EACH YEAR, APPROXIMATELY 50,000 PATIENTS WORLDWIDE UNDERGO hematopoietic-cell transplantation. This procedure, which is used to treat a wide range of malignant and nonmalignant diseases, may involve either a myeloablative or reduced-intensity conditioning regimen; the use of alternative allogeneic donors (i.e., haploidentical or mismatched donors); cells from bone marrow, cord blood, or peripheral-blood stem cells; and new immunomodulatory agents to prevent graft-versus-host disease (GVHD)\(^1\) (Table 1).

Despite the overall improvement in outcomes after hematopoietic-cell transplantation, kidney injury remains a frequent complication and contributes to the morbidity and mortality associated with the procedure.\(^2\)-\(^11\) The onset of acute kidney injury and chronic kidney disease, which affect from 10 to 70% of transplant recipients,\(^2\),\(^7\),\(^12\),\(^13\) varies from days after transplantation to months or years afterward. Acute injury is generally indicated by elevated levels of serum creatinine up to 100 days after transplantation, and chronic injury by elevated levels at or after 100 days. Acute kidney injury that persists for 3 months or longer is usually reclassified as chronic kidney disease.

The overall health of the patient at the time of transplantation is generally assessed with use of a hematopoietic-cell transplantation–specific comorbidity index that includes the serum creatinine level.\(^14\) In this index, which includes 17 categories of organ dysfunction, scores for organ-specific coexisting conditions range from 0 to 3, with higher scores indicating a greater severity of the condition. The risk categories are not fixed and can vary according to conditioning regimens. Scores on the comorbidity index range from 0 to 12. Higher scores on the index (the weighted sum of all the scores for organ-specific conditions and other pre-transplantation characteristics) indicate a greater risk of death that is not associated with relapse. In general, patients with a score of 0 are considered to be at low risk of death that is not associated with relapse, those with a score of 1 or 2 are considered to be at intermediate risk, and those with a score of 3 or greater are considered to be at high risk. A score of 1 or more is correlated with a risk of acute post-transplantation kidney injury.\(^3\) Such kidney injury may be caused by conditioning chemotherapy, total-body irradiation, nephrotoxic agents, infections, the hepatic sinusoidal obstruction syndrome (previously called veno-occlusive disease of the liver), transplantation-associated thrombotic microangiopathy, and GVHD.\(^1,7,15-19\) This article reviews the causes, diagnosis, and management of complications and disorders of the kidney after hematopoietic-cell transplantation.

**Definition and Epidemiology of Kidney Injury**

Acute kidney injury after transplantation was initially defined as a doubling of the baseline serum creatinine level within the first 100 days after transplantation.
However, more recent studies have used other criteria such as the risk, injury, failure, loss, and kidney function, and end-stage kidney disease (RIFLE) system and the Acute Kidney Injury Network (AKIN) criteria for kidney injury (Box 1).\(^2,5-7\)

A doubling of the serum creatinine level is correlated with RIFLE-I (injury to the kidney) and AKIN stage 2 (Box 1).

The incidence of acute kidney injury varies from 10% among recipients of autologous transplants (all of whom undergo myeloablative conditioning) to almost 50% among patients who receive allogeneic transplants after reduced-intensity conditioning and as much as 73% among patients who receive allogeneic transplants after myeloablative conditioning. The median time to the onset of acute kidney injury is 33 to 38 days after transplantation.\(^2,7,12,13\)

Both increasing severity\(^2,5-7\) and the early appearance of acute kidney injury (within the first 30 days after transplantation)\(^11,23\) are associated with a stepwise increase in the risk of death and a decrease in overall survival. Among patients who require dialysis, mortality ranges from 55 to 100%.\(^23,25\)

Chronic kidney disease is defined according to serum creatinine levels or estimated measurements of the glomerular filtration rate (GFR). In transplant recipients, these measurements, which are calculated with equations based on serum creatinine and cystatin C levels, are less precise than direct measurement with the use of iohexol to determine the GFR.\(^26\) The more accurate measurements should be used, since eligibility criteria for transplantation, the conditioning regimens, and the donor source are determined with the GFR.\(^26\)

### Table 1. Features of Hematopoietic-Cell Transplantation Procedures.*

<table>
<thead>
<tr>
<th>Types of Cells Transplanted</th>
<th>Source</th>
<th>Conditioning Regimen†</th>
<th>Prophylaxis against GVHD</th>
<th>Prophylaxis against Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous or syngeneic</td>
<td>Self or identical twin</td>
<td>Myeloablative</td>
<td>NA</td>
<td>Acyclovir or valacyclovir for VZV and HSV; fluconazole for fungi; trimethoprim–sulfamethoxazole for <em>Pneumocystis jiroveci</em> and toxoplasmosis; fluconazole or posaconazole, voriconazole, or micafungin for fungi</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>HLA-matched related or unrelated donor, cord blood, HLA-mismatched, haploidentical donor</td>
<td>Myeloablative or reduced intensity</td>
<td>Calcineurin inhibitor, methotrexate, mycophenolate mofetil, antithymocyte globulin, alemtuzumab, prednisone, sirolimus, cyclophosphamide</td>
<td>Acyclovir or valacyclovir for VZV and HSV; high-dose acyclovir, ganciclovir, or foscarnet for cytomegalovirus; trimethoprim–sulfamethoxazole for <em>P. jiroveci</em> and toxoplasmosis; fluconazole or posaconazole, voriconazole, or micafungin for fungi</td>
</tr>
</tbody>
</table>

* HSV denotes herpes simplex virus, NA not applicable, and VZV varicella–zoster virus.

† Examples of myeloablative regimens are cyclophosphamide plus high-dose total-body irradiation, cyclophosphamide plus busulfan, and fludarabine plus busulfan. Reduced-intensity regimens include fludarabine plus 200 cGy of total-body irradiation.

*AKIN denotes Acute Kidney Injury Network, ESRD end-stage renal disease, GFR glomerular filtration rate, KDIGO Kidney Disease: Improving Global Outcomes, and RIFLE risk, injury, failure, loss of kidney function, and ESRD.*

### Box 1. Criteria for Acute Kidney Injury.*

**RIFLE system**\(^20\)

- **Risk (RIFLE-R):** 1.5× baseline serum creatinine level or >25% decrease in GFR.
- **Injury (RIFLE-I):** 2× baseline serum creatinine level or >50% decrease in GFR.
- **Failure (RIFLE-F):** >3× baseline serum creatinine level, >75% decrease in GFR, or serum creatinine level >4.0 mg/dl with a rapid increase of 0.5 mg/dl within 48 hr. Urine output: <0.3 ml/kg/hr for >24 hr or anuria for >12 hr.
- **Loss (RIFLE-L):** Dialysis >4 wk.
- **ESRD (RIFLE-E):** Dialysis >3 mo.

**AKIN criteria**\(^20\)

- **Stage 0:** Decrease in GFR to <25% of baseline value.
- **Stage 1:** Serum creatinine level increased by less than a factor of 2 with decrease in GFR from 25 to <50%.
- **Stage 2:** Serum creatinine level increased by more than a factor of 2, but no dialysis.
- **Stage 3:** Serum creatinine level increased by more than a factor of 2 and dialysis.

**KDIGO staging**\(^21\)

- **Stage 1:** 1.5–1.9× baseline serum creatinine level or ≥0.3 mg/dl above baseline. Urine output: <0.5 ml/kg/hr for >6 hr.
- **Stage 2:** 2.0–2.9× baseline serum creatinine level. Urine output: <0.5 ml/kg/hr for >12 hr.
- **Stage 3:** ≥3.0× baseline serum creatinine level or serum creatinine level ≥4.0 mg/dl with a rapid increase of 0.5 mg/dl within 48 hr, or need for renal-replacement therapy. Urine output: <0.3 ml/kg/hr ≥24 hr or anuria for >12 hr.

**Grade 0–3 staging**\(^22\)

- **Grade 0:** Decrease in GFR to <25% of baseline value.
- **Grade 1:** Serum creatinine level increased by less than a factor of 2 with decrease in GFR from 25 to <50%.
- **Grade 2:** Serum creatinine level increased by more than a factor of 2, but no dialysis.
- **Grade 3:** Serum creatinine level increased by more than a factor of 2 and dialysis.

\(^*\)Box 1. Criteria for Acute Kidney Injury.*

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and the adjustments in medication dosing are based on a threshold for the GFR.

**PATHOPHYSIOLOGY OF KIDNEY INJURY**

**ACUTE KIDNEY INJURY**

Although common causes of acute kidney injury (such as that seen in patients in an intensive care unit) may occur in transplant recipients, the pathophysiology of causes among patients who have undergone transplantation remains unclear (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Risk factors that are unique to patients who have undergone hematopoietic-cell transplantation include acute GVHD, the hepatic sinusoidal obstruction syndrome, use of calcineurin inhibitors, and viral infections (Fig. 1). Acute GVHD involves the release of inflammatory cytokines, activation of antigen-presenting cells, the presence of cytotoxic T lymphocytes, and damage to target cells in the skin, gastrointestinal tract, and liver. Studies have shown that GVHD affects the kidney and is a risk factor for acute kidney injury. The hepatic sinusoidal obstruction syndrome, which is caused by the use of high-dose conditioning regimens, results in acute portal hypertension because of injury to sinusoidal endothelial cells and activation of stellate cells. The portal hypertension that results from hepatic sinusoidal injury may lead to decreased renal perfusion and renal tubular injury, as indicated by a low urinary sodium concentration. The hepatic sinusoidal obstruction syndrome is a risk factor for acute kidney injury; the presence of both these conditions is associated with poor outcomes. It was initially thought that most kidney injury after hematopoietic-cell transplantation was a result of the use of calcineurin inhibitors; however, neither the dose nor the blood level of cyclosporine is significantly associated with the development of acute kidney injury, although calcineurin inhibitors can cause acute renal arteriolar vasoconstriction. Risk factors for acute kidney injury among patients who undergo reduced-intensity conditioning regimens include an incomplete HLA match between the donor and recipient, the presence of multiple complications after transplantation, severe GVHD, the use of prophylactic methotrexate to prevent GVHD, more than three prior courses of chemotherapy, and the presence of diabetes before transplantation. CHRONIC KIDNEY DISEASE

One year after transplantation, the GFR is below 60 ml per minute per 1.73 m² (chronic kidney disease stage 3) in many recipients of hematopoietic-cell transplants. The cumulative incidence of chronic kidney disease varies widely — from 7 to 48% — and it may develop from 6 months to 10 years after transplantation. Risk factors for chronic kidney disease include previous acute kidney injury, acute and chronic GVHD, an age of 45 years or older at the time of transplantation, a baseline GFR below 90 ml per minute per 1.73 m², hypertension, survival more than 1 year after transplantation, and exposure to high-dose total-body irradiation. Progression to end-stage renal disease occurs in approximately 4% of patients with chronic kidney disease.

**GVHD-RELATED CHRONIC KIDNEY DISEASE**

The relationship between kidney injury and GVHD is controversial. A histologic diagnosis of renal GVHD is rarely made, since formal pathological criteria have not been established. However, a mouse model of GVHD revealed up-regulation of intrarenal pathways involved in antigen processing, chemotaxis, and adaptive and innate immune responses; inflammation with CD3+ T cells; and expression of vascular-cell adhesion molecules and intracellular adhesion molecules, both of which indicated endothelial injury. Infiltration of CD3+, CD4+, and CD8+ T cells and CD68+ macrophages into the renal interstitium has also been described in rat models of acute GVHD. As the inflammatory process worsened in that model, peritubular capillaritis, tubulitis, glomerulitis, and endarteritis, together with increased expression of major histocompatibility complex class II in renal tubules, were observed. These findings were associated with kidney dysfunction (indicated by elevated blood urea nitrogen levels) and tubular injury (as measured by urinary N-acetyl-β-D-glucosaminidase levels). Glomerulitis, renal tubulitis, and peritubular capillaritis with infiltration of CD3+ T cells have also been observed on kidney biopsy in patients (Fig. 2A).

There is some evidence that proinflammatory
Cytokines are present in the urine, and it is speculated that this finding may reflect the inflammatory milieu of GVHD in the kidney.41,42 Either the kidney may be a direct target of T-cell-mediated renal damage or the chronic systemic inflammatory state of GVHD could lead to nephropathy with tubular and endothelial injury. Support for the inflammatory-injury hypothesis comes from measurements of urinary cytokines and urinary elafin, an endogenous serine protease inhibitor produced by epithelial cells and macrophages in response to tissue inflammation, the release of proteolytic enzymes, and the disruption of epithelial integrity.41 Elafin has previously been identified as a serum marker of GVHD of the skin.42 Elevated urinary elafin levels are associated with both acute kidney injury and chronic kidney

Figure 1. Kidney Injury after Hematopoietic-Cell Transplantation.
The mechanisms (Panel A) and the time course (Panel B) of kidney injury after hematopoietic-cell transplantation are shown. GVHD denotes graft-versus-host disease.
The presence of elafin in the distal and collecting tubules but not in the glomeruli or proximal tubules of the kidneys in recipients of hematopoietic-cell transplants who have kidney dysfunction (Fig. 2B) may indicate a local response to distal tubule injury, rather than filtration or excretion of circulating elafin by the kidney.43

Elevated urinary levels of interleukin-6, interleukin-15, and monocyte chemoattractant protein 1 (MCP-1) are associated with the development of albuminuria and proteinuria at day 100 after transplantation; this suggests intrarenal inflammation. MCP-1 has also been found to be associated with chronic kidney disease at 1 year.13

The association between kidney injury and GVHD after hematopoietic-cell transplantation mirrors the association between allograft dysfunction and rejection after transplantation. These associations provide support for immune-mediated mechanisms of renal damage.

**Figure 2. Pathologic Changes in the Kidney after Hematopoietic-Cell Transplantation.**
Panel A shows tubulointerstitial nephritis. Moderate interstitial fibrosis separates dilated and focally atretic tubules, cellular debris fills many lumens (arrow), and inflammation is present (Masson’s trichrome stain, low magnification). Panel B shows the expression of elafin. Finely granular cytoplasmic staining is most often distributed diffusely within the cytoplasm of distal tubules (arrow), whereas coarse granules (arrowhead) typically accumulate toward the luminal aspect (3,3′-diaminobenzidine, high magnification). In rare cases, staining for elafin is restricted to the basal aspect of tubular cells (not shown). Panel C shows a normocellular glomerulus (left) with slightly thickened basement membranes and barely visible membrane spikes. The beaded hyalinosis (arrow) of the artery may be a result of treatment with calcineurin inhibitors (periodic acid–Schiff, medium magnification). An electron micrograph of the same kidney-biopsy specimen (right) shows scattered epimembranous and intramembranous electron-dense deposits (arrow) and effacement of the foot process focally (uranyl acetate). Panel D shows acute and chronic changes due to thrombotic microangiopathy. The glomerulus (left) has capillary congestion with focal mesangial lysis and extensive fibrin thrombi (arrow). Membrane duplication is visible only in rare segments (Jones’s methenamine silver stain, high magnification). The normocellular glomerulus (right) has diffuse membrane duplication (arrows) and narrowed capillary lumens (hematoxylin and eosin, high magnification). Panel E shows BK virus nephropathy. Many tubular epithelial cells (left) are enlarged and have marginalized nuclear chromatin (arrow); detached and necrotic epithelial cells mixed with debris fill tubular lumens (hematoxylin and eosin, medium magnification). Several enlarged tubular epithelial cells (arrow) and parietal epithelial cells of Bowman’s capsule (right) are stained positively with antibodies against simian virus 40 (arrowheads) (3,3′-diaminobenzidine, high magnification).
plantation include treatment with total-body irradiation, the use of calcineurin inhibitors, the combined use and elevated levels of sirolimus and tacrolimus, acute GVHD grade 2 to 4, infections, nonmalignant conditions, and transplantation of peripheral-blood stem cells.\textsuperscript{10,37,44-47} BK viremia has also been associated with thrombotic microangiopathy.\textsuperscript{48} In an autopsy study, however, the association between GVHD and the presence of thrombotic microangiopathy in the kidney was independent of the use of calcineurin inhibitors and conditioning with total-body irradiation.\textsuperscript{49} Regardless of the cause, endothelial damage is thought to initiate thrombotic microangiopathy by activating the coagulation system, which in turn leads to the formation of thrombin and the deposition of fibrin. Repair after such injury in the transplant recipient depends on the balance between fibrinolytic and coagulant activity.\textsuperscript{50}

One hypothesis is that the vascular endothelium is a target of GVHD, with the implication that diffuse alveolar hemorrhage and thrombotic microangiopathy may be manifestations of acute endothelial GVHD.\textsuperscript{51,52} Levels of plasma markers of endothelial injury, markers of coagulation activation, and soluble adhesion molecules are generally elevated in patients with endothelial injury in whom thrombotic microangiopathy develops after transplantation.\textsuperscript{53} However, one study showed no association between plasminogen-activator inhibitor type 1, tissue plasminogen activator, and d-dimer levels and subsequent kidney injury soon after transplantation.\textsuperscript{54} Recent studies have investigated abnormalities of the coagulation cascade and the complement system. These studies implicate deletions in the gene encoding complement factor H and factor H autoantibodies in transplantation-associated thrombotic microangiopathy.\textsuperscript{10,55,56}

Examination of kidney-biopsy specimens obtained from patients with thrombotic microangiopathy shows mesangiolysis and loss of endothelial cells, with expansion of the subendothelium and occlusion of capillary lumens (Fig. 2D). The fact that C4d, a complement fragment, may be detected in glomerular and peritubular capillaries in biopsy and autopsy specimens suggests the presence of an antibody-mediated process and complement activation.\textsuperscript{40,55} Infiltration of inflammatory cells, including CD3+ and CD8+ T cells and cytotoxic T cells, has also been detected in the glomeruli, tubules, and interstitium.\textsuperscript{40} A predominance of natural killer cells in the kidney (thought to be due to chronic inflammation) may also exacerbate endothelial injury.\textsuperscript{57} A final common pathway to injury probably links inflammatory mediators and tubular and endothelial damage, ultimately leading to chronic kidney disease.

THE NEPHROTIC SYNDROME

GVHD, with or without renal insufficiency, may also be manifested as a frank nephrotic syndrome (characterized by proteinuria, hypoalbuminemia, and edema) as early as 2 months after transplantation, although it more typically appears 6 to 12 months later.\textsuperscript{58} The incidence of the nephrotic syndrome in adult recipients ranges from 0.4 to 6.0%.\textsuperscript{59,60} Most patients with the nephrotic syndrome have evidence of membranous nephropathy on biopsy, with subepithelial deposits that are thought to be antigen–antibody complexes that indicate GVHD in the kidney (Fig. 2C). When the nephrotic syndrome appears after hematopoietic-cell transplantation, it usually occurs in the context of chronic and protracted acute GVHD, after the dose of immunosuppressive medication has been tapered; few cases occur in the absence of GVHD.\textsuperscript{61-63}

Minimal-change nephrotic syndrome after hematopoietic-cell transplantation, which is considered to be a T-cell–mediated process, has also been described, sometimes in the absence of overt GVHD elsewhere in the body.\textsuperscript{64-66} Elevated serum levels of interferon-γ and tumor necrosis factor-α have been reported, and in one case, anti–phospholipase A\textsubscript{2} receptor antibodies were present; these findings suggest a role for both cytokine- and antibody-mediated injury.\textsuperscript{59,60,65} Case reports of membranoproliferative glomerulonephritis, class III lupus nephritis, focal segmental glomerulosclerosis, and IgA nephropathy in transplant recipients have also been published.\textsuperscript{63,66,67}

EVALUATION AND CARE OF PATIENTS

The initial evaluation of a patient who has undergone hematopoietic-cell transplantation and has an elevated creatinine level should focus on determining the cause of the increase. It is important to obtain a complete urinalysis, urinary
survival rate was 80%.68 Regardless of the kidney function or urine output, the therapy was initiated along with mechanical ventilation, 10 children in whom renal-replacement therapy was initiated early,25,68 before the occurrence of excessive volume overload. Fluid overload is defined as a fluid overload value greater than 10%. In one small study involving those who received convective therapy (continual venovenous hemofiltration or hemodiafiltration) than among those who received diffusive therapy (dialysis) (59% vs. 27%), especially when therapy was initiated early,25,68 before the occurrence of excessive volume overload. Fluid overload is calculated as follows:

\[
\text{[(fluid intake − fluid output) ÷ weight] × 100,}
\]

with fluid intake and fluid output measured from the time of admission to the intensive care unit to the initiation of continuous renal-replacement therapy and with body weight measured in kilograms at the time of admission to the intensive care unit.25,69,70 Excessive volume overload is defined as a fluid overload value greater than 10%. In one small study involving 10 children in whom renal-replacement therapy was initiated along with mechanical ventilation, regardless of kidney function or urine output, the survival rate was 80%.65 Regardless of the method used, early initiation of renal-replacement therapy is associated with improved outcomes. Microalbuminuria, defined as a urinary albumin-to-creatinine ratio of 30 to 299 (calculated as milligrams of albumin to grams of creatinine), is a putative marker of endothelial dysfunction and inflammation.71 In patients who have received hematopoietic-cell transplants, both microalbuminuria and macroalbuminuria (defined as an albumin-to-creatinine ratio of ≥300) at any point in the first 100 days after transplantation are associated with an independent increase in the risk of death within 1 year after transplantation. If either or both of these conditions are present at 80 to 100 days after transplantation, the risk of chronic kidney disease is also increased.13,72 In one study, the risk of death was 74% higher among patients with microalbuminuria at day 100 than among those without it (hazard ratio, 1.74; 95% confidence interval [CI], 1.08 to 2.81) and the risk of death among those with macroalbuminuria at day 100 was almost four times the risk among those without it (hazard ratio, 3.62; 95% CI, 1.91 to 6.87).13 Urinary albumin-to-creatinine ratios that are measured 80 to 100 days after transplantation appear to be clinically useful in predicting both the risk of subsequent kidney dysfunction and death.13,34,73 A renal biopsy may be beneficial in the care of individual patients, since the results can clarify their histologic status and its correlation with the degree of macroalbuminuria. These results can also be used to identify a possible role of GVHD, endothelial injury, and chronic inflammation in the development and progression of a given lesion. Since macroalbuminuria may be a marker of renal GVHD, it may be useful to continue immunosuppression after 80 to 100 days following transplantation, even in the absence of evidence of GVHD in organ systems outside the kidney. Macroalbuminuria and hypertension have also been identified as early markers of clinical thrombotic microangiopathy in recipients of hematopoietic-cell transplants.10,47

Hypertension
Elevations in blood pressure are common after hematopoietic-cell transplantation. In adult patients who are younger than 60 years of age, the target blood pressure to be achieved with treatment is below 140/90 mm Hg.74 In children and adolescents, hypertension is defined as a sys-
tolic or diastolic blood pressure above the 95th percentile for sex, age, and height as measured on at least three occasions. A 24-hour ambulatory blood-pressure monitoring study at 80 days after transplantation may be beneficial in the care of some patients because it provides a more accurate assessment of blood pressure, including nocturnal blood pressure, than would otherwise be available.

As many as 70% of children and adults who receive hematopoietic-cell transplants have hypertension during the first 2 years after the procedure (median time to onset, 1 month). Independent predictors of hypertension include treatment with cyclosporine, acute kidney injury, total-body irradiation, receipt of an autologous transplant (primarily in patients with neuroblastoma), obesity, and diabetes. Hypertension has been associated with an increased odds of the development of chronic kidney disease (odds ratio, 4.03; 95% CI, 1.04 to 13.06) and with the development of transplant-associated thrombotic microangiopathy.

Effective treatment of hypertension is important as a means to decrease both the risk of cardiovascular disease and the progression of chronic kidney disease. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers should be considered as first-line therapy for such patients. Additional therapeutic options include dietary and lifestyle modifications.

**TRANSPLANTATION-ASSOCIATED THROMBOTIC MICROANGIOPATHY**

The risk of death from causes other than relapse of the primary disease within 1 year after hematopoietic-cell transplantation is higher among patients with clinical evidence of thrombotic microangiopathy than among other transplant recipients. A clinical diagnosis of thrombotic microangiopathy after transplantation is based on the presence of microangiopathic hemolytic anemia (red-cell fragmentation), elevated lactate dehydrogenase levels, kidney dysfunction (a >50% increase from the baseline serum creatinine level or a 50% decrease in creatinine clearance from baseline), neurologic involvement without other identifiable causes, and negative results on direct and indirect Coombs’ tests. A revised grading system assesses the severity of thrombotic microangiopathy primarily on the basis of the serum creatinine level, the need for dialysis, the presence of encephalopathy, or a combination of these factors. However, the requirement for the presence of concurrent renal and neurologic dysfunction and a schistocyte count of 4% or greater on a peripheral-blood smear does not identify patients with probable thrombotic microangiopathy who are also at high risk for a poor outcome. Therefore, Cho et al. propose that concurrent renal and neurologic dysfunction and a defined schistocyte count not be required for the diagnosis. In addition, in one study, histologic evidence of thrombotic microangiopathy in the kidney was not correlated with elevations in serum creatinine levels. A kidney biopsy may therefore be required to confirm the diagnosis.

Options for the treatment of thrombotic microangiopathy after hematopoietic-cell transplantation are limited. Most clinicians discontinue the use of calcineurin inhibitors and switch to mycophenolate mofetil, sirolimus, or both for prophylaxis against GVHD. In some patients, however, treatment of GVHD with increasing doses of calcineurin inhibitors can lead to the resolution of thrombotic microangiopathy. Other therapies include plasma exchange that is initiated soon after diagnosis and rituximab in conjunction with plasma exchange. Recent studies have shown that certain genetic variations in complement factors are associated with thrombotic microangiopathy, that plasma levels of C5b–9 are elevated in these patients, and that C4d may be present in renal-biopsy specimens. These findings have led to the use of eculizumab to treat transplant-associated thrombotic microangiopathy, with mixed results. Data from randomized clinical trials to identify the most appropriate therapy for transplantation-associated thrombotic microangiopathy are lacking.

**THE NEPHROTIC SYNDROME**

Renal biopsy is warranted in patients in whom the nephrotic syndrome develops after hematopoietic-cell transplantation. The nephrotic syndrome usually resolves after treatment with high-dose prednisone, reinstitution of treatment with calcineurin inhibitors, or both. Rituximab has been used successfully in patients with the nephrotic syndrome, typically in those with membranous nephropathy.
VIRAL INFECTIONS

Hemorrhagic cystitis is a common complication after hematopoietic-cell transplantation; it is usually caused by BK virus or adenovirus. Clinical syndromes vary and may include microscopic or macroscopic hematuria, dysuria, and flank pain, with or without renal insufficiency. Among the risk factors for hemorrhagic cystitis are treatment with rabbit antithymocyte globulin, high levels of BK virus, receipt of a cord-blood or peripheral-blood stem-cell transplant, the presence of acute GVHD (grade 2 to 4), an age older than 7 years, and coinfection with other viruses.\textsuperscript{24,90,91} Plasma levels of BK virus are more indicative of renal involvement and renal injury due to BK nephropathy\textsuperscript{92} than are urinary levels of BK virus (Fig. 2E).

Studies have shown that children with a peak plasma BK virus load of 10,000 copies per milliliter or more during the first year after transplantation, regardless of the urinary viral load, have worse renal disease (with 70% requiring dialysis), more severe hemorrhagic cystitis leading to urologic complications requiring surgical interventions, and a lower rate of survival at 1 year than those with fewer than 10,000 copies per milliliter.\textsuperscript{48,93} In patients with BK viremia or nephropathy, the first-line therapy is often the reduction of immunosuppression, when possible, before the initiation of treatment with cidofovir or other antiviral agents, including leflunomide. Cidofovir has been used to treat severe cases of hemorrhagic cystitis, with mixed results.\textsuperscript{24,81,94,95} Brincidofovir has also been used to treat BK virus nephropathy in patients who have received hematopoietic-cell transplants.\textsuperscript{96} A renal biopsy should be performed in patients with BK viremia and elevated serum creatinine levels before treatment with cidofovir begins in order to confirm the diagnosis of BK virus nephropathy. In the absence of biopsy-proven BK virus nephropathy, treatment with cidofovir may not be indicated. Adenovirus, which has also been identified as a cause of acute kidney injury in patients after hematopoietic-cell transplantation,\textsuperscript{97} is sensitive to both cidofovir and brincidofovir.

END-STAGE KIDNEY DISEASE AND RENAL TRANSPLANTATION

Data on risk factors for end-stage kidney disease after hematopoietic-cell transplantation are limited; the prevalence of this condition has been reported to be as high as 4%.\textsuperscript{33,34,77} Successful kidney transplantation has been reported in both children and adults who have end-stage kidney disease after hematopoietic-cell transplantation.\textsuperscript{98-100} Some patients have received a kidney transplant from the original hematopoietic-cell donor, so that a reduction or even discontinuation of immunosuppression has been possible.\textsuperscript{99}

CONCLUSIONS

Current evidence suggests a need to rethink the causes of acute and chronic kidney injury in patients after hematopoietic-cell transplantation. Most such kidney injury is not related to total-body irradiation or treatment with calcineurin inhibitors. At the same time that physicians who perform transplantations have worked to decrease toxicity and complications after the procedure by administering agents other than amphotericin, adjusting conditioning regimens to prevent the hepatic sinusoidal obstruction syndrome, and implementing prophylactic regimens against viral infections, acute and chronic GVHD has emerged as a major cause of kidney injury after transplantation. However, it is difficult to separate out the contributions of calcineurin inhibitors from those of GVHD to post-transplantation renal injury; in fact, their roles may not be mutually exclusive. T-cell–mediated injury in patients with GVHD is intertwined with the effects of cytokines, and the effects of cyclosporine can be potentiated in a chronic inflammatory state.

In order to design therapeutic trials and improve outcomes in this high-risk population, it will be necessary to increase understanding of the mechanisms of the cellular, antibody-mediated, and complement-directed pathways of kidney disease. It will also be necessary to obtain renal-biopsy specimens so that GVHD of the kidney and the pathologic effects of GVHD on the kidney can be better understood and defined.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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