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Renal Transplantation: An Update for Anaesthetists

Emma Aitken[1]*, Richard Stevenson[1], Faisal Hanif[1], Diana Raj[2], Karen Stevenson[1] and David Kingsmore[1]

[1]Department of Renal Surgery, Queen Elizabeth University Hospital, Glasgow, UK
[2]Department of Anaesthetics, Queen Elizabeth University Hospital, Glasgow, UK

***Corresponding author:** Emma Aitken, Department of Renal Surgery, Queen Elizabeth University Hospital, Glasgow, UK, Tel: +44-141-201-1100, E-mail: EmmaAitken@nhs.net*

Summary

Renal transplantation (RTx) is well established as the optimal method of renal replacement therapy (RRT); however the imbalance between organ supply and demand has led to increased numbers of organs coming from marginal donors. This in conjunction with an increase in the number of "marginal recipients", necessitates optimisation of other aspects of transplantation including perioperative care to maintain the excellent outcomes and survival benefit previously published in the literature. This review highlights the important elements of perioperative care including pre-operative cardiovascular risk assessment, fluid balance and minimising cold ischaemic times which are essential for the anaesthetic management of the renal transplant recipient and may have implications for future workforce planning and delivery of expectant care in a speciality with a high "out-of-hours" workload.

Renal transplantation (RTx) is the optimal method of renal replacement therapy (RRT) for patients with end stage renal disease (ESRD) with significant benefits for both quality of life [1,2] and survival [3,4]. Five-year survival on haemodialysis (53%) [5] is worse than that of many cancers [6]; compared to 5-year graft and patient survival following cadaveric transplantation of 86% and 89% respectively [7] and 92% and 92% for living donor (excluding HLA incompatible donors) [8]. Long-term survival is increased by 48-82% in patients receiving a renal transplant compared to those on the transplant waiting list with a survival benefit of transplantation seen within 8 months of surgery [3]. Furthermore, RTx is the most cost-effective strategy for the treatment of ESRD. In the United Kingdom (UK), there are nearly 50,000 patients with ESRD requiring RRT. Dialysis costs an average of £38,000 per patient per year with 3% of the total National Health Service (NHS) budget spent on kidney failure services. RTx costs approximately £17,000 per transplant and £5,000 per year thereafter for maintenance immunosuppression, resulting in cost savings of £31,300 per patient per year assuming a median graft survival time of 10 years [9].

Last year in the UK 2,930 renal transplants were performed (Figure 1). With the exception of the 2014-2015 year (for which there was a 5% reduction in both living and deceased donor numbers), donor numbers have increased steadily by about 5% per year since the introduction of the Organ Donation Taskforce in 2008. Despite this, the demand for organs continues to outweigh the supply and the number of patients on the waiting list to receive a cadaveric kidney at 31st March 2016 was 5275, a reduction of 7% from the previous year reflecting the overall increased number of transplants performed nationally over recent years [10]. Given that the mortality on the renal transplant waiting list is approximately 5.8% per annum and another 10.4% of patients are removed from the waiting list every year due to deterioration in their overall health [9], many patients on the waiting list will never ultimately receive an organ.

In recent years, the imbalance between supply and demand for organs has resulted in a drive to increase the donor pool. Primarily this has focussed on an extension of the criteria of suitable donors to include extended criteria donors (ECD)- marginal donors who would have previously been considered unsuitable and donation after cardiac death (DCD). Organs from such donors are known to have a higher incidence of primary non-function and delayed graft function (DGF) and are associated with poorer long-term outcomes [11]. It is therefore essential that other aspects of surgical and perioperative care be optimised to ensure that the benefits of RTx demonstrated in historical series are maintained.

Perhaps more than any other surgical specialty, RTx has undergone profound changes in the past ten years, with increasing workload and a plethora of novel pharmacological agents that have emerged following several decades of clinical trials. The volume of recent research in transplantation may be appreciated by comparing the number of publications on the internet to other surgical condition (Figure 2). As many of these advances have been implemented with such rapidity and in such number, medical staff not directly involved in the care of patients with ERSD may struggle to assimilate. This review aims to highlight the key recent changes that have occurred in RTx and their relevance to anaesthetists involved in delivering a renal transplant service, particularly the implications of this increasingly intense workload on workforce planning.

Changes in Donor Characteristics

The classical "ideal" deceased donor, a young male with no history of hypertension or diabetes who has been declared brainstem dead after a road traffic accident, is now rare with less than 20% of kidney donors now under the age of 35-years-old [9]. The on-going imbalance between the number of people on the waiting list and number of donated kidneys available has therefore led to an expansion of the donor pool beyond standard criteria donors (SCD).

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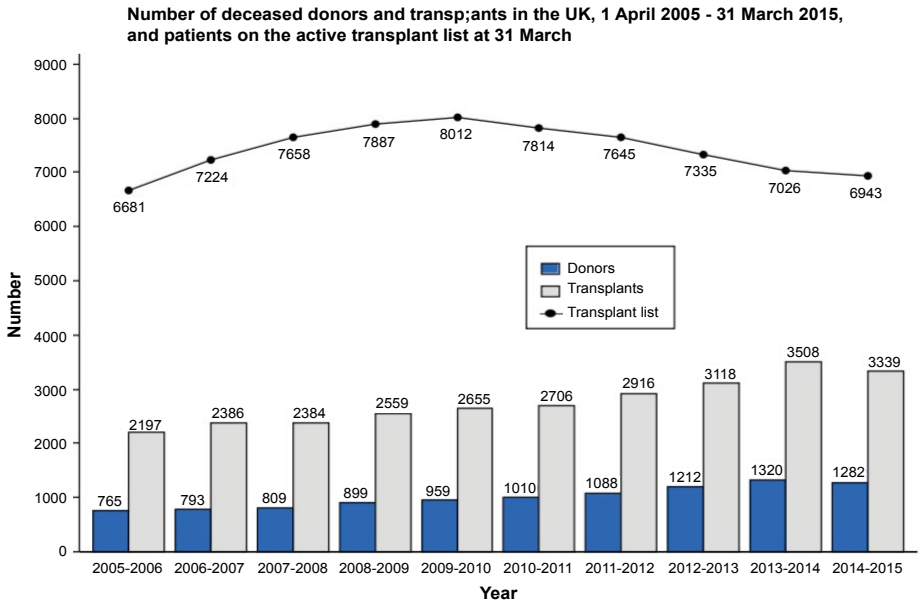

Figure 1: Patients on active waiting list in the UK at 31 March 2015 and number of deceased donors and transplants in recent years.

(Figure obtained from NHS Blood and Transplant,Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland).

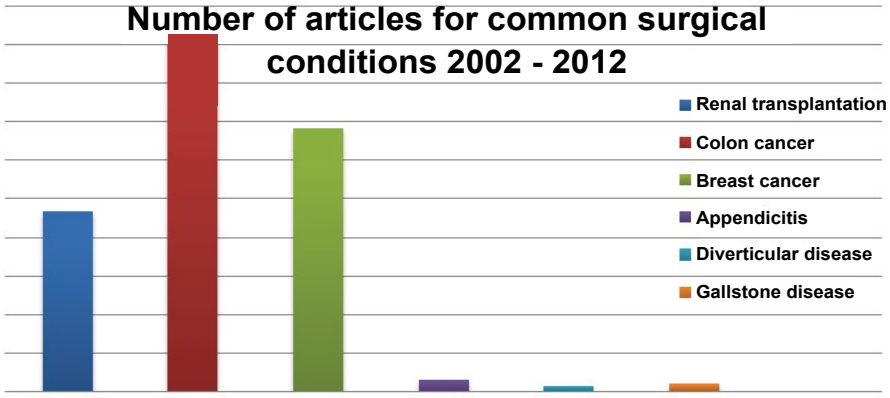

Figure 2: Number of articles available on Google Scholar for common surgical conditions 2002-2012.

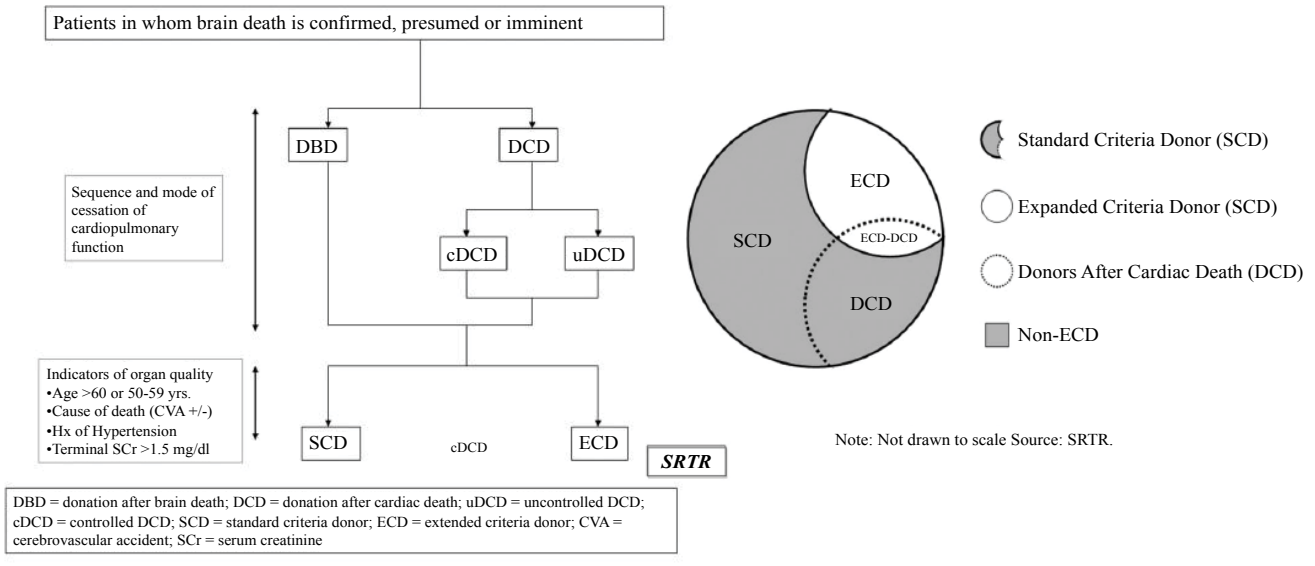

Figure 3: Definitions of donation after brainstem death (DBD), donation after cardiac death (DCD) and expanded criteria donation (ECD).

Donation after brainstem death (DBD) remains the most common type of deceased donor transplant. The recognition that kidneys from older donors with adverse characteristics may still be transplantable has led to increased numbers of expanded-criteria donors (ECD) (Figure 3). Half of all kidney transplants performed within the Eurotransplant zone in 2011 came from ECD donors [12]. Several studies have demonstrated acceptable outcomes from ECD donors, defined as a donor age more than 60 years or between 50 to 59 years with two or more associated risk factors (hypertension; creatinine > 1.5 mg/dL; cerebrovascular accident (CVA) as cause of death) [4,13] and mortality following transplantation of an ECD is 17% lower than remaining on the waiting list without a transplant [14]. Nevertheless ECD kidneys are associated with a 70% greater risk of graft loss that SCD kidneys [14] and the added life-years provided by a SCD renal transplant is 10 years compared to only 5.1 years following ECD transplantation [15,16], illustrating the importance of appropriate donor-recipient pairing, pre-operative counselling and optimisation of the rest of the transplant process. Molecular aging of the renal allograft is of particular importance with regard to ECD donors given the associated functional decline. Aging is a multi-factorial process bringing with it natural degradation. Like all organs, the kidney is affected in asimilar fashion, however the chronological age of the graft is a poor indicator of the biological function. The Glasgow Renal Prognostic Scoring System (GRPSS) uses molecular markers, such as CDKN2A to predict DGF and these have been shown to be a superior method of predicting post-transplant outcomes [17]. Future research focusing on cellular senescence, stem cells and the genomic pathways key to the aging process will aid the understanding of this complex problem with the ultimate aim of translating this knowledge to improved outcomes for RTx.

Donation after cardiac death (DCD) (non-heart beating donation) refers to a donor who does not meet the criteria for brainstem death but in whom cardiac standstill occurs before the organs are retrieved. The overwhelming majority of DCD organs are obtained from "controlled" DCD donors (Maastricht category III and IV) [18] i.e. following consent, life support is withdrawn from the donor and due to poor haemodynamic or respiratory status, cardiac death rapidly ensues, then the organs are retrieved in the operating theatre. After considerable ethical, legal and morale consideration, there are also a small number of emerging "uncontrolled" (category II) DCD retrieval programmes [18,19] i.e. the donor dies after unsuccessful resuscitation in the emergency department and catheters are placed in the femoral vessels to permit cooling of organs until consent for donation can be obtained. These programmes are likely to expand over the next 5-10 years and open up access to an entirely new potential donor pool.

Outcomes following DCD RTx are comparable to that of standard criteria DBD donors with regards to graft and patient survival and acute rejection episodes [20-22]. DGF (the phenomenon whereby the kidney does not begin to function immediately after transplantation, normally a result of acute tubular necrosis secondary to the insults sustained during retrieval, cold storage and re-implantation) occurs more frequently in DCD than DBD kidneys (44% vs. 24%) [20]. However, the negative impact of DGF on long-term graft function which is seen in DBD kidneys [23], does not occur in DCD kidneys [20,21,24]. The reasons behind this phenomenon are unclear and need to be further investigated, but may relate to the multiple processes involved in brain-stem death [24]. DCD organ donation does however pose a number of additional insults and challenges. In addition to the cold ischaemic insult which DBD kidneys receive whilst placed on ice for cold storage between the time of retrieval and transplantation, DCD kidneys also receive a significant additional warm ischaemic insult during the time between withdrawal of care to the donor, cessation of cardiac activity and commencement of the procedure for organ preservation (Figure 4). Both increasing cold ischaemic time (CIT) and warm ischaemic time (WIT) can have deleterious effects on the kidney (particularly marginal kidneys). The key to successful transplantation of these vulnerable kidneys is to minimise additional cold ischaemic time with streamlined perioperative care [25].

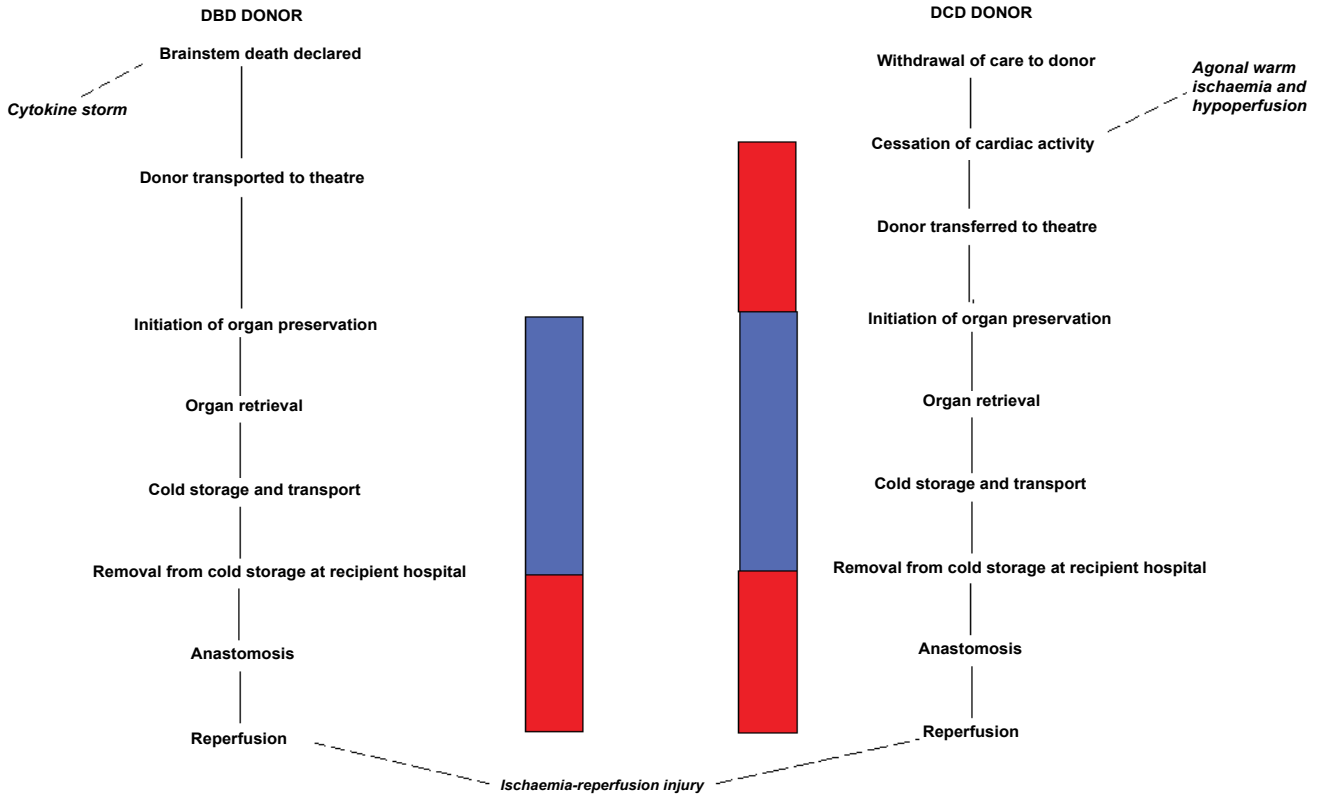

Figure 4: Diagrammatic representation of the events which organ during organ retrieval and implantation. Insults to the organ are highlighted in italics and cold ischaemic time (CIT) represented by the blue bar and warm ischaemic time (WIT) represented by the red bars for DBD and DCD organs.

Table 1: Changing cardiovascular risk profile of the renal transplant recipient.

	2001	2005	2010	2012
Age (S.D.)	39.2 (3.1)	41.7 (3.2)	48.7 (3.3)	50.8 (3.3)
Co-morbidties				
CAD	5.8% (n = 5)	12.8% (n = 10)*	31.2% (n = 25)**	34.4% (n = 42)**
PVD	10.4% (n = 9)	14.1% (n = 11)	18.7% (n = 15)*	21.3% (n = 26)*
Diabetes mellitus	9.3% (n = 9)	19.2% (n = 15)**	27.5% (n = 22)**	27.9% (n = 34)**
Stroke	0% (n = 0)	1.3% (n = 1)	7.5% (n = 6)**	9.8% (n = 12)**
BMI (kg/m^2)				
< 30	100% (n = 86)	94.9% (n = 74)	72.5% (n = 58)**	64.8% (n = 79)**
30-35		5.1% (n = 4)	26.25% (n = 21)	27.0% (n = 33)
> 35			1.25% (n = 1)	8.2% (n = 10)
Smoker (%)	40.7% (n = 35)	32.1% (n = 25)*	25.0% (n = 20)**	24.5% (n = 30)
Abnormal Resting ECG	5.8% (n = 5)	12.8% (n = 10)*	26.2% (n = 21)**	25.4% (n = 31)**
Exercise tolerance test				
Failed to complete 10 mins Bruce protocol/ achieve target heart rate	5.6% (n = 1)	12.0% (n = 3)	45.5% (n = 25)**	40.3% (n = 25)**
ECG changes consistent with ischaemia	5.6% (n = 1)	16.0% (n = 4)*	27.3% (n = 15)**	33.9% (n = 21)**
Echocardiography				
LV ejection fraction < 50%	0% (n = 0)	0% (n = 0)	2.2% (n = 1)	5.8% (n = 3)**
Left ventricular hypertrophy	33.3% (n = 4)	23.8% (n = 12)	55.6% (n = 25)*	42.3% (n = 22)*
Valvular heart disease	0% (n = 0)	0% (n = 0)	0% (n = 0)	0% (n = 0)
NHYA functional status				
1	60.5% (n = 52)	52.5% (n = 41)	26.2% (n = 21)**	25.4% (n = 31)**
2	39.5% (n = 34)	41.0% (n = 32)	60.0% (n = 48)	53.8% (n = 65)
3		6.4% (n = 5)	13.8% (n = 11)	21.3% (n = 26)
4				
ASA				
3	100% (n = 86)	100% (n = 78)	100% (n = 80)	97.5% (n = 120)
4				2.5% (n = 2)

Results are displayed as the percentage of the total transplant population/ year with each risk factor (or percentage of patients who had imaging with a positive result in cases when the whole population were not imaged). Coronary artery disease (CAD) was defined as previous myocardial infarction or symptomatic coronary artery disease with angiographic changes of stenosis > 50% in any vessel. Peripheral vascular disease (PVD) was defined as intermittent claudication with claudication disease < 50 metres, critical ischaemia or previous major lower limb amputation. Hypertension was defined as a systolic blood pressure repeatedly > 140/90. Diabetes was defined as two fasting blood sugars > 7 mmol/l. Hyperlipidaemia was defined as a fasting cholesterol > 5 mmol/l. Significant valvular heart disease was defined as a gradient across the aortic valve > 30 mHg or > 5 mmHg across the mitral valve. Left ventricular hypertrophy on echo was defined as a left ventricular mass index > 150 g/m^2. ASA is the American Society of Anaesthetics classification of peri-operative risk. All results were compared to 2001 as the baseline. *indicates a statistically significant difference from baseline ($p < 0.05$) and **indicates a highly statistically significant difference ($p < 0.001$) (Reproduced from Aitken, et al., 2013).

Live donor (LD) RTx is the optimal method of kidney transplantation with favourable short and long-term results [26]. Five year graft survival from LD transplants is in excess of 90% [9,26]. Promotion of living donor RTx along with paired pooled donation in those with direct incompatibility and altruistic donation may go some way to making up the shortfall of organs. Additionally, ABO incompatible transplantation and desensitisation programmes may assist in the acquisition of organs for individuals in whom it would have previously been very difficult to match an organ for [27]. Advances in donor selection, work-up and follow-up are aimed at minimising risk to the donor, though long-term follow-up on living kidney donors remain scanty. Surgical advances in donor nephrectomy including totally laparoscopic and hand-assisted techniques have resulted in reduced analgesic requirements and the length of hospital stay for donor [28]. The perioperative and anaesthetic care of live donors is outwith the scope of this article, however there are several recent excellent reviews on the subject in the literature [26,29].

Changes in Recipient Characteristics

In the early years of RTx when surgical and immunological experience was limited, only the fittest patients with ESRD were placed on the transplant waiting list. This waiting list has now had over three decades of "maturing", so that the current cohort of patients is a heterogenous mix of those who are surgically challenging, patho-physiologically complex, immunologically sensitised (often undergoing a second or subsequent transplant) and have extensive co-morbidities which are often accompanied by great psychological burdens that can complicate pre-operative assessment [30] (Table 1). Currently 12.3% of patients on the Eurotransplant renal transplant waiting list are > 65 years old and 33.7% have been on dialysis for over 5 years [12]. The mean age of a patient on the waiting list has increased from 46 years old in 1990 to 52-years-old in 2014. Over 70% of patients on the waiting list have two or more risk factors for cardiovascular disease (hypertension, cigarette smoking, diabetes mellitus or left ventricular hypertrophy) and nearly 35% had abnormal dipyridamole-stress myocardial perfusion scans [31]. Furthermore, median waiting time for deceased donor transplantation has increased from 2.5 years in 1990 to 3 years in 2014 [7], with many highly sensitised patients waiting considerably longer. There is a progressive, malignant, systemic attrition from the effects of ERSD, dialysis and the underlying disease that caused the renal failure during this time. As with the "marginal donors", good pre-operative assessment and perioperative care is paramount in the "marginal recipient". Perhaps equally important is the realisation that these patients have potentially the most to gain from transplantation. The low rates of cardiac complications in transplanted patients would support that despite the co-morbidity of this cohort, the operative procedure and anaesthetic considerations make this a sensible treatment of choice where possible.

Pre-Operative Assessment

Pre-operative assessment for RTx is generally performed at the time of appointment to the waiting list in most renal transplant centres. A transplant surgeon and/or nephrologist routinely perform it with anaesthetists rarely being involved in this initial assessment. The assessment should include an evaluation of all the technical and

anatomical aspects of the surgical procedure (suitability of vessels and bladder for implantation etc.); assessment of the immunological risk and immunosuppression; assessment of cardiovascular and perioperative risk and an opportunity for patient education. Major contraindications to renal transplant are rare (active malignancy or infection, severe vascular disease, recent myocardial infarction) and many conditions previously considered absolute contraindications are now regarded as relative (old age, obesity (BMI > 30 kg/m^2), poorly controlled diabetes, a primary renal disease with high recurrence rate in the transplanted kidney).

One of the major challenges that presents to all involved with transplantation is how to manage the waiting list to ensure that any changes to a patient's health are re-evaluated appropriately. Patients are warned at the time of appointment that in the event of deterioration in their general health their names could be temporarily or permanently suspended depending upon the severity of their illness. Bearing in mind the length of time on the waiting list, for patients with ERSD, deterioration of health during this time period is inevitable with an attrition rate of approximately 9% per annum dying whilst on the waiting list and 6% per year being permanently removed from the waiting list as a result of ill health [12]. It is inevitable that when presented with a potential recipient for a deceased renal transplant that there will be limited contemporary information available.

Elderly Patients

This attrition rate is particularly important given the increasing numbers of elderly patients awaiting RTx. Whilst RTx is known to improve survival in selected patients even > 70 years old (relative risk of death 0.59 compared to wait-listed patients) [32], only patients expected to survival the waiting time and still derive benefit should be considered for transplantation. There is some evidence that transplantation of elderly patients with ECD kidneys in an attempt to reduce waiting times is associated with improved survival (average life expectancy 5.6 years vs. 5.3 years) [33], however this combination of marginal donor and marginal recipient is associated with increased perioperative risk.

Cardiovascular Disease

ESRD is more than a single diagnosis, rather part of a catastrophic cascade of multi-organ disease that subsequently brings considerable co-morbidity particularly to the cardiovascular system. Atherosclerosis and left ventricular hypertrophy combine in patients with ESRD to make them a high-risk group for major adverse cardiac events [34]. The death rate from ischaemic heart disease is five times higher in patients with ESRD than that of the general population [35] and cardiovascular disease is the leading cause of death following transplantation accounting for 40-50% of all mortality [36]. Death with a functioning graft is now the leading cause of graft loss following RTx [34].

Although this is a high-risk patient group for perioperative cardiac complications, the actual Major Adverse Cardiac Events (MACE) rate is considerably lower than for other major procedures such as re-vascularisation surgery for critically ischaemic limbs-a procedure that is undertaken without question. Perhaps this reflects the assumption that there is a valid alternative to transplantation in haemodialysis, but this assumption is not borne out in the life expectancies. Nevertheless, almost all patients with significant cardiac risk factors tolerate the surgery well [37] and the challenge is to correctly identify pre-operatively those patients who will develop complications and intervene to reduce any modifiable risk. Numerous guidelines and recommendations exist for pre-operative cardiovascular risk assessment of patients being placed on the renal transplant waiting list. Most recommend cardiac stress-testing in all symptomatic patients and asymptomatic patients with risk factors for coronary artery disease i.e. those with advancing age (primarily those > 60 years old), diabetes, smoking, hypertension, dyslipidemia, long duration of time on dialysis, left ventricular hypertrophy or left ventricular ejection fraction < 40% [38-40]. Coronary angiography should be performed if an abnormality is detected on initial work-up or in patients with prior coronary events (this can pose difficult in pre-emptive patients due to the reluctance to administer nephrotoxic contrast to patients with residual renal function). Considerable variation in these guidelines perhaps represents the uncertainty about the optimal management strategy, with significant aortic stenosis perhaps being the only contra-indication.

Pre-operative physiological and functional assessment is very difficult to determine in patients with end stage renal failure due to the combination of impairment by the multifactorial diseases related to ESRD and the influence of fluid balance and fluid shifts between dialysis sessions. Exercise tolerance is likely to be influenced by fluid status (overloaded pre-dialysis, dehydrated post-dialysis), cardio-respiratory disease, anaemia, fatigue, uraemia and neuromuscular complications associated with long-term dialysis. These factors are, at least in part (anaemia, uraemia and left ventricular hypertrophy) likely to be reversed by transplantation [41]. Studies of routine cardiological assessment (ECG, echocardiogram and myocardial perfusion scans) have failed to demonstrate any increased ability to discriminate between patients who should be either removed or included on the waiting list [37,42]. Despite this lack of objective stratification, transplant surgeons and nephrologists make a subjective assessment of overall fitness that, along with intensive perioperative management, results in low cardiovascular complication rates despite being a high-risk patient group [37].

Perioperative Management

When an organ becomes available, the transplant surgeon and anaesthetist review the potential recipient. Essential basic investigations include haemoglobin, coagulation, urea and electrolytes, ECG and chest x-ray. Bloods will also be taken to confirm HLA-typing and formal "cross-matching" of donor and recipient serum. Depending on fluid balance and metabolic status patients may require dialysis pre-operatively, however it is essential that hypovolemia be avoided as hypotension and intravascular volume depletion increase the likelihood of acute tubular necrosis within the transplant [43]. In the past, prior to the availability of recombinant erythropoietin, chronic anaemia was common necessitating perioperative blood transfusion; however the need for perioperative transfusion is now rare and should be avoided if possible due to the additional immunological risks. Uraemia results in a prolonged bleeding time due to reduced platelet numbers and function. Prothrombin time and partial thromboplastin times are usually normal, but anticoagulation should be avoided in pre-operative dialysis. The surgical team will prescribe immunosuppressive drugs, several of which require to be administered in the perioperative period (often by the anaesthetist). The mainstay therapy is usually a calcineurin inhibitor such as tacrolimus, an antiproliferative agent e.g. mycophenolate mofetil and steroids in addition to an intravenous monoclonal antibody e.g. basiliximab or anti-thymocyte globulin. The anaesthetist is commonly asked to administer intravenous steroids and/or diuretics prior to reperfusion. The monoclonal antibodies are generally administered pre-operatively however can result in a cytokine storm on rare occasions [44]. This manifests clinically with fever, hypotension and erythema and is therefore essential for anaesthetists to be aware of.

The Surgical Procedure

The right iliac fossa is generally preferred as the site for the renal allograft if there is no contraindication. The muscles of the lower abdominal wall are divided to expose the iliac vessels and bladder. Two end-to-side vascular anastomoses are performed of donor renal artery on external iliac artery and donor renal vein on iliac vein. The anastomotic time should be kept as short as possible to minimise warm ischaemic damage, and usually takes about 30 minutes. The time when the vascular clamps are removed is a critical time for the anaesthetist in terms of blood pressure and fluid management (see below). Following this the ureteric anastomosis onto the bladder is performed.

Anaesthesia

General anaesthesia is routinely used for RTx, although regional anaesthesia has been successfully used in some centres [45]. Careful positioning of the patient is essential to protect arterio-venous fistulae and permit central access. Blood pressure cuffs and venous cannulae must be sited in the opposite arm from any existing arterio-venous fistulae and wherever possible the cephalic vein should be preserved for future vascular access for haemodialysis. Central venous monitoring is standard practice in most units to assist in the assessment of fluid balance, however routine invasive arterial monitoring is generally avoided, unless the patient is at very high cardiovascular risk, due to the risk of damage to the radial artery. Routine cardiac, neuromuscular and temperature monitoring are required. The patient should be kept normothermic using forced air warmers and warmed intravenous fluids if required.

The patient's airway should be protected with an endotracheal tube due to the risk of aspiration in uraemic patients [46]. Patients should be pre-oxygenated and a rapid sequence induction may be indicated, particularly in diabetic patients with a history of autonomic neuropathy. Anaesthesia is routinely induced with propofol, thiopentone or etomidate. Total intravenous propofol anaesthesia has been used for RTx and is associated with a lower risk of post-operative nausea and vomiting [47]. Isoflurane is traditionally the inhalational agent of choice as only 0.2% is metabolised and it causes few cardiac arrhythmias, unlike halothane. Emerging evidence from the VAPOR-trial has shown that sevoflurane significantly reduces acute rejection 2 years after living donor transplant compared with propofol [48] and offers an exciting avenue for mechanistic research. Enflurane should be avoided as there is a theoretical risk of nephrotoxicity [49]. There is little data on the role of the newer volatile agents in RTx.

Suxamethonium in intubating doses will cause a rise in serum potassium of ~0.5 mmol/l in patients with renal failure and repeated doses have led to cardiac arrest [49]. Rapid sequence induction should be modified to avoid suxamethonium wherever possible in patients with ESRD and it is absolutely contraindicated in patients with serum potassium > 5.5 mmol/l. Non-depolarising muscle relaxants are generally favourable. Atracurium has theoretical advantages as it is also broken down by Hofmann elimination, whilst pancuronium is best avoided as it is 80% renally excreted therefore its action may be prolonged [46]. Rocuronium, 30% excreted by the kidney and reversed by Sugammadex offers a good, safe alternative [50,51], however this complex is renally excreted and prolonged exposure is inevitable in this patient population and should be bourn in mind. Short-acting intravenous opioids may be used to blunt the stress response to laryngoscopy, particularly since many of these patients are hypertensive pre-operatively.

Intra-operatively fentanyl, which is metabolised primarily by the liver, can be used in normal doses. Morphine however may have prolonged sedative effects in patients with renal failure as its active metabolite, morphine-6-glucuronide, accumulates.

Fluid Balance and Perfusion

Converse to surgery in other patients with renal failure in which fluid administration is minimised to prevent fluid overload, kidney transplant recipients require liberal volumes of intravenous fluid intra-operatively. This is of particular importance when the vascular clamps are removed and blood flow is restored to the kidney. The anaesthetist has a crucial role to play at this point, as the best chance of immediate graft function is reliant upon adequate intravascular volume and avoidance of hypotension. The target central venous pressure should be ≥ 10-12 mmHg [52]. Similarly, intra-operative hypotension is an independent risk factor for DGF, with an odds ratio of 1.51 for every 5 mmHg incremental decrease in mean arterial blood pressure [53]. In particular, rapid fluctuations in blood pressure in the perioperative period are associated with allograft damage, with patients with high pre-operative blood pressure most likely to experience the greatest drop [43]. A surprising volume of fluid may be required to achieve such targets, with some studies requiring as much as 30 ml/kg/hour [54,55]. The specific type of fluid used is less important, although normal (0.9%) saline seems a logical choice, as it is high in sodium (particularly if osmotic diuretics are given intra-operatively) and free of lactate and potassium.

Dopamine may be administered in the intra-operative and early post-operative period for two purposes. There is theoretical benefit for the use of a DA_2-receptor agonist (in doses of 2-3 mcg/kg/min) to promote renal blood flow, although no outcome benefit has ever been demonstrated [56]. At doses of 5-10 mcg/kg/min, β-adrenergic effects may help in maintaining normotension, however at higher doses (10-20 mcg/kg/min) the α-adrenergic effects predominate and blood flow to the grafted kidney may actually be reduced. Similarly α-adrenergic agonists e.g. phenylephrine, cause large reductions in blood flow to the transplanted kidney and should be avoided if possible. If hypotension persists despite adequate filling, β-agonists such as dobutamine and dopexamine are preferable [49]. It often is forgotten that effective removal of fluid and potassium is routine in the dialysis units in which these patients are cared for. In the era of ERAS and minimal perioperative fluid, many feel uncomfortable in aggressive perioperative fluid administration, but with pre-operative dialysis, patients are often dehydrated with consequent impairment of transplant perfusion and this can be readily demonstrated in theatre.

Post-Operative Management

As with the intra-operative period, accurate fluid balance post-operatively is essential. Fluid administration is guided by urine output, central venous pressure, blood pressure and daily weights. Again it is important to avoid prolonged periods of hypo- or hyper-tension. Work from our own centre has demonstrated that a mean arterial blood pressure < 70 mmHg at any point during the post-operative period is associated with DGF [57]. Haemodialysis may be required in the immediate post-operative period for treatment of hyperkalaemia or pulmonary oedema. The volume of fluid administered in the perioperative period will vary greatly depending on whether or not the kidney has DGF. In many patients with immediate function, patients rapidly become polyuric of large volumes of unconcentrated urine. These patients will require large volumes of intravenous fluid to replace urinary and insensible losses. It is also important to monitor serum electrolytes in such patients as they can become profoundly hypokalemic and hypocalcemic. In patients who have DGF, judicious administration of intravenous fluid is required to avoid periods of hypotension and hypoperfusion but not overload an oligo- or an-uric patient.

Thromboprophylaxis

Primarily as a result of co-morbidities, patients undergoing RTx are atmoderate-high risk of deep venous thrombosis. Early mobilisation on the first post-operative day is encouraged and all patients should have anti-embolism stockings. Prophylactic heparin (either low-molecular weight or unfractionated) is administered post-operatively until the patient is fully mobile, although low-molecular weight heparin is unlicensed in the UK for patients with an eGFR < 30.

Analgesia

Non-steroidal anti-inflammatory agents must be avoided as they can cause vasoconstriction and reduce renal blood flow. Epidural anaesthesia has been used successfully for RTx, however hypotension must be avoided. Generally, patient-controlled opiate analgesia provides excellent pain relief in the early post-operative period. It is important to be aware that if immediate kidney function does not occur, active metabolites of morphine can accumulate leading to drowsiness and respiratory depression. For this reason repeat doses of morphine should be reduced accordingly (e.g. 1 mg boluses with 15 minute lockout) or shorter acting agents e.g. fentanyl should be used instead.

Immunosuppression

As indicated previously, immunosuppression in transplantation

has been the subject of numerous large multi-centre trials over the past 30 years. Vast improvements in both short and long-term outcomes are associated with the development of novel drugs and treatment regimens. The gold standard immunosuppressive regimen is now well established with an intravenous induction agent e.g. basiliximab (a monoclonal antibody to IL-2), a calcineurin inhibitor e.g. tacrolimus, an anti-proliferative agent i.e. mycophenolate mofetil and steroids (which are also administered intravenously in the perioperative period) [58]. Many centres will use variations on this protocol for specific patients i.e. those with higher than normal immunological risk. All antibodies given as immunosuppression have the risk of inducing cytokine storm and should be given with circumspection. In particular the alternative induction agents, alemtuzumab (a monoclonal antibody to CD52) and anti-thymocyte globulin, should be given in conjunction with steroids and anti-histamines to minimise adverse reactions. All drug regimens should be clarified with the transplanting surgeon and perioperative risks discussed.

Early Complications

With accurate blood grouping HLA-matching and formal cross matching for donor and recipient blood/serum (see below), hyperacute rejection is now vanishingly rare. Acute rejection (either cellular or humoral) can however occur in the early post-operative period. This can manifest as either prolonged DGF or deterioration in renal function and is often accompanied by oliguria and pain over the transplanted kidney. Rejection is treated with high dose steroids, alternative immunosuppressive regimens or techniques such as plasma exchange to remove antibodies if appropriate. Eculizumab, a C5 complement inhibitor has been shown to be effective in both the treatment of antibody-mediated rejection, and also in cases of atypical haemolytic uraemic syndrome in the allograft, although long-term results and duration of treatment are still unclear.

Vascular complications are rare (occurring in 2-3% of kidney transplants), but carry significant morbidity. They must be identified and acted upon urgently in an attempt to salvage the graft. Renal artery thrombosis is normally a technical complication which presents within 48 hours of surgery. It can rapidly lead to graft loss and the need for allograft nephrectomy. A kink in the renal artery, severe volume depletion, hypotension, and a prolonged warm ischemia time may precipitate this devastating complication. Typically it presents with abrupt onset anuria within the first 48 hours of transplantation and is an indication for immediate re-exploration. Renal vein thrombosis occurs within the first week after transplantation. The clinical presentation includes sudden oliguria or anuria, graft tenderness and swelling, haematuria and ipsilateral lower limb oedema. Duplex ultrasound often shows high resistance waveforms and may visualise clot within the vein. Urgent re-exploration is required. Significant bleeding from the vascular anastomoses is rare, but can be dramatic and life-threatening manifesting as severe hypotension and hypovolaemic shock. Resuscitation and rapid operative control of the bleeding is required.

Ureteric complications such as urine leak or ureteric stricture causing hydronephrosis occur in approximately 5% of patients. They rarely represent a surgical emergency though may present with acute deterioration in graft function or anuria. Often such complications are managed by interventional radiology and definitive operative intervention can be delayed.

Cold Ischaemic Time, DGF and its Prevention

It is now well recognised that the duration of cold ischaemia preservation (cold ischaemic time (CIT)) imparts significant consequences including a higher likelihood of DGF, higher chance of acute rejection, poorer ultimate graft function and increased early graft loss. There is little clear data to determine absolute cut-offs for the length of cold ischaemia associated with adverse outcomes, and there is likely to be a plethora of compounding factors. A large multinational analysis has clearly demonstrated that beyond 18 hours of cold ischaemia the risk of graft failure increases exponentially [59]. For this reason many efforts have focussed on minimising any unnecessary delays to reperfusion.

Organisational Issues

The drive to minimise preventable insults to the kidney requires significant organisational changes both locally and nationally. For example, the UK national allocation system for cadaveric kidneys has recently been revised to ensure a higher priority is given to geographic location of donor and recipient and the distance required to transplant the kidney when deciding whom a kidney is offered to. Additionally a reorganisation of local surgical and anaesthetic services with additional workforce planning may be required to facilitate the increasing burden of out-of-hours work as it becomes apparent that kidney transplants can no longer wait until the morning. Furthermore, given that RTx is often performed in an emergency theatre shared by several specialities, local agreements are essential to ensure that whilst the sickest patients receive the optimal timing of intervention, that RTx is recognised as equally important in life preservation, requiring immediate surgery that should not be delayed if possible.

Selective Omission of the Donor-Recipient Crossmatch ("Virtual Crossmatch")

Prior to any transplant a series of tests are required to confirm that the donor and recipient are immunologically compatible. Patients are initially tested for ABO incompatibility and then HLA matching is undertaken at three important loci-A, B and DR-for which there are a total of 6 possible antigens. This matching is carried out nationally based on prior reported blood group, HLA type and known antibodies. Finally a formal cytotoxic crossmatch of donor T-cells against recipient serum has traditionally been performed to confirm compatibility and the absence of preformed antibodies to the donor which could lead to hyperacute rejection, prior to transplantation. This final cross matching process takes approximately 6 hours and can only be performed once the kidney has arrived at the recipient's hospital. The delay for this cross matching process adds significantly to CIT.

The "virtual crossmatch" process permits selective omission of the final donor-recipient crossmatch in patients of very low immunological risk who have no known preformed antibodies or sensitising events (transplants, transfusions or pregnancies). This process has significantly reduced both CIT and incidence of DGF [60]. Locally nearly half of renal transplants performed in the past year have been transplanted in this manner.

Machine Perfusion

Another novel approach to improving and assessing organ viability involves machine perfusion in a "pod" that pumps cold perfusion fluid through the kidney in a pulsatile manner whilst measuring flow and resistance. It is particularly useful for kidneys that may have undergone ischaemic damage during the retrieval process, and can be used to predict organ viability (particularly useful for kidneys from ECD and DCD donors). Studies have demonstrated that machine perfusion is associated with a reduction in DGF (adjusted odds ratio 0.57) and superior graft survival at 1-year (94% vs. 90%; $p = 0.04$) [61]. There are several on-going clinical trials assessing the value of machine perfusion in specific donor groups.

Conclusions

RTx is well established as the optimal method of RRT; however the imbalance between organ supply and demand has led to increased number of organs coming from marginal donors. This, in conjunction with an increase in the number of "marginal recipients", necessitates optimisation of other aspects of transplantation including perioperative care to maintain the excellent outcomes and survival benefit quoted in the literature. This review article has highlighted some important elements of perioperative care including pre-operative cardiovascular risk assessment, fluid balance

and minimising cold ischaemic times which are essential for the anaesthetic management of the renal transplant recipient and may have implications for future workforce planning and delivery of expectant care in a speciality with a high "out-of-hours" workload.

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