AJKD
In Practice

Delayed Graft Function After Kidney Transplantation: The Clinical Perspective

Adnan Sharif, MD,[1] and Richard Borrows, MA[1,2]

Delayed graft function continues to pose a significant challenge to clinicians in the context of kidney transplantation. With the present disparity between supply and demand for organs, transplantation is proceeding with more marginal kidneys and therefore the problem of delayed graft function is likely to increase in the future. Although our understanding of the mechanism and risk factors for delayed graft function has improved, translation of this understanding into targeted clinical therapy to attenuate or manage established delayed graft function has been elusive. Based on current trends, the use of kidneys from expanded criteria or cardiac death donors will continue to expand, which will increase the prevalence of delayed graft function in the immediate postoperative setting. The aim of this article is to discuss and critique the available clinical evidence for targeted intervention in the prevention and management of delayed graft function and review emerging and experimental therapies.
Am J Kidney Dis. 62(1):150-158. © *2013 by the National Kidney Foundation, Inc.*

INDEX WORDS: Delayed graft function; acute kidney injury; expanded criteria donor; donation after cardiac death; marginal kidneys; machine perfusion; preservation solution.

CASE PRESENTATION

A 62-year-old man wth end-stage kidney disease treated with hemodialysis for 4.5 years has a history of diabetes (2 oral antiglycemic agents), obesity (body mass index, 33 kg/m^2), and hypertension (3 antihypertensive agents). He is admitted to the hospital for kidney transplantation. The kidney is from a 59-year-old donor with normal kidney function, donated after cardiac death (DCD), with a background history of only hypertension (1 antihypertensive agent only). The kidney has been preserved by static cold storage with University of Wisconsin solution. Warm ischemic time is 15 minutes and cold ischemic time is 12 hours. Prior to transplantation, the recipient was counseled with regard to the risk of delayed graft function (DGF) and the strategies available to ameliorate its incidence and sequelae.

BACKGROUND

Kidney DGF represents acute kidney injury in the immediate postoperative period after transplantation and continues to pose a significant challenge in kidney transplantation. The Organ Procurement and Transplantation Network database (http://optn.transplant.hrsa.gov) demonstrates remarkable consistency in DGF incidence for deceased donor transplants during the last decade, with a rate of 24.3% (1997-2007). Contemporary approaches to expand donor pools by using more marginal kidneys such as those from expanded criteria donors (ECDs) or DCD donors entail an increased burden of DGF. The last few years have seen advances in the clinical interpretation of DGF and its mechanism; these were the subject of a recent comprehensive review,[1] which raised multiple potential targets for future therapy.

Key advances in the field include refining the definition of DGF, advances in the ability (or lack thereof) to predict DGF, and perhaps most importantly, the emergence of several randomized controlled trials to guide practice more robustly. For the practicing nephrologist, these important clinical advances will influence the approach to and management of patients with or at risk of DGF. It therefore is timely to review these advances, describe the consequences and management of DGF in the present era, and finally, speculate on future developments.

DEFINITION AND CLINICAL SEQUELAE OF DGF

Although DGF traditionally is defined as dialysis requirement in the first week posttransplantation, a recent systematic review by Yarlagadda et al[2] identified no fewer than 18 unique definitions of DGF in the literature. The dialysis-based definition is criticized for its subjectivity and whether dialysis requirement reflects true transplant function or clinician practice. This was illustrated by Akkina et al,[3] who compared data from the University of Minnesota Medical Center and Hennepin County Medical Center. The latter program showed a 2- to 3-fold higher rate of dialysis in the first week posttransplantation, but without dif-

From the [1]Department of Nephrology and Kidney Transplantation, Queen Elizabeth Hospital Birmingham; and [2]Centre for Translational Inflammation Research, University of Birmingham, Birmingham, United Kingdom.

Received June 15, 2012. Accepted in revised form November 14, 2012. Originally published online February 13, 2013.

Address correspondence to Richard Borrows, MA, Department of Nephrology, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom B15 2WB. E-mail: richard.borrows@uhb.nhs.uk

0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2012.11.050

ferences in either donor or recipient characteristics, or in subsequent transplant failure rates.

A more objective DGF definition has emerged and is termed functional DGF, based on failure of serum creatinine level to decrease by 10% on 3 consecutive days during the first postoperative week. When compared with the dialysis-based definition, Moore et al[4] demonstrated that functional DGF, but not dialysis requirement, was associated independently with subsequent death-censored transplant failure. This study supports adoption of functional DGF as a classifier for clinical/research use, although further validation is required.

The consequences of DGF also were addressed in a recent meta-analysis. Yarlagadda et al[5] showed a 14% increase in failure rate of kidneys showing DGF (heterogeneously defined) after 3.2 years of follow-up. In addition, DGF was associated with a 38% increase in acute rejection and 0.66-mg/dL higher creatinine level at the end of follow-up. In a recent registry analysis of 50,246 first-time transplant recipients of deceased donor kidneys (of whom 23% required postoperative dialysis), Tapiawala et al[6] demonstrated a 53% increase in death for patients with DGF. Cause-specific deaths were similar between the DGF and non-DGF groups, although acute rejection accentuated the association between DGF and mortality.

Although the long-term clinical consequences of DGF are well documented, the differential risk from contributing DGF risk factors is less clear. For instance, an accepted risk factor for DGF is prolonged cold ischemic time, yet recent publications report minimal influence of cold ischemic time–induced DGF on longer term transplant survival. Kayler et al[7] analyzed paired kidney transplants between 2000 and 2009 and demonstrated an increased risk of DGF with prolonged cold ischemic time, but no difference in transplant survival. This mirrors other paired kidney analyses in which prolongation of cold ischemic time has not resulted in decreased transplant survival.[8,9] Similarly, although DCD kidneys have a significantly higher risk of DGF posttransplantation compared with kidneys donated after brain death, 5-year survival is shown to be equivalent for first-time transplants.[10] It therefore is unclear whether the clinical consequences of DGF are related to individual contributors or a sum of all the parts, and it is becoming clear that although certain kidneys are more likely to accrue a risk of DGF, this may not necessarily have long-term implications. The optimal definition of DGF, particularly with regard to its adverse effect on longer term outcome, may need to evolve from simple dialysis- or function-based definitions to more mechanistic or pathophysiologic frameworks.

MECHANISM OF DGF

A full discussion of the mechanism of DGF is beyond the scope of this review, but the reader is referred to a recent comprehensive review on this subject.[1] Historically, kidney tubular damage was considered the predominant insult leading to DGF (due to ischemia/anoxia either prior to retrieval, during preservation, or after implantation). However, recent investigations suggest that other mechanisms involving the generation of cytotoxic mediators and activation of innate and even adaptive immunity are responsible for cell injury. Of particular relevance is how existing and emerging therapeutic strategies may target these pathways, as discussed later.

As a brief summary, it is clear that endothelial ischemia results in cell damage and swelling, impaired blood flow, and reperfusion that adversely influence transplant outcome.[11] Cerebral injury and brain death induce intense microvascular vasoconstriction (catecholamine storm), thrombosis (tissue factor release), and inflammation (cytokine storm). In addition, a reduction in shear stress during static preservation augments thrombosis and inflammation, exacerbating endothelial damage, while reperfusion generates free radical and reactive oxygen species.[12] DGF therefore represents an example of ischemia-reperfusion injury, rather than mere ischemia.

In addition, other mechanisms of cell injury are now considered relevant, including damage from the generation of cytotoxic mediators and activation of innate and adaptive immune responses.[13-19] Although at a relatively speculative stage, these mechanisms are adding to the overall understanding of the phenomenon.

RISK FACTORS AND PREDICTION OF DGF

Irish et al[20] recently described risk factors for DGF from a large registry data set (Box 1). Although this registry was unable to capture specifics of patient management and organ preservation, the analysis unveiled the most important epidemiologic associations as cold ischemic time, use of DCD kidneys, donor age, donor body mass index, and donor creatinine level. The authors noted that with time, the importance of donor kidney function has increased, whereas that of immunologic risk factors has lessened, the latter possibly related to enhanced immunosuppression protocols in current use. The authors subsequently proceeded to develop a mathematical nomogram to predict the risk of DGF, although discrimination afforded by this model was moderate (C statistic = 0.70) and calls into question whether this (or any other) nomogram is of true predictive utility.