

CLINICAL PRACTICE GUIDELINES

Assessment of the Potential Kidney Transplant Recipient

UK Renal Association

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Dr Chris Dudley, Consultant Nephrologist,

Richard Bright Renal Unit, Bristol

&

Dr Paul Harden, Consultant Nephrologist

Oxford Kidney Unit

Posted at www.renal.org/guidelines

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Please send feedback for the next version to:

Dr Chris Dudley at chris.dudley@nbt.nhs.uk

Dr Paul Harden at paul.harden@orh.nhs.uk

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Introduction

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2. Evaluation, selection and preparation of the potential transplant recipient
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Acknowledgements

Introduction

This clinical practice guideline addresses access to kidney transplantation together with the evaluation, selection and preparation of the potential kidney transplant recipient. Guidance on the medical management of the kidney transplant recipient is provided in another module of the Renal Association guidelines available at www.renal.org. Readers should refer to the joint British Society for Histocompatibility and Immunogenetics/British Transplantation Society document for guidelines on the detection and characterization of HLA antibodies in renal transplantation and to the NHS Blood and Transplant/British Transplantation Society guidelines for consent for solid organ transplantation (www.bts.org.uk/standards-and-guidelines.htm)¹.

In this guideline Chronic Kidney Disease Stage 5 (CKD 5) includes pre-dialysis and transplant patients with $\text{eGFR} < 15 \text{ ml/min/1.73m}^2$ as well as patients on dialysis i.e. CKD 5, CKD 5T and CKD 5D. This guideline is an updated version of the Renal Association guidance developed by the same lead co-authors published in 2007 and is based on a review of the literature between 2007 and 2010. Where evidence was available from RCTs and systematic reviews recommendations were based on these publications. Where there was a lack of evidence from high-quality studies, recommendations were based on the best available evidence taking in account the previous clinical practice guidelines on evaluation of the potential kidney transplant recipient from North America² and the European Renal Best Practice (ERBP) guidelines for renal transplantation³.

The recommendations in this update have been graded using the modified GRADE system to indicate both the strength of each recommendation (strong or weak) and level of evidence for the recommendation (A-D)^{4,5}. These guidelines on the assessment of the potential kidney transplant recipient have been endorsed by the British Transplantation Society.

References

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Summary of clinical practice guidelines for assessment for renal transplantation

1. Access to renal transplantation (Tx) (Guidelines Tx 1.1 – 1.9)

Guideline 1.1 – Tx : Access to renal transplantation

We recommend that kidney transplantation should be the renal replacement therapy of choice for the patient with chronic kidney disease stage 5 who is considered fit for major surgery and for chronic immunosuppression. All patients predicted to have an increased life expectancy post-transplantation should be assessed for transplantation. Placement on the transplant waiting list will be limited by individual co-morbidity and prognosis. (1A)

Guideline 1.2 – Tx : Access to renal transplantation

We recommend that living donor transplantation should be considered the treatment of choice for all patients suitable for renal transplantation when there is an appropriate donor. (1A)

Guideline 1.3 – Tx : Access to renal transplantation

We recommend that patients with progressive deterioration in renal function suitable for transplantation should be placed on the national transplant list within six months of their

anticipated dialysis start date. Pre-emptive transplantation should be the treatment of choice for all suitable patients whenever a living donor is available. (1A)

Guideline 1.4 – Tx : Access to renal transplantation

We recommend that there must be demonstrable equity of access to deceased donor kidney transplantation irrespective of gender, ethnicity or district of residence. (1A)

Guideline 1.5 – Tx : Access to renal transplantation

We recommend that age is not a contra-indication to transplantation but age related co-morbidity is an important limiting factor. (1B)

Guideline 1.6 – Tx : Access to renal transplantation

We recommend that all transplant units should have written criteria for acceptance on to the waiting list. The benefits and potential risks associated with transplantation should be fully explained both verbally and in writing. Potential transplant recipients should be informed of all donor options including living related and unrelated donation and the NHSBT/BTS guidelines for consent for solid organ donation should be followed. (1C)

Guideline 1.7 – Tx : Access to renal transplantation

We recommend that all CKD 5 patients and CKD 4 patients with progressive disease should have their suitability for transplantation assessed annually and that appropriate patients should be referred to a transplant centre. When transplantation is considered inappropriate the reason(s) should be documented. All patients on the transplant list should be assessed annually to determine whether transplantation remains appropriate. Patients should be placed on, or removed from the waiting list only after discussion and agreement with the nephrologist, transplant surgeon and the patients themselves according to local practice. (1C)

Guideline 1.8 – Tx : Access to renal transplantation

We recommend that the care of the renal transplant recipient is best undertaken by a multi-disciplinary team. (1C)

Guideline 1.9 – Tx : Access to renal transplantation

We recommend that simultaneous kidney-pancreas transplantation or living donor renal transplantation is the treatment of choice for patients with Type 1 diabetes mellitus who are suitable for renal transplantation. (1B)

2. Evaluation, selection and preparation of the potential transplant recipient (Tx) (Guidelines Tx 2.1 – 2.9)

Guideline 2.1 – Tx : Pre-transplant assessment

We recommend that the object of pre-transplant assessment is: a) to ensure transplantation is technically possible; b) to ensure the recipient's chances of survival are not compromised by transplantation; c) to ensure that graft survival is not limited by premature death (maximum benefit obtained from a limited resource); d) to ensure pre-existing conditions are not exacerbated by transplantation; e) to identify measures to be taken to minimise peri- and post-operative complications; f) to inform patients of the likely risks and benefits of transplantation. (1C)

Guideline 2.2 – Tx : Pre-transplant cardiac assessment

We suggest that there is no compelling evidence that pre-transplantation screening tests for coronary artery disease in asymptomatic patients with established renal failure is effective in preventing future cardiac events or reducing mortality after transplantation.

Until better evidence emerges, screening tests may be best used to identify high-risk patients for exclusion from the transplant waiting list. (2C)

Guideline 2.3 – Tx : Preparation of the renal transplant recipient

We suggest that the use of pre-operative beta-blockers may be considered in patients at high cardiovascular risk undergoing renal transplantation but should be introduced at least 1 month before transplantation. Beta-blockers should not be discontinued abruptly peri-operatively. Low dose aspirin and clopidogrel therapy are not contraindications to transplantation. (2C)

Guideline 2.4 – Tx : Preparation of the renal transplant recipient

We recommend that patients should be strongly encouraged to stop smoking before and after transplantation. Formal smoking cessation programmes should be offered and accessed in primary care. (1A)

Guideline 2.5 – Tx : Preparation of the renal transplant recipient

We suggest that obese patients ($\text{BMI} > 30 \text{ kg/m}^2$) present technical difficulties and are at increased risk of peri-operative complications. They should be screened rigorously for cardiovascular disease and each case considered individually. Although obesity is not an absolute contra-indication to transplantation, individuals with a $\text{BMI} > 40 \text{ kg/m}^2$ are less likely to benefit. (2B)

Guideline 2.6 – Tx : Preparation of the renal transplant recipient

We recommend that all potential transplant recipients should be tested for prior exposure to viral infections including: cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), hepatitis B and C and human immunodeficiency virus (HIV). Immunisation should be offered to all hepatitis B (if not already immunised) and

VZ virus antibody negative patients before transplantation. Patients otherwise suitable for renal transplantation with evidence of chronic hepatitis B and/or C or HIV infection should be managed according to British Transplantation Society and European Best Practice Guidelines prior to transplantation. (1A)

Guideline 2.7 – Tx : Evaluation and selection of the renal transplant recipient

We recommend that renal transplantation should only be considered in potential recipients with previous malignancy (excluding non-melanoma skin cancer) if there is no evidence of persistent cancer. It is recommended that the waiting time between successful tumour treatment/remission and transplantation be at least 2 years. For certain malignancies the waiting time may need to be extended to more than 5 years. The Israel Penn International Transplant Tumour Registry should be consulted for tumour specific advice (www.ipitr.uc.edu/Home.cfm). (1A)

Guideline 2.8 – Tx : Evaluation and selection of the renal transplant recipient

We recommend that patients who are at risk of developing recurrence of original renal disease should be managed according to the European Best Practice Guidelines (EBPG). (not graded)

Guideline 2.9 – Tx : Screening investigations in the renal transplant recipient

We suggest that there is no evidence that asymptomatic potential transplant recipients require screening for diverticular disease, peptic ulceration or gall bladder stones. (2C)

Summary of audit measures in assessment for renal transplantation

1. The proportion of patients with and without diabetes mellitus < 65 years old with CKD stage 5 listed for transplantation.
2. The proportion of transplant patients who receive a living donor transplant.
3. The time to placement on the UK Transplant national transplant list in relation to start date of dialysis.
4. The proportion of living donor transplant recipients transplanted before starting dialysis.
5. A comparison between renal units of the proportion of dialysis patients placed on the national transplant list corrected for differences in identified unit and patient specific variables including co-morbidity.
6. The proportion of CKD stage 5 patients with a transplant status recorded.
7. The proportion of CKD stage 5 dialysis patients with Type 1 diabetes mellitus listed for simultaneous kidney-pancreas transplantation.
8. The proportion of patients who smoke (or have given up within the last year)
 - a. whilst listed for transplantation
 - b. one year after renal transplantation.
9. The number of patients with BMI >40 kg/m² who are on the transplant waiting list and the reason for their inclusion.
10. The proportion of patients on the transplant waiting list whose viral status is known for CMV, EBV, VZV, hepatitis B and C and HIV.
11. The proportion of VZV and HBc antibody negative patients on the transplant waiting list who have been immunised against these viruses.

Rationale for clinical practice guidelines for assessment of the renal transplant recipient

1. Access to renal transplantation (Tx) (Guidelines Tx 1.1 – 1.9)

Guideline 1.1 – Tx : Access to renal transplantation

We recommend that kidney transplantation should be the renal replacement therapy of choice for the patient with chronic kidney disease stage 5 who is considered fit for major surgery and for chronic immunosuppression. All patients predicted to have an increased life expectancy post-transplantation should be assessed for transplantation. Placement on the transplant waiting list will be limited by individual co-morbidity and prognosis. (1A)

Audit measure

The proportion of patients with and without diabetes mellitus < 65 years old with CKD stage 5 listed for transplantation.

Rationale

Patients' survival following renal transplantation is better compared to age-matched individuals remaining on the transplant waiting list¹. In a series of 46,164 patients on the transplant waiting list in the USA between 1991-97, mortality was 68% lower for transplant recipients than for those remaining on the transplant waiting list for >3 yrs follow-up¹. This resulted in a mean increase in projected survival of 10 years, maximised in the 20-39 year old age group, who were predicted to live 17 years longer than their counterparts remaining on the transplant waiting list. The increased survival benefit was seen in both sexes and was even more marked in diabetics. This analysis was confined to those patients admitted to the waiting list using the criteria for fitness for transplantation in use at the time of the study in the USA, and therefore cannot safely be extrapolated to higher risk potential transplant candidates. Although a smaller study from Scotland replicated these findings, a similar more recent analysis from the UK showed that patients

over the age of 65 years did not experience any survival advantage compared with matched patients who were listed but not transplanted^{2,3}.

References

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Guideline 1.2 – Tx : Access to renal transplantation

We recommend that living donor transplantation should be considered the treatment of choice for all patients suitable for renal transplantation when there is an appropriate donor. (1A)

Audit measure

The proportion of transplant patients who receive a living donor transplant

Rationale

The demand for renal transplantation has consistently and increasingly outstripped the number of available deceased donor organs for the last 20 years. In 2005 this shortfall had increased to over 6000 patients¹. Donation of a kidney from a living donor increased by 12% in 2008/9 in the UK and is the most realistic option to expand organ donation^{1,2}. Living donor kidney transplantation provides most patients with the best chance of long-term rehabilitation and it also facilitates access to deceased donor transplantation for those without a living donor. The opportunity for planned transplantation before dialysis is required is an attractive option for patients and evidence suggests that there is improved graft survival of transplants performed pre-emptively³. During the last 5 years

there has been substantial increase in living donor kidney transplantation in the UK which now accounts for 38% of the total kidney transplant programme (living donor kidney transplantation rate has increased from 9.2 per million population pmp in 2005 to 17.2 pmp in 2010 in the UK¹). Living kidney donation also enables scheduling of transplantation at a time when the recipient is in optimal medical and psychological condition and may be the only option in high-risk recipients.

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Guideline 1.3 – Tx : Access to renal transplantation

We recommend that patients with progressive deterioration in renal function suitable for transplantation should be placed on the national transplant list within six months of their anticipated dialysis start date. Pre-emptive transplantation should be the treatment of choice for all suitable patients whenever a living donor is available. (1A)

Audit measures

1. The time to placement on the national transplant list in relation to the start date of dialysis.
2. The proportion of living donor transplant recipients transplanted before starting dialysis.

Rationale

In a series of 25,758 recipients of first deceased donor kidney transplants in the USA between 1995-8, pre-emptive transplantation was associated with a 25% reduction in graft failure and 16% reduction in mortality compared to recipients receiving a transplant when already established on dialysis¹. In 13,078 pre-emptive living related transplant

recipients from the same series, there was a 31% reduction in mortality and a 27% reduction in graft failure¹. Transplant survival is negatively influenced by the duration of dialysis before transplantation, with a 5 year allograft survival of approximately 85% in pre-emptive transplantation compared with 75% in those receiving dialysis for 3-4 years before transplantation². Patients with advanced CKD should receive a renal transplant as soon as possible to optimise clinical outcomes. Under Standard Two of The National Service Framework for Renal Services (Part One), a marker of good practice is the placement of patients on the national transplant list within six months of their anticipated dialysis start date if clinically appropriate³. Early pre-emptive transplantation with a higher eGFR (≥ 15) does not improve graft survival after kidney transplantation, compared to pre-emptive transplantation with a lower eGFR (<10)⁴. Within the UK there is evidence of significant differences between renal units in the time taken to register patients on the national transplant list that cannot be explained by differences in patient characteristics⁵.

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Guideline 1.4 – Tx : Access to renal transplantation

We recommend that there must be demonstrable equity of access to deceased donor kidney transplantation irrespective of gender, ethnicity or place of residence. (1A)

Audit measure

A comparison between renal units of the proportion of dialysis patients placed on the national transplant list corrected for differences in identified unit and patient specific variables including co-morbidity.

Rationale

Renal transplantation remains the most successful and cost-effective treatment for suitable patients with established renal failure. Not all patients receiving dialysis are suitable for kidney transplantation and there is evidence that selection criteria vary widely throughout the UK¹⁻³. At the beginning of 2009, 38% of all patients treated with dialysis were active (or suspended) on the national transplant waiting list. NHS Blood and Transplant coordinates deceased-donor kidney allocation according to a nationally agreed algorithm. In 2004, the UK Transplant Kidney and Pancreas Advisory Group commissioned an Equity of Access Task Force to identify factors that may lead to inequity of access to renal transplant waiting lists, to recommend methods through which unjustified inequity may be removed and to determine methods through which this could be identified. The report from this Task Force contributed in part to the development and implementation of a new national renal allocation algorithm in 2006 and modified further in 2008. A key recommendation from this group was the above audit measure⁴. Recent data from the UK suggests that whilst gender had no effect on the probability of placement on the national transplant waiting list, ethnic minorities were less likely to be listed within 2 years of start of dialysis compared to white patients, although this difference could be explained by differences in patient characteristics and social deprivation^{5,6}. However, patients cared for in non-transplanting renal units were less likely to be registered for transplantation compared to patients cared for in transplanting renal centres⁵. Furthermore, there were significant differences between renal units in the probability of being activated on the waiting list within 2 years of starting dialysis that could not be explained by case-mix (age, ethnicity and primary renal diagnosis)⁵.

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Guideline 1.5 – Tx : Access to renal transplantation

We recommend that age is not a contra-indication to transplantation but age related co-morbidity is an important limiting factor (1B)

Rationale

There is an imbalance between the availability of donor organs and demand for renal transplantation in the UK¹. The shortfall of deceased donor organs has resulted in the national allocation scheme - coordinated by NHS Blood and Transplant. New allocation criteria were introduced in a phased manner in 2006 and in 2008 to minimise racial and geographical inequities². Population studies have shown reduced rates of access to transplantation for African Americans in the USA and British Asians in the UK^{3,4} although recent data from the UK suggests that after correction for patient characteristics and social deprivation, no such reduced access exists⁵.

There is evidence that selection criteria for placement on the transplant waiting list vary significantly throughout the UK⁶. It is important that centres managing patients with Stage 4 and 5 CKD follow standardised procedures for evaluation of suitability for transplantation. Each transplant centre should have written protocols for transplant assessment consistent with European and North American Guidelines^{7,8}. Improved life expectancy of first deceased donor transplant recipients over patients remaining on the waiting list is seen in all age groups in a US study⁹. Transplant recipients between ages 60-74 had a 61% reduction in mortality and increased predicted survival of 4.3 years over matched patients remaining on the transplant waiting list⁹. In contrast, in a more recent

UK analysis, patients over the age of 65 years did not experience any survival advantage compared with matched patients who were listed but not transplanted over 5 years of follow-up¹⁰. Quality of life, however, may be improved. Potential recipients aged 50 or greater should have a careful evaluation of cardiovascular co-morbidity.

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10. Ansell D, O'Neill JO, Johnson R et al. Transplantation of older patients does not improve survival compared with those wait listed. Analysis of 9,700 wait listed patients in the UK. *Transplantation* 2008;86(2S):314

Guideline 1.6 – Tx : Access to renal transplantation

We recommend that all transplant units should have written criteria for acceptance on to the waiting list. The benefits and potential risks associated with transplantation should be fully explained both verbally and in writing. Potential transplant recipients should be informed of all donor options including living related and unrelated donation and the NHSBT/BTS guidelines for consent for solid organ donation should be followed. (1C).

Rationale

It is important that all potential transplant recipients should receive comprehensive information on the risks of transplantation, the results compared with dialysis and the options in terms of different types of donor. All patients should receive education about all forms of living donor transplantation including paired/pooled exchange and antibody incompatible transplantation. Recommendations made in the NHSBT/BTS guidelines for consent for solid organ donation should be adhered to¹.

References

1. <http://www.bts.org.uk/transplantation/standards-and-guidelines/>

Guideline 1.7 – Tx : Access to renal transplantation

We recommend that all CKD 5 patients and CKD 4 patients with progressive disease should have their suitability for transplantation assessed annually and that appropriate patients should be referred to a transplant centre. When transplantation is considered inappropriate the reason(s) should be documented. All patients on the transplant list should be assessed annually to determine whether transplantation remains appropriate. Patients should be placed on, or removed from the waiting list only after discussion and agreement with the nephrologist, transplant surgeon and the patients themselves according to local practice. (1C)

Audit measure

The proportion of CKD stage 5 patients with a transplant status recorded.

Rationale

Clinical practice differs from centre to centre with regard to selection for transplantation¹. It is important to review all patients with stage 4 and 5 CKD as potential transplant recipients according to local written protocols. Limitation of access to transplantation by

age, gender, social and ethnic background is unacceptable and must be prevented by a standardised assessment mechanism.

The median waiting time to transplantation in the UK for adult patients registered on the kidney transplant waiting list during 2001-2004 was 902 days². CKD is associated with accelerated cardiovascular disease³ requiring regular review of patients on the waiting list to detect emerging co-morbidities which may compromise the outcomes of renal transplantation. Surveillance for cardiovascular disease may need to be more frequent in high risk groups such as individuals with previous cardiac intervention or re-transplantation.

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Guideline 1.8 – Tx : Access to renal transplantation

We recommend that the care of the renal transplant recipient is best undertaken by a multi-disciplinary team. The supporting role of transplant nurse specialists in living donor/recipient preparation and recipient care is highly desirable. (1C)

Rationale

Optimal early and maintenance care post-transplantation requires close co-operation between health care professionals of different disciplines including H&I scientist, transplant surgeon, nephrologist, anaesthetist, radiologist, histopathologist, renal pharmacist and specialist in infectious disease. Nurse practitioners are increasingly providing a pivotal role in transplant assessment and subsequent co-ordination of maintenance transplant recipients^{1,2}.

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Guideline 1.9 – Tx : Access to renal transplantation

We recommend that simultaneous kidney-pancreas transplantation or living donor renal transplantation is the treatment of choice for patients with Type 1 diabetes mellitus who are suitable for renal transplantation. (1B)

Audit measure

The proportion of CKD stage 5 dialysis patients with Type 1 diabetes mellitus listed for simultaneous kidney-pancreas transplantation.

Rationale

In diabetic patients, kidney transplantation leads to a marked improvement in patient and graft survival compared with continued dialysis¹. A number of studies have demonstrated improved survival for diabetic recipients of simultaneous pancreas-kidney (SPK) transplants compared with deceased donor kidney alone transplants (KA)^{2,3}. Furthermore, US Registry data suggest that diabetic recipients of deceased donor SPK and living donor KA transplants have similar 5 year mortality risks that are significantly better than that of diabetic recipients of deceased donor KA transplants⁴. However, a recent analysis reports enhanced graft survival rates in living donor KA transplantation compared to SPK⁵. It is recommended that all type 1 diabetics with advanced CKD suitable for transplantation should be considered for living donor transplantation if available, particularly as the waiting time for SPK is increasing. All these studies are potentially flawed by selection bias and re-analysis of the UNOS database after correction for differences in donor and recipient risk factors gives similar short-term patient and graft survival between recipients of SPK and KA transplants⁶. However, some studies show that recipients of SPK transplants report better physical health and quality of life in areas that are diabetes

specific compared with recipients of KA transplants^{7,8}, Furthermore, there is accumulating, but as yet inconclusive, evidence that pancreas transplantation may halt and potentially improve some of the long-term complications of diabetes mellitus including retinopathy⁹, nephropathy¹⁰ and neuropathy¹¹.

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2. Evaluation, selection and preparation of the potential transplant recipient (Tx) (Guidelines Tx 2.1 – 2.9)

Guideline 2.1 – Tx : Pre-transplant assessment

We recommend that the object of pre-transplant assessment is: a) to ensure transplantation is technically possible; b) to ensure the recipient's chances of survival are not compromised by transplantation; c) to ensure that graft survival is not limited by premature death (maximum benefit obtained from a limited resource); d) to ensure pre-existing conditions are not exacerbated by transplantation; e) to identify measures to be taken to minimise peri- and post-operative complications; f) to inform patients of likely risks and benefits of transplantation. (1C)

Rationale

The main goal of renal transplantation is to improve the life expectancy and quality of life of patients with established renal failure. It follows, therefore, that patients who are predicted to have their lives shortened by transplantation or to experience a worsening quality of life should be excluded from the transplant waiting list. It is acknowledged that making such predictions is often difficult and imprecise and that the quality of data to support rational decision making is generally inadequate. There is evidence that selection criteria vary widely throughout the UK as reflected by variation in the proportion of patients who are on the transplant waiting list at different renal units¹. In July 2003, the British Transplantation Society and Renal Association published waiting list criteria for potential renal transplant recipients based, with some minor modifications, on the European Best Practice Guidelines (2000)². The major difference was in the exclusion of patients with a predicted survival of less than 5 years compared with 2 years in the EBPG. The general principles of the pre-transplant assessment listed above are not controversial and constitute best practice. However, the exact mechanism by which some of the individual objectives may be met remain unclear and inevitably results in an element of subjectivity.

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Guideline 2.2 – Tx : Pre-transplant cardiac assessment

We suggest that there is no compelling evidence that pre-transplantation screening tests for coronary artery disease in asymptomatic patients with established renal failure is effective in preventing future cardiac events or reducing mortality after transplantation. Until better evidence emerges, screening tests may be best used to identify high-risk patients for exclusion from the transplant waiting list. (2C)

Rationale

Although age, diabetes mellitus and pre-existing coronary artery/peripheral vascular disease are factors that identify individuals at a higher risk of cardiac mortality after transplantation¹⁻³, it is uncertain whether revascularisation of coronary artery lesions reduces the risk of postoperative events or prolongs survival of patients before transplantation. In a prospective observational cohort study of 300 consecutive patients screened for cardiovascular disease in Glasgow prior to listing for transplantation, there was no significant survival difference between those patients referred for coronary angiography compared to those who were not, despite the higher perceived cardiovascular risk of patients undergoing invasive tests⁴. There was also no apparent survival difference between patients who underwent percutaneous coronary intervention (PCI) compared with those who underwent angiography without intervention, or those who had no angiography although the numbers were small and the rate of intervention was low. While the results of screening (including the inability to perform an exercise stress test for >6 minutes) were important predictors of survival, they did not lead to intervention and did little more than exclude patients from transplantation. Furthermore, trials in the non-renal population have shown that prophylactic coronary artery revascularization does not reduce long term all cause mortality or improve outcomes in high risk patients undergoing major non-cardiac surgery⁵. To answer the question of

whether pre-transplant screening and subsequent coronary intervention improves survival in patients with established renal failure and coronary artery disease requires a large prospective multi-centre randomised study. Until then it remains uncertain whether screening and subsequent intervention in high-risk patients is effective in preventing future cardiac events or reducing mortality after transplantation⁶. When performed, screening tests may be best used to identify high-risk patients for exclusion from the transplant waiting list.

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Guideline 2.3 – Tx : Preparation of the renal transplant recipient

We suggest that the use of pre-operative beta-blockers may be considered in patients at high cardiovascular risk undergoing renal transplantation but should be introduced at least 1 month before transplantation. Beta-blockers should not be discontinued abruptly peri-operatively. Low dose aspirin and clopidogrel therapy are not contraindications to transplantation. (2C)

Rationale

Despite recommendations by a number of guideline committees for the use of beta-blockers in high-risk patients undergoing non-cardiac surgery to prevent peri-operative

cardiovascular events, evidence of the efficacy of this approach from randomised clinical trials is limited and untested in the context of renal transplantation¹. Recent evidence from a large randomised controlled trial (POISE) of peri-operative beta-blockers started 2-4 hours before non-cardiac surgery showed that although the primary end-point of cardiac death, non-fatal myocardial infarction or cardiac arrest was reduced in the beta-blocker group, this was at the cost of an increased incidence of total mortality and stroke². The most recent meta-analysis of 33 randomised trials including over 12,000 patients, of whom over 8000 were from POISE, has concluded that although peri-operative beta-blockers reduced the risk of non-fatal myocardial infarction (NNT 63) and myocardial ischaemia (NNT 16) there was no significant reduction in all cause mortality, cardiovascular mortality or heart failure. Indeed, their use increased the risk of bradycardia and hypotension needing treatment and increased the risk of non-fatal strokes (NNH 293)³. A large US cohort study in which the outcome of patients undergoing non-cardiac surgical procedures was analysed according to whether or not they received beta-blockers within the first 2 days of hospitalisation concluded that high-risk patients who received beta-blockers were significantly less likely to die in hospital. However, low risk patients receiving beta-blockers were more likely to die⁴. Evidence from the DECREASE study suggests that if pre-operative beta-blockers are used they should be introduced at least one month prior to transplantation⁵. For patients already taking a beta-blocker, therapy should be continued given the risks of sudden cessation. The recently published guideline update from the American College of Cardiology/American Heart Association provides sensible advice on pre-operative beta-blocker use based on the current published evidence⁶. The guidelines state that beta-blockers titrated to heart rate and blood pressure are *probably* recommended for patients undergoing intermediate- or high-risk surgical procedures whose pre-operative assessment identifies coronary heart disease or high cardiac risk. To avoid peri-operative bradycardia and hypotension, it would be prudent to start beta-blockers at least one month prior to transplantation.

Aspirin has a major role in the primary and secondary prevention of myocardial infarction and reduces the severity of silent myocardial ischaemia in both stable and unstable angina. Peri-operative aspirin therapy is associated with a significant reduction

in mortality in patients undergoing coronary bypass surgery and is not associated with an increased risk of bleeding or gastritis⁷. It interferes with platelet aggregation induced by thromboxane A₂ but not by either thrombin or high concentrations of collagen. Therefore, clinically significant bleeding should not be made worse by peri-operative aspirin⁸. Furthermore, the use of low dose peri-operative aspirin may reduce the risk of transplant renal vein thrombosis⁹. Patients taking clopidogrel may be more likely to bleed peri-operatively and require blood transfusions but this should not be considered a contraindication to renal transplantation. The use of platelet infusions may reduce this risk^{10,11}.

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Guideline 2.4 – Tx : Preparation of the renal transplant recipient

We recommend that patients should be strongly encouraged to stop smoking before and after transplantation. Formal smoking cessation programmes should be offered and accessed in primary care. (1A)

Audit measure

The proportion of patients who smoke (or have given up within the last year)

a) whilst listed for transplantation.

b) one year after renal transplantation.

Rationale

Cigarette smoking increases the risk of cancer and cardiovascular disease in the general population. Only a few studies have examined the effect of cigarette smoking on renal transplantation but all show an association with reduced patient and graft survival. In one study of patients with a functioning graft at least one year after transplantation, cigarette smoking correlated with reduced patient survival and the magnitude was quantitatively similar to that conferred by diabetes¹. In a larger single centre North American study, smoking more than 25 pack-years at the time of transplantation (compared to smoking less than 25 pack-years or never having smoked) was associated with a 30% higher risk of graft failure after correcting for multiple known risk factors². The increase in graft failure was largely due to an increase in deaths. Stopping smoking more than 5 years before transplantation reduced the relative risk of graft failure by 34%. The relative risks of major cardiovascular disease events and invasive malignancies were significantly increased in smokers. Similar results have been observed in another study in which pre-transplant smoking was associated with reduced transplant and death-censored graft survival, although death-censored graft survival was significantly higher in patients who

stopped smoking before transplant evaluation³. Evidence suggests that with appropriate interventions, many patients can stop smoking⁴⁻⁵.

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Guideline 2.5 – Tx : Preparation of the renal transplant recipient

We suggest that obese patients (BMI >30 kg/m²) present technical difficulties and are at increased risk of peri-operative complications. They should be screened rigorously for cardiovascular disease and each case considered individually. Although obesity is not an absolute contra-indication to transplantation, individuals with a BMI >40 kg/m² are less likely to benefit. (2B)

Audit measure

- a). The proportion of obese patients (BMI >30 kg/m²) on the transplant waiting list who have had a cardiac assessment.
- b). The number of patients with BMI >40 kg/m² who are on the transplant waiting list and the reason for their inclusion.

Rationale

Body mass index (BMI) is the most widely used marker of obesity despite its limitations. According to the WHO classification a BMI of 30-34.9 kg/m² is defined as obese class I (mild), 35-39.9 kg/m² as obese class II (moderate) and >40 kg/m² as obese class III

(morbid). The impact of obesity on outcome after renal transplantation has been controversial. For obese patients overall, registry data have demonstrated a significant survival advantage for recipients of both deceased and living donor transplantation compared with remaining on dialysis¹. However, recipients of deceased donor transplants with a BMI >41 kg/m² had no survival benefit. Some single centre studies have shown that wound infection, delayed graft function and weight gain are more common complications in moderately and morbidly obese transplant recipients although patient and graft survival are unchanged²⁻⁴. In a small paired kidney analysis of 28 pairs, obesity defined as a BMI >30 kg/m² was associated with decreased graft survival at 5 years⁵. In another study in which patients were rigorously screened (and excluded) for cardiovascular disease before acceptance for transplantation, 5 year patient and graft survival were no different in the obese (BMI >30 kg/m²) group although wound breakdown was commoner⁶. A recent analysis of 27,377 patients from the UNOS database showed that compared with normal weight patients, a BMI >35 kg/m² was independently associated with an increased risk of delayed graft function, prolonged hospitalisation, acute rejection and decreased overall graft survival, although a high proportion of such individuals were African Americans and had diabetes mellitus⁷.

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Guideline 2.6 – Tx : Preparation of the renal transplant recipient

We recommend that all potential transplant recipients should be tested for prior exposure to viral infections including: cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), hepatitis B and C and human immunodeficiency virus (HIV). Immunization should be offered to all hepatitis B (if not already immunised) and VZ virus antibody negative patients before transplantation. Patients otherwise suitable for renal transplantation with evidence of chronic hepatitis B and/or C or HIV infection should be managed according to British Transplantation Society and European Best Practice Guidelines prior to transplantation. (1A)

Audit measure

- a). The proportion of patients on the transplant waiting list whose viral status is known for CMV, EBV, VZV, hepatitis B and C and HIV.
- b). The proportion of VZV and HBc antibody negative patients on the transplant waiting list who have been immunised against these viruses.

Rationale

It is important to know if potential transplant recipients have had exposure to certain viruses, notably Epstein-Barr virus (EBV), cytomegalovirus (CMV) and varicella zoster virus (HZV). EBV negative recipients of an EBV positive transplant have a seven-fold increased risk of post-transplant lympho-proliferative disorder (PTLD)¹. Knowledge of recipient CMV serology at transplantation is essential to guide antiviral prophylactic strategies².

Potential recipients who are hepatitis B surface antigen positive will require assessment by a hepatologist with liver biopsy if circulating viral DNA is present before placement on the waiting list³. Active viral replication, chronic active hepatitis or cirrhosis has a poor prognosis if untreated before transplantation⁴. In hepatitis C, survival post-transplantation is increased over remaining on dialysis⁵. It is recommended that the potential transplant recipient has a liver biopsy to assess liver damage and consideration of treatment before transplantation⁶.

The advent of highly active antiviral therapy has revolutionized the prognosis of HIV, and early experience suggests similar early graft and patient survival rates between HIV – positive and negative renal transplant recipients⁷. Guidelines for the management of potential kidney transplant recipients with HIV infection should be followed.⁸

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Guideline 2.7 – Tx : Evaluation and selection of the renal transplant recipient

We recommend that in potential recipients with previous malignancy (excluding non-melanoma skin cancer), renal transplantation should only be considered if there is no evidence of persistent cancer. It is recommended that the waiting time between successful tumour treatment/remission and transplantation be at least 2 years. For certain malignancies the waiting time may need to be extended to more than 5 years. The Israel Penn International Transplant Tumour Registry should be consulted for tumour specific advice (www.ipittr.uc.edu/Home.cfm). (1A)

Rationale

The risk of several forms of malignancy is markedly increased after transplantation¹, due in part to alteration of immune surveillance mechanisms with maintenance immunosuppression. Patients with successfully treated cancer can be considered for renal transplantation however it is important to estimate the risk of cancer relapse before placement on the transplant waiting list. Relapse of solid organ tumours is dependent upon tumour type and time interval between treatment and transplantation. Overall 53% of recurrences occur in patients transplanted within 2 years of cancer treatment, falling to 34% if the interval between treatment and transplantation is 2-5 years and 13% if the interval is more than 5 years². The risk of recurrence is very low for non-melanoma skin cancer and in-situ carcinoma of the cervix or bladder such that no delay in placement on the waiting list is required. The risk of recurrent colorectal cancer, melanoma, and breast cancer is higher and the disease-free interval may need to be at least 5 years before transplantation depending on circumstances². Liaison with an oncologist is advised. Although there is evidence that dialysis patients have an increased incidence of cancer compared with the general population³, currently there is no evidence that dialysis patients on the transplant waiting list should have increased cancer surveillance strategies over that recommended for the general population⁴. Previous post-transplant lymphoproliferative disease (PTLD) is not a contraindication to re-transplantation.

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Guideline 2.8 – Tx : Evaluation and selection of the renal transplant recipient

We recommend that patients who are at risk of developing recurrence of original renal disease should be managed according to the European Best Practice Guidelines (EBPG) and the UK Guidelines for Living Donor Kidney Transplantation. (not graded)

Rationale

Recurrent disease accounts for approximately 5% of all allograft loss¹; primary focal segmental glomerulosclerosis, IgA nephropathy, mesangiocapillary glomerulonephritis type II and diabetic nephropathy are the commonest causes. Pre-transplantation counselling should include the potential risk of recurrent disease in appropriate patients. In rare circumstances transplantation may be contraindicated because of the very high risk of recurrent disease for example in recipients who have lost their first allograft early from recurrent disease^{2,3}.

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Guideline 2.9 – Tx : Screening investigations in the renal transplant recipient

We suggest that there is no evidence that asymptomatic potential transplant recipients require screening for diverticular disease, peptic ulceration or gall bladder stones. (2C)

Rationale

Colonic perforation due to diverticular disease is rare with modern immunosuppressive regimes which use low dose corticosteroids. In a retrospective study in which all transplant candidates aged more than 50 years underwent screening, none of the patients with significant diverticular disease had symptomatic disease post-transplantation¹. Patients with clinically significant disease should be assessed and managed according to standard practice. Peptic ulceration is now rarely a serious problem and there is a low morbidity rate even in patients with past peptic ulcer disease². Most transplant centres

ignore incidental cholelithiasis and there is no published evidence from the recent era to support a role for screening and intervention before transplantation.

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