Acute kidney injury in pediatric hematopoietic stem cell transplant recipients

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Abstract. Acute kidney injury is common after pediatric hematopoietic stem cell transplant with a reported incidence of 21–55% in the first 3 mo after transplant. Acute kidney injury is associated with decreased survival and the development of chronic kidney disease in this patient population. In this review, current definitions of acute kidney injury are discussed. The epidemiology and risk factors for acute kidney injury in this patient population are described, and current hypotheses on the pathophysiology are reviewed. Current and emerging ideas about changes to management strategies to mitigate acute kidney injury are presented, and areas for further research are proposed.

Keywords: Pediatric hematopoietic stem cell transplant, acute kidney injury, chronic kidney disease

1. Introduction

Hematopoietic stem cell transplantation (HSCT) can be a curative therapy for many malignant and non-malignant diseases in childhood. About one third of these children will require admission to a pediatric intensive care unit (PICU) and intensive care support [1–3]. Multiple studies have demonstrated improved outcomes among children admitted to the PICU and requiring intensive care support after HSCT [1, 4, 5]. Most recent survival estimates in patients need-

ing intensive care support after HSCT in single center studies are 44–63% [1, 2, 4, 5]. A multicenter study of pediatric HSCT patients requiring intensive care support described a hospital survival of 50% in this population, compared to 99% in the patients who did not require intensive care support, with a 1 yr survival of 40% and 65% in the two groups, respectively [3]. Acute kidney injury (AKI) represents one factor that may place these children at increased risk for both mortality and morbidity from later chronic kidney disease (CKD).

Pediatric HSCT patients requiring dialysis during their PICU admission have a 5-fold increased odds of death during that admission [1, 5]. The etiology of AKI is multifactorial in HSCT recipients, and can be related to exposures such as nephrotoxic medications including those administered during the

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conditioning regimen and to prevent graft versus host disease (GVHD), the underlying disease process itself (e.g. a history of tumor lysis syndrome, malignant infiltration of the kidney), the systemic inflammatory response that can accompany engraftment, episodes of sepsis related to the significant immunocompromised state and indwelling medical devices, and the development of veno-occlusive disease (VOD) or thrombotic microangiopathy (TMA), which are frequently associated with AKI. The risk factors for alterations in renal function and the subsequent impact on outcome can now be studied in a more uniform manner with the introduction of accepted standard definitions of AKI in children.

2. AKI in the general PICU population

AKI can be defined by a categorical score of increasing severity based on the change in serum creatinine or by a decrease in urine output. Three very similar categorical scoring systems exist for defining AKI (Table 1): the pediatric risk injury failure loss end stage (pRIFLE) score [6], the AKI network (AKIN) criteria [7], and the kidney disease: improving global outcomes (KDIGO) staging [8]. While the KDIGO staging is the most recent, and can be applied to both adults and children, the pRIFLE score has been the most studied and

validated in children [6, 9–12]. While the AKIN and KDIGO staging systems use change in serum creatinine to determine the stage of AKI, the pRIFLE score uses the change in estimated creatinine clearance calculated by the original Schwartz formula [13, 14] to assign the categorical score.

AKI, using these definitions, has been repeatedly found to be strongly associated with poor outcome in PICU populations. AKI is associated with increased mortality, longer duration of mechanical ventilation, and increased length of stay [6, 9, 10, 15, 16]. These associations are even stronger as the severity of AKI worsens [6, 15, 16].

Recently, the concept of renal angina has been proposed [17]. This concept describes a method to predict AKI in children, so that at risk patients may be identified. Once identified, these patients can be candidates for increased screening or use of novel diagnostic tests for AKI. The renal angina index was subsequently validated in critically ill children, and a high renal angina index on day 0 of PICU admission was found to be a good predictor of AKI on day 3 of PICU admission [18]. The renal angina index includes a component for the risk factors for AKI and a component for any early clinical indication of AKI such as change in estimated creatinine clearance or fluid overload (FO). There are three risk factors identified in the renal angina index: PICU admission (moderate risk), stem cell

Table 1
Comparison of acute kidney injury categorical scoring system definitions

Score	Defining criteria - Either creatinine change or urine output criteria may be used		
	Stage	eCCl/Serum creatinine	Urine output
pRIFLE	Risk	eCCl decrease by 25%	<0.5 mL/kg/hr for 8 hr
	Injury	eCCl decrease by 50%	<0.5 mL/kg/hr for 16 hr
	Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m ²	<0.3 mL/kg/hr for 24 hr or anuric for 12 hr
AKIN		Serum creatinine	Urine output
	1	Increase by 1.5–2x baseline or increase by ≥0.3 mg/dL	<0.5 mL/kg/hr for >6 hr
	2	Increase by 2–3x baseline	<0.5 mL/kg/hr for >12 hr
KDIGO	3	Increase by >3x baseline or increase ≥0.5 mg/dL if baseline is ≥4.0 mg/dL	<0.3 mL/kg/hr for 24 hr or anuric for 12 hr
		Serum creatinine	Urine output
	1	Increase by 1.5–1.9x baseline or increase by ≥0.3 mg/dL	<0.5 mL/kg/hr for 6–12 hr
	2	Increase by 2–2.9x baseline	<0.5 mL/kg/hr for ≥12 hr
	3	Increase by ≥3x baseline or increase to ≥4.0 mg/dL or initiation of renal replacement therapy or eCCl <35 mL/min/1.73 m ²	<0.3 mL/kg/hr for ≥24 hr or anuric for ≥12 hr

pRIFLE = Pediatric risk injury failure loss end-stage; AKIN = Acute kidney injury network; KDIGO = Kidney disease improving global outcomes; eCCl = Estimated creatinine clearance.

transplantation (high risk), and need for ventilation and inotropy (very high risk). Thus, any HSCT patient in the PICU is at high risk of AKI, and this risk increases greatly if they also require mechanical ventilation and inotropic support.

3. Epidemiology of AKI in the pediatric HSCT patient

Several single-center studies of AKI after allogeneic pediatric HSCT have been published (Table 2). Ileri et al. [19] described 57 children undergoing allogeneic transplant with myeloablative conditioning between 1999 and 2007, and used the AKIN criteria to define AKI up to 100 days after transplant. The incidence of AKI in this cohort was 42%: 21% with stage 1, 16% with stage 2, and 5% with stage 3 AKI. The median time to the development of AKI after transplant was 31 days, and the median time for patients to return to baseline creatinine was 7 days. Risk factors associated with AKI were cyclosporine toxicity, amphotericin therapy, and VOD. Five of the 24 patients with AKI died (21%), and there was increased risk of mortality for those with stage 2 or 3 AKI.

An earlier study by Kist-van Holthe et al. [20] followed 66 children receiving an allogeneic HSCT between 1998 and 2000. AKI was defined as a doubling of the serum creatinine (equivalent to AKIN stage 2 or greater) in the first 3 mo after transplant. The incidence of stage 2 and 3 AKI was the same as the previous study at 21%. Risk factors associated with AKI in this cohort were similar: elevated cyclosporine levels, foscarnet therapy, and VOD. Hazar et al. [21] studied 34 children receiving allogeneic HSCT between 2005 and 2006. They also defined AKI as a doubling of serum

creatinine in the first 100 days, and reported a similar incidence of AKI of 26.4% in their patients.

In the largest study to date, Satwani et al. [22] followed 170 children receiving allogeneic HSCT between 2001 and 2007. They included patients receiving myeloablative as well as reduced intensity conditioning, and made comparisons between these regimens. They defined AKI as a decrease in the estimated creatinine clearance of at least 50% (equivalent to the second pRIFLE category of injury). The 55% incidence of AKI in this cohort at 3 mo following transplant was higher than the prior studies. Fifteen percent of the patients required renal replacement therapy (RRT) in the first year after transplant, and 96% of these patients (24/25) died. Patients who received myeloablative conditioning had a significantly higher rate of AKI at 1 mo after transplant than those receiving reduced intensity conditioning. This trend remained through all time points measured in the first year, but was not significant after the first month. In a multivariable model describing risk factors for death in this cohort, only myeloablative conditioning and AKI at 1 mo after transplant were independent risk factors for death.

4. Pathophysiology of AKI in pediatric HSCT

Given the common occurrence of AKI in the pediatric HSCT population, and its association with increased morbidity and mortality, a clear understanding of the underlying pathophysiology is important to the care of these children. Understanding this pathophysiology requires a review of the risk factors that are believed to contribute to AKI [23, 24].

Table 2
Epidemiologic studies of acute kidney injury after pediatric hematopoietic stem cell transplantation

Studies	Number of patients	Type of transplant	Frequency of acute kidney injury	Acute kidney injury risk factors	Frequency of chronic kidney disease
Ileri et al. [19]	57	Allogeneic	21% stage 1, 21% stage 2 or greater	Cyclosporine A, amphotericin B, veno-occlusive disease	10%
Kist-van Holthe et al. [20]	66	Allogeneic	21% stage 2 or greater	Elevated cyclosporine A levels, foscarnet, veno-occlusive disease	11%
Hazar et al. [21]	34	Allogeneic	26.4% stage 2 or greater	None found	Not reported
Satwani et al. [22]	170	Allogeneic	55% stage 2 or greater	Myeloablative conditioning	36%

4.1. Conditioning regimen

The intense conditioning regimen associated with myeloablative allogeneic HSCT is speculated to be a main risk factor for the development of AKI. Myeloablative conditioning regimens are used to eradicate all residual cancer cells and then to induce immunosuppression that allows donor cell engraftment. With nonmyeloablative conditioning, sufficient immunosuppression is provided to allow engraftment of the transplanted donor cells and the therapy relies on a graft-versus-tumor effect to kill tumor cells. The nonmyeloablative regimen is less toxic, and therefore, is more commonly used in older patients or patients with substantial co-morbidities [5]. Small studies of adults have found that nonmyeloablative conditioning for allogeneic HSCT is associated with a lower incidence of AKI [24–26]. One such study reported that the frequency of AKI increased significantly from autologous HSCT (21% incidence) to nonmyeloablative allogeneic (40% incidence) to myeloablative allogeneic (69% incidence) HSCT. Additionally, a subsequent parallel increase in mortality in the 6–12 mo after HSCT was reported (7% to 34% to 58% for autologous, nonmyeloablative allogeneic, and myeloablative allogeneic, respectively) [26]. Similar associations have been reported in a pediatric study of AKI after HSCT [22].

In addition to a decrease in the direct toxic effects of a less intensive conditioning regimen, there is also a lower incidence of hepatic VOD and GVHD using nonmyeloablative conditioning [24, 27, 28]. Further, nonmyeloablative HSCT has a faster engraftment time resulting in less cytopenia, and therefore, potentially less sepsis and nephrotoxicity associated with antimicrobials [24]. Although the use of nonmyeloablative conditioning has been associated with less nephrotoxicity, several retrospective studies have offered mixed reviews on the outcome of these patients, especially because nonmyeloablative regimens can still be quite immunosuppressive, and thus, this area of study warrants further work [29–32].

4.2. Decreased renal perfusion

Several processes may result in a decrease in renal perfusion. The development of capillary leak syndrome, the vasodilatation associated with infection and sepsis, and poor cardiac output (e.g. myocardial dysfunction, pericardial effusion, cardiac tamponade

secondary to radiation or chemotherapy) can all play a role in decreased renal perfusion and the development of pre-renal AKI [23, 28]. If this compromised perfusion of the renal vasculature persists, it may result in intrinsic kidney injury.

4.3. Intrinsic kidney injury

Several factors contribute to the development of intrinsic kidney injury. As described prior, failure to re-establish renal perfusion after the development of pre-renal AKI is a common cause. Poor perfusion combined with the use of nephrotoxic agents (e.g. non-steroidal anti-inflammatory drugs, diuretics, intravenous contrast, antimicrobials, and calcineurin inhibitors) are a set up for further debilitating disease [23, 28]. The injury invokes a local imbalance of vasoactive substances, which enhance the release of vasoconstrictors such as endothelin and decrease the levels of vasodilators such as endothelium-derived nitric oxide thereby fostering compromise of renal perfusion [33].

For those patients undergoing HSCT for treatment of a malignancy, the associated tumor lysis causes the release of cellular components that may also scavenge circulating nitric oxide [34]. Furthermore, free iron released from red blood cells during episodes of hemolysis now recognized as a generator of free radicals that exacerbate cellular injury at the renal level [33, 35].

Patients who develop additional endothelial injury secondary to factors such as complement deficiency, toxin exposure, and bacterial infection may have an increased risk of developing TMA in the setting of HSCT. Typically, TMA presents within the first 3 mo after HSCT. These patients develop AKI associated with microangiopathic hemolytic anemia and thrombocytopenia [28]. The earliest markers of TMA are elevated lactate dehydrogenase, proteinuria, and hypertension; and those with proteinuria have a lower survival [36]. The clinical manifestations of TMA overlap with calcineurin inhibitor toxicity, and calcineurin inhibitors, as well as rapamycin, unrelated donors, allogeneic transplantation, and certain viral infections are all potential risk factors for TMA after HSCT [37].

4.4. Hepatic VOD

Also known as hepatic sinusoidal obstruction syndrome, hepatic VOD affects approximately 10% of patients who undergo allogeneic HSCT. Hepatic VOD

is commonly observed within 30 days of HSCT and is diagnosed when a patient presents with jaundice, ascites, and painful hepatomegaly [28, 38–40]. The process is triggered by conditioning-related sinusoidal endothelial injury, resulting in thrombosis, vascular stasis, portal hypertension, hepatocyte injury, and a form of AKI that is very similar to hepatorenal syndrome [41]. Portal hypertension and tubular injury are thought to contribute to the AKI that occurs after the development of VOD [40]. Hepatic VOD is predominantly observed in the setting of myeloablative HSCT [24, 41].

4.5. GVHD

The contribution of GVHD to the development of AKI is multifactorial. First, AKI can occur through direct cytokine and immune-related injury leading to the development of nephrotic syndrome and the development of interstitial nephritis. Second, the associated dehydration that occurs due to stool losses and poor intake by mouth can affect intravascular volume leading to pre-renal AKI. Further, there is a direct nephrotoxic effect from the medications used to prevent and treat GVHD such as the calcineurin inhibitors [24, 28, 42, 43]. A prospective study of 57 pediatric HSCT patients noted an AKI incidence of 42% among the cohort; the use of cyclosporine was reported as the main risk factor [44]. In addition, the use of additional immune modulating medications and high-dose prednisolone in refractory GVHD increases the risk for cytomegalovirus reactivation, and additional viral, bacterial, and fungal infections including organisms that infect the kidney such as adenovirus and BK polyomavirus [40].

4.6. Marrow infusion toxicity

The kidneys may be damaged by cell lysis products and free hemoglobin during marrow infusion. In addition, dimethyl sulfoxide, a cryoprotectant for stem cells, may cause intravascular hemolysis, increasing exposure to red cell breakdown products and free hemoglobin, leading to renal nephropathy [44].

5. Practice changes over time in AKI diagnosis and management and innovative aspects of care

Historically, a doubling of the baseline serum creatinine concentration was considered to be diagnostic

of AKI [20, 21]. However, with serum creatinine levels dependent upon age, gender, and muscle mass, using this strategy has limitations in the HSCT population and high risk for low muscle mass [45]. Use of a radio labeled diethylenetriaminepentaacetic acid, iothalamate, or an inulin clearance method provide better measures of the true glomerular filtration rate (GFR) compared to serum creatinine [21, 46, 47]. Inulin clearance is considered the gold standard measure of GFR; however, it is rarely used in clinical practice. Newer methods such as the clearance of iothexol or the measurement of serum cystatin C—a small housekeeping protein correlated with the GFR in patients with CKD [14] may become more widely used in the future to measure and estimate kidney function in those with AKI.

Scoring systems have also been employed to provide consistency in the description of AKI. Systems such as the pRIFLE criteria, AKIN criteria, and KDIGO criteria, as described above, are now used as standards to define AKI [6–8]. While these scoring systems rely on changes in serum creatinine, estimated creatinine clearance, and urine output for the diagnosis of AKI, they are easier to use in real time than conventional methods of measuring GFR and provide a common platform allowing meaningful comparisons to be made between studies.

Recently, several studies have suggested that urinary biomarkers hold promise as a method to detect the onset of AKI earlier than changes in serum creatinine or urine output. For example, urine neutrophil gelatinase associated lipocalin (NGAL) is a protein upregulated in the renal tubules and is released in the urine with the onset of AKI [33, 48]. Additionally, serum cystatin C levels have also been found to correlate well with elevation in serum creatinine concentration and conventional methods of evaluating GFR such as 99mTc-diethylenetriaminepentaacetic acid radio labeling [21]. Moreover, a urinary microalbumin level exceeding 400 mg per g of urinary creatinine has predicted AKI well after surgery in cardiac patients similar to that of NGAL [49, 50]. Another study detailed the time course of elevation of four urinary biomarkers of AKI after pediatric cardiopulmonary bypass, demonstrating the potential utility of urine biomarkers to predict AKI after a known “insult”. In this study, which tested levels of NGAL, interleukin-18, liver fatty acid-binding protein, and kidney injury molecule-1, all four biomarkers were increased by 12 hr after cardiopulmonary bypass surgery in patients who developed AKI

[51]. NGAL was elevated as early as 2 hr after surgery. Importantly, in those who developed AKI, as defined by increase in creatinine, time of diagnosis was 1 day after surgery in 98%. Thus, the use of biomarkers of AKI may facilitate earlier diagnosis of AKI than the use of creatinine alone, especially in high-risk populations where the timing of risk factors for AKI is predictable, such as in the setting of cardiopulmonary bypass surgery or induction therapy for HSCT. The use of urinary biomarkers as diagnostic tools of AKI appears to be an ever growing field of study, and studies of using biomarkers to predict AKI in the HSCT population, although currently lacking, may be quite useful.

5.1. Potential changes in current HSCT practice to minimize AKI

Unfortunately, many current therapies used in HSCT conditioning and supportive care are nephrotoxic. There exist some methods to potentially reduce this toxicity. For example, the use of the chemoprotectant amifostine may be of benefit in minimizing toxicity associated with high-dose chemotherapy and HSCT [44, 52]; however, the data on the use and success of amifostine for reducing toxicity in the setting of pediatric HSCT is limited and more study appears warranted [53]. In addition, nonmyeloablative HSCT pre-conditioning regimens, as routinely used for older patients and those with multi-organ dysfunction, may be associated with a lower incidence of AKI [24]. Moreover, other opportunities may exist to adjust planned conditioning regimens for those pediatric patients who are at increased risk of developing AKI.

5.2. The role of RRT

Currently, the mainstay of therapy is to treat AKI after it has developed. Children receiving HSCT are at risk for FO due to many aspects of their management. These patients receive frequent colloid in the form of blood product infusions, and large volumes of crystalloid in the form of total parenteral nutrition, conditioning medications with associated required fluid, and prophylactic antimicrobials [54]. To address the problem of FO and associated AKI, some centers have established protocols to initiate therapies at a certain level of FO in the setting of AKI. Protocols exist that recommend the administration of intravenous diuretics and inotropic therapy at 5% FO above baseline,

followed by the initiation of RRT at 10% FO either with worsening AKI [54, 55] or with evidence of worsening respiratory status or increasing inflammation [55]. Such an approach has been met with mixed reviews as the need for RRT has traditionally been associated with increased risk of mortality, reported to be as high as 70–80% [28, 56, 57].

However, studies exist which suggest a potential role for RRT in critically ill pediatric HSCT patients. Over a decade ago, DiCarlo et al. [58] reported the use of continuous RRT initiated concurrently with intubation among 10 children receiving chemotherapy or following HSCT with acute respiratory distress syndrome. Six of the 10 children in this study were HSCT patients, and four of them survived to ICU discharge [58]. Although a small study, these encouraging results spawned further interest and study. Another single center study of 21 children with acute lung injury after allogeneic HSCT and treated with continuous RRT between 1994 and 2006 showed the encouraging result that PaO₂:FiO₂ ratio improved at 24 and 48 hr after initiation of RRT, however, only five of 21 survived to ICU discharge [59]. In a follow-up study at the same institution of 29 children after allogeneic HSCT treated with continuous RRT between 2003 and 2007, 33% survived to PICU discharge, but the median survival after RRT initiation was only 31 days and only patient survived beyond 6 mo after RRT initiation [60]. While this survival may seem discouraging, results from a larger multicenter study show higher survival, although possibly related to broader indications for RRT initiation. Using the pediatric continuous RRT registry, Flores et al. [61], analyzed 51 patients who received HSCT at multiple centers. The median age was 13.6 yr (range 0.5–23.5 yr). The majority of patients were started on continuous RRT secondary to FO and electrolyte imbalance, and a large proportion were started on continuous RRT for FO only. In that report, 45% of the cohort survived to ICU discharge. The most common modality of continuous RRT used in the study was continuous veno-veno hemodialysis, however, use of convective modalities such as continuous veno-veno hemofiltration or continuous veno-veno hemodiafiltration was associated with higher survival. In survivors, the mean airway pressure at the end of continuous RRT had decreased from that at the time of RRT initiation. In addition, it was significantly lower in survivors as compared to non-survivors at the end of RRT suggesting an association with the ability to treat FO, ventilator requirements and survival. The authors speculated that

pulmonary disease secondary to infection or fibrosis from conditioning, and less related to FO, may be present in many non-survivors, and not as amenable to treatment specifically targeted at decreasing FO.

While continuous RRT is generally considered the safest and most easily controlled RRT modality in a critically ill child, intermittent hemodialysis and peritoneal dialysis are other RRT modalities available in the PICU. Peritoneal dialysis is an especially important consideration in resource limited settings, is generally very safe and well tolerated, but must be used cautiously in the HSCT population at very high risk of infection and gastrointestinal disease from infection and/or GVHD. The use of continuous RRT and other modalities of RRT early in the course of critically ill children after HSCT deserves further, more rigorous study to determine the true value of RRT in this population, the optimal timing of initiation, and the duration of therapy needed to achieve the best outcomes.

6. Long term effects on renal function of HSCT and AKI in pediatric patients

Several studies have followed pediatric patients after HSCT to examine the development of AKI, CKD, hypertension, and proteinuria. The studies by Ileri et al. [19] and Satwani et al. [22] both describe CKD at 12 mo after allogeneic HSCT. Ten percent of patients surviving to 1 yr post-transplant had stage 2 or 3 CKD in the former study, and 36% in the latter study (which defined CKD as >50% decrease in estimated creatinine clearance from pre-transplant baseline). The study by Ileri et al. [19] was underpowered to detect an association between AKI and the development of CKD. Although the Satwani et al. [22] study did not assess the association between AKI and the development of CKD, it did describe an association between AKI at

1 mo post-transplant and decreased overall survival. Additionally, 15% of the patients in that study were treated with RRT in the first year, with a 4% overall survival in this group.

Kist-van Holthe et al. [20] reported an 11% incidence of stage 2 or 3 CKD at 1 yr post-allogeneic HSCT and, AKI after HSCT predicted the development of CKD in this cohort. Two percent of these patients were being treated with anti-hypertensive medications at one year post-transplant. Long term follow up of this same group of patients (mean 5 yr post-transplant), still revealed a 10% incidence of CKD, but anti-hypertensive medications were no longer required for any patient [62]. In contrast, Hoffmeister et al. [63] reported a 15% prevalence of hypertension in children surviving at least 5 yr after receiving HSCT between the years 1969 and 2004. In that report, the 30 yr cumulative incidence rate was 36%. The age-based prevalence of hypertension in this cohort is two-three times the prevalence in the general population of the United States. Also, in that study, AKI after HSCT was associated with the development of hypertension [63].

Proteinuria is another important prognostic indicator for CKD development in survivors of AKI. In studies of adult and pediatric HSCT patients, albuminuria within the first 100 days after transplant showed a strong association with CKD and death [64, 65]. Patzer et al. [44] followed 41 children who received HSCT for 1 to 2 yr after HSCT and did not find any increase in urine albumin excretion from baseline during the follow-up period. In a study with much longer follow-up, Frisk et al. [66] followed a group of 18 children receiving HSCT for a median of 18 yr and found that the albumin excretion was higher in these patients compared to control patients from the community of similar age. Taken together, these studies indicate that children receiving HSCT are at increased risk of long-term decreases in

Fig. 1. A schematic for prevention, diagnosis, and treatment of acute kidney injury in the pediatric hematopoietic stem cell transplant patient.

renal function, but larger studies are needed to more accurately characterize this risk.

7. Future directions and conclusion

As the role of HSCT continues to expand, it is vital to discover areas for improvement in care. The collaboration of physicians from hematology/oncology, nephrology, and critical care has greatly assisted patients in recovering from the most critical of illness. In addition, to continuing to improve outcomes from acute illness, long term outcomes must also be addressed. The incidence of CKD in children who undergo HSCT is estimated to be between 10–36% [19, 21, 22, 44, 67], depending on the definition used and the duration of follow-up. AKI after pediatric HSCT has been associated with the development of both CKD and chronic hypertension [20, 63]. Therefore, improved protection of the kidney and preservation of renal function is essential. Figure 1 demonstrates a theoretical framework for incorporating the methods discussed in this article to prevent, diagnose, and treat AKI in children receiving HSCT. Areas of promising study for the future include the early use of RRT as the percent of FO at the time of RRT initiation has independently been associated with lower survival in pediatric intensive care patients who developed AKI [68, 69]. Further, the utility of serum and urinary biomarkers (such as NGAL, microalbumin, and cystatin C) may assist providers in the real time adjustment of therapies, including the proper dosing of medications to prevent further kidney injury, and is an area of research warranting further study in the HSCT population. As point of care testing is becoming available for these markers, their potential benefit is only likely to escalate. Additionally, the systematic use of a common scoring system (pRIFLE, AKIN, and KDIGO) has improved the identification and standardization of AKI. Further study is needed to best refine their use and implementation among this population of patients. Finally, a better understanding of the impact of the conditioning regimen on renal function and overall outcomes remains an area of intense study. It is hoped that continued work in this area will improve outcomes for this high-risk patient population. Clearly, much has been accomplished, but there is still much work to be performed. The ongoing desire to investigate methods to prevent and treat AKI in this vulnerable population is vital to continuing the current improvement reported.

References

- [1] Chima RS, Daniels RC, Kim MO, Li D, Wheeler DS, Davies SM, et al. Improved outcomes for stem cell transplant recipients requiring pediatric intensive care. *Pediatr Crit Care Med* 2012;13(6):e336–42.
- [2] Cole TS, Johnstone IC, Pearce MS, Fulton B, Cant AJ, Gennery AR, et al. Outcome of children requiring intensive care following haematopoietic SCT for primary immunodeficiency and other non-malignant disorders. *Bone Marrow Transplant* 2012;47(1): 40–5.
- [3] Duncan CN, Lehmann LE, Cheifetz IM, Greathouse K, Haight AE, Hall MW, et al; Pediatric Acute Lung Injury and Sepsis (PALISI) Network. Clinical outcomes of children receiving intensive cardiopulmonary support during hematopoietic stem cell transplant. *Pediatr Crit Care Med* 2013;14(3):261–7.
- [4] Kache S, Weiss IK, Moore TB. Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. *Pediatr Transplant* 2006;10(3):299–303.
- [5] Tamburro RF, Barfield RC, Shaffer ML, Rajasekaran S, Woodard P, Morrison RR, et al. Changes in outcomes (1996–2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. *Pediatr Crit Care Med* 2008;9(3):270–7.
- [6] Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007;71(10):1028–35.
- [7] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al; Acute Kidney Injury Network. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11(2):R31.
- [8] Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). *Crit Care* 2013;17(1): 204.
- [9] Plötz FB, Bouma AB, van Wijk JA, Kneyber MC, Bökenkamp A. Pediatric acute kidney injury in the ICU: An independent evaluation of pRIFLE criteria. *Intensive Care Med* 2008;34(9):1713–7.
- [10] Soler YA, Nieves-Plaza M, Prieto M, García-De Jesús R, Suárez-Rivera M. Pediatric Risk, Injury, Failure, Loss, End-Stage renal disease score identifies acute kidney injury and predicts mortality in critically ill children: A prospective study. *Pediatr Crit Care Med* 2013;14(4):e189–95.
- [11] Zappitelli M, Moffett BS, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: A retrospective cohort study. *Nephrol Dial Transplant* 2011;26(1):144–50.
- [12] Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. *Clin J Am Soc Nephrol* 2008;3(4):948–54.
- [13] Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58(2):259–63.
- [14] Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20(3):629–37.

- [15] Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: A two-center retrospective cohort study. *Crit Care* 2011;15(3):R146.
- [16] Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit Care Med* 2010;38(3):933-9.
- [17] Basu RK, Chawla LS, Wheeler DS, Goldstein SL. Renal angina: An emerging paradigm to identify children at risk for acute kidney injury. *Pediatr Nephrol* 2012;27(7):1067-78.
- [18] Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, Chawla LS, et al. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. *Kidney Int* 2014;85(3):659-67.
- [19] Ileri T, Ertem M, Ozcakar ZB, Ince EU, Biyikli Z, Uysal Z, et al. Prospective evaluation of acute and chronic renal function in children following matched related donor hematopoietic stem cell transplantation. *Pediatr Transplant* 2010;14(1):138-44.
- [20] Kist-van Holthe JE, Goedvolk CA, Brand R, van Weel MH, Bredius RG, van Oostayen JA, et al. Prospective study of renal insufficiency after bone marrow transplantation. *Pediatr Nephrol* 2002;17(12):1032-7.
- [21] Hazar V, Gungor O, Guven AG, Aydin F, Akbas H, Gungor F, et al. Renal function after hematopoietic stem cell transplantation in children. *Pediatr Blood Cancer* 2009;53(2):197-202.
- [22] Satwani P, Bavishi S, Jin Z, Jacobson JS, Baker C, Duffy D, et al. Risk factors associated with kidney injury and the impact of kidney injury on overall survival in pediatric recipients following allogeneic stem cell transplant. *Biol Blood Marrow Transplant* 2011;17(10):1472-80.
- [23] Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: An update. *J Am Soc Nephrol* 2005;16(1):151-61.
- [24] Lopes JA, Jorge S. Acute kidney injury following HCT: Incidence, risk factors and outcome. *Bone Marrow Transplant* 2011;46(11):1399-408.
- [25] Ando M, Mori J, Ohashi K, Akiyama H, Morito T, Tsuchiya K, et al. A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT. *Bone Marrow Transplant* 2010;45(9):1427-34.
- [26] Schrier RW, Parikh CR. Comparison of renal injury in myeloablative autologous, myeloablative allogeneic and non-myeloablative allogeneic haematopoietic cell transplantation. *Nephrol Dial Transplant* 2005;20(4):678-83.
- [27] Parikh CR, Sandmaier BM, Storb RF, Blume KG, Sahebi F, Maloney DG, et al. Acute renal failure after nonmyeloablative hematopoietic cell transplantation. *J Am Soc Nephrol* 2004;15(7):1868-76.
- [28] Singh N, McNeely J, Parikh S, Bhinder A, Rovin BH, Shidham G. Kidney complications of hematopoietic stem cell transplantation. *Am J Kidney Dis* 2013;61(5):809-21.
- [29] Alyea EP, Kim HT, Ho V, Cutler C, Gribben J, DeAngelo DJ, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood* 2005;105(4):1810-4.
- [30] Diaconescu R, Flowers CR, Storer B, Sorror ML, Maris MB, Maloney DG, et al. Morbidity and mortality with non-myeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. *Blood* 2004;104(5):1550-8.
- [31] Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A children's oncology group study. *J Clin Oncol* 2009;27(7):1007-13.
- [32] Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood* 2008;111(1):446-52.
- [33] Devarajan P. Update on mechanisms of ischemic acute kidney injury. *J Am Soc Nephrol* 2006;17(6):1503-20.
- [34] Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: A novel mechanism of human disease. *JAMA* 2005;293(13):1653-62.
- [35] Dragsten PR, Hallaway PE, Hanson GJ, Berger AE, Bernard B, Hedlund BE. First human studies with a high-molecular-weight iron chelator. *J Lab Clin Med* 2000;135(1):57-65.
- [36] Jodele S, Davies SM, Lane A, Khoury J, Dandoy C, Goebel J, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: A study in children and young adults. *Blood* 2014;124(4):645-53.
- [37] Copelovitch L, Kaplan BS. The thrombotic microangiopathies. *Pediatr Nephrol* 2008;23(10):1761-7.
- [38] Carreras E, Bertz H, Arcese W, Vernant JP, Tomás JF, Hagglund H, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: A prospective cohort study of the European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood* 1998;92(10):3599-604.
- [39] Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* 2008;41(3):229-37.
- [40] Kogon A, Hingorani S. Acute kidney injury in hematopoietic cell transplantation. *Semin Nephrol* 2010;30(6):615-26.
- [41] Parikh CR, Coca SG. Acute renal failure in hematopoietic cell transplantation. *Kidney Int* 2006;69(3):430-5.
- [42] Kusumi E, Kami M, Hara S, Hoshino J, Yamaguchi Y, Murashige N, et al. Postmortem examination of the kidney in allogeneic hematopoietic stem cell transplantation recipients: Possible involvement of graft-versus-host disease. *Int J Hematol* 2008;87(2):225-30.
- [43] Reddy P, Johnson K, Uberti JP, Reynolds C, Silver S, Ayash L, et al. Nephrotic syndrome associated with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2006;38(5):351-7.
- [44] Patzer L, Kentouche K, Ringelmann F, Misselwitz J. Renal function following hematological stem cell transplantation in childhood. *Pediatr Nephrol* 2003;18(7):623-35.
- [45] Laskin BL, Goebel J, Davies SM, Khoury JC, Bleesing JJ, Mehta PA, et al. Early clinical indicators of transplant-associated thrombotic microangiopathy in pediatric

- neuroblastoma patients undergoing auto-SCT. Bone Marrow Transplant 2011;46(5):682-9.
- [46] Hilson AJ, Mistry RD, Maissey MN. 99Tcm-DTPA for the measurement of glomerular filtration rate. Br J Radiol 1976;49(585):794-6.
- [47] Rahn KH, Heidenreich S, Brückner D. How to assess glomerular function and damage in humans. J Hypertens 1999;17(3):309-17.
- [48] Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365(9466):1231-8.
- [49] Kern W, Braess J, Kaufmann CC, Wilde S, Schleyer E, Hidde-mann W. Microalbuminuria during cisplatin therapy: Relation with pharmacokinetics and implications for nephroprotection. Anticancer Res 2000;20(5C):3679-88.
- [50] Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol 2008;48:463-93.
- [51] Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Piyaphanee N, Ma Q, et al. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol 2011;58(22):2301-9.
- [52] Chauncey TR, Gooley TA, Lloid ME, Schubert MM, Lilleby K, Holmberg L, et al. Pilot trial of cytoprotection with amifostine given with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Am J Clin Oncol 2000;23(4):406-11.
- [53] Ozkaynak MF, Sahdev I, Gross TG, Levine JE, Cheerva AC, Richards MK, et al. A pilot study of addition of amifostine to melphalan, carboplatin, etoposide, and cyclophosphamide with autologous hematopoietic stem cell transplantation in pediatric solid tumors-A pediatric blood and marrow transplant consortium study. J Pediatr Hematol Oncol 2008;30(3):204-9.
- [54] Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol 2004;19(1):91-5.
- [55] DiCarlo J, Alexander SR. Acute kidney injury in pediatric stem cell transplant recipients. Semin Nephrol 2008;28(5):481-7.
- [56] Bunchman TE, McBryde KD, Mottes TE, Gardner JJ, Maxvold NJ, Brophy PD. Pediatric acute renal failure: Outcome by modality and disease. Pediatr Nephrol 2001;16(12):1067-71.
- [57] Rajpal JS, Patel N, Vogel RI, Kashtan CE, Smith AR. Improved survival over the last decade in pediatric patients requiring dialysis after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2013;19(4):661-5.
- [58] DiCarlo JV, Alexander SR, Agarwal R, Schiffman JD. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. J Pediatr Hematol Oncol 2003;25(10):801-5.
- [59] Elbahlawan L, West NK, Avent Y, Cheng C, Liu W, Barfield RC, et al. Impact of continuous renal replacement therapy on oxygenation in children with acute lung injury after allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer 2010;55(3):540-5.
- [60] Rajasekaran S, Jones DP, Avent Y, Shaffer ML, Elbahlawan L, Henderson N, et al. Outcomes of hematopoietic stem cell transplant patients who received continuous renal replacement therapy in a pediatric oncology intensive care unit. Pediatr Crit Care Med 2010;11(6):699-706.
- [61] Flores FX, Brophy PD, Symons JM, Fortenberry JD, Chua AN, Alexander SR, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. Pediatr Nephrol 2008;23(4):625-30.
- [62] Kist-van Holthe JE, Bresters D, Ahmed-Ousenkova YM, Goedvolk CA, Abbink FC, Wolterbeek R, et al. Long-term renal function after hemopoietic stem cell transplantation in children. Bone Marrow Transplant 2005;36(7):605-10.
- [63] Hoffmeister PA, Hingorani SR, Storer BE, Baker KS, Sanders JE. Hypertension in long-term survivors of pediatric hematopoietic cell transplantation. Biol Blood Marrow Transplant 2010;16(4):515-24.
- [64] Hingorani S, Gooley T, Pao E, Sandmaier B, McDonald G. Urinary cytokines after HCT: Evidence for renal inflammation in the pathogenesis of proteinuria and kidney disease. Bone Marrow Transplant 2014;49(3):403-9.
- [65] Hingorani SR, Seidel K, Lindner A, Aneja T, Schoch G, McDonald G. Albuminuria in hematopoietic cell transplantation patients: Prevalence, clinical associations, and impact on survival. Biol Blood Marrow Transplant 2008;14(12):1365-72.
- [66] Frisk P, Arvidson J, Neveus T. Glomerular and tubular function in young adults treated with stem-cell transplantation in childhood. Pediatr Nephrol 2010;25(7):1337-42.
- [67] Van Why SK, Friedman AL, Wei LJ, Hong R. Renal insufficiency after bone marrow transplantation in children. Bone Marrow Transplant 1991;7(5):383-8.
- [68] Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous veno-venous hemofiltration. Pediatrics 2001;107(6):1309-12.
- [69] Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 2005;67(2):653-8.