CHAPTER

38 Acute Kidney Injury following Hematopoietic Cell Transplantation and Severe Burns

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Acute kidney injury (AKI) occurs, with varying prevalence, across virtually all hospital settings. The most common etiologies of hospital-based AKI—acute tubular necrosis (ATN), contrast induced nephropathy, and prerenal azotemia—are familiar to every practicing nephrologist. However, AKI can also be uniquely associated with specific conditions. Two such situations are following hematopoietic cell transplantation (HCT) and in the setting of severe burns. Care for HCT and burn patients is highly specialized, typically restricted to tertiary care centers, and involves a limited number of patients. Thus, many nephrologists may have limited experience evaluating and managing AKI in these settings. However, although not commonly encountered, HCT and burns are associated with a remarkable incidence of AKI that portends subsequent worse outcomes. Therefore, this chapter explores the epidemiology, pathogenesis, and outcomes of AKI in these unique settings.

BACKGROUND

HCT is an increasingly common treatment that offers the possibility of cure for a variety of once fatal malignant and nonmalignant disorders. Initially conceived in the late 1950s as a treatment for hematologic malignancies, the spectrum of illnesses treated with HCT has burgeoned to include solid tumors,[1] red blood cell dyscrasias,[2] inborn errors of metabolism,[3] and autoimmune disorders.[4] The coming years hold the potential of an even greater role for HCT including the tantalizing possibility of inducing tolerance in solid organ transplantation and treating chronic ailments such as Parkinson disease and diabetes mellitus.[5] Current common indications for transplantation are listed in Table 38.1. Overall, approximately 50,000 to 60,000 HCTs are performed annually worldwide with roughly 40% of these occurring in the United States (www.cibmtr.org). The 5-year survival rate has improved steadily and now stands at over 50%. Additional improvements have been achieved over the past two decades in engraftment time, graft-versus-host disease (GVHD), relapse or malignant progression, and nonrelapse mortality.[12] Much of this improvement is attributable to more accurate human lymphocytic antigen (HLA) matching, more effective and tolerable infection prophylaxis, and a reduction in the intensity of chemoradiation conditioning regimens. Despite these striking advances, the procedure remains fraught with potential complications, one of the most severe of which is AKI.

The development of AKI can be detrimental, beyond its own sequelae, because it interferes with the usual adequate dosing of immunosuppressants and thus predisposes for GVHD, rejection, and interruption of treatment. AKI can also contribute to other organ dysfunction, such as lung and liver, due to volume overload, coagulation abnormalities, and cytokine mediated pulmonary dysfunction. There are at present three types of transplantation: myeloablative autologous (autologous), myeloablative allogeneic (allogeneic), and nonmyeloablative allogeneic, or reduced intensity conditioning (RIC). In the United States, 57% of transplants are autologous with the remainder being conventional and reduced intensity allogeneic.[6,7] The incidence, risk factors for development, etiology, severity, and outcomes of AKI differ markedly among the three transplant modalities.

Sources of Cells

In the early days of HCT bone marrow was the source of cells for most transplants, reflected in the older term "bone marrow transplant." However, the potential sources of cells for HCT have expanded over time. The use of recombinant human granulocyte colony stimulating factor, which can increase the entry of stem cells into the peripheral blood by up to 1,000-fold, has allowed cytapheresis harvested peripheral cells to become the current dominant source for HCT. Autologous transplants involve the harvesting of one's own bone marrow or peripheral blood cells or, most recently, the use of banked umbilical cord cells. Allogeneic transplants utilize family members or HLA-matched unrelated donors and can again derive

38.1 Common Indications for Hematopoietic Cell Transplantation

Autologous	Allogeneic
Multiple myeloma	Acute myelogenous leukemia
Non-Hodgkin lymphoma[a]	Acute lymphocytic leukemia
Hodgkin lymphoma	Myelodysplastic syndrome/ myelodysplastic disorder
Other cancers[c]	Non-Hodgkin lymphoma[a]
Neuroblastoma	Nonmalignant disease[b]
Breast cancer	–AL amyloidosis –Paroxysmal nocturnal hemoglobinuria –Thalassanemia –Sickle cell disease –Systemic lupus erythematous Chronic myelogenous leukemia Aplastic anemia Multiple myeloma

[a]Non-Hodgkin lymphomas include lymphoblastic, Burkitt, diffuse large B cell, follicular, mantle cell, T cell.
[b]Nonmalignant disease includes Fanconi anemia, Blackfan-Diamond anemia, rheumatoid arthritis, Crohn disease, multiple sclerosis, systemic sclerosis, juvenile rheumatoid arthritis, Evan syndrome, chronic inflammatory demyelinating polyneuropathy, Niemann-Pick disease, Kostmann syndrome, osteopetrosis, Hurler syndrome, adrenoleukodystrophy (ALD)/metachromic dystrophy (MLD), Di-George syndrome, chronic granulomatous disease, common variable disease, severe combined immunodeficiency, Wiskott-Aldrich syndrome, POEMS syndrome, familial erythrophagocytic lymphohistiocytosis.
[c]Other cancers include chronic lymphocytic leukemia, Ewing sarcoma, rhabdomyosarcoma, medulloblastoma, Wilms tumor, osteogenic sarcoma, hepatic blastoma, juvenile chronic myeloid leukemia, desmoplastic small round cell tumor, germ cell, ovarian, renal cell, small-cell lung, soft cell sarcoma.
Data is from references 6 to 11.

cells from bone marrow, peripheral blood, or umbilical cord blood. By 2007, 80% of allogeneic and nearly 100% of autologous transplants involved the use of peripheral blood cells.[6,7] AKI has been found to be more common in recipients of marrow transplant as opposed to peripheral stem cells in some studies[11] but not in others.[13] Conversely, chronic GVHD (cGVHD) may be more prevalent in recipients of peripheral stem cell transplantation due to the greater dose of delivered T cells.[13,15–17] No association has been established between the number of infused stem cells per body weight and AKI.[18]

Myeloablative versus Nonmyeloablative

Conventional myeloablative allogeneic HCT involves high-dose chemotherapy and radiation to eradicate the underlying disease and immunosuppression to prevent rejection of the transplant graft. The allograft then serves to reconstitute the marrow and correct the treatment associated pancytopenia. Survival is contingent on recovery from the cytoablative therapy, successful engraftment, prevention and treatment of infections and GVHD, and eradication of the underlying disease. The potent myeloablative procedure is associated with significant rates of acute conditioning associated complications due to its high-dose chemotherapy and total-body irradiation (TBI), restricting its use to younger, healthier HCT recipients. However, many of the hematologic and malignant conditions wherein HCT holds the greatest potential for cure present primarily in patients older than the standard myeloablative cutoff of 55 to 60 years old or with baseline organ dysfunction or previous high-dose chemotherapy sufficient to render them ineligible for the procedure.

For years these patients were necessarily excluded from treatment. In 1997, a nonmyeloablative procedure was proposed wherein a reduced intensity conditioning regimen would allow its use in older patients and those with significant burdens of comorbidities.[19] Unlike in myeloablative transplant, the low dose chemoradiation in RIC is not intended to kill all residual cancer cells but to provide sufficient immunosuppression so as to allow engraftment of the transplanted stem cells, facilitating their subsequent eradication of the cancer via a donor mediated immune response known as the graft-versus-tumor effect.[19–23] RIC has demonstrated low toxicity and similar efficacy compared to conventional myeloablation in several malignancies without an increased rate of disease recurrence.[19,20] RIC constituted approximately 20% of allogeneic transplants in 2006 and it is increasingly employed in low-grade lymphoma, chronic leukemia, acute leukemia in remission, renal cell carcinoma, and multiple myeloma.[24] Utilization of RIC is likely to continue to increase given the aging population, expanded indications, and technologic advances for transplants across histocompatibility barriers. Distinguishing features of the three types of hematopoietic cell transplants are charted in Table 38.2.

Conditioning Treatments and Prophylaxis

Although all modalities of HCT expose recipients to potentially nephrotoxic medications in the course of conditioning and infection prophylaxis, the specific risks vary by type of transplant. Myeloablative allogeneic regimens typically are cyclophosphamide based along with either TBI or busulfan whereas autologous recipients receive a combination of cyclophosphamide or busulfan along with other agents. For RIC, a very low dose of TBI or fludarabine is substituted for cyclophosphamide or cyclophosphamide dosing is individualized. Allogeneic recipients receive prophylaxis against acute graft-versus-host disease (aGVHD) with

38.2 Distinguishing Features of the Three Modalities of Hematopoietic Cell Transplant

	Myeloablative Autologous	Myeloablative Allogeneic	Nonmyeloablative Allogeneic
Number in U.S. (annual)	21,000	4,300	2,700
Age % recipients age >60	Mostly younger 34%	Younger <10%	Older 40%
Conditioning regimen Radiation Cytotoxic therapy	 +/− High dose	 12 Gy High dose	 2 Gy Low dose
Donor cells	PB (98%) Other (2%)	PB (68%) BM (24%) CB (8%)	PB (96%) Other (4%)
GVT effect	None	Mild/moderate	Main effect
SOS (incidence)	4%–7%	2%–54%	Rare
TM (incidence)	0%–27%	0%–76%	Extremely rare
Pancytopenia	Shorter (~2 weeks)	Longer (~3 weeks)	Shorter (~2 weeks)
Acute GVHD (II-V) Timing Incidence Prophylaxis	 N/A N/A N/A	 Early (weeks) 7%–91% MTX/CsA ±Pred	 Later 13%–77% CsA or Tac ±Pred
Chronic extensive GVHD (incidence)	N/A	13%–71%	11%–73%
Overall mortality 100 days 1 year	 ~5%–20% ~25%–30%	 ~20%–25% ~40%–45%	 ~5%–15% ~35%–40%

HCT, hematopoietic cell transplantation; U.S., United States; Gy, Gray; PB, peripheral blood; BM, bone marrow; CB, cord blood; GVT, graft-versus-tumor; SOS, sinusoidal obstruction syndrome; TM, thrombotic microangiopathy; GVHD, graft-versus-host disease; N/A; not applicable; MTX, methotrexate; CsA, cyclosporine; Tac, tacrolimus; Pred, prednisone.
Adapted and modified from reference 10. Data from references 6, 7, 10, and 25 to 29.

immunosuppressive drugs, typically cyclosporine or tacrolimus plus methotrexate, although mycophenolate mofetil and sirolimus can also be used.[30] Prophylactic drugs may be withdrawn earlier in RIC to facilitate graft-versus-tumor effect. Prophylaxis for infection includes acyclovir for patients seropositive for herpes simplex virus (HSV), trimethoprim/sulfamethoxazole to prevent Pneumocystis jiroveci infection, oral fluconazole for fungal prevention, and preemptive ganciclovir or foscarnet for cytomegalovirus (CMV) infection in viremic recipients.[31,32] Amphotericin, voriconazole, or micafungin are used for patients at risk for aspergillus infection.[33] Comparing outcomes in allogeneic recipients in the periods between 1993 and 1997 and 2003 and 2007, there has been a significant decrease in bacterial, fungal, and CMV infections.[12] In addition to improvements in the use of prophylactic antimicrobials, the increased use of peripheral blood donor cells has resulted in significantly faster neutrophil engraftment and earlier reconstitution of immunity.

Epidemiology of Acute Kidney Injury

Estimates of the incidence of AKI post-HCT vary widely, ranging from 14% to 100%.[14,34] The likelihood of kidney injury is impacted by transplant type (allogeneic or autologous), donor type (related or unrelated), degree of HLA matching (full match or mismatched), conditioning regimen (myeloablative or nonmyeloablative), and specific

38.3 Commonly Utilized Definitions of Acute Kidney Injury in Hematopoietic Cell Transplant Studies

RIFLE	
Risk	Increase in Scr ≥ 1.5 × baseline or decrease in GFR ≥25%
Injury	Increase in Scr ≥ 2 × baseline or decrease in GFR ≥50%
Failure	Increase in Scr ≥ 3 × baseline or decrease in GFR ≥75% or an absolute Scr ≥4.0 mg/dL with an acute rise of at least 0.5 mg/dL
Loss	Persistent AKI >4 weeks
ESRD	ESRD >3 months
AKIN	
Stage 1	Increase in Scr ≥0.3 mg/dL or increase to 150%–199% (1.5–1.9 fold) from baseline
Stage 2	Increase in Scr 200–299% (>2.0–2.9 fold) from baseline
Stage 3	Increase in Scr ≥300% (≥3-fold) from baseline or Scr ≥4.0 mg/dL with an acute rise of at least 0.5 mg/dL
Parikh-Schrier	
Grade 0	Decrease in GFR <25% of baseline
Grade 1	Increase in Scr <2-fold from baseline with a decrease in GFR >25% but <50% of baseline
Grade 2	Increase in Scr ≥2-fold from baseline but not requiring dialysis
Grade 3	Increase in Scr ≥2-fold from baseline and need for dialysis

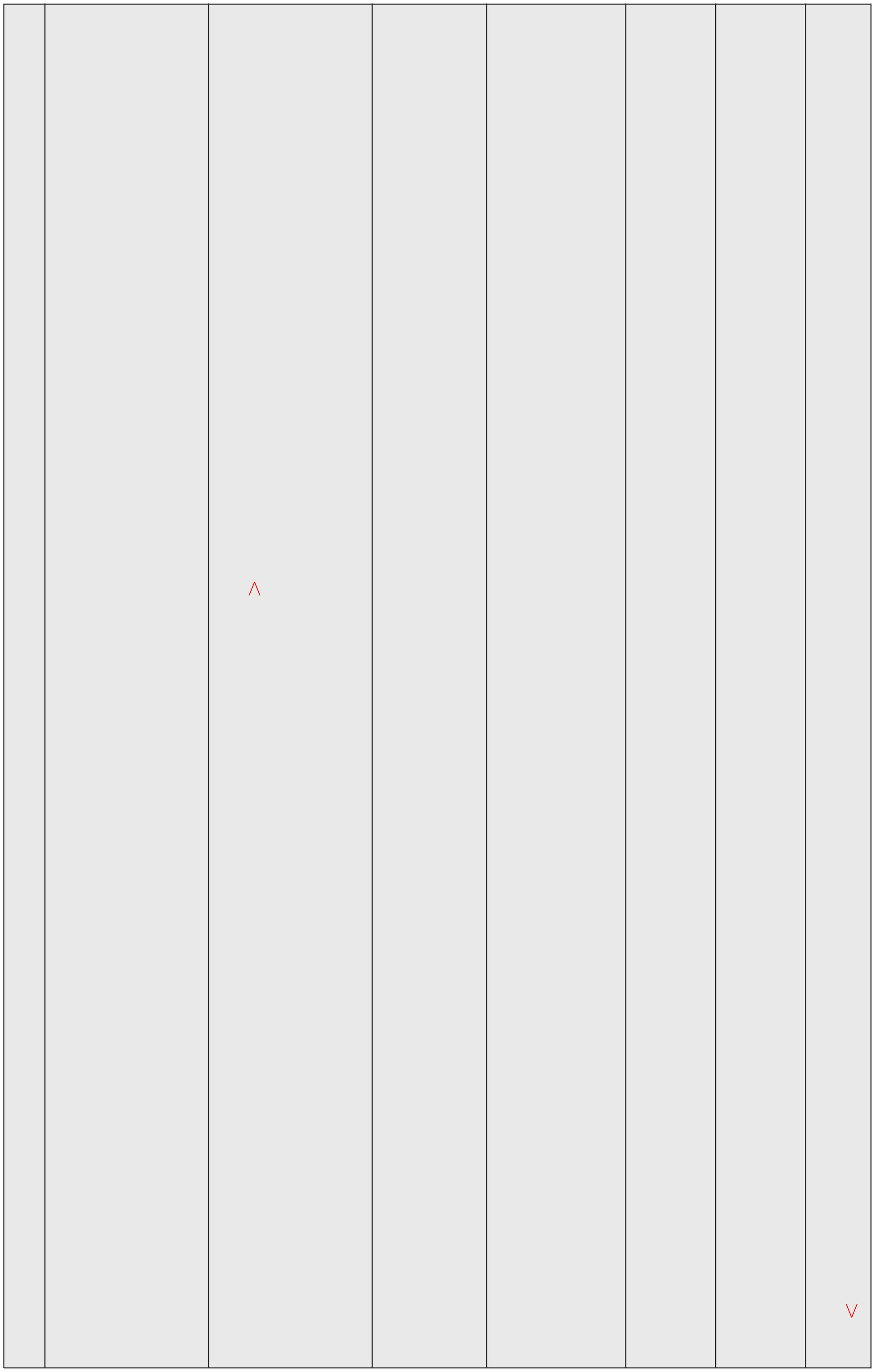
AKI, acute kidney injury; RIFLE, risk, injury, failure, loss, end-stage renal disease; Scr, serum creatinine; GFR, glomerular filtration rate; mg/dL; milligrams/deciliter; ESRD, end-stage renal disease; AKIN, Acute Kidney Injury Network.

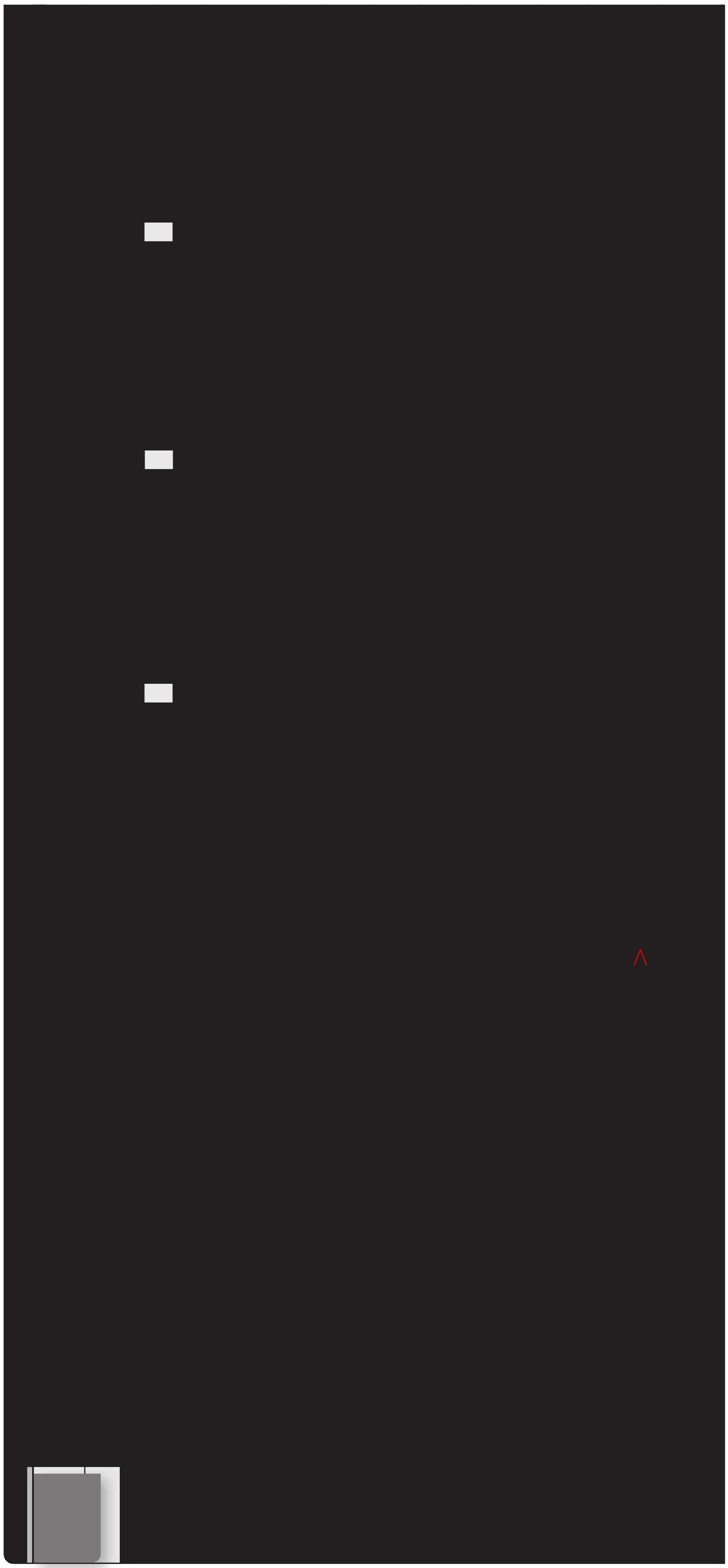
conditioning regimens, immunosuppressants, prophylactic medications, and length of follow-up. In addition, the lack of a standardized definition for AKI has been vexing to those seeking to understand the epidemiology of the disease. Two recently proposed sets of diagnostic criteria, RIFLE (risk, injury, failure, loss of kidney function, end-stage kidney disease)[35] and AKIN (Acute Kidney Injury Network),[36] have facilitated diagnostic standardization and allowed for significant advances in understanding the epidemiology and outcomes of AKI at large.[37] The definitions employed by three common classification systems for AKI following HCT are shown in Table 38.3. Although many studies of post-HCT AKI have used a variation of the classification system utilized by Parikh et al.,[38] the sensitivity of the RIFLE and AKIN criteria has recently been evaluated for diagnosis and prediction of long-term, all-cause mortality associated with post-HCT AKI.[39] AKIN identified the smallest number of patients as having AKI across all three modalities due to a reduced sensitivity for identifying the lowest category of AKI. For severe AKI, denoted as RIFLE ≥ injury, AKIN ≥ stage 2, or Parikh ≥ grade 2, all three systems performed identically. As seen in multiple other settings,[40,41] RIFLE and AKIN stages, along with those of the Parikh classification, were associated in a stepwise manner with mortality. The HCT-Comorbidity (HCT-CI) index is composed of cardiac, pulmonary, hepatic, gastrointestinal, and renal function tests that are sensitive for the detection of subclinical organ impairment and has been shown to predict nonrelapse mortality.[42,43] Both intermediate, hazard ratio (HR) 2.42, and high risk, HR 4.69, HCT-CI scores were independently associated with the development of RIFLE "I" and "F" in a combined cohort of myeloablative and RIC allogeneic recipients.[43]

INCIDENCE AND TIMING OF ACUTE KIDNEY INJURY

Myeloablative Allogeneic

Following the initial seminal study by Zager et al.,[44] AKI has been recognized as a common and devastating complication of myeloablative allogeneic HCT. In that initial cohort of 272 patients, 53% developed AKI at a median of 14 days. Numerous retrospective and prospective studies have since evaluated the incidence of AKI following myeloablative allogeneic HCT (Tables 38.4 and 38.5). Utilizing multiple definitions, AKI has been noted in 21% to 100% of patients with a weighted mean of 60%. Severe AKI occurs in a weighted mean of 40% of recipients. Although AKI following myeloablative allogeneic HCT has historically been thought to occur primarily in the first 2 to 3 weeks posttransplant, reflective of conditioning toxicity,[44,52] the median onset across all studies ranges from 15 to 60 days with a weighted mean of 30 days. The requirement for dialysis has ranged from 0% to 36%,[8,18,28,44,49,51–55,60,62,64,67,68] with some the lowest incidences[18,64] occurring more recently, perhaps reflecting refinements in conditioning and prophylactic regimens.





Befitting the discrepant patient populations, conditioning regimens, and prophylactic medications seen in these studies, myriad risk factors have been found for AKI. Conflicting results have been reported for multiple factors. Additionally, many studies have not utilized adjusted analysis, calling the true influence of postulated risk factors with potential colinearity into question. Those that have been found significant after adjustment in multiple studies include sinusoidal obstruction syndrome (SOS),[28,48,50,51,52,53,63,67,68] cyclosporine use/toxicity,[45,53,64] hyperbilirubinemia/jaundice,[46,48] amphotericin,[28,50] aGVHD,[48,51] and chronic kidney disease (CKD).[46,55] A full listing of risk factors for AKI in myeloablative allogeneic as well as autologous and RIC HCT are provided in Table 38.6.

Nonmyeloablative Allogeneic

Given the older age, poorer performance status, and increased comorbidities in those patients selected for RIC, a higher incidence of AKI than is seen with myeloablative transplant might be expected. Instead, when compared directly, RIC has consistently been associated with equal[14,43] or reduced rates of AKI.[39,63] Overall, the reported incidence is similar to myeloablative, ranging from 17% to 94% with a weighted mean of 65%. However, severe AKI is less common, occurring in a weighted mean of 30% of recipients. Reflecting this, the need for dialysis is lower and has been noted in 0% to 5% of patients.[14,25,26,29,38,39,43,58,59,63] Comparing the two modalities concurrently, myeloablative HCT was associated with an odds ratio (OR) of 4.8 for AKI.[14] Because the level of posttransplant immunosuppression and the rate of GVHD are similar between the two regimens, it appears to be the milder preconditioning regimen that reduces the incidence and severity of AKI. A gentler chemoradiation procedure alleviates both direct nephrotoxicity as well as damage indirectly caused by myeloablative associated SOS, infection, and thrombotic microangiopathy (TMA).[38] The median onset of AKI in RIC studies ranges from 17 to 60 days with a weighted mean of 46 days. This is 2 weeks later than in myeloablative, again reflecting the lesser role of conditioning toxicity in the etiology of RIC associated AKI. The onset of AKI is fairly evenly distributed over the first 3 months but subsequently tapers off significantly.[25,38] As with myeloablative allogeneic HCT, there has been little agreement between studies on independently significant risk factors for AKI following RIC HCT, with only aGVHD[25,58] noted in multiple studies.

An additional contribution to the discordant incidence and severity of AKI in MA and RIC may lie in the recipient's capacity to repair conditioning mediated tubular injury. Hematopoietic stem cells have shown the capacity to differentiate into renal tubular cells and home to the site of injury after ischemic renal insults.[69,70] It is possible such cells may contribute to the repair and regeneration of damaged tubular cells and thus mitigate AKI. Renoprotective activity of stem cell lineages has been documented in ischemically injured kidneys,[71,72] as well as with cisplatin-induced toxicity.[73,74] It is possible obliteration of endogenous stem cells in myeloablative regimens contributes to the higher observed rates of AKI.

Myeloablative Autologous

Although autologous transplants outnumber allogeneic worldwide,[6,7] comparatively few studies have investigated renal outcomes following this procedure.[29,35,40,44,58,59,61–64] The incidence of AKI after myeloablative autologous HCT is significantly lower than in either myeloablative allogeneic or RIC, ranging from 7% to 56%, with a weighted mean of 30%. Severe AKI occurs in a weighted mean of 19% of recipients. Dialysis is required following 0% to 9% of transplants.[29,35,44,58,59,61,63] Few studies have evaluated the timing of AKI onset following autologous transplantation. The lower incidence of AKI occurs despite an older patient population and the corresponding prevalence of more comorbidities.[8,9,39,67] This paradoxical outcome is due to several factors. First, autologous recipients receive comparatively mild chemoradiation conditioning regimens, thus affording protection from many conditioning associated complications. Second, autologous recipients by definition cannot suffer from acute or chronic GVHD, both of which expose the kidney to direct and indirect damage. Correspondingly, there is no need to treat autologous recipients with calcineurin inhibitors to prevent or treat GVHD and these patients are thus spared the risk of calcineurin inhibitor nephropathy (CIN). Third, associated with the milder conditioning and lack of GVHD, SOS and TMA are much less common.[13,38,75] Finally, there is more rapid engraftment without foreign cells, shortening neutropenia, lessening sepsis, and minimizing exposure to nephrotoxic antimicrobials.[64] No risk factors have been found across studies to independently associate with AKI following autologous HCT.

General Risk Factors

Chronic Kidney Disease

CKD is a well-established risk factor for AKI in the setting of potential kidney insults with nephrotoxins such as radiocontrast media[76] and aminoglycosides.[77] Surprisingly, the inverse has been found in multiple studies of HCT. Zager assessed the relationship in 3,325 patients between pretransplant eGFR and renal function at 1 year following HCT.[78] Outcomes included both "renal functional impairment," defined as a 25% reduction in eGFR from baseline, as well as absolute change. A striking inverse correlation was seen between baseline function and 25% decrease, $r = 0.92$, and absolute decrease, $r = 0.97$. The authors speculate it may be a form of acquired cytoresistance as seen in several animal models.[79–84] Although not universally noted,[55] a similar finding of elevated pretransplant GFR as a risk factor for AKI has been found in several RIC[38,58] and myeloablative allogeneic studies.[50] Although the concept of ischemic preconditioning to prevent AKI is intriguing,[85,86] some part of the effect in this setting is likely due to the utilized AKI definitions in that the

38.6 Risk Factors Independently Associated with Acute Kidney Injury Following Hematopoietic Cell Transplant

Risk Factors	MA	Autologous	RIC
SOS/liver toxicity	6 (8)[a]	1 (1)	– (0)
Cyclosporine use/toxicity	3 (7)	– (0)	1 (0)
Ventilator use	2 (2)	1 (1)	– (0)
aGVHD	2 (8)	– (0)	2 (2)
Amphotericin	2 (6)	– (1)	– (0)
Hyperbilirubinemia	2 (5)	– (0)	– (0)
Diminished baseline renal function	2 (7)	– (1)	– (0)
Sepsis/septic shock	1 (5)	1 (1)	– (0)
Hypertension	1 (3)	– (0)	– (0)
ICU admission	1 (1)	– (0)	– (0)
Unrelated donor/incomplete HLA-match	1 (9)	– (0)	1 (4)
Foscarnet	1 (2)	– (0)	– (0)
Age	1 (7)	– (2)	1 (3)
Methotrexate	– (3)	– (0)	1 (1)
Diabetes mellitus	– (0)	– (0)	1 (1)
(GVHD, sepsis, SOS) composite	– (0)	– (0)	1 (1)
>3 cycles of prior chemotherapy	– (0)	– (0)	1 (1)
Absence of vascular disease	– (0)	– (9)	1 (1)
High baseline GFR	– (0)	– (0)	1 (1)
Bacteremia	– (0)	1 (0)	– (0)
Melphalan	– (0)	1 (0)	– (0)
Proteinuria	– (0)	1 (0)	– (0)

[a]Number of studies with statistically significant increased risk of AKI (number of studies where risk factor has been evaluated for independent association).
AKI, acute kidney injury; HCT, hematopoietic cell transplantation; MA, myeloablative allogeneic; RIC, reduced intensity conditioning allogeneic; SOS, sinusoidal obstruction syndrome, aGVHD, acute graft-versus-host disease; ICU, intensive care unit; GFR, glomerular filtration rate.

absolute change required for doubling of serum creatinine is less in patients with lower baselines, with the same following for GFR, and thus those patients with preserved baseline function require smaller changes to meet AKI criteria.

Genetics

SNPs in genes associated with the urea cycle (CPSI) and hemochromatosis (HFE) have been shown to influence susceptibility to SOS.[87–90] Additionally, donor–recipient genotype combinations in the killer immunoglobulin-like receptors (KIRs) present on NK and some T cells are important determinants of aGVHD.[91] Finally, the presence of the DD allele in the ACE gene may slow the decline in creatinine clearance in the year following HCT.[92]

Additional Markers of Kidney Injury

Despite the tremendous incidence of AKI documented in these studies, they are likely to be significantly underestimating the true occurrence of kidney injury following HCT. As is widely recognized in nephrology, serum creatinine is a poor and insensitive marker for kidney function. Due to renal functional reserve and tubular creatinine secretion, serum creatinine can remain in the normal range even when the glomerular filtration rate (GFR) has fallen to 50% of baseline. In addition to actual changes in GFR, creatinine levels are also influenced by body weight, race, age, gender, muscle mass, protein intake, and drugs. In HCT patients in particular, given the severity of their disease, it is common to see significant weight loss, loss of muscle mass, and decreased protein intake.

^{99m}Tc-DTPA was used to sequentially measure GFR in pediatric patients post-HCT.[47] GFR fell precipitously from baseline at 30 and 100 days but rebounded somewhat by 180 days. The estimated GFR utilizing creatinine was significantly higher than ^{99m}Tc-DTPA measured GFR. N-acetyl-β-D-glucosaminidase (β-NAG), a biomarker of tubular damage,[93] was significantly elevated at 30 days but returned to baseline by 180 days. Near ubiquitous early elevation in urinary α-1 microglobulin and β-NAG and a decrease in phosphate reabsorption after conditioning indicated rampant tubular damage.[28] After 2 years, although only 5% of the children had inulin measured GFR $<$90 mL/min, approximately 40% maintained elevated urinary α-1 microglobulin levels or decreased phosphate reabsorption. Based on these more sensitive markers it appears nonspecific tubular damage in the peritransplant period is ubiquitous and recovery is often incomplete, even if subclinically so.

Additional novel markers may assist in ascertaining the true incidence of injury. Cystatin C, a low molecular weight protein (13kDa) synthesized by all nucleated cells, freely crosses the glomerular filtration barrier and is almost completely reabsorbed by the cells of the proximal tubule. Cystatin C has demonstrated superior diagnostic sensitivity for the detection of AKI compared with creatinine.[94] Cystatin-C has retrospectively been assessed as a marker for post-HCT kidney dysfunction.[45] Although noting a strong inverse correlation between cystatin C and estimated GFR, the authors did not compare the ability of cystatin C and creatinine to detect AKI. A significantly higher rate of worsening of preexisting chronic kidney disease (CKD) was found during the first year post-HCT in patients with a pretransplant cystatin C level $\geq$0.90 mg per L relative to patients with levels below this cutoff.

In the context of validating the results of a urine proteomic study of novel markers predictive of clinical AKI, an AKI-specific peptide panel was assessed in 31 patients undergoing allogeneic HCT, 13 of whom developed AKI.[95] Although absolute peptide levels differed from those of patients studied in an intensive care unit (ICU) setting, the panel showed excellent discriminatory ability with an area under the receiver operating curve (AUC) of 0.90, a sensitivity of 94%, and a specificity of 82% to predict AKI as defined by a rise in serum creatinine of $\geq$50% within 48 hours.

ETIOLOGIES OF ACUTE KIDNEY INJURY

AKI seen in the context of HCT is often multifactorial and identifying a specific etiology can be challenging. Several factors unique to the transplant patient and procedure contribute to the extreme incidence and severity of AKI observed post-HCT. Various classification systems have attempted to distinguish between causes associated with early, middle, and late onset, as variably defined.[50,96–98] The most common etiologies will be discussed in chronological order, beginning at the time of induction.

Medullary Infusion Toxicity

Infusion of cryopreserved marrow or blood progenitor cells may lead to kidney injury via two mechanisms. Cell lysis products and debris associated with the freeze/thaw cycle can cause direct glomerular damage and proteinuria. Additionally, dimethyl sulfoxide, a cryopreservative primarily used in autologous cell storage, may cause hemolysis and hemoglobinuria mediated nephrotoxicity.[99–101]

Tumor Lysis Syndrome

Tumor lysis syndrome is a condition in which the rapid obliteration via radiation and chemotherapy of a high bulk of tumor cells results in a massive release of nephrotoxic debris. Renal injury is primarily mediated via hyperphosphatemia as well as urate and xanthine nephropathy. Precipitation of these products in the renal tubules leads to intratubular obstruction and AKI. Additionally, hyperuricemia has been associated with renal vasoconstriction and pro-oxidative and pro-inflammatory mediators.[102] Those at greatest risk are patients with high tumor bulk such as acute leukemias with high white cell counts and Burkitt's lymphoma.[103] Fortunately, due the fact that many patients are in remission at the time of therapy and are treated appropriately with

prophylactic intravenous fluids, urinary alkalinization, and allopurinol, the incidence of tumor lysis syndrome following HCT is rather low (approximately one in 400).[101]

Sepsis

Patients undergoing HCT are at tremendous risk for bacterial and fungal infection and resulting sepsis due to the profound neutropenia engendered by induction chemotherapy and radiation, which is then compounded by the use of immunosuppressants to prevent aGVHD. The inflammatory response to disseminated infection leads to systemic arterial vasodilatation and capillary leak, precipitating hypotension and renal hypoperfusion with resultant pre-renal azotemia and acute tubular necrosis. This hypoperfusion can be potentiated by vomiting and diarrhea associated with the intense conditioning regimens. However, even in the absence of hypotension, sepsis may provoke AKI via cytokine and chemokine mediated renal vasoconstriction and direct intrarenal inflammatory and complement associated kidney injury.[104] Additionally, the antimicrobials used in the prevention and treatment of sepsis are often nephrotoxic (see later).

Nephrotoxic Medications

Many of the chemotherapy agents used for induction have the potential to be nephrotoxic including carboplatin, vincristine, melphalan, busulfan, etoposide, carmustine, cytarabine, and cyclophosphamide.[100,105–107] The nephrotoxicity of antineoplastic medications is treated in depth elsewhere in this text. Amphotericin B is utilized for patients at risk for or with evidence of aspergillus infection and is a well-recognized nephrotoxin. Though liposomal amphotericin has generally been associated with lessened nephrotoxicity,[108] studies show both preparations confer an equal increase in risk of AKI following HCT.[28,50] The use of aminoglycosides has declined with the advent of alternative broad spectrum antibiotics but when utilized still carry a marked potential for nephrotoxicity. Additional medications found to associate with AKI following HCT include vancomycin[33,43] and methotrexate.[25] Given the potential nephrotoxicity of calcineurin inhibitors (see later), sirolimus has been investigated for GVHD prophylaxis. Although there is no data on monotherapy, sirolimus has been shown to potentiate the risk of TMA (OR 2.79)[109] and SOS (OR 2.76)[27] when used with calcineurin inhibitors without affecting mortality. The risk of SOS was even higher when sirolimus was used in conjuncture with busulfan.

Calcineurin Inhibitors

Calcineurin inhibitors (cyclosporine [CSA] and tacrolimus) are routinely used as immunosuppressants to prevent GVHD. In myeloablative allogeneic transplant patients, they are frequently combined with methotrexate or mycophenolate mofetil while they are used with steroids in non-myeloablative transplantation. Calcineurin inhibitors are well-known nephrotoxins, inducing potent renal vasoconstriction, direct endothelial injury, and provoking thrombotic microangiopathy. Toxicity has been thought to correlate well with serum drug concentration.[110] Although the expected association was seen between CSA exposure and AKI in several older studies,[19,20,111] the majority of recent studies have failed to replicate this finding.[25,38,44,49,50,58,112] There does not appear to be any difference in the incidence of AKI utilizing cyclosporine versus tacrolimus.[54] In two studies where the etiology of AKI was chart adjudicated, elevated CSA levels were associated with AKI in 67% of all patients[28] and 100% of patients with grade 2 AKI.[38] However, despite this clinical association and the biologic plausibility of causation, CSA levels were not found in either study to be independent risk factors for AKI on multivariable analysis.

This discordance between statistical analysis and chart reviewed diagnosis may be due to variability of levels and troughs within a given patient and the transient effect of CSA on short-term renal function. Additionally, targeted CSA therapeutic ranges vary significantly across studies (see Table 38.4) and, in analyzing CSA as a risk factor, it has sometimes been treated as a continuous variable based on levels and sometimes categorical regarding its use or the surpassing of the designated toxic threshold. Renal dysfunction may also lag peak concentration.[67] Finally, CSA toxicity can occur despite low or normal serum concentrations and thus may be complicated by a patient's genetic susceptibility. Woodhahl et al. investigated four single nucleotide polymorphisms (SNPs) in genes regulating cyclosporine metabolism and transport which may affect tubular intracellular drug levels in 121 patients following myeloablative transplant.[113] Although no findings reached statistical significance, there was a trend toward a higher OR for AKI with SNPs in ABCB1, encoding the transporter P-glycoprotein.

Sinusoidal Obstruction Syndrome

SOS, formerly known as hepatic veno-occlusive disease, is initiated by chemoradiation-induced injury to sinusoidal epithelial cells. Damage to these cells leads to activation of stellate cells and deposition of extracellular matrix in sinusoids and zone 3 hepatocytes with resulting thrombosis and necrosis. Subsequent portal hypertension stimulates a shift in fluid from the intravascular to extravascular space, increased activation of the renal-angiotensin-aldosterone system, sodium and water retention, ascites formation, and ultimately AKI in a presentation similar to hepatorenal syndrome.[75] However, patients with SOS and AKI have also been found to have higher β-NAG, α-1 microglobulin, and albumin excretion than those without AKI, implying there is a component of tubular and perhaps glomerular injury as well.[100] Signs and symptoms include hepatomegaly, right upper quadrant pain, ascites, weight gain, and increased serum aminotransferase and bilirubin levels.[114] SOS is only rarely seen with RIC[14] and is less common in autologous than allogeneic transplants.[62] In myeloablative regimens, the development of SOS is strongly associated with post-HCT AKI,[14,44,52,68] with an incidence of 0% to 60%,[8,30,114] and

increases with AKI severity. Ileri et al. documented SOS in 6% of pediatric recipients without AKI, 8% with grade 1, 22% with grade 2, and 100% with grade 3.[28]

Risk factors for the development of SOS include age, preexisting hepatic disease, hepatitis C, TBI, CMV seropositivity, and multiple medications including cyclophosphamide, busulfan, vancomycin, amphotericin B, acyclovir, and methotrexate.[64,114,115] Although the exact contribution of individual medications can be difficult to untangle in overlapping regimens, cyclophosphamide in particular is thought to directly contribute to liver injury.[116] Using personalized dosing based on measurement of carboxyethylphosphoramide mustard, a metabolite that functions as a reporter molecule for hepatotoxins from cyclophosphamide, and utilizing Bayesian parameter estimates, patients that received reduced cyclophosphamide had lower bilirubin levels, and suffered less AKI, 62% vs 77% ($P = .03$), than those receiving conventional dosing.[117]

HCT Associated Thrombotic Microangiopathy

Thrombotic microangiopathies (TMA) are characterized by systemic or intrarenal platelet aggregation, thrombocytopenia, and microvascular fragmentation of erythrocytes. Diagnostic evaluation divulges schistocytes on peripheral smear and increased serum lactate dehydrogenase (LDH). In the archetypal TMA, thrombotic thrombocytopenia purpura (TTP), abnormalities in ADAMTS-13 von Willebrand factor cleaving protease activity have been associated with inherited and acquired disease. Decreased ADAMTS-13 activity results in a preponderance of large multimers of von Willebrand factor and subsequent platelet aggregation.[118] However, ADAMTS-13 deficiency is not involved in the pathophysiology of HCT associated TMA.[119–123] Additionally, autopsy studies have demonstrated post-HCT TMA to be primarily renally dominant, similar to hemolytic uremic syndrome rather than TTP.[119,124] Correspondingly, the neurologic features of TTP are typically absent.[124]

The inciting event in post-HCT TMA is endothelial damage initiated by the conditioning regimen, particularly TBI and busulfan.[121,125] The initial injury is potentiated by infections, lipopolysaccharides, calcineurin inhibitors, sirolimus, and aGVHD.[122,126,127] GVHD may mediate endothelial damage in the kidney via circulating inflammatory cytokines related to systemic disease or may inflict direct injury to endothelial cells in the kidney due to localized activated donor cells.[128] This kidney specific GVHD may also be associated with reduced VEGF function.[128–130] Owing to this damage, a loss of endothelial resistance to thrombus formation, subsequent leukocyte adhesion, and an increased vascular shear stress ensue and augment the injury. In addition to AKI, patients often present with anemia, thrombocytopenia, hypertension (HTN), edema, proteinuria, and hematuria. Disease onset typically is within 100 days of HCT. The clinical spectrum of kidney disease in HCT patients with TMA ranges from an indolent course resulting in CKD to a fulminant presentation with AKI and death.[128] Different forms of overlapping thrombotic microangiopathic syndromes have been described. Patients with TMA after HCT have thus been diagnosed with HCT nephropathy, radiation nephropathy, hemolytic uremia syndrome, TTP, or transplant associated microangiopathy.[127] Making a confident diagnosis is challenging because anemia, thrombocytopenia, and elevations in LDH and creatinine are common post-HCT due to delayed engraftment, fungal and viral infections, medications, and GVHD.[121,131] Biopsy is often contraindicated due to patient instability and thrombocytopenia. Confounding the confusion, no fewer than 28 different sets of diagnostic criteria have been proposed in 35 articles detailing post-HCT TMA.[124] Two distinct consensus definitions have also been set forth.[120,131]

Not surprisingly, the estimated incidence of TMA in the setting of HCT varies widely from 0.5% to 76%[34,122,128] with the alleged mortality ranging from 0% to 100%. Changsirikulcai et al. retrospectively analyzed autopsy samples from 322 patients who had died a median of 43 days posttransplant; 41% had suffered AKI within 2 weeks preceding their deaths.[128] On biopsy, 20% met criteria for TMA whereas an additional 15% had a singular glomerular or vascular thrombus. There was no statistically significant difference in serologic abnormalities (hematocrit, platelets, LDH, elevated creatinine) between patients with these findings and those with negative biopsies. Histologic evidence of TMA in the kidney did not correlate with the laboratory evidence of AKI in the 2 weeks prior to death. On chart review, a clinical diagnosis or suspicion of TMA correlated with histologic evidence of TMA in 35.5% of the positive samples versus 4.5% of the negative ($P < .001$). Other studies have shown mixed results in the correlation between TMA as diagnosed by clinical criteria and histologic findings on autopsy.[99,119,124] An extensive litany of risk factors for post-HCT TMA have been described including advanced age, female sex, female recipient–male donor, unrelated donor, HLA-mismatch, T-cell depletion, high intensity conditioning regimens, high dose busulfan, fludarabine, TBI, sirolimus, calcineurin inhibitors, sirolimus with calcineurin inhibitors, aGVHD, methylprednisolone therapy, adenovirus, fungal or viral infection, and SOS.[38,109,128,132–137]

Treatment options for post-HCT TMA, outside of withdrawing any identifiable inciting agents, are scarce. Indeed a review article found that any attempt at treatment led to increased mortality as opposed to no treatment at all, although this finding may suffer confounding by indication.[121] Although plasma exchange, a staple of treatment in ADAMTS-13 associated TMA, has been reported to be effective in rare instances,[138,139] the majority of studies have seen little or no benefit.[124,131,140–143] Rituximab, an anti-CD20 monoclonal antibody, showed promise in a small series treating post-HCT TMA which had failed plasma exchange.[144] In patients who have developed GVHD and TMA, withdrawal of calcineurin inhibitors and treatment with daclizumab, a humanized anti-CD25 antibody, have shown promise in the treatment of TMA but poor response in terms of complete remission of

GVHD.[126] Defibrotide, a polydeoxyribonucleotide salt, protects against endothelial damage by inhibiting tumor necrosis factor (TNF)-α mediated endothelial cell apoptosis and exhibits profibrinolytic, antithrombotic, and anti-inflammatory activity.[122] It has been used in treating SOS associated with HCT and with some success in small studies in TMA.[145]

Graft-versus-Host Disease

GVHD has classically been thought not to involve the kidney. aGVHD develops in 50% to 60%[146] of sibling-matched allografts and cGVHD involves 30% to 60%.[147] Any association between GVHD and AKI in these patients has been attributed to volume depletion due to gastrointestinal tract involvement with diarrhea and an increased need of nephrotoxic drugs for GVHD treatment. Recent evidence, however, suggests that GVHD may affect the kidney directly. aGVHD has been found an independent risk factor for post-HCT AKI in multiple studies.[25,48,58,63] Such toxicity may be due to cytokine mediated inflammatory injury, glomerular deposits leading to nephrotic syndrome (see later), and tubulitis secondary to activated cytotoxic T cells. Documentation of severe renal infiltration by cytotoxic T cells during GVHD has been documented in mice,[148] but confirmation of the role of GVHD in human AKI awaits further study.

Biopsy Data for Etiologies

Biopsies are rarely performed in patients with AKI following HCT due to thrombocytopenia, hemodynamic instability, and infection. Several series have been performed, often retrospectively, in patients with AKI or worsening CKD months to years out from transplant.[149–153] Among frequently overlapping pathology, findings consistent with TMA, polyoma virus nephropathy, ATN, interstitial nephritis, tubulointerstitial scarring, and podocytopathy are commonly found. El-Seisi et al. performed an autopsy study of 26 patients who had died a median 3 months after transplant; 15 had AKI.[99] Global segmental sclerosis, tubular epithelial atypia, tubular calcification, mild tubulitis, interstitial fibrosis, and thrombotic microangiopathy were all common. Despite the expected renal insults common in hospital-based death, very little classical ATN was noted. No association was seen between clinical SOS and histology consistent with TMA. Interestingly, only 1/12 patients with TMA on biopsy had clinical evidence of the disease on retrospective chart review. In assessing the generalizability of these findings to all AKI post-HCT, the study suffers from selection bias in that patients would have been much less likely to be autopsied if they died of disease relapse or at home.

PROGNOSIS

Mortality

Nonrelapse mortality after HCT occurs primarily due to complications of the HCT procedure, with AKI being one of the most prominent. The pathway linking HCT associated

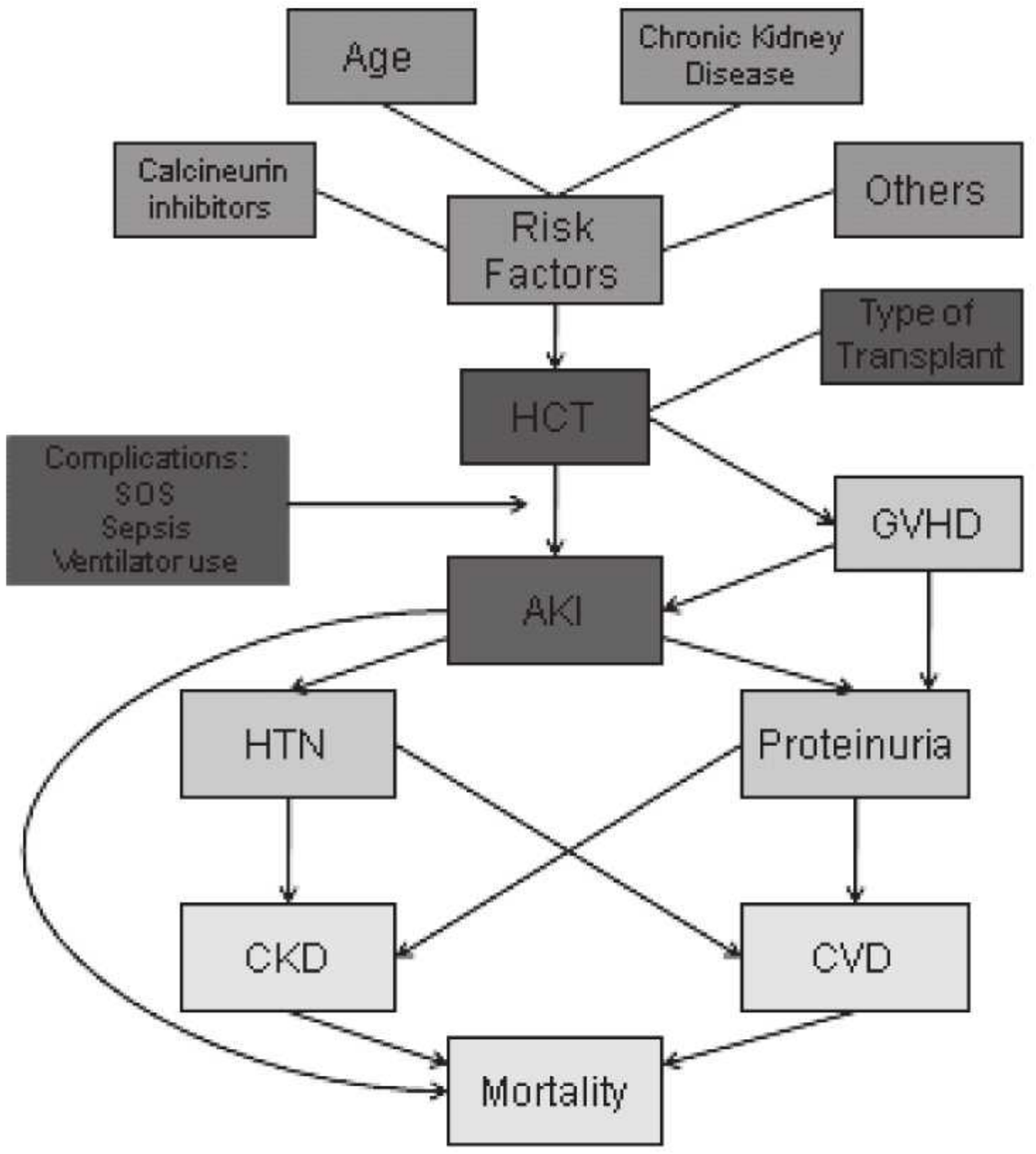


FIGURE 38.1 Mechanisms and outcomes of hematopoietic cell transplant associated acute kidney injury. AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; GVHD, graft-versus host disease; HCT, hematopoietic cell transplant; HTN, hypertension; SOS, sinusoidal obstruction syndrome.

AKI with mortality and other long-term outcomes is shown in Figure 38.1. AKI can cause mortality directly via consequences of compromised renal function including metabolic acidosis, cardiac dysrhythmias, HTN, electrolyte imbalances, gastrointestinal dysfunction, and hemorrhage.[154] AKI can also contribute to dysfunction in other organ systems such as lung and liver via volume overload and confers an increased risk of sepsis due to altered leukocyte function.[154–156] Additionally, cytokine or immune-mediated injury may be culpable for the dysfunction in distant organs seen with AKI.[157] Finally, AKI interferes with adequate dosing of immunosuppressants and may predispose to GVHD and rejection while complicating their treatment.[158]

Across modalities, AKI following HCT has consistently been linked with an increased risk of death on both short- and long-term follow-up. Overall mortality following AKI has been found to range from 4% to 61%.[34,64] In one of the earliest studies involving myeloablative allogeneic transplant, Zager et al. found an index hospitalization mortality of 17% in those without AKI, 37% in non–dialysis-requiring AKI, and a whopping 84% in dialysis-requiring AKI.[44] AKI has since been found to confer a significant independent risk for mortality in myeloablative allogeneic,[14,33,49,50,52,67] myeloablative autologous,[67,114] and RIC[25,28,38] transplants. The strength of this association has consistently been found to be dose dependent and contingent on the severity of the

AKI as well as the length of follow-up.[14,25,43,52,58,59,66,67,112,159] Increased mortality has been found at 100 days,[28,52,67] 6 months,[46,49] 1 year,[25,38] and 5 years.[26] Patients with AKI have significantly decreased 1-, 2-, and 3-year survival when stratified by AKIN stage.[66] Utilizing the Parikh scale, Yu et al. found 29% mortality without AKI, 57% with Grade 1. and 79% with Grade 2-3.[63] In a prospective study evaluating the RIFLE, AKIN, and Parikh diagnostic criteria in 249 patients receiving a mixture of myeloablative allogeneic, RIC, and myeloablative autologous transplants, the mortality rates at 1,000 days for patients with AKI were approximately 54% in myeloablative allogeneic, 48% to 50% in RIC, and 11% to 20% in autologous recipients.[39] The variance in mortality rates may be due to the previously noted different etiologies of AKI in these three modalities. A very significant stepwise increase in mortality hazard ratio was seen in all three classification systems. On multivariable analysis, RIFLE "I" and "F" were associated with overall nonrelapse mortality, HR 2.1 ($P = .01$) and 6.15 ($P < .01$). Finally, a meta-analysis of over 1,200 patients receiving a myeloablative allogeneic transplant revealed a doubling of the relative risk of death 6 months after AKI.[86] The adjusted odds of 6-month mortality were elevated nearly sevenfold. The outlook for patients requiring dialysis is especially grim, with mortality ranging from 75% to 100%.[10,25,38,43,44,49,51,54,58,60,62,68,112]

Significantly, AKI is an independent predictor of overall and nonrelapse 5-year mortality even in RIFLE stage "R," demonstrating that small changes in creatinine may be associated with long-term mortality.[26] Such a connection between mild AKI and mortality has also been demonstrated in cardiac surgery, acute myocardial infarction (MI), and the critically ill.[160–163]

AKI has been postulated to drive mortality by means of instigating HTN, CKD, and increased cardiovascular disease. Specific to HCT, AKI interferes with dosing of immunosuppressive medications, including calcineurin inhibitors, and may thus contribute to the development of cGVHD and resultant mortality.[155] The extent to which the association between AKI and long-term mortality is causal remains unknown.[164] Although it plausibly could be a direct mediator through the above mechanisms, AKI may associate with mortality merely as a surrogate for unappreciated or inadequately adjusted comorbidities. Additionally, many of the causes of AKI, including SOS, infection, and GVHD, independently lead to mortality.[97] In one study where AKI had a marked dose response association with mortality, correcting for aGVHD, SOS, TMA, and ICU admission abrogated the association.[49] However, another study showed AKI continuing to confer a robust OR of 6.8 for mortality even on a model adjusted for comorbidities and complications.[112]

Chronic Kidney Disease

The increased incidence of CKD following AKI has been well established.[162–165] The first report of CKD following HCT was in 1978.[166] Since then, estimates of the incidence of CKD in survivors of AKI have ranged from 3.6% to 89%.[153] The marked discrepancy in these estimates is due to variation in the definition of CKD, changes in conditioning regimens and posttransplant prophylactic and therapeutic medications, as well as evolving patient populations. Additionally, autologous, conventional allogeneic, and RIC transplants all confer different risks for AKI and their proportional representation among cohorts will influence the observed CKD rate. AKI following HCT has been identified as an independent risk factor in the development of CKD in multiple studies.[45,50,53,153,167,168] Indeed, in some pediatric populations, AKI has been identified as the only consistently significant risk factor for post-HCT CKD.[53,55] A systematic review by Ellis et al. identified 28 studies containing 5,337 patients who survived at least 100 days following HCT and who were evaluated for CKD.[169] With significant heterogeneity in definitions, 16.6% of all patients were reported to have developed CKD with 0.8% progressing to end-stage renal disease (ESRD). AKI following HCT was assessed as a risk factor for the development of CKD in four studies involving 2,038 patients. The cumulative OR for CKD after AKI was found to be 2.57. Worldwide, 5,100 post-HCT patients develop CKD annually whereas 300 progress to ESRD.[170] Survival in patients with HCT associated ESRD may be worse than in the general ESRD population.[171]

On systematic review, the incidence of CKD following allogeneic and autologous transplants is similar.[169] In addition to AKI, multiple risk factors for post-HCT CKD have been identified, although inconsistently, including age, prior transplant, aGVHD, cGVHD, calcineurin use >60 days, baseline GFR, microalbuminuria, multiple myeloma, and female gender.[31,32,153,167,169] Although TBI has often been found to be weakly, if at all, associated with CKD,[32,167,172,173] other studies have found a strong and indeed preeminent association.[169,174,175]

Post-HCT CKD can be secondary to glomerular (see later) or interstitial and vascular disease. Although many cases of interstitial CKD are readily attributable to TMA (often associated with TBI), from 17.5% in myeloablative to 66% in nonmyeloablative recipients have idiopathic disease.[32] This CKD is multifactorial but it seems likely that AKI plays a prominent role in its development. In a retrospective study of 123 patients receiving allogeneic transplants, CKD developed in 40% within 24 months.[167] The occurrence of AKI post-HCT conferred an OR of 4.54. Additional risk factors included age and baseline GFR <90 mL per minute. Patients who would and would not go on to develop CKD had a near identical drop in GFR at 3 months (28 vs. 26). However, by 24 months, GFR had dropped further to −36 mL per minute from baseline in CKD patients but rebounded to −17 mL per minute in those not destined for CKD. Only 3% of recipients developed CKD subsequent to 24 months. It may be that much of this "early" CKD is secondary to progression of AKI in patients with lower baseline GFR and less renal functional

reserve.[168] Indeed, nonrecovery of GFR by 100 days post-HCT has been documented even in mild AKI.[62]

Proteinuria

On systematic review, the rate of proteinuria following HCT is 7.8%[169] but was rarely reported. Thought to be a marker of endothelial dysfunction and inflammation, proteinuria post-HCT may reflect systemic endothelial injury. As such, proteinuria is intricately associated with SOS and GVHD. Hingorani et al. prospectively followed 142 patients receiving myeloablative allogeneic, RIC and autologous transplants.[31] Microalbuminuria was present in 37% at baseline and 64% at day 100, with an overall prevalence of 94% in the first 100 days post-HCT. Overt proteinuria was seen in 4% at baseline and in 15% by day 100. Mean proteinuria peaked at 35 days and declined at 100 days and again by 1 year. The development of SOS was associated with a markedly higher level of albuminuria in the first week post-HCT. Median albuminuria was significantly higher in allogeneic recipients than autologous at 35 and 100 days. Interestingly, albuminuria was not associated with the development of AKI but was, as a time-varying term, a risk factor for the development of aGVHD. On multivariable analysis, overt proteinuria at 100 days conferred an HR 2.4 for overall mortality and 6.8 for nonrelapse mortality.

The presence of albuminuria prior to the clinical presentation of aGVHD suggests it as an early marker of systemic and renal inflammation and endothelial damage. It also implies the kidney as a target of aGVHD. Such targeting is also insinuated by the association between SOS, strongly associated with aGVHD, and proteinuria. Both membranous nephropathy and minimal-change disease post-HCT are thought to be renal manifestations of GVHD. In minimal change, the lack of infiltrates on biopsy and the increased production of tumor necrosis factor-α and interferon-γ suggest cytokine mediated glomerular injury in response to extrarenal alloantigens.[176] In contrast, in membranous nephropathy, subepithelial immune complex deposition is present along the basement membrane, consisting of antigen-antibody complexes that resemble GVHD. GVHD may thus cause proteinuria via both inflammation and direct glomerular and tubular injury. The near universal incidence of microalbuminuria see by Hingorani and others[57] may thus suggest ubiquitous subclinical immune mediated kidney injury in HCT despite the observation that only 30% of patients in this study met clinical diagnostic criteria for AKI.

Frank nephrotic syndrome is rare after HCT, with an incidence of 0.4% to 0.8%.[96,177] The most common etiology, membranous nephropathy (MN), was first reported in 1989,[178] and has been documented in nearly 60 cases.[151] Although the antigenic target has yet to be elucidated, MN following HCT is intimately associated with cGVHD. Much like chronic allograft nephropathy, cGVHD is increasingly recognized to feature a role for B cells and antibodies in its pathophysiology, altering the classically understood T-cell centric paradigm.[45] Additional glomerulopathies reported after HCT include MCD, focal segmental glomerular sclerosis, membranoproliferative glomerulonephritis, diffuse proliferative glomerulonephritis, antineutrophil cytoplasmic antibody (ANCA)-associated GN, and IgA nephropathy.[151,179–186] Case reports suggest nephrotic syndrome associated with post-HCT MN may be responsive to treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).[187]

Hypertension

HTN is an integral component of the classically described transplant nephropathy. Few prospective studies have evaluated the incidence of new-onset HTN following HCT. Hoffmeister et al. followed 689 pediatric patients receiving a mixture of myeloablative allogeneic, RIC, and autologous transplants.[188] Seventeen percent of recipients developed new-onset HTN during a median follow-up of 16 years. In those who experienced AKI within 100 days of transplant, HTN developed in 22% versus 14% in those without AKI. On multivariable analysis, the hazard ratio for HTN given post-HCT AKI was 2.53 ($P < .0001$). Additional risk factors for the development of HTN were high dose TBI, autologous transplant, and time-dependent obesity, diabetes, and growth hormone usage. Overall rates of HTN on follow-up were found to be two to three times higher than the age appropriate population prevalence. In 73 autologous recipients, 72% developed new-onset or worsening of prevalent HTN at 1 year post-HCT. HTN rates were higher in those patients that had developed CKD. Although HTN was also associated with calcineurin inhibitor use, elevated blood pressure persisted in 64% of hypertensive patients 6 months after stopping calcineurin inhibitors.[153] A systematic review showed HTN developing in 108/873 (12.4%) patients across modalities but was unable to assess risk factors or the time frame of HTN onset in HCT recipients.[169]

Conclusion

AKI is remarkably prevalent following all modalities of HCT and is independently associated with mortality. The etiology is multifactorial and varies by conditioning regimen. Although the incidence of AKI has fallen over the past two decades,[12] it remains one of the most common and devastating complications of HCT. Given the data on biomarkers for tubular damage, it is likely that the incidence of subclinical injury following HCT far outstrips even the remarkable rates noted in studies to date. With the survival rate following HCT improving, the importance of the long-term effects associated with peritransplant complications such as AKI will become increasingly preeminent. The relationship between even mild AKI and both CKD and mortality is now well established.[189] It is possible that strategies to minimize AKI post-HCT, while improving short-term outcomes, may also mitigate the subsequent incidence of these devastating long-term sequelae.

ACUTE KIDNEY INJURY FOLLOWING SEVERE BURNS

In the United States, approximately 45,000 people are hospitalized annually for burn injuries.[190,191] The prognosis for these patients depends substantially on the extent of their burns. Although burn patients are increasingly receiving specialized care in dedicated burn units, their hospitalizations continue to be associated with significant complications resulting in a mean length of stay of 9 days and mean hospital costs of $60,000. One of the most devastating of these complications is AKI. Indeed, it was not until 1965 that a patient was reported to survive the combined insults of a severe burn and AKI.[192] As seen in general critical care, AKI following burns is often the heralding sign of impending multiorgan failure. The impact of severe AKI requiring renal replacement therapy (RRT) on postburn outcomes has long been recognized but only recently has the significant sequelae of milder disease been appreciated. Over the past 20 years, survival rates following severe burns have improved modestly associated with evolving critical care techniques and burn specific therapeutic protocols,[193,194] but the diagnosis of AKI complicating a severe burn continues to portend a grim prognosis. For the purposes of this review, severe burns will be understood to involve at least 10% of total body surface area (TBSA), with more stringent requirements present as noted.

Epidemiology and Risk Factors

Estimates of the incidence of AKI following severe burns vary widely. A portion of this variance can be attributed to differences amongst the literature in what constitutes a "severe" burn and to heterogeneous patient populations, types of burns, and ranges of TBSA percentage burns included in different studies. However, the primary source of the discordant findings in the epidemiology of AKI following burns has been the lack of a standardized definition for AKI. A recent systematic review identified 57 pediatric and adult studies providing data on the prevalence and mortality of AKI in patients with severe burn injuries, 9 of which were prospective.[195] An astounding 23 different definitions of AKI were used, illustrating the difficulty in comparing results across the literature. Definitions were founded on fixed serum creatinine cutoffs, relative increases in creatinine, urine output, blood urea nitrogen (BUN) levels, and need for RRT.

In this review, a total of 34,868 patients were evaluated across studies. In those studies permitting assessment of AKI prevalence, 1,872/34,771 (5.4%) patients developed AKI. The prevalence of AKI varied considerably and ranged from 0.2% to 64%. Unsurprisingly, AKI rates are highly contingent on diagnostic criteria, ranging from 34.9% in those studies utilizing a fixed serum creatinine cutoff to 3.5% in those identifying AKI based on urine output. When employing the sensitive RIFLE criteria, AKI was seen in 608/2,111 (30.9%) of patients versus 334/9,443 (17%) where AKI was more stringently defined by a requirement for RRT. It is likely that even those studies utilizing a definition involving relative changes in serum creatinine, such as the RIFLE system, may actually underestimate the true prevalence of AKI. Major burn patients are often initially resuscitated at an outside hospital prior to transferring to a specialized burn center and patients' initial presenting creatinine may thus already be elevated from their true baseline. Overall, the median prevalence was noted to be 14.5%, which is lower than that seen in ICU populations at large.[196,197] This discrepancy may be due to burn patients often being younger and with fewer comorbidities than are present in the general ICU population.

Across studies, RRT was performed in 30% of AKI patients or 3% of the total population with burn injuries.[195] This is slightly less than seen in studies of general ICU populations. This lower utilization of RRT may again reflect younger, healthier patients who are better able to withstand AKI without progressing to a requirement for RRT. However, the mortality of burn patients on RRT (see below) is worse than even the dreadful rates of 50% to 70% witnessed in general ICUs,[196–199] indicating the extreme severity of these patients' critical illness. It is thus possible that lower prevalence of RRT use in burn patients may alternatively be related to withholding of treatment for perceived therapeutic futility. Finally, difficulties in obtaining access or concerns of possible catheter associated infection may induce a reluctance to initiate RRT in patients with severe burns.

Utilizing a Pearson correlation test, Brusselaers et al. found the prevalence of AKI has increased over time ($r = 0.31$; $P = .02$) but the prevalence of AKI requiring RRT has declined ($r = 0.36$; $P = .05$).[195] This discrepancy can be explained by changes in the sensitivity and specificity of AKI definitions concurrent with improvements in critical care techniques and protocols for the treatment of burn victims.

The primary risk factor for the development of AKI following a severe burn is the size of the burn itself, as expressed in TBSA percentage.[200–204] Greater burn size predisposes to greater fluid and albumin loss as well as increasing the likelihood of infection. The incidence of AKI begins to increase with burns of >10% TBSA.[200] AKI is associated with burn size in a dose-dependent manner, with each 10% increase conferring an increased risk of death up until approximately 60%, when mortality levels off, albeit at a level of close to 50%.[200] A burn size of >65% of TBSA is associated with RR for AKI of 9.9 compared to <65% on multivariable analysis.[203]

Additional risk factors noted in the literature include sepsis,[190,202,204,205] inhalation injury (IHI),[190,200,204] age,[201,205,206,207] overall severity of critical illness or multiorgan dysfunction (acute physiology and chronic health evaluation II [APACHE II], pediatric risk of mortality [PRISMA]),[204,206–208] catheter infections,[190] adequacy of preadmission fluid resuscitation,[205] percentage of full thickness burns (FTB),[201] and admission thrombocytopenia and elevated bilirubin.[201] Interestingly, whereas Steinvall et al. noted age, TBSA percentage, and extent of FTB to be associated with

the development of AKI, these factors did not correspond to severity by RIFLE stages.[201]

ETIOLOGIES

Early Acute Kidney Injury

Renal Hypoperfusion

AKI associated with burns is bimodal, occurring either within the first 7 days after injury or during the second to third week. Causes of AKI in these early and later periods are listed in Table 38.7. Burns lead to an intense inflammatory response and release of vasoactive agents, increasing capillary permeability to fluid and albumin.[209] Albumin exhibits a significant leak within 6 to 18 hours postburn.[210] As compared to other critically ill patients, burn victims experience inflammation of a greater intensity and significantly longer duration.[211] The resulting loss of oncotic pressure is compounded by a decrease in albumin synthesis after severe burns.[212] As a result, fluid is shifted from the intravascular to extravascular space. Additionally, compromise of the barrier integrity of the skin engenders massive insensible fluid losses. The resulting intravascular hypovolemia and subsequent renal hypoperfusion are the primary cause of early AKI. Severe burns with extensive tissue destruction also decrease cardiac inotropism via endotoxin mediated apoptosis[213] while simultaneously elevating local and systemic stress-related hormones such as catecholamines, angiotensin II, aldosterone, and vasopressin with resulting systemic and renal vasoconstriction, a condition known as burn shock.[200,202,203,214–216]

These physiologic responses to a severe burn occur within hours and thus compel rapid and aggressive fluid resuscitation to prevent renal hypoperfusion and resulting oliguria. Indeed, a delay in adequate fluid resuscitation has been associated with poor prognosis in burn associated AKI.[217,218] Fluid requirements are contingent on the patient's initial weight, burn size, and need for mechanical ventilation.[193] With recognition of the importance of timely resuscitation and the adaptation of aggressive, standardized protocols[219,220] early AKI following severe burns has become less frequent.[200] In modern studies, however, there is not always an association between resuscitation volume and the development of AKI.[205] It may be that once a critical volume threshold is reached, no further benefit may be realized as etiologies other than hypovolemia come to predominate. Indeed, administration of fluid >25% more than that predicted as appropriate by the Parkland burn formula has been associated with increased odds of pneumonia, acute respiratory distress syndrome (ARDS), multisystem organ failure (MOF), and death.[221]

38.7 Common Causes of Acute Kidney Injury Following Severe Burns

Early
Volume depletion/hypoperfusion
Inhalation injury
Rhabdomyolysis/hemolysis
Late
Sepsis
Abdominal compartment syndrome
Nephrotoxic medications
Hypercalcemia

Inhalation Injury

Early AKI is often preceded by or concurrent with systemic inflammatory response syndrome (SIRS) and respiratory disease.[201] Pulmonary injury associated with trauma or burns promotes pathogenic systemic inflammation and the development of MOF, including AKI.[222] The extravasation of intravascular fluid initiated by the burn may be potentiated by inflammation triggered by IHI. Supporting this, burn victims with IHI have been documented as having significantly higher fluid and sodium replacement requirements than those without IHI.[223] IHI associated respiratory failure results in hypoxia and acidemia, further compromising vascular tone. Renal dysfunction is more common among patients with the most severe respiratory dysfunction.[224] Prevalence of inhalation injury is higher and the number of days on mechanical ventilation is greater in pediatric burn patients with AKI than in those without.[204]

Rhabdomyolysis/Hemolysis

Rhabdomyolysis (RML) and hemolysis can result in AKI via the release of free hemoglobin and myoglobin. Both molecules are freely filtered by the glomerulus, absorbed by tubular epithelial cells, and degraded into heme and globin, respectively. Each of these pigment molecules can be directly toxic to tubular cells via generation of oxygen free radicals as well as causing cast precipitation and tubular obstruction. AKI is associated with RML in one third of patients with myoglobinuria due to this oxidative stress and myoglobin cast nephropathy.[225,226] In patients with RML, myoglobinuria is strongly associated with the development of AKI, with an area under the receiver operating curve (AUC) of 0.88 and an optimal cutoff of 3865 ng per mL.[227] In the early period following a severe burn, patients are at substantial risk for AKI secondary to RML and, to a lesser degree, hemolysis.

RML is most frequently associated with electrical burns.[228–230] However, RML can also follow deep flame burns which produce direct myocyte damage or else induce limb ischemia and secondary RML through circumferential burns resulting in eschar formation and compartment syndrome.[231] Burn victims are at additional risk for RML due to prolonged immobilization, IHI, sepsis, pharmacologic

agents, obesity, and large surgical surface areas, which promote the destruction of striated muscle cells.[206,232] Once present, the nephrotoxic effects of RML are potentiated by such frequent comorbidities of burns as acidosis, intravascular volume depletion, and oliguria.[202]

In a retrospective study of 714 burn victims, RML, diagnosed by serum creatinine phosphokinase (CPK) and myoglobin levels as well as the documented presence of pigmented urine, was noted in 8/714 (1%) of patients,[206] six of whom (75%) developed AKI. Although serum CPK levels were similar between those with and without AKI, myoglobin trended toward being higher in the AKI patients, 10,600 μg per L versus 4989 μg per L, but the results were not statistically significant. While RML can develop several weeks after a severe burn, it is a significantly more common cause of AKI in the early period. Patients with AKI due to RML are more likely to present with early injury, 12/16 (75%), than those with AKI secondary to other causes, 31/77 (40%), and RML induced AKI requires RRT more frequently 9/16 (56%) than other AKI etiologies 23/77 (30%).[233] In a study of 48 patients with AKI requiring RRT, myoglobinuria occurred significantly more frequently in those with AKI <5 days postburn than those with later injury ($P < .0001$).[200] Although not statistically significant, Steinvall et al. examined 31 patients with burn-associated AKI and found mean myoglobin levels were higher in those with early AKI as opposed to late, 1,167 μg per L versus 220 μg per L.[201]

Outcomes following RML are better after electric burn than flame due to the severity of burn required to cause RML with thermal injury.[233] Early escharotomies and fasciotomies so as to minimize tissue ischemia are key to reducing the incidence of RML.[233] Although of unproven benefit, urine alkalinization and forced diuresis using lactated Ringer's (LR) solution, sodium bicarbonate, and mannitol or furosemide is typically employed. Myoglobin has a molecular weight of 17 kD and can theoretically be eliminated by ultrafiltration but the half-life of systemic myoglobin has not been shown to differ in burn-associated AKI patients treated with continuous venovenous hemodiafiltration (CVVHDF) as compared to LR alone.[206,234]

Proteinuria

Burn shock associated with sepsis may incite lesions in the glomerulus and tubules and is often associated with high and low molecular weight proteinuria.[235] Plasma from septic burn victims with AKI induces a pro-apoptotic effect in tubular cells and podocytes that correlates with the extent of proteinuria. Specifically, alteration of polarity in tubular cells and reduced expression of megalin, nephrin, and the tight junction protein ZO-1 have been demonstrated.[236]

The development of proteinuria may be a more sensitive indicator of kidney injury than definitions predicated on serum creatinine. Kang et al. evaluated 24-hour urine protein excretion daily for 3 days and then weekly for 3 weeks in 12 patients following a severe burn injury.[237] None of the patients experienced a rise in serum creatinine or a decrease in urine output. Mean proteinuria rose from 139 mg per 24 hours on day 0 to 835 mg per 24 hours by day 3 and remained above baseline at 3 weeks with the majority of protein being nonalbumin. Additional confirmation of tubular injury was found by a sustained elevation in N-acetyl-β-D-glucosaminidase (NAG), a specific marker of renal tubular pathology.[238] Sabry evaluated 40 patients with TBSA burns >20%, nine (22.5%) of whom developed AKI.[202] Although serum creatinine in those patients with AKI was not significantly higher than in those without AKI until hospital day 7, the patients with AKI were found to have significantly higher microalbuminuria at admission. It is unclear if this is an example of microalbuminuria being an early biomarker of tubular injury or if these patients had microalbuminuria at baseline and hence were at higher risk for AKI.

Late Acute Kidney Injury

Patients who develop AKI in the later period following burns are younger with lower TBSA percentage burns and less FTB.[201] Due to the profound and prolonged inflammation engendered by burns, patients 2 to 3 weeks postinsult continue to express elevated cytokines, including TNF-α and IL-1, with resulting vasoconstriction and renal hypoperfusion. These ongoing physiologic derangements render them highly susceptible to the predominant renal insults, sepsis, and nephrotoxic medications, encountered in this period. The resulting development of ATN compromises the kidney's ability to retain sodium and concentrate urine and thus perpetuates intravascular volume depletion. With improved resuscitation protocols having minimized hypoperfusion associated early AKI, late-onset injury now predominates.[200] The factors influencing the development of late AKI are shown in Figure 38.2.

Sepsis

The primary causes of late AKI following severe burns are sepsis and associated MOF.[200,203,217,218,239] Sepsis has been noted in 64% of late-onset AKI compared to 28% in early AKI[233] although such a disparity is not always seen.[201] Holm et al. found sepsis to be present in 30/33 (91%) of burn victims whose AKI developed >5 days postinjury but in 0/15 of those with AKI within the first 5 days.[200] Despite the extensive use of topical and systemic antibiotics, the nidus of infection in postburn sepsis remains the burn itself. However, as seen in ICU populations at large, impairment of the GI mucosal barrier with subsequent bacterial translocation and endotoxemia may be an additional contributor to late onset sepsis after burns.

The onset of sepsis in a burn patient is an ominous development. In a study of 76 patients with AKI, sepsis was seen in 96% of nonsurvivors versus 44% of survivors ($P < 0.001$).[217] However, not all episodes of severe sepsis cause AKI and the chronology is not always consistent. Among survivors of AKI, Chrysoloulo et al. found kidney injury often preceded clinical evidence of sepsis, rather than following

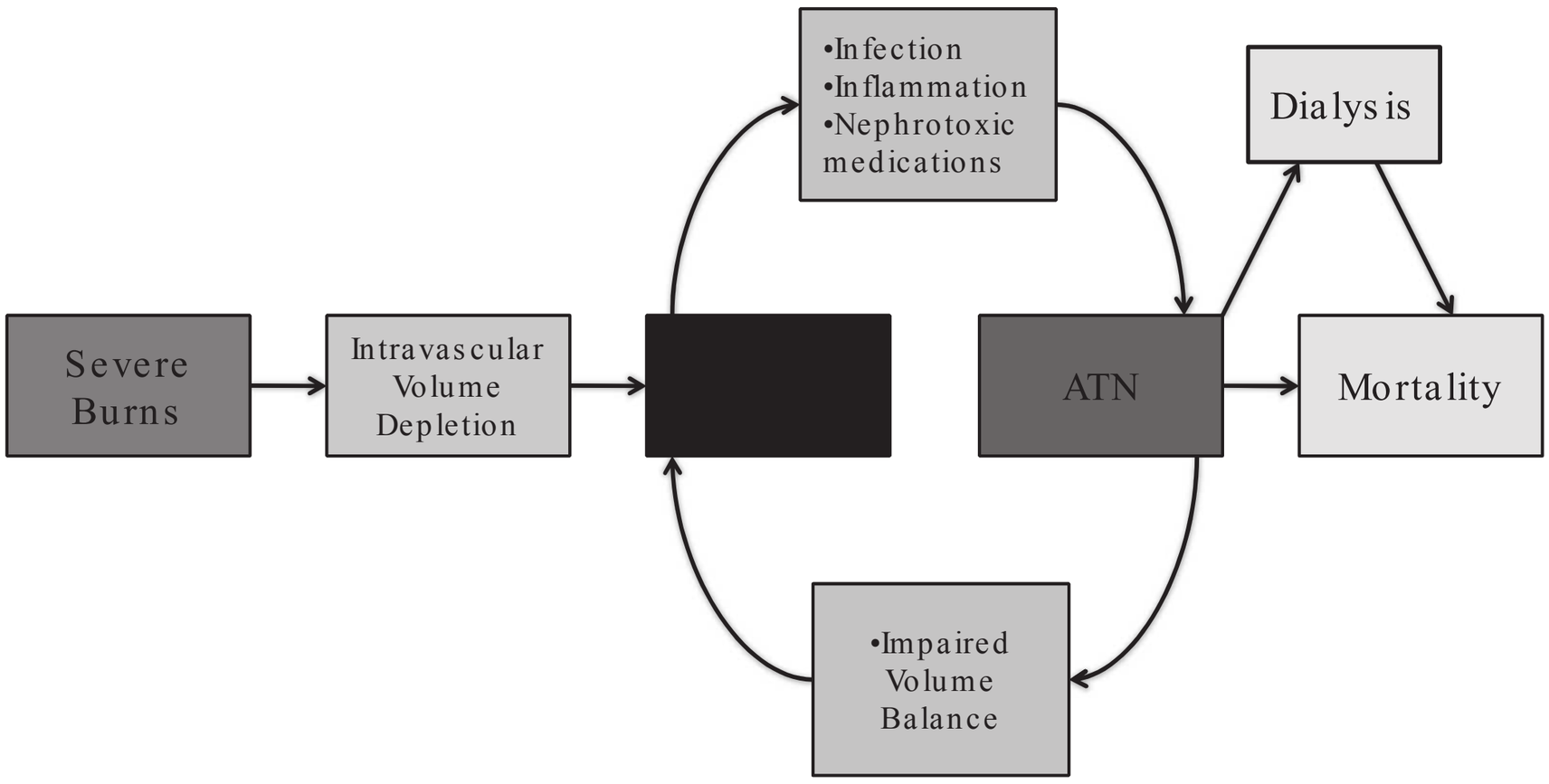


FIGURE 38.2 Progression of late kidney injury after severe burns. AKI, acute kidney injury; ATN, acute tubular necrosis.

it.[217] Remarkably, all diagnoses of sepsis occurred after onset of AKI in survivors whereas nonsurvivors were stricken both before and after inception of AKI. Taken together, these findings suggest that when AKI follows sepsis, it is part of MOF and results in the expected devastating mortality. The mere development of sepsis in the setting of prevalent AKI, however, allows for the possibility that the AKI's initial etiology was primarily hemodynamic and thus may be associated with more favorable outcomes.

Abdominal Compartment Syndrome

Aggressive volume resuscitation, although minimizing early intravascular hypovolemia, hypotension, and renal hypoperfusion, may ultimately lead to a significantly positive fluid balance. In the setting of increased capillary permeability and subsequent fluid translocation, excessive extravascular volume puts patients at risk for intra-abdominal hypertension and abdominal compartment syndrome.[240–242] First reported following a burn in 1994,[243] abdominal compartment syndrome has been diagnosed in 40% of patients meeting RIFLE "F,"[204] although the temporal relationship between intra-abdominal hypertension and AKI is not always clear. Abdominal compartment syndrome impairs cardiac function, reduces pulmonary compliance, and truncates renal perfusion.[243–245] In a study of 123 burn victims, 9/56 (16%) of those with AKI were diagnosed with compartment syndrome whereas none of the 67 without AKI developed this complication.[204] Surgical decompression has been shown to improve APACHE scores and increase urine output in post-burn compartment syndrome.[244]

Nephrotoxic Medications

Nephrotoxic medications, particularly antibiotics, are well-known risk factors for AKI. The use of potentially nephrotoxic antibiotics has been reported as nearly ubiquitous in late onset AKI after severe burns.[200,233] Additionally, in patients diagnosed with AKI by RIFLE criteria, use of known nephrotoxic medications was much more prevalent in those patients who ultimately progressed to a higher stage of AKI severity (86%) than in those who did not (27%) ($P = .02$).[208] However, the concurrent presence of sepsis in nearly all patients on antibiotics is an obvious potential confounder and confirmation of the independent role of nephrotoxic medications in the development of late AKI awaits future controlled studies. The use of nephrotoxic antibiotics has also been reported in up to 57% of early AKI cases but the drugs were only initiated 1 to 3 days prior to occurrence of AKI and thus cannot be said to be causal.[233]

Hypercalcemia

Burn injuries and their management frequently result in hypercalcemia. Kohut et al. found hypercalcemia in 22/73 (30%) of patients with TSBA >20% burns and/or ICU stay >20 days.[246] Elevation of calcium in this setting is multifactorial but primarily related to prolonged immobility, with subsequent increase in bone resorption, and high protein feeds stimulating calcium mobilization and hypercalciuria.[247] Hypercalcemia leads to renal hypoperfusion both through direct vascular action causing renal vasoconstriction and by stimulation of natriuresis and aquaresis. Treatment of hypercalcemia involves aggressive hydration, volume expansion, and early mobilization. Bisphosphonates have also proven successful in preserving bone mass following severe burns.[248]

Treatment

Volume Resuscitation

The critical impact of volume depletion on outcomes following severe burns has long been recognized.[249] Immediate and aggressive fluid resuscitation so as to maintain circulating

blood volume and ensure adequate tissue perfusion and oxygenation is a critical component of the acute treatment of burn patients. The time between burn injury and fluid resuscitation is significantly less in survivors than nonsurvivors.[217] Of multiple proposed resuscitation formulas,[219,220] the Parkland formula[250] is one of the most widely utilized. This protocol calls for the administration of LR at 4 mL/kg/TBSA percentage burned, half to be given in the first 8 hours and the remainder over the next 16 hours. Fluids are then adjusted to maintain urine output of 0.5 to 1.0 mL/kg/hr. Resuscitation guided by the Parkland formula has been shown to result in less volume administered without difference in cardiac output parameters than that guided by pulmonary artery catheter.[251] Colloid solutions have increasingly fallen out of favor as they have not been shown superior to saline in general ICU patients[252] and a decrease in GFR following colloid administration has been observed in burn victims.[253]

Early wound excision and grafting may temporize the inflammatory response and subsequent release of inflammatory mediators, thereby improving renal blood flow and mitigating AKI. However, the effect of early excision on mortality has been variable.[217,218]

Vitamin C

Vitamin C has been utilized following thermal injury due to its antioxidant properties. Activation of mast cells is instigated by burns, resulting in histamine release, increased xanthine oxidase activity, and resultant free radical production.[254] By serving as a free radical scavenger, vitamin C may reduce postinjury membrane lipid peroxidation and attenuate vascular permeability.[255] Concerns have been expressed about the potential of vitamin C to initiate an osmotic diuresis and worsen renal injury. However, addition of vitamin C to resuscitation fluids has been shown to reduce fluid requirements, minimize weight gain, and lessen wound edema.[256] Patients receiving vitamin C experienced fewer ventilator days and demonstrated improved PaO2:FiO2 ratios.[256] Kahn et al. prospectively compared conventional LR resuscitation and LR with vitamin C at 66 mg/kg/hr.[257] The vitamin C group displayed a decreased fluid requirement but increased urine output. Although no difference was noted in mortality, the study involved only 33 patients and was likely underpowered for such hard outcomes.

Fenoldopam

Fenoldopam, a highly selective dopamine-1 receptor agonist, decreases renal vascular resistance, increases glomerular filtration rate (GFR), stimulates natriuresis through inhibition of the Na/H exchanger and Na/K/ATPase mediated sodium reabsorption, and facilitates aquaresis via antagonism of antidiuretic hormone (ADH).[258] Fenoldopam administration has been associated with increased cortical and medullary renal blood flow via nonnitric oxidase mediated arterial dilitation.[259,260] In a retrospective study of 758 patients admitted to an intensive care burn unit, 76 diagnosed with AKI on AKIN criteria were treated with fenoldopam.[258] Serum creatinine improved within 48 hours across all AKIN stages and urine output increased without adjustment in fluid administration in AKIN stages 2 and 3. The study, however, was not powered to assess RRT requirement, length of stay, or mortality.

Outcomes

Progression/Resource Utilization

Palmieri et al. evaluated the prognostic ability of the RIFLE criteria in 60 patients, 32 of whom (53%) were diagnosed with AKI.[208] Following initial fulfillment of criteria, 13 patients subsequently progressed over a mean of 9 days to a higher class. Mortality was 0% in those without AKI, 8% in those who did not progress beyond their initial stage ("R" or "I"), and 46% in those who progressed to a higher class. Progression was not associated with age, comorbidities, or severity of illness scores at admission but rather factors arising subsequent to admission such as sepsis, use of nephrotoxic drugs, cumulative fluid balance, and number of surgeries.

Evaluating the impact of AKI on length of hospital stay is difficult due to the competing risk of death associated with AKI. Nonetheless, significantly longer ICU,[200,204,208] and overall hospital[201,204] stays have been noted in patients with AKI. Similarly, the number of required ventilator days has also been demonstrated to be higher with AKI[200,204,208] and to increase in a stepwise manner with AKI severity.[200]

Dialysis

Although the first report of survival in a burn victim with AKI requiring RRT was in 1965,[192] the subsequent 20 years continued to produce very poor outcomes. Burn patients typically have massive obligatory fluid input in the service of maintaining hemodynamics, providing parenteral nutrition, and administering medications. Given these patients' low oncotic pressure and increased capillary permeability, much of this fluid is extravasated into third spaces, resulting in anasarca and placing patients at risk for impaired wound healing, skin breakdown, and pulmonary edema. During the period preceding the mid-1980s, the only treatment option was standard intermittent hemodialysis, which typically was employed daily in an attempt at aggressive ultrafiltration. With sepsis often compounding patients' hypotension and intravascular volume depletion, intermittent intense fluid removal was often impossible and outcomes were very poor. In the mid-1980s, continuous arteriovenous, followed by continuous venovenous, methods of RRT were introduced and are now preeminent in ICUs. Continuous RRT offers the advantage of gentle yet large volume ultrafiltration, allowing for aggressive nutritional support. The physiology of burn patients makes such techniques an especially appealing option in this setting.

Multiple venovenous therapeutic modalities (hemodialysis, hemofiltration, hemodiafiltration) have been successfully employed in patients with AKI and severe burns.[261] In a review of 16 studies, the incidence of renal replacement therapy after severe burns ranged from 0.7% to 14.6%.[201] A 10-year experience at a large burn unit showed 1% of all admissions, and 2.7% of patients with TBSA >10% burns, required RRT.[239] A systemic review found RRT was performed in 30% of AKI patients or 3% of the total population with burn injuries.[195] RRT is typically initiated approximately 2 weeks after hospital admission, consistent with the period of late onset sepsis/MOF associated AKI.[201,239,261,262] Reported mean duration of treatment has ranged from 10 to 24 days.[201,239,261,262]

Early studies reported a significantly higher rate of bleeding complications in burn patients receiving CRRT than in general ICU CRRT patients, 56% versus 15% (P = .002).[261] This increased risk may have resulted from the interaction of anticoagulation and the frequent thrombocytopenia and consumptive coagulopathy seen following burns. The patients in this study received a mixture of arteriovenous and venovenous dialysis. When the same investigators assessed a later cohort using only venovenous techniques, no bleeding complications were noted.[262] Encouragingly, survival improved from 18% in the first time period (1987–1994) to 50% in the second (1995–1998) within the same institution.

Inpatient Mortality

Prior to the widespread availability of RRT, the survival rate in patients with severe burns and AKI was abysmal. Of 119 patients in the literature published between 1953 and 1979, only 8/119 (7%) survived.[216] In the ensuing years, outcomes have improved considerably but the diagnosis of AKI following a severe burn still portends a grim prognosis. Analyzing data culled from nearly 30 years of experience at a single center, Jeschke et al. identified 60 children who had experienced AKI following a severe burn. Dividing the patients into those presenting before and after 1984, they found that the mortality rate had decreased from 100% to 56%.[218]

On systematic review, mortality rates vary by AKI definition, ranging from a median of 35% in studies utilizing RIFLE criteria to 88% in three older studies where AKI status was determined by elevations in BUN levels.[195] The overall mean mortality in severely burned patients with AKI was 55%, with a median across studies of 77%. The median mortality in burn patients not afflicted with AKI was 13%. In the 30 studies with data available on control populations, AKI was clearly associated with an increased risk for mortality with an RR of 4.85. An increased risk of mortality has been documented with both early and late AKI. Retrospectively examining 62 patients meeting RIFLE criteria within 24 hours of admission, Mosier et al. found hospital mortality significantly elevated compared to burn patients without early AKI, 36% versus 13% (adjusted OR 2.32).[205] Forty-seven out the remaining 159 study patients (30%) developed AKI later in their hospital stay with a mortality of 16/47 (34%). As compared to mortality in burn victims who would be discharged without AKI, 6/112 (5%), late AKI conferred an unadjusted OR for death of 10.9.

The RIFLE criteria have been shown to provide incremental prognostic value regarding mortality in several settings of AKI.[263–267] In eight studies examining the utility of the RIFLE criteria following severe burns, mean mortality across categories was 42% with a median of 35%.[195] Mortality increased in a stepwise manner, both across studies with fixed serum creatinine cutoffs as well as across RIFLE stages.[195,201,204] Although the RR for mortality with AKI was 6.17 in those studies employing the RIFLE criteria, there was not a statistically significant increase in mortality for patients in the "R" category.[195] However, in 62 patients who developed RIFLE "R" or "I" within 24 hours of admission, 18 of whom progressed from their initial RIFLE stage to a more advanced one, Mosier et al. found mortality was significantly elevated in those who progressed versus those who stabilized or improved, 72% versus 20%.[205]

Despite refinements in continuous RRT techniques, the outlook for patients requiring dialysis remains harrowing and the need for dialysis is the strongest predictor of death in burn victims with AKI.[233] In a study of 1,360 burn patients admitted over 13 years to an ICU, mortality was found to be 6.9% in patients without AKI, 34.4% with AKI without RRT, and 62.5% in patients requiring dialysis.[233] Mortality in burn patients requiring RRT ranges across reported studies from 63% to 100%.[200,203 205,233,261,268–270] The median mortality in studies defining AKI by the need for RRT is 80%.[195]

Although need for RRT is the dominant risk factor for death in burn patients with AKI, multiple additional associations been reported including sepsis/MOF,[205,208,217] TBSA%,[190,233] RIFLE "F,"[190,208] age,[233] IHI,[190] serum albumin on presentation,[203] and SOFA score.[208] Burn size >65% TBSA confers a dramatic RR of 14.2 on multivariable analysis for mortality.[203] In 76 diagnosed with AKI, Chrysopoulo et al. noted 64/67 (94%) nonsurvivors as compared to 4/9 (44%) survivors were diagnosed with sepsis (P < .001).[217] As with AKI at large,[271] the development of oligo/anuria following a severe burn is predictive of worse outcomes. Mustonen et al. examined 32 patients requiring RRT.[233] Although 20/20 (100%) nonsurvivors were oliguric and 18/20 (90%) were anuric, only 6/12 (50%) survivors were oliguric and 2/12 anuric (17%). Mortality rates have alternatively been reported as higher in early AKI[200,233] and in late AKI[217] with another study finding them nearly identical.[205] With early AKI having larger TBSA percentage burns and higher rates of RML whereas late AKI involves more prevalent comorbidities and sepsis, both findings are plausible and the question awaits resolution in larger, multicenter studies.

It is interesting to note that in several studies only more severe AKI as evidenced by RIFLE "I" or "F" is associated with increased mortality.[190] This finding stands in clear distinction to that seen in multiple other populations where even

minor AKI confers an elevated risk for mortality.[163,272–275] It may be that other risk factors for mortality in burns such as TBSA percentage burned and IHI are so overwhelmingly impactful that the association between milder forms of AKI and death is overshadowed. Similarly, although TBSA percentage burned is an extremely strong predictor of mortality in multivariable models, once AKI develops, survival is similar across ranges of TBSA percentage burns. Especially in the late period, AKI is often associated with sepsis and MOF. It is possible that once such devastating complications have arisen, the power of TBSA percentage burned as a predictor of mortality is overwhelmed.

Encouragingly, there has been a strong trend toward decreasing mortality overall ($r = -0.5$; $P < .001$) and in those patients requiring RRT ($r = -0.6$; $P = .001$).[195] No prospective studies have evaluated long-term proteinuria, hypertension, or renal function in this patient population. Full inpatient renal recovery, variably defined, has been reported in multiple studies for many if not all survivors of burn associated AKI.[201,261,262] However, evidence is now overwhelming that even mild AKI is associated with increased risk for long-term CKD.[276–278] In light of this data, such optimistic findings seem premature and the long-term renal outcomes in survivors of postburn AKI await eliciting in future longitudinal studies.

Conclusion

AKI following burns is highly prevalent and conveys a grim prognosis. As the etiology is frequently multifactorial, interventions to reduce the incidence and severity of AKI must necessarily involve multiple targets. The prognosis following the onset of AKI has improved, even for those patients requiring dialysis, but remains poor. It remains to be seen whether the continued application and refinement of specialized burn therapies and RRT techniques will appreciably impact prevalence and mortality. Early, aggressive fluid resuscitation, control of infection, timely excision of eschars, and minimizing nephrotoxic medications remain the cornerstones of prevention for this devastating complication of an already horrific injury.

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