



The Voice of Transplantation in the UK

# Management of the Failing Kidney Transplant



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## **1 INTRODUCTION**

### **1.1 The need for guidelines**

It is estimated that patients with failed transplants currently constitute approximately 4% of the incident dialysis population (1). With the increasing number of kidney transplant recipients (KTRs) it is inevitable that, despite improvements in graft survival, failing grafts will become progressively more common. While some patients will be retransplanted, increasing age and comorbidity means that most KTRs whose transplants fail will never return to the transplant list.

Alongside this increase in the absolute number of failing grafts, there is evidence that KTRs with poor graft function receive suboptimal care when compared to patients with native renal disease (2). Possibly unrelated, but a subject of concern, is the observation that poor allograft function is associated with an increased risk of death that increases as the need for dialysis approaches (3). This risk mainly results from higher rates of cardiovascular and infective death. Returning to dialysis after graft failure is an especially risky time, with mortality rates significantly greater than those of patients with poorly functioning allografts (4).

As a result of these findings a number of centres in the UK have set up specialist transplant low clearance services. Other units currently manage failing transplants in advanced kidney care (low clearance) clinics, or in standard transplant clinics with additional input from multidisciplinary teams as required. Whatever the set up, the increasing numbers and significant excess morbidity associated with graft failure means that guidelines for the management of the failing kidney graft are overdue.

These are the first guidelines on this subject published by the British Transplantation Society. This document aims to provide a comprehensive summary of all aspects of the management of the failing kidney transplant, including outcome data. Guidelines for the management of patients with failing grafts are inevitably similar in many respects to those for general KTRs which have been previously published (5,6). This document should be read in conjunction with these existing guidelines, but will focus on areas with special relevance to KTRs with poor renal function.

## **1.2 Process of writing and methodology**

This document has been written under the auspices of the BTS Standards Committee. The guidance has been produced in line with the BTS Clinical Practice Guideline and the recommendations of NHS Evidence (7). It has been produced with wide representation from UK clinicians and professional bodies involved in kidney transplantation.

A systematic review of the relevant literature and synthesis of the available evidence was undertaken by selected clinical experts. This was followed by peer group appraisal and expert review. Draft proposals were collated by the editor and draft guidelines were presented to a meeting of the British Renal Society in Manchester in May 2013. Following this, appropriate levels of evidence were added to the recommendations by group consensus. The draft of the document was placed on the BTS website in April 2014 for a period of open consultation, to which patient and transplant groups were actively encouraged to contribute. The final document was posted in June 2014.

Where available, these guidelines are based upon published evidence. With the exception of descriptive studies, the evidence and recommendations have been graded for strength. A small number of conference presentations have been included where relevant. Data relating to UK transplantation and outcomes were kindly provided by NHSBT. With minor exceptions where relevant results became available, the publication 'cut off' date for evidence was June 2013.

It is anticipated that these guidelines will next be revised in 2019.

## **1.3 Writing committee**

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#### **1.4 Disclaimer**

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

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

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

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

## **1.6 Grading of recommendations**

In these guidelines, the GRADE system has been used to rate the strength of evidence and the strength of recommendations. This approach is consistent with that adopted by KDIGO in guidance relating to renal transplantation, and also with guidelines from the European Best Practice Committee, and from the Renal Association (5,8).

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

- A (high)
- B (moderate)
- C (low)
- D (very low)

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

- Level 1 (we recommend)
- Level 2 (we suggest)
- Not graded (where there is not enough evidence to allow formal grading)

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of the evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice and is similar to the approach adopted by KDIGO (8).

## **1.7 Definitions and abbreviations**

The following definitions and abbreviations are used in this document:

ACR	Albumin: creatinine ratio
DSA	Donor specific antibody
GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcomes
KTR	Kidney transplant recipient
PCR	Protein:creatinine ratio
PRA	Panel reactive antibody
RFKT	Recipient with failing kidney transplant

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## **2 EXECUTIVE SUMMARY OF RECOMMENDATIONS**

### Principles of management of the failing graft

*We suggest that:*

- Patients with failing grafts have ready access to the low clearance multi-disciplinary team. (2C)
- Joint transplant/advanced kidney care be initiated at least 6-12 months before the anticipated need for dialysis or retransplantation, or when graft eGFR falls below 20 mL/min. (2C)
- Where appropriate, retransplantation be undertaken when the eGFR of the recipient with a failing kidney transplant (RFKT) has fallen to 10-15 mL/min. (2C)
- Given the increased morbidity seen in the RFKT, especial care be paid to the attainment of cardiovascular and other targets. (2C)
- Immunosuppression be reduced in the late stages of graft dysfunction, with reduction of target tacrolimus or ciclosporin blood concentrations or complete withdrawal of these agents. (2C)
- Given the possibility of immunological damage following reduction of immunosuppression, transplant biopsy be considered before deciding upon the preferred course of action. (2D)

### Management of immunosuppression

*We recommend that:*

- Consideration be given to the relative risk of maintaining recipient immunosuppression after return to dialysis and re-listing for a repeat kidney transplant, the clinical benefit of immunosuppressive drug tapering/withdrawal, and the risk of *de novo* allosensitisation that may preclude options for future kidney transplantation. This is particularly relevant for paediatric recipients and young adults who are likely to require retransplantation within their lifetime. (1D)
- All immunosuppression apart from steroids be stopped immediately after transplant nephrectomy, with subsequent gradual withdrawal of steroids. (1D)

- In the event of severe acute rejection following withdrawal of immunosuppression, we recommend that steroid therapy be restarted, followed by transplant nephrectomy when acute inflammation has settled. (1D)
- For patients that are re-listed for transplantation, that the clinical team notify the histocompatibility laboratory of significant changes in immunosuppression and that additional serum samples be obtained for HLA-specific antibody screening four weeks after any such changes. (1C)

*We suggest that:*

- Immunosuppressive therapy be continued to avoid immunological sensitisation if a living kidney donor is available and there is the prospect of retransplantation pre-emptively or within one year of starting dialysis. (2C)
- Immunosuppressive treatment be withdrawn after graft failure when there are immunosuppression-related complications such as skin cancer and an anticipated delay in retransplantation. (2C)

### Cardiovascular & other risk factor management

*We recommend that:*

- Smoking be actively discouraged in RFKTs. (1B)
- RFKTs be vaccinated with inactivated viruses as per the normal population, except for HBV. (1D)
- RFKTs receive annual influenza vaccination unless contraindicated. (1C)
- RFKTs are thoroughly assessed for the cause of their graft failure and counselled appropriately regarding future transplantation. (1D)

*We suggest that:*

- Blood pressure be recorded at each clinic visit and maintained <130/80 mmHg (125/75 mmHg if PCR >50 or ACR >35 mg/mmol). (2C)
- There is no evidence to support the use of any particular antihypertensive agent. The focus is to achieve absolute blood pressure targets rather than the use of individual agents. (2D)

- Inhibitors of the renin-angiotensin system may be more effective in reducing proteinuria but may worsen anaemia. (2C)
- Resistant hypertension is often due to salt and water retention and should be addressed by dietary measures and the use of diuretics. (2D)
- Treatment of dyslipidaemia in RFKTs is the same as treatment in KTRs. Pravastatin and fluvastatin are preferred statins. Fibrates are contraindicated. (2C)
- Nicotinic acid compounds and ezetimibe may be safely used in RFKTs. (2B)
- Low level consumption of alcohol is safe in RFKTs. (2D)
- Control of diabetes can be erratic as renal function deteriorates and is improved by monitoring in specialist clinics. (2C)
- RFKTs be counselled regarding diet, weight loss and exercise. (2D)
- Anaemia is common and can be treated according to existing guidelines. (2C)
- RFKTs have their skin examined at 1-3 yearly intervals by a trained healthcare professional. (2C)
- Sirolimus may be considered in RFKTs with previous squamous cell carcinoma. (2B)
- Acitretin can be safely used in RFKTs. (2B)
- There is no evidence to support aggressive immunosuppression in RFKTs with late recurrent disease. (2D)
- RFKTs have HBsAb levels rechecked annually and be revaccinated if antibody titres fall below 10 U/mL (2D); do not receive live attenuated vaccines (2C); and receive pneumococcal vaccine and one booster after five years. (2D)

#### Surgical issues in the management of the failing renal transplant

- Widely accepted indications for graft nephrectomy include:
    - localising symptoms (pain, infection, bleeding) that are resistant to medical therapy in a failed graft
    - to create space for retransplantation
    - to enable complete withdrawal of immunosuppression
    - risk of graft rupture
    - graft malignancy
    - refractory anaemia with raised CRP
- (Not graded)

*We suggest that:*

- In the absence of prospective data, decisions on whether to remove a failed or failing graft be made on perceived benefits and risks and on a case-by-case basis. (2B)
- The surgical technique used for graft nephrectomy is dependent on timing post-transplantation and operator preference. There is no compelling evidence favouring either the intracapsular or extracapsular approach in the late phase post-transplantation. (2C)
- The role of percutaneous embolisation of the failing or failed renal allograft is uncertain. At present, it is reserved for patients at high operative risk where malignancy is not a consideration. (2D)
- Data on outcomes after graft nephrectomy in the paediatric group are limited. Local and regional specialist opinion should be followed. (2D)

#### Patient education and options for renal replacement therapy

*We recommend that:*

- While there are some important transplant-specific issues, the decision making process and management of end-stage kidney disease are largely the same as for patients with chronic kidney disease and are covered by the Renal Association guideline ‘Planning, Initiating and Withdrawal of Renal Replacement Therapy’. (1C)
- Pre-emptive retransplantation in suitable candidates is the best option for ongoing renal replacement therapy, and should ideally occur when eGFR is 10-15 mL/min. (1D)
- If the patient is returning to a local centre for dialysis or conservative care, the transfer of care be completed in time (at least 6 months before graft failure) to ensure that patients are adequately prepared. (1D)
- Appropriately skilled psychological support be made available to patients with failing transplants, with ongoing support on return to dialysis or conservative management.
- Patients with squamous cell carcinoma have all current lesions resected prior to retransplantation and be clear of metastatic disease. However, there is no requirement to wait for a disease-free interval prior to retransplantation. (1C)
- Patients with graft loss due to BK nephropathy be considered for retransplantation, but preferably avoiding highly potent immunosuppressive regimens. (1C)

- Potential non-concordance is not an absolute contraindication to retransplantation. However, there will clearly be cases where the clinical team assesses the risk of non-concordance to be unacceptably high. (1D)

#### Outcomes following return to dialysis or retransplantation

*We recommend that:*

- Following graft failure, repeat transplantation offers the best survival and quality of life. This is particularly true for pre-emptive repeat transplantation. (1A)
- Patients suitable for retransplantation be evaluated for repeat transplantation when graft survival is anticipated to be <1 year (1B)
- The optimum kidney for retransplantation comes from a well matched living donor. (1A)

### **3 PRINCIPLES OF MANAGEMENT OF THE FAILING TRANSPLANT**

#### **Statements of Recommendation**

*We suggest that:*

- Patients with failing grafts have ready access to the low clearance multi-disciplinary team. (2C)
- Joint transplant/advanced kidney care be initiated at least 6-12 months before the anticipated need for dialysis or retransplantation, or when graft eGFR falls below 20 mL/min. (2C)
- Where appropriate, retransplantation be undertaken when the eGFR of the recipient of a failing kidney transplant (RFKT) has fallen to 10-15 mL/min. (2C)
- Given the increased morbidity seen in the RFKT, especial care be paid to the attainment of cardiovascular and other targets. (2C)
- Immunosuppression be reduced in the late stages of graft dysfunction, with reduction of target tacrolimus or ciclosporin blood concentrations or complete withdrawal of these agents. (2C)
- Given the possibility of immunological damage following reduction of immunosuppression, that transplant biopsy be considered before deciding upon the preferred course of action. (2D)

#### **3.1 Organisation of patient follow up**

In the UK, most patients with poor kidney graft function are managed in specialist transplant clinics held either at the transplant centre, or more conveniently at the local non-transplanting renal centre. Transplant follow up is most commonly performed by nephrologists, although long term follow-up is shared in some centres with transplant surgeons and specialist nurses.

Poor kidney transplant function is associated with an increased risk of death that increases as the need for dialysis approaches (1). This risk mainly results from higher rates of cardiovascular and infective death, and is particularly high at the time of returning to dialysis (see chapter 8) (2).

In addition to this increased risk of death, there is considerable evidence that kidney transplant recipients with poor graft function receive suboptimal care when compared to patients with native renal disease (3). Thus, for example, the mean Hb of patients reported to the UK Renal Registry in 2011 was 110 +/- 18 g/L in stage 5T, compared to 117 g/L for patients on dialysis (4). In the same populations, there were significantly worse results for the percentage of transplant patients with Hb >100 g/L, ferritin <100 ng/mL, systolic BP <130 mmHg, diastolic BP <80 mmHg, and cholesterol <200 mg/dL (table 3.1). Similar data have been reported in studies from France, Spain and the UK (5-7).

**Table 3.1 Variation in CKD management in dialysis and CKD5T populations**

Parameter	Dialysis Patients	Stage 5T (eGFR <15 mL/min)
Hb mean	117	110 $\pm$ 18
% Hb <100 g/L	14	32 *
% Hb <110 g/L	30	51 *
Ferritin median ng/mL	393	202 *
Ferritin % <100 ng/mL	6	28 *
% Systolic BP >130 mmHg	53	74 *
% Diastolic BP >80 mmHg	62	68 *
% Cholesterol >200 mg/dL	17	34 *

\*p<0.001 Data from UK Renal Registry 2011 (4)

At least some of this variation relates to the continuing need for immunosuppression in transplant recipients, with associated effects on blood pressure and other variables. However, another factor is the wide variation in the location where such patients are managed, with few

transplant centres having the critical mass to see patients with failing grafts in an appropriate low clearance environment.

In most centres in the UK, failing kidney transplant recipients are managed in transplant clinics with additional input from low clearance teams as required, and less commonly in low clearance clinics. However, as a result of concerns regarding morbidity and mortality, a number of centres have established specialist transplant advanced kidney care services where these two specialties are co-located. There is no hard evidence to support this model, but there is considerable logic in centralising transplant and advanced kidney care services where a critical mass is available.

Whatever the model of care adopted, which will vary according to geography and the availability of resources, RFKTs should have ready access to the low clearance multi-disciplinary team. In line with pre-dialysis patients and other published guidelines, joint transplant/advanced kidney care should be initiated at least 6-12 months before the anticipated need for dialysis or retransplantation for deceased donor listing, or when graft eGFR falls to 20 mL/min for preparation for living donor transplantation (8,9). The optimal timing of repeat transplantation will depend upon many factors such as the symptom burden of the recipient, rate of change of graft function and donor/recipient convenience, but preparations for retransplantation should usually be completed by the time the eGFR has fallen to 10-15 mL/min.

### **3.2 Specific issues in the failing kidney transplant**

Most of the physiological changes that occur with loss of graft function mimic those seen in progressive renal disease from other aetiologies. It is logical, therefore, to manage these in a similar way to the non-transplant population and previous guidelines have made recommendations to this effect (9,10). However, there are a number of significant differences, such as an increased susceptibility to bruising and infection in transplant recipients, almost certainly related to the longer history of renal disease and the effects of immunosuppression.

Recommendations with regard to cardiovascular risk factor management, anaemia, skin disease and infection risk are detailed in chapter 5. These include recommendations regarding blood pressure control and targets, dyslipidaemia, glycaemia, smoking, anaemia, and lifestyle. Given the increased morbidity seen in the failing transplant, attention to the attainment of cardiovascular risk reduction is especially important, especially given data that hypertension control may confer lasting benefit even in the late stages of graft dysfunction (11).

It should be noted that the observed failure to achieve cardiovascular and other risk factor targets starts early, and the frequency increases as graft function declines. For example, a study from the UK Renal Registry demonstrated serial increases in PTH, serum phosphate, and systolic and diastolic blood pressure as graft function moved from stage 1-2T (eGFR >60 mL/min) to 5T (eGFR <15 mL/min), and significant falls across this range in Hb and serum bicarbonate (7). Similarly, a Spanish study showed sequential worsening of risk factors as graft function deteriorated from stage 1T to 5T (table 3.2) (6). In this latter study, cardiovascular risk factors deteriorated despite increases in the use of epoetin, blood pressure agents and phosphate binders. Given the recognition that cardiovascular comorbidity increases at even low reductions in renal function (12), this highlights the need for aggressive risk factor management at all stages of the graft history.

**Table 3.2 Variation in CKD parameters related to stage of graft dysfunction (6)**

	1T	2T	3T	4T	5T	P
<b>Hb (g/L)</b>	145	142	134	124	113	<0.001
<b>Phosphate (mg/dL)</b>	3.1	3.1	3.3	3.9	5.1	<0.001
<b>iPTH (pg/mL)</b>	68.5	102.4	138.6	233.0	383.1	<0.001
<b>Total CO<sub>2</sub> (mmol/L)</b>	25.3	25.4	24.5	23.3	20.3	<0.001
<b>Systolic BP (mmHg)</b>	136	137	143	146	144	<0.001
<b>Diastolic BP (mmHg)</b>	82	82	82	83	83	0.809
<b>Triglycerides (mg/dL)</b>	119	127	144	150	157	<0.001
<b>Albumin (g/L)</b>	44	44	44	42	41	0.001

## **Immunosuppression**

As graft function declines, there is good evidence to suggest that immunosuppression may be safely reduced in most long term kidney transplants. For example, the ‘creeping creatinine’ study examined the effect of substituting mycophenolate mofetil for calcineurin inhibitor-based immunosuppression and found modest improvement of graft survival with few side effects (13).

More recently, and in contrast to the above, the finding of C4d deposition in a significant number of failing grafts has resurrected the possibility that graft loss may be an immunologically mediated process, even after many years of apparent stability (14). Studies are underway to assess whether increased immunosuppression may be beneficial in this context.

In most transplant units, immunosuppression is reduced as graft function deteriorates, with reduction of target tacrolimus or ciclosporin blood concentrations, or complete withdrawal of these agents at the point of graft failure or return to dialysis. Given the possibility of immunological damage which may be treatable if graft function has not deteriorated too far, it is appropriate to consider transplant biopsy before deciding upon preferred management in these circumstances.

If immunosuppression is reduced, care is required to minimise the risk of acute rejection or the formation of donor specific antibodies which may complicate future treatment. This is considered further in chapter 4.

## **Depression**

Many patients with graft dysfunction will develop depression. This should be actively sought and treated along conventional lines (see chapter 7.4). Reduced libido may be a prominent feature of depression and usually responds to phosphodiesterase inhibitors (e.g. sildenafil).

## **Drugs**

ACE inhibitors and ARBs are not contraindicated in graft dysfunction, although their use should be reviewed in the event of hyperkalaemia or if transplant renal artery stenosis is suspected. Their use may exacerbate anaemia, especially if used with mycophenolate or azathioprine.

Diuretics may be required to manage hypertension and fluid overload, especially as urine output declines and drug resistance increases. Potassium sparing diuretics are usually best avoided.

Drug doses should be adjusted according to eGFR and the manufacturer's recommendations. Particular care is advised re the use of oral hypoglycaemic agents (see chapter 5.4).

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## **4 MANAGEMENT OF IMMUNOSUPPRESSION**

### **Statements of Recommendation**

*We recommend that:*

- Consideration be given to the relative risk of maintaining recipient immunosuppression after return to dialysis and re-listing for a repeat kidney transplant, the clinical benefit of immunosuppressive drug tapering/withdrawal, and the risk of *de novo* allosensitisation that may preclude options for future kidney transplantation. This is particularly relevant for paediatric recipients and young adults who are likely to require retransplantation within their lifetime. (1D)
- All immunosuppression apart from steroid be stopped immediately after transplant nephrectomy, with subsequent gradual withdrawal of steroids. (1D)
- In the event of severe acute rejection following withdrawal of immunosuppression, we recommend that steroid therapy be restarted, followed by transplant nephrectomy when acute inflammation has settled. (1D)
- For patients that are re-listed for transplantation, that the clinical team notify the histocompatibility laboratory of significant changes in immunosuppression and that additional serum samples be obtained for HLA-specific antibody screening four weeks after any such changes. (1C)

*We suggest that:*

- Immunosuppressive therapy be continued to avoid immunological sensitisation if a living kidney donor is available and there is the prospect of retransplantation pre-emptively or within one year of starting dialysis. (2C)
- Immunosuppressive treatment be withdrawn after graft failure when there are immunosuppression-related complications such as skin cancer and an anticipated delay in retransplantation. (2C)

#### **4.1 Introduction**

The majority (up to 60%) of patients listed for repeat transplantation are sensitised and many such patients are highly sensitised with a concomitant low probability of receiving a suitable crossmatch negative re-graft. Recent studies have shown that the development of high HLA specific sensitisation after transplant failure occurs most often after returning to the transplant waiting list, when awaiting repeat kidney transplantation. This usually coincides with immunosuppression tapering or withdrawal [1] and is independent of graft nephrectomy [2,3]. It is therefore important to consider the timescale in which repeat transplantation is likely to be achieved through, for example, imminent live donor transplantation in the coming months (in which case continuing immunosuppression may be justified), or return to the deceased donor kidney transplant waiting list where waiting time may vary from months to years (in which case continuing immunosuppression may be undesirable). This is particularly relevant for paediatric recipients and young adults who are likely to require retransplantation within their lifetime.

#### **4.2 Immunosuppression management with transplant nephrectomy**

In the event of transplant nephrectomy, there is no need for ongoing immunosuppression to preserve residual graft function or prevent acute rejection and consideration should be given to stopping immunosuppressive treatment. However, this needs to be balanced against the risk of development of *de novo* HLA-specific antibodies that frequently occurs after withdrawal of immunosuppression (see above).

There are no robust data to guide the optimal timing of withdrawal. Donor-specific antibody concentrations often rise after transplant nephrectomy. While this may be due to the graft having acted as an ‘antibody sink’ with the rise in serum anti-HLA antibody occurring after nephrectomy without any change in antibody production (4,5), it is more likely to be a consequence of the withdrawal of immunosuppression. Some data suggest new antibody formation for up to six weeks after nephrectomy (6).

In the absence of a clear evidence base, we recommend that all immunosuppression apart from steroid be stopped immediately after transplant nephrectomy, with gradual steroid withdrawal as outlined below.

#### **4.3 Immunosuppression management with failed transplant left *in situ***

If the transplant is left *in situ*, there are arguments for and against continuing some immunosuppression, with no good trial data to guide practice. Ongoing immunosuppression can preserve residual renal function which may make a continuing contribution to dialysis adequacy and water elimination, in particular for patients on peritoneal dialysis (7). Continued immunosuppression may reduce the chronic inflammatory stimulus of the graft and therefore reduce epoetin resistance and general morbidity. The risk of HLA-sensitisation outlined above should also be taken into consideration. However, these factors are balanced by the myelotoxicity of some immunosuppressive agents that may contribute to epoetin resistance. Patients also continue to accrue the generic risks of immunosuppressive treatment, most importantly malignancy and infection.

A reasonable approach is to minimise the risk of immunological sensitisation by continuing immunosuppressive therapy if a living kidney donor is available and there is the prospect of retransplantation pre-emptively or within one year of starting dialysis. If a longer period is anticipated before repeat transplantation, the risk:benefit ratio of gradual immunosuppression withdrawal may favour withdrawal of treatment and should be considered on an individual basis. This is particularly the case when there have been immunosuppression-related complications such as skin cancer or dyslipidaemia. (2C)

#### **4.4 Approach to withdrawal of immunosuppression**

A staged approach to immunosuppressive withdrawal is probably safest. Anti-proliferative agents (azathioprine, mycophenolate) can be stopped immediately, followed by gradual taper of the CNI or mTOR inhibitor. There are no published data on the optimum rate of taper. One approach is to reduce the dose by 25% per week until withdrawn. Steroids should be the last component to be withdrawn. In order to avoid problems due to hypoadrenalinism, prednisolone should not be withdrawn faster than 1 mg per month once the dose is below 5 mg daily. In the event of clinical manifestations of adrenal insufficiency such as hypotension or hypoglycaemia, it is appropriate to reintroduce steroids at the previous dose and to attempt a slower steroid taper.

Severe acute rejection with manifestations such as a painful, tender graft, fever, haematuria, raised inflammatory markers and thrombocytopenia is a recognised complication of

immunosuppression withdrawal. In this event, steroid therapy should be immediately re-instituted, followed by transplant nephrectomy when the acute inflammation has settled.

#### **4.5 HLA-specific antibody screening**

Recipients with a failing kidney transplant are at high risk of developing *de-novo* sensitisation. This is particularly the case after starting dialysis or re-listing for transplantation, when immunosuppression is commonly changed, reduced or withdrawn.

For patients that are re-listed, the clinical team should notify the histocompatibility laboratory of any such events and send serum samples for HLA-specific antibody screening at four weeks after all significant changes in immunosuppression. Antibody screening after graft failure and on return to the transplant waiting list should be undertaken according to the BTS/BSHI Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Solid Organ Transplantation [8].

Depending on the HLA-specific antibody status of the patient at the time of first antibody screening assessment, the clinical benefits and risks associated with immunosuppression tapering/withdrawal must be considered, taking account of future options for repeat transplantation. If a patient is already sensitised and has high levels of broadly reactive antibodies at the time of graft failure, the risk of additional sensitisation occurring subsequent to changes in immunosuppression is low. If, however, a patient has received a previous HLA mismatched transplant and is non-sensitised or has low antibody levels, tapering and/or immunosuppression withdrawal is likely to result in the patient becoming highly sensitised.

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## **5 CARDIOVASCULAR & OTHER RISK FACTOR MANAGEMENT**

### **Statements of Recommendation**

*We recommend that:*

- Smoking be actively discouraged in RFKTs. (1B)
- RFKTs be vaccinated with inactivated viruses as per the normal population, except for HBV. (1D)
- RFKTs receive annual influenza vaccination unless contraindicated. (1C)
- RFKTs are thoroughly assessed for the cause of their graft failure and counselled appropriately regarding future transplantation. (1D)

*We suggest that:*

- Blood pressure be recorded at each clinic visit and maintained <130/80 mmHg (125/75 mmHg if PCR >50 or ACR >35 mg/mmol). (2C)
- There is no evidence to support the use of any particular antihypertensive agent. The focus is to achieve absolute blood pressure targets rather than the use of individual agents. (2D)
- Inhibitors of the renin-angiotensin system may be more effective in reducing proteinuria but may worsen anaemia. (2C)
- Resistant hypertension is often due to salt and water retention and should be addressed by dietary measures and the use of diuretics. (2D)
- Treatment of dyslipidaemia in RFKTs is the same as treatment in KTRs. Pravastatin and fluvastatin are preferred statins. Fibrates are contraindicated. (2C)
- Nicotinic acid compounds and ezetimibe may be safely used in RFKTs. (2B)
- Low level consumption of alcohol is safe in RFKTs. (2D)
- Control of diabetes can be erratic as renal function deteriorates and is improved by monitoring in specialist clinics. (2C)
- RFKTs be counselled regarding diet, weight loss and exercise. (2D)
- Anaemia is common and can be treated according to existing guidelines. (2C)
- RFKTs have their skin examined at 1-3 yearly intervals by a trained healthcare professional. (2C)
- Sirolimus may be considered in RFKTs with previous squamous cell carcinoma. (2B)

- Acitretin can be safely used in RFKTs. (2B)
- There is no evidence to support aggressive immunosuppression in RFKTs with late recurrent disease. (2D)
- RFKT have HBsAb levels rechecked annually and be revaccinated if antibody titres fall below 10 U/mL (2D); do not receive live attenuated vaccines (2C); and receive pneumococcal vaccine and one booster after five years. (2D)

## 5.1 Introduction

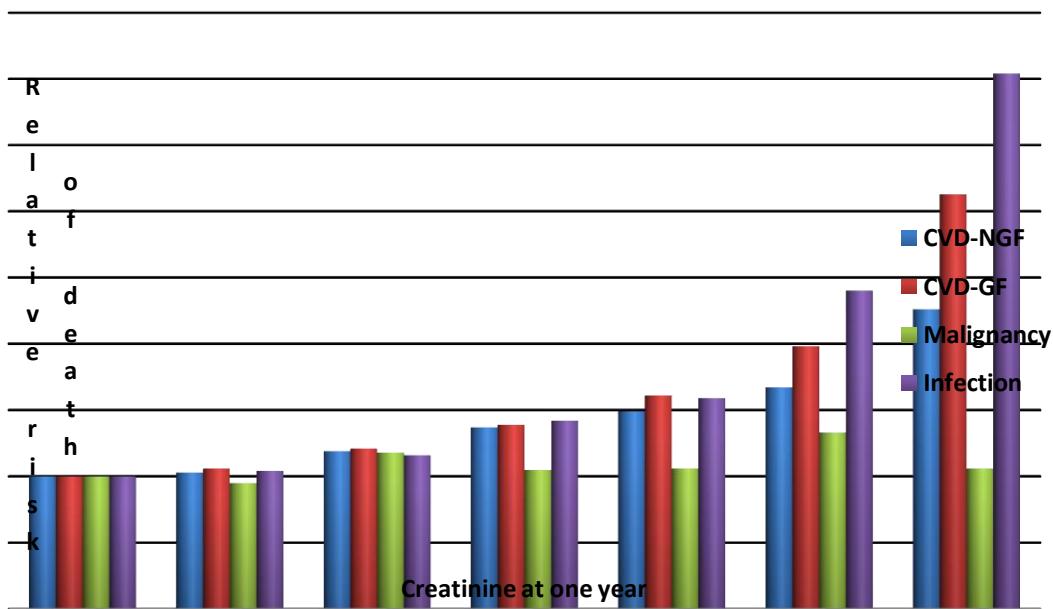
It is clear that poor allograft function is associated with an increased risk of death that escalates as the need for dialysis approaches. This risk mainly results from higher rates of cardiovascular and infective death. The period around the resumption of dialysis can be considered particularly high risk (1).

Returning to dialysis after graft failure is an especially hazardous time with mortality rates greater than those of patients with poorly functioning allografts (2). Data from the United States suggest that such patients have a one year mortality of 16% and a three year mortality of 33% (3) (see chapter 8).

Given that the three major causes of death in KTRs are vascular disease, infection and neoplasia, the question arises whether there is anything different about KTRs with poorly functioning grafts. This was addressed in a large US database of nearly 60,000 transplant recipients who were assessed at 12 months after grafting (figure 5.1) (4).

This study showed that while the overall death rate was markedly increased, the risk of death from malignancy was relatively unaffected by poor graft function. Instead, the increased death rate was largely accounted for by significant increases in mortality from vascular disease and infection. This correlation between low eGFR and high rates of cardiovascular disease has been confirmed in another large study (5). Indeed, recent evidence has suggested that renal function may be the strongest independent determinant of cardiovascular risk in KTRs (6). In this study, once the eGFR dropped below 45 mL/min/1.73m<sup>2</sup>, each 5 mL/min/1.73m<sup>2</sup> drop in eGFR conferred a 15% increase in both death rate and the incidence of cardiovascular disease. Of note, this suggests that absolute transplant function may be more important than pre-existing comorbidity.

**Figure 5.1** Relative risk of death stratified by serum creatinine concentration at 12 months.



CVD-NGF = cardiovascular death with graft failed by 12 months; CVD-GF = cardiovascular death with functioning graft.

There is evidence that KTRs with poor graft function receive suboptimal care when compared with patients with native renal disease (7). As a result of these findings a number of centres have set up specialist transplant low clearance services. Although the resource implications are large, this is an attractive model of care since KTRs are often resistant to rejoining the routine low clearance service, and such specialist clinics will retain the services of transplant-orientated clinicians.

Guidelines for the management of patients with failing grafts are inevitably similar to those for general KTRs which have been published previously (8,9). The recommendations below should be read in conjunction with these existing guidelines, but will focus on areas with special relevance to RFKTS, usually defined as having CKD 4T or CKD 5T.

## 5.2 Blood pressure

There is a strong correlation between blood pressure control and outcome after kidney transplantation (10-12). There is some evidence that improving blood pressure control may be

associated with better outcomes (13). However, there are no prospective randomized controlled trials demonstrating that intervention is of value.

Poor allograft function is closely associated with hypertension (14). Given that death rates due to cardiovascular disease are much higher in the CKD4T and 5T populations and that blood pressure is one of the major risk factors for cardiovascular disease, it seems sensible to target blood pressure aggressively in this population. Blood pressure should be recorded at each clinic visit, and the clinic blood pressure be maintained at <130/80 mmHg (<125/75 mmHg if urine PCR >50 or ACR >35 mg/mmol).

The main determinant of benefit of blood pressure control is probably the achieved blood pressure rather than the agent chosen. There is no evidence to suggest that blood pressure treatment should be any different in KTRs with lower eGFRs, although treatment regimens incorporating the use of diuretics make sense given the increase in salt and water retention with deteriorating graft function.

As with other KTRs, drug treatment should be tailored to the individual and side effect profiles. Care should be exercised with drugs that have potassium-retaining properties. In particular, inhibitors of the renin-angiotensin system may be more effective in reducing proteinuria but may worsen anaemia in RFKTS.

### **5.3 Lipids**

The causes of post transplantation dyslipidaemia are multi-factorial and include (15):

- immunosuppressive medication e.g. steroids, CNIs, and mTOR inhibitors
- diabetes
- genetic predisposition
- obesity
- diet
- alcohol intake
- hypothyroidism
- nephrotic syndrome
- other medication

Epidemiological studies have shown that hypercholesterolaemia is a risk factor for cardiovascular disease after transplantation (16). However, there are no data on the effects of

statins specifically in the RFKT population and there is little evidence upon which to base treatment decisions (17). The major randomized controlled trial of the treatment of hypercholesterolaemia with fluvastatin in KTRs showed no significant benefit in the primary composite vascular outcome, although there were significant benefits in some secondary cardiovascular outcomes (18). An extension of the original study demonstrated a 21% reduction in cardiac events but no effects on graft survival (19). Recent trial evidence has also shown some benefits in statin-induced lipid lowering in patients with CKD and meta-analysis of the available data suggests that statins are beneficial in patients with CKD, but that the benefit wanes as function declines (20-22).

Studies suggest that the uptake of medication is relatively low and registry data suggest poor lipid control in the UK KTR population (23,24). Guidelines have cited higher adverse effect rates with the use of statins in patients with decreased renal function, although meta-analyses do not substantiate this assertion (15,21,22,25). Statins interact with drugs that are also metabolized by the CYP3A4/A5 pathway such as tacrolimus, ciclosporin and sirolimus. This usually results in elevated blood concentrations of the statins and appears to be more problematic with simvastatin and atorvastatin. Simvastatin is probably best avoided since it should not be used with ciclosporin and is limited to a maximum dose of 20 mg daily when co-administered with either diltiazem or amlodipine (26).

Drugs that are not extensively metabolized by CYP3A are less toxic i.e. fluvastatin and pravastatin. There is some evidence that rosuvastatin may be associated with adverse renal events at high doses and its use should probably be restricted to low doses in RFKTs (27). The combination of a statin and a fibrate is associated with significantly increased morbidity and should be avoided in RFKTs (28). Fibrates alone also have significant toxicity in patients with eGFR <30 mL/min/1.73m<sup>2</sup> and are therefore not recommended in RFKTs (29).

Ezetimibe is safe to use in RFKTs although the benefits of therapy are uncertain beyond simply lowering cholesterol concentrations. Nicotinic acid may safely be used to treat hypertriglyceridaemia although reduced doses of short acting preparations are recommended. Extended release preparations appear to be safe in patients with advanced CKD and so can be used in RFKTs (29).

On balance, given the absence of evidence to the contrary, dyslipidaemia in RFKTs should be treated according to existing target levels for KTRs. RFKTs with dyslipidaemia should be counselled regarding diet, weight loss, alcohol intake and the use of exercise.

An example of a typical treatment regimen is shown below (table 5.1).

**Table 5.1 Typical treatment regimen for dyslipidaemia in CKD5T**

Lipid abnormality	Definition	Conservative treatment	Drug treatment
Hypertriglyceridaemia	TG >5.65 mmol/L	Diet, exercise, weight loss	Ezetimibe, nicotinic acid
Raised LDL	LDL >2.59 mmol/L	Diet, exercise, weight loss	Statin, ezetimibe
Low HDL	HDL <1.03 mmol/L	Diet, exercise, weight loss	Statin
Total cholesterol	Chol >5.0 mmol/L in primary prevention, (>4.0 mmol/L in secondary prevention)	Diet, exercise, weight loss	Statin, ezetimibe

#### **5.4 Glucose**

Hyperglycaemia should be managed according to standard guidelines, but certain principles need to be highlighted in transplant patients with a low eGFR. As renal function declines, insulin requirement may vary due to insulin resistance and altered proximal tubular metabolism. Although insulin requirements usually fall, the outcome of these conflicting influences is not always predictable and diabetic KTRs should be monitored closely, usually under specialist supervision.

The use of some oral hypoglycaemic drugs is contraindicated and declining kidney function may therefore require the alteration of medication. There is particular confusion regarding metformin, which is a particularly useful agent with positive impacts on weight gain and mortality, as well as upon glycaemia. Although the British National Formulary recommends that metformin is stopped when eGFR falls <30 mL/min or serum creatinine rises >150 µmol/L, the evidence base for this is very weak and there are few data to support withdrawal at any particular level of function (30-

32). In practice, given the lack of proven alternatives, it seems appropriate to use metformin until renal function drops below 20 mL/min/1.73m<sup>2</sup>.

Recommendations for other hypoglycaemic agents based on other publications (8,33) include (table 5.2):

**Table 5.2 Hypoglycemic drug use in CKD5T**

Class	Drug	Dose by eGFR	Interactions
2 <sup>nd</sup> generation sulphonylurea	Gliclazide, glipizide, glimepiride	Normal	↑ CsA
Alpha-glucosidase inhibitor	Acarbose	Avoid if eGFR <30 mL/min	
Biguanide	Metformin	Caution if eGFR <30 mL/min; avoid if <20mL/min	
Meglitinide	Repaglinide, mitiglinide	Start at low doses	↑ Repaglinide levels with CsA
Thiazolidinedione	Pioglitazone	Normal	
Incretin mimetic	Exenatide	Avoid if eGFR <30 mL/min	
	Liraglutide	Normal	
Amylin analogue	Pramlintide	Avoid if eGFR <20 mL/min	
DDP-4 inhibitor	Sitagliptin	↓ 50% if eGFR <50 mL/min ↓ 75% if eGFR <30 mL/min	
	Vildagliptin	Start at low dose	

## **5.5 Lifestyle modification**

Healthy lifestyle measures are recommended in RFKTs, although energy levels may be reduced as function deteriorates. Regular exercise has been shown to achieve weight loss, reduce blood pressure and also improve glucose tolerance (34). Low physical activity is linked to both cardiac and all cause mortality after transplantation, although there are no prospective data that demonstrate improved outcomes with increased exercise (35).

It seems sensible to encourage moderate exercise in RFKTs. A low salt diet will also help control blood pressure and may become more important with deteriorating function and increasing salt and water retention. Regular dietetic review is important to ensure adequate calorie and protein intake while minimizing the risk of sodium, potassium and phosphate retention, and maintenance of a healthy weight. Low level alcohol consumption is associated with good outcomes and there is no need to prohibit alcohol consumption (36).

## **5.6 Smoking**

There is unequivocal evidence that smoking adversely affects outcomes in kidney transplantation (37-40). RFKTs should strongly be encouraged to stop smoking and ready access to smoking cessation services should be available. Both bupropion and varenicline may be prescribed, although low doses should be used if renal function is significantly reduced (eGFR <30 mL/min/1.73m<sup>2</sup>).

## **5.7 Anaemia**

Anaemia is common in the KTR population and may be associated with poor outcome (41). It is commoner in RFKTs and may be exacerbated by immunosuppressant therapy, especially anti-proliferative agents and sirolimus. Management should be similar to other patients with CKD, but studies consistently show poor control in KTRs (41-43).

## **5.8 Skin disease**

Benign skin disease is very common after transplantation and a recent UK study of 308 adult KTRs at a mean of 10.7 years post transplantation recorded the following incidence (44):

- seborrhoeic warts 55%
- viral warts 38%
- skin tags 33%
- folliculitis 27%
- fungal infection 18%
- seborrhoeic dermatitis 9.5%

These lesions may cause considerable morbidity and also may affect adherence to medication. In KTRs with poor graft function it is recommended that regular skin examination takes place (usually 1-3 yearly according to skin type, history of skin disease and severity of immunosuppression), and that immunosuppression is reviewed regularly. The role of HPV vaccination is unclear, but as it is an inactivated vaccine it could be administered safely either before or after transplantation.

Skin neoplasia are more common in KTRs due to impaired immuno surveillance. KTRs with skin neoplasia have worse outcomes than members of the general population. Preventative strategies are therefore paramount. These include screening and the minimisation or modification of immunosuppressive therapy. Certain patient groups are at higher risk of non-melanoma skin cancer, particularly the fair-skinned who are living in a sunny climate. Other risk factors include occupation, behaviour, previous skin cancer, childhood sun exposure and family history. It is sensible to minimise exposure and use high factor sun block.

Acitretin (0.2-0.4 mg/kg/day) may prevent recurrence in those with previous skin cancer and can be used safely in patients with a low eGFR (45). Registry data suggest that mTOR inhibitors may be associated with fewer non-melanoma skin cancers (NMSCs), particularly cutaneous Kaposi's sarcoma (46). Recent studies have suggested that switching KTRs with previous cutaneous squamous cell carcinomas to sirolimus is beneficial when compared to continued CNI-based therapy (47-49). However, this should be counterbalanced by the increase in adverse effects seen in KTRs with eGFR <40 mL/min/1.73m<sup>2</sup> or with significant proteinuria who switch to sirolimus (50). There is limited evidence that mycophenolic acid compounds may be less likely to cause NMSC than azathioprine (51).

## **5.9 Vaccination**

Inactivated vaccines can be safely used in KTRs, but live attenuated vaccines should be avoided because of the small risk associated with immunosuppression (see table 5.3). There is no link between vaccination and rejection.

**Table 5.3 Vaccination in kidney transplant recipients**

<b>Inactivated Vaccines</b>	<b>Live Attenuated Vaccines</b>
Inactivated influenza	Measles
Hepatitis A	Mumps
Hepatitis B	Rubella
Inactivated polio	Varicella
Diphtheria	BCG
Tetanus	Smallpox
Pneumococcal	Yellow fever
Meningococcal	Oral salmonella
Human papilloma virus	Oral polio
Rabies	
Anthrax	
Intramuscular salmonella	
Japanese encephalitis	
Inactivated intravenous cholera vaccine	

Patients with failed kidney transplants have impaired responses to vaccines and serological evidence of conversion should be sought where possible (e.g. HBsAb levels) (52). All vaccination should ideally be carried out before transplantation, but in reality many RFKTS will require vaccination either for diseases that require recurrent immunization (e.g. influenza) or because they were never previously vaccinated.

RFKTs should receive annual influenza vaccination unless contraindicated and pneumococcal vaccine plus one booster after five years.

It is recommended that RFKTs are vaccinated for HBV prior to restarting dialysis, although their response may be suboptimal in the face of immunosuppression. Vaccination for HBV is administered at double the usual dose and accelerated schedules should not be used as seroconversion is likely to be low. If the primary course is not successful then one further course should be tried before abandoning the process (53).

## **5.10 Management of recurrent/*de novo* glomerular disease**

A distinction must be made between histological recurrence on biopsy and graft failure due to recurrent disease. In most glomerular diseases, histological recurrence is quite common, but is rarely associated with graft loss. The best data, from Australia and New Zealand, recorded the rate of graft loss after 10 years due to recurrent disease as (54):

- |   |       |
|---|-------|
| • mesangiocapillary glomerulonephritis type I | 14.4% |
| • focal segmental glomerulosclerosis          | 12.7% |
| • membranous nephropathy                      | 12.5% |
| • IgA nephropathy                             | 9.7%  |
| • pauci-immune crescentic glomerulonephritis  | 7.7%  |
| • other types                                 | 3.1%  |

Other important recurrent diseases include diabetic nephropathy, primary oxalosis, haemolytic uraemic syndrome and Fabry disease. Thorough evaluation of failing allografts suggests that approximately 22.6% of graft failures are lost due to recurrent (16%) or *de novo* glomerular disease (6.6%) (55). Excellent guidelines on the management of native glomerular disease have recently been published (56).

Recurrent disease will usually be diagnosed by a renal biopsy, usually performed for deterioration in eGFR or proteinuria. Treatment of early recurrent disease will not be covered here and the reader is referred to several excellent reviews (57-59).

There are few good data to guide the treatment of late recurrent disease, and virtually no data on recurrence when eGFR is <30 mL/min/1.73m<sup>2</sup>. Unless the deterioration has happened acutely and the biopsy shows a great deal of acute inflammation with little interstitial fibrosis and tubular atrophy, there is no evidence to support the disease-specific treatment of late disease

recurrence. Management involves attention to conservative measures, in particular blood pressure control and anti-proteinuric therapy.

Patients must be counselled regarding the risk of recurrence in a subsequent transplant. There is some evidence that antibody titres can be used to predict relapse in patients with membranous nephropathy who have anti-PLA<sub>2</sub>R1 antibodies, although this requires confirmation (60,61). For patients with recurrent FSGS, retransplantation strategies may include prophylactic treatment with rituximab or plasma exchange (62). Another group of patients who may benefit from pre-emptive strategies are those with recurrent disease due to complement disorders (C3 nephropathy, dense deposit disease and atypical haemolytic uraemic syndrome) since they may benefit from prophylactic inhibition of complement e.g. eculizumab (63).

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## **6 SURGICAL ISSUES IN THE MANAGEMENT OF THE FAILING RENAL TRANSPLANT**

### **Statements of Recommendation**

- Widely accepted indications for graft nephrectomy include:
    - localising symptoms (pain, infection, bleeding) that are resistant to medical therapy in a failed graft
    - to create space for retransplantation
    - to enable complete withdrawal of immunosuppression
    - risk of graft rupture
    - graft malignancy
    - refractory anaemia with raised CRP
- (Not graded)

*We suggest that:*

- In the absence of prospective data, decisions on whether to remove a failed or failing graft be made on perceived benefits and risks and on a case-by-case basis. (2B)
- The surgical technique used for graft nephrectomy is dependent on timing post-transplantation and operator preference. There is no compelling evidence favouring either the intracapsular or extracapsular approach in the late phase post-transplantation. (2C)
- The role of percutaneous embolisation of the failing or failed renal allograft is uncertain. At present, it is reserved for patients at high operative risk where malignancy is not a consideration. (2D)
- Data on outcomes after graft nephrectomy in the paediatric group are limited. Local and regional specialist opinion should be followed. (2D)

## **6.1 Introduction**

Removal of a renal transplant (graft nephrectomy) is commonly performed in patients who return to dialysis after kidney transplantation. In an analysis of almost 20,000 adult renal transplant recipients re-starting dialysis in the US, nearly a third had undergone transplant nephrectomy (1). This chapter summarises the existing evidence on when the operation should be performed, the surgical techniques available, expected post-operative outcomes, and non-surgical means of devascularising a transplanted kidney. In general, the available evidence is weak, consisting predominantly of small retrospective case-series. Where larger retrospective analyses are available, they often span multiple eras of immunosuppression, making interpretation difficult.

## **6.2 Indications for graft nephrectomy**

Unlike many other solid organ transplants, the presence of alternative forms of renal replacement therapy means that renal allograft failure rarely leads directly to patient death. As a result, leaving a failing or failed renal allograft *in situ* may be a reasonable long-term option. Because of the absence of prospective data on the best approach to managing the patient with a failed renal allograft, decisions on whether to remove the graft should be made on perceived benefits and risks on a case-by-case basis.

The benefits of leaving a failed or failing renal allograft *in situ* include residual graft function (urine and hormone production), the avoidance of the morbidity and mortality associated with graft nephrectomy, and the possible immunogenic stimulus of graft removal. The risks include the possible need for ongoing immunosuppression (and the side-effects associated with this); the potential for the graft to act as a focus of infection, malignant transformation, or as a persistent nidus of immunoreactivity; and persistent localising symptoms such as graft pain and haematuria.

Current widely accepted indications for allograft nephrectomy include:

- Patients with pre-existing graft failure or poor graft function who have significant localising symptoms consistent with an alloimmune response (e.g. graft pain, haematuria) that fail to settle with a period of increased immunosuppression. Other causes for these symptoms should be excluded by urine culture, imaging, and/or cystoscopy.

- Patients with recurrent or severe graft pyelonephritis that fails to improve with appropriate antibiotic therapy.
- To create space in an iliac fossa for retransplantation where the contralateral iliac fossa is unavailable.
- Emergency graft nephrectomy where there is a significant risk of graft rupture, e.g. renal vein thrombosis or severe acute rejection resistant to immunosuppressive therapy.
- To enable complete withdrawal of immunosuppression when significant infective or malignant conditions are resistant to other treatments, e.g. post-transplant lymphoproliferative disease refractory to standard therapy (2), or BK virus nephropathy refractory to reduced immunosuppression and antiviral therapy (3,4).
- Graft malignancy that is not amenable to other forms of therapy, e.g. partial nephrectomy, radiofrequency ablation, cryotherapy (5).
- Early renal arterial thrombosis. This is an uncommon complication after transplantation, and failed thrombectomy or prolonged graft ischaemia may prompt graft nephrectomy.
- Patients with renal failure and non-specific systemic symptoms with raised inflammatory markers and epoetin resistance may also benefit from graft nephrectomy (6,7).

### **6.3 Surgical technique**

After extraperitoneal kidney transplantation, the capsule of the allograft becomes progressively adherent to surrounding soft tissues and peritoneum. When a renal allograft requires removal within 3-6 weeks of implantation, it is usually possible to remove the kidney, its vessels, ureter and capsule in their entirety (extracapsular technique). Early after transplantation, an extracapsular technique is preferred. After this point, the plane between the capsule and the peritoneum becomes lost and the renal hilum is difficult to identify, though it is still possible to remove the allograft by separating the renal parenchyma from the capsule (intracapsular technique) (8).

Late post-transplantation, an extracapsular technique can be used by dissecting the capsule off the peritoneum and excising the vessels and the ureter separately. Extracapsular graft nephrectomy has theoretical advantages over the intracapsular technique as a greater volume of allergenic material is removed. However, complete removal of donor tissue is likely to

require placement of recipient vein patches at sites of vascular anastomosis, adding significantly to the complexity and potential morbidity of the surgery.

No prospective trials have been performed comparing the two approaches and retrospective data are limited in the modern era of immunosuppression. Touma *et al* retrospectively compared the post-operative outcomes of 67 graft nephrectomies performed more than a month post-transplantation (44 extracapsular and 23 intracapsular) (9). The changes in percentage panel reactive antibody (PRA) levels were very similar between the two groups, though post-nephrectomy immunosuppression was not described and the authors did not state if their extracapsular technique included removal of all allergenic material and placement of vein patches. Estimated blood loss was higher with the extracapsular technique (483 mL vs 226 mL;  $p<0.05$ ), but there was no difference in morbidity.

Although other studies have compared outcomes after graft nephrectomy using the two techniques, these papers combined early and late graft nephrectomy (10,11). This approach makes a meaningful comparison difficult as the indications for surgery, intra-operative blood loss and post-operative morbidities may vary with the time after transplantation.

In later phases, there is no strong evidence favouring either technique. Whichever technique is used, careful surgery with meticulous haemostasis is essential.

## **6.4 Post-operative outcomes**

As with all operations, post-operative morbidity and mortality are important benchmarks by which to judge the degree of physiological stress placed upon the patient. The impact of graft nephrectomy can also be determined by assessing changes in the allosensitisation status, and whether surgery has an adverse effect on the function of subsequent renal transplants.

### **6.4.1 Surgical morbidity and mortality**

Graft nephrectomy has traditionally been thought to be associated with significant morbidity and mortality, with retrospective case series from previous eras showing post-operative mortality of up to 39% (7). Recent registry analyses have provided more reliable mortality estimates.

Johnston *et al* examined outcomes in 6213 patients undergoing graft nephrectomy in the US between 1995 and 2003 (1). One percent of patients died during their hospital admission, and

approximately 5% of patients died within 90 days of surgery. Death was more common in patients undergoing nephrectomy for graft failure within a year of transplantation, presumably because of the heavier immunosuppressive burden during this period. A further US registry analysis showed a 30-day mortality rate of 1.5% after allograft nephrectomy (12). However, this study excluded patients whose renal allograft failed within 90 days of transplantation.

The morbidity after graft nephrectomy is more difficult to quantify, as retrospective coding of post-operative complications is highly subjective. As yet, no study has used an objective, standardised, validated complication classification tool (13). Within 90 days of admission for graft nephrectomy, sepsis occurs in 6-10% of patients and congestive heart failure in 7% (1). Small retrospective case series describe complication rates between 10-50% (10,14,15), with median blood loss between 200 and 500 mL (9,10). Major vascular complications have been reported to occur in 5%, including severe haemorrhage requiring ligation of the external iliac artery (16).

#### **6.4.2 Allosensitisation and subsequent graft outcomes**

One of the postulated benefits of graft nephrectomy is to remove the source of alloantigen and therefore diminish subsequent sensitisation. In addition, the presence of residual donor tissue post-nephrectomy (e.g. at the vascular or ureteric anastomoses) may stimulate an alloimmune response when immunosuppression is weaned. Alternatively, leaving a failed kidney transplant *in situ* may enable the graft to act as a ‘sponge’ for alloantibody and minimise serum alloantibody levels (17).

Studies that have attempted to define the impact of graft nephrectomy on alloantibody responses have been observational and have compared patients undergoing nephrectomy with those with grafts left *in situ*. It is therefore difficult to distinguish between the relative effects of the process leading to the need for graft nephrectomy, and the surgery itself (and associated blood transfusions). In addition, weaning of immunosuppression after graft failure has been shown to be associated with allosensitisation, independent of graft nephrectomy (18). As yet, no randomised studies have been performed to control for these confounding factors.

Given the flaws in retrospective analyses, it is unsurprising that findings have been inconsistent. Schleicher *et al* examined 166 patients undergoing retransplantation, 121 of whom had undergone previous graft nephrectomy (19). Sensitisation to human leucocyte antigens (HLA) was greater prior to retransplantation in the nephrectomy group, though sensitisation data were

not present before the initial transplant and the graft nephrectomy. In a registry analysis of 3,496 transplant failure patients who underwent repeat transplantation, sensitisation to HLA prior to retransplantation was higher in those who had undergone graft nephrectomy, but only in those with PRA levels <30% before their first transplant (1). In contrast, smaller retrospective case series have found no association between graft nephrectomy and allosensitisation (14, 20).

All of these studies used PRA as a marker of allosensitisation. However, the ability to identify donor specific antibody (DSA) provides a more relevant marker of the alloimmune response after transplantation. The development of solid phase assays has enabled more accurate characterisation of anti-HLA antibodies. Using the Luminex® single antigen assay, Del Bello *et al* examined DSA production in 69 patients who had renal allograft failure (21). All patients had undergone withdrawal of immunosuppression, allowing an analysis of the impact of graft nephrectomy on DSA independent of this potential confounding factor. Steroids were stopped six months after starting dialysis. At graft loss, the proportion of patients with DSA was similar in those who had subsequent graft nephrectomy (n=48) and those who did not (n=21). Patients undergoing allograft nephrectomy were more likely to develop post-operative DSA than those with grafts left *in situ*. At last follow-up, nephrectomised patients were more likely to have DSA (81% vs 52%; p=0.02). Previous studies have similarly suggested that graft nephrectomy can reveal or stimulate DSA production (22,23), even when performed within days post-transplantation (24).

Although it appears that graft nephrectomy may be associated with higher levels of DSA, a large US registry analysis showed that dialysis patients with a failed first kidney transplant that had been removed were more than twice as likely to receive a second transplant as those who had not undergone graft nephrectomy (12). Moreover, graft nephrectomy was associated with a 32% reduction in the relative rate of death after adjusting for socio-demographic factors, co-morbidity, donor characteristics, and other potential confounders.

After graft loss within 12 months of transplantation, graft nephrectomy is associated with a decreased risk of second graft failure (1). This protective effect appears to be due to reduction in death with a functioning graft. However, if graft loss and subsequent nephrectomy occur after 12 months, the risk of repeat transplant failure is increased, even after censoring for death with a functioning graft.

## **6.5 Non-surgical devascularisation techniques**

Devascularisation of a renal allograft is usually achieved surgically, but can also be accomplished by embolising the graft via percutaneous puncture of the femoral artery (25). A variety of different materials have been used to induce graft thrombosis including ethanol, polyvinyl alcohol microspheres, stainless steel coils, and combinations of the above. Small, retrospective case series describing post-embolisation outcomes have been reported, but no prospective studies have been published comparing graft nephrectomy and the percutaneous approach.

Graft embolisation is minimally invasive and may avoid the need for prolonged post-operative recovery and the risk of requiring a blood transfusion. However, renal allografts present for long periods post-transplantation may develop a collateral blood supply and embolisation of the transplant renal artery may fail to render the graft ischaemic in 10-30% of cases (26-28). Other possible complications of graft embolisation include abscess formation in the graft, migration of embolisation coils into the distal circulation, puncture site complications, and the ‘post-embolisation syndrome’ (fever, pain, malaise, haematuria, and graft swelling). This has been reported to occur in up to 60% of patients (26,28). In addition, this technique fails to provide complete graft histology. The impact of embolisation on development of DSA has not been reported.

Embolisation followed by immediate graft nephrectomy has been described in a retrospective analysis of 13 cases (29). This approach may enable lower intra-operative blood loss and reduce transfusion requirements, but prospective studies have not been reported.

In summary, the role of embolisation in the management of the failing or failed renal allograft has not yet been determined. Embolisation may have a place in patients at high operative risk, but post-embolisation complications are common. Patients at high risk of intra-operative bleeding who require graft nephrectomy may be suitable for embolisation followed by immediate open surgery. Where there is a suspicion of graft malignancy, embolisation alone is not appropriate.

## **6.6 Graft nephrectomy in the paediatric transplant population**

The effective management of failed renal allografts is especially important in the paediatric population due to the need to minimise long-term allosensitisation and reduce morbidity and mortality. Unfortunately, data are particularly sparse on outcomes after graft failure in the

paediatric group with little or no information on the impact of graft nephrectomy on sensitisation, rates of subsequent retransplantation, or later graft survival. Both surgical and percutaneous approaches to graft devascularisation have been advocated (30,31). Zerouali *et al* performed graft nephrectomy on 53 of 63 children with failed kidney transplants (30). Complications occurred in 38% of patients, but all patients had symptom resolution. In contrast, an analysis of eleven children with graft failure found that open surgery was necessary in just two patients (31). Percutaneous embolisation was used to treat seven children, and medical therapy with high-dose prednisolone (1-2 mg/kg/day) and indomethacin was used successfully in three.

Insufficient data are available to recommend a specific strategy in the paediatric population, and local opinion and expertise should be followed.

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## **7 PATIENT EDUCATION AND OPTIONS FOR RENAL REPLACEMENT THERAPY**

### **Statements of Recommendation**

*We recommend that:*

- While there are some important transplant-specific issues, the decision making process and management of end-stage kidney disease are largely the same as for patients with chronic kidney disease and are covered by the Renal Association guideline ‘Planning, Initiating and Withdrawal of Renal Replacement Therapy’. (1C)
- Pre-emptive retransplantation in suitable candidates is the best option for ongoing renal replacement therapy, and should ideally occur when eGFR is 10-15 mL/min. (1D)
- If the patient is returning to a local centre for dialysis or conservative care, the transfer of care be completed in time (at least 6 months before graft failure) to ensure that patients are adequately prepared. (1D)
- Appropriately skilled psychological support be made available to patients with failing transplants, with ongoing support on return to dialysis or conservative management.
- Patients with squamous cell carcinoma have all current lesions resected prior to retransplantation and be clear of metastatic disease. However there is no requirement to wait for a disease-free interval prior to retransplantation. (1C)
- Patients with graft loss due to BK nephropathy be considered for retransplantation, but preferably avoiding highly potent immunosuppressive regimens. (1C)
- Potential non-concordance is not an absolute contraindication to retransplantation. However, there will clearly be cases where the clinical team assesses the risk of non-concordance to be unacceptably high. (1D)

### **7.1 General principles**

While there are some important transplant-specific issues, the decision-making process and the management of end-stage renal failure in the context of the failing graft are largely the same as for patients with chronic kidney disease and are covered by the Renal Association guideline ‘Planning, Initiating and Withdrawal of Renal Replacement Therapy’ (1).

Key recommendations of this guideline that apply to transplant recipients with a failing graft are:

- Patients should have access to a dedicated clinic staffed by a multidisciplinary team. (1B)
- Patients with an eGFR <20 mL/min/1.73m<sup>2</sup> and declining should receive timely and personalised information regarding established kidney failure and renal replacement therapy options so they can make an informed decision about future treatment. (1B)
- Patients with severe CKD (stage 5 and progressive stage 4), together with their families and carers, should be offered an appropriate education programme aimed at improving their knowledge and understanding of their condition, and of the options for treatment. (1B)
- Unless for conservative management, patients with a failing transplant should start renal replacement therapy in a controlled manner, without the need for hospital admission and using an established access (arteriovenous fistula, arteriovenous graft, peritoneal dialysis catheter), or by pre-emptive renal transplantation. (1B)
- Consideration should be given to starting renal replacement therapy in patients with an eGFR <6 mL/min/1.73m<sup>2</sup>, even if the patient is asymptomatic. (2C)
- Patients with advanced kidney disease who are referred for conservative kidney management, and those patients who have imminent or immediate end-of-life care needs, should be identified and their care prioritised. (1C)
- Patients should wait for at least three months after nephrectomy before retransplantation. (2D)
- Suitable patients should be listed for deceased donor transplantation six months before the anticipated date of transplant failure. This usually equates to a GFR <15 mL/min and falling, aiming to transplant when the GFR is 10-15 mL/min. Preparation for living donor transplantation should be initiated at a GFR of 20 mL/min, aiming to transplant at between 10 and 15 mL/min.
- Unless there is a reason to suppose that the clinical course will be different after a subsequent transplant, recurrent primary renal disease within one year of transplantation is a relative contra-indication to retransplantation. (2C)

## **7.2 Timing and practical issues relating to return to advanced kidney care management**

In the UK, patients with advanced chronic kidney disease are usually managed in specialist multi-professional advanced kidney care (low clearance) clinics in line with the Renal Association guideline referenced above. However, this model has been less widely used for RFKTs despite their needs being broadly similar.

Where sufficient numbers and facilities exist, a dedicated clinic devoted to the RFKT and containing staff familiar with both transplantation and dialysis preparation is ideal. Failing this, a reasonable approach is for clinic visits to be alternated between staff and clinics with the appropriate expertise. Depending on the rate of change of graft function, the frequency of review may need to be adjusted to avoid the unplanned initiation of dialysis.

Patients are often followed up in a transplant centre which is geographically remote from their home and returned to a more local renal centre when close to starting dialysis. Transfer to a local centre should be completed in time (at least 6 months before graft failure) to ensure adequate preparation for a return to dialysis or for engagement with conservative care services.

## **7.3 Choice of renal replacement modality or conservative management**

### **7.3.1 Retransplantation**

The mortality following return to dialysis is higher than in patients starting renal replacement for the first time (3,4).

Most believe that pre-emptive retransplantation is the optimal option in suitable candidates. However, while pre-emptive retransplantation may result in better outcomes, there are few robust supporting data (5). Indeed, there is one report of an increased risk of transplant failure following pre-emptive retransplantation (6). On balance, however, the evidence suggests that pre-emptive retransplantation in suitable candidates is the best option for ongoing renal replacement therapy, both from the perspectives of quality of life and survival.

If living donor transplantation is an option, suitable living donors should be identified and assessed in a timely fashion. The optimal timing of retransplantation should be guided by the same principles as patients approaching ESRF with primary CKD. The Renal Association Guideline states: 'We recommend that all suitable patients should be listed for deceased donor

transplantation six months before the anticipated date of transplant failure' (1). In practice, this equates to a GFR <15 mL/min and falling, aiming to transplant when the GFR is between 10 and 15 mL/min.

Patients with very early graft failure and transplant nephrectomy need sufficient time to recover from the initial transplant surgery before retransplantation. Usual practice is to recommend that patients wait for at least three months after graft nephrectomy prior to retransplantation.

### **7.3.2 Contra-indications to retransplantation**

The contra-indications to retransplantation are largely the same as those for initial transplantation and are covered in the Renal Association guideline 'Assessment of the Potential Kidney Transplant Recipient' (2).

However, there are some issues that are specific to r-transplantation.

#### **Recurrent disease**

A number of systemic primary diseases recur following renal transplantation. As a general principle, recurrent disease in a first transplant makes further recurrence following retransplantation more likely. The most commonly encountered recurrent glomerular disease is focal segmental glomerulosclerosis with a reported incidence of up to 30% in primary transplants, increasing to nearly 100% in retransplants where there has been recurrence in the initial transplant (7,8).

The timing of recurrence in a first transplant may inform the likely prognosis following retransplantation. This is especially true where the initial cause of renal failure was not certain before transplantation.

Depending upon the primary disease, new treatments may have become available which would influence the chance of recurrent disease in a second graft. An example would be in atypical HUS. However, unless there is a reason to suppose that the clinical course will be different, recurrent primary renal disease within 1 year of transplantation is a relative contra-indication to retransplantation.

#### **Squamous cell carcinoma**

Squamous cell carcinoma (SCC) is a common problem in longstanding renal transplant recipients, with field change in the skin leading to the development of new cancers after initial

presentation. Around 50% of patients with at least one SCC will develop a further lesion within 12 months (9). Stipulation of a waiting time after removal of a SCC prior to transplantation is likely to debar many patients from transplantation with no proven benefit on prognosis.

Patients with SCC must have all current lesions resected prior to retransplantation and be clear of metastatic disease. However there is no requirement to wait for a disease-free interval prior to retransplantation.

### **Post-transplant lymphoproliferative disease (PTLD)**

There are small case series describing successful retransplantation in patients with PTLD (10,11). The joint guideline of the British Committee for Standards in Haematology and the British Transplantation Society recommends that patients with PTLD wait for at least one year after achieving disease remission prior to consideration of retransplantation (12).

### **Kaposi's sarcoma**

Kaposi's sarcoma often resolves on withdrawal of immunosuppressive therapy but the rate of recurrence after retransplantation is high (13). Regression on treatment with sirolimus provides the option for retransplantation with sirolimus as primary immunosuppressive therapy but outcomes using this approach are uncertain, as is the appropriate interval prior to retransplantation (14).

### **BK nephropathy**

BK nephropathy is an indicator of over-immunosuppression and does not constitute a contraindication to retransplantation. In one study, the recurrence rate of BK infection was lower in patients retransplanted after resolution of previous BK viraemia (15). Patients with graft loss due to BK nephropathy should be considered for retransplantation, but preferably avoiding highly potent immunosuppressive regimens.

### **Non-concordance**

Loss of one transplant through non-concordance with medication or medical advice is not a reliable predictor of concordance in subsequent transplantation, particularly in young children and adolescents. It follows that non-concordance should not be regarded as a contraindication to retransplantation. However, there will clearly be cases where the clinical team assesses the risk of non-concordance to be unacceptably high.

### **7.3.3 Choice of dialysis modality**

The principles of choice of dialysis modality are the same as those for patients approaching end-stage renal disease for the first time and are covered by the relevant Renal Association Guideline (1).

### **7.3.4 Formation of dialysis access**

The Renal Association guideline ‘Vascular Access for Haemodialysis’ recommends formation of an arteriovenous fistula at a minimum of three months prior to starting haemodialysis and probably not more than one year before the expected date of dialysis. For prosthetic grafts, a prolonged maturation period is not required (16). Consequently, in individuals where an arteriovenous graft is deemed to be the appropriate access, placement can be delayed until a time closer to the expected date of dialysis.

### **7.3.5 Conservative management**

In patients undergoing conservative management, a balance needs to be struck between preserving residual renal function and the side-effects of immunosuppressive therapy. In this situation, it is appropriate to adjust immunosuppression to minimise any side-effects.

## **7.4 Psychosocial issues**

Little has been written about the emotional implications and consequences for patients whose transplants are failing or have failed. However, graft failure can have profound psychological effects on patients which can result in depression and suicidal ideation, and close family members can be similarly affected. This is particularly true in the case of graft failure from a living donor, where there are additional issues of guilt and failure for both the donor and recipient.

There is often psychological resistance from both the patient and clinician to accept that a transplant is failing, posing a barrier to timely planning for return to RRT or conservative management. When transplant failure does occur, patients are often ill-prepared to cope with the emotions experienced. Commonly experienced emotions associated with graft failure are grief, guilt (particularly if a living donor was involved), anger, loss of self-esteem, and fear. In contrast to patients starting dialysis for the first time, memories of what it is like to undergo dialysis can become exaggerated and negative, however well the patient adjusted to treatment

the first time round. Concern over practical issues such as the impact of a return to dialysis on work and personal life can also have a major psychological impact.

Transplanted patients may be out of touch with current treatments and need to receive up to date information regarding available treatment modalities and help with any misconceptions based on their previous experience.

Clinicians should be aware of the psychological impact of transplant failure for the patient and their family, with particular recognition of the potential for depression and suicidal ideation. Appropriately skilled psychological support should be available to patients with failing transplants, with ongoing support on return to dialysis or conservative management.

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## **8 OUTCOMES FOLLOWING RETURN TO DIALYSIS OR RETRANSPLANTATION**

### **Statements of Recommendation**

*We recommend that:*

- Following graft failure, repeat transplantation offers the best survival and quality of life. This is particularly true for pre-emptive repeat transplantation. (1A)
- Patients suitable for retransplantation be evaluated for repeat transplantation when graft survival is anticipated to be <1 year. (1B)
- The optimum kidney for retransplantation comes from a well matched living donor. (1A)

#### **8.1 Introduction**

In this chapter, a number of unreferenced statistics relating to UK transplant outcomes are presented which are either unpublished or in press. We gratefully acknowledge the support of the Department of Statistics and Clinical Studies, NHS Blood and Transplant (NHSBT). We also thank Professor Gerhard Opelz for permission to report new data from the Collaborative Transplant Study.

#### **8.2 Incidence of graft failure**

With the increasing number of kidney transplant recipients (KTRs) and improved patient survival after transplantation, it is inevitable that recipients surviving with failing grafts will become progressively more common. US data suggest that patients with failed transplants constitute 4.1% of the incident dialysis population and are now the fifth commonest cause of starting dialysis in the US (1,2).

In the UK, 1332 kidney transplant recipients died in 2011-12. Of these, 360 (27%) had suffered graft failure before death (Table 8.1).

**Table 8.1 – Incidence of graft failure in deceased patients in 2011 and 2012**

	Living Donor	Deceased Donor	Total
Number of transplanted patients who died in 2011/12	180	1152	1332
Number of deceased patients with failed graft at time of death	38	322	360
Percentage of deceased patients with failed graft at time of death	21.1%	28.0%	27.0%

### 8.3 What happens to RFKTs?

In the US, about 85% of RFKTs will never return to the transplant waiting list (1,2). While this is mainly due to increasing age and comorbidity, it also reflects the high death rate observed after graft failure (see below).

When censored for patient death, 49.3% of patients who suffered graft failure in the UK in 2008-12 subsequently returned to the deceased donor transplant waiting list. The median time before returning to the transplant waiting list was 261 days after starting dialysis and the median wait for a repeat transplant was a further 715 days, meaning the median time to retransplantation from a deceased donor was 976 days (2.6 years). For those patients with graft failure who received a second transplant from a living donor, the median time to repeat transplantation was 313 days.

In the above cohorts, the median age at first graft failure was 51.3 (SD  $\pm$ 14.2) years for first transplants and 50.2  $\pm$ 11.5 years for second transplants, the discrepancy relating to an increased need for repeat transplantation in paediatric recipients.

#### **8.4 Prognosis after graft failure**

Poor allograft function is associated with an increased risk of death that increases as the need for dialysis approaches. This risk is largely accounted for by higher rates of cardiovascular and infective death (see chapter 7) (3,4).

There have been numerous studies comparing mortality rates for KTRs returning to dialysis against other dialysis patients, with mixed results. There is an inherent problem with the control group, but one US study compared the mortality of KTRs returning to dialysis against dialysis patients who were active on the renal transplant list and found a 78% increase in mortality, most of which occurred in the first two months after restarting dialysis (5). Another US study compared the mortality of KTRs returning to dialysis against patients with poorly functioning allografts and showed a one year mortality of 16% and a three year mortality of 33% (6).

In the UK, a similar study showed that the adjusted hazard ratio for death in the first year after first graft failure was 4.2 when RFKTs were compared with those patients who had started dialysis as initial renal replacement therapy and who been wait-listed for transplantation (i.e. fitter dialysis patients) (7). In this study, the increased hazard ratio for death was 3.5 at 1-2 years and 2.6 at 2-3 years, and an increased risk persisted for at least 5 years after graft failure. Even when RFKTs listed for further transplantation were considered (i.e. fitter RFKTs), an excess mortality risk remained with a hazard ratio of 3.1 in the first year, falling to 1.5 in years 3-5.

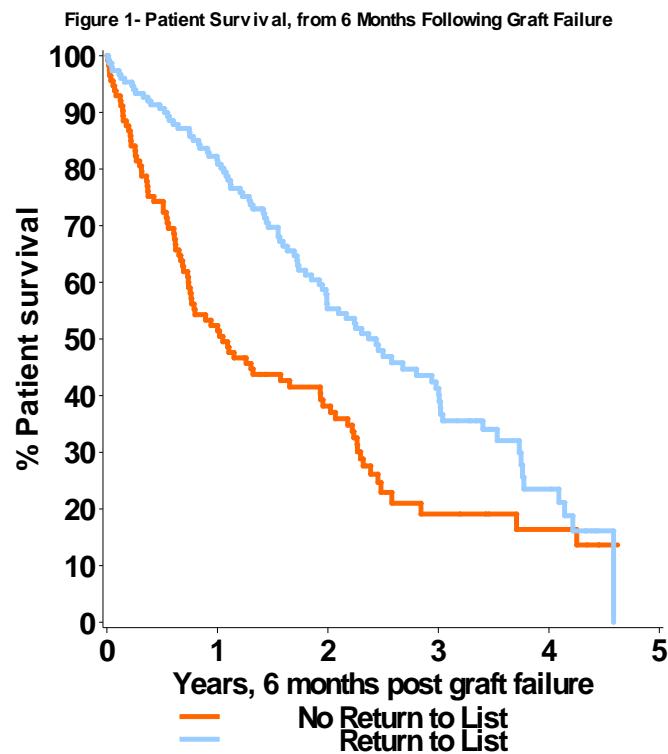
Epidemiological data suggest that the risk of death after transplant failure is associated with (6,8):

- White race
- Female gender
- Peripheral vascular disease
- Congestive heart failure
- Diabetes
- Long allograft life

## 8.5 Prognosis of failed RFKts on dialysis

Without retransplantation, the prognosis after graft failure is poor. Recent data from NHSBT indicate that <20% of RFKts live more than 4 years after graft failure unless they are retransplanted. In a cohort of 259 patients with graft failure followed from 6 months after graft failure in 2008-12, the mean actuarial survival was 18 months if the patient had not been re-entered onto the deceased donor waiting list, and 34 months if the patient had been relisted for transplantation but not transplanted (figure 8.1). These poor outcomes reflect the cardiovascular and other comorbidities associated with a long history of renal disease, graft failure, and return to dialysis.

**Figure 8.1 Patient survival from 6 months following graft failure, UK 2008-12**



## **8.6 Prognosis of RFKTs following repeat transplantation**

Patient survival is considerably better following repeat transplantation, which is not surprising given that patients receiving second transplants are on average younger and fitter, and also benefit from the survival advantage conferred by transplantation. This is despite an increased risk of death in the peri-transplant period when compared to first transplants (9,10).

The literature regarding graft survival in repeat transplantation is confused because of the large number of small studies and the difficulty in matching patient groups. However, the overall prognosis of second and subsequent grafts appears to be poorer than that of first transplants, with a median graft survival 14 years for first vs 10 years for second grafts (9,10).

Early studies showed that second transplants had worse graft survival in association with high levels of circulating HLA antibodies (11,12). Later studies showed better survival following improved immunosuppression regimes and the avoidance of antibody incompatibility and -DR mismatches (13,14). In addition to better overall graft survival, the gap between graft survival of first and subsequent transplants has significantly narrowed, although late graft loss remains a concern even in the absence of discrete episodes of rejection (15,16). Improved outcomes have been particularly noted following pre-emptive repeat transplantation, which in a retrospective analysis of the UNOS data was found to be associated with a lower incidence of acute rejection, delayed graft function, and death with a functioning graft (2).

In the UK, the percentage of repeat kidney transplants over the last 5 years has remained steady at around 11% of the total transplant number. The ratio of deceased and living donor repeat transplantation is unchanged, the latter comprising 485/1384 (35%) of repeat kidney transplants. The percentage of third and subsequent kidney transplants has remained steady at ~1.6% of the transplant total, although the absolute numbers are small (table 8.2).

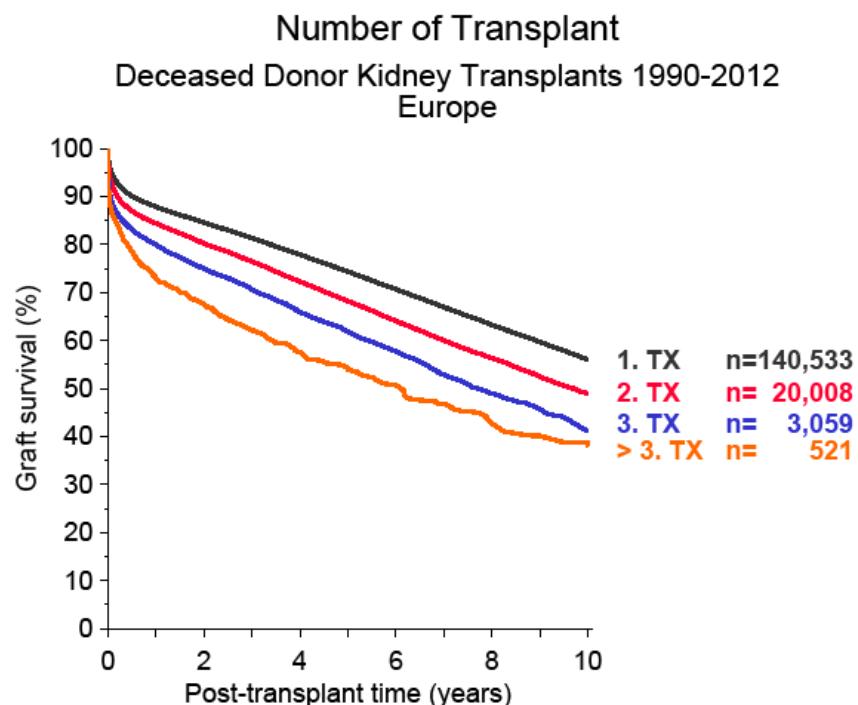
**Table 8.2 UK patients undergoing repeat kidney transplantation 2008-12**

Transplant number		1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	Total	Repeat transplants as a percentage of total transplants
2008	Living donor	803	73	8	3	887	9.5%
	Deceased donor	1390	143	25	4	1562	11.0%
2009	Living donor	819	89	24	1	933	12.2%
	Deceased donor	1384	136	27	4	1551	10.8%
2010	Living donor	859	98	10	0	967	11.2%
	Deceased donor	1452	157	14	1	1624	10.6%
2011	Living donor	864	85	13	3	965	10.5%
	Deceased donor	1452	170	26	5	1653	12.2%
2012	Living donor	872	78	16	0	966	9.7%
	Deceased donor	1621	161	25	1	1808	10.3%
<b>Total</b>	Living donor	4217	423	71	7	4718	10.6%
	Deceased donor	7299	767	117	15	8198	11.0%

The UK data mirror the international experience that transplant outcome deteriorates with increasing number of retransplants (17). Representative data from the Collaborative Transplant Study indicate that median graft survival for 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and >3<sup>rd</sup> kidney transplants in Europe was 11.8, 9.8, 7.7 and 6.1 years respectively in the cohort 1990-2012 (figure 8.2) (18). Comparison with previous equivalent analyses shows a gradual improvement over time, with the corresponding figures for the cohort 1985-2011 being 10.9, 9.2, 7.0 and 5.1 years respectively (18).

**Figure 8.2 Graft survival of deceased donor kidney transplants, Europe 1990-2012**

Data from the Collaborative Transplant Study (18)



## 8.7 Influence of donor organ type upon outcome

In a recent UK analysis, outcome data from patients receiving second kidney grafts in 2001-12 were examined to investigate whether the transplantation of a living or deceased donor organ influenced long term outcome. These data suggest that patient survival is affected by the type and the order of organ transplantation, with poorer outcomes when the second kidney transplanted is from a deceased donor (table 8.3). However, these data should be interpreted with caution. While an analysis of data from the Collaborative Transplant Study yielded similar results, the median age of the DD then DD cohort was significantly higher than other patient groups and this may have significantly affected patient outcome.

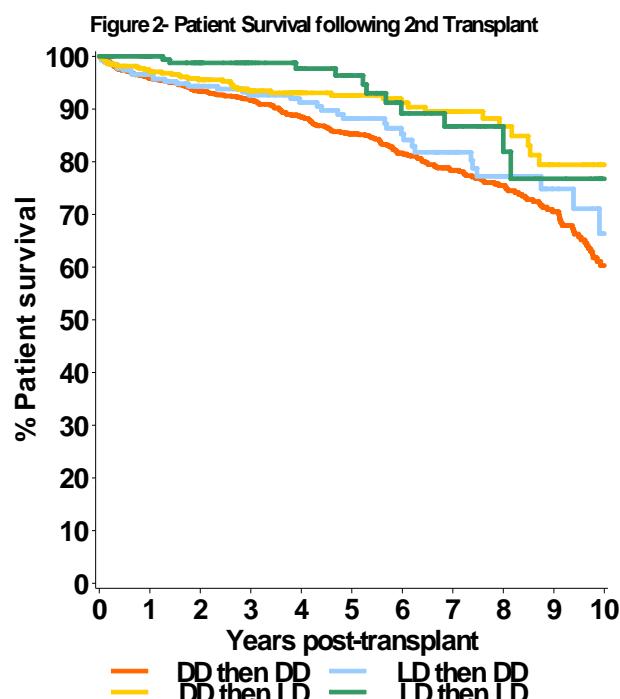
**Table 8.3 Patient survival following second transplantation by donor organ type**

	No at risk on day 0	% Patient survival (95% confidence interval)					
		One year		Three year		Five Year	
DD then DD	1441	96	(94,97)	91	(90,93)	85	(83,87)
DD then LD	503	97	(95,98)	93	(90,95)	92	(89,94)
LD then DD	277	96	(93,98)	92	(87,95)	87	(81,91)
LD then LD	201	99	(96,100)	98	(93,99)	95	(87,98)

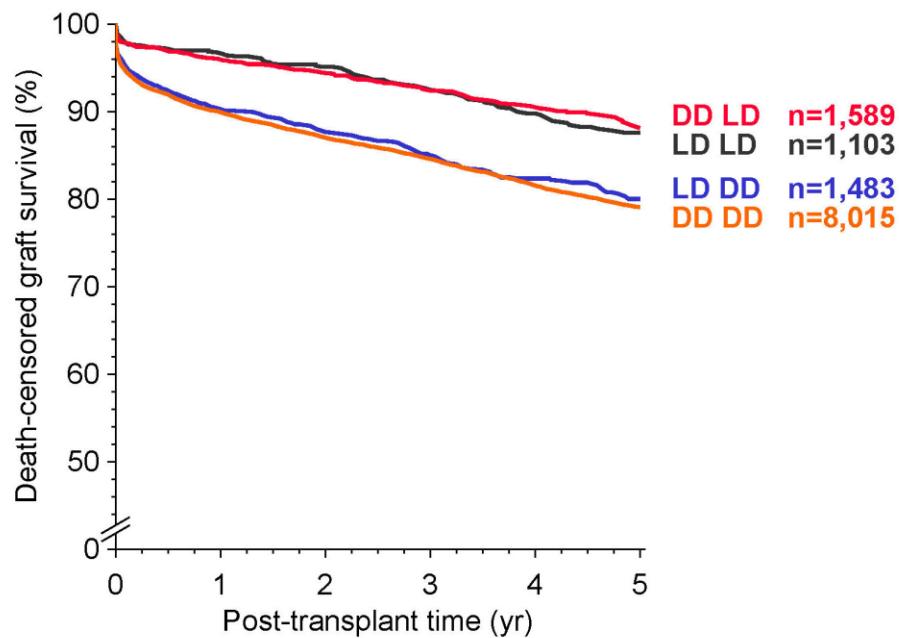
LD = living donor transplant, DD = deceased donor transplant

When graft survival was examined in the UK study, recipients of first and second kidneys from deceased donors exhibited worse graft survival than those of receiving other combinations of donor organs (log rank  $p<0.0002$ ) (figure 8.3). These data were confirmed by data from the Collaborative Transplant Study (figure 8.4).

**Figure 8.3 Graft survival following second transplantation, UK 2002-12**



**Figure 8.4 Graft survival following second transplantation, Europe 2002-12**



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