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Specific etiologies associated with the multiple organ dysfunction syndrome in children: Part 2

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Abstract

Objective—To describe a number of conditions and therapies associated with multiple organ dysfunction syndrome (MODS) presented as part of the *Eunice Kennedy Shriver* National Institute

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of Child Health and Human Development MODS Workshop (March 26–27, 2015). In addition, the relationship between burn injuries and MODS is also included although it was not discussed at the Workshop.

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 and therapies 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—Sepsis and trauma are the two conditions most commonly associated with MODS both in children and adults. However, many other pathophysiologic processes may result in MODS. In this paper, we discuss conditions such as liver failure and pancreatitis, pathophysiologic processes such as ischemia and hypoxia, and injuries such as trauma and burns. Additionally, therapeutic interventions such as medications, blood transfusions, transplantation may also precipitate and contribute to MODS. The purpose of this manuscript is to describe the association of MODS with a variety of conditions and therapies in an attempt to identify similarities, differences and opportunities for therapeutic intervention.

Keywords

Multiple organ dysfunction syndrome; pancreatitis; liver failure; solid organ transplant; cirrhosis; burns; trauma; transfusion; pediatrics

Introduction

There are a number of pathophysiologic processes that may result in the multiple organ dysfunction syndrome (MODS) in children. To begin, underlying diagnoses such as cancer and congenital heart disease as described in Part 1 of this manuscript, as well as inborn errors of metabolism, rheumatologic diseases and various others have 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 insults and rheumatologic disorders are not addressed in this, or its accompanying manuscript. The available literature contains a host of publications and reviews addressing these individual topics and their association with MODS. The purpose of this manuscript, in

conjunction with Part 1, 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 other disciplines, and identify opportunities for future study.

Hepatic failure/Solid organ transplantation

MODS is a critical problem for patients who receive solid organ transplantation, as well as those with disease processes that put them at risk for requiring a transplant such as acute and chronic liver failure. As with other causes of MODS, disordered regulation of the immune system and endothelial dysfunction play a central role in these processes. Consequently, an understanding of the clinical phenotypes and/or mechanisms of injury associated with MODS in patients with acute and/or chronic liver failure or in solid organ transplant recipients may help inform MODS in other disease processes.

Cirrhosis

In cirrhosis, vasodilatation occurs in the systemic vasculature and in the splanchnic vascular bed in response to liver fibrosis as portal hypertension results in poor clearance of vasoactive peptides which promotes endothelial dysfunction. This endothelial dysfunction, in turn, decreases afterload and promotes excessive myocardial contractility. As a result, systolic function is not only disproportionately high, but diastolic function, or relaxation becomes compromised (1,2). Such alterations in cardiac function may be clinically silent, until made evident by intercurrent stress. Moreover, dilatation of the pulmonary vasculature in cirrhosis may result in hepatopulmonary syndrome secondary to right to left shunting of blood through pulmonary angiomas. Further, the renin-angiotensin-aldosterone system is activated in response to the dilatation of the systemic vascular bed resulting in the release of vasopressin and an increased risk for hepatorenal syndromes Type I and II. Each of the pulmonary and renal changes is associated with pre-transplant morbidity and justifies Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) exception points. In the end, all changes directly or indirectly reflect altered endothelial function.

Acute on Chronic Liver Failure

Acute decompensation of cirrhosis versus acute on chronic liver failure (ACLF) is distinguished by the presence of organ failure (1,3,4). In the former, increased fibrosis and portal hypertension is associated with vasodilatation and complications of portal hypertension. With acute on chronic liver failure, bacterial translocation across the intestine occurs in the setting of decreased immune surveillance of the innate and adaptive immune systems. This bacterial infection is associated with worsening systemic hemodynamics and MODS. Transplant free mortality is increased 5-fold in adults with ACLF (51%, 90-day mortality) compared to acute decompensation of cirrhosis (10%, 90-day mortality). The number of organ failures is directly related to the risk of mortality and disease severity tools for liver disease (i.e. MELD, PELD) do not accurately reflect risk.

Acute Liver Failure

Acute liver failure is a devastating condition which may commonly be associated with MODS including renal, bone marrow and central nervous system failure (4). The primary etiology is not established in almost 50% of children (5). Liver transplantation can serve as directed therapy for patients with acute liver failure when treatment fails to rescue the patient from clinical deterioration. While liver transplantation may be life-saving, the decision to proceed with transplantation is irreversible and has profound consequences, both on organ allocation and on long term challenges faced by the patient and family. Patients who receive transplantation for pediatric acute liver failure have increased short-term and long-term mortality risk compared to those with chronic liver disease. Death in the immediate post-transplant period is usually attributed to MODS, sepsis, or cerebral edema. Patients with indeterminate acute liver failure have excess late mortality risk most commonly related to sepsis; they are also at increased risk for developing aplastic anemia.

As part of the pediatric acute liver failure effort (U01 DK072146 Squires), markers of immune activation were measured in 77 children with acute liver failure (6). The normalized serum sIL2Rα level was higher in patients who died ($p=0.02$) or underwent liver transplant ($p=0.01$) compared to those who survived with native liver (7). Of the 15 subjects with markedly high sIL2Rα levels (≥5000 IU/mL), 5 survived with their native liver, 2 died, and 8 underwent liver transplant (7). The investigators subsequently analyzed serum inflammatory mediators and found that liver transplant recipients had a biomarker pattern more similar to spontaneous survivors than those of non-survivors (8). If confirmed, such findings might allow for the use of immunomodulatory therapy to improve outcomes and potentially decrease the use of liver transplants (Table).

Solid Organ Transplantation

Thrombotic microangiopathy (TMA), recognized as a cause of morbidity and mortality in stem cell transplant recipients (see Part 1), is increasingly detected in solid organ transplant recipients (9,10). TMA results from dysregulation of complement activation. With solid organ transplant recipients, endothelial injury and microangiopathy are likely multifactorial reflecting ischemia reperfusion injury associated with transplant, infections, inherited or acquired complement dysregulation and injury from exposure to medications such as calcineurin inhibitors. As a result of uncontrolled complement activation, patients with TMA have hemolytic anemia, pulmonary hypertension and renal insufficiency with evidence of gastrointestinal and central nervous system injury. The risk of death is related to the number of involved organs. Early data suggest that blockage of terminal steps in complement activation with ecluzimab may mitigate injury (11).

Summary

MODS is a critical problem with acute and chronic liver failure and for those who receive solid organ transplant. It appears that immune dysregulation and endothelial dysfunction play a central role in the pathogenesis of MODS. Current disease stratification tools are inadequate, and therefore, we cannot effectively predict which patients are at risk or how risk evolves over time. Understanding the pathobiology, and the development of risk stratification tools using molecular and computational techniques would guide risk

stratification, permit trials targeted to mitigate injury, improve organ allocation and decrease mortality.

Pancreatitis

In addition to liver disease, other disease processes of the gastrointestinal tract may be associated with MODS. For example, there has been a rising trend in the number of patients presenting with acute pancreatitis in the past decade (12). With this increase, there has also been an increase in the number of patients who are developing MODS in the setting of acute pancreatitis. However, the reasons that drive a sub-population of patients with pancreatitis to develop MODS and the process by which acute pancreatitis transitions to MODS are not well understood (Table). Some experts are unsure whether pancreatitis is a primary driver or a byproduct of MODS.

In recent years, the pathophysiology of pancreatitis has been the focus of multiple laboratories throughout the world. Still, the molecular details of the events that lead to pancreatitis remain uncertain. A number of hypotheses have been offered (12–14). Many center on the premature activation of trypsinogen within the acinar cell. Other models invoke excessive activation of the unfolded protein response, which results in activation of cell-death pathways. In each case, the damage to acinar cells triggers an inflammatory response and the release of digestive enzymes into the circulation.

Some experts speculate that the increased levels of pancreatic digestive enzymes in the bloodstream may lead to an imbalance in cytokines resulting in MODS (12,15). Others propose that MODS develops as a result of a robust local inflammatory response (15). Still others suggest that MODS occurs primarily in the setting of infected pancreatic necrosis and sepsis (16). Regardless of the trigger, patients with MODS present with a systemic inflammatory response syndrome (SIRS) and/or a compensatory anti-inflammatory response syndrome (CARS) (14,17). In the case of SIRS, there is an activation of the vascular endothelium, neutrophils, and biological defenses, which results in early-phase complications and morbidity, eventually resulting in the occurrence of MODS (13). In CARS, there is an excessive anti-inflammatory response and compromised immune function, which leads to late-phase complications such as infected pancreatic necrosis and abscess formation. The data supporting these models are sparse. It is important to gain a better understanding of the pathophysiological changes at the level of the pancreas that incite the downstream effects that culminate in MODS.

In addition, there would appear to be an immediate need for the validation in children of criteria used in adults to diagnose acute pancreatitis including prospective studies that standardize etiological classifications (12,17). Additionally, multicenter studies on the natural history of this disease in children would also appear needed in order to understand factors predicting disease severity and complications (12). Finally, it would seem important for a better understanding of the molecular details of acute pancreatitis to be attained (Table). The development of better research models, particularly to elucidate the mechanisms of genetic risk factors, would seem essential to facilitating such an understanding.

Acute Kidney Injury

Acute kidney injury (AKI) occurs between 20–60% of children and neonates admitted to critical care units (18). This wide range likely reflects, to some degree, the variability in definitions used to identify and diagnose AKI. Over the past decade, the use of the RIFLE, pRIFLE, AKIN and KDIGO guidelines have been created to give a more definitive ranking of the degree of AKI based on a rising serum creatinine level and/or diminishing urine output (19). Additionally, biomarkers (e.g. NGAL, KIM1, IL-18) are being used as research tools to identify “subclinical” AKI (20). Prior to these various tools, the literature based definition of AKI was often simply the need for renal replacement therapy (RRT) (21). Data suggest that the need for RRT is associated with a greater risk of death (22). In fact, the presence of AKI is associated with increased mortality in children; recent data reveal that early AKI is associated with a seven-fold increase in mortality (23). Among children with acute decompensated heart failure, the presence of worsening renal function (defined as a serum creatinine increase ≥ 0.3 mg/dL) was associated with a ten-fold increase in the combined endpoint of either death or the need for mechanical circulatory support (24). Among children with sepsis and MODS, the development of AKI is a discouraging prognostic sign (25)

As with other organ injuries, AKI may be the precipitant of MODS or one of the organs injured as part of the syndrome. Not surprisingly, the presence of MODS has been associated with increased mortality among children who receive continuous RRT (CRRT) for any indication (26). The use of CRRT associated with MODS is frequently in the setting of sepsis. In the Surviving Sepsis Management Guidelines, CRRT is suggested to facilitate fluid management in hemodynamically unstable septic patients, and specifically for children, to prevent ≥ 10% fluid overload (27). The indication for CRRT commencement in this setting is often for hypermetabolic syndrome associated with fluid overload. In this clinical condition, CRRT may facilitate effective fluid management removing sufficient fluid to prevent symptomatic overload and allowing for the provision of adequate nutrition and necessary medications. Temperature control is also effectively achieved and maintained with the use of CRRT. Although the true benefit of CRRT in this setting remains to be clearly established, some data suggest benefit with its use among children with multiple organ failure (28). A miniaturized Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM®) has been developed and published case reports suggest its benefit in neonates with MODS (29,30).

Burn patients

In addition to medical conditions, MODS has also been associated with a host of external injuries including multiple trauma patients and burn victims. Although not discussed as a separate topic at the Workshop, this section is included given the prevalence of burn injuries in children and their association with MODS. For example, a recent, relatively large single center trial reported MODS to occur in 19% of children with a burn area that encompassed at least 30% of the body surface area (31). Moreover, pediatric burn patients represent a unique group with a profound and poorly understood dysfunctional immune, metabolic, and catabolic response commensurate to the original size of the thermal injury (32).

Physiologically, the post burn response is manifested by metabolic rates well above normal, increased cardiac work, muscle protein catabolism, profound lipolysis, insulin resistance and liver dysfunction (33). Virtually every organ system is affected by major burn injury with perturbations mediated by surges in catecholamines, cortisol, glucagon and pro- and anti-inflammatory cytokines (33). In one study, MODS was found to be associated with the size of the burn, full thickness burns, and an associated inhalational injury. Not surprisingly, the occurrence of MODS was associated with a longer length of ICU stay, a greater number of major infections, and a substantially higher mortality.

Research over the last fifty years has focused on defining the clinical challenges encountered from the onset of thermal injury: the resuscitation, the acute hospitalization, and the rehabilitation. Encouragingly, substantial gains in the understanding of the clinical response have resulted in improvements in morbidity and mortality. Current standards of care underscore these advances and awareness: early excision and grafting, early enteral nutrition, and environmental thermoregulation (33). As knowledge is gained and care informed, new and deeper questions arise that must be addressed. For example, the hyperdynamic metabolic and catabolic response associated with major pediatric burn clearly contributes to the risk of MODS (Table). To address these concerns and attenuate the pervasive growth retardation after severe burns, early enteral nutrition, based on metabolic carts has become standard (33). Other strategies, such as increased ambient temperatures in the operating and hospital room successfully limit metabolic rates and substantially improve gains associated with early enteral nutrition (33). However, as composition of standard tube feedings change, maintaining the balance between increasing lean body mass versus fat gain has been a challenge. It is not definitively established whether supplementation with arginine, high dose glutamine, or other amino acids will benefit this patient population (34).

Additionally, propranolol administration during acute hospitalization has been found to mitigate the marked tachycardia and increased cardiac work observed in severely burned children (35–43). Benefits associated with propranolol use include decreased metabolic rates, lean body mass gains, and more efficient myocardial oxygen consumption. However, the definitive role of propranolol in this population is still not fully known, and multi-center study is ongoing to best delineate its value. Further, oxandrolone has been found to decrease whole body catabolism, and counter the decreased strength and growth retardation observed in large burns. However, the long term effects of this agent need to be demonstrated, both alone and in combination with other anti-catabolic agents such as propranolol (43–48). Insulin resistance has been noted in severely burned pediatric patients starting during the acute hospitalization and lasting for three years. Better blood glucose control has led to better outcomes in some populations, but optimal management of hyperglycemia and insulin resistance in these children remains unknown (49–52).

Given the magnitude of the physiological response to major burn injury, there is a need to understand the role of genetics in the response, whether it be in the response to resuscitation or in the development of hypertrophic scars. Several groups are focusing on the genomic and proteomic response to burn injury in children and identifying the genotypes and phenotypes of survivors and non-survivors in order to evaluate treatment algorithms and/or predict outcomes (53–55). Specifically, groups are looking at genomic and proteomic profiles to try

to determine who is a risk for developing MODS in order to improve morbidity and mortality (31). In one small, multicenter study of burn victims, proteomic analysis revealed differences in the level of acute phase reactants, proteins of inflammation, complement, hepatic signaling proteins, and proteins associated with insulin resistance that distinguished survivors from non-survivors. In particular, among the cytokines assessed, non-survivors were characterized by higher serum levels of GM-CSF, IL-8, IL-4 and MCP-1 ($p < 0.05$) (53).

Trauma

Pediatric major trauma patients are also at risk for MODS; data suggest that MODS occurs in as many as 12% of children admitted to a pediatric intensive care unit with an injury severity score greater than nine (56). Much of that morbidity would appear to be associated with traumatic brain injury as the incidence of MODS in pediatric trauma patients decreases substantially when TBI patients are excluded from analysis (57). The pathogenesis of MODS associated with pediatric trauma is just beginning to be elucidated, but would appear to emanate from a variety of potential causes including inflammation, immune dysfunction, endothelial injury, secondary infection and hemorrhage. Data suggest that IL-6 levels are elevated in critically injured children with some data suggesting an association between these levels and the occurrence of MODS (56, 58). Additionally, immune paralysis has also been reported in critically injured pediatric trauma patients using *ex vivo* lipopolysaccharide-induced tumor necrosis factor alpha production capacity assessments (58). Moreover, nosocomial infections appear to be more common in the trauma patients who have this documented impediment in their immune response.

In addition to the inflammatory changes and perturbations, hemorrhage, the associated coagulopathy and the use of transfusion may also contribute to the promulgation of MODS among the pediatric trauma population (Table). For example, among the 8–10% of pediatric trauma patients who require transfusion under current Advanced Trauma Life Support (ATLS) guidelines, mortality is reported to approximate 30% (59).

Recent data suggest that 30–77% of pediatric trauma patients have some degree of coagulopathy upon admission, with a higher incidence and severity in patients with a concomitant traumatic brain injury (59–61). Many adult trauma centers have recognized this “trauma associated coagulopathy” (TAC), and early balanced ratio transfusion/resuscitation protocols have been implemented. Typically, these protocols use 1:1:1 ratios of packed red blood cells (RBCs), fresh frozen plasma (FFP), and platelets, or some variation initially—followed by thromboelastography (TEG)-driven component transfusions. Such an approach has not gained widespread acceptance among the pediatric community. The natural history of TAC in children needs to be better delineated and understood in the context of injury severity. The role of TEG-driven resuscitation protocols in decreasing the morbidity and mortality associated with pediatric trauma including the occurrence of MODS should be established. Given the body of evidence suggesting an association between transfusion and organ dysfunction, a better understanding of the optimal approach to transfusion therapy in pediatric trauma patients may result in improved outcomes.

Red blood cell transfusion therapy

The association of RBC transfusion as well as native RBC dysfunction with organ failure progression in the setting of MODS has been broadly reported and is an active field of investigation (62). The principle RBC function is to enable oxygen (O_2) delivery, the maintenance of which is fundamental to supporting those with critical illness and is an integrated function of blood O_2 content and flow. It is essential to note that blood flow (rather than O_2 content) is the focus of physiologic control in O_2 delivery homeostasis (63). O_2 content varies within a fairly narrow range, whereas flow is scalable by several orders of magnitude. Thus, the volume and distribution of blood flow vary to maintain coupling between O_2 delivery and demand (64–66). In addition to conventionally appreciated features of RBC physiology influencing O_2 delivery (O_2 affinity and rheology), mounting evidence supports an expanded paradigm for O_2 delivery homeostasis based on coordinated gas transport (O_2, carbon dioxide (CO_2), and nitric oxide (NO)) which is linked to vascular signaling by RBCs (67,68). Thus, it has come to be understood that the trapping, processing and delivery of NO by RBCs has emerged as a conserved mechanism through which regional blood flow is linked to biochemical cues of perfusion sufficiency (69,70). By coordinating vascular signaling in a fashion that links O_2 and NO flux, RBCs couple small vessel caliber (and thus blood flow) to O_2 need in the tissues (71–74). Malfunction of this signaling system is implicated in a wide array of pathophysiologic processes and may be explanatory for the dysoxia frequently encountered in the critical care setting (62).

Moreover, it is now recognized that donor RBCs are fundamentally altered during processing and storage in a manner that both impairs O_2 transport efficacy and introduces additional risk by perturbing both immune and coagulation systems in transfusion recipients (75–80). The protean biophysical and physiological changes in RBC function arising from storage are termed the “storage lesion”; many have been understood for some time. For example, it is known that the O_2 affinity of stored blood rises during the storage period and that intracellular allosteric regulators, notably 2,3-disphosphoglyceric acid and adenosine triphosphate (ATP), are depleted during storage (78,81). The appreciation of other storage lesion features has emerged with improved understanding of coagulation, immune, and vascular signaling systems (75). Recent data further implicate RBC processing and storage in disturbance of key RBC signaling regulating the linkage between regional blood flow and regional O_2 consumption (by regulating the bioavailability of key vasoactive mediators in plasma as described above). In summary, RBC transfusion always results in an increased arterial O_2 content, but the signaling disturbance and the compensatory mechanisms to anemia described above may explain the surprising lack of efficacy for transfusion in improving O_2 delivery in critically ill patients with anemia (82–89). The failure of RBC energetics and antioxidant systems is emerging as a likely mechanism for both the ‘storage lesion’ and the acquired dysfunction of endogenous RBCs in the setting of MODS (90,91).

Although RBC transfusion increases hemoglobin concentration, and thereby blood O_2 content, it does not necessarily follow that O_2 delivery is likewise increased unless blood O_2 content is rate-limiting in the transfer of O_2 from lung to tissue. The current approaches to transfusion decision-making in the critical care setting are to maintain an ‘adequate’ RBC mass well above a threshold that may limit tissue O_2 delivery. Historically, ‘normal’ values

have been presumed necessary for ‘adequate reserve’ during stress, although awareness of the tolerance for anemia in this population is developing (92–94). With an improved understanding of vascular signaling and gas transport by RBCs (67,69,95), and of the full array of defects comprising the RBC ‘storage lesion’ (75,83), it is now appreciated that this strategy must be balanced by consideration that: (1) donor and recipient RBCs do not exhibit similar physiology and (2) RBC transfusion may cause harm (beyond transfusion reactions and transmission of infection) – and that this harm appears progressive with transfusion volume, frequency and donor exposure. Consequently, newer ‘restrictive’ hemoglobin thresholds for transfusion (approximately 7 gm/dL) are now appreciated to be at least non-inferior (and in many cases, superior) to more ‘liberal’ hemoglobin thresholds (approximately 9 gm/dL) for a broad array of conditions (96–102), even in actively bleeding patients (103). While traditional transfusion thresholds are currently undergoing a broad ‘reset’, a comprehensive paradigm shift is emerging in the approach to the critically ill, with re-consideration of the ‘hemoglobin trigger’ strategy. Clearly, it is not feasible to define specific hemoglobin boundaries across the complex interaction of developmental-, condition- and stress-specific situations in the intensive care unit. Ideally, the decision to transfuse should be based upon individual and context-specific considerations of the degree to which anemia contributes to tissue O_2 delivery lack (and/or reserve) (104–107). This distinction is exemplified by employing ‘physiologic’ triggers (e.g. transfusing only to rectify abnormal measures of perfusion sufficiency (or reserve)), rather than to maintain a specific hemoglobin concentration, irrespective of context (108,109). In order to do so, it is necessary to identify the specific physiologic goal(s) most linked to outcome as well as to determine appropriate thresholds for putative goals. An enhanced ability to assess the functionality of the circulating RBC mass and its specific relationship to tissue oxygen delivery is pivotal to such determinations.

Transfusion decisions, particularly among the critically ill, should maintain hemoglobin levels above thresholds that limit O_2 delivery. Historically, normal values were presumed necessary during stress. There is now a better appreciation of anemia tolerance and donor RBC impairment; consequently, conservative transfusion approaches are emerging, based upon non-inferiority trials of permissive anemia (e.g. restrictive hemoglobin-based thresholds). However, there is a lack of decision-making structure that identifies specific individuals for whom permissive anemia is unsafe and guides transfusion both in terms of timing and amount based upon outcome-linked physiologic O_2 delivery targets. Prior to implementation of this approach, the ability to quantify O_2 delivery/consumption and sufficiency/reserve relationships (global/organ/tissue) and the ability to specifically attribute these parameters to anemia must be developed (Table).

Conclusion

In summary, there are a number of medical conditions, external injuries and therapeutic interventions that are associated with multiorgan dysfunction and the MODS. The intent of this manuscript was to highlight a handful of those conditions, injuries 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 the understanding of this process from that of a syndrome, a collection of symptoms, to a well defined clinical entity with established pathophysiologic causes, genetic predispositions and targeted therapies.

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Table

Identified Knowledge Gaps and Potential Opportunities for Study

- Current disease stratification tools of acute and chronic liver failure are inadequate, and therefore, it is difficult to effectively predict which patients are at risk or how risk evolves over time. Understanding the pathobiology, and the development of risk stratification using molecular and computational techniques would potentially guide risk stratification, permit trials targeted to mitigate injury, improve organ allocation and decrease mortality.
- A better understanding of serum inflammatory mediators and biomarker patterns in acute liver failure might help distinguish spontaneous survivors from non-survivors and allow for the use of immunomodulatory therapy to improve outcomes and potentially decrease the use of liver transplants.
- There appears to be a need for the validation in children of criteria used in adults to diagnose acute pancreatitis including prospective studies that standardize etiological classifications.
- The natural history of pancreatitis in children needs to be better established in order to understand factors predicting disease severity, complications and the progression to MODS.
- A better understanding of the molecular details associated with acute pancreatitis and their relationship to MODS needs to be attained.
- The mechanisms by which acute kidney injury precipitate dysfunction in other organs are not clearly established; conversely, the mechanisms by which the kidney is secondarily injured as part of MODS are also not well understood.
- An expansion of the understanding of the manner by which the hyperdynamic metabolic and catabolic responses associated with major pediatric burn contribute to the risk of MODS may result in better outcomes.
- Further work assessing the genomic and proteomic profiles associated with burn injury may help to improve morbidity and mortality and reduce the incidence of MODS in this patient population.
- A better understanding of the inflammatory and counter-inflammatory changes associated with major trauma is needed; such insight might afford opportunities to intervene and mitigate the occurrence and severity of associated MODS.
- The natural history of trauma associated coagulopathy in children needs to be better delineated and understood in the context of injury severity. The role of thromboelastography driven resuscitation protocols in decreasing the morbidity and mortality associated with pediatric trauma warrants investigation.
- A decision-making structure is needed to guide red blood cell transfusion both in terms of timing and amount based upon outcome-linked physiologic O_2 delivery targets.
- The ability to quantify O_2 delivery and consumption measurements, to relate these measurements to O_2 sufficiency and reserve at the whole body, organ, and tissue levels, and to attribute these parameters to anemia must be developed.