Published in final edited form as:

Pediatr Crit Care Med. 2017 March ; 18(3 Suppl 1): S50–S57. doi:10.1097/PCC.0000000000001048.

Specific etiologies associated with the multiple organ dysfunction syndrome in children: Part 1

Jeffrey S. Upperman, MD,
Division of Pediatric Surgery, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, California

Jacques Lacroix, MD,
Division of Pediatric Critical Care Medicine, Department of Pediatrics, Sainte-Justine Hospital, Université de Montréal, Montreal, QC, Canada

Martha A.Q. Curley, RN, PhD, FAAN,
School of Nursing, Departments of Anesthesia and Critical Care Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Paul A. Checchia, MD, FCCM, FACC,
Sections of Critical Care and Cardiology Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

Daniel W. Lee, MD.,
Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Virginia, Charlottesville, Virginia

Kenneth R. Cooke, MD, and
Pediatric Blood and Marrow Transplantation Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Address for correspondence: Robert Tamburro, MD, MSc, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), 6710B Rockledge Drive, Room 2331-C, Bethesda, Maryland, 20817, Phone: 301-480-2619, robert.tamburro@nih.gov.

Copyright form disclosure: Dr. Tamburro's former institution received funding from US FDA Office of Orphan Product Development Grant Program, and from Ony, LLC (provided the calfactant free of charge for the above grant which assessed the efficacy of exogenous surfactant in pediatric hematopoietic stem cell transplant patients with acute lung injury). He also has received royalties from Springer Publishing for serving as an associate editor on a Pediatric Critical Care Study Guide: Text and Review. Dr. Tamburro disclosed government work, and he disclosed off-label/unapproved drugs or products: Serum IL-6 levels in responding patients have been measured to be greater than 3000 pcg/mL (normal <10 pcg/mL) and the fever and hemodynamic instability reported in CRS can be reversed within hours of the administration of the anti-IL-6 receptor monoclonal antibody, tocilizumab (23–25, 27). Clinical experience suggests that the timely administration of tocilizumab with or without corticosteroids to the patient with moderate-grade CRS is of paramount importance in preventing severe, life-threatening CRS characterized by multiple organ dysfunction although this has not been confirmed in phase II or III trials. Drs. Upperman, Curley, and Lee received support for article research from the National Institutes of Health (NIH). Dr. Curley's institution received funding from National Heart, Lung, and Blood Institute and the National Institute of Nursing Research, NIH (grant U01 HL086622). Dr. Lee also disclosed support from the St. Baldrick's Foundation. Dr. Cooke received funding from NIH (grant), and received funding from Jazz pharmaceuticals, advisory board (money paid had no influence on his efforts for this study). The remaining authors have disclosed that they do not have any potential conflicts of interest.

Robert F. Tamburro, MD
Pediatric Trauma and Critical Illness Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services, Bethesda, Maryland

Abstract

Objective—To describe a number of the conditions associated with multiple organ dysfunction syndrome (MODS) presented as part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development MODS Workshop (March 26–27, 2015).

Data Sources—Literature review, research data, and expert opinion.

Study Selection—Not applicable.

Data Extraction—Moderated by an expert from the field, issues relevant to the association of MODS with a variety of conditions were presented, discussed and debated with a focus on identifying knowledge gaps and research priorities.

Data Synthesis—Summary of presentations and discussion supported and supplemented by relevant literature.

Conclusions—There is a wide range of medical conditions associated with MODS in children. Traditionally, sepsis and trauma are the two conditions most commonly associated with MODS both in children and adults. However, there are a number of other pathophysiologic processes that may result in MODS. In this paper, we discuss conditions such as cancer, congenital heart disease and acute respiratory distress syndrome. In addition, the relationship between MODS and clinical therapies such as hematopoietic stem cell transplantation and cardiopulmonary bypass are also considered. The purpose of this manuscript is to describe the association of MODS with a variety of conditions in an attempt to identify similarities, differences and opportunities for therapeutic intervention.

Keywords

Multiple organ dysfunction syndrome; sepsis; acute respiratory distress syndrome; congenital heart disease; cytokine release syndrome; graft-versus-host disease; idiopathic pneumonia syndrome; hepatic veno-occlusive disease/sinusoidal obstruction syndrome; thrombotic microangiopathy; pediatrics

Introduction

There are a number of pathophysiologic processes that may result in the multiple organ dysfunction syndrome (MODS) in children. To begin, certain underlying diagnoses including, but not limited to cancer, congenital heart disease, inborn errors of metabolism, and rheumatologic diseases have all been associated with a predisposition to the syndrome. Similarly, acute conditions such as sepsis, acute respiratory distress syndrome, acute kidney injury, liver failure, and pancreatitis have also been associated with the process. Additionally, pathophysiologic processes such as hypoxia (of any source) can be potent triggers of MODS as observed following cardiopulmonary arrest. Further, acute insults such

as multiple trauma and thermal injuries have also been found to result in MODS. Conversely, numerous treatments and therapeutic regimens such as anti-neoplastic therapies, blood transfusions, hematopoietic and solid organ transplantation have all been reported to elicit MODS. Given the breadth of these various topics, any attempt to provide a comprehensive review of the many etiologies of MODS would be grossly insufficient, and thus, that is not the intent of this manuscript. Conditions commonly associated with MODS such as inborn errors of metabolism, brain injury and neurologic insult and rheumatologic disorders are not addressed in this, or its accompanying manuscript. The available literature contains a host of publications and reviews addressing the individual topics and their association with MODS. The purpose of this manuscript is simply to encourage investigators to consider the topic from the perspective of other disciplines to hopefully identify areas of commonality, enhance the body of knowledge of respective disciplines, and identify opportunities for future study (Table).

Sepsis

Sepsis is a common cause of MODS. It is defined in its simplest form as a systemic inflammatory response syndrome (SIRS) caused by an infection (1). Although sepsis has most recently been redefined for adults (2), those definitions have not been applied to children to date. Thus, this discussion will continue to utilize the definitions initially proposed at the International Pediatric Sepsis Consensus Conference held in 2005. Based on those proceedings, the proposed diagnostic criteria of SIRS include the presence of alterations in at least two of four criteria including temperature, heart rate, respiratory rate and/or white blood cell count (1). This set of diagnostic criteria for SIRS has subsequently been found to demonstrate excellent inter-observer reliability (3). In addition to SIRS, several other definitions were proposed at the International Pediatric Sepsis Consensus Conference. For example, "*infection*" was defined as a suspected or proven infection (by positive culture, tissue stain, or polymerase chain reaction test) caused by any pathogen OR a clinical syndrome associated with a high probability of infection (1). Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid; perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans). "*Severe sepsis*" was defined as sepsis plus cardiovascular organ dysfunction *or* acute respiratory distress syndrome (ARDS) *or* two or more other organ dysfunctions. "*Septic shock*" was defined as sepsis and cardiovascular organ dysfunction as defined in the MODS diagnostic criteria. Sepsis may be caused by all forms of microbes including bacteria, viruses, protozoans and fungi. The most frequent causes of community- and hospital-acquired infection in the PICU are, in decreasing order: respiratory infections (37%), bacteremia (25%), urinary tract infections, intra-abdominal infections, soft tissues infections, central nervous system infections, endocarditis, fasciitis, etc. (4).

Of the many etiologies of MODS, the association between MODS and sepsis is perhaps the most studied in children, and it is important to understand that relationship (Figure 1). Although not all cases of MODS are caused by an infection, all severe infections can progress to MODS. Moreover, septic patients must receive antibiotics as soon as possible; even a delay as short as 30 minutes increases the risk of MODS and death (5). The

relationship between MODS and sepsis is exemplified by the cumulative effect on mortality of MODS severity and the septic state. Leclerc analyzed the cumulative influence of organ dysfunctions and the presence of sepsis on mortality using the PELOD score among 593 consecutive admissions of critically ill children to one of three PICUs (6). In that study, 514 patients had SIRS; 269 of whom had two or more organ dysfunctions (severe sepsis). The hazard ratio (HR) of death associated with SIRS or sepsis was similar (9.039), and was significantly higher than the risk of death in patients without SIRS or sepsis ($p = 0.031$). The SIRS/sepsis patients were grouped together for further analysis. The HR of death significantly increased with worsening of the diagnostic category of the septic state: 18.8 with severe sepsis ($p = 0.007$) and 32.6 with septic shock ($p < 0.001$). Additionally, each increase of one unit in the PELOD score multiplied the HR of each septic state by 1.096 ($p < 0.0001$). The formula that can be used to estimate the cumulative HR of death is: HR (death) = HR^{PELOD} × (HR septic state). For example, for children with severe sepsis and a PELOD score of 24, the HR of death = 169.7 as illustrated below:

$$\mathrm{HR}^{\mathrm{PELOD\ score}}=1.096^{24}=9.025;\ \mathrm{HR}_{\mathrm{severe\ sepsis}}=18.8,\ \mathrm{thus:}$$
$$\mathrm{HR\,(death)}=\mathrm{HR}^{\mathrm{PELOD}}\times(\mathrm{HR\,septic\,state})$$
$$\mathrm{HR\,(death)}=1.096^{24}\times 18.8$$
$$\mathrm{HR\,(death)}=9.025\times 18.8=169.7.$$

Thus, the description of the severity of illness is improved in critically ill children by consideration of both the severity of MODS and the status of the septic condition. The predictive value of this combined evaluation is better than the predictive value of MODS or septic state alone. Although these definitions of SIRS and sepsis are imperfect and likely to be soon revised for children, they add useful information.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a syndrome of inflammation and increased permeability in the lungs associated with a pattern of clinical, radiological, and physiological abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension (7). Although there are similarities in the pathophysiology of ARDS between adults and children, pediatric-specific practice patterns, comorbidities, and differences in outcome prompted the recent development of a pediatric-specific operational definition for ARDS by the Pediatric Acute Lung Injury Consensus Conference (PALICC) Group (Figure 2) (8). In pediatrics, the incidence and mortality of ARDS is lower than published rates for adults. Specifically, pediatric ARDS (PARDS) incidence ranges from 2–12.8 per 100,000 person-years while mortality rates span from 18–27% (9). However, despite these documented differences with adults, most of our knowledge related to PARDS is derived from studies in adult patients or in mature animals with very few studies performed in children or in young animal models (10). This void in pediatric-specific inquiry presents a problem because pulmonary and immune system maturation may impact the pathophysiology of PARDS and may be significantly different then what has been described in adult ARDS. Differences in the innate immunologic response to critical illness may account for the variation in the rate of multiple organ failure between critically ill

children and adults (11). These fundamental differences may impact the diagnosis, severity, and optimal therapeutic approach in the management of PARDS.

PARDS can be associated with MODS either as the precipitant of the other organ dysfunctions, or as an additional organ dysfunction incited by another trigger. Either way, MODS at the onset of PARDS is an important independent clinical risk factor for mortality in children (12–14). Moreover, as mortality from PARDS continues to decrease, rates of new or progressive organ system dysfunction and organ failure-free days have been recommended as alternative endpoints for clinical trials of PARDS (15).

Congenital Heart Disease/Cardiopulmonary Bypass

In the United States alone, there are approximately 400,000 cardiac surgical operations performed employing cardiopulmonary bypasses (CPB) each year, of which 10,000 are performed on children. In nearly all cases, cardiac surgical operations performed on children employing CPB induce ischemia with subsequent reperfusion injury resulting from the reinitiation of flow following circulatory arrest and removal of the cross clamp. These pathophysiologic processes not only cause injury themselves through myocardial necrosis, renal injury, and neurologic injury; they also activate a systemic inflammatory response characterized by multisystem organ dysfunction and failure. The sum total of these pathologic processes is postoperative morbidity and mortality that is significantly worse in the infant than compared to the adult (16). However, unlike other triggers associated with whole-body inflammatory reactions such as trauma or sepsis, cardiac surgical teams have the advantage of knowing when the trigger will occur (i.e., during CPB) and hence have an opportunity for preemptive intervention in an effort to attenuate or minimize the response.

The vast majority of patients undergoing congenital cardiac repair with bypass have some degree of MODS. Published reports indicate that this rate varies between 4 and 80% (17). If cardiac dysfunction is included, virtually all patients have MODS. However, the outcomes in this population are excellent. This raises the possibility that MODS following this type of injury is fundamentally different than that in other critical disease processes. It is possible that this population requires separate definitions of MODS.

The fact that the injury in this population is initiated through the necessity of performing a cardiac repair provides an opportunity to investigate the mechanisms involved. There are very few situations in which the timing of the injury can be controlled, and thus, it is incumbent upon investigators to leverage this factor. Certainly, there are challenges to such investigations including diverse baseline cardiac diseases and physiologic states, as well as unique bypass strategies, operative approaches, and anesthetic management. However, this represents an opportunity for not only study, but for also preemptive intervention. Current interventional approaches involve modulation of the inflammatory response including steroids and nitric oxide (16, 18–19). Moreover, such study also allows investigation into the roles of the multiple variables such as preoperative state and age. It is clear that cardiac injury and recovery from inflammation is affected by the age of the patient (20). This may be particularly true in the cardiac surgical patient. Within this particular population, we have

the opportunity to examine the response to injury and progression to MODS across the spectrum of age from the neonate to the 90-year-old patient receiving a valve replacement.

Additionally, there exists the potential to examine a single population, or even a single patient, across multiple surgical exposures and insults due to the requirement for several staged surgical palliative procedures throughout a lifetime. Moreover, since complex congenital cardiac disease is now considered a survivable disease, mortality is not an appropriate endpoint for investigations. Due to the extensive follow up inherent in this population, an opportunity for long-term endpoints exists. While MODS and critical cardiac disease have been traditionally thought of as an acute problem; the congenital heart disease population allows examination of the chronicity and long-term outcomes of MODS.

Cancer and antineoplastic therapies

Cancer has long been associated with multiple organ dysfunction (21,22). The organ dysfunction may not only be a result of the disease process and its associated co-morbidities such as sepsis, but may also emanate from the anti-neoplastic therapies. As innovative therapies emerge and are implemented for an ever-expanding list of high-risk patients and refractory disease processes, the ability to recognize and address adverse organ dysfunction in a prompt and effective manner will be necessary to optimize treatment outcomes. When organ dysfunction is associated with specific anti-neoplastic regimens, it is similar to congenital heart surgery with cardiopulmonary bypass, in that both represent scheduled interventions with a known propensity to incite organ injury. Clinical situations such as these in which the known insult can be anticipated would appear to foster greater opportunity for successful intervention.

Recently, after decades of investigation, effective methods of utilizing immune cells to recognize and eliminate cancer are becoming reality. Most notably, genetic engineering of autologous T-cells with chimeric antigen receptors (CARs) and T-cell receptors (TCRs) have resulted in unprecedented responses in children and adults with relapsed, refractory pre-B cell acute lymphoblastic leukemia (ALL) (23–25), synovial cell sarcoma or melanoma (26), respectively. However, this transformative therapy has also been reported to be associated with a pathophysiologic process known as the cytokine release syndrome.

Cytokine release syndrome (CRS) is a constellation of symptoms along a spectrum ranging from mild with only fever to severe with very high fever, rigors, headache, flushing, tachypnea, severe tachycardia, coagulopathy, hypoxia, pulmonary edema, hypotension requiring vasopressors, and/or respiratory failure (27). Severity of CRS appears related to overall tumor burden, and almost all patients who respond have some degree of CRS (23). Left unchecked, severe CRS will result in multiorgan failure typically beginning with the rapid development of biventricular cardiac dysfunction then failure, acute pulmonary edema resulting in hypoxemic respiratory failure, acute kidney injury at times requiring renal replacement therapy, hepatic dysfunction and severe coagulopathy. Neurotoxicities observed in CAR therapy for ALL appear to be related to CRS, but often present as an isolated phenomenon outside the context of typical multisystem CRS (23,25).

Activated CAR T-cells produce massive quantities of inflammatory cytokines such as interferon gamma (INF-γ), tumor necrosis factor alpha (TNF-α), and IL-2, which in turn activate other aspects of cellular immunity inducing robust production of IL-6 (27). IL-6 clearly drives the symptoms noted in CRS. Serum IL-6 levels in responding patients have been measured to be greater than 3000 pcg/mL (normal <10 pcg/mL) and the fever and hemodynamic instability reported in CRS can be reversed within hours of the administration of the anti-IL-6 receptor monoclonal antibody, tocilizumab (23–25, 27).

Clinical experience suggests that the timely administration of tocilizumab with or without corticosteroids to the patient with moderate-grade CRS is of paramount importance in preventing severe, life-threatening CRS characterized by multiple organ dysfunction although this has not been confirmed in phase II or III trials. This is one instance where MODS may actually be prevented. However, early recognition and treatment is critical as patients who have already progressed to organ failure are rarely rescued even with anti-cytokine therapy. Moreover, it will be important to assess if such an approach can be successful in other clinical conditions in which cytokine release drives multiple organ dysfunction.

Hematopoietic stem cell transplantation

Hematopoietic cell transplantation (HCT) is another anti-neoplastic therapy that has emerged over the past 25 years as the only curative therapy for children with a number of malignant, as well as nonmalignant, disorders of the blood and immune systems. In its more traditional mode, HCT recipients are treated with supra-lethal doses of anti-cancer therapy (chemo- and/or irradiation-therapy) and subsequently “rescued” by the infusion of hematopoietic stem cells. Despite significant advances in critical care and transplantation medicine, optimal outcomes following allogeneic HCT continue to be limited by the occurrence of organ dysfunction as the result of the development of acute graft-versus-host disease (GVHD), acute pulmonary dysfunction, thrombotic microangiopathy and veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) of the liver.

GVHD describes a disease process wherein immune cells in the donor stem cell “graft” respond to foreign antigens in the “host”. Immunologic dysregulation occurring after allogeneic-HCT contributes to GVHD. However, donor T-cell activation also enhances the therapeutic potential of HCT through powerful graft versus tumor effects that persist long after the chemo- and irradiation-therapy effects have passed. The pathophysiology of acute GVHD is complex (28–30). Immune dysregulation can be conceptualized in three distinct phases (29) and involves diffuse damage and activation of host tissues by HCT conditioning regimens (**Phase 1**), the activation of donor T-cells by host antigen presenting cells (**Phase 2**) and the culmination of target organ damage by soluble and cellular effectors (**Phase 3**). While components of this paradigm have been challenged and refined (30), the hypothesis identifies areas where novel agents can be explored. The onset of acute GVHD typically occurs within the first two months after allogeneic HCT, and the classic target organs include the gastrointestinal tract, liver, and skin. Historically, the incidence and severity of GVHD has correlated with donor type (related vs. unrelated) and the degree of antigenic disparity between donor and host. Advanced (grade 3 to 4) GVHD remains life-threatening

and often times requires critical care support to manage direct (organ dysfunction) and indirect (opportunistic infection) manifestations of disease.

Pulmonary complications in a variety of forms occur in 25% to 55% of HCT recipients and can account for approximately 40% of transplant-related mortality. Historically, approximately 50% of cases were determined to be noninfectious in origin, but the judicious use of broad-spectrum antimicrobial prophylaxis in recent years has tipped the balance of pulmonary complications from infectious to non-infectious causes (31). The idiopathic pneumonia syndrome (IPS) refers to noninfectious lung injury that occurs acutely within the first 120 days following HCT (31–34). Diagnostic criteria of IPS include signs and symptoms of pneumonia, non-lobar radiographic infiltrates, abnormal pulmonary function and the absence of infectious organisms as determined by broncho-alveolar lavage (BAL) or lung biopsy. IPS has been a frequently fatal complication of HCT, associated with mortality rates in excess of 70% with a median time from diagnosis to death of only 2 weeks (31–34). Potential etiologies for IPS include direct toxic effects of HCT conditioning regimens, occult pulmonary infections, and the release of inflammatory cytokines that have been implicated in other forms of pulmonary injury (31). Clinically, the diagnosis of IPS has been linked to the development of acute GVHD. Although this association suggests the importance of alloreactivity to lung injury that occurs after HCT, a causal relationship between IPS and GVHD has yet to be firmly established.

Clinical syndromes presenting with microangiopathic hemolytic anemia, consumptive thrombocytopenia, and often with renal insufficiency and encephalopathy, have long been recognized as potentially devastating multisystem complications after HCT (35). While several terms have been used in the literature to describe these microangiopathic processes, transplant-associated thrombotic microangiopathy (TA-TMA) is now widely accepted as an umbrella term to cover these disorders (36). The diagnosis of TA-TMA is based on clinical criteria and the classic presentation which includes the relatively acute onset of anemia and thrombocytopenia with evidence of RBC fragmentation in the peripheral blood smear (37). Concomitant acute renal dysfunction, often associated with proteinuria and hypertension, occurs in the majority of patients, and neurologic deficits, including but not restricted to confusion and seizures, are also commonly observed. The onset of TA-TMA usually occurs within the first 100 days after HCT, and the median time of onset ranged from 44 to 67 days in two large retrospective reports (38,39). TA-TMA occurs less frequently after autologous HCT (up to 2.6%) compared to the allogeneic setting where the incidence is in the 10–15% range and even higher in some recent pediatric reports given the close association of TA-TMA with calcineurin inhibitors, GVHD and infections (38,40). Recognizing the need to standardize definitions for toxicity reporting in multi-center clinical trials and to facilitate future clinical investigative efforts, U.S. and European working groups have recently proposed specific sets of clinical criteria for reporting TA-TMA (39,41).

The primary inciting events leading to the development of TA-TMA remain poorly understood, but evidence suggests that damage to the vascular endothelium is central to its pathogenesis and may represent a common thread underlying several of the other post-transplant complications (37). In this context, TA-TMA is now believed to be a multi-visceral disorder and should be included in the differential diagnosis of usual HCT

complications (36). For example, pulmonary TMA presenting as pulmonary hypertension should be considered in patients with respiratory failure (42,43). Recent reports have also found that TMA can affect the intestinal tract and present with abdominal pain and bloody diarrhea, thereby imitating enteric GVHD or infectious colitis (44,45). The diagnosis of intestinal TMA relies primarily on histopathologic evaluation demonstrating hyaline thrombi in the capillaries of intestinal biopsies, or the presence of thrombonecrotic arteriolar lesions in the intestine on autopsy (44,45). Recent reports have revealed that activation and dysregulation of the complement alternative pathway may be a major contributor to endothelial damage incurred during TA-TMA (46,47). These findings are significant as they may identify a genetic susceptibility for disease development and ultimately guide the institution of novel treatment strategies to improve outcomes.

Approximately 12–18% of patients with TA-TMA will have severe disease affecting their outcome. Proteinuria and activated terminal complement at TA-TMA diagnosis are very poor prognostic markers and prompt clinical interventions should be considered (40). Unfortunately, there is currently no standard treatment for TA-TMA, but there is consensus that rapid withdrawal of potential offending drugs such as calcineurin inhibitors or sirolimus should be the primary intervention. Aggressive management of concurrent GVHD and infections is crucial since these are common causes of mortality in patients with TA-TMA. While often used, plasma exchange (PE) has demonstrated limited efficacy and has not been endorsed as a standard treatment; response rates are generally less than 50%, and mortality rates among patients treated with PE remain unacceptably high (41). Early implementation of PE in pediatric patients may rescue some patients with renal failure, but outcomes remain poor (48). The fact that TA-TMA results from direct injury to endothelial cells and not from circulating antibody may explain the low response rates to plasma exchange and supports the use of other agents that inhibit complement (ecluzimab) (49) or stabilize vascular endothelial integrity and function (50) to improve outcomes. VOD/SOS is recognized as another complication associated with high dose chemotherapy and HCT that may result in multiorgan dysfunction. It results from direct injury to sinusoidal endothelium, hepatocytes, and the central venules in zone 3 of the liver acinus that ultimately progresses to veno-occlusion and sinusoidal obstruction (51–54).

VOD/SOS is characterized clinically by painful hepatomegaly, jaundice, and fluid retention as manifested by weight gain and ascites that typically occurs within 30 days of HCT. The clinical diagnosis of VOD/SOS is based on the classical triad of weight gain, painful hepatomegaly, and jaundice as characterized by the Seattle (51) and Baltimore (55) transplant groups. Making the diagnosis of VOD/SOS can be challenging because the signs and symptoms of this condition often overlap those of other processes (54). In this context, the time of onset is often useful in narrowing the differential diagnosis. The severity of VOD/SOS ranges from mild to severe depending upon the degree of hyperbilirubinemia, the amount of fluid retention and the pace of disease progression (56–58). When associated with MODS, specifically involving pulmonary and renal impairment, VOD/SOS has historically been associated with unacceptably high mortality rates that approach 100% despite advances in mechanical ventilation and continuous renal replacement therapy (54,58).

Optimization of care in the immediate post-HCT period and minimization of potential organ dysfunction is essential for successful outcomes as the degree of MODS has clearly been associated with survival in the HCT population (21,59). Indeed, the development of novel strategies that reduce transplant-related toxicity, regulate GVHD, preserve graft versus tumor effects, and facilitate engraftment and long-term immune reconstitution remains the most significant challenge to broadening the scope of allogeneic HCT. The development of novel therapies to treat and prevent acute GVHD, translational research efforts underscoring a critical role for TNF inhibitors in the management of IPS (60,61), and the introduction of an endothelial stabilizing agent (defibrotide) for the management of hepatic VOD/SOS (62,63) have represented major advances in the field. These breakthroughs in combination with the discovery of biomarkers that may predict the development, severity and response to therapy of these complications (64–67) are being considered in the development of rationally designed, translational research trials aimed at identifying patients at risk, limiting the occurrence of MODS and improving patient outcomes after allogeneic HCT.

Conclusions

In summary, there are a number of medical conditions and therapeutic interventions that are associated with multiorgan dysfunction and the MODS. The intent of this manuscript, as with the accompanying manuscript, is to highlight a handful of those conditions and therapies in an attempt to identify areas of commonality, areas of difference, and opportunities for further study and intervention; it was not to present an exhaustive list of the many etiologies that may result in MODS. It is hoped that by considering this syndrome in relation to a number of disparate conditions, investigators may gain new insight and avenues for study that will advance our understanding of this process from that of a syndrome (i.e simply, a collection of related symptoms), to a well-defined clinical entity with established pathophysiologic causes, genetic predispositions and targeted therapies.

Acknowledgments

Support: National Heart, Lung, and Blood Institute and the National Institute of Nursing Research, National Institutes of Health (U01 HL086622 Dr. Curley); St. Baldrick's Foundation Scholar Award with generous support from the Hope From Harper Fund (Dr. Lee).

We thank the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and their Office of Science Policy, Analysis and Communications for their support of this Workshop.

References

1. Goldstein B, Giroir B, Randolph A. the International Concensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005; 6:2–8. [PubMed: 15636651]
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315:801–810. [PubMed: 26903338]
3. Juskewitch JE, Prasad S, Salas CF, Huskins WC. Reliability of the identification of the systemic inflammatory response syndrome in critically ill infants and children. Pediatr Crit Care Med. 2012; 13:e55–57. [PubMed: 21926661]
4. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med. 2003; 167:695–701. [PubMed: 12433670]

5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34:1589–1596. [PubMed: 16625125]
6. Leclerc F, Leteurtre S, Duhamel A, et al. Cumulative influence of multiple organ dysfunction syndrome and septic state on mortality of critically ill children. Am J Respir Crit Care Med. 2005; 171:348–353. [PubMed: 15516535]
7. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994; 149:818–824. [PubMed: 7509706]
8. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015; 16:428–439. [PubMed: 25647235]
9. Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015; 16:S23–S40. [PubMed: 26035358]
10. Sapru A, Flori H, Quasney MW, Dahmer MK. for the Pediatric Acute Lung Injury Consensus Conference Grou. Pathobiology of Acute Respiratory Distress Syndrome. Pediatr Crit Care Med. 2015; 16:S6–S22. [PubMed: 26035365]
11. Wood JH, Partrick DA, Johnston RB Jr. The inflammatory response to injury in children. Curr Opin Pediatr. 2010; 22:315–320. [PubMed: 20386451]
12. Flori H, Dahmer MK, Sapru A, Quasney MW. Pediatric Acute Lung Injury Consensus Conference Group. Comorbidities and assessment of severity of pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015; 16:S41–S50. [PubMed: 26035363]
13. López-Fernández Y, Azagra AM, de la Oliva P, et al. Pediatric Acute Lung Injury Epidemiology and Natural History (PED-ALIEN) Network. Pediatric Acute Lung Injury Epidemiology and Natural History study: Incidence and outcome of the acute respiratory distress syndrome in children. Crit Care Med. 2012; 40:3238–3245. [PubMed: 22990455]
14. Leclerc F, Duhamel A, Deken V, Le Reun C, Lacroix J, Leteurtre S. Groupe Francophone de Reanimation et d'Urgences Pediatriques. Nonrespiratory pediatric logistic organ dysfunction-2 score is a good predictor of mortality in children with acute respiratory failure. Pediatr Crit Care Med. 2014; 15:590–593. [PubMed: 24977439]
15. Quasney MW, López-Fernández YM, Santschi M, Watson RS. Pediatric Acute Lung Injury Consensus Conference Group. The outcomes of children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015; 16:S118–S131. [PubMed: 26035362]
16. Checchia PA, Gandhi SK. Defining vasodilatory shock following cardiac surgery in children: when, where, how often? Pediatr Crit Care Med. 2009; 10:409–410. [PubMed: 19433948]
17. Taggart DP, Hadjinikolas L, Hooper J, et al. Effects of age and ischemic times on biochemical evidence of myocardial injury after pediatric cardiac operations. J Thorac Cardiovasc Surg. 1997; 113:728–735. [PubMed: 9104982]
18. Checchia PA, Backer CL, Bronicki RA, et al. Dexamethasone reduces postoperative troponin levels in children undergoing cardiopulmonary bypass. Crit Care Med. 2003; 31:1742–1745. [PubMed: 12794414]
19. Checchia PA, Bronicki RA, Muenzer JT, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children--a randomized trial. J Thorac Cardiovasc Surg. 2013; 146:530–536. [PubMed: 23228403]
20. Checchia PA, Schierding W, Polpitiya A, et al. Myocardial transcriptional profiles in a murine model of sepsis: evidence for the importance of age. Pediatr Crit Care Med. 2008; 9:530–535. [PubMed: 18679145]
21. Dursun O, Hazar V, Karasu GT, Uygun V, Tosun O, Yesilipek A. Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. J Pediatr Hematol Oncol. 2009; 31:481–484. [PubMed: 19564740]

22. Fiser RT, West NK, Bush AJ, Sillos EM, Schmidt JE, Tamburro RF. Outcome of severe sepsis in pediatric oncology patients. Pediatr Crit Care Med. 2005; 6:531–536. [PubMed: 16148811]
23. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015; 385:517–528. [PubMed: 25319501]
24. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014; 371:1507–1517. [PubMed: 25317870]
25. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19–28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014; 6:224ra25.
26. Robbins PF, Kassim SH, Tran TL, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. Clin Cancer Res. 2015; 21:1019–1027. [PubMed: 25538264]
27. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014; 124:188–195. [PubMed: 24876563]
28. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol. 2012; 12:443–458. [PubMed: 22576252]
29. Ferrara, JL., Cooke, KR., Teshima, T. The Pathophysiology of Graft-vs-Host Disease. In: FerraraCooke, Degg, editors. Graft-vs-Host Disease. 3. New York: Marcel Dekker, Inc; 2005. p. 1-34.
30. Shlomchik WD. Graft-versus-host disease. Nat Rev Immunol. 2007; 7:340–352. [PubMed: 17438575]
31. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. American Thoracic Society Committee on Idiopathic Pneumonia Syndrome. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med. 2011; 183:1262–1279. [PubMed: 21531955]
32. Clark JG, Hansen JA, Hertz MI, Parkman R, Jensen L, Peavy HH. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. Am Rev Respir Dis. 1993; 147:1601–1606. [PubMed: 8503576]
33. Crawford SW, Hackman RC. Clinical course of idiopathic pneumonia after bone marrow transplantation. Am Rev Respir Dis. 1993; 147:1393–1400. [PubMed: 8503550]
34. Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. Transplantation. 1997; 63:1079–1086. [PubMed: 9133468]
35. Cooke KR, Jannin A, Ho V. The contribution of endothelial activation and injury to end-organ toxicity following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2008; 14:23–32.
36. Jodele S, Laskin BL, Dandoy CE, et al. A new paradigm: Diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. Blood Rev. 2015; 29:191–204. [PubMed: 25483393]
37. Fuge R, Bird JM, Fraser A, et al. The clinical features, risk factors and outcome of thrombotic thrombocytopenic purpura occurring after bone marrow transplantation. Br J Haematol. 2001; 113:58–64. [PubMed: 11328282]
38. George JN, Li X, McMinn JR, Terrell DR, Vesely SK, Selby GB. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. Transfusion. 2004; 44:294–304. [PubMed: 14962323]
39. Ruutu T, Barosi G, Benjamin RJ, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica. 2007; 92:95–100. [PubMed: 17229640]
40. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood. 2014; 124:645–653. [PubMed: 24876561]
41. Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2005; 11:571–575. [PubMed: 16041306]

42. Dandoy CE, Hirsch R, Chima R, Davies SM, Jodele S. Pulmonary hypertension after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2013; 19:1546–1556. [PubMed: 23891748]
43. Jodele S, Hirsch R, Laskin B, Davies S, Witte D, Chima R. Pulmonary arterial hypertension in pediatric patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Biol Blood Marrow Transplant. 2013; 19:202–207. [PubMed: 22960385]
44. Nishida T, Hamaguchi M, Hirabayashi N, et al. Intestinal thrombotic microangiopathy after allogeneic bone marrow transplantation: a clinical imitator of acute enteric graft-versus-host disease. Bone Marrow Transplant. 2004; 33:1143–1150. [PubMed: 15077133]
45. El-Bietar J, Warren M, Dandoy C, et al. Histologic Features of Intestinal Thrombotic Microangiopathy in Pediatric and Young Adult Patients after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2015; 21:1994–2001. [PubMed: 26150023]
46. Jodele S, Licht C, Goebel J, et al. Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Blood. 2013; 122:2003–2007. [PubMed: 23814021]
47. Jodele S, Zhang K, Zou F, et al. The genetic fingerprint of susceptibility for transplant associated thrombotic microangiopathy. Blood. 2016; 127:989–996. [PubMed: 26603840]
48. Jodele S, Laskin BL, Goebel J, et al. Does early initiation of therapeutic plasma exchange improve outcome in pediatric stem cell transplant-associated thrombotic microangiopathy? Transfusion. 2013; 53:661–667. [PubMed: 22804695]
49. Jodele S, Fukuda T, Vinks A, et al. Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow Transplant. 2014; 20:518–525. [PubMed: 24370861]
50. Corti P, Uderzo C, Tagliabue A, et al. Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. Bone Marrow Transplant. 2002; 29:542–543. [PubMed: 11960280]
51. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984; 4:116–122. [PubMed: 6363247]
52. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med. 1993; 118:255–267. [PubMed: 8420443]
53. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. Blood. 1995; 85:3005–3020. [PubMed: 7756636]
54. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transpl. 2010; 16:157–168.
55. Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation. 1987; 44:778–783. [PubMed: 3321587]
56. Blostein MD, Paltiel OB, Thibault A, Rybka WB. A comparison of clinical criteria for the diagnosis of veno-occlusive disease of the liver after bone marrow transplantation. Bone Marrow Transplant. 1992; 10:439–443. [PubMed: 1464007]
57. Bearman SI, Anderson GL, Mori M, Hinds MS, Shulman HM, McDonald GB. Veno-occlusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. J Clin Oncol. 1993; 11:1729–1736. [PubMed: 8355040]
58. Carreras E. How I manage sinusoidal obstruction syndrome after hematopoietic cell transplantation. Brit J Hematol. 2015; 168:481–491.
59. Tamburro RF, Barfield RC, Shaffer ML, 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; 9:270–277. [PubMed: 18446105]
60. Yanik GA, Grupp SA, Pulsipher MA, et al. TNF-receptor inhibitor therapy for the treatment of children with idiopathic puenmonia syndrome. A joint Pediatric Blood and Marrow Transplant Consortium and Children's Oncology Group Study (ASCT0521). Biol Blood Marrow Transplant. 2015; 21:67–73. [PubMed: 25270958]

61. Klein O, Cooke KR. Idiopathic Pneumonia Syndrome Following Hematopoietic Stem Cell Transplantation. J Ped Intensive Care. 2014; 3:147–157.

62. Richardson PG, Ho VT, Giralt S, et al. Safety and efficacy of defibrotide for the treatment of severe hepatic severe hepatic veno-occlusive disease. Ther Adv Hematol. 2012; 3:253–265. [PubMed: 23606935]

63. Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in pediatric hematopoietic stem cell transplantion: an open-label, phase 3, randomized controlled trial. Lancet. 2012; 379:1301–1309. [PubMed: 22364685]

64. Schlatzer D, Dazard JE, Ewing RM, et al. Human plasma biomarker discovery to expand the disease pathway of idiopathic pneumonia syndrome following allogeneic stem cell transplantation. Mol and Cell Proteomics. 2012; 11 M111.015479.

65. Paczesny S, Krijanovski OI, Braun TM, et al. A biomarker panel for acute graft-versus-host disease. Blood. 2009; 113:273–278. [PubMed: 18832652]

66. Vander Lugt MT, Braun TM, Hanash S, et al. ST2 as a marker for risk of therapy-resistant graft-verus-host disease and death. N Eng J Med. 2013; 369:529–539.

67. Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host-disease based upon biomarkers: a multicenter study. Lancet Hematol. 2015; 2:e21–e29.

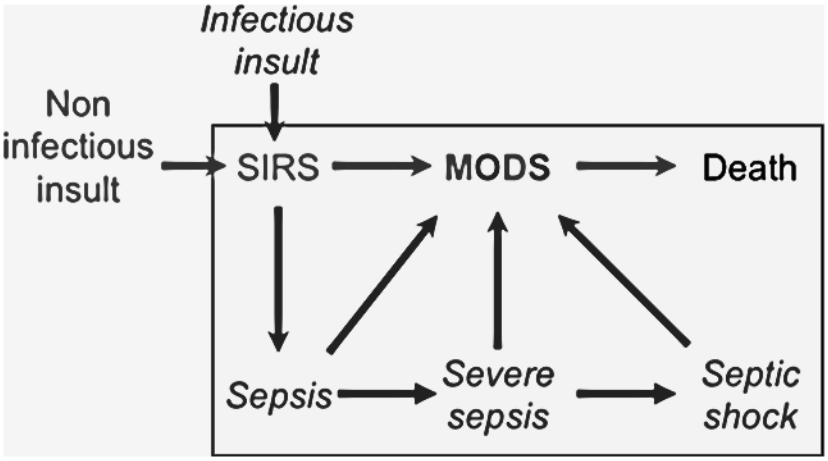

Figure 1.
Relationship between the systemic inflammatory response syndrome (SIRS), the multiple organ dysfunction syndrome (MODS) and three septic states (sepsis, severe sepsis and septic shock).

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Figure 2. Pediatric Acute Respiratory Distress Definition

[1]Use PaO_2-based metric when available. If PaO_2 is not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate the SpO_2/FiO_2 (SF) ratio or the oxygen saturation index (OSI) where

$$\mathrm{OSI}=\frac{(\mathrm{FiO_2}\times \text{mean airway pressure}\times 100)}{\mathrm{SpO_{2.}}}$$

[2] Non-intubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation are categorized using the “at-risk” definition.

[3]Acute respiratory distress syndrome severity stratification based on OSI or oxygenation index (OI) where

$$\mathrm{OI}=\frac{(\mathrm{FiO_2}\times \text{mean airway pressure}\times 100)}{\mathrm{SpO_2}}$$

should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease.

CPAP = continuous positive airway pressure, PF = PaO_2/FiO_2.

Taken from: Khemani RG, Smith LS, Zimmerman JJ, Erickson S; Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16:428–439 (Figure 2).

Table

Identified Knowledge Gaps and Potential Opportunities for Study

- An enhanced understanding of the sepsis pathophysiology that drives multiple organ dysfunction (MODS) needs to be better established and potential therapeutic targets need to be identified.
- A better understanding of the influence that pulmonary and immune system maturation have on the pathophysiology of acute respiratory distress syndrome (ARDS) needs to be established with an attempt to explain the differences between children and adults in terms of outcomes and the occurrence of MODS associated with ARDS.
- The impact of age on the occurrence of MODS following cardiac surgery and cardiopulmonary bypass needs to be better established. Moreover, similarities and differences between MODS in the setting of cardiac repair and other etiologies such as sepsis and trauma need to be elucidated; such study may improve outcomes in each of these settings.
- Established triggers of MODS with well-defined timelines such as cardiopulmonary bypass and anti-neoplastic therapy need to be used as models for studying MODS. The conditions associated with these interventions such as congenital heart and cancer represent opportunities for long-term follow up of MODS and the impact of multiple insults.
- The role of anti-cytokine therapy in conditions associated with MODS needs to be determined. However, to do so, mediating biomarkers must first be identified that can be assessed in a clinically relevant time frame as has been accomplished for the cytokine release syndrome.
- Mortality among pediatric hematopoietic stem cell patients remains unacceptably high and there is a clear association of mortality with MODS in this patient population. In order to advance this field, early predictors of patient at risk need to be identified. The development of novel strategies that reduce transplant-related toxicity in combination with the discovery of biomarkers that may predict the development, severity and response to therapy of these complications must be further established.