CHAPTER 213

Acute Renal Failure in Kidney Transplant Recipients

Paolo Cravedi, Madhav Menon, Norberto Perico, and Giuseppe Remuzzi

OBJECTIVES

This chapter will:

1. Discuss the causes and risk factors of delayed graft function (DGF).
2. Describe the pathophysiology of ischemia/reperfusion damage.
3. Address the question of whether DGF is associated with an increased risk of acute rejection and long-term graft dysfunction.
4. Discuss allograft acute kidney injury (AKI) as a template for studying mechanistic aspects of AKI.
5. Discuss strategies to prevent ischemia/reperfusion injury and DGF.
6. Discuss future therapeutic perspectives.

Acute kidney injury (AKI) is a common clinical problem. Similar to native kidneys, transplanted kidneys are prone to all forms of AKI. Transplanted organs also are predisposed to a number of additional and specific acute insults related to immunologic injury, toxicity of immunosuppressive agents, ischemia–reperfusion injury, and surgical complications.[1] Fig. 213.1 lists common causes of AKI specifically important to allografts along with the time frame posttransplantation that these causes commonly are encountered in clinical practice. Importantly, the timing of the initial AKI that occurs in most allografts is preset and known ahead of time, serving as an excellent platform to study mechanisms that may be common to all forms of acute renal dysfunction. Delayed graft function (DGF) represents a stereotypic form of AKI after kidney transplantation that results in posttransplantation oliguria, increased allograft immunogenicity, and risk of acute rejection. Rarely, a graft never functions (primary nonfunction). Experimental studies have shown that ischemia and reinstitution of blood flow in ischemically damaged kidneys after hypothermic preservation activate a complex sequence of events that sustain renal injury and play a pivotal role in the development of DGF.[2]

The incidence of DGF has been reported variously to occur in 8% to 50% of primary cadaveric renal transplants in the United States[3] and in 35% of cadaveric transplants in a European multicenter study report.[4] According to the United Network for Organ Sharing (UNOS) Renal Transplant Registry, the frequency of DGF in cadaver transplants declined only slightly, from about 29% to 23% during the 1990s,[5] despite improvements in donor and recipient management and in diagnostic and therapeutic tools. In recent unpublished data from Mount Sinai Hospital, New York, including 96,236 transplants from 1995 to 2012, DGF rate was still 21.9% for recipients of cadaveric kidney transplants. These data showing minimal reduction in DGF rates can be explained partly by the expansion of criteria for acceptable donors, including use of marginal and older donors,[6] as well as recipients that may be more predisposed to develop DGF.

CAUSES AND RISK FACTORS OF DELAYED GRAFT FUNCTION

Prerenal, renal, or postrenal factors may cause DGF (Box 213.1). Recipient hypovolemia is the most common prerenal cause of DGF, and it is generally reversible with proper fluid

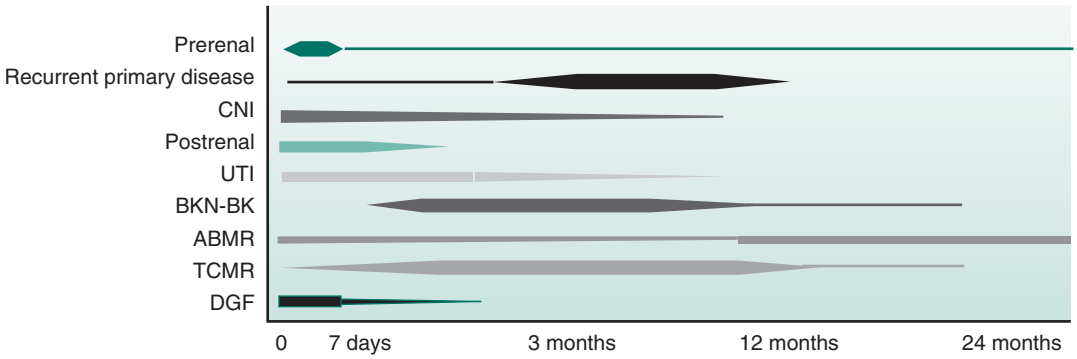

FIGURE 213.1 Timing and cause of allograft acute kidney injury (AKI): the common causes of allograft AKI by the usual time frames of their occurrence after transplantation. The thickness of the lines depicts frequency of occurrence in the respective time frames, which are plotted on the X-axis. *ABMR,* Antibody-mediated rejection; *BKN,* BK nephropathy; *CNI,* calcineurin inhibitors; *TCMR,* T cell–mediated rejection; *UTI,* urinary tract infection.

BOX 213.1

Risk Factors for Delayed Graft Function

Procurement Factors
Kidney from non–heart-beating donor
Inotropic support of the donor
Cold storage preservation
Cold ischemia time

Donor Factors
Age (>55 years)
Marginal kidney from diabetic or hypertensive donor

Recipient Factors
Prerenal
Recipient hypovolemia
Intraoperative albumin administration
Nocturnal hemodialysis
Hemodialysis with ultrafiltration within 24 hours before transplantation
Recipient or donor body weight
Number of previous transplants
Renal
Inherited thrombophilia
Factor V Leiden mutation
OKT3 monoclonal antibody therapy
Antiphospholipid antibodies
Preformed antidonor antibodies
Acute tubular necrosis
Cyclosporine nephrotoxicity
Postrenal
Ureteral leakage
Ureteral obstruction

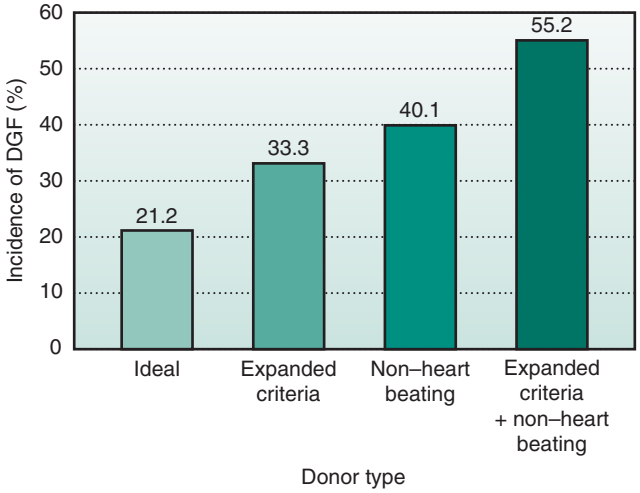

FIGURE 213.2 Incidence of delayed graft function (DGF) in kidney transplant recipients from ideal, expanded criteria, non–heart-beating and non–heart-beating with expanded criteria donors between 2000 and 2004 in the United States. Expanded criteria donors were all donors aged 60 years or older and those between 50 and 59 years of age with at least two of the following criteria: serum creatinine concentration greater than 1.5 mg/dL, history of hypertension, or cerebrovascular accident as cause of death. (From U.S. Department of Health and Human Services. 2005 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1995-2004. Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2005.)

management. One rare form of prerenal DGF, which is yet a major cause of early graft failure, is vascular thrombosis.[7,8] Risks associated with graft loss from thrombosis are increased with a pediatric recipient or donor, with prolonged cold ischemia time, and with acute tubular necrosis (ATN). OKT3 monoclonal antibody treatment (commonly used in the past, but no longer employed because of the high risk of cytokine release syndrome) also may increase the risk of thrombosis by inducing the expression of tissue factor on endothelial cells and monocytes.[9] The primary intrinsic renal causes of DGF in renal transplantation are hyperacute rejection, ATN, and calcineurin inhibitor (CNI) nephrotoxicity. Postrenal causes of DGF, found in up to 4% of kidney recipients, usually are related to ureteral leakage rather than obstruction.[10]

Risk Factors Related to the Donor

The source of donors is particularly important (see Box 213.1). ATN, for example, is remarkably higher in recipients of cadaveric kidney transplants than in those receiving a living kidney. The difference is accounted for mainly by the massive release of cytokines and growth factors associated with brain death that contributes to ischemia and inflammation[11] of the kidney and, together with the hemodynamic instability, which leads to ATN. The modality of organ procurement represents another important risk factor for donor-related DGF. The growing shortage of organs for transplantation has increased interest in using non–heart-beating and expanded criteria donors. Renal grafts from non–heart-beating donors[12] have twice the risk for DGF as those from heart-beating donors, despite similar outcomes at 1 year. There are now considerable data and experience to support the policy that no marginal or suboptimal graft should be discarded because of donor age, diabetes, or hypertension, provided that the pretransplantation kidney biopsy is acceptable.[13] Over the short term, the use of marginal kidney donors has resulted in successful increased use of organs that normally would not be considered for transplantation, particularly kidneys from older donors. Nevertheless, the successful use of marginal donors has been associated with a significant increased risk of DGF (Fig. 213.2), an event that is expected to become more important in the future.[14,15] Recent studies have examined the role of preprocurement AKI in donors and its effects on DGF in the recipients, and concluded a significant association between donor-AKI and recipient DGF, without significant effects on long-term allograft function in this context.[16,17]

Organ preservation also plays a role (see Box 213.1). Pulsatile perfusion generally has been reported to be superior to simple cold storage preservation.[10] A small prospective controlled paired-kidney study using good-quality kidneys coming from donors after cardiac death (DCD) with lower cold-ischemia times suggested no added benefit of pulsatile perfusion over cold storage of these kidneys.[18] However, more recent data from the United States, including larger cohorts, have reported significantly reduced DGF rates with pulsatile perfusion, with benefit observed in organs obtained from DCD and donors after brain death (DBD) organs, especially when cold-ischemia time was greater than 6 hours.[19,20] Prolonged cold ischemia time, which is now more common in organ transplantation, appears to be an additional independent risk factor for DGF.[21] This is supported by data from the U.S. Renal Data System Registry that demonstrated a 23% increase in risk of DGF

for every 6 hours of cold ischemia.[3] Improved allocation policies that reduce ischemia times therefore represent a central instrument to reduce the incidence of DGF in the near future.[22] Donor age is a further important risk factor for DGF. Analysis of the U.S. Scientific Renal Transplant Registry from 1990 to 1998 showed a doubling of DGF risk for recipients of kidneys from donors 55 years of age or older.[23] Kidneys from older donors are also more susceptible to damage from cold ischemia.

Risk Factors Related to the Recipient

Allosensitization of the recipient represents one of the key factors influencing early graft function. Almost all patients (90%) with pretransplantation panel reactive antibodies (PRA) greater than 50% required posttransplantation dialysis, compared with 45% of those with PRA 10% to 50% and 27% of those with PRA less than 10%.[24] Based on capillary deposition of complement component C4d, it has been suggested that humoral reactivity may contribute to DGF in as many as 50% of cases.[25] In addition, donor-recipient HLA mismatching at class I and II loci reportedly has been associated with increased risk of DGF.[26] Further, the beneficial effect of thymoglobulin induction on DGF-risk compared with nonlymphocyte depleting strategies also strongly implies the role of immune responses in DGF.[27] However, these effects of polyclonal thymoglobulin may result from direct inhibition of leukocyte-endothelial interactions rather than effects on adaptive immunity and are discussed later.[28] It also must be kept in mind that initial CNI doses often are reduced when thymoglobulin is used, a factor that may contribute to the observed benefit with this form of induction therapy.[29]

Nonimmunologic factors additionally may contribute to enhance the risk of DGF. In 158 consecutive living-related kidney transplant recipients, the mean recipient/donor weight was significantly higher in patients with DGF compared with those without DGF.[30] Further, increased donor and recipient body mass index (BMI) have been associated independently with higher risk of DGF.[31] Dialysis modality at the time of transplantation and race also have been recognized as risk factors for DGF.[32] In one study, after adjustment for confounding factors, the relative risk of oliguria in the first week after surgery was 60% higher in hemodialyzed African-American patients than in those on peritoneal dialysis. This finding was not confirmed by others.[33] Additional recipient risk factors include the number of previous transplants, poor quality of reperfusion, absence of intraoperative diuresis, pretransplantation anuria or oliguria,[4] and lower mean perioperative diastolic blood pressure,[33] possibly reflecting the exacerbation of ischemia in hypotensive patients (see Box 213.1). In case series, the mammalian target of rapamycin (mTOR) inhibitor sirolimus, especially in association with cyclosporine, has been associated with prolongation of DGF, without change in DGF-incidence (discussed later).[34,35]

PATHOPHYSIOLOGY OF RENAL ISCHEMIA-REPERFUSION INJURY

Ischemia starves the tissue of oxygen and nutrients and causes accumulation of metabolic waste products. At the cellular level, the biochemical changes occurring during ischemia induce rapid anaerobic glycolysis, resulting in accumulation of lactic acid that lowers intracellular pH[36] and lysosomal instability with activation of lytic enzymes. One of the cell functions requiring the most energy is sodium and water homeostasis via the sodium-potassium pump. In hypoxic conditions, this pump fails, and cellular, mitochondrial, and nuclear swelling and eventual rupture can occur.[37]

In response to renal ischemia, cytoprotective mechanisms, such as a rapid decrease of cellular metabolic activity,[38] are activated as well. However, in cadaveric donor kidneys, the expression of genes encoding for factors relevant to the adaptive graft response, such as heme-oxygenase-1 (HO-1), vascular endothelial growth factor (VEGF), and Bcl-2, is lower than normal.[39] This reflects a defective adaptation against ischemia/reperfusion (IR) injury that would affect graft function in the short term.

Reinstitution of blood flow in ischemically damaged kidneys after hypothermic preservation activates a sequence of events that sustain renal injury and play a pivotal role in the development of DGF. This reperfusion injury is mediated by an array of inflammatory mechanisms that cause direct tissue damage by initiating a cascade of deleterious cellular responses. In the reperfusion phase, the adherent leukocytes plug capillaries, generate proteolytic enzymes, and release cytokines. The vasa recta become congested, peritubular capillary perfusion is impaired, and endothelial permeability is increased.[40] Activated leukocytes, particularly the polymorphonuclear cells, generate oxygen free radicals and ultimately infiltrate renal tissue. The complex interplay among reactive oxygen radicals, chemokines/cytokines, complement factors, adhesion receptors, and leukocytes leads to an inflammatory process that eventually damages renal epithelial cells, particularly those of the proximal tubule. These mechanisms may impair graft function beyond the injury associated with ischemia.

ISCHEMIA/REPERFUSION INJURY ENHANCES ALLOGRAFT IMMUNOGENICITY

Risk of Acute Rejection

Ischemic renal injury increases the risk of acute rejection because of the effects of innate immunity in response to injury on the foreign tissue of the graft.[41] The relationship between increased IR or early posttransplant injury and immunologic events is reflected clinically as the association between DGF and subsequent cellular rejection.[42] IR injury initiates a chain of events starting with the release of damage-associated molecular patterns (DAMPs) from injured graft cells, which include several intracellular proteins, DNA, RNA, and nucleotides. Activation of polymorphonuclear leukocytes (PMNs), eicosanoids, cytokines, reactive oxygen species (ROS), and complement products have been shown by many groups to be involved in this initial phase.[43] Complement pathway genes are among the highest upregulated in transcriptomic studies from donor organs predisposed to DGF compared with those without.[44] In murine models, complement components C3-, C5-, and C6-knockout mice have been protected from IR injury and complement deposition, suggesting a role for complement activation in IR injury. Interestingly, C4-knockout mice have not shown protection, suggesting lack or minimal involvement of classical pathway of complement in IR injury.[45] DAMPs from injured cells activate Toll-like receptors on innate immune cells,[46,47] inducing the maturation and

migration of antigen-presenting cells (APCs) to secondary lymphoid tissues, where they trigger primary T cell and B cell responses, that is the adaptive immune system.[48] Aside from eliciting this nonspecific inflammation, innate-immune cells recently have been shown to have allo- or "non-self" recognition capacities.[49] Therefore IR injury may be superseded by immunologic events and, conversely, the latter may propagate IR injury. Furthermore, ischemia upregulates the expression of major histocompatibility complex (MHC) class I and II molecules on the kidney,[50] predominantly in tubular cells for class I and in interstitial cells for class II. MHC antigens are responsible for alloreactivity, either via direct recognition of MHC alloantigen molecules on the surface of the graft or via indirect recognition of processed peptides derived from those molecules and presented to the recipient immune system by recipient antigen-presenting cells.[51] Consequently, acute rejection occurs more frequently in patients who experience DGF than in those with immediate function,[52] although this is not a uniform finding.[53] In 308 recipients of cadaveric renal transplants, the incidence of acute rejection was 53% in those with DGF and 46% in those without DGF.[54] However, detection of acute rejection in the kidney with DGF is difficult because the rising serum creatinine concentration and oliguria cannot be used to make the diagnosis, and only protocol biopsy every 7 to 10 days, as is done in some centers, can be of help.

Risk of Long-Term Graft Dysfunction

Recovery from ischemic damage may initiate a cascade of events leading to chronic graft injury. Experimental studies of kidney transplantation in rats documented that IR injury and uninephrectomy may interact to produce progressive fibrotic changes in the graft.[55] In the clinical setting, data show an association between the occurrence of DGF and impaired long-term graft function (Fig. 213.3). In the precyclosporine era, a multicenter analysis to address this issue reported a significant correlation between early posttransplantation renal function (at day 1 and week 1) and long-term graft survival.[56] Despite an overall improvement of kidney graft survival with cyclosporine use, the effect of DGF was still evident, with lowering of 1-year graft survival by 20% to 30% in most single-center studies.[21] A multivariate analysis

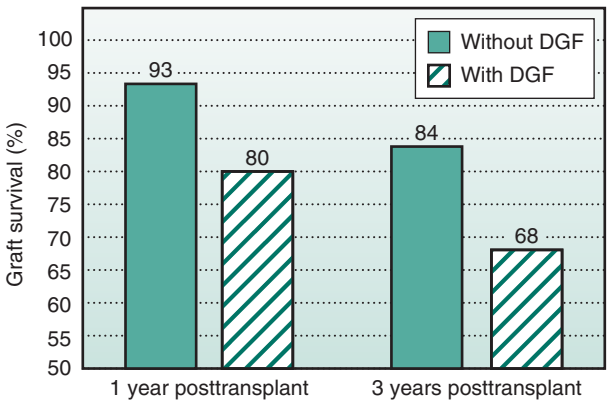

FIGURE 213.3 Kidney graft survival at 1 and 3 years for recipients with or without delayed graft function (DGF). (From U.S. Department of Health and Human Services. 2005 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1995-2004. Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2005.)

confirmed DGF as an independent predictor of graft loss and showed a relative risk of graft loss 2.9 times greater for DGF compared with immediate kidney function.[57] The importance of DGF in long-term graft outcome is supported further by findings that, in cadaver transplants from 1994 to 1998 in the United States, the half-life of kidneys with no DGF was 11.5 years, compared with 7.2 years with DGF.[23] Multivariate analysis of factors affecting graft survival confirmed that DGF was associated significantly with graft loss, independent of other factors, including donor age and human leukocyte antigen (HLA) mismatches.[57] Other studies confirmed that the presence as well as the duration of DGF negatively affects long-term graft function. In addition, the analysis from the U.S. Renal Data System, involving more than 37,000 primary cadaveric renal transplants, revealed that DGF was independently predictive of 5-year graft loss (relative risk, 1.53), and the presence of DGF and early acute rejection further reduced the rate of 5-year graft survival.[58] Even in the absence of overt DGF (defined by dialysis requirement), slow graft function, a subtler form of early injury, also has been associated with long-term impact on GFR in smaller studies.[59]

Whether DGF is harmful in the absence of rejection is an important issue that has not been clearly addressed yet. It is a difficult interaction to dissect, because kidneys with DGF have a higher incidence of acute rejection, and biopsy is not always performed during the DGF period, so rejection may be underdiagnosed. Nevertheless, in a multicenter study of 57,000 first cadaveric transplants reported to the UNOS registry, DGF showed a strong effect independent of rejection.[50] In the presence of rejection, the effect of DGF was even stronger, with graft half-life decreasing from 9.4 to 6.2 years.[50] The impact of DGF alone or in combination with acute rejection on kidney graft survival in the long term was analyzed recently.[60] At 10 years after transplantation, the actuarial graft survival rate was 64% in patients with no history of DGF or rejection episodes, 44% in those with DGF, 36% in those with history of rejection, and 15% if both risk factors were present, further suggesting an additive negative effect on graft outcome. More recent data analyzing data from mate kidney transplants to balance the effects of donor-kidney quality have suggested that DGF contributed the highest hazard toward 1-year graft survival, especially when additive to acute rejection.[42]

However, not all studies support the conclusion that DGF is a strong predictor of long-term outcome of the graft. Indeed, some investigators reported that DGF was an independent risk factor for graft loss in the first 6 months but not later.[61] Similarly, others found DGF to be associated with increased graft loss during the first year but not in the later posttransplantation period.[62] In a cohort of 3800 cadaveric renal transplant recipients, patients with well-recovered graft function by 1 month after DGF had a significantly reduced 4-year graft survival rate, compared with patients with no prior history of DGF.[63] However, patients with a history of DGF but good graft function at 6 months showed long-term graft survival similar to that of patients with no history of DGF. Similarly, in the recent analysis by Gill et al., among allografts without AR, DGF contributed only minimally to graft survival after the first posttransplant year.[42]

Overall, the discrepancies among these studies can be explained at least partly by the presence of different policies on performing biopsies during the anuria period in different centers. Therefore to evaluate the relative impact of DGF and acute rejection on long-term graft outcomes, future studies should include per protocol biopsies within 7 to 10 days after transplantation, to exclude the occurrence of acute rejection in those patients who develop DGF.

Besides DGF, AKI occurring after graft function recovery has been associated with chronic graft function impairment. In kidney transplants, among data from 27,232 Medicare beneficiaries, a diagnosis of AKI was associated with an increased risk of allograft failure with greater effects of AKI seen at higher levels of baseline kidney function.[64] These data include clinically diagnosed AKI from all causes and cannot parse apart differential effects from rejection episodes. Therefore similar to data in native kidneys,[65] AKI occurring early or late after graft function recovery represents a negative prognostic factor for graft loss.

Strategies to Prevent Ischemia-Reperfusion Injury and Delayed Graft Function

The improvement in understanding of the pathophysiology of renal ischemia and reperfusion injury has contributed to the evolution of strategies to decrease the rate of DGF, which have focused on donor management, organ procurement and preservation techniques, recipient fluid management, and pharmacologic agents (Box 213.2).

BOX 213.2

Proposed Strategies to Prevent Ischemia-Reperfusion Injury and Delayed Graft Function

Preservation Solutions
University of Wisconsin solution
Histidine-tryptophan-ketoglutarate solution
Celsior solution
Pulsatile perfusion machine

Recipient Fluid Management
Fluid expansion with colloid or crystalloids
Mannitol or furosemide

Vasodilatory Agents
Calcium channel blockers
Prostacyclin
Atrial natriuretic peptide
Selective and nonselective endothelin receptor antagonists

Antioxidants
Heme-oxygenase-1 induction or overexpression in the graft
N-Acetylcysteine
Propionyl-L-carnitine
Inhibitors of inducible nitric oxide synthase

Antiinflammatory Agents
Antagonists of platelet-activating factor receptor
Monoclonal antibodies to TNF-α
Inhibitors or antagonists of cytokines: interleukins 1, 10, and 13; CXCL-8; MCP-1
Monoclonal antibodies to ICAM-1 and leukocyte function-associated antigen 1
Soluble P-selectin glycoprotein ligand
Immunosuppressants (CTLA4-Ig fusion protein, mycophenolate mofetil)
Complement inhibitors
Statins

Growth Factors
Insulin-like growth factor

Cell Therapy

CTLA4, Cytotoxic T-lymphocyte antigen 4; *CXCL-8,* interleukin-8; *ICAM-1,* intercellular adhesion molecule 1; *Ig,* immunoglobulin; *MCP-1,* monocyte chemotactic protein 1; *TNF,* tumor necrosis factor.

Preservation Solutions

Regardless of the method of kidney storage, preservation solutions have been designed to minimize ischemic damage (see Box 213.2). Particular components are added to these solutions to decrease cell swelling, maintain calcium homeostasis, decrease free radical generation, and provide high-energy substrates. The University of Wisconsin solution of Belzer and Southard[66] has emerged as the standard, effective preservation solution; it has proved superior to the EuroCollins solution in reducing DGF rates at all but the shortest cold ischemia times.[67] Modified solutions that omit the hydroxyethyl starch seem equally effective but are potentially less expensive.[68] A new solution, Celsior, is already used for heart, lungs, and liver transplants and recently has been proposed for kidney preservation. In a multicenter trial on 187 renal transplants in a clinical setting, the preservation of kidneys in Celsior solution resulted in a DGF rate similar to that observed with the use of University of Wisconsin solution (31.3% vs. 33.9%).[69] Similar results were obtained using the Solution de Conservation des Organes et des Tissus (SCOT), a solution that combines an extracellularlike composition with 20-kDa polyethylene glycol, which is known for its cell-protection properties.[70] Research on preservation is focused on additives that could supplement the standard solutions, such as trimetazidine,[71] dextrans,[72] and bioflavonoids.[73]

The method of preservation also may have a role in decreasing DGF, and a pulsatile perfusion machine has been reported to be superior to simple cold storage in most recent data. When two kidneys from each donor were split between pulsatile perfusion and cold storage, no significant improvement in early graft function was found in the perfusion group, even with cold ischemia times greater than 24 hours.[74] However, as discussed above, more recent studies have shown that the use of pulsatile perfusion may decrease the rate of DGF, particularly in the setting of expanded criteria donor kidneys.[19,20,75]

Recipient Fluid Management

Patients are often volume contracted before surgery because of recent dialysis. Fluid expansion with colloid or crystalloids[76] under central venous monitoring can reduce the incidence of DGF. The role of adequate hydration of the recipient is supported by the finding of lower DGF rates in patients previously receiving peritoneal rather than hemodialysis treatment. Mannitol, because of its diuretic and antioxidant properties, has been shown to improve early graft function when given to the recipient just before reperfusion.[77] Furosemide often is given during the vascular anastomosis to promote diuresis, although whether it actually improves early function or simply increases urine output from a functioning kidney is unclear.[78]

Immunosuppressive Management of Delayed Graft Function

Many centers change their immunosuppression regimen when faced with DGF or a high risk of DGF. A common change is to reduce or delay the introduction of CNI and to switch to a depleting antibody, because cyclosporine may affect recovery from ATN negatively and may increase the risk of dysfunction or even failure of the graft. Furthermore, the fact that poorly functioning kidneys complicate the differential diagnosis of rejection[52] makes treatment with

antibody induction therapy attractive. Studies have evaluated the effects of thymoglobulin (rabbit antithymocyte globulin, or RATG) and monoclonal antibodies such as anti-CD3 antibodies (OKT3), which are devoid of appreciable nephrotoxicity but are powerful immunosuppressants.[23] A clinical trial documented that intraoperative administration of RATG in adult cadaveric renal transplant recipients was associated with a significant decrease in DGF, better early allograft function in the first month after transplantation, and a decreased posttransplantation hospital length of stay, compared with postoperative treatment.[27] Previous studies suggested that the intraoperative administration of RATG may help to prevent DGF by blocking adhesion molecules, because this polyclonal agent contains antibodies to a variety of adhesion molecules.[79] However, the clear short-term advantage of RATG may be offset to some extent by an increased risk of opportunistic infections and post-transplantation lymphoproliferative disease (PTLD).[29] As an alternative, the novel monoclonal antibodies to block interleukin-2 receptor (IL-2R) on T cells (basiliximab, daclizumab) have been shown to be extremely safe in transplantation, with encouraging although not always consistent results in DGF.[80] In addition, recent findings indicate that, under induction therapy with basiliximab, early or delayed introduction of cyclosporine results in similar function in renal transplant patients regardless of DGF risk level.[81] Add-on therapy with anti-IL-2R antibody in an induction protocol based on the use of low-dose RATG also has been proposed as a rational strategy to fully inhibit T cell function even without achieving a complete T cell depletion. Very promising are the results of a pilot, explorative study performed to test the possibility that basiliximab, given to kidney transplant recipients who are at increased immunologic risk or who have DGF, in combination with low-dose RATG, is at least as effective as RATG at standard dose but has a more favorable safety profile.[82]

As an alternative to cyclosporine, mTOR inhibitors such as sirolimus and everolimus have been proposed, because they initially were thought to be devoid of direct nephrotoxicity.[83] Small series have even suggested sirolimus conversion as rescue therapy for DGF while on CNI.[84] However, analysis of data from the Scientific Registry of Transplant Recipients have suggested an increased risk of DGF while on sirolimus-based regimens.[85] Further, in a retrospective analysis of 132 consecutive cases of DGF at the University of California, San Francisco, sirolimus appeared to delay recovery from DGF.[34] Similarly, a randomized prospective study in kidney transplant recipients showed that the addition of sirolimus to low-dose cyclosporine, corticosteroids, and basiliximab delayed the recovery from DGF but did not affect graft function at 1 year, compared with triple therapy with conventional cyclosporine dose, mycophenolate mofetil, and corticosteroids.[35] These observations indicate that sirolimus may not be the first-line alternative immunosuppressive agent in the DGF setting when use of CNIs raises concern. Belatacept, currently FDA approved for kidney transplantation, on the other hand, may hold promise for use in DGF once superseding rejection has been ruled out.[86]

Allograft Acute Kidney Injury as a Template for Genomic Studies on Acute Kidney Injury

Although acute kidney injury is a common clinical problem, information regarding the molecular phenotype of AKI in native kidneys has been difficult to procure because most episodes are self limited, and performance of native kidney biopsies for each AKI episode entails high risk. Kidney transplants experience AKI and are suited ideally to investigate the transcriptional profiles of the AKI syndrome.[87] Investigators interrogated postperfusion, wedge biopsies from 75 allografts applying quantitative PCR targeted toward 15 genes with immunologic, proinflammatory, and antiapoptotic roles. They correlated gene expression patterns to DGF, acute rejection (AR), and 6-month graft function.[88] They identified that a similar pattern of intragraft gene expression changes including amplified expression of proinflammatory cytokines (TNF-α, TGF-β, and either IL-10 or IL-6), T cell activation/T cell (CD25/CD3), and expression of inflammation-induced (ICAM-1, HO-1, or A20) transcripts at the zero-hour was linked to DGF and AR. Not surprisingly, the presence of DGF in turn was predictive of AR within 3 months. A multiple logistic model incorporating gene expression events and clinical covariates (including donor-type, warm- and cold-ischemia time) predicted AR within the first 3 months accurately ($R^2 = 0.88$) but was less predictive of 6-month allograft function ($R^2 = 0.48$). The same group analyzed longer-term follow-up in this cohort with zero-hour transcriptional information and showed prediction of proteinuria (AUC = 0.859, $p = .0001$), and graft loss (AUC = 0.724, $p = .027$) using distinct combinatorial logistic models with gene-expression and clinical variables.[89]

Hauser et al. applied microarrays to preperfusion biopsies to evaluate the transcriptional profiles of 14 living-donor (LD) kidneys, 15 cadaveric kidneys with immediate function, and 14 cadaveric grafts with DGF (defined by dialysis requirement in first week). First, they observed that transcriptional profiles of LD-kidneys clustered separately from cadaveric kidneys (132 genes). They further observed that transcripts related to cell cycle regulation, cell growth/metabolism, and signal transduction were significantly differentially regulated in allografts with DGF compared with those with immediate function. Interestingly, upregulation of several complement pathway related genes was identified as associated with DGF in this setting, a finding that may have future therapeutic implications.[90]

The transcriptional profiles of subsequent AKI episodes in transplant kidneys also have been studied. Famulski et al. examined gene-expression profiles of AKI allografts using 6-week protocol biopsies, and identified 394 transcripts that were differentially expressed in AKI compared to simultaneously obtained carefully selected pristine allograft biopsies.[91] Using the geometric mean of the fold increase in the top 30 differentially regulated genes (compared with control nephrectomies), they devised an injury-repair-response-associated-transcript (IRRAT) score that correlated inversely with renal function at the time, and directly with eGFR improvement thereafter. IRRAT score also significantly was associated with the presence of DGF, brain death (i.e., deceased donor status), and interstitial inflammation. Histology, interestingly, did not correlate with these parameters. IRRAT scores since have been observed to be elevated in cellular and B-mediated rejection[92] and may represent allograft injury accompanying different pathologic entities. Interestingly, AKI related gene-expression profiles identified by different groups in transplantation have shown significant overlaps with both mouse orthologs identified in ischemia-reperfusion models of native kidneys,[87,93] and with each other implying the molecular homogeneity in the injury response whether native or allograft kidneys.[90,91,94] Data emerging from transcriptional profiles could improve our understanding of AKI in allografts and native kidneys, and ultimately could lead to development of diagnostic signatures and therapeutic targets.[95]

FUTURE THERAPEUTIC PERSPECTIVES

Although these approaches are finalized to accelerate recovery from DGF, effective treatments for preventing its occurrence are still lacking. Several new drugs show promise in animal studies in preventing or ameliorating ischemia/reperfusion injury and possibly preventing DGF, but definite clinical trials are lacking (see Box 213.2). In various experimental models, pharmacologic manipulation of cytokine and chemokine activities through specific antibodies or receptor antagonists has been reported to attenuate postischemic injury.[96] The goal of monotherapy for the prevention or treatment of DGF may, however, be unattainable, and multidrug approaches or single drugs targeting multiple signals may be the next step to reduce posttransplantation injury and DGF.

An increasing body of evidence also has revealed that injury to a target organ may be sensed by bone marrow stem cells that migrate to the site of damage, undergo differentiation, and promote structural and functional repair. This remarkable stem cell plasticity has been shown to be effective in repairing injured kidney in mouse models of ischemia/reperfusion or toxic injury, in which bone marrow–derived hematopoietic or mesenchymal stem cells differentiated into tubular epithelial cells or facilitate tubular cell regeneration through release of growth factors, eventually restoring renal structure and function.[97,98] The evidence that mesenchymal stem cells, by virtue of their renoprotective property, can restore renal tubular structure and also ameliorate renal function during experimental acute renal failure provides opportunities for novel therapeutic interventions for DGF. Novel data indicates that mesenchymal stem cells also have immunemodulating effects, which would concur in improving graft and patient outcomes.[99]

Key Points

1. Delayed graft function is a form of acute renal dysfunction that results in posttransplantation oliguria and has been associated with an increased risk of acute rejection episodes and decreased long-term survival.
2. Prerenal, renal, and postrenal factors related to the transplant donor or the recipient can cause delayed graft function.
3. Experimental studies have shown that ischemia and reinstitution of blood flow in ischemically damaged kidneys after hypothermic preservation activate complex sequences of events that sustain renal injury and play a pivotal role in the development of delayed graft function.
4. Strategies to decrease the rate of delayed graft function are focused on donor management, organ procurement and preservation techniques, recipient fluid management, and pharmacologic agents (vasodilators, antioxidants, and antiinflammatory agents).
5. Genomic studies in allograft AKI generally reflect homogeneity in response to injury and represent an opportunity for development of diagnostic signatures and potential therapeutic targets.
6. Multidrug approaches and cell therapy will be the next steps to reduce posttransplantation injury and delayed graft function.

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