Chapter 9: Hematopoietic Stem Cell Transplant–Related Kidney Disease

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INTRODUCTION

Acute and chronic kidney diseases are common following hematopoietic cell transplantation (HCT) and can lead to long-term effects. Additionally, the occurrence of kidney disease in the setting of HCT can negatively affect mortality and morbidity. Etiologies of HCT-associated kidney injury are often multifactorial, including conditioning chemotherapy, radiation, nephrotoxic medications, sepsis, sinusoidal obstruction syndrome (SOS), transplantation-associated thrombotic microangiopathy (TA-TMA), and graft-versus-host disease (GVHD). Continued improvement in survival following HCT highlights the importance of monitoring renal function both before and after transplant and continued follow-up of patients with CKD.

AKI

Pretransplant evaluation of renal function

Serum creatinine (SCr) is the most widely used marker of kidney function in patients undergoing HCT (1). Measurement of SCr provides estimation of renal function at the bedside and allows for following trends in renal function. GFR prediction formulas, such as the Modification of Diet in Renal Disease (MDRD) equation for adults and the Schwartz formula in children, are available (2,3). However, several shortcomings are inherent in the properties of SCr as a functional biomarker of AKI. These include the delay between the onset of kidney injury and an increase in SCr, limiting its utility to provide the earliest window for intervention (4). In addition, SCr is affected by factors such as age, muscle mass, and hydration status, issues particularly relevant for HCT patients. Even small changes in SCr in this population can represent significant decline in kidney function. Other methods of GFR estimation include 24-hour urine creatinine clearance, inulin clearance, and use of radioactive isotopes (Tc-DTPA or Cr-EDTA) or iodinated contrast agents (iothalamate or iohexol).

Defining AKI

Current definitions of AKI are based on increases in SCr and decreased urine output. Two scoring systems, RIFLE (risk, injury, failure, loss, ESRD) and Acute Kidney Injury Network (AKIN), have been developed to standardize stratification of AKI severity (5,6). RIFLE criteria include two additional categories (loss, ESRD) describing two post-AKI clinical outcomes. For children, a modified version of RIFLE criteria, pRIFLE, has been developed (7). Several studies have shown a correlation between these scores and clinical outcomes (8). Recently, a new staging criteria for AKI was created by KDIGO; however, this newer definition has not been prospectively studied in the HCT population.

Epidemiology of AKI

The incidence of AKI varies, based on the definition of AKI, type of HCT, and chemotherapeutic conditioning regimen. When AKI is defined as a doubling of SCr during the first 100 days after stem cell infusion, the prevalence ranges from 15% to 73% (9). Severity of AKI also varies. In a study of pediatric and adult allogeneic HCT recipients, up to a third of all patients doubled their SCr in the first 100 days, and 5% required acute dialysis (10). Severity of AKI is associated with increased risk of morbidity and mortality (11–13).

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For those receiving high-dose conditioning regimens and allogeneic HCT, the incidence of AKI is as high as 69%. It often occurs before day 28, and risk factors include lung toxicity, hepatic toxicity, SOS, amphotericin exposure, and sepsis (14,15).

For patients receiving reduced-intensity chemotherapy (RIC) and allogeneic HCT, AKI occurs less frequently, later after transplant, and less often results in the need for dialysis. A retrospective cohort study found that 47% of RIC patients developed AKI compared with 73% in the high-dose treatment group, developing at a median of 26–60 days after transplant in the RIC group. Fewer RIC patients required dialysis, and mortality was significantly lower (11,16,17). Compared with allogeneic HCT, AKI incidence is lower in autologous HCT, occurring in approximately 21% of these patients (18).

Causes of AKI

Common risk factors and causes of AKI after HCT include volume depletion, sepsis, nephrotoxic medication exposure, SOS, and GVHD (Table 1). Owing to a propensity for increased gastrointestinal (GI) fluid losses and poor oral intake, HCT patients are highly susceptible to volume depletion. Close tracking of fluid intake, urine output, fluid losses via the GI tract and insensible losses, and daily weight measurement are required. Additional measures that can discriminate prerenal AKI from other types include BUN/Cr ratio, fractional excretion of sodium (FENa), and fractional excretion of urea (FEurea) (Table 2).

Sepsis can result in decreased effective circulating volume and hypotension and is a major risk factor for AKI. Sepsis-induced inflammation leads to increased capillary permeability and intravascular fluid leak, resulting in total body volume overload while depleting effective circulating volume and end organ perfusion (19).

GVHD is unique to HCT and likely causes tissue and endothelial damage via T cell– and cytokine-mediated injury (20). The GI mucosa is a common site of GVHD, contributing to inadequate fluid intake and increased GI losses.

Table 1. Risk factors for AKI in HCT

Intravascular volume depletion
Vomiting and diarrhea associated with acute gut GVHD
Systemic vasodilatation
Sepsis
Renal vasoconstriction
Sinusoidal obstruction syndrome
Calcineurin inhibitors
Endothelial injury
Acute GVHD
Calcineurin inhibitors
Total body irradiation
Thrombotic microangiopathy
Tubular injury
Medications: amphotericin, vancomycin
Conditioning chemotherapy

Table 2. Urinary indices for AKI classification

AKI classification	BUN/Cr ratio	FENa*	FEurea†
Prerenal AKI	>20	<1%	<35%
Intrinsic AKI	Variable	>3%	>35%
Obstructive AKI	Variable	Variable	Variable

*FENa = (urinary Na × SCr)/(serum Na × urinary Cr).
†FEurea = (urinary urea × SCr)/(serum urea × urinary Cr).

SOS and hepatorenal syndrome (HRS) have been identified as an independent risk factor for AKI. HRS results in decreased resistance in the systemic and splanchnic vasculature, leading to renal hypoperfusion and compensatory increase in renal salt and water reabsorption. It presents as oligo-anuric prerenal AKI with edema and low urinary sodium. Septic shock and other causes of AKI must be ruled out. Defibroitide exhibits antithrombotic and fibrinolytic properties and has been studied for use in SOS (21).

Common medications related to AKI include vancomycin, aminoglycosides, and amphotericin. Calcineurin inhibitors (CNIs) can lead to renal arteriolar vasoconstriction and have been associated with development of TA-TMA.

Management of AKI

The management of AKI is mainly supportive and specific to the underlying cause. For situations of renal hypoperfusion, prompt administration of intravenous fluids is required to restore effective circulating volume. However, a critical point is that fluid overload (FO) can itself be an independent predictor of mortality in critically ill patients (22,23). Stem cell transplant recipients are a population that may be particularly sensitive to FO, with one study of critically ill children suggesting that >10% FO in HCT patients correlates with decreased survival (%FO = [Fluid In – Fluid Out]/Intensive Care Unit Admission Weight in kilograms) (24,25). Judicious use and dose adjustment of antimicrobials should be used to decrease risk of AKI from nephrotoxin exposure. For those not responsive to medical interventions, dialysis is used as supportive therapy for management of AKI-related fluid and metabolic derangements.

CKD AFTER HCT

CKD stage 3 is defined as a GFR of <60 mL/min per 1.73 m^2 for ≥3 months. This is often the definition of CKD used in studies of HCT patients. The five stages of CKD (Table 3) range from mild to ESRD. The prevalence of CKD after HCT, using this definition, is between 20% and 30% (26). Cohorts including children and adults have shown a CKD prevalence of 19% at 1 year and 7% at least 2 years after HCT, with a mean estimated GFR of 46 mL/min per 1.73 m^2 (27,28). Other chronic kidney disorders following HCT include albuminuria, hypertension, and renal tubular dysfunction. Regardless of underlying cause, CKD can progress to ESRD and increases mortality risk after

Table 3. Stages of CKD (67)

Stage	Description	GFR (mL/min per 1.73 m^2)
1	Kidney damage with normal GFR	≥90
2	Mild	60–89
3a	Moderate	30–44
3b		45–59
4	Severe	15–29
5	ESRD	<15

HCT. For those who progress to ESRD, this mortality risk can be as high as 90% (29). Monitoring changes in renal function and management of any existing chronic renal disease are important to the long-term survival and quality of life for post-HCT patients.

Clinical entities associated with CKD after HCT

Preexisting CKD before HCT

Preexisting CKD is not a contraindication to HCT. A study of 141 adult patients with leukemia and pretransplant kidney dysfunction showed that, at 1 year, these patients did not have worse survival than those who initially had normal kidney function. In addition, for some cancer diagnoses, CKD is related to the underlying disease process and HCT can slow the progression of CKD.

Important points in managing patients with preexisting CKD include accurate assessment of renal function prior to HCT, appropriate changes to medication dosing, and avoidance of nephrotoxins.

Transplantation-associated TMA

TMA is defined by hemolytic anemia with erythrocyte fragmentation, thrombocytopenia, and renal failure. It is characterized by endothelial damage, leading to thickened glomerular and arteriolar vessels, the presence of fragmented red blood cells, thrombosis, and endothelial cell swelling (30). Two consensus guidelines outline the clinical criteria for the diagnosis of TA-TMA. Both require the presence of schistocytes on peripheral smear and an elevated lactate dehydrogenase. The BMT Clinical Trials Network also includes AKI (doubling of serum creatinine), unexplained CNS dysfunction, and a negative Coombs test. The International Guidelines from the European Group for Blood and Marrow Transplantation include thrombocytopenia, anemia, and decreased haptoglobin (31–33).

In the setting of HCT, the incidence of TMA ranges from 2% to 21% (31). The clinical course of TMA can be rapid with severe AKI but commonly follows a more indolent course, resulting in CKD and, possibly, progression to ESRD (34). Risk factors for the development of TMA after HCT include CNI use, total body irradiation, and GVHD (35).

The mainstay of TA-TMA management remains reduction in dose or stoppage of CNI and therapeutic plasma exchange. A response rate of 50%–63% has been reported using these two interventions (33). Given that GVHD itself can be a risk factor for the development of TA-TMA, an approach with close monitoring of levels rather than complete cessation of CNI may be more appropriate (36,37). In patients not responsive to these interventions, pharmacologic therapies include rituximab, defibrotide, and eculizumab (33,38,39). Eculizumab, a monoclonal immunoglobulin that binds complement factor 5, has been used for treatment of TA-TMA. A retrospective analysis of 12 patients with post-HCT TMA treated with eculizumab reported hematologic response of 50% and overall survival of 33% (40). In some cases, there may be dysregulation of the complement system; elevated levels of C5b-9, the membrane attack complex, have been identified; and eculizumab has been used in these patients with mixed results (41).

IDIOPATHIC OR GVHD-RELATED CKD

Many HCT survivors will not present with a clear etiology for CKD and are labeled as idiopathic CKD. Some data support a label of GVHD-related CKD, with renal disease resulting from T cell– and cytokine-mediated tissue damage related to the chronic inflammatory state of GVHD (42,43). The presence of albuminuria in this patient population may be a marker of the renal involvement of GVHD either directly or indirectly as described above. Clinically, albuminuria is monitored using urine albumin to creatinine ratio (ACR) on a spot urine sample. Microalbuminuria is defined as an ACR of 30–300 mg albumin/g creatinine, whereas macroalbuminuria is defined by ACR ≥300 mg/g creatinine. Albuminuria is common after HCT and can have long-term effects. In a cohort of 142 HCT patients, 94% developed albuminuria within 100 days after HCT, 50% developed it at 1 year, and 4% had an ACR demonstrating overt proteinuria. Microalbuminuria at day 100 was associated with a four times greater risk of CKD, and macroalbuminuria was associated with a seven times greater risk of nonrelapse mortality (28). In a more recent study, both micro- and macroalbuminuria in the first 100 days after HCT were associated with an increased risk of nonrelapse mortality at 1 year (43). Albuminuria can also provide a readily available indicator of other underlying pathologic processes, such as TA-TMA (37).

Recent consensus guidelines recommend screening urinalyses and ACR as part of the day +80 post-HCT evaluation and then yearly screening after HCT. If macroalbuminuria is present, more frequent monitoring every 3–6 months is indicated (44). Given its utility as a marker of underlying pathology and the association between macroalbuminuria and long-term outcomes, renal biopsy is indicated in patients with persistent macroalbuminuria.

Glomerular disorders

Glomerular lesions related to HCT are typically discussed in association with chronic GVHD (cGVHD). HCT-related glomerular disease results in albuminuria, ranging from mild to nephrotic range proteinuria. Rarely, post-HCT glomerular disease presents as glomerulonephritis (45). In

contrast to albuminuria, more severe glomerular diseases are less common. Among these, membranous nephropathy (67%) and minimal change disease (33%) are the two most common pathologies (45,46). Both tend to occur fairly late after transplant, 8–14 months, and often within several months of development of GVHD or lowering of immunosuppression for GVHD prophylaxis (27,47). Treatment for HCT-associated nephrotic syndrome is similar to that in other settings, with corticosteroids being most common, as well as resumption of GVHD prophylaxis with CNIs (27,48). HCT patients with macroalbuminuria are likely to benefit from antiproteinuric therapy with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) (27,49).

Hypertension

Elevations in BP are a common complication of HCT. In a retrospective analysis of a cohort of children and adults followed for a median of 16 years after HCT, the prevalence of hypertension was 17% (50). Risk factors associated with the development of hypertension include prior AKI, total body irradiation, autologous transplant, TA-TMA, obesity, and diabetes.

Consensus recommendations are for BP measurement at each clinic visit, with a maximum interval of yearly (51). Thresholds for treating hypertension in the HCT population follow those of the general population, as recommended in the Report from the Panel Members of the Eighth Joint National Committee. For those >60 years of age, treatment goals are based on a threshold of ≥150/90 mmHg. For all other adults (≥18 years old), including those with CKD, the threshold for treatment initiation is ≥140/90 mmHg (52). In children, the Fourth Report on the Diagnosis, Treatment, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents defines hypertension as a systolic or diastolic BP >95th percentile, based on sex, age, and height (53).

Effective treatment of hypertension can decrease cardiovascular disease risk and slow the progression of CKD. Initial interventions are lifestyle modifications, including dietary sodium restriction and regular exercise. Due to antiproteinuric and renoprotective properties, ACE-I or ARB therapy should be first choice for pharmacologic treatment of hypertension. For patients in which ACE-I/ARB use is contraindicated, choice of antihypertensive should be individualized.

BK nephropathy

BK virus is a double-stranded DNA virus in the polyomavirus family with a seroprevalence of 80% reported in healthy blood donors (54). After infection, BK remains dormant in the urothelial cells without clinical effects in immunocompetent individuals. In the immunosuppressed, BK virus has been associated with nephropathy after both kidney transplant HCT; however, hemorrhagic cystitis is more common in the HCT population. In post-HCT patients, BK virus–associated hemorrhagic cystitis occurs in 10%–25% of patients and can lead to obstructive AKI, long-term urologic dysfunction, need for invasive intervention, and increased mortality. A prospective study in pediatric HCT patients reported a 22% prevalance of hemorrhagic cystitis, developing at a median of 35 days after HCT, which was associated with worse survival (55). Risks for developing BK-related complications include unrelated donor, myeloablative conditioning, and GVHD (56).

Despite a reported prevalence of 10%–30% for BK viremia, less is known about the relationship between BK viremia and nephropathy in the HCT population. In a study of 124 adult allogeneic HCT recipients, 65% developed viruria and 17% developed viremia after a median follow-up of 454 days. Only 2 of 21 patients had persistent viremia and biopsy-proven nephropathy; the remaining cases of viremia were mild and transient. BK viremia was an independent risk factor for an increase in post-HCT creatinine (57). In children after HCT, BK viremia has been reported as more predictive of poor renal outcomes than viruria, supporting the use of plasma BK polymerase chain reaction (PCR) levels when monitoring for the development of nephropathy (58). For those with elevations in SCr suspected to be related to BK nephropathy, definitive diagnosis requires kidney biopsy.

Current treatment options for hemorrhagic cystitis include pain control, continuous bladder irrigation, and urologic intervention for clearance of clots causing obstruction. Pharmacologic interventions include cidofovir, leflunomide, and fluoroquinolones (59). CMX100 is an oral formulation of cidofovir and may have less kidney toxicity (60). Another novel therapy being investigated is the use of exogenous BK-specific T cells and manipulation of immunosuppression to maximize the patient's own immune response (61,62).

ESRD AND KIDNEY TRANSPLANT AFTER HCT

There are limited data on the risk of ESRD after HCT. The reported prevalence ranges from 0.4% to 4.4% (63). One study calculated a risk of end-stage kidney disease as being 16 times higher than the general population 20 years after HCT (64). For those progressing to ESRD, dialysis and renal transplant remain the treatment options. There are several reports of successful kidney transplantation in both children and adults (65,66).

CONCLUSION

HCT patients are a population clearly at risk for the development of kidney disease, necessitating close monitoring with a multidisciplinary approach involving both oncologists and nephrologists.

TAKE HOME POINTS

- Acute and chronic kidney problems are common following HCT and are associated with an increased risk of nonrelapse mortality and a decrease in overall survival.

- Micro- and macroalbuminuria are associated with an increased risk of mortality and CKD at 1 year after HCT. It is unclear if the presence of albuminuria is a marker of systemic or local inflammation or a marker of GVHD.
- Hypertension should be managed with ACE-Is or ARBs.
- A multidisciplinary approach is needed to insure appropriate management of renal issues occurring after HCT.

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REVIEW QUESTIONS

1. Following hematopoietic stem cell transplant your patient is having a progressive rise in serum creatinine. A recent CBC and blood smear showed anemia, thrombocytopenia, and the presence of schistocytes. Considering the possibility of transplant-associated thrombotic microangiopathy, labs are sent and show an elevated lactate dehydrogenase level, an undetectable haptoglobin level, and the Coombs test is negative. Of the following, the best first step(s) in the treatment of this patient is:

   a. Administration of rituximab
   b. Therapeutic plasma exchange (TPE)
   c. Red blood cell and platelet transfusion
   d. Decreasing dose of calcineurin inhibitor therapy
   e. Both b and d

Answer: e is correct. Calcineurin inhibitor therapy, used for GVHD prophylaxis, has been associated with TA-TMA in the HCT population. First-line therapy includes lowering of CNI dose or stoppage and TPE, with the majority of patients responding to these two interventions. Other therapies being studied include rituximab, defibrotide, and eculizumab.

2. In septic HCT patients, the pathophysiologic mechanism most likely to lead to total body volume overload and edema is:

   a. Increased capillary leak related to sepsis-induced inflammatory response
   b. Heart failure
   c. Administration of pressors
   d. Endothelial damage related to high-dose antibiotics
   e. Decreased venous return related to positive pressure ventilation

Answer: a is correct. Sepsis results in a cytokine and complement-stimulated systemic inflammatory response causing increased capillary leak, total body volume overload, and decreased effective circulating volume. Sepsis is a common cause of AKI following HCT. Other common causes include volume depletion, nephrotoxic medication exposure, sinusoidal obstruction syndrome, and GVHD. Volume overload has been associated with increased morbidity and mortality in critically ill patients and HCT specifically.

3. As part of annual screening after HCT, your patient is noted to have a urine albumin/creatinine ratio of 500 mg/g Cr. Your frequency of monitoring for proteinuria should be changed to:

   a. Monthly
   b. Weekly
   c. Continue with annual monitoring
   d. Every 3–6 months
   e. You no longer need to check for proteinuria

Answer: d is correct. Albuminuria is a common long-term consequence of HCT and has been associated with progression to CKD and non–relapse-associated mortality. Microalbuminuria is defined as an ACR of 30–300 mg albumin/g creatinine, whereas macroalbuminuria is defined by ACR $\geq$ 300 mg/g creatinine. Recent consensus guidelines recommend screening ACR as part of the day +80 post-HCT evaluation and then yearly screening after HCT. If proteinuria is present, more frequent monitoring every 3–6 months is indicated. Additionally, for those with persistent macroalbuminuria, renal biopsy is indicated to make definitive diagnosis of the underlying etiology.