

Delayed graft function: a dilemma in renal transplantation

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INTRODUCTION

'Delayed graft function' (DGF) is a term used to describe the lack of acceptable autonomous function in a kidney which, after transplantation, requires intervention in the form of dialysis. Historically, DGF was defined by the requirement for dialysis within the first week of renal transplantation. However, the postoperative requirement of haemodialysis or peritoneal dialysis is not standardized, and is very subjective, reflecting considerable difficulty in deciding when someone requires dialysis. This is a clinical decision that varies among consultants and hospitals, and a certain amount of medical dogma applies to the decision. Variables include the amount of urine being produced, serum creatinine levels, fluid overload, and uraemic status of the patient. Recently, efforts have been made to quantify DGF more scientifically. This has led to different levels of severity of DGF being described and the introduction of different descriptions, e.g. (i) DGF requiring dialysis or not [1]; (ii) intermediate delayed function and slow graft function [2]; and (iii) poor early graft function [3].

The looseness of the definition explains why there is so much variation in different clinical studies. Efforts to redefine DGF using a more measurable method have been available for some time. Because of the inability to define DGF by a measurable factor there is wide variation in its reported incidence.

ALTERNATIVE DEFINITIONS OF DGF

- (a) The number of days to achieve a creatinine clearance of >10 mL/min, calculated by the Gault-Cockcroft formula, which is the threshold for minimal graft function [4].
- (b) A serum creatinine level of >3 mg/dL on the fifth day after surgery [5].
- (c) The need for dialysis within 72 h after transplantation [6].
- (d) If the serum creatinine level increased, remained unchanged, or decreased by less

than 10% per day immediately after surgery during three consecutive days for >1 week [7].

(e) A rising serum creatinine level above that before surgery, or urine output of <300 mL within 6 h of transplantation, despite diuretics and adequate volume [8].

(f) Urine output of <1 L in the first 24 h or a decrease in serum creatinine of <20 – 30% , reflected in a poor GFR [9].

(g) Calculating the creatinine reduction ratio on post-transplant day 2 (serum creatinine on day 1 minus serum creatinine on day 2, multiplied by 100, and divided by serum creatinine on day 1) where $\leq 30\%$ was deemed poor [10].

INCIDENCE

DGF does not occur after all renal transplantations; there is a wide variation in reporting (5–93%) depending on the source of the graft [3,11], but most centres report a DGF rate of 20–40% [12]. There is very little difference in the incidence of reported DGF in the multi-centre reviews in Europe and the USA [12,13]. As people attempt to redefine the parameters of DGF, they influence its rate of presentation. The factors that predispose to DGF also differ between centres, contributing to this variation. Factors associated with an increased occurrence of DGF can be categorised in to three areas, i.e. donor, recipient and transplant procedure [14]. Donor factors include: increased age, hypertension (>10 years), creatinine clearance <80 mL/min, vascular sclerosis, weight, female gender, and atraumatic death. Recipient factors are pre-sensitization, ethnicity, pre-transplant levels of pro-inflammatory cytokines, pre-transplant anuria, pre-transplant mean arterial pressure (<100 mmHg), and American Society of Anesthesiology physical status category IV (a patient with an incapacitating systemic disease that is a constant threat to life). Transplant procedural factors comprise cold ischaemia time, warm ischaemia

time, anastomotic time, and selection of preservation solution. There is a difference between the occurrence rate of living donor and cadaveric donor kidney transplantation-induced DGF [3]. In living donor transplants the two dominant aspects that predict the occurrence of DGF are the recipient's preponderance to microvascular disease resulting from their diabetic status, and warm ischaemia time [3]. Cold ischaemia time is also strongly associated with DGF, with a 23% increase for every 6 h [15].

There have been efforts to expand the donor pool by addressing different aspects of accepted exclusion criteria. Previously, the following were exclusion criteria, but efforts have been made to alter these in certain circumstances: donor ≥ 60 years old or 50–59 years old with two of the following characteristics: donor history of cerebrovascular accident, donor history of hypertension, and elevated creatinine (>1.5 mg/dL) at any time during donor management [16]. Also, changes in the view of what would have been thought to be a surgically suboptimal kidney (with a vascular, parenchymal or urological anomaly that would have been rejected as unsuitable) are now being reassessed. These abnormalities would have included a kidney with more than two arteries on a single patch, noticeable parenchymal damage to the kidney (macroscopic sclerosis or sutured polar branches accidentally damaged during removal), and kidneys with complex anomalies of the excretory system. These anomalies increase the operation time and extend the ischaemia time of the kidney [17].

ROLE OF ISCHAEMIA TIME

'Warm ischaemia time' is measured from the time at which the renal vessels are ligated during harvesting to when the temperature of the kidney is reduced to 4 °C. 'Cold ischaemia time' is measured from when a kidney is cooled to 4 °C at the time of procurement to

the time it is implanted into the recipient. There is the potential for a second warm ischaemia time during the anastomosis of the graft; the influence has been shown to be significant but it is not often recorded accurately [9]. The time constraint on this part of the procedure falls at 45 min, after when there is an increased risk of DGF [18]. Increases in cold and warm ischaemia time increase the incidence of DGF [3,7,18]. Warm ischaemia time is becoming more prevalent with the use of donors with no heartbeat. In living donors, the actual ischaemia time is minimal, and the quality of the transplanted graft is better from a healthy living donor [3]. The duration of cold ischaemia is variable, but has a direct effect on the presence of DGF and graft survival [7]. Several innovative approaches have been attempted to minimise damage during this period, including pulsatile perfusion [19], inhibition of calcium uptake by cells [19], and thrombolysis before cold storage and addition of protective agents to the transport medium [20]. Currently the solution for perfusion and storage is University of Wisconsin Solution (Viaspan®). Attempts to change the transport medium to other solutions to ease the transition from donor to recipient are ongoing, as it has been shown that the greater the ischaemic reperfusion injury the higher the risk of DGF [20]. The difference between machine perfusion and cold-storage solutions has been examined; machine perfusion gives fewer episodes of DGF, but this depends on flow and resistance, and levels of calcium in the solution [21]. These authors showed that maintaining vascular viability at the molecular level and mitigating the apoptotic process during ischaemia reduced the incidence of DGF and increased the 1- and 2-year survival. The advantage of machine perfusion is that 'poor' kidneys (those with high perfusion pressures) are discarded.

HISTOPATHOLOGY

Many pathological findings are associated with DGF, the most common being acute tubular necrosis. Other pathological processes that can mimic DGF include antibody-mediated rejection, cortical necrosis/infarction, endothelial damage, acute calcineurin inhibitor toxicity, thrombotic microangiopathy, drug-induced interstitial nephritis, and fulminant disease recurrence [9]. While DGF implies eventual function, the processes of antibody rejection and infarction are usually irreversible and lead to primary

graft nonfunction. Typical histological findings of DGF are dilatation of tubules, loss of proximal epithelial cell brush border, epithelial cell necrosis/apoptosis, and cellular casts [14]. Many of these findings depend on the source of the graft and on the conditions during transplantation. Cadaveric and living donor kidneys show tubular cell apoptosis. A higher percentage of this apoptosis occurs in the cadaveric kidney, but the transplant conditions of a living donor are optimal, with cold ischaemia time being at a minimum.

DGF is also thought to up-regulate MHC class II antigens, thus predisposing the transplanted graft to an increased incidence of acute rejection, which can be recognized histologically by the presence of tubulitis and infiltration of leukocytes into the tubular epithelium. A key clinical sign of acute rejection is a baseline rise in serum creatinine of 25% in the asymptomatic patient with no other apparent explanation. In the clinical setting, DGF can mask the presentation of acute rejection. The clinical difficulties of acute rejection are through the effects on the functional unit of the kidney, the tubular cells of the nephron. DGF is marked by apoptosis and necrosis of tubular cells, which produces chemoattractants for immune cells. This added insult of immune-mediated damage to tubular cells means that the kidney function is further compromised. So, in the presence of DGF, the kidney is more likely to have episodes of acute rejection.

Since the introduction of the Banff classification of kidney transplant pathology there has been conformity in the reporting of biopsies taken from allografts. This classification was initially agreed in 1991, and with improvements in techniques and the introduction of different immunohistochemical markers, it is continuously being updated. The histological changes are in the architecture of renal parenchyma, which include vascular, glomerular and tubulo-interstitial changes. The histological assessment of chronic change in the renal transplant has led to the development of the term 'chronic allograft nephropathy' (CAN). CAN has replaced the term 'chronic rejection', which was a misnomer, as the damage being accrued is caused more by parenchymal and architectural changes than actual immune-mediated damage. Historically, CAN has been characterized as an ill-defined spectrum of changes including mesangial matrix

expansion, mesangial proliferation, basement membrane thickening with double contours, and peripheral mesangial interposition, sometimes with focal segmental sclerosis. Currently, the presence of double contours is regarded as the most specific histopathological change [8]. The insult of DGF induces changes in the kidney parenchyma that lead to earlier presentation of and more severe prognosis for CAN. It has been shown that the early development of interstitial fibrosis in renal biopsies shows a progressive decline in creatinine clearance, and there is very little structural or functional reserve within the allograft to compensate for additional insults [22]. Thus, as the transplanted kidney ages it struggles to compensate with not only the normal loss of renal function from the ageing process, but also the added difficulties of antigen-dependent and -independent host responses. Alterations in the filtration system have been shown in the transplanted kidney compared with the normal kidney of patients after nephrectomy: the function and histological structure was inferior in the transplanted kidney to that in the normal kidney, and the kidney with DGF was in an even poorer condition [23]. DGF has been well described in association with an inferior functioning kidney at 1 and 2 years after transplantation [18,24].

MANAGEMENT

When DGF is diagnosed, the main management strategy is to support the patient with dialysis and to monitor for rejection with serial biopsies. A question arises about the use of alternative immunosuppressants. The general consensus is to try to spare the renal allograft from toxic effects, so a substitute for calcineurin inhibitors is sought. Daclizumab and basiliximab inhibit stimulation of T cells by binding to the interleukin-2 receptor. Concerns have been raised about the long-term effects of the original form of this type of immunosuppression (monoclonal and polyclonal antibody), with a reported increase in long-term malignancy-related deaths, deaths from cardiovascular complications, and a rise in the rate of infectious complications after surgery [25]. However, these two immunosuppressants have not shown these effects.

Many centres have different regimens for managing DGF. Most patients continue on

corticosteroids and mycophenolate mofetil (inosine monophosphate dehydrogenase inhibitor). The introduction of sirolimus (Rapamune®) was felt to be the answer to dealing with DGF, as it was supposedly not nephrotoxic. Unfortunately it rapidly became apparent that sirolimus caused a lengthening of DGF instead of shortening it [26], probably because of its ability to influence the proliferation of tubular cells. The prospect of reducing the occurrence of DGF with highly immunosensitized patients has been introduced with the possibilities of induction therapy, where a patient is commenced on a monoclonal or polyclonal antibody before receiving a transplant (OK3 and ATG); however, OKT3 actually increases the occurrence of DGF [27]. The ideal regimen is the use of polypharmacy and one that is tailored to each patient.

DISCUSSION

How is the success and failure of kidney transplantation defined? Treatment success is currently measured by graft and patient survival. The current worldwide rate of 1- and 5-year graft survival is 95% and 80%, respectively, with death with a functioning graft the commonest cause of graft loss after 1 year. The presence or absence of DGF will give an indication of the life-expectancy of the renal graft. The effects of DGF can be converted into more measurable events such as an increase in creatinine levels, hospitalization, and in rejection episodes, and these all indicate poorer survival rates at 3 and 5 years. The serum creatinine level at 1 week after surgery is a strong predictor of eventual graft and patient survival, as is the absence of acute cellular rejection, and these predictors have been shown to be influenced by the initial presence of DGF.

The presence of DGF is influenced by: (i) the surgical management of the donor (warm ischaemia time); (ii) cold ischaemia time, which predicts the occurrence of DGF with the risk increasing by 23% for every 6 h [6]; (iii) immunosuppressant management also plays a role in the presentation of DGF. The use of calcineurin inhibitors does not increase DGF, but prolongs it, while the use of OKT3 increases the incidence of DGF [7]; (iv) kidney sharing on an HLA basis results in longer cold ischaemia times and therefore offsets any benefit of the HLA matching by increasing the risk of DGF; (v) the transport solution that

leads to the lowest risk of DGF is University of Wisconsin solution (Viaspan®), both for cold storage and machine perfusion.

DGF is mainly the presentation of a transplanted kidney in the process of replacing its tubular cells that were damaged during the storage period. The process means that the kidney is not functioning optimally; the replacement of cells leads to an increase in the presence of immunotactic materials produced by cells undergoing apoptosis and necrosis. This increases the risk of acute rejection by leading to an overwhelming immune response to the allograft. The presence of raised immune material leads to increasing production of fibrotic material and to a decrease in functioning tubules, increasing the prevalence and severity of CAN. It is therefore imperative to lessen the occurrence of DGF to attempt to increase the long-term survival of renal allografts.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: DGF, delayed graft function; CAN, chronic allograft nephropathy.