Acute Kidney Injury in Pediatric Stem Cell Transplant Recipients

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Summary: Because respiratory dysfunction after hematopoietic stem cell transplantation is a manifestation of a continuum of dysfunction temporarily induced by the transplant process, a proactive rather than reactive approach might prevent or attenuate its progression to acute respiratory distress syndrome. Organ dysfunction in this population results from cytokine-driven processes, of which the first manifestation includes fluid accumulation. We describe a multistep protocol that first targets fluid balance control, both through restriction of intake and through augmentation of output using dopamine and furosemide infusions. If these steps fail to stem the tide of water accumulation, we advocate the relatively early use of continuous renal replacement therapy, its use triggered by a continued increase in body weight (>10% above baseline), an increasing c-reactive protein level, and an increasing oxygen need. Renal function parameters do not figure in this protocol. We recommend continuous renal replacement therapy at 35 mL/kg/h (2,000 mL/1.73 m^2/h), a dose that allows adequate flexibility in fluid management and that may provide effective clearance of proinflammatory (and anti-inflammatory) mediators that drive the evolving dysfunction. Proactive intervention improves the clinical status such that the transition to mechanical ventilation may proceed smoothly or in some cases even may be avoided altogether.

Keywords: *Stem cell transplant, idiopathic pneumonia syndrome, respiratory failure, hemofiltration*

The case presented by Symons and Picca[1] of a pediatric stem cell transplant patient who develops acute kidney injury (AKI) highlights the clinical complexity of such cases. The conditioning regimen, severe immunosuppression and routine requirement for nephrotoxic medications and high volumes of blood products place stem cell transplant recipients at high risk for AKI and present unique challenges for fluid management and renal replacement therapy provision. The stem cell transplant (SCT) patient narrative describes a scenario familiar to practitioners of hematopoietic stem cell transplantation, nephrology, and critical care medicine. Inevitably, all 3 disciplines will work together in support of this child who has developed the idiopathic pneumonia syndrome (IPS) after transplantation. In fact, the level of organ dysfunction described likely fulfills the clinical criteria for the acute respiratory distress syndrome (ARDS). The case report delineates both the classic time course for the development of respiratory complications and the usual therapeutic maneuvers used in dealing with the evolving crisis. The multidisciplinary team in this case may in fact be able to support this child, but some therapeutic decisions (and omissions) have made the job more difficult.

We discuss why respiratory dysfunction exists after transplantation, how it evolves, and how the caregivers can monitor its evolution. With an appreciation of posttransplantation ARDS as the unfortunate end result of a continuum of dysfunction, one might envision a more proactive approach to the care of the child (and perhaps the adult) developing IPS, with the goal of preventing or attenuating its progression to ARDS.

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ORIGINS OF ORGAN DYSFUNCTION

Chemotherapy and total body irradiation are used routinely in the preparation for hematopoietic stem cell transplantation, both of which are capable of damaging native cells and triggering an inflammatory response. In addition, during engraftment donor cells may contribute to ongoing inflammation. The majority of hematopoietic stem cell recipients manifest some degree of systemic (and therefore pulmonary) inflammation, subsiding over days to weeks. In a few, the process escalates insidiously, resulting in respiratory insufficiency and failure. Multiple factors contribute to respiratory failure after hematopoietic SCT, including hydrostatic pulmonary edema, capillary leak, alveolar hemorrhage, infection, and direct cytotoxic injury induced by radiation or chemotherapy. Large volumes of intravenous fluids are administered to hematopoietic stem cell recipients, but it is unlikely that hydrostatic pulmonary edema alone is responsible for respiratory failure. Most patients with respiratory failure show a prodrome of ongoing inflammation that includes fever, a progressive need for supplemental oxygen, and hemodynamic instability, often requiring support with cardiotropic agents such as dopamine. In the first 60 days after transplantation, respiratory infection is documented in only a minority of patients with respiratory insufficiency. The more common scenario is of smoldering lung damage (IPS) accompanied by systemic inflammation that has been initiated by the preparatory regimen.[2]

Animal models of allogeneic transplantation provide evidence that pulmonary and systemic inflammation are an inevitable result of cytokine-driven feedback loops. Initial activity is triggered by intestinal mucosal damage and translocation. Increased levels of neutrophils, endotoxin (lipopolysaccharide), components of the lipopolysaccharide amplification system (lipopolysaccharide-binding protein [LBP] and soluble CD14), and tumor necrosis factor-α (TNF-α) can be found in bronchoalveolar lavage fluid. Evidence suggests that because intestinal injury precedes lung changes by a week or more, endotoxin enters the bronchoalveolar fluid after translocating across the damaged gut endothelium.[3] Pharmacologic neutralization of TNF-α delays lung injury induced by donor T cells, but injury ultimately still occurs, probably through other proinflammatory pathways.[4] As engraftment occurs, donor cells also contribute to ongoing inflammation in allogeneic transplant recipients. Minor histocompatibility antigens on host cell surfaces can be important constant stimuli to donor cells in the pathogenesis of IPS.[5] For instance, pneumonitis and mononuclear cell infiltration around vessels and bronchioles are observed 6 weeks after allogeneic transplantation, but not in animals undergoing syngeneic transplantation. T-cell reactivity to host antigens is centered on the lung (ie, it is not present in the spleen). Perhaps small numbers of mature immunocompetent donor T cells can induce relatively isolated pulmonary damage.

CLINICAL MANIFESTATIONS

In the clinical setting, cytokine-driven inflammation manifests as mild to moderate pulmonary and cardiac insufficiency that tends to peak around the tenth posttransplant day. The cytokine profile is dominated by interleukin-2 (IL-2), IL-6, and interferon-γ in the first few days (the aplastic phase).[6] By the 14th day (leukocyte recovery phase), the profile is dominated by IL-8 and TNF-α. The c-reactive protein (CRP) level correlates well with the degree of IL-6 activity in transplant recipients.[7] The few patients who go on to develop serious pulmonary complications show a relatively more robust degree of inflammation, manifested as a CRP level well above 10 mg/dL (100 mg/L) on the 10th day.[8,9]

Although direct invasion of lung tissue by a pathogen, such as aspergillus or certain viruses, can be responsible for respiratory failure in the transplant recipient, bronchoalveolar lavage fluid obtained at bronchoscopy identifies an offending agent in only 46% to 52% of attempts.[10,11] But even in the infected host, the severity of the pulmonary dysfunction is influenced greatly by the degree of capillary leak induced by the cytokine-instigated process described earlier. Epidemiologic reports on posttransplant respiratory failure tend to cluster patients by type of transplant (donor matched or unmatched, related or unrelated), and by the

presence or absence of a pulmonary or systemic pathogen, a system that tends to mask the severely deleterious impact of IPS on transplant outcomes. In pediatric and adult SCT recipients who require mechanical ventilatory support, mortality rates have been reported to range from 56% to as high as 90%.[12-15] Although transplant epidemiologic data are not usually configured to track the incidence of ARDS, the criteria for that clinical diagnosis probably were met more often than not. In our own center, before the addition of early hemofiltration to the treatment regimen, mortality rates had been 85% for children posttransplant who developed respiratory failure meeting ARDS criteria and who needed mechanical ventilatory support for more than 48 hours.[16]

Clinically relevant organ dysfunction develops in many recipients in the days to weeks after transplantation. The driving force is the cytokine sequence that begins in the damaged gastrointestinal tract and smolders in most recipients for 1 to 3 weeks after transplantation. In a minority, however, the dysregulated immune response persists. It is perhaps most useful to envision that in the immediate posttransplant period, respiratory insufficiency might be caused by the presence of an invading pathogen, but it always is influenced by the degree of capillary leak induced by a systemic cytokine-driven process, which itself was initiated by cellular damage from the preparatory regimen. Pulmonary insufficiency may seem to precede cardiac and renal dysfunction, but they are more likely developing in parallel, not in series. Although pulmonary function worsens most dramatically, cardiac and renal dysfunction are developing concomitantly. ARDS and multiple organ failure are the clinical end points of a process that is triggered by an infectious or noninfectious cause but is mediated by unchecked cytokine and chemokine feedback loops.

Contemporary critical care for ARDS centers on the nonprovocative support of the lungs for a period of days during which time immunoregulatory mechanisms might restore order. In the previously normal young host this is a reasonable expectation. However, in the setting of immune dysregulation that characterizes the immediate posttransplant period, once cytokine-driven multiple organ dysfunction is entrenched, it may last for weeks if the patient survives at all. In this setting, inflammatory activity continues relatively unabated, and restoration of order seems an unlikely prospect. But is it? Or are we missing opportunities, both to minimize pulmonary mechanical difficulties and to slow the cytokine-driven component? If we can control the overall accumulation of water, will we provide more time for the restoration of order? And if we can somehow reduce the overall load of proinflammatory (and anti-inflammatory) cytokines and other dysregulatory biochemicals, will order be restored more quickly?

THERAPEUTIC STRATEGIES

Two assumptions inform our strategy for the support of the child with evolving respiratory insufficiency after transplantation (or chemotherapy). The first is that pulmonary, cardiac, and renal dysfunction are the clinical manifestations of an uncontrolled cytokine-driven process triggered by the transplant preparatory regimen and possibly worsened by an infectious agent. The second is that those pulmonary, cardiac, and renal dysfunctions are developing in parallel, not in series. With these assumptions in mind, we propose the following therapeutic approach: (1) accurately record and track the intake and output of fluids, and (2) weigh the patient daily.

Despite being standard components of posttransplantation care, serial patient weights and the careful tracking of intake and output of fluids often are used ineffectively in monitoring for evolving organ dysfunction. Intake and output should be totaled over several days as well as within a discrete 24-hour period. Daily weighing of the patient is essential and must be continued despite patient discomfort or increasing complexity of care.

Obtain Serial Measurements of CRP Levels (Perhaps Every 3 Days)

Serial measurement of the CRP level may help to identify patients most at risk of serious pulmonary complications.[9] A strong upward trend

may strengthen the case for proactive intervention as described later; likewise a trend toward normalization may parallel a clinical impression of diminishing inflammatory activity. Serum ferritin concentration also has been suggested as a useful marker of inflammation after transplantation. Dramatic increases in ferritin levels (ie, >5,000 ng/mL [5,000 mcg/L]) seem to occur most commonly in the hemophagocytic syndrome and in patients with serious complications after chemotherapy or hematopoietic stem cell transplantation.[17,18]

Furosemide and Dopamine Infusions

A threshold increase in weight (such as 5% above baseline) should trigger the initiation of infusions of furosemide at adequate doses (0.1-0.4 mg/kg/h) and dopamine infusion at 3 to 8 mcg/kg/min.[19] The goal of these therapies is to prevent worsening fluid overload.

Diminishing urine output in the face of significant weight gain in the transplant recipient is tied to cytokine-mediated capillary leak phenomena. Urine output less than a certain threshold (eg, <1 mL/kg/h) should not prompt increased infusions of crystalloid or colloid unless there is unequivocal evidence of dehydration (ie, weight is less than baseline, and, if accessible, central venous pressure is low). In oliguric patients in whom the clinical picture is not clear, commonly used indices of renal function such as the fractional excretion of sodium or urea may help to identify those prerenal patients who will benefit from further fluid loading. However, in the posttransplant setting as described earlier these patients are uncommon; most often, increasing the fluid intake simply drives pulmonary edema formation.

In the case described earlier[1] the proper time to have initiated nephrology and/or critical care consultation and a protocol-driven, step-wise approach to fluid management intervention would have been with the first sign of dwindling urine output (ie, at least 2 days earlier). The patient's weight should have been documented daily. When her weight increased from 40 kg to 42 kg (ie, a 5% increase), a furosemide infusion should have been started at 0.1 to 0.2 mg/kg/h. The furosemide infusion is incompatible with many common medications, so it will likely monopolize an intravenous lumen. She might need a new peripheral intravenous line or an additional central line. The infusion should be increased to 0.3 to 0.4 mg/kg/h if need be, with a goal of keeping her weight less than 42 kg. In addition, we recommend an infusion of dopamine beginning at 5 mcg/kg/min. This may be all that is needed to avoid respiratory failure.[20]

In some children, the response to the furosemide and dopamine infusion is brisk, and the cardiovascular system compensates for the decrease in filling volumes by efficiently mobilizing tissue fluid. Within 1 to 3 days the CRP level peaks and then declines, and oxygen needs diminish. Furosemide and dopamine are discontinued when clinically indicated.

In others, however, symptoms of pulmonary insufficiency persist. Chest roentgenograms should be obtained frequently (eg, daily if symptoms and oxygen needs increase).

At this point discussions should commence on the advisability of a bronchoscopy if a causative infectious agent is being sought. The practical issue with bronchoscopy is that the procedure itself, which includes the instillation of saline to obtain diagnostic material, might bring the patient one step closer to invasive mechanical ventilation. At 5% above baseline weight, pulmonary insufficiency may be apparent but the child likely has plenty of reserve.

CRRT if Fluid Accumulating

A subsequent increase in weight (to 10% above baseline), or progression in pulmonary edema despite negative fluid balance, should trigger the initiation of continuous renal replacement therapy (CRRT) at an adequate dose, at least 35 mL/kg/h (2,000 mL/1.73 m^2/h).

Worsening pulmonary edema despite a consistently negative fluid balance enabled by the furosemide infusion is an entirely realistic scenario in the face of cytokine-induced capillary leak. Usually the CRP concentration remains increased, and pulmonary function and symptoms worsen. The child may now show significantly increased work of breathing, and may need high-flow nasal cannula oxygen or continuous or bilevel positive airway pressure venti-

lation delivered by mask to maintain oxygen saturation above 93%.

A confluence of clinical thresholds dictates the next step in the protocol: (1) progression in symptomatic respiratory insufficiency manifested by escalating noninvasive support, (2) continued accumulation of edema in the lungs, (3) lack of renal response to an escalating dose of furosemide, and (4) laboratory evidence of ongoing inflammation (eg, increased CRP levels). With most or all of these components present there is a high likelihood of further clinical deterioration, subsequent endotracheal intubation, and mechanical ventilation. At this point CRRT should be initiated, with the aim of preventing that eventuality, or attenuating the severity and duration of respiratory failure.

Although CRRT has been in use in critical care units worldwide for more than 20 years, practice patterns remain heterogeneous both in terms of time of initiation and the mode used. It is used most commonly in the patient with established multiple organ failure. In severe septic shock, failure of the cardiac, pulmonary, and renal systems may progress swiftly and are apparent at presentation. CRRT typically is initiated in the first to third day after endotracheal intubation and therapy with cardiotonic agents. When multiple organ failure evolves from a predominantly pulmonary presentation (ARDS) in the normal host, cardiac and renal function are relatively spared initially and CRRT often is delayed a number of days until renal failure is fully established. In a given institution the timeline may be moved up if the clinicians ascribe some weight to an immunomodulatory role for continuous hemofiltration in addition to its renal replacement capabilities, or if excess lung and total body water pose mechanical difficulties for pulmonary function.

In the SCT population with evolving ARDS (and in other patients with serious immunodeficiency, such as after chemotherapy) we recommend the early deployment of CRRT in a step-wise escalation of therapy.[21] In a penultimate step we attempt to establish a negative fluid balance with infusions of furosemide and dopamine.[19] A lack of renal response to the diuretic and cardiotonic, coupled with a further increase in weight, triggers the initiation of CRRT, which in our center is typically in the form of continuous venovenous hemodiafiltration. In deference to its potential immunomodulatory function the prescription should include a hemofiltration dose of at least 35 mL/kg/h (2,000 mL/1.73 m^2/h). Strategic objectives with hemofiltration in this setting include (1) strict fluid balance control with a return to and maintenance of baseline weight; and (2) the constant exchange of extracellular water, and concomitant with this exchange, the mobilization of water-soluble components of the inflammatory cascade. The purely diffusive mode of continuous renal replacement, continuous venovenous hemodialysis (CVVHD), promotes a modest degree of interstitial fluid and solute movement through gradual re-equilibration. In the convective modes (hemofiltration [CVVH] and diafiltration [CVVHDF]), each hour 500 to 3,000 mL of crystalloid replacement fluid is infused intravenously to offset removal of ultrafiltrate. A significant portion of the crystalloid redistributes to the extracellular space and may help to wash out the interstitium, mobilizing mediators, proteins, extracellular matrix material (eg, hyaluronan, whose fragments function in inflammatory signaling), and cellular wastes, some of which might be removed at the hemofilter. But mobilization also might facilitate removal or metabolism of these toxins, waste products, and mediators at various organs and other sites as well (eg, the liver, spleen, and red blood cell).[22]

In the setting of respiratory failure that is likely being driven by cytokines and other tissue-derived inflammatory mediators, we believe that diffusive and convective modes of hemofiltration are likely not fully interchangeable from a therapeutic standpoint. Unlike with CVVH and CVVHDF, when diffusion alone (CVVHD) is used there is no large-volume replacement fluid infusion that has the potential to maximize exchange of water and solutes at the level of the interstitium. Recent data from the Prospective Pediatric CRRT (ppCRRT) Registry group showed increased survival in SCT recipients who received convective CRRT versus CVVD (59% versus 27%; $P < .05$).[23]

We have set the target for minimum ultrafiltrate production somewhat arbitrarily at 35 mL/kg/h

(2,000 mL/1.73 m^2/h), extrapolating from a prospective survival comparison of 3 doses of convective clearance (20, 35, and 45 mL/kg/h) conducted in a large series of adult patients with acute renal failure.[24] The survival advantage of the higher clearance goals in this randomized series held up in the subgroup with sepsis/ARDS. In our own experience, early introduction of CVVHDF targeting ultrafiltration at these rates in the setting of IPS after stem cell transplantation or chemotherapy has been associated with a reduction in mortality to less than 30%.[21]

SUMMARY

We thus advocate a proactive approach to the child with evolving multiple organ dysfunction after transplantation. Monitoring of all transplant recipients should emphasize the fundamentals of fluid balance to detect and follow extracellular water accumulation as a clinical correlate for disease severity. Serial laboratory measurements of CRP concentrations and perhaps ferritin concentrations can corroborate the clinical impression of disease progression. Therapeutic interventions then should focus on amelioration of water accumulation rather than targeting biochemical parameters of renal function, with furosemide and dopamine infusions giving way to CRRT in the form of CVVH or CVVHDF if fluid balance (ie, body weight) targets are not met. It is highly likely that the symptomatic child who has accumulated extracellular water in excess of 10% of baseline body weight will continue to accumulate water, contributing to pulmonary dysfunction that eventually may reach the crisis stage. CRRT initiated in response to a fluid accumulation threshold rather than according to biochemical renal parameters may improve the clinical status such that the transition to mechanical ventilation may proceed smoothly or in some cases even may be avoided altogether.

REFERENCES

1. Symons JM, Picca S. Acute kidney injury and dialysis in children: illustrative cases. Sem Neph. 2008;28:431-5.
2. Clark JG, Madtes DK, Martin TR, Hackman RC, Farrand AL, Crawford SW. Idiopathic pneumonia after bone marrow transplantation: cytokine activation and lipopolysaccharide amplification in the bronchoalveolar compartment. Crit Care Med. 1999;27:1800-6.
3. Cooke KR, Hill GR, Gerbitz A, Kobzik L, Martin TR, Crawford JM, et al. Tumor necrosis factor-alpha neutralization reduces lung injury after experimental allogeneic bone marrow transplantation. Transplantation. 2000;70:272-9.
4. Clark JG, Mandac JB, Dixon AE, Martin PJ, Hackman RC, Madtes DK. Neutralization of tumor necrosis factor-alpha action delays but does not prevent lung injury induced by alloreactive T helper 1 cells. Transplantation. 2000;70:39-43.
5. Cooke KR, Krenger W, Hill G, Martin TR, Kobzik L, Brewer J, et al. Host reactive donor T cells are associated with lung injury after experimental allogeneic bone marrow transplantation. Blood. 1998;92:2571-80.
6. Takatsuka H, Wakae T, Mori A, Okada M, Okamoto T, Kakishita E. Effects of total body irradiation on the vascular endothelium. Clin Transplant. 2002;16:374-7.
7. Chasty RC, Lamb WR, Gallati H, Roberts TE, Brenchley PE, Yin JA. Serum cytokine levels in patients undergoing bone marrow transplantation. Bone Marrow Transplant. 1993;12:331-6.
8. Schots R, Van Riet I, Othman TB, Trullemans F, De Waele M, Van Camp B, et al. An early increase in serum levels of C-reactive protein is an independent risk factor for the occurrence of major complications and 100-day transplant-related mortality after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2002;30:441-6.
9. Schots R, Kaufman L, Van Riet I, Lacor P, Trullemans F, De Waele M, et al. Monitoring of C-reactive protein after allogeneic bone marrow transplantation identifies patients at risk of severe transplant-related complications and mortality. Bone Marrow Transplant. 1998;22:79-85.
10. McCubbin MM, Trigg ME, Hendricker CM, Wagener JS. Bronchoscopy with bronchoalveolar lavage in the evaluation of pulmonary complications of bone marrow transplantation in children. Pediatr Pulmonol. 1992;12:43-7.
11. Eikenberry M, Bartakova H, Defor T, Haddad IY, Ramsay NK, Blazar BR, et al. Natural history of pulmonary complications in children after bone marrow transplantation. Biol Blood Marrow Transplant. 2005;11:56-64.
12. Keenan HT, Bratton SL, Martin LD, Crawford SW, Weiss NS. Outcome of children who require mechanical ventilatory support after bone marrow transplantation. Crit Care Med. 2000;28:830-5.
13. Jacobe SJ, Hassan A, Veys P, Mok Q. Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. Crit Care Med. 2003;31:1299-305.
14. Bojko T, Notterman DA, Greenwald BM, De Bruin WJ, Magid MS, Godwin T. Acute hypoxemic respiratory failure in children following bone marrow transplantation: an outcome and pathologic study. Crit Care Med. 1995;23:755-9.

15. Rossi R, Shemie SD, Calderwood S. Prognosis of pediatric bone marrow transplant recipients requiring mechanical ventilation. Crit Care Med. 1999;27:1181-6.
16. Litalien CDM, DiCarlo J. Oxygenation index and alveolar-arterial oxygen gradient predict mortality in pediatric bone marrow transplantation. Pediatr Res. 1998;43:39A.
17. Rajantie J. Hyperferritinaemia in children undergoing bone marrow transplantation. Bone Marrow Transplant. 1989;4 Suppl 3:92.
18. Or R, Matzner Y, Konijn AM. Serum ferritin in patients undergoing bone marrow transplantation. Cancer. 1987;60:1127-31.
19. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol. 2004;19:91-5.
20. Reising CA, Chendrasekhar A, Wall PL, Paradise NF, Timberlake GA, Moorman DW. Continuous dose furosemide as a therapeutic approach to acute respiratory distress syndrome (ARDS). J Surg Res. 1999; 82:56-60.
21. 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;25:801-5.
22. Di Carlo JV, Alexander SR. Hemofiltration for cytokine-driven illnesses: the mediator delivery hypothesis. Int J Artif Organs. 2005;28:777-86.
23. 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;23:625-30.
24. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356:26-30.