Differential diagnosis of renal allograft dysfunction

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INTRODUCTION — The most common complication of renal transplantation is allograft dysfunction, which in some cases leads to graft loss. Although there is a wide intercenter variability, data from the United States indicate that overall one year survival of a renal allograft is approximately 90 percent [1].

A number of risk factors have been identified for lower one-year cadaver renal allograft survival, including second or third cadaver transplantation, prior sensitization with more than 50 percent panel reactivity, the presence of delayed graft function (defined as the requirement for dialysis during the first week after transplantation), the number of rejection episodes, donor age less than five and greater than 60 years, greater degrees of HLA mismatching, and allograft dysfunction at discharge (plasma creatinine concentration above 2 mg/dL [176 µmol/L]) [2].

The causes of renal allograft dysfunction vary with the time after transplantation. As a result, the differential diagnosis is best approached by considering the time periods separately. This topic review will serve as an overview in those areas in which the major issues are discussed in detail elsewhere.

IMMEDIATE POSTTRANSPLANTATION — Renal failure persisting after transplantation is called delayed graft function (DGF). The definition of DGF varies in different studies, but generally refers to oliguria or the requirement for dialysis in the first week posttransplantation. Less then 5 percent of kidneys with DGF never function (primary nonfunction).

The major causes of DGF, which has a major impact on graft survival [3,4], are:

- Postischemic acute tubular necrosis (ATN)
- Hyperacute and acute antibody mediated rejection (AMR)
- Accelerated rejection superimposed on ischemic ATN
- Urinary tract obstruction due to ureteral necrosis with a urinary leak or to a hematoma
- Atheroemboli or thrombosis of the renal artery or vein

Among patients with DGF, limited retrospective evidence suggests that allograft function may recover faster with the continued administration of an ACE inhibitor/angiotensin II receptor post-surgery [5]. Further study is required to better clarify this issue.

Postischemic acute tubular necrosis — Postischemic ATN is the most common cause of DGF (show histology 1). The incidence of this complication increases with:
- A cold ischemia time exceeding 24 hours, with cyclosporine induction therapy (especially at doses above 10 mg/kg per day) [6]. (See "Risk factors for graft failure in kidney transplantation").

- Prior sensitization in retransplanted patients, indicating that in some cases DGF may be mediated by immunologic injury.

- The type of dialysis performed immediately prior to transplantation. (See "Dialysis issues prior to and after renal transplantation").

Additional factors that may enhance the risk of ATN include higher donor age, preservation of the allograft in Eurocollins solution, severe vascular disease in the donor and recipient, administration of sirolimus, and possibly laparoscopy [7-12]. (See "Benefits and complications of laparoscopic donor nephrectomy" and see "Sirolimus in renal transplantation").

**Hyperacute and acute antibody mediated rejection** — Hyperacute antibody mediated reaction is caused by preformed donor specific antibodies, such as ABO isoagglutinins, anti-endothelial antibodies and anti-HLA antibodies, that frequently results in allograft loss within the first 24 hours. Acute antibody mediated reaction (AMR) is used to describe an antibody mediated rejection that occurs after the first 24 hours [13].

The diagnosis of hyperacute rejection is usually made by the surgeon in the operating room, as the pink kidney becomes mottled and cyanotic. There is little or no urine output, and no renal blood flow by renal scan or duplex Doppler. Renal biopsy shows intrarenal coagulopathy with thrombi occluding the small arteries and glomeruli and renal cortical necrosis (show histology 2). The differential diagnosis includes pulsatile perfusion-induced endothelial injury, cryoglobulinemia, disseminated intravascular coagulation, fat emboli, and anti-GBM disease.

The diagnosis of AMR, which relies upon C4d staining in the allograft, characteristic histologic changes, and/or positive donor specific antibodies (DSA) occurring in the proper clinical setting, is discussed separately. (See "Acute renal allograft rejection: Diagnosis" and see "C4d staining in renal allografts and treatment of antibody mediated rejection").

**Atheroemboli** — Atheroemboli can come from either the recipient's native vascular tree or from the donor's aorta at the time of procurement and/or during angiographic evaluation [14,15]. A donor source may result in a greater atheromatous load and little likelihood of recovering a significant degree of renal function [15].

**Thrombosis** — Thrombosis may arise with or without rejection (secondary and primary thrombosis, respectively) [16-19]. Primary thrombosis of the allograft is an uncommon event, occurring in 0.5 to 6 percent in most series, which usually leads to loss of the graft [20]. One series of 558 consecutive cadaveric renal transplants found that primary thrombosis occurred in 34 patients and was responsible for nearly 45 percent of early graft loss (defined as less than 90 days posttransplant) [20].

Causes of thrombosis may result from technical problems. These include intimal dissection or kinking of the artery, or angulation or kinking of the vein [19]. Additional risk factors/causes for thrombosis may vary with the vessel involved [19]:
• Hypotension, hyperacute or unresponsive acute rejection, a hypercoaguable state, multiple renal arteries, and unidentified intimal flaps increase the risk of arterial thrombosis.

• For venous thrombosis, causes include a hypercoaguable state, hematomas or lymphocelecs causing compression, anastomotic stenosis, and extension of a deep venous thrombosis.

As observed in children with congenital nephrotic syndrome, adults with massive proteinuria may also be at increased risk for thrombosis. In this setting, prophylactic nephrectomy reduces the risk of posttransplant vascular thrombosis.

Another specific risk factor for thrombosis is the presence of antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids [16]. Thus, patients with lupus nephritis, antiphospholipid antibodies, and a history of thromboembolic events, as well as those with the antiphospholipid syndrome may benefit from continued warfarin therapy after renal transplantation. If untreated, these patients appear to be at risk for both intrarenal and systemic clotting events. (See "Antiphospholipid syndrome and the kidney").

Whether inherited thrombophilias predispose to renal allograft thrombosis has not been well studied [21]. At least two inherited thrombophilias, a prothrombin gene mutation and heterozygosity for the factor V Leiden mutation, may increase the risk of this complication [16,22,23]. (See "Prothrombin gene mutation").

Very limited evidence suggests that the prophylactic administration of low dose aspirin (75 mg/day for one month posttransplant) may help prevent renal vein thrombosis. In a retrospective single-center study, the use of such a regimen decreased the incidence of renal thrombosis from 5.6 to 1.2 percent among all transplant recipients [24]. Whether such therapy has a role in this setting requires further study.

Thrombosis of the renal artery and vein are both associated with a sudden decrease in urine [19]. Renal vein thrombosis, but not usually artery thrombosis, is associated with a tender, swollen allograft.

**Diagnosis** — The diagnosis of allograft rejection in patients with DGF who are maintained on dialysis can be made only by renal biopsy. Doppler ultrasonography is utilized to diagnose thrombosis of the renal vein or artery [19].

**EARLY (1 TO 12 WEEKS) POSTTRANSPLANTATION** — The differential diagnosis is substantially different in patients with initial graft function who then develop renal insufficiency. The major causes in this setting are:

• Acute rejection, which is most common (see "Acute renal allograft rejection: Diagnosis").

• **Cyclosporine** or tacrolimus nephrotoxicity (see "Cyclosporine and tacrolimus nephrotoxicity").

• Urinary tract obstruction (show radiograph 1) or decreased renal perfusion due to effective circulating volume depletion [19].

• Infection, possibly reflecting renal disease induced by cytomegalovirus, or polyoma (BK) virus (see "BK virus-induced (polyomavirus-induced) nephropathy and renal
transplantation" and see "Clinical manifestations and diagnosis of JC, BK, and other polyomavirus infections" and see "Cytomegalovirus infection in renal transplant recipients").

- Recurrence of the primary disease, such as focal glomerulosclerosis, hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura, and anti-GBM antibody disease in hereditary nephritis \[25\]. (See appropriate topic reviews).

Limited data also suggests that drug-induced acute interstitial nephritis may be an infrequent cause of renal allograft dysfunction in this setting \[26\].

**Diagnosis** — Early allograft dysfunction is characterized by a plasma creatinine concentration that is stable at an elevated level or is increasing. Unless there is suggestive evidence of infection or recurrent disease (such as heavy proteinuria or a nephritic urine sediment with red cells and red cell casts), we begin the evaluation of such patients by measuring the plasma calcineurin inhibitor concentration. If the drug level is elevated, we reduce the dose. A renal biopsy is performed if no improvement is noted within one to two days.

If, on the other hand, the plasma calcineurin inhibitor concentration is normal or low, we treat empirically for acute rejection. This is discussed separately. (See "Acute renal allograft rejection: Treatment").

Renal ultrasonography should be performed prior to renal biopsy to exclude a urinary leak or obstruction.

**LATE ACUTE DYSFUNCTION** — The following conditions should be considered when acute allograft dysfunction develops more than three months after transplantation \[27\]:

- Prerenal azotemia due to volume depletion. (See "Diagnosis of acute tubular necrosis and prerenal disease").

- Cyclosporine or tacrolimus nephrotoxicity (see "Cyclosporine and tacrolimus nephrotoxicity").

- Acute rejection, possibly due to reduced dose of immunosuppressive medications or noncompliance. (See "Acute renal allograft rejection: Diagnosis").

- Urinary tract obstruction (show radiograph 1). (See "Diagnosis of urinary tract obstruction and hydronephrosis").

- Recurrence of the primary diseases noted above. (See appropriate topic reviews).

- Renal artery stenosis, which is associated with hypertension. (See "Hypertension after renal transplantation").

- De novo renal disease, such as acute tubular necrosis due to sepsis or nephrotoxins, or drug- or infection-induced interstitial nephritis. Human polyomavirus type BK-associated interstitial nephritis is an increasingly recognized cause of graft dysfunction \[28-30\]. (See "BK virus-induced (polyomavirus-induced) nephropathy and renal transplantation" and see "Clinical manifestations and diagnosis of JC, BK, and other polyomavirus infections").
**Diagnosis** — Our initial approach in this setting is to repeat the plasma creatinine concentration after adequate hydration and to measure the plasma calcineurin inhibitor level. As an example, the cyclosporine dose should be reduced by 0.5 to 1 mg/kg per day if the plasma concentration is elevated (>150 ng/mL in plasma or >300 ng/mL in whole blood).

Renal ultrasonography and, if negative, renal biopsy are performed in the plasma creatinine concentration remains elevated or rises further and renal artery stenosis is not suspected clinically.

**LATE CHRONIC DYSFUNCTION** — Many patients have slowly progressive renal disease over a period of years after renal transplantation, often associated with persistent proteinuria [31]. (See "HLA matching and graft survival in kidney transplantation", see section on Long-term graft survival).

- Chronic allograft nephropathy (see "Chronic renal allograft nephropathy")
- Calcineurin inhibitor nephrotoxicity (see "Cyclosporine and tacrolimus nephrotoxicity")
- Hypertensive nephrosclerosis from poorly controlled hypertension.
- Urinary tract obstruction
- Renal viral infection, particularly cytomegalovirus or polyomavirus (as above)
- Recurrent or de novo renal disease. Late recurrence may be seen in many diseases, including focal glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy, and diabetic nephropathy [32,33]. (See appropriate topic reviews).

Most recurrent or new renal diseases in the allograft are diagnosed by renal biopsy, with full evaluation being essential. Even in this setting, it is often difficult to determine whether the allograft dysfunction is caused by these disorders or by concurrent chronic rejection.

Therapy for chronic allograft nephropathy is discussed separately. (See "Chronic renal allograft nephropathy").

**REFERENCES**


27. Frem, GJ, Rennke, HG, Sayegh, MH. Late renal allograft failure secondary to


Acute tubular necrosis in renal transplant

Renal allograft biopsy showing acute tubular necrosis with sloughed and swollen epithelial cells (arrow) and, in the upper tubule, scalloping of the epithelial cells and an intratubular cast. Courtesy of Ann Crosson, MD.

Hyperacute rejection light

Light micrograph of a glomerulus in hyperacute rejection. There is a thrombus in the afferent arteriole (arrow) and there is extensive necrosis of the glomerular tuft (which has few cells) and the surrounding parenchyma. Courtesy of Helmut Rennke, MD.
Light micrograph in hyperacute rejection showing marked vascular injury with visible fibrin strands on the intimal surface (arrow). The vascular wall is largely replaced by fibrinoid necrosis; there is only minimal neutrophil infiltration despite the extensive vascular damage. Courtesy of Helmut Rennke, MD.

Immunofluorescence microscopy in hyperacute rejection showing extensive fibrin deposition in a glomerulus (right) and in the vascular wall and lumen of an artery (left). The arterial lumen is markedly narrowed due to intraluminal fibrin deposition. Courtesy of Helmut Rennke, MD.
Hyperacute rejection IF IgM

Immunofluorescence microscopy in hyperacute rejection showing the almost pathognomonic deposition of IgM around the wall of a small artery. The lumen (L) is markedly narrowed by intraluminal fibrin deposition (arrow) which comprises most of the space between the remaining lumen and the immunoglobulin positive vascular wall. Courtesy of Helmut Rennke, MD.

Hydronephrosis in renal allograft

A noncontrast-enhanced pelvic CT scan of a renal allograft (small arrows) demonstrates marked dilatation of the renal collecting system and ureter (large arrow). This abnormality, which was due to a stricture at the neoureterovesical junction, was amenable to balloon dilatation, resulting in prompt disappearance and resolution of the hydronephrosis. Courtesy of Jonathan Kruskal, MD, PhD.