration and confirmed before inclusion in each matching run to avoid exchanges not proceeding due recipient withdrawal after the matching run.

Nominated contacts from the living donor co-ordinator team at each transplant centre and/or referring hub are responsible for ensuring that all eligible pairs are

registered and that information is complete and up to date. Each H&I laboratory also has nominated contacts for the schemes to co-ordinate scientific information for donor-recipient pairs. Key responsibilities for the nominated living donor co-ordinator contacts include:

- Close collaboration with the H&I key contacts to ensure recipient HLA antibody screening is up to date, unacceptable antigens are registered, and donor HLA preferences are specified before confirmation of inclusion in each matching run.
- Close collaboration with clinical colleagues to ensure that donor and recipient assessments are up to date and complete before confirmation of inclusion in a matching run.
- With the exception of multiple donors for one recipient, ensuring that donor-recipient pairs are assessed by an Independent Assessor and approved by the HTA before inclusion in the matching run.
- Particular donor information that is relevant to the acceptance of a kidney by a recipient centre must be cited with the registration according to the agreed clinical criteria, which include complex vascular or non-vascular anatomy, relevant medical history, and absolute GFR for all complex potential donors.
- 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 that 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 must be discussed in advance to minimise the risks.
- Collation and confirmation of information to register and positively confirm inclusion of relevant pairs in the scheme at the notified times.

Matching Runs and Scoring Systems

There are four matching per year, at quarterly intervals. Each matching run identifies all potential matches within the pool according to a scoring system developed in collaboration with experts in matching algorithms at the University of Glasgow. Scoring is necessary to optimise the number of transplants overall and the best transplant option for a single recipient from multiple possibilities. The number of

transplants and the scores of different possibilities are optimised over all options involving both 2-way and 3-way exchanges and altruistic donor chains. Identification of possible matches takes into account any donor age or HLA restrictions specified at the time of registration. Typically there are approximately 250 pairs in any one matching run and up to 70 transplants may be identified.

Scoring is based on the:

- Calculated level of sensitisation (to promote matches for sensitised patients where such are identified)
- Waiting time in the scheme (after the first matching run)
- HLA mismatch level of the potential transplant (to promote good matching where possible)
- Age difference between the two donors, which is a tie-breaker to optimise outcome

The scheme continues to evolve. For example, a restriction on blood group O donor kidneys only being allocated to blood group O recipients has been removed to maximise transplant opportunities for highly-sensitised HLA recipients. Current matching arrangements, statistics related to the scheme, and on-line resources to support clinical decision-making can be found at www.odt.nhs.uk (1-3).

One week before each matching run, a ‘pre-run’ is performed to identify any potential matches between complex donors (see above) and the recipients in the scheme. Transplant teams are requested to review the potential matches for their patients and discuss with them if they wish to be included with the potential donor in the final matching run. This pre-run and the discussions with clinical teams and recipients before the actual matching run is finalised are essential to minimise the number of potential transplants that may not proceed.

When a matching run has taken place, NHSBT notifies the nominated scheme leads with a report specifying all the donor-recipient pairs that have been successfully matched. The nominated scheme leads in transplanting centres are responsible for:

- Liaising with local referring units and donor-recipient pairs to inform them that they are in a potential match, pending initial crossmatch between all pairs. Recipients must be reminded that they are automatically suspended from the

national transplant list until confirmation of the initial crossmatch test. The initial crossmatch must be arranged as soon as possible after the matching run so that it is reported within a maximum of 14 days after the notification of identified transplants. In the event of a positive crossmatch, the recipients from the provisionally matched group are reinstated on the national transplant list unless an alternative match within the same group can proceed. Transplant centres are responsible for reinstating recipients on the national transplant list.

- 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 if this has not been completed prior to registration in the schemes (see Chapter 5). Transport arrangements for essential samples and organs before and 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 LKD Schemes Co-ordinators within NHSBT of the progress of the matched group, including the outcomes of crossmatch results, prompt reporting of problems, e.g. non-proceeding transplants, delay to the scheduled dates of surgery, and response to requests for further information (including the investigation of incidents and action to prevent future risk or recurrence).
- Liaising with the wider in-centre teams to facilitate arrangements for admission, co-ordinating the start of simultaneous donor lists on the day of surgery, and ensuring colleagues are updated and informed throughout the process. Designated weeks of surgery are scheduled within 8 weeks of the notification of the outcome of the matching scheme and dates are included in the annual timetable distributed by NHSBT. All participating transplant centres in the UK are requested to 'ring-fence' operating lists within the 'sharing period' to accommodate as many exchanges as possible. This is important to reduce delay and to incentivise donor-recipient pairs and non-directed altruistic donors (NDADs) to enter into the scheme.

Special considerations

The expectations of donor-recipient pairs entering the paired/pooled scheme must be managed. The potential benefit from a compatible living donor transplant must be balanced with realistic information about the likelihood of being matched, tailored

to their individual circumstances (e.g. degree of sensitisation, blood group mismatch, etc.). In addition to the latest statistical information and decision-making aids related to the scheme available at www.odt.nhs.uk, the NHSBT 'Incompatible Pairs' calculator enables clinicians to assess the likelihood of a particular incompatible donor-recipient being matched in the scheme (3).

Approximately 25% of identified transplants will not proceed due to reasons that cannot be foreseen before the matching run, i.e. positive crossmatch or clinical/social considerations for either the donor or recipient. The schemes are formally monitored by the Directorate of Organ Donation and Transplantation (ODT) within NHSBT to identify when transplants do not proceed due to modifiable reasons and to make recommendations for remedial action to reduce the risk of recurrence.

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:

- Before confirming inclusion in each matching run, donor-recipient pairs must agree, if matched, to be available for crossmatch testing and to proceed to surgery within the designated timeframes.
- All incompatible donor-recipient pairs are entitled to know the treatment choices that are available to them. Practices vary between centres but, increasingly in HLA or high titre ABO blood group incompatible scenarios, up to 3 or 4 matching runs (1 year) in the paired-pooled scheme are often recommended before considering other interventions. An annual review of all unmatched donor-recipient pairs in the scheme is recommended to ensure that appropriate treatment options are reconsidered.
- Multiple donors with different HLA types and blood groups can be assessed and registered for a single recipient, to increase potential for matching.
- Recipients can be registered with 'extended criteria' for both HLA and ABO matching to facilitate a lower risk transplant (see above).
- Compatible donor-recipient pairs are eligible for the scheme and benefit the whole UKLKSS by increasing the donor-recipient pool. For individual recipients, this is recommended if an improved age or HLA match might be achieved (e.g. for children or young adults).

- 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.
- Donors from outside the UK for NHS recipients, non-UK donor-recipient (non-NHS entitled) pairs, and privately funded pairs can be included in the UKLKSS if they meet the requirements for registration and inclusion and the timeframes involved to avoid impact on other pairs in the scheme. Such cases are reviewed on an individual basis. In the case of private patients or non-NHS entitled donor-recipient pairs, the terms of participation in the schemes must be made explicit and it is recommended that they are referred and managed in collaboration with a NHS multi-disciplinary transplant team that is familiar with the schemes.
- Donor-recipient pairs must be made aware of the implications of late withdrawal on other matched pairs and encouraged to carefully consider this before registration in the scheme and at the time of each subsequent matching run.
- Although simultaneous donor surgery is the default position for all matched donor-recipient pairs, non-simultaneous surgery may be the preferred option to overcome logistical complexities and to facilitate timely transplantation. If this approach is adopted, although the risk of a recipient missing out on a transplant opportunity is low, donor-recipient pairs must be consented to ensure that they understand the possible risks involved.
- If a paired/pooled recipient misses out on a transplant and his/her donor has donated but all the exchanges cannot be completed, he/she can be prioritised for transplantation from either a living or deceased donor, according to their preference. Details are available from https://www.odt.nhs.uk/living-donation/

Transplants and Outcomes

It is usual for the retrieved kidneys to travel between donor and recipient hospitals, but arrangements for donors and recipients to move can be made if all parties agree. Usually, 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. However, there is flexibility for centres to stagger the start time of donor surgery within the same day or on adjacent days to accommodate matched transplants within the scheduled sharing weeks (see also section 8.2).

To streamline the transplant process and minimise delay at implantation, the retrieved kidney should be prepared in the retrieval centre so that it is ready for implantation into the recipient on arrival. If a kidney cannot be transplanted into the intended recipient on the day of surgery and the donor has consented to the option of transplantation into an alternative recipient (see HTA consent, Chapter 2), the kidney is re-offered to all UK centres via NHSBT according to the offering process for a deceased donor kidney.

Five-year transplant survival rates (not censored for patient death) are comparable for paired donation transplantation and other forms of living donor transplantation (2).

Anonymity

The scheme relies upon anonymity between matched donor and recipient pairs to avoid disclosure of identity before donation-transplantation (4). 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, usually initiated by the recipient, after the exchange transplant has been performed and it is recommended that this is facilitated through the respective living donor co-ordinators.

8.2 Altruistic Donation (Directed and Non-directed)

Increased public awareness since 2011 has led to more people volunteering to be considered for altruistic kidney donation and this is a valuable means of expanding

the donor pool. Five year transplant survival rates (not censored for patient death) are comparable for recipients of non-directed altruistic donor kidneys with other forms of living donor transplantation (2).

Terminology

The Human Tissue Authority (HTA) classifies the different types of altruistic living organ donation according to whether the donation is made to a specific individual or to a stranger (4).

Donation to a specific individual: Directed Altruistic Donation

The HTA defines two categories of directed altruistic donor (DAD)

1. Where there is no genetic relationship or established emotional relationship between the donor and recipient (e.g. distant family member who has not seen their potential recipient for many years; relative with whom there has been no contact previously; friend of a friend)
2. Where there is no pre-existing relationship between the donor and recipient before the identification of the recipient's need for a transplant (i.e. contact is made through a third party such as through social networking, media campaign, Facebook, bespoke website, local newspaper)

This is a challenging and controversial area in living organ donation. To provide a framework for an approach to the management of DAD referrals, the British Transplantation Society (BTS) has published specific guidelines to support clinical practice (5).

It is particularly important to manage the expectations of category 2 DAD donors and their potential recipients so that both sides are clear about the likelihood of finding a suitable donor through social media/media appeals. More guidance is available at https://www.organdonation.nhs.uk//about-donation/living-donation/ and https://www.nhsbt.nhs.uk/get-involved/promoting-donation-hub/download-digita

Donation to unspecified individuals: Non-Directed Altruistic Donation

Non-directed altruistic donors (NDAD) donate an organ to an individual who is unknown to them. These donations account for approximately 10% of all living

kidney donations in the UK (1). Different names are used to describe this type of donation within the transplant literature (e.g. altruistic, anonymous, non-directed, “Good Samaritan”, unspecified). To remain consistent with the terminology used in the Human Tissue Act 2004 and by the Human Tissue Authority (4), the term *Non-directed Altruistic Donation* is used by the BTS and within these guidelines.

From January 2018, provided that there is no patient with higher priority on the national transplant list to whom their kidney could be allocated, all NDADs donate into the paired / pooled scheme to create altruistic donor chains (ADCs) of up to three transplants. The NDAD is used to ‘prime’ a chain of transplants between two or more donor-recipient pairs to maximise transplant opportunities within the UKLKSS. The remaining organ from the paired donor at the end of the chain is donated to the best-matched recipient on the national waiting list (see Figure 8.2). Options to use the last paired donor as a ‘bridge donor’ to initiate an ADC in the next LDKMR may be considered for the future.

Assessment of Directed Altruistic and Non-Directed Altruistic Donors

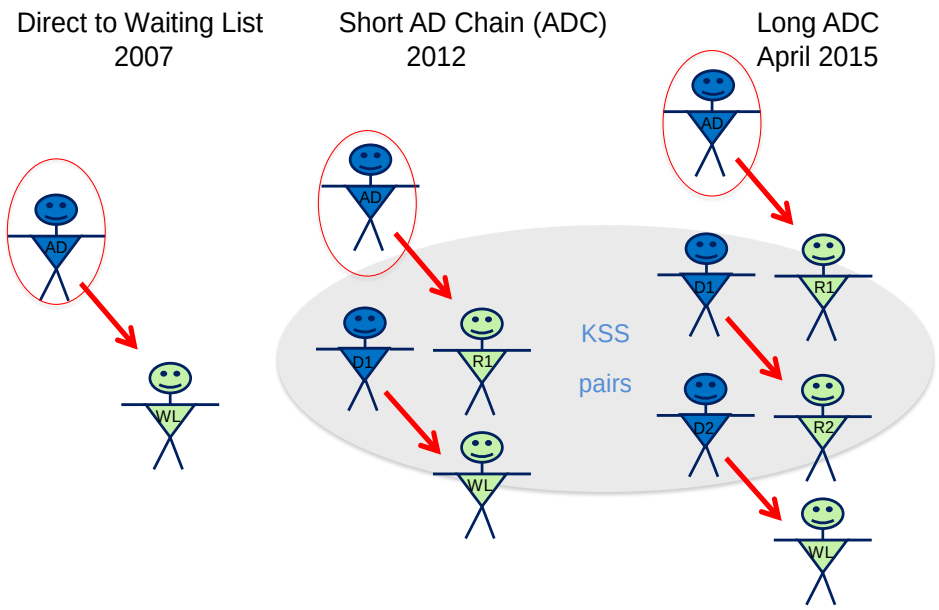
Directed altruistic donors (DADs) and Non-Directed altruistic donors (NDADs) must complete the same living donor assessment as required for directed donors, with the additional requirement of a formal mental health assessment (see Chapter 8, Appendix 1).

Registration and Allocation

Most DADs donate directly to an identified, compatible recipient and will proceed as per directed donations within a single centre or by agreement between two centres. If a DAD is incompatible with their recipient, they may also enter the paired/pooled scheme as donor-recipient pair, provided that they can meet the requirements of the scheme and are aware of their roles and responsibilities within it (see section 8.1).

Once they have been fully evaluated and HTA approved, all NDADs are registered with NHSBT. Registration is 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.

Figure 8.2 Allocation Options for NDAD Kidneys



The allocation of NDAD kidneys, including altruistic donor chains identified in the living donor kidney matching run and the possible default to a high priority patient on the national transplant list, must be discussed with all NDADs at an early stage of assessment so that the arrangements and timeframes for donation are clear.

If an altruistic donor chain falls through, the NDAD can choose to donate directly to the waiting list to avoid further delay to their donation, or wait for the next quarterly matching run (2).

Once a NDAD has been matched to a recipient (through a chain or directly via the waiting list), 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. The following principles of best practice are established:

- Specific donor information that is relevant to the acceptance of a kidney by a recipient centre must be cited with the registration according to the agreed clinical criteria, which include complex vascular or non-vascular anatomy, relevant medical history and absolute GFR for all complex donors.

- Donors must be made aware that they cannot request specific dates for donor surgery but that every effort will be made to accommodate their donation within the shared weeks of surgery attached to each matching run. In exceptional circumstances **only**, if a donor is unable to donate within the shared weeks of surgery, this must be specified in the special considerations at registration to allow other centres to accept/decline an offer for a potential recipient.
- For donations into the UKLKSS, the same principles that apply to the paired/pooled scheme (detailed in section 8.1) are applicable to NDADs entering into an altruistic donor chain.

Receiving an altruistic donor offer to a recipient on the national transplant list

After an offer of a kidney from a NDAD has been made for a recipient on the national transplant list from NHSBT, 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 negotiated between the participating centres, but consideration should be given to the preferences of the donor and the expectations of both donor and recipient in scheduling a date.
- Before accepting an offer in principle and **before** informing the potential recipient, the following must be identified as a priority: recipient clinical issues; suitability of offer for the intended recipient; and centre logistics. Once the recipient has been informed about the offer, it can cause unnecessary distress 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 so that it is reported within fourteen 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 are met by the recipient centre.

- 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.

Specific Considerations in Directed and Non-directed Altruistic Donation

Psychosocial assessment

A formal mental health assessment by a mental health professional (psychiatrist or psychologist) remains a mandatory stage in the work-up of both DADs and NDADs. Research into non-directed altruistic donation has demonstrated that there is no significant difference in psychosocial outcomes between those donating to a stranger and those donating to someone that they know (6). The same study also showed that a mental health history in NDADs does not prohibit donation, nor does it increase the likelihood of adverse post-operative outcome.

There are currently no data regarding the sensitivity or specificity of mental health assessments or whether they can be safely removed without an increase in pre- or post-operative mental health problems within these donor subsets, yet there are still large numbers of potential altruistic donors who are screened out for a variety of psychosocial reasons (7). Given the positive psychosocial outcomes reported after NDAD in the UK and the reliance on positive outcomes to further expand the programme, it is prudent for formal mental health assessments to remain best practice until further evidence is available. The UK and Ireland Group of Renal Transplant Psychiatry has produced a Consensus Guidance Statement on the Mental Health Assessment of Altruistic Donors as a framework for assessment (Appendix 1, Chapter 8).

Age

An issue commonly discussed within the field of directed and non-directed altruistic donation is that of age: particularly young adults aged between 18-25 years. Separate from considerations about long-term health, the majority of concerns relate to whether younger donors may be more likely to regret their decision. There is no evidence to suggest that this is the case. A helpful discussion with younger donors may include questions regarding why it is important to them that they donate now

and whether it is something that they would consider at a later point in their life. A period of time to reflect on the decision may also be encouraged.

Donor motivation

Research into non-directed donation has dispelled many pre-existing concerns regarding donor motivation. Donors have been found to be most commonly motivated by a desire to help another individual, and that donation would make a significant impact on someone in need with minimal inconvenience to themselves. NDADs are most commonly made aware of altruistic donation through the media or through researching other forms of donation. Religious motivations are relatively uncommon (6).

Social support

One area in which conventional directed donors and DADs/NDADs appear to differ is social support; the perception of being cared for and supported by those around us. A number of studies have demonstrated that NDADs commonly do not experience the same level of social support as conventional directed donors. The loved ones of those choosing to donate altruistically are not always fully supportive of the donation, principally due to a lack of understanding regarding the motivations behind the donation and fears related to complications. Some donors may also choose not to tell their loved ones about their decision to donate until quite late into their work-up.

Anecdotally, a lack of social support has been shown to be a significant reason behind altruistic donors withdrawing from the donation process. Therefore, the issue should be raised with all directed altruistic and non-directed altruistic donors during the early stages of their work-up and they should be encouraged to notify their loved ones of their decision to become a donor. This is so that issues specific to social support can be identified early and addressed as necessary.

Anonymity

Anonymity between NDADs and their recipient prior to surgery is required (4,8). 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, the 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.

Donor expectations

There are particular considerations about the lack of proximity between the donor and recipient that are unique to NDADs. It is essential for the expectations of all NDADs to be carefully explored during the assessment process, so that there are realistic expectations about feedback and contact after transplantation. NDADs should be prepared for how they would feel should they hear nothing from or about their recipient, or should they find out that the transplant was unsuccessful. Their expectations of the process should also be clearly elicited alongside the psychological impact of unmet expectations.

NDADs differ considerably on how much contact they would like with the recipient after donation. UK NDADs have found that 50% of donors received a card or letter after donation and of those who didn't, the majority "would have liked or maybe would have liked" to receive one (87%). This implies that the majority of NDADs would like to hear something from the recipient. A large number had found out whether the donated kidney had worked, and only a minority regretted finding out this information. Further contact was minimal with the majority of donor-recipient pairs never meeting in person (6).

Donors with terminal illnesses

Enquiries have been made from individuals with terminal illnesses who wish to donate a kidney before they die and a handful of transplants from such donors have now taken place. It is important for each case to be considered on an individual basis with regular involvement of the multidisciplinary team. In the absence of additional physical risks (to either the donor or the recipient) or psychological contraindications, there is no reason why donations from these individuals should not take place (9). Transplant centres must accept that whilst these donors may be passed as fit to donate, they are inherently different from other types of NDADs and

as a result may have additional healthcare needs which have implications on resources, such as nursing and social care.

Logistical considerations

The NDAD scheme differs from the UKLKSS in that there is no specific requirement for the recipient to be automatically suspended from the national transplant list when an offer of a kidney has been made, or even when the initial crossmatch has been performed. It is nearly always 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 against the possibility that the transplant will not occur. There is also the potential for 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 notifying that decision to NHSBT.

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. If it is a more permanent issue, clinical or otherwise, it may be advisable to re-offer the kidney with the donor's agreement. If a kidney cannot be transplanted into the intended recipient on the day of surgery, it is re-offered to all UK centres via NHSBT according to the offering process for a deceased donor kidney.

To streamline the transplant process and minimise delay at implantation, the retrieved kidney should be appropriately prepared in the retrieval centre so that it is ready for implantation into the recipient on arrival.

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 Living Donor Transplantation

Antibody incompatible transplantation (AIT) accounted for 2.5% (n=27) of living donor transplants in the UK in 2016-17 (1). The decline in activity in the past five years may be due to the development of the UKLKSS and the improved transplant opportunities through the schemes, as well as the better outcomes from HLA-compatible transplants. The BTS has published specific guidelines on antibody incompatible transplantation (10). These are also summarised in section 7.5.

Such transplantation falls into two categories: ABO incompatible transplantation (ABOi), 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 (HLAi), where the recipient has antibodies against one or more specific HLA antigens present in the donor resulting in a positive flow cytometric or CDC crossmatch.

Compared with 'compatible' transplants, both categories of AIT carry increased risks and it is important that the donor is aware of these and of the alternatives to AIT. In general, ABOi carries a small (1-2%) additional risk of early accelerated antibody mediated rejection but otherwise has short and long term results which are comparable with compatible transplantation (11-13). However, HLAi carries an increased risk of severe rejection, serious morbidity from infection due to increased immunosuppression, and death (14-16). These risks should ideally be discussed with the donor and recipient together, prior to transplantation. As a minimum, the donor must be aware that the transplant is high risk and that the long term outcome may be suboptimal.
Options for antibody incompatible living donor pairs are listed below:

i) Deceased donor transplantation - i.e. the recipient remains on the waiting list and does not proceed with LDKT
ii) Entry of the pair into the UKLKSS
iii) Direct antibody incompatible transplantation
iv) Acceptance of a lower risk antibody incompatible transplant within the UKLKSS (e.g. ABOI rather than HLAi)

Discussions around these options are complex and depend on a number of factors, but pairs are in general encouraged to enter the UKLKSS in the first instance. The

‘Incompatible Pairs Living Donor Kidney Application’ available at www.odt.nhs.uk (3) provides information on how long pairs can expect to wait for a transplant based on the characteristics of the pair. It should be used to inform discussions with the donor-recipient pair and to determine a strategy in which alternative approaches can be considered over time.

Sources of Information

NHS Blood and Transplant www.odt.nhs.uk or www.organdonation.nhs.uk
Human Tissue Authority www.hta.gov.uk
British Transplantation Society, Standards & Guidelines
https://bts.org.uk/guidelines-standards/

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8.4 APPENDIX TO CHAPTER 8

MENTAL HEALTH ASSESSMENT OF ALTRUISTIC KIDNEY DONORS: CONSENSUS GUIDANCE STATEMENT

BACKGROUND

Altruistic kidney donation (aka non-directed, anonymous, Good Samaritan, unspecified), previously well-established elsewhere, first became legal in the UK in 2006.

The relevant regulatory body, the Human Tissue Authority (HTA) at first mandated a psychiatric assessment of all potential donors before invasive investigation, but said little about the purpose and nothing about the process of such assessment. It also recommended that psychiatric assessments be made available to Independent Assessors (IAs), who are individuals trained and appointed by them who undertake final donor assessments before a date for surgery is set.

The HTA requirement for mandatory psychiatric assessment was withdrawn in 2012 on legal advice, but the BTS and NHS-BT do still recommend it, albeit without further elaboration. (The HTA further recommend that the only information to go to the IA is a referral letter from the transplant co-ordinator. It does not specifically *exclude* the sending of other background information, including psychiatric assessment where these have been undertaken, but it does not see a need for it).

After a slow initial take-up, altruistic donor numbers currently account for approximately 10 % of all living donors.

Practice varies widely across the UK in regard to:

- The proportion of donors referred for mental health assessment
- The professional affiliation of the assessor
- The nature of the assessment

Anecdotally, up to 20-30% of potential donors are turned down on mental health grounds. Some donors have reported the process of mental health assessment as intrusive and unwelcome ("worse than the angiogram").

There is therefore a clear need to attempt standardisation of these assessments in an effort to reduce unjustified variation in practice, improve acceptability to donors, and justify decisions to decline donors, preferably on a growing evidence base.

In recognition of this need, a consensus guidance workshop was convened in London in March 2015 by the UK and Ireland Transplant Psychiatry and Psychology Group, an informal multidisciplinary network covering most of the mental health professionals undertaking this work.

Draft guidance was developed and circulated before the workshop, and then used as a basis for detailed discussion on the day, with follow-up comment by e-mail. This document is the outcome of that process. It is the hope of the group that the guidance it contains will be helpful to clinicians in the field and the relevant clinical and regulatory bodies.

QUESTIONS

1. Which potential donors should be referred?
2. Who should undertake assessments?
3. At what stage of work-up?
4. With what information to hand?
5. What is the purpose of assessment?
6. How should it be undertaken?
7. To whom should the report be sent?
8. What are the follow-up requirements
    - for those who go on to donate?
    - for those who are declined on mental health grounds?
9. Should reports be collated centrally as a research resource?

1 Which potential donors should be referred?

The HTA's originally mandated requirement and the continuing recommendations from NHSBT and BTS reflect concerns in the transplant community that a significant proportion of potential donors might come forward as a result of mental disorder which they were not well placed, as transplant clinicians, to identify or assess. Accumulating clinical experience has reduced, but not abolished, this concern. Given the high rates of psychopathology reported in altruistic donors and the frequency of declining donation on mental health grounds, there are clear risks which are best addressed by ensuring all altruistic donors undergo mental health assessment.

Recommendation

- ***There is clear, emphatic consensus among mental health clinicians working in the field that ALL potential altruistic donors should be referred for mental health assessment.***

2 Who should undertake assessments?

Transplant centres' access to mental health specialists varies widely across the UK, as it does in other countries. Some centres specifically fund or part-fund embedded psychiatrists, psychologists or nurse specialists (though few will have direct access to more than one such type of mental health clinician). Others have service level agreements which establish routes of referral to specific individuals with dedicated funding streams, while some still fall back to generic mental health services allocated according to the patients' address or GP. But however the mental health services to individual transplant centres are aligned and funded, they need to work in broadly the same way.

Any mental health clinician working in this field should be able to assess motivation, capacity and mental disorder (including substance misuse and personality disorder), though there are different emphases in training and clinical practice across the disciplines. What is more important than the professional affiliation of the assessing mental health clinician is their familiarity with transplantation procedures, timescales, risks and outcomes. *Competencies* matter more than formal *roles*.

Recommendations

- ***Mental health assessments of potential altruistic donors can be undertaken by any suitably qualified and sufficiently senior mental health clinician (whether psychiatrist, psychologist, social worker, counsellor or nurse specialist) who is sufficiently familiar with transplant procedures, risk and outcomes, ideally because they are embedded within or affiliated to transplant services.***

- ***Centres with access to more than one type of clinician can direct referrals accordingly (for example preferring that potential donors with a history of mental disorder treated by medication see a psychiatrist, rather than psychologist, initially). Some cases may require assessment by more than one professional.***

3 At what stage of work-up?

Transplant units usually undertake initial donor screening via a transplant co-ordinator, who provides information (verbal, written and via DVD) about the process (including the risks), gathers a basic health history, takes baseline blood samples, and makes contact with the GP to confirm the history. If this does not identify obvious contraindications (and in a significant minority it will), patients are then usually seen by a transplant physician and/or surgeon, who emphasises again the nature of the risks involved. Referral for mental health assessment is usually undertaken at this stage, and definitely before any invasive investigation (such as renal biopsy or angiography), in order to ensure that potential donors who might be excluded on mental health grounds are not exposed to undue risk.

Recommendation

- ***Referral for mental health assessment of potential altruistic donors should be made after initial screening, clinical assessment, and provision of information by the transplant team, but before any investigations which carry risk. However, to avoid delay in the assessment process and in discussion with the donor, it may be***

appropriate to perform mental health assessment in parallel with physical assessment.

4. With what information to hand?

One risk of making mental health assessments mandatory is that referrals may be perfunctory, when instead they should set out clearly any particular causes for concern. These might, for example, arise from a potential donor's age, a history of contact with mental health services or treatment for mental disorder in primary care, psychological symptoms evident at initial assessment, or doubts about the nature of the motivation involved.

Transplant teams routinely request information from potential donors' GPs which may be relevant to donor's suitability on medical and mental health grounds. Information regarding the latter is clearly relevant to the mental health assessment and normally passed on with the referral, but it is open to the mental health clinician receiving the referral to request further background information from GPs and mental health services (e.g. discharge summaries, outpatient letters) before and after seeing the potential donor. Such requests are an integral part of mental health assessment, and any reluctance by potential donors to grant them is relevant to their suitability to proceed as donors.

Recommendation

- ***Referral information should include, at a minimum, a clear description of any specific mental health concerns or a statement that there are none. Where concerns relate to past episodes of treatment, available details obtained from the GP should be forwarded to the referee. Mental health clinicians receiving referrals should be free to gather further information directly if they judge it relevant, either on referral or after interview. Potential donors should be advised by the referrer that this gathering and sharing of information will happen (just as it would if they had a cardiac history and were being referred for cardiology assessment), and should be asked to agree to it.***

5. What is the purpose of assessment?

The HTA's (now withdrawn) mandatory requirement was vague about the *purpose* of mental health assessment, and the NHSBT and BTS recommendations say little more. Clinicians in the field identify several overlapping purposes, some specifically *psychiatric* (i.e. related to the subset with mental disorder), others *psychological* (applying to all donors). They include:

- To confirm the donor's *capacity* (i.e. their ability to understand, remember and weigh up the information presented to them, and to then make and convey their decisions).
- To explore *motivation*. This is particularly important in cases of altruistic donation. Where significant concerns about motivation emerge, they may amount to reasons for exclusion from donation.
- To explore *resilience* and available practical and emotional *support,* including the views of significant others.
- To explore *expectations*. This is mainly a role for transplant co-ordinators, but drawing out the expectations of altruistic donors bring may help prevent and manage "post-donation blues".
- To identify those who bring *additional risks* of mental health complications (e.g. relapse of a recurrent condition) during assessment and after surgery and who therefore may require specific mental health treatment in the peri-operative and post-operative period. In some cases, these potential risks may be sufficient to contraindicate donation.
- To clarify the appropriate route by which to access specialist mental health services for *follow-up* in the event of mental health problems arising after donation (or exclusion from donation).
- To identify those whose wish to donate arises from mental disorder, and who should therefore be *excluded from donation*. While few living related kidney donors are excluded on mental health grounds, anecdotal evidence suggests the proportion rises for altruistic non-directed donors, the main reasons being personality disorder, substance misuse, and recurrent depression.

It should be made explicit at the outset that mental health assessment of altruistic donors is not intended to be therapeutic (although it may identify a need for treatment), but is an integral part of the whole process of assessing altruistic donors.

Confirming capacity, clarifying support, and (less explicitly) exploring motivation are also in part the remit of the HTA's IA assessment, though in that context the main focus in assessing motivation is to consider any evidence of coercion, duress or financial incentive.

Where a mental health assessment has covered these areas it is therefore important the conclusions should be available to the IA.

Recommendation

- ***The multiple potential purposes of mental health assessment listed above should be acknowledged, together with their overlap with each other and with the IA role. Referral should, where possible, clarify the purpose(s) for which referral is made. Mental health clinicians should clarify the specific purpose(s) they have addressed in their assessment.***

6. How should it be undertaken?

Different disciplines approach mental health assessment in different ways. None should be expected to radically depart from their usual methods in this context, and each is free to use whatever methods they judge appropriate to answer the questions put to them in the referral.

Assessment will always involve a clinical interview with the potential donor. This may be supplemented with standardised instruments (questionnaires, structured interviews) as judged appropriate by the assessor. For example, a clear cut clinical diagnosis of current depression may suffice for the purpose of the assessment, or the assessor may judge it necessary to supplement this with the use of recognised depression scales (HAD, BDI etc.).

Assessment may necessitate interviews with informants such as partners or other next of kin, according to the judgment of the assessor. Issues arising may require repeat interviews with potential donors.

A referral suggesting the possibility of cognitive impairment (and thus possible impaired capacity) will normally require a clinical interview, a standardised assessment (e.g. ACE-III and/or other instruments), *and* a third party interview which itself may need to be standardised.

Assessments will vary widely depending on the questions to be answered and their underlying complexity. Some will be straightforward, requiring no standard scales or third party interviews, and should be possible within the customary one-hour interview. Others will be more complex and require multiple elements spread over more than one appointment. It is unlikely any such assessment should take more than three hours in total.

Recommendation

- ***The nature of the assessment should be tailored to the referral question, the clinical circumstances, and the professional background of the assessor. Repeat interviews, third party interviews, standardised questionnaires and structured assessments may all be necessary, but the only element of assessment required in all cases is a clinical interview***

7. To whom should the assessment report be sent?

The report should obviously go the referrer and the GP, as well as to any mental health services with which the donor has had, or may foreseeably require, contact.

Some renal services share all correspondence (including mental health referral letters) with patients, including potential donors, but this is not standard practice in all units. Mental health services also vary in the degree to which they routinely share assessment letters with patients.

The mental health assessment of a potential altruistic donor may draw upon information which has not previously have been shared with the donor. The conclusion of the report should not be automatically shared, even if this is usual practice.

Given the identified overlap between some aspects of mental health assessment and the IA assessment, reports should be forwarded to the IA with the HTA referral when donor work-up reaches that point.

Recommendation

- ***As a minimum, the assessment report should go to the referring clinician in the transplant team, the GP, and any mental health services with which the potential donor is in (or may foreseeably require) follow up. Reports may also go directly to the patient, where this is consonant with practice in local mental health and renal services. The report should also be forwarded to the HTA-IA in due course. The patient should be informed about, and consent to, this dissemination of information.***

8 What are the follow-up requirements for those who go on to donate, and for those who are declined on mental health grounds?

Mental health assessment may identify vulnerabilities in potential donors which are not so great as to prevent donation, but which bring identifiable risks such as a relapse of depression in the event of medical complications.

Pre-donation assessment should seek to identify the appropriate routes to specialist mental health services for such donors. In the short term, this might be a referral back to the assessing mental health clinician in the transplant service; for problems arising in longer term follow-up, this may mean a referral (back) to local generic mental health teams. Altruistic donors will normally be followed up annually for life by transplant clinics, sometimes at a distance from the patients' home. Clinicians need signposting guidance if follow-up identifies emerging mental health problems.

This issue is more acute for those turned down on mental health grounds, especially as the decision to decline them may intensify distress and heighten risk. Where such potential donors are in current follow-up with mental health services, those services should be informed promptly (with copies to the GP) of the decision and the reasons for it. Where they have been in recent follow-up, and may need to be seen again, the assessor should also inform the mental health services (copied to the GP). Where there is no current or recent mental health follow-up, the GP should be informed promptly and advised of the potential need to refer the donor on. If the clinical urgency is requires it, the assessing clinician may need to refer the donor directly.

Recommendation

- ***Assessing clinicians should identify routes to mental health follow-up for those who may need it in the short- or long-term after donation. For potential donors who are declined there should be direct liaison with relevant mental health services and the GP.***

9 Should reports (or data extracted from them) be collated routinely for purposes of audit, clinical governance and research? If so, what elements form the core data set?

There is a strong case for the central collation of data abstracted from mental health reports, in order to better understand the issues raised and to relate outcomes to factors identified at assessment. There is at present no obvious candidate body to undertake such collation; however it is to be done, the task requires agreement on a standard minimum data set, and there is nothing to prevent data being collected locally under a standard national template. The first step is therefore to agree a core data set which should quickly and easily codeable (5 minutes, no free text), and ideally should take up no more than one A4 page.

(There is also a case for a central mechanism to identify donors who, after being declined by one transplant centre on mental health or other grounds, approach other centres. These two aims can probably not be met by the same central service, especially as the first will require removal of patient-identifiable information while the later relies on it).

Proposed Minimum Data Set

Assessor

Professional affiliation (social worker, psychiatrist, psychologist, nurse therapist, counsellor, other)

Number of appointments

Total time taken

Method: clinical interview

Plus standardised instruments

Plus collateral informant interview

Demographics

Age

Gender

Postcode (for DepCat scores)

Employment status (f/t, p/t, u/e, retired, student, etc.)

Marital status / domestic circumstances

Any dependent children? Number, ages

Mental Health History

Treatment

G/P, O/P, I/P, detention

Current, recent, remote (?df),

Drugs, specific psychological Rx, supportive

Diagnosis

Current, Recent, Remote (?df),

ICD-11, DSM-V codes

Any history of self-harm or factitious disorder?

Current psychological symptoms

Evident, subclinical, absent

Mood, anxiety, psychotic

Cognitive impairment

Evident (ACE-III score), subclinical, absent

Capacity

Intact, impaired, borderline

Alcohol and substance (mis)use

Substance (s)

Dependent, harmful, hazardous, non-problematic

Current, recent, remote

Significant family psychiatric history

Forensic history

Current/previous probation or prison

Pending proceedings

Motivation

General altruism

Consistent with other behaviour (blood & bone marrow donor, charity, community, volunteering etc.)

Inconsistent

Specific trigger

Bereavement

Other

Attitude of family

Supportive, opposed, indifferent, unaware

Decision

No specific mental health concerns

Donation contraindicated on mental health grounds

Donation not contraindicated but additional measures required

Donation deferred pending mental health intervention

Mental Health Follow-up

Already in place with relevant service

New need identified and acted on

With assessor

Not specifically required but routes of referral identified

Outcome

Donation declined on mental health grounds

Donation declined on other grounds

Donor withdrew

Donation pending

Donation progressed

- post-donation MH problems: Y/N/unknown

9 LOGISTICAL CONSIDERATIONS

Recommendations

- ***Wherever possible, the aim is to ensure that the financial impact on the living donor is cost neutral by the reimbursement of legitimate expenses incurred as a direct result of the preparation for and/or act of donation. There are clear policies across the four UK countries to ensure that claims are settled in full and in a timely manner (B1)***

- ***Donors who are non-UK residents present unique logistical challenges. To ensure that the process is clinically effective and to comply with Visa and Immigration requirements, there is an agreed entry visa application process and maximum duration of stay in the UK (six months) for the donor. Visa extensions will only be considered in exceptional or unforeseen circumstances. (B1)***

9.1 Reimbursement of Living Donor Expenses

The reimbursement of legitimate expenses to a living donor, including loss of earnings that are directly attributable to the organ donation, is supported by the Health Departments in all four UK countries and forms part of national commissioning arrangements. NHS England has combined its separate kidney and liver policies to provide a single pathway. The policy has been developed in conjunction with both clinicians and commissioners, is compatible with the policies in each of the other UK countries, and sets out the framework and responsibilities of those involved in achieving a successful claim (1). Reimbursement does not contravene the current UK legislation under the Human Tissue Act 2004, which forbids payment for supplying a human organ, provided that the donor does not gain any financial advantage as a result (see section 3.8).

The policy is underpinned by some key principles:

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

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

9.1.1 Reimbursement of Expenses within the UK Living Kidney Sharing Schemes and for Non-directed altruistic kidney donors

In cases of paired/pooled donation and non-directed altruistic donation, living donor kidneys are exchanged across the UK between different transplant centres and may cross country borders with different mechanisms of donor reimbursement. Once exchanges have been identified and dates of surgery are scheduled, there is limited time to obtain prior approval for donor reimbursement from the recipient's commissioners.

In cases of paired/pooled donation, an application to the *local* recipient Commissioners should be made by the donor at the time of registration into the scheme (as for a direct living donation). This facilitates prior approval of anticipated expenses and timely reimbursement when the transplant proceeds. Reciprocity between each donor/recipient pair involved in an exchange means that the costs to the local commissioners are 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 schemes. However, any recipient

in the UK may be a potential beneficiary of such a kidney and so the accepted mechanism for donor reimbursement is by application to the recipient's commissioners. If a non-directed donor donates into an altruistic donor chain, expenses should be reimbursed by the commissioners for the recipient on the national transplant list, i.e. at the end of the chain. This leaves the local arrangements for the paired donors and recipients in the middle of the chain unaffected (see above).

9.2 Donors who are Non-UK Residents

Donors who are non-UK residents present logistical challenges. Policies have been jointly developed to facilitate the entry of genuine donors into the UK for the purposes of donation to either an NHS entitled recipient or to a private patient. The current immigration rules provide a clear process for consideration of Entry Visa applications and define the supporting information that is required to support the donor application, including a letter from the recipient's transplant centre/referring nephrology unit, using an agreed template (see Appendix to Chapter 9) to clinically endorse the application (2). Using a template letter ensures that the application is recognised by Visa and Immigration personnel in individual posts (embassies) and processed correctly. Posts in individual countries are responsible for approving and issuing Entry Visa applications. Appeals on compassionate grounds may be considered on a case-by-case basis if supporting evidence is available. Please contact NHSBT for further advice. Non directed altruistic donors and directed altruistic donors that fall into category 2 within the HTA's revised legal framework (i.e. where donor and recipient have no pre-existing relationship, having met only for the purposes of living donor transplantation) are not considered for donation in the UK or eligible to apply for a UK Entry Visa (3).

Potential non-resident donors must be provided with clear and comprehensive information about their rights and entitlements whilst in the UK for the purposes of organ donation. Before coming to the UK, prospective donors must be provided with a letter which explains that the costs associated with treatment to donate a kidney will be covered by the NHS, including those costs related to immediate post-operative complications (see Appendix 9). However, it must be made clear that any medical or dental treatment outside of the donor process (such as the detection of previously unsuspected malignancy) would not be covered by the NHS and that any

treatment would require payment in person or through medical insurance, or that the donor would need to return to his/her country of residence for treatment.

Successful applicants will be issued with a six-month visa under the visitor rules, during which time they must be assessed and prepared for donation, undergo donor nephrectomy and return to their country of origin following initial post-operative recovery. It is the responsibility of clinical teams to ensure that, pending unforeseen circumstances, donors comply with the terms of the Entry Visa and that extensions to stay in the UK are only applied for in exceptional circumstances.

The Council of Europe (CoE) identified some core principles to underpin the evaluation and protection of non-resident donors, including national oversight, a regulatory framework and clear clinical and organisational pathways (4,5). These same principles are also relevant to donor-recipient pairs who wish to travel to the UK for the purposes of LDKT and are managed within the private sector. Tables 9.2.1 and 9.2.2 summarise the information requirements and a best practice model for clinicians working with donors who are non-resident in the UK and wish to donate to a NHS entitled recipient in the UK.

Potential recipients are discouraged from travelling outside the UK to receive a transplant. As the national focal point for transplant-related crimes, NHSBT is responsible for collecting registry data for all LDKTs that take place outside the UK. Transplant centres are required to submit annual data to NHSBT so that this activity is monitored and accurately captured within the UK Registry.

9.3 Prisoners as Living Donors

In response to a small number of offers from prisoners to donate an organ altruistically, the British Transplantation Society (BTS) has collaborated with the relevant agencies to produce guidance for clinicians who receive requests to consider offers of living organ donation from this source, for both family members and unknown recipients. The guidance provides a framework for management of such referrals, with particular emphasis on the logistical aspects that need to be addressed along the clinical pathway (6).

Useful website sources of information:

NHS Blood and Transplant www.odt.nhs.uk; www.organdonation.nhsbt.nhs.uk

Visas and Immigration www.gov.uk/apply-uk-visa

Human Tissue Authority www.hta.gov.uk

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3. UK guidelines for directed altruistic donation. British Transplantation Society, 2014. https://bts.org.uk/wp-content/uploads/2016/09/16_BTS_Directed_Altruistic_2-1.pdf
4. Council of Europe, Guide to the Quality and Safety of Organs for Transplantation, 6th Edition https://www.edqm.eu/en/organ-tissues-cells-transplantation-guides-1607.html
5. Council of Europe, Resolution CM/Res (2017)1. On principles for the selection, evaluation, donation and follow-up of the non-resident living organ donors. https://www.edqm.eu/sites/default/files/cmres_2017_1-on_principles_for_selection_eval_donation_and_follow_up_of_nrld.pdf
6. UK Guidelines for living organ donation from prisoners. British Transplantation Society, 2014. https://bts.org.uk/wp-content/uploads/2016/09/04_BTS_Donation_Prisoners-1.pdf

Table 9.2.1

Information Requirements for Assessment of Non-UK Living Donors Before Travel to the UK

Information	Minimum requirement	Desirable
1. Personal details	Name Date of birth Address Nationality Occupation	Email address Telephone number Passport number and country of issuance
2. Relationship to recipient	Description of relationship	Documentary evidence Letter from elder/post
3. Medical History	Medical and surgical history Including yes/ no for diabetes, hypertension, kidney disease Medication history	Documentation by a medical professional Full family history
4. Physical status	Weight Height Blood pressure	Full physical examination by local doctor
5. Investigations	Urine dip Creatinine FBC Fasting blood glucose HIV, Hep B and Hep C	U&E, LFT, Bone PCR or ACR Haemoglobin electro MSU
6. H&I	Blood group	Virtual or wet crossmatch

Table 9.2.2

Summary Flowchart for Assessment of Non-UK resident Living Donors for NHS Entitled Recipients

Action	Responsible Person/s
1. Recipient contacts living donor co-ordinator (LDC) with potential non-UK resident donor	Recipient
2. Recipient provided with medical questionnaire letter/proforma, blood pack for virtual cross match and information pack with link to relevant web sites e.g. NHSBT, HTA, Visas and Immigration	LDC
3. Donor investigations and medical review arranged in own country. Copies of results and completed donor medical questionnaire returned back to LDC	Donor
4. Donor blood drawn for virtual cross match and either sent by courier or returned with potential recipient	Donor +/- recipient
5. Medical questionnaire, blood results and virtual cross match reviewed in transplant centre/referring unit and decision made whether donor appears to be suitable	Multi-disciplinary team (MDT)
6. Donor contacted directly (or through recipient if not able to contact directly) to relay results and suitability after MDT discussion	LDC
7. Supporting letter for donor Entry Visa application (if required) provided by transplant/medical team using agreed template (see Appendix 9.4)	LDC/donor clinician
8. Donor Entry Visa attained and LDC informed about estimated date of arrival in the UK	Donor +/- recipient
9. Donor registered in transplant centre/referring unit and investigations arranged to start as soon as possible after donor arrives in UK	LDC

10. On arrival, donor passport, Entry Visa and incoming airline ticket are copied and retained in the donor record for monitoring purposes (e.g. Home Office tracking)	LDC
11. Donor assessed medically and surgically, as per usual protocol. If suitable, independent assessment and donation date arranged	MDT and HTA Independent Assessor (IA)
12. Donor progresses to donation. Donor is offered immediate follow-up in the transplant centre.	MDT
13. When recovered and before expiry of Entry Visa, the donor is discharged back to country of origin with written information about recommended life-long follow-up. Donor should be given contact details in the UK +/- country of origin, in case of medical issues when he/she returns home	MDT

9.4 APPENDIX TO CHAPTER 9

Template Letter for Potential Overseas Donors to Support Entry Visa Applications to the UK

Trust headed paper
[include contact details for living donor coordinator]

[Name and address (in country of residence) for non-resident potential donor]

Hospital No/ID
NHS No
Date of Birth

Dear [Donor's name]

RE: PROPOSED LIVING KIDNEY DONATION FOR UK RECIPIENT: (NAME, HOSPITAL ID, DOB, ADDRESS IN UK)

I am writing to you because you have volunteered to be assessed as a living kidney donor for your [relationship donor to recipient].

Thank you for the medical information that you have provided. To make sure that you can safely donate a kidney and understand everything that you need to know about it, you will need to complete your assessment in the United Kingdom (UK). We are pleased to accept you for further donor assessment at ['X'] Hospital, [Name of City/Town/UK].

We have planned appointments for you starting from [Day, Date]. You now need to apply for a UK Entry Visa to start as close to this date as possible. **Please do not book your travel arrangements until your visa has been issued**. This letter tells you what to do to apply for your visa and to arrange your travel to the UK. Please read it carefully before you make your plans.

Next Steps:

1. Your application to travel to the UK

To travel to the UK to be a kidney donor, you can apply for a Standard Visitor Visa and stay for up to 6 months. You need to comply with UK immigration requirements and apply to your local British Diplomatic Mission, stating that you plan to donate an organ to your relative. **Your relative, the potential recipient of your kidney, must be a resident in the UK and entitled to kidney transplant treatment on the National Health Service (NHS).** He/she must check this with the hospital in the UK before you submit an application, otherwise it will not be valid.

You will find all the information you need to apply for your visa on the UK Visas and Immigration website at: https://www.gov.uk/standard-visitor-visa or at your local British Diplomatic Mission. **To make sure that your application can be processed quickly and has the best chance of success, you must make sure that you include all the information that is requested – your visa will be refused if there is missing information.**

You need to apply for your visa a minimum of 4 weeks (maximum 12 weeks) before you plan to travel to the UK. Your visa is only valid for **6 months from the date it is issued. To make the most of your time in the UK, please contact us to discuss the best date to attend the hospital before you apply for your visa. This date must be included on the visa application form.**

2. Your medical testing and donation in the UK

To complete the kidney donation process within your 6-month visa, your medical assessment, operation and recovery in the UK must be planned ahead. Once your assessment is complete, we will confirm if you are able to donate and check that you still wish to go ahead. You will need to recover in the UK after donation for up to 4 weeks before you travel back to your own country.

You must arrange to stay with your family in the UK throughout your stay or find suitable accommodation before you arrive (you will have to provide evidence of this in your visa application to travel to the UK). When you are sent home from hospital, it is important that you live with someone who can support you whilst you recover from your operation.

3. Your checklist

To help us plan everything as smoothly as possible for you, you can help us by:

1. Making sure that you have discussed with the hospital when you wish to travel to the UK **before submitting your application**. This is very important – if you do not check with the hospital first, you will not have enough time in the UK to complete the assessment, donate a kidney and recover from the operation before you need to travel home again. Your visit to the UK will be wasted.

2. Following the guidance on the https://www.gov.uk/standard-visitor-visa website when applying for your visa so that you include all the information that is requested **before** you submit your application. Incomplete information is the most common reason for visas to be refused.

3. Attaching this letter to your visa application and submitting it with all your other supporting information to your local British Diplomatic Mission, where an Entry Clearance Officer will deal with it. If your application is approved, it will start on the date that you requested in your application, as agreed with the hospital in the UK. Please keep a copy of all these documents - you will need them when you travel to the UK.

4. **It is your responsibility to let us know if there is any delay in submitting your visa application or in approving it so that we know when to expect you to arrive. Contact details are at the top of this letter.**

Costs

It is important that you know which costs and expenses are covered during your visit. The costs of your medical treatment to donate a kidney (donor assessment, donor operation and out-patient appointments) are covered by the NHS whilst you are in the UK. Once you return home at the end of the 6-month period, you are not entitled to NHS care in your own country.

Whilst you are in the UK, any medical or dental treatment outside of the donor process, is not covered by the NHS and, if you do not have medical insurance, you would 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 can apply for reimbursement of expenses (e.g. travel) due to the donation process from the NHS. You will need to keep a record and receipts of expenses. We can give you the information that you need to make a claim once you arrive in the UK.

Please ensure that you and your family have read this letter and understand all the information before applying for a visa. I will be coordinating your donor assessment at the hospital. Please contact me directly or through your recipient if you have any questions.

Yours sincerely

Living Donor Coordinator/member of Transplant/Referring team

cc: [potential recipient]

10 DONOR FOLLOW-UP AND LONG-TERM OUTCOME

Recommendations

- ***Counselling and consent of potential living kidney donors must include acknowledgement that the baseline risk of ESRD is increased by donation (see also section 5.5). (A1)***

- ***Discussion with potential donors must be informed by those factors known to increase ESRD risk post-donation, including donor age, sex, race, BMI, and a family history of renal disease (see also sections 5.6-5.9). (A1)***

- ***Risk calculators predicting lifetime ESRD risk may help inform the consent process. (C2)***

- ***The risk of ESRD in living donors mandates lifelong follow-up after donor nephrectomy. For donors who are resident in the UK, this can be offered locally or at the transplant centre according to the wishes of the donor, but such arrangements must secure the collection of data for submission to the UK Living Donor Registry. (B1)***

- ***Donors who are non UK residents and travel to the UK to donate (privately or to a NHS entitled recipient) are not entitled to NHS follow-up but must be given advice about appropriate follow-up before returning to their country of origin. (C1)***

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

- ***Women must be informed of a greater risk of pregnancy-induced hypertension following kidney donation. (A1)***

- ***Close monitoring of blood pressure, creatinine and foetal well-being is advisable in kidneys donors during pregnancy. (C1)***

- ***Kidney donors may be offered Aspirin 75 mg daily for pre-eclampsia prophylaxis. (D2)***

- ***There is no evidence to support the benefits of right or left nephrectomy to prevent pregnancy induced hydronephrosis. (Not graded)***

- ***Births after kidney donation should be reported to the Living Donor Registry as 'a significant medical event' at each annual review. (Not graded)***

10:1 Long Term Outcome Following Living Kidney Donation

The continued success of living donation depends upon ensuring the safety and excellent long-term outcomes of the donor. In particular, donors must be reassured that the risk both of developing progressive CKD and of premature cardiovascular death remain low following nephrectomy. Studies in Sweden (1,2) and the USA (3-5) have demonstrated that longevity remains greater and the risk of developing ESRD remains lower in cohorts of donors when compared to the general population.

Although favourable outcomes in donors when compared to the general population provide reassurance, such studies are not able to determine whether donor nephrectomy increases the risk of adverse outcomes when compared to pre-donation risk. To do so would require a control group of those assessed as able to donate, but who did not – a group that is not readily available. Two recent studies (6,7) have compared donors to 'healthy non-donor' controls in an attempt to address this question.

Muzaale *et al* reported the long-term follow-up of 96,217 donors who had donated a kidney in the USA between 1994 and 2011, and compared outcomes to a control group of 20,024 participants in the NHANES III study (6). Median follow-up was 7.6 years for donors and 15 years for matched healthy non-donors. ESRD developed in 99 kidney donors at a mean of 8.6 years after donation, compared to 36 non-donors. The estimated risk of developing ESRD at 15 years post-donation was 30.8 per 10,000 for donors and 3.9 per 10,000 in the control group ($p<0.001$). The risk was higher in black compared to non-black donors (74.7 vs 22.7, $p<0.001$). The lifetime

risk of ESRD was estimated as 14 in 10,000 non-donors, 90 in 10,000 donors, and 326 in 10,000 of the US general population. The same authors previously reported that the risk of long-term mortality was not increased in donors compared to controls (5)

Subsequent analyses of up to 133,824 US living kidney donors between 1987 and 2015 identified male sex (hazard ratio (HR) 1.88), black race (HR 2.96), first-degree biologic relationship to the recipient (HR 1.70), BMI (HR 1.61 for each 5 kg/m^2) and age (HR 1.4 for each 10 years in non-black donors) as risk factors for ESRD in the donor population (8). ESRD in the first 10 years post-donation (10 in 10,000 donors) was predominantly caused by glomerulonephritis; whilst by 25 years post-donation ESRD (85 in 10,000 donors) was predominantly attributed to diabetes and hypertension (9).

Mjoen *et al* reported long-term renal function, and both cardiovascular and all-cause mortality, in 1901 donors who had donated in Norway between 1963 and 2007 and compared the outcomes to 32,621 non-donors who could have been considered for donation over the same period (7). The median follow-up was 15.1 years for donors and 24.9 years for non-donors. The hazard ratio for all-cause death was 1.3 for donors when compared to controls, 1.4 for cardiovascular death, and 11.38 for ESRD. Importantly, the substantial HR for ESRD reflected only 9 cases of ESRD developing at a median of 18.7 years post-donation, with immunologic renal disease accounting for 7 of these cases.

Methodological concerns have been raised regarding both studies. In the US report (6), 9,364 of the 20,024 NHANES III participants were considered as potential donors. Each of these 9,364 controls was matched to multiple donors. Thus, if ESRD were by chance under-represented in the much smaller control group then the risk of ESRD in the donors would be falsely amplified. In this context, it is of note that none of the white control group developed ESRD. In the Norwegian study (7), the control group was drawn from the HUNT1 study that included subjects from a single county (Nord Trondelag), which is a largely rural area with several small towns. The control group was younger than the donors and less likely to smoke. Perhaps most importantly, 80% of the Norwegian donors were first-degree relatives of their recipient, and all cases of ESRD were in this group. Similarly, 84% of ESRD cases in US donors occurred in the 67.6% of donors biologically related to their recipient. In contrast, the majority of the controls were unlikely to have had a family history of

renal disease. Accordingly it is possible that the background risk of ESRD in the control groups underestimates the pre-donation risk of ESRD in donors.

Notwithstanding these concerns, the US and Norwegian studies are important. Both provide comprehensive data on large cohorts of living kidney donors with long-term follow-up, and for the first time provide accurate predictions of the risk of ESRD following donation. Both are reassuring, indicating that the lifetime risk of ESRD after kidney donation is low, occurring in less than 1:200 donors (0.5%). However, it appears clear that, for an individual at low baseline risk, donating a kidney does increase the risk of later developing ESRD. This risk remains substantially less than that in the general (unscreened) population. By contrast, it is not clear that kidney donation has a detrimental effect on long-term cardiovascular or all-cause mortality, with conflicting results from the US (5) and Norwegian (7) studies.

Both studies identify that the increase in ESRD risk in donors is largely due to genetic and immunologic factors. The most potent risk factor for ESRD is black race, identified both in the US study and in previous reports from the USA (6,10). The estimated ESRD risk at 15 years post-donation was 74.7 and 22.7 per 10,000 in black and white donors respectively (6). It is not clear if the excess risk in black donors is related to the future development of hypertension, socio-economic factors, or to a genetic predisposition to ESRD, possibly including at-risk APOL1 polymorphisms (11). At present there is no evidence to support APOL1 genetic testing, but black donors must be counselled with due regard to the increased risk of developing ESRD. This is especially important for young black donors, in whom the cumulative risk of ESRD is greatest.

Donor age is also an important consideration. The risk of ESRD is less in young when compared to older donors when followed for a fixed period of time. In the US study the 15 year ESRD risk was 29.4 per 10,000 donors aged 18-39, 17.4 for those aged 40-49, 54.6 for ages 50-59 and 70.2 for those aged >60, with statistical significance when those aged <50 are compared to those aged >50 (6). However, the cumulative time post-donation is necessarily longer in young donors. For example a 20-year-old donor may have 60 years to accumulate the complications of donor nephrectomy, whereas a 60-year-old donor only 20 years. Thus the lifetime risk of ESRD is greater in young donors. This is particularly important since immune-mediated renal disease (the commonest cause of ESRD in donors) has a peak incidence in middle age. Young donors must be counselled accordingly.

Risk calculators provide a means of estimating ESRD risk both at baseline (12) and post-donation (8). It is not clear that such calculators can be applied to the UK population, but they may be useful in illustrating risk to potential donors.

In summary, living kidney donation remains a safe and acceptable surgical procedure. Recent studies have provided evidence to estimate ESRD risk in donors, demonstrated a numerically small increase in ESRD risk, and identified those groups at particular risk (black donors, young donors, donors genetically related to patients with ESRD, donors with increased BMI). Importantly, the absolute risk of ESRD in donors remains low when compared to the general population. This data must inform donor assessment and consent, and emphasises the importance of long-term donor follow-up.

10.2 Arrangements for Follow-up

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

All centres have arrangements in place for immediate and life-long follow-up of living donors. The minimum standard includes a follow-up appointment within four to six weeks after donation at the transplant centre and an annual review thereafter, either at the transplant centre, the referring nephrology unit or in primary care. Additional reviews are arranged if clinically indicated. Within a maximum of twelve weeks, it is anticipated that the donor will have made a full recovery and returned to normal activities.

A survey of UK transplant centres in 2016 (13) demonstrated wide variations in regional practice with 56% of transplant centres performing life-long donor follow-up in 80-100% of previous donors ‘in-centre’ with face-to-face appointments. Living donor co-ordinators perform 80% of life-long follow-up with nephrologists or surgeons performing the remaining 20%. A minority of transplant centres and referring units refer donors back to primary care for annual review and the majority of these only do so after the first anniversary (or subsequent anniversary) appointments. Telephone or virtual clinics are rarely used. Most non-UK resident

donors are lost to follow-up unless individual arrangements are put in place once they have returned to their countries of origin.

Long-term annual follow-up provides an opportunity for specific clinical review as well as a general health and wellbeing check, including psychosocial aspects (see Figure 10.1). The European Organ Donation Directive (EUODD) specifies the requirement for life-long donor follow-up data to be collected on all living organ donors (14) and this principle is embedded in the UK Living Donor Registry administered by NHSBT (2). While not all donors wish to return for regular review, many welcome the continuing support and interest in their welfare.

There are some logistical challenges in achieving life-long follow-up for all donors, particularly for non-UK residents and/or those who are not NHS entitled. This is especially the case in countries where living donor transplantation is not an established practice or where individuals pay for healthcare. These donors must be provided with written advice about appropriate annual monitoring. Depending upon the country, it may be possible to put the donor in contact with a local hospital or nephrology/transplant service to facilitate annual review.

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 and psychological support.

Latest statistics show variation in the quantity and completeness of donor follow-up data contributed to the UK Registry data between transplant centres (16). Figure 10.2 provides a template toolkit, which has been developed by the Living Donor Kidney Transplantation 2020 (LDKT 2020) Strategy Implementation Group as a flexible resource for clinical teams to plan and improve the consistency of life-long follow-up. A donor reported outcome measures (DROM) survey is under development and will be available in 2018.

Figure 10.1 Pathway for Follow Up After Living Donor Nephrectomy

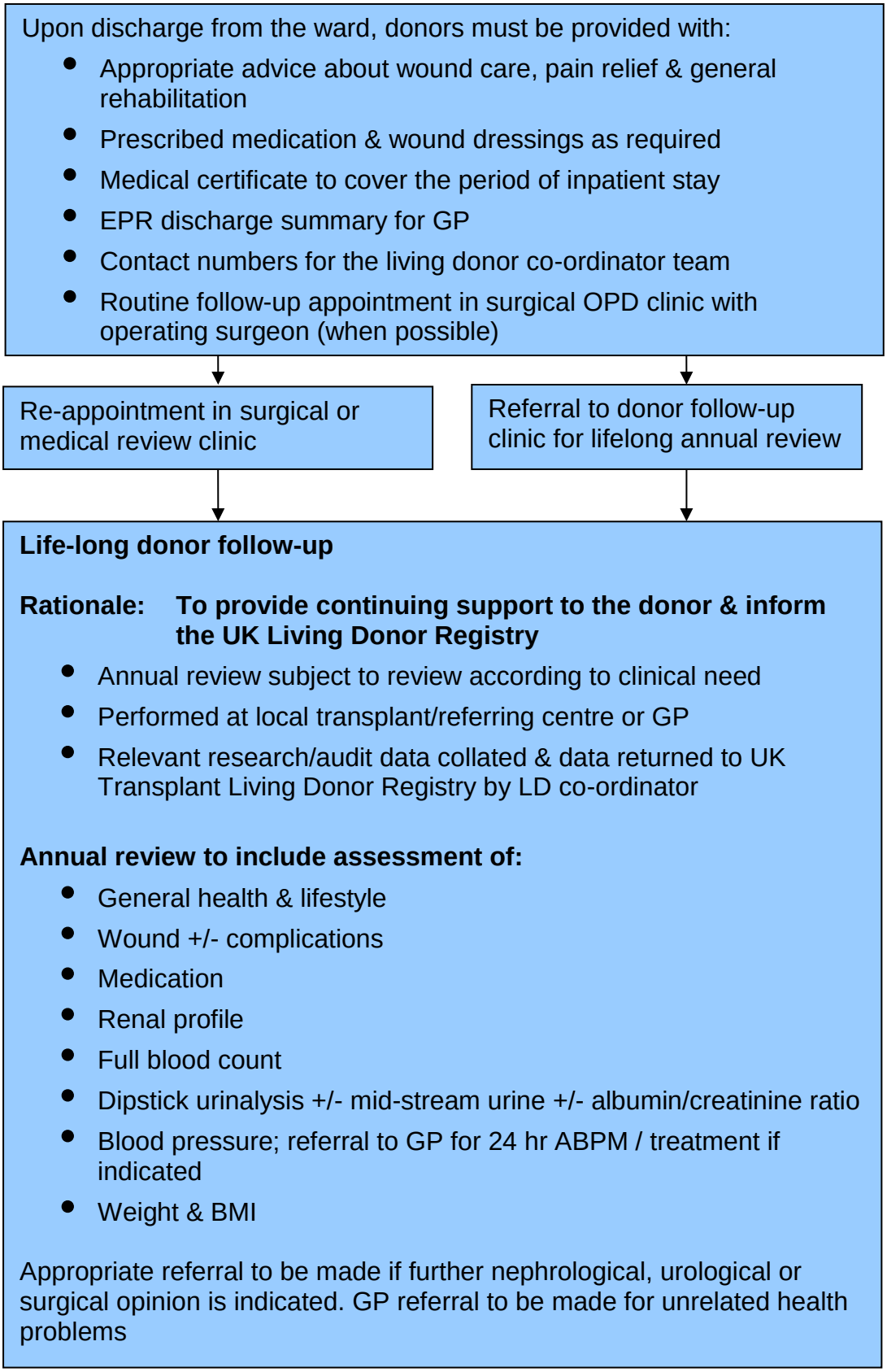

Figure 10.2 Toolkit to Support Centres to Provide Lifelong Donor Follow Up Return Data to the UK Registry*

TOOLKIT: PART 1 - ELEMENTS AND REQUIREMENTS

ELEMENT	WHO	REQUIREMENT
Clinical Standard **What is best for the donor?**	**BTS/RA UK Guidelines for LDKT**	**Annual follow-up** **Clinical Review Registry Data** **Donor Reported Outcome Measures (DROMs)**
Legal Standard **What is required by law?**	**EU Organ Donation Directive** **Human Tissue Authority**	**Annual follow-up**
UK Registry **What informs best practice?**	**UK Registry** **NHS Blood and Transplant** **Pan EU Registry**	**Collection of outcome data 1,2,5,10 and every 5 years thereafter**

TOOLKIT: PART 2 - WHERE TO PERFORM FOLLOW UP AND BY WHOM

WHERE?	BY WHOM?
1. **Transplant Centre:** Minimum year 1 +/- 1st anniversary appointment if returning to referring unit/GP, or lifelong if donor originated in transplant centre wishes to stay 2. **Referring nephrology centre:** All donors before or after 1st anniversary appointment 3. **Primary Care (GP):** Donor choice, after 1st anniversary appointment 4. **Non-UK Countries:** By local arrangement +/- written referral	Appropriately qualified healthcare professional Nurse-led after discharge from medical/surgical review clinic Face to face Telephone Telemedicine

TOOLKIT: PART 3 - HOW TO PERFORM FOLLOW-UP

HOW

• Annual review in month of nephrectomy anniversary (tailored to clinical need in 1st year)
• Transplant centre responsible for return of data from Tx centre and GP
• Referring units responsible for return of own data
• Electronic/paper submission of annual data to NHSBT within 3/12 of anniversary (EU Registry uploaded from NHSBT Registry)
• Ensure all donors are given a positive choice about where/how they are followed up and decision is recorded and reviewed at each visit
• Administrative processes in place in transplant centres & referring centres to support clinics and correspondence, i.e.
  • Maintaining local databases re donor preference for follow-up, anniversary appointment dates
  • Reminder appointment letters to donor +/- GP for anniversary visits
  • Receipt and return of donor data from GP & non-UK resident donors

* developed and approved by the LDKT 2020 Strategy Implementation Group

10.3 The Unsuitable Donor

It is essential to provide appropriate care and follow-up for people who start the donor assessment process but who do not subsequently donate. If the person is unsuitable to donate because of health concerns, appropriate arrangements must be 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 to manage feelings of failure or guilt about the recipient and any subsequent adverse outcomes should they occur (see Chapter 5).

10.4 Pregnancy following Kidney Donation

Many kidney donors are women of child bearing age and accurate assessment of potential pregnancy complications after donation is needed to inform decision making. Early small studies (including 39 and 23 pregnancies) did not identify any increased risk of pregnancy complications in women after donation (17,18). However, larger survey and population studies have reported higher rates of hypertensive complications during pregnancy. Comparison of pregnancy outcomes pre- and post-donation in 326 donors from the Norwegian Birth Registry identified that pre-eclampsia occurred more frequently after donation (5.7%) than before donation (2.6%), but the absolute numbers affected were low (19). Similarly, the incidences of pre-eclampsia and gestational hypertension were higher (5.5% and 5.7% respectively) after donation compared to pre-donation (0.8% and 0.6% respectively) in a survey study of 1085 donors reporting 3213 pregnancies from Minnesota (20). However, the rate of pre-donation pre-eclampsia in these studies may be low due to selection bias, as women with a history of pre-eclampsia may have been advised not to donate.

In the Minnesota study, post-donation pregnancies were also more likely than pre-donation pregnancies to be complicated by fetal loss (19.2% v 11.3%), gestational diabetes (2.7% v 0.7%), and delivery before 36 weeks gestation (26.3% vs 15.4%) (20). There were no differences in pre-pregnancy eGFR between women with and without complications post-donation. Greater maternal age after donation may contribute to worse outcomes; however, the mean maternal age at pregnancy after donation was 28.8 ± 5.5 years and is therefore unlikely to exclusively explain these differences. These findings have not been confirmed by other studies.

More recently, a Canadian population study compared pregnancy outcomes in 131 pregnancies in 85 kidney donors with 510 healthy non-donor women selected from the general population matched for demographics and number of previous pregnancies (21). In keeping with previous findings, the rates of gestational hypertension or pre-eclampsia (11%) were higher in kidney donors compared to non-donors (5%). Again this study is limited by the small number of women affected and the diagnosis of pre-eclampsia was determined by coding rather than by clinical criteria. Importantly, there were no differences between the mode of delivery, gestation at delivery or birth weight (i.e. features of poor placental function associated with pre-eclampsia) between kidney donors and matched controls.

It is recommended that women are informed of a potential greater risk of pregnancy induced hypertension following kidney donation which may require specialist antenatal care, but it does not appear to lead to adverse outcomes for either mother or offspring. Close monitoring is advisable in donors during pregnancy, with monitoring of blood pressure, creatinine and fetal well-being. Although direct evidence of benefit is lacking, kidney donors can be offered Aspirin 75 mg daily for pre-eclampsia prophylaxis (22). There is a theoretical risk of increased complications in women with a single right kidney due to pregnancy-induced hydronephrosis but there is no evidence at present to support a preference for right or left nephrectomy.

Women who develop pre-eclampsia, particularly in those with early onset disease, are more likely to develop long term health consequences (e.g. hypertension, cardiovascular disease) than women with normal blood pressure during pregnancy (23). Pre-eclampsia occurs in late pregnancy in the majority of kidney donors, but the risk of future cardiovascular disease in kidney donors who develop pre-eclampsia is unknown. 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 (24). This should be encouraged in order to improve the evidence base.

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11 RECIPIENT OUTCOME AFTER LIVING DONOR KIDNEY TRANSPLANTATION IN ADULTS

Recommendations

- ***Graft and patient survival after living donor kidney transplantation should be within the national range of expected outcomes. (A1)***

- ***Transplant centres should regularly audit secondary outcomes 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 of complications and a poor outcome, due to immunological status or co-morbidities, should be considered for transplantation when the clinical team regard the risk / benefit ratio to be favourable. Due process will include careful consideration of the likely outcome for that individual without transplantation. The potential donor must be fully appraised of the issues. A summary of these discussions (between the clinical team and the donor-recipient pair) should be documented in the clinical records and a copy should also be given to the donor and recipient. (C2)***

Continuous and careful consideration of recipient outcomes is an important aspect of any living donor kidney transplant programme. This section will consider the outcomes in:

- Living versus deceased donor transplantation
- Extended criteria living donors
- Living donor transplantation versus dialysis
- High risk recipients

11.1 Living versus Deceased Donor Transplantation

It is long established that recipients of living donor kidney transplants have superior graft and patient survival compared to those from deceased donor organs. Pre-mortal renal injury is avoided, donors are generally healthier, cold ischaemic times are shorter, and operative conditions for the recipient are optimised in an elective setting. Additionally, it is often possible to arrange pre-emptive transplantation or minimisation of dialysis duration.

The UK Transplant Registry, managed by the Organ Donation and Transplant (ODT) division of National Health Service Blood and Transplant (NHSBT) authority, provides contemporaneous supportive data (1).

For example, 10 years after transplantation, 75% of adults who received their first (kidney only) deceased brainstem death donor transplant in 1998-2000 were still alive. This compares to 90% of those transplanted in the same period with a first kidney transplant from a living donor. Hence, there was a 20% improvement in 10-year patient survival with living versus deceased donation for those transplanted in that period (1).

The annual activity reports provided by ODT also allow for the comparative assessment of graft and patient outcomes for individual centres. Such comparative national audit is of great value and necessitates an ongoing commitment to data return from each centre (see Chapter 10).

11.2 Extended Criteria Living Donors

The persistent disparity between the number of patients waiting for a kidney transplant and the organs available from the deceased donor pool, coupled with increasing familiarity of the outcomes for living donors and their recipients, has led the transplant community to consider potential donors who would previously been discounted due to demographic characteristics or medical issues.

The areas of uncertainty related to short and long-term outcomes for the donor in medically complex volunteers is covered in detail in other sections of these guidelines.

In terms of recipient outcome, consideration must be given to the alternative options: the likelihood of receiving a standard or extended criteria deceased donor transplant, the outcome of such a transplant, the morbidity and potential mortality risk while waiting for a suitable deceased organ, the suitability / risks associated with emergency versus elective surgery, the likely outcome of this living donor organ in comparison with projected life expectancy of this individual etc.

The literature is sufficiently developed to advocate transplantation from older living donors for at least a cohort of patients (see section 5.6.4 for detailed discussion). In a similar manner, the appropriateness of giving what may be a 'non-ideal' living donor kidney (due to function, matching, co-morbidities) to a patient must be considered on an individual basis for the particular recipient. Entry of a donor-recipient pair into the UK Living Kidney Sharing Scheme (UKLKSS) should be considered when it may be possible to achieve a better living donor option, particularly in terms of age or matching for younger recipients. As of 31 Dec 2016, 66 compatible pairs were registered in the UKLKSS; in 12 pairs the age difference between donor and recipient exceeded 20 years; in 58 pairs the HLA mismatch was level 4 (2). It is expected that in due time, more data on outcomes for recipients from more complex donors will be available to guide decision-making.

11.3 Transplantation versus Dialysis

It must be remembered that the long-term outcome for patients on maintenance dialysis therapy remains limited. The decision for a recipient is seldom between a 'sub-optimal' and an 'ideal' living donor kidney transplant. The alternative to living donor transplantation, of whatever quality, is to remain on dialysis waiting for a suitable deceased donor organ.

The quality of deceased donor kidneys now available for transplantation in the UK must also be taken into consideration. For example, a living donor kidney may be declined for a recipient on the basis of age but, in 2016-17, 36% of all deceased donors in the UK were at least 60 years old (1).

The duration of dialysis therapy before transplantation remains an important (potentially modifiable) factor in long-term survival after transplantation. Of those listed for kidney transplantation in the UK in 2011-12, 56% had received a transplant

after 3 years, 6% had been removed from the waiting list and 5% had died while waiting (1). This is another important issue when considering potential living donor transplant options.

11.4 High Risk Recipients

The success of a transplant programme cannot be judged solely by recipient and graft survival, but in the outcomes for the entire end-stage renal disease (ESRD) population. A conservative approach to risk is more likely to result in excellent graft and patient survival after transplantation, but potentially be associated with inequity of access to transplantation for patients at higher anaesthetic, surgical or immunological risk and an increased risk of death on the waiting list. A measure of the approach of individual units to risk is less easily measured than survival outcomes in those transplanted. The proportion listed for transplantation is one such measure. Of note, the Access to Transplantation and Transplant Outcome Measure (ATTOM) national observational study has identified significant disparities in age, ethnic, socio-economic and geographical factors living donor transplant utilisation (3).

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. Statistically, this equates to an expected outcome that is outside the 95% confidence interval for graft and patient survival in the UK. There is currently no robust, clinically applicable scoring system upon which to base this assessment of risk. Although models are likely to be developed in due course (4,5), it is recognised that with the uncertainty of prediction tools there is on-going dependency on the clinical judgement of the transplant professionals involved.

Living donor kidney transplantation can provide opportunity for individuals whose peri-operative risks for an emergency procedure are considered unacceptably high, but who may be suitable for an elective transplant. The advantages include:

- Optimisation of the recipient
- Availability of senior staff from across the multidisciplinary team (surgeons, anaesthetists and intensivists, H&I scientists, nursing staff in theatre and ward, nephrologists etc.)
- Pre-transplant immunosuppression or immunomodulation
- Good quality organ with low risk of delayed graft function

The key issue is that, whilst these patients may expect a relatively poorer outcome from transplantation compared with individuals considered to be at standard 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 whether they have a transplant or are dialysis dependent (6,7).

The premise of undertaking higher risk living donor transplantation is already established. Antibody incompatible transplants, for example, are excluded from the survival analysis on living donor kidney transplant outcomes in the annual NHSBT report as the survival rates are not as good as antibody compatible transplants. However, for some patients, such a transplant represents the only option for dialysis independency.

Given the insufficient data available to give clear guidance on this issue to individual high-risk recipients, risk assessment in each case must, by default, be based on combined expert opinion. Careful consideration of all higher risk living donor transplants must be in a multi-disciplinary meeting, with clear documentation of discussions.

In a similar manner, the risks and likely outcomes must be conveyed to both the donor and recipient. Although such discussion is applicable to living donation in general, it is particularly important for the high risk recipient where the risk of an adverse outcome is greater than for standard transplantation.

The following are recommended when considering potential higher risk recipients:

- If it is unlikely that the patient would survive with a functioning graft for at least 2 years, then living donor transplantation should not be considered

- The risks and benefits of living donor transplantation must be described along with other management options (deceased donor transplantation, dialysis, maximal conservative care)
- It must be established what the recipient wants and expects from transplantation in terms of quality and extension of life
- If considering living donor transplantation, particularly for patients who are high risk due to established co-morbidities, the goal should be pre-emptive transplantation
- The donor must be fully appraised of the risks and the potentially poor outcome for the recipient
- The details of the final understanding must be compliant with the NHS consent process, and documentation of the issues must be given to both the donor and recipient
- If 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 must be discussed with the potential recipient and donor

It is important that the decision to transplant high risk recipients is not influenced by undue concern about outcome data. It is not possible to set national standards for transplant outcomes in this group given the patient heterogeneity and unit variation in definition of high risk. It is recommended that each centre maintains detailed records of relevant clinical features for each high risk recipient. This will be useful for internal or external review, and may be valuable for future audit.

It is recommended that, for all living donor transplants, data are also collected locally by each unit. There are many parameters that are not currently reported centrally but which are important measures of service provision that should be audited regularly. The following list is not exhaustive:

- Delayed graft function
- Return to theatre
- Urological complications
- Acute rejection
- Infective complications

- Transplant artery stenosis
- Renal function at 1 and 5 years

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12 RECURRENT RENAL DISEASE

Summary of Recommendations

- ***A wide range of diseases that cause renal failure may recur in a 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 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 atypical HUS potential de novo disease in a related donor needs to be addressed directly. The risks of recurrent disease in the recipient need to be mitigated through regulated approval and consideration of the use of an inhibitor of complement activation, currently eculizumab. (A1)***

- ***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 following text.***

12.1 Introduction

Many native kidney diseases can recur following transplantation and may result in allograft failure. These 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 cause of graft dysfunction and/or failure (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. This is an evolving field and it may be necessary to review source data or seek specialist advice to estimate risk and decide upon the 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 (8,9).

There is increasing definition of single genes associated with familial FSGS, which may in fact present as sporadic disease. This has implications for assessment of any related donor but also improves quantification of the risk of disease recurrence.

In atypical haemolytic uraemic syndrome (HUS) the risk of unrecognised genetic susceptibility to disease in the donor and in the recipient is now well recognised and has significantly influenced clinical practice with respect to the assessment of any donor (10). Similarly, the availability of eculizumab, an inhibitor of complement C5 cleavage has changed practice with respect to the prevention of disease recurrence in the recipient (10).

12.2 Diabetic Nephropathy

Histological recurrence of diabetic nephropathy is relatively common following renal transplantation (11). The time required for recurrent diabetic disease to cause significant graft dysfunction is long and it is therefore not a contraindication to living donor transplantation. Living donor transplantation significant benefits with respect to both patient and graft outcomes (12-14). Where appropriate, the balances of risk and benefit should also be compared with the option of combined kidney and pancreas transplantation from a deceased donor.

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.***

12.3 Primary Focal Segmental Glomerulosclerosis

Recurrent focal segmental glomerulosclerosis (FSGS) is a significant problem following renal transplantation and is estimated to occur in 20% to 50% of cases (1,2,15). This wide range in reported frequency of recurrence is likely to reflect heterogeneity in the underlying diagnoses associated with FSGS. The histological description of FSGS in the context of proteinuria and renal failure frequently occurs as a non-specific finding in many forms of kidney disease, including transplantation. 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 (5,15-17)
- Rapid progression to end stage renal failure (18)
- Recurrent disease in a previous transplant (5,6,19)

In these situations the rate of graft loss secondary to recurrent disease may be significantly above 50%. This generalisation is, however, not true in familial forms of FSGS, which can have an early presentation and rapid course of deterioration but have a relatively low risk for disease recurrence (20-24). This is also true of sporadic forms of FSGS in which a genetic diagnosis is nevertheless established. A contemporary strategy for age-stratified identification of genetic causes of FSGS is therefore recommended (20). The detail of this strategy is likely to evolve with increased availability of genetic data.

Even primary FSGS presenting with the nephrotic syndrome seems not to be a single disease entity, and this may account for differences in the rate of recurrence in different groups. For example, there is evidence that recurrent disease is more common in whites than blacks (25), pointing towards genetic heterogeneity and potential future risk stratification (25,26).

Recurrent primary FSGS generally occurs in the first 6 months following transplantation, an important point if transplant recipients are not to be incorrectly labelled as having recurrent disease. The very rare recurrence of nephrotic syndrome consequent upon *de novo* antibody formation to a nephrin determinant absent in the recipient in congenital nephrotic syndrome of the Finnish type is an exception to this generalisation (22).

There is now sufficient information to believe that previous suggestions of a relationship between HLA matching and risk of recurrence are not a concern, but probably arose from co-linearity with other risk factors (26,27).

Recommendations

- ***Living donor kidney transplantation is a reasonable option in patients with primary FSGS. Both the donor and recipient need to be specifically counselled about the risk of recurrent disease, which may occur early and result in rapid graft loss. In those in whom a genetic aetiology has been established the risk of recurrent disease is low but not absent. A potential living related donor must also be investigated for evidence of the same genetic abnormality.***

- ***Transplantation in an individual with unequivocal evidence of graft loss secondary to recurrent disease constitutes a high risk of subsequent failure such that some centres consider this a contraindication to repeat transplantation (28). 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. Equally it is incumbent upon that team to assess the circumstances of the original graft failure with absolute rigor. The risk of recurrence is low when the previous graft did not fail due to recurrent disease.***

12.4 IgA Nephropathy

Histological evidence of recurrent IgA nephropathy commonly occurs in transplanted kidneys, but is less frequently of 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). The importance of recurrent disease may be reducing in the context of modern immunosuppression (29).

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.***

12.5 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 (30,31). In the report of Briganti and colleagues, recurrent membranous nephropathy was responsible for 12.5% of the 40.1% of failed transplants at 10 years (7).

Recurrent disease may relate to the persistence of antibody to PLA2 receptor but this remains to be proven (32). At the time of transplantation, approximately 50% of patients have detectable antibody and its presence is associated with recurrent disease; however, the correspondence is imperfect and at present there is no evidence to suggest that this should alter the approach to treatment. 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.***

12.6 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. Living donor kidney transplantation is a reasonable treatment option in some circumstances, after adequate control of the underlying disease has been achieved (33,34). The donor and recipient 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.***

12.7 Systemic Lupus Erythematosus

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 (35), although this is not always directly attributable to disease activity.
The treatment of active lupus should be optimised before transplantation, although it is recognised that serological markers of disease, native renal histology and duration of dialysis are poor 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 before transplantation and increased peri-operative anti-thrombotic prophylaxis should be 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)***

12.8 ANCA Associated Systemic Vasculitis

The risk of recurrent disease in ANCA associated systemic vasculitis (AASV) is small when patients are transplanted in remission: reportedly between 1% and 2.8% per year of patient follow-up The consequences of recurrence may, however, be significant, with increased mortality and graft loss (36).

There is a particular 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 after 1 year of disease quiescence, although this should be balanced against the potential risks of staying on dialysis (37). 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 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.***

12.9 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 (38,39).

Recommendation

- ***The 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.***

12.10 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 (40). It is reported to occur mainly in patients with a juvenile type X-linked Alport syndrome and truncation mutations of the COLIVA5 gene. When a patient has lost one transplant due to post-transplant anti-GBM disease, repeat transplantation is difficult because of the high risk of recurrence. The decision to proceed should be considered only after careful discussion between the multi-professional team, the donor, and the 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)***

12.11 Mesangiocapillary Glomerulonephritis

There has been a significant change in the description of mesangiocapillary glomerulonephritis (MCGN) based upon improved understanding of the mechanisms underlying its pathogenesis. MCGN may be associated with predominant deposition of monoclonal or polyclonal immunoglobulin. This may be secondary to haematological, autoimmune or infectious disease with a small number of 'idiopathic' cases. MCGN may also be associated with dysregulated activation of the alternate pathway of complement encompassed in the term C3 glomerulopathy (41). C3 glomerulopathy may be divided on the basis of electron microscopic appearance into Dense Deposit Disease (DDD) and C3 glomerulonephritis. Assessment of these diseases is described in detail elsewhere.

In patients with C3 glomerulopathy, detailed complement testing should be performed to identify any underlying complement abnormality as it may inform the risk of recurrence. The identification of genetic complement regulatory abnormalities in a proband also has implications for other family members who may be affected.

The description of outcomes following transplantation has until recently relied upon histological differentiation primarily reporting on MCGN class I and II. These provide much of the context for the reported literature and the recommendations that follow, albeit with additional insights provided by contemporary understanding of C3 glomerulopathy.

Type I 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% (9). The risk of graft loss in patients with recurrent type 1 MCGN is therefore around 15% at

5 years. This represents a significant cause of transplant failure (7,8,42). The risk of recurrence may be higher in living donor transplantation (8,9). It may be that the risk of secondary MCGN is low following successful control of the underlying disease. On the other hand, this histological classification includes a significant mix of cases, some with immunoglobulin deposition and others with C3 glomerulonephritis. In these cases it is thought that the likelihood of recurrent disease in C3 glomerulonephritis is likely to be high and comparable to that of DDD.

DDD (Type II MCGN) is the primary glomerulonephritis most likely to recur after renal transplantation and does so in virtually all cases. The outcome after transplantation is variable. In 75 patients reported by the North American Pediatric Renal Transplant Cooperative Study, 5 year graft survival was 65.9% and 34.1% in living and deceased donor transplantation respectively (42). Poor outcome has been associated with heavy pre-transplant proteinuria and increased glomerular proliferation (43).

Recommendations

- ***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 transplantation should only be undertaken following careful discussion between the multi-professional team, the donor and the recipient. This is particularly the case if there is an identified abnormality of a soluble complement regulatory protein.***
- ***Transplantation in an individual with unequivocal evidence of graft loss secondary to recurrent C3 glomerulopathy constitutes a high risk of subsequent failure such that some centres consider this a contraindication to repeat transplantation (44)***
- ***Among patients with genetic abnormalities in complement proteins or with an unknown cause of C3 glomerulopathy, a comparison with atypical HUS suggests that consideration should be given to avoiding living related donors in whom similar genetic mutations may predispose to the future development of C3 glomerulopathy after nephrectomy (44)***

12.12 Haemolytic Uraemic Syndrome

The recommendation for renal transplantation in HUS has changed significantly since the previous edition of these guidelines because effective therapy has become available for the treatment and prevention of recurrent disease in atypical HUS. In England, use of this medication, eculizumab, is co-ordinated through a national expert centre. There remain, however, important considerations with respect to the recipient and donor. The principles of this management are discussed in a publication from 2009: 'Clinical Practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom' (10). Additional information relevant to the use of eculizumab has been prepared by the national expert centre and is accessible through rarerenal.org. Further advice on genetic testing and evaluation of potential donors is available through the aHUS National Service (contact details on rarerenal.org).

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 medication.

Patients presenting with atypical HUS or wishing to be considered for transplantation should be assessed in accordance with the aforementioned guidelines and the national expert centre. The rate of recurrence following transplantation is high in patients known to have mutations in Factor H or gene re-arrangements involving Factor H or Factor H related proteins, gain of function mutations in Factor B or C3, or who have lost a previous transplant due to disease recurrence. The risk of recurrence is intermediate for mutations of factor I, in the presence of autoantibodies against factor H, and when mutations of uncertain functional significance or when no mutation or autoantibody is detected. Patients carrying an MCP (CD46) 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 (10).

Living unrelated transplantation may therefore be considered after appropriate counselling of donor and recipient. Patients at low risk do not require prophylaxis with eculizumab but should be warned of the possibility of recurrence and monitored closely. In patients at medium or high risk of recurrence it is recommended that

treatment with eculizumab be offered, although the necessary duration of treatment is uncertain.

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 carefully discussed.

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 (40).

Recommendations

- ***Living related renal transplantation should be avoided in atypical HUS unless the cause of the disease in the recipient is known and this has been excluded in the donor. Even then related donors may be at a greater risk of aHUS and should be warned of this risk.***
- ***In patients in whom the underlying cause has unequivocally been attributed to Shiga-toxin, the recurrence rate of HUS is low and living donor transplantation may be considered.***

12.13 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 (45).

Primary hyperoxaluria type 1 is generally treated with combined liver and kidney transplantation (46,47) or early liver transplantation alone (48). However, some groups in North America have advocated early living donor kidney transplantation, particularly if there is evidence of pyridoxine responsiveness (49) in particular in patients homozygous for the G170R mutation (50).

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 (51).

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.***

12.14 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 (52).

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.***

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13 LIVING DONOR KIDNEY TRANSPLANTATION IN CHILDREN

Recommendations

- ***Pre-emptive living related renal transplantation is the gold standard therapy for children with end-stage renal disease. (2C)***

- ***The aim should be for children to receive a renal transplant from a blood group compatible well-matched donor, although ABO and/or HLA incompatible renal transplantation is feasible in children. (2C)***

- ***Every effort should be made to minimise HLA mismatches (especially with common antigens) to reduce the risk of future sensitisation. (2D)***

- ***All children with stage 4 and 5 chronic kidney disease should be assessed by a multi-disciplinary team, including a paediatric nephrologist, transplant surgeon, anaesthetist and urologist (where appropriate) prior to renal transplantation. (Not graded)***

- ***In general, children who are ≥10 kg in weight are suitable to receive a kidney from an adult living donor. (2C)***

13.1 Introduction

Pre-emptive living related renal transplantation is the gold standard therapy for children with end-stage renal disease (ESRD) (1). The aim should be for children to receive a blood group compatible well-matched donor minimising HLA mismatches (to reduce the risk of future sensitisations), although ABO and/or HLA incompatible renal transplantation is feasible in children (2-6). All children with Stage 4 and 5 chronic kidney disease (CKD) should be assessed by a multi-disciplinary team, including a paediatric nephrologist, transplant surgeon, anaesthetist and urologist (where appropriate) prior to transplantation.

When transplanting children from living donors, there are some specific issues that require consideration. This Chapter highlights 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.

13.2 Donor Selection

Parents are the usual source of living donor kidneys for children. However, any suitable adult may be considered as a potential donor, including unrelated and altruistic donors, who may come forward from the UK Living Kidney Sharing Scheme (UKLKSS) (2).

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) (3). One parent may fortuitously be better than a one haplotype match, or may mismatch on less common antigens and therefore be the preferred donor. The involvement of an expert in histocompatibility is critical in advising upon such decisions.

ABO incompatible transplantation

This should be considered when an ABO compatible transplant is not available, including after consideration of UKLKSS. Younger children tend to have lower antibody titres and there may be reduced risk, although ABO incompatible transplantation should only be performed in centres with appropriate support for the additional treatment required (4,5).

HLA incompatible transplantation

This should be considered when a highly sensitised patient has not been able to receive a transplant (usually retransplant as highly sensitised from previous transplant) via a deceased donor, living donor or via the UKLKSS. However, it should only be performed in centres with appropriate support for the additional treatment required (6).

Immunisations and infection

Children are less likely to have been exposed to infectious agents and, where possible, should be immunised before transplantation to reduce the subsequent infection risk (7). This risk may be reduced by considering the use of less immunosuppression for children who receive a well-matched kidney.

Special note should be made that many children are EBV naïve at the time of transplantation, with no currently available vaccination, whereas most adult donors are EBV positive. When available, the use of an EBV negative kidney donor should be considered to reduce the risk of post-transplant lymphoproliferative disorder.

Social aspects

Choosing a donor must include assessment of the psychosocial aspects of the family. It should be noted that parental donors may be cared for in a different hospital from the recipient and clear plans should be made for supporting the donor, the recipient, and other family members during the post-operative period.

13.3 Recipient Considerations

The commonest causes of ESRD in children are congenital anomalies of the kidney and urinary tract, with renal dysplasia and/or reflux and/or obstructive uropathy in over half of cases; obstructive uropathy accounts for 18% of cases (8). All children should be seen by a paediatric urologist with appropriate urological investigation (including flow studies and video-urodynamics) before living donor transplantation. The most appropriate timing of any urinary tract reconstructive surgery should be discussed between the transplant surgeon and paediatric urologist (9).

Glomerular disease accounts for 10% of children with ESRD (8). 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 FSGS. Pre-transplant genetic studies may identify those at risk of disease recurrence in the transplant and provide additional information to inform the selection and consent process of potential living donors (10).

In children, particularly those requiring dialysis in infancy, there is a risk of thrombosis of major intra-abdominal vessels and this requires careful evaluation before surgery (11).

13.4 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, and this may be retrieved by laparoscopic surgery (12,13). 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 inferior vena cava (IVC) for attachment of the donor renal vessels. Some transplant 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 IVC or other anatomical abnormalities (14).

In 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 (15). 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 may be considered (16).

The implantation of an adult kidney into a paediatric recipient requires close cooperation between the paediatric nephrology, transplant surgical and anaesthetic teams with intensive care involvement in smaller and/or ventilated children (17). 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 ongoing fluid loss is required, remembering that the urine output from both the native and donor kidney may be significant. The surgical and anaesthetic team should note a target

blood pressure for adequate renal perfusion during the surgical procedure which should guide the post-operative management.

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, and these should be replaced with regular monitoring of renal function, urine and plasma electrolytes and blood sugar levels. 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. Elective ventilation may be considered in young children for the first 24 to 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 or enteral medication. Rarely, 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 (11).

It may be necessary to perform the donor and recipient procedures in separate hospitals and, provided that the kidney is transported safely and efficiently between the two centres to minimise the cold ischaemia 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 using webcam technology (such as FaceTime or Skype), to facilitate contact between the donor, child and their carers.

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14 APPENDIX

14.1 Conflicts of Interest

The authors make the following statements in relation to potential conflict of interest related to this guideline:

Dr Peter Andrews	None
Dr Richard Baker	None
Prof Simon Ball	Travel support from Astellas. Research support and honorarium from Oxford Immunotec
Dr Kate Bramham	None
Mr Tim Brown	No details available
Ms Lisa Burnapp	Advisory board membership for Chiesi, medical advisor to the 'Gift of Life' donor information booklet sponsored by Astellas and Sandoz
Prof Jamie Cavenagh	No details available
Mr Marc Clancy	Research grants from Astellas. Advisory board Sandoz. Speaker fees from Astellas and Sandoz. Educational meeting sponsorship from Astellas and Sanofi. Research collaboration Cytori
Dr Aisling Courtney	None
Dr Sam Dutta	None
Dr Robert Elias	Support to attend conferences from Janssen and funding for a shared decision making network from the Association of Renal Industries
Dr A Fenton	None
Prof Susan Fuggle	Honoraria and support to attend conferences from Astellas
Mr Keith Graetz	None
Dr Siân Griffin	None
Dr Brendan Healy	None
Dr Rachel Hilton	Research grants, honoraria and/or support to attend conferences from Astellas, Genetech, Novartis, Oxford Immunotec, and Roche
Dr Gareth Jones	None

Prof Graham Lipkin	None
Dr Adam Mclean	Research funding from Astellas, invited delegate at Astellas, Novartis-funded meetings
Prof Nizam Mamode	Payment for consultancy work from Alexion Pharmaceuticals, and unrestricted educational grants from Astellas and Glycorex
Ms Hannah Maple	Co-applicant on an NIHR study further investigating the topic of altruistic donation
Dr Stephen Marks	Principal investigator in randomised controlled trials with Novartis and Astellas but no direct payments
Dr E Montgomery	None
Dr P Nightingale	None
Mr Jonathan Olsburgh	None
Dr Michael Picton	None
Dr Stephen Potts	None
Dr Nicola Price	None
Dr Richard Sandford	None
Dr Alastair Santhouse	Expenses (but not lecture fees) from Novartis and the World Transplantation Congress
Prof Neil Sheerin	None
Ms Lisa Silas	None
Ms Karen Stevenson	No details available
Dr Craig Taylor	None
Dr Raj Thuraisingham	None
Dr Nicholas Torpey	None
Dr Caroline Wroe	None

14.2 Search Strategies

Authors of this guideline have notified the following search strategies:

Dr Peter Andrews	PubMed search, review of national guidelines and NICE website, review of ODT and UNOS websites
Dr Richard Baker	PubMed search, review of national and international guidelines

Prof Simon Ball	Combinations of recurrent disease, transplant, kidney, and renal alone or along with one of the following: mesangiocapillary glomerulonephritis, C3 glomerulopathy, haemolytic uremic syndrome, HUS, FSGS, focal segmental glomerulosclerosis, Goodpasture's disease, ANCA , systemic lupus erythematosus, SLE , IgA nephropathy, IgA disease, membranous nephropathy, diabetic nephropathy, hyperoxaluria, oxalosis, cystinosis, Alport, inherited nephropathy
Dr Kate Bramham	None
Mr Tim Brown	No details available
Ms Lisa Burnapp	Search strategies for my sections are largely covered by the general statements that include guideline review but, specifically, also include direct on-line search for specific policies, guidance and statistics from national and global donation and transplantation organisations and PubMed
Prof Jamie Cavenagh	No details available
Mr Marc Clancy	PubMed, NHSBT website and direct online searches
Dr Aisling Courtney	PubMed, NHSBT website
Dr Sam Dutta	PubMed
Dr Robert Elias	We searched PubMed through to 01 September 2015, using keywords "HIV", "transplant", "transplantation", "consent", "informed consent", "confidentiality" and "ethics". We also searched reference lists of review articles, relevant studies, and clinical practice guidelines. We considered all systematic reviews, randomised controlled trials, observational cohort studies, ethics reports and case reports looking at people with HIV infection treated with kidney and/or pancreas transplantation. Our search was limited to articles in English and studies conducted in adult humans. One study published in 2016 was added at editorial review
Dr A Fenton	Search strategy-Pub Med, references from related articles, review of BTS, EBPG, KDIGO guidelines

Prof Susan Fuggle	All relevant articles and review of national guidelines
Mr Keith Graetz	Online, PubMed, NICE, OVID
Dr Siân Griffin	A literature search was performed using PubMed to identify the relevant evidence. Related guidelines were also considered (Guidelines for Hepatitis E and Solid Organ Transplantation, first edition, BTS 2017; Guidance on the microbiological safety of organs, tissues and cells used for transplantation, Advisory Committee on the Safety of Blood. Tissues and Organs (SaBTO) 2011 and KDIGO Clinical Practice Guideline on the Evaluation and Follow-Up Care of Living Kidney Donors, draft 2015)
Dr Brendan Healy	As per Dr Griffin
Dr Rachel Hilton	I searched PubMed through to 01 November 2016 using the keywords "proteinuria", “albuminuria”, “pyuria”, “living donor”, "kidney", “renal”, "transplant" and "transplantation". I considered all systematic reviews, randomised controlled trials, observational cohort studies and case reports looking at living kidney donors. I also searched reference lists of review articles, relevant studies, and clinical practice guidelines. Specifically, I looked at European Best Practice guidelines (2013) on donor and recipient evaluation and perioperative care and also the KDIGO chronic kidney disease guidelines (2012). My search was limited to articles in English and studies conducted in humans
Dr Gareth Jones	NHSBT website and BTS guidelines
Prof Graham Lipkin	All relevant articles from PubMed and review of latest versions of KDIGO+EBPG guidance
Dr Adam Mclean	1) PubMed searches using "Kidney Transplantation" (Mesh Terms) AND "Living Donors" (Mesh Terms) AND "Obesity" (Mesh Terms), and equivalent (All Fields) search 2) PubMed searches using "Kidney Transplantation" (Mesh Terms) AND "Living Donors" (Mesh Terms)

	AND "Risk Factors" (Mesh Terms) and equivalent (All Fields) search
Prof Nizam Mamode	PubMed search, along with NHSBT website
Ms Hannah Maple	Search strategy adapted from PhD
Dr Stephen Marks	Search strategies are covered by the general statements that include guideline review but, specifically, also include direct on-line search for specific policies, guidance from national and international transplantation organisations, and PubMed
Dr E Montgomery	Search strategy: PubMed, references from related articles, review of BTS, EBPG, KDIGO guidelines
Dr P Nightingale	Search strategy: PubMed, references from related articles, review of BTS, EBPG, KDIGO guidelines
Mr Jonathan Olsburgh	PubMed search using the search terms kidney transplant, kidney donor, donor nephrectomy, ex-vivo ureteroscopy, kidney stones
Prof Michael Peters	Search strategy: PubMed, references from related articles, review of BTS, EBPG, KDIGO guidelines
Dr Michael Picton	PubMed search
Dr Stephen Potts	I did not use a formal search strategy
Dr Nicola Price	As per Dr Griffin
Dr Richard Sandford	PubMed and NCBI website search, review of current national guidelines, review of UNOS, UKGTN, BSHG and genetics education websites as stated
Dr Alastair Santhouse	As per Dr Elias
Prof Neil Sheerin	Hypertension search on PubMed using terms hypertension, living donor, kidney donation
Ms Lisa Silas	As per Dr Elias
Ms Karen Stevenson	No details available
Dr Craig Taylor	All relevant articles and review of national guidelines.
Dr Raj Thuraisingham	PubMed search
Dr Nicholas Torpey	No details available
Dr Caroline Wroe	PubMed, references from related articles, review of BTS, EBPG, KDIGO guidelines