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Allan Doctor, *Washington University in Saint Louis*

Jerry Zimmerman, *University of Washington*

Michael Agus, *Harvard University*

Surender Rajasekaran, *Michigan State University*

Juliane Bubeck Wardenburg, *University of Chicago*

[James Donald Fortenberry](#), *Emory University*

Anne Zajicek, *National Institute of Child Health and Human Development*

Katri Typpo, *University of Arizona*

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Pediatric Multiple Organ Dysfunction Syndrome: Promising Therapies

Allan Doctor¹, Jerry Zimmerman², Michael Agus³, Surender Rajasekaran⁴, Juliane Bubeck Wardenburg⁵, James Fortenberry⁶, Anne Zajicek⁷, and Katri Typpo⁸

¹Departments of Pediatrics (Critical Care Medicine) and Biochemistry, Washington University in Saint Louis

²Department of Pediatrics (Critical Care Medicine), University of Washington, Seattle, WA

³Department of Pediatrics (Critical Care Medicine), Harvard University, Boston, MA

⁴Department of Pediatrics (Critical Care Medicine), Michigan State University, Grand Rapids, MI

⁵Departments of Pediatrics (Critical Care Medicine) and Microbiology, University of Chicago

⁶Department of Pediatrics (Critical Care Medicine), Emory University, Atlanta, GA

⁷Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD

⁸Department of Pediatrics (Critical Care Medicine), University of Arizona, Phoenix, AZ

Abstract

Objective—To describe the state of the science, identify knowledge gaps, and offer potential future research questions regarding promising therapies for children with multiple organ dysfunction syndrome (MODS) presented during the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Workshop on Pediatric Multiple Organ Dysfunction Syndrome (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—Among critically ill children, MODS is relatively common and associated with significant morbidity and mortality. For outcomes to improve, effective therapies aimed at

Address Correspondence to: Allan Doctor, MD, Professor of Pediatrics and Biochemistry, Director, Division of Pediatric Critical Care Medicine, Washington University School of Medicine, Campus Box 8208, 5th Floor McDonnell Pediatric Research Building, 660 South Euclid Avenue, Saint Louis, MO 63108, doctor@wustl.edu.

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preventing and treating this condition must be discovered and rigorously evaluated. In this manuscript, a number of potential opportunities to enhance current care are highlighted including the need for a better understanding of the pharmacokinetics and pharmacodynamics of medications, the effect of early and optimized nutrition, and the impact of effective glucose control in the setting of MODS. Additionally, a handful of the promising therapies either currently being implemented or developed are described. These include extracorporeal therapies, anti-cytokine therapies, anti-toxin treatments, anti-oxidant approaches and multiple forms of exogenous steroids. For the field to advance, these and other therapies must be assessed in rigorous manner and implemented accordingly.

Keywords

Multiple organ dysfunction syndrome; pediatrics; nutrition; bacterial translocation; microbiome; extracorporeal membrane oxygenation; therapeutic plasma exchange; continuous renal replacement therapy; hemophagocytic lymphohistiocytosis; macrophage activation syndrome; anti-cytokine therapy; bacterial toxin-mediated disease; anti-toxin therapy; corticosteroids; hydrocortisone; mineralocorticoids; aldosterone; gonadocorticoids; oxandrolone; tight glucose control; anti-oxidant therapy

Introduction

For outcomes to improve for children with the multiple organ dysfunction syndrome (MODS), effective therapies aimed at preventing and treating this condition must be developed, rigorously evaluated and applied. Currently, the standard of care comprises treatment targeted at the precipitating etiology while providing robust supportive care. Given the diverse etiologies, presentations and courses of this syndrome, developing effective therapies is challenging. Moreover, the standard of care is complicated by alterations in organ function and by knowledge gaps in other pertinent issues such as optimal medication dosing and nutritional support. To advance the field, gains in the understanding of these issues must be made. Additionally, innovative therapies that have been proposed must be tested in a rigorous manner. Therapies found to be effective in one MODS phenotype should be considered in others, as appropriate. In this manuscript, we will highlight potential innovative therapies for MODS as well as identify knowledge gaps requiring further research to inform care and advance therapeutic interventions.

Influence of MODS upon Pharmacokinetics and Pharmacodynamics

Medical treatment of MODS is highly complex, and many unanswered questions remain. Additional research is needed to understand and model pharmacokinetic (PK) changes in MODS patients receiving a wide variety of medications and other therapeutic interventions and to develop and validate pharmacodynamic (PD) measures, biomarkers, as well as outcome measures in children with MODS (Table).

MODS affects drug PK and PD in a complex relationship with both the fluctuation in organ dysfunction and the institution of other therapies to support the child. A large variety of medications and therapeutic modalities are commonly used: vasoactive infusions to support blood pressure and tissue perfusion; immune-modulating agents to control the inflammatory

response; antimicrobials to treat infectious etiologies; devices including mechanical ventilation, hemodialysis, and extracorporeal membrane oxygenation (ECMO) to facilitate fluid management and to support tissue oxygenation; and complex sedative/analgesic regimens to enable tolerance of the above.

The dynamic complexity of a child's clinical status, the effects and interactions of administered medications, and the removal of medications via hemodialysis and other means have led to difficulties in developing PK models that incorporate this myriad of factors and provide appropriate drug dosing adjustments. For example, present data indicate substantial variability and a lack of predictability in drug behavior for children on ECMO(1). The most common mechanisms by which ECMO affect PK are sequestration in the circuit, increased volume of distribution, and decreased drug elimination(2). While lipophilic drugs and highly protein-bound drugs (e.g. voriconazole and fentanyl) are significantly sequestered in the circuit, hydrophilic drugs (e.g. β -lactam antibiotics, glycopeptides) are significantly affected by hemodilution and other pathophysiologic changes that occur during ECMO(3-5). However, it is unknown if, and unlikely that, the published data and PK models are generalizable between circuit systems and over the wide, complex range of patient pathologies and physiology given the influence of drug molecular weight, volume of distribution, lipid solubility, protein binding, drug-drug interactions, circuit-related factors and the degree of hepatic and renal injury. The development of rapid sample assay methods and personalized, bedside PK modeling would be highly desirable, so that real-time drug dosing changes could be made.

As a result, there appears to be great diversity and heterogeneity in the pharmacologic approach to critical illness. For example, the Collaborative Pediatric Critical Care Research Network published an evaluation of the treatment of children admitted to the PICU with status asthmaticus across a number of clinical sites(6). Although outcomes were similar across the sites, there was a clear lack of consistency in pharmacological therapies, and widespread treatment variability across the institutions(6). One consistent, key finding of that study was the significant over-representation of African-American children requiring PICU admission for status asthmaticus, with no clear explanation. If such a disparity is observed in MODS, this could significantly influence future research endeavors given the potential influence of racial and ethnic differences upon drug metabolism and effect. Additionally, the use of glucocorticoids (discussed below) in the treatment of the hemodynamic instability and inflammatory dysregulation of children with MODS is another example of the wide variability in use of pharmacologic therapies in this setting. Moreover, data to inform the use of narcotic analgesics and sedating agents (e.g. benzodiazepines) is lacking in critically ill children, including PK/PD data. For example, in studying opioid tolerance in mechanically ventilated children, the need for a doubling of the initial opioid doses in order to achieve the same pharmacological effects has been offered as a definition of tolerance(7). Although a reasonable definition, the actual dosages of opioids were influenced by many other factors including subjective assessments of pain or discomfort, varying expectations by the physicians or nurses, and a wide range of practice patterns. Such findings reinforce the contention for more informed use of these medications in critically ill children.

In summary, there is need for development and validation of PK models which incorporate the complexity observed in MODS. Additionally, the development and validation of PD endpoints and biomarkers, as well as outcome measures and endpoints applicable to the range of therapeutic areas in pediatric critical care medicine, are equally needed. This research might be completed more efficiently with the use of research networks and their close research collaborations and infrastructure. Using a virtualized secure web service with strong data governance, Frey demonstrated that data could be shared rapidly and effectively within a research network(8). The ability to increase the scope and accessibility of research could ultimately contribute to the identification of promising therapies and improvements in current ones for children with MODS.

Nutrition and Nutrients as Primary Therapy

Nutrition is fundamental to the provision of pediatric critical care and yet, we lack prospective data to inform the timing, route, and amount of nutrition to support organ function(9, 10). Adequate macronutrient delivery is thought to prevent initiation or progression of MODS through multiple mechanisms: preservation of lean body mass, providing adequate substrate for acute phase and immune protein production, preserving or improving intestinal barrier function, modulating intestinal microbiome and host-microbe interactions, and attenuation of the immune and inflammatory responses to critical illness(10-17).

Both the delivery of prescribed nutrition and the precision with which energy requirements for critically ill children can be determined present important clinical challenges. Although RCT results evaluating the issue in adults have not been uniform, the preferential delivery of nutrition by the enteral route is associated with reduced 60-day mortality in critically ill children (18-23). Yet, despite early enteral nutrition (EN) guidelines, prescribed macronutrient needs fail to be met during pediatric critical illness and median daily protein and calorie delivery remains only 40-75% of goal(18, 19, 24, 25). The reasons for this failure to deliver adequate EN include, but are not limited to, fluid restriction, feeding intolerance, interruption of EN for procedures and hemodynamic instability(25, 26). Practice variation related to perceived risks of EN or symptoms of feeding intolerance often result in avoidable interruptions to EN delivery, thereby limiting delivery of appropriate nutrition(26). Objective biomarkers to monitor the safety of EN could guide initiation, advancement, and withdrawal of enteral feeding, and limit practice variation. Biomarker development is needed to limit subjective decision-making, which is currently the rule with regard to EN delivery (Table).

Energy requirements during pediatric critical illness vary greatly between patients and over time within patients, making the estimation of calorie needs challenging(27, 28). As both over- and under-feeding calories during pediatric critical illness are associated with worse organ function, the delivery of energy to meet, but not exceed, needs may prevent or improve MODS(25, 29). Precision is lacking for the prescription of energy and protein, which may be optimally tailored to patient needs on a daily basis. Technology for the convenient measurement of energy requirements could facilitate precise and individualized energy prescriptions which would vary over time and with illness severity, preventing both over-

and under-feeding(30). Adequate protein intake during pediatric critical illness prevents loss of lean body mass and provides adequate substrate for acute phase and immune protein production. Sufficient protein is also necessary to realize the benefits of several adjuvant therapies targeted to prevent progression of MODS(11). Agus examined protein turnover rates in response to insulin and found improved protein turnover rates only in patients who received adequate protein intake(31). Adequate macronutrient delivery is a necessary first step to examine nutritional and other adjuvant therapies as potential pathways to mitigate organ failure initiation/progression in pediatric MODS.

The gut is thought to be central to the initiation and progression of MODS during critical illness(32, 33). Putative mechanisms for the gut as a “motor” of organ dysfunction are via loss of intestinal barrier functions and altered intestinal microbiome diversity(33). In healthy states, the intestinal epithelium acts as a selectively permeable barrier to allow absorption of nutrients while excluding pathogens, to produce hormones, cytokines and antimicrobial peptides, and to interact with commensal intestinal microbes(34). During critical illness, there are direct and downstream negative effects of intestinal barrier dysfunction and diminished intestinal microbiome diversity which may lead to MODS: a systemic inflammatory response, remote organ dysfunction, loss of intestinal and remote organ immune function, and a shift of the intestinal microbiome towards pathogenic organisms(15, 35-39).

Dietary composition modulates intestinal epithelial barrier function and is an essential determinant of intestinal microbiome diversity(40, 41). Emerging lines of evidence regarding the impact of the gut microbiome on systemic inflammation, nutrient absorption, and the intestinal barrier highlight the potential therapeutic impact of medical nutrition on MODS severity and progression(42, 43). In fact, diet is the most important determinant of intestinal microbiome diversity, more important than genetic background in mice(40). Given the importance of nutrition in the maintenance of intestinal barrier function and microbiome diversity, nutrition as a primary rather than supportive therapy may represent an exciting approach to prevent the initiation or progression of pediatric MODS.

The absence of EN results in impaired intestinal epithelial barrier function in humans and animals, with loss of enterocyte integrity and increased paracellular permeability via apical tight junctions, leading to the translocation of bacteria and bacterial products(14, 44-46). While the composition of EN modulates the intestinal microbiome, the absence of EN leads to a shift of microbiota to predominantly gram negative proteobacteria with a subsequent increase in pro-inflammatory cytokines and loss of epithelial tight junction proteins(42). Loss of intestinal barrier function may be a direct result of nutrient deprivation, or as a downstream effect of reduced microbial population diversity. Changes in microbiome and intestinal epithelial barrier function may worsen feeding intolerance, creating a cycle of nutrient deprivation and worsening barrier function. The minimum dose and timing of enteral macronutrient or micronutrient delivery necessary to preserve intestinal barrier function or microbiome diversity during pediatric critical illness remains unknown.

Immunonutrition, or the delivery of specific nutrients with antioxidant, immune-modulating or anti-inflammatory properties at pharmacological doses has demonstrated promise in small

single-center studies and in animal models of critical illness, but has failed to reveal benefit, and in some cases, has demonstrated harm in large adult critical care trials(47-49). The Randomized Comparative Pediatric Critical Illness Stress-Induced Immune Suppression (CRISIS) Prevention Trial which compared enteral zinc, selenium, glutamine, and intravenous metoclopramide to enteral whey protein was stopped early due to lack of efficacy(50). The study did not provide data regarding the adequacy of enteral protein delivery, but diet was not controlled. In each of the large adult clinical trials of immunonutrition, patients failed to achieve the recommended protein delivery, which may limit or mask the observed effect of immunonutrition(47-49). In the absence of adequate protein (substrate), patients may fail to realize benefits from immune-modulating nutrients. In addition, each of these large clinical trials involved the use of combination immunonutrition therapy. Combination therapy might alter the function or absorption of individual immune-modulating nutrients. Further studies are needed to investigate the pharmacokinetics and pharmacodynamics of mono and combination immune-modulating nutrients both in the absence and presence of sufficient protein intake.

Extracorporeal Approaches to Patient Support

Sepsis remains a major source of mortality and morbidity in children(51). While overall mortality has improved, the subset of sepsis patients with MODS remains at high risk for death. For these patients, extracorporeal therapies could potentially serve as “desperate appliances” to support or reverse organ dysfunction(52). Extracorporeal therapies have been used to provide organ support while resolution of the homeostatic dysfunction wrought by sepsis takes place. Certain extracorporeal approaches could also have the theoretical potential for a direct therapeutic effect on the underlying inflammatory and coagulation disorders in sepsis. Potential direct and indirect benefits of extracorporeal therapies in MODS include:

- Management of sepsis-associated acute kidney injury and fluid overload [continuous renal replacement therapies (CRRT)]
- Provision of immunohomeostasis of pro-/anti-inflammatory mediator pathways (CRRT/plasma exchange)
- Mechanical support of organ perfusion and function [extracorporeal membrane oxygenation (ECMO)]
- Improvement of coagulation response with decreased organ microthrombosis [plasma exchange].

CRRT offers the direct benefit of temporary renal replacement to manage uremia and electrolyte disturbances of septic patients with acute kidney injury. CRRT also allows for direct management of fluid balance in a continuous fashion. Fluid overload has been increasingly recognized as a risk factor for worsened risk-adjusted outcomes in both adults and children. While survival benefits are clearly observed with early and appropriate fluid resuscitation, the development and persistence of fluid overload has now been recognized as a significant risk factor for worsened outcomes in both adults(53) and pediatric patients(54). In contrast, early CRRT intervention at lower fluid overload levels has been associated with

improved survival(55). Conservative fluid management and tighter fluid balances also demonstrated outcome benefit in an adult randomized trial(56). While long theorized to provide the indirect benefit of removal of mediators of the inflammatory cascade, randomized controlled trials (RCT)(57) have not been able to demonstrate an overall outcome benefit of specific use or degree of intensity of CRRT in adults with sepsis and MODS. The role of CRRT in improving outcomes in pediatric MODS and sepsis remains unclear.

plasma exchange (TPE) is an intriguing extracorporeal therapy with potential direct and indirect organ benefits. TPE can directly improve coagulopathy with exchange of functional fresh frozen plasma to improve acute bleeding. Several small RCTs in adults with sepsis have suggested benefit of TPE in adult sepsis/MODS. The largest adult trial to date randomized septic patients to plasmapheresis or standard therapy, with a reduction in death with plasmapheresis(58). A recent meta-analysis of published TPE trials to date(59) found a small treatment effect on mortality in adults. However, an attempt at a pediatric RCT of TPE in patients with sepsis(60) was stopped due to poor enrollment, without clear trends in improvement.

TPE could have greater impact in a subgroup of patients with a MODS subphenotype similar to thrombotic thrombocytopenic purpura (TTP); those with deficiency of ADAMTS-13, elevated ultra-long von Willebrand factor multimers, and end-organ microthrombi. TTP survival has been positively impacted by treatment with TPE. The benefit of TPE in pediatric MODS may be most notable in a subset of patients with features of TTP(61). Nguyen has defined a specific TTP-like phenotype, known as thrombocytopenia-associated multiple organ failure (TAMOF) that correlated with low ADAMTS-13 activity, end-organ microthrombi and increased mortality(62). In a small associated RCT of 10 children(62), all five TAMOF patients who received TPE survived, compared to only one of the five children with standard therapy. A retrospective cohort analysis of Turkish PICU patients with TAMOF(63) found a similar significant decrease in mortality with TPE compared to standard therapy. Preliminary findings from a larger prospective multicenter pediatric observational trial(64) of 81 TAMOF patients have found a clinically and statistically significant reduction of severity of illness scores (Pediatric Logistic Organ Dysfunction Score, PELOD) and risk-adjusted mortality in children with sepsis and MODS who received TPE compared to those receiving standard therapy.

ECMO offers the advantage of immediate, direct respiratory and cardiac support in the child with MODS whose cardiorespiratory function is not responsive to other standard and less invasive therapies. The use of ECMO in MODS has been demonstrated to enhance cardiorespiratory stability. While an ECMO RCT in MODS patients has not been performed, studies have supported good outcomes for patients predicted to be at high risk of death(65). Consideration for the use of ECMO support for MODS unresponsive to other standard treatments is in fact recommended in the pediatric sepsis guidelines of the American College of Critical Care Medicine for patients failing or not responding to other interventions(66). The therapeutic effect of ECMO is essentially to “buy time” while recovery on both an organ- and cell-based level can occur. ECMO provides an additional advantage in that its provision of cardiorespiratory stability and readily available vascular access offers a

“platform” for additional delivery of CRRT and TPE, if indicated. Recent experience with the simultaneous use of TPE on ECMO suggests improvement with the combination(67). In summary, extracorporeal therapies may be recommended for consideration of use in direct and indirect organ support for MODS patients with potentially reversible disease processes, but further research is needed (Table).

Anti-Cytokine Therapy: Anakinra (IL-1 receptor antagonist)

Research is being conducted on applying the principles of genomics and genetics in caring for patients with sepsis who are at risk for developing MODS(68). Multi-systemic injury can result from infection, trauma and macrophage activation, leading to considerable morbidity and mortality. The progression from insult to MODS is at least partially dependent on the nature of the injury and the patient’s genetic susceptibility.

The response of patients with secondary hemophagocytic lymphohistiocytosis / macrophage activation syndrome / MODS (HLH/MAS/MODS) to anakinra, a highly selective IL-1 receptor blocker was recently assessed(69). Therapy was directed at ameliorating inflammation by selectively blocking the IL-1 contribution to the hypercytokinemia (or what has been termed the “cytokine storm”) while simultaneously supporting failing organs. In patients with HLH/MAS/MODS, infections serve primarily as triggers, and it is thought that functional deficiencies in NK cells and cytotoxic T cells drive a dysfunctional response of the host to the infection(70). This cytokine surge, and not the original infection, characterizes the systemic manifestation of secondary HLH leading to end-organ damage and mortality.

Previously used therapies for HLH including agents such as steroids, chemotherapy, and stem cell transplantation have led to opportunistic infections and further organ damage. In a recent report, eight patients (median age 14 years) with findings atypical for sepsis that fulfilled a majority of the modified Henter criteria for HLH were identified(71). All patients had some combination of multi-organ injury with radiological evidence of pulmonary disease, myelogenous involvement, elevated liver enzymes and / or the need for vasoactive infusions. Once HLH was suspected, anakinra was initiated using a wide dosing range of 2-12 mg/kg/day SQ every 8 hours depending on the initial degree of inflammation. The dose was then titrated on a daily basis depending on the patient’s response. Patients were treated for a median duration of 8.5 days (range, 5–31 days).

Inflammation appeared to wane with therapy as C-reactive protein (CRP) levels decreased by 55% from 150 ± 28 to 68 ± 36 mg/L ($p = 0.03$) at the end of one week of therapy. At the same time, ferritin levels dropped by 60% from 8098 ± 4696 to 3210 ± 1178 ng/mL although that difference failed to achieve statistical significance. One patient (12.5%) died, who in spite of an extensive workup, did not exhibit any of the markers of primary HLH.

More than any other cytokine family, the IL-1 family of ligands and receptors is associated with the inflammatory response(72). Studies have found that IL-1 receptor stimulation plays a key role in the evolution and persistence of end-organ injury and its down-regulation leads to improved cardiopulmonary function in animal models(72). In addition, it has been

demonstrated that the IL-1 receptor antagonist (IL1RN) single nucleotide polymorphism (SNP) rs315952C is associated with decreased risk of acute respiratory distress syndrome (ARDS) in three populations with heterogeneous ARDS risk factors(73). It has been hypothesized that these patients have a protective level of IL-1 receptor antibody (IL1RA) which may attenuate ARDS risk.

In patients with HLH/MAS/MODS, it is believed that an anti-inflammatory, negative feedback loop induced by innate immune responses to IL-1 and IL-6 may favor conditions leading to an alternative pathway of macrophage differentiation, and thereby, facilitate development of the so-called CD163 “scavenger” phenotype(74). The activation of CD163 has been linked to higher serum ferritin levels and mortality(75, 76). The elevation of serum ferritin in certain subsets of patients may be related to this phenotype and may benefit from a targeted anti-cytokine therapy. The goal of therapy for HLH/MAS in the above study was to attenuate inflammation. Anti-cytokine therapy in the past has been used to treat sepsis without success. It remains unclear why in many instances anti-cytokine therapies have failed. One hypothesis is that these therapies are initiated too late as MODS appears to be established very early in patients with sepsis(77, 78). Additionally, it may also be argued that such therapies have been directed to a diverse, heterogeneous group of patients generically labeled as “septic” which diffused the potential observed benefit in select subsets that may have responded.

Anti-Toxin Therapy; Understanding Targets, Optimizing Interventions

Bacterial toxins have long been considered highly targetable for the prevention of human disease. The success of childhood vaccination against *Bordetella pertussis*, *Clostridium tetani*, and *Corynebacterium diphtheriae* stems from active immunization with inactivated bacterial exotoxins, illustrating the possibility that strategic neutralization of specific toxins may ameliorate the pathologic consequences of infection. Secreted toxins are widely expressed by bacterial pathogens associated with MODS in the modern ICU including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*. Commensurate with the prominent role of bacterial toxins in human disease, basic research efforts spanning decades have provided keen insight on the cellular mechanisms of toxin action. Toxins contribute to overt cell lysis, cessation of protein synthesis, impaired cytoskeletal reorganization, and alteration of cellular second messenger and trafficking systems among other biological activities. As a common feature, bacterial toxins cause cell injury and an ensuing pro-inflammatory state in the infected host.

Relevant to human critical illness, *S. aureus* α -toxin (Hla) and the secretion system that facilitates *P. aeruginosa* toxin delivery to human cells (PcrV) have emerged as leading targets for vaccine and immunotherapy development (79-86). Clinical trials examining high-affinity monoclonal antibodies capable of neutralizing Hla or precluding toxin delivery by PcrV illustrate that the field is currently poised from a technologic perspective to apply such highly targeted preventatives and therapies (79, 80). Given the precise targeting of toxin-modifying therapies and preventatives, a detailed understanding of molecular toxin action in the context of life-threatening disease and clinical identification of patient populations that can most benefit from anti-toxin therapies are needed for successful implementation.

Molecular and cellular insights from bacterial toxin biology shed light on the complexity of serious toxin-mediated disease, underscoring the challenges of this approach. Utilizing the very well-studied *S. aureus* α -toxin, a strategic integration of pre-clinical molecular knowledge with refinement of the targeted patient population through clinical epidemiology and predictive modeling can be proposed as a paradigm that will yield efficacious clinical implementation of anti-toxin-directed therapies.

α -toxin is a pore-forming cytotoxin produced by almost all clinical *S. aureus* isolates. The toxin has been implicated in the pathogenesis of pneumonia, sepsis, skin infection, and central nervous system infection (87). α -toxin utilizes ADAM10 as a cellular receptor (88). This cell-surface exposed zinc-dependent metalloprotease is widely expressed throughout all tissues (89). Studies of the toxin-ADAM10 interaction strongly suggest that all ADAM10-expressing cells can be injured by α -toxin (82, 90-94). Multiple lines of experimental evidence demonstrate that toxin expression is required for the progression of lethal staphylococcal infection (82, 95-97). Similarly, protection against experimental disease is conferred by toxin-neutralizing vaccines, monoclonal antibodies, genetic deletion of ADAM10 or modulation of ADAM10 expression, and small molecules that antagonize the toxin-ADAM10 interaction or disrupt toxin function (81, 82, 90, 91, 98-102). Coupled with serologic evidence that humans mount antibody responses to α -toxin following infection (103-105), this toxin has emerged as one of the leading targets of vaccine and monoclonal antibody development in the field (106-111).

While it is tempting to speculate that delivery of toxin-neutralizing antibodies may prevent the progression of MODS, a thoughtful analysis of this approach raises key questions that warrant consideration. Namely, what cells does the toxin injure to potentiate lethal sepsis? When does the toxin act in the course of disease? How does a single toxin contribute to the injury of multiple organs in the pathogenesis of severe systemic infection? Are there humans that are naturally protected against lethal intoxication – or conversely, humans that are uniquely susceptible? If so, who are these individuals and how should clinical trials of potential interventions be designed? Existing studies on α -toxin shed some light on these questions, highlighting additional areas of focused investigation that will advance the therapeutic potential of toxin neutralization.

Pre-clinical modeling of lethal *S. aureus* sepsis has led to the observation that α -toxin acts on endothelial cells, platelets, and myeloid lineage cells to potentiate host death (82, 93, 101). The pathologic upregulation of ADAM10 by α -toxin on endothelial cells and platelets contributes to loss of endothelial barrier function, while intoxication of myeloid lineage cells induces prominent inflammation (92, 93). Multi-cellular targeting on the tissue level contributes directly to organ injury in staphylococcal sepsis; acute lung injury is observed within hours of infection while necrotic injury to the liver is evident later in the course of disease (93). Highly relevant to planned interventions, these clinicopathologic features of disease are discernable prior to systemic clinical evidence of overt infection. While these detailed molecular insights are confined to a tractable animal modeling system, they urge the question of how much toxin-induced organ injury is present in humans upon presentation to medical attention. The answer to this question is not objectively known, but it is certainly suggested from available models that toxin-induced cellular injury is a primary inciting

event that elicits the clinical manifestations measurable as MODS (112). This finding has several clinical implications: 1) we must be able to identify patients at risk for life-threatening infectious disease or patients in the earliest stages of disease, and 2) toxin-neutralizing antibodies or vaccines may be best deployed in patient populations at highest risk for infection *prior to pathogen encounter*.

The marriage of these pre-clinical insights with human disease epidemiology is therefore needed to define the patient populations that can most clearly benefit from such highly focused interventions. Defining a specific patient population at risk for *S. aureus* infection has proven increasingly complex in the current era of epidemic drug-resistant staphylococcal disease in both the community setting and the hospital (113). Populations at high risk include those undergoing complex surgical procedures, those requiring mechanical ventilation or intensive care support, individuals with underlying immunodeficiency or illnesses that perturb innate immune function, and those who reside in institutionalized settings. However, the prominent occurrence of life-threatening disease in otherwise healthy children and adults also prompts the question of whether there is a need to achieve population-based protection against the effects of this toxin (103, 113). At present, a limited number of clinical studies have examined the human response to *S. aureus* infection to define immunologic correlates of protection against disease, or alternatively, to enable risk stratification (103-105). While the existing data suggest that targeting α -toxin may be a beneficial approach, further investigation is needed to refine the patient populations for intervention and importantly to define the time windows in which intervention will be efficacious.

The state of investigation on *S. aureus* α -toxin can be leveraged to construct a framework approach for the translation of toxin-targeting therapies and preventatives. Basic science, pre-clinical studies can afford clear insights on the molecular pathogenesis of disease and enable rigorous experimental analysis of candidate toxin-targeting approaches. Together, these insights should inform the approach to investigation of the human response to toxin-mediated injury to ensure the translational applicability of pre-clinical findings. Technologies that enhance early diagnosis of bacterial infection and pathogen identification must be clinically available to facilitate the delivery of toxin-targeted therapies prior to the development of an advanced disease state. When complemented by the advancing field of host biomarker discovery to facilitate early identification of patients with progressive disease, risk stratification algorithms may be within reach to pinpoint those individuals optimally suited for highly focused anti-toxin therapies. While such toxin-targeted approaches cannot be reasonably expected to mitigate all forms of severe bacterial infection that contribute to MODS, the contribution of these host-injurious proteins to human disease now presents an ideal opportunity to capitalize on multidisciplinary research to advance these novel interventions.

Steroid Therapy

As described above, sepsis remains one of the most common causes of MODS. Multiple investigations have demonstrated that the number of dysfunctional organs is associated with the risk of mortality among critically ill children including those with sepsis(114-117). In

severe sepsis, MODS may be facilitated by a reciprocating double jeopardy pathophysiology involving inflammation as well as ischemia/dysoxia(118). These events, in turn, may mediate other hypothesized causes of MODS including widespread energy failure, generalized apoptosis and diffuse epithelial injury. Typically, the focus of steroid therapy for sepsis-associated MODS involves corticosteroids. However, it should be appreciated that considerable pre-clinical and clinical data examining mineralocorticoids and gonadocorticoids have been generated, and suggest that these other steroid classes may also have potential therapeutic benefit for sepsis-associated MODS.

Corticosteroids - Hydrocortisone

At the time of this publication, a large adult interventional trial examining adjunctive hydrocortisone for recalcitrant septic shock is in progress(119). Previously well-conducted interventional clinical trials addressing this subject have resulted in conflicting outcomes(120, 121). Review of the published trials indicates that corticosteroids are nearly uniformly beneficial in terms of hastening resolution of septic shock. However, the majority of published data to date indicate no improvement in enduring, clinically meaningful, patient-centered outcomes for septic shock patients treated with corticosteroids. It can be argued that one of the most perplexing research questions in critical care medicine involves this observation that corticosteroids hasten resolution of shock, and hence, presumably decrease the risk of organ dysfunction, while not providing any decreased risk for mortality. Reasons for this paradox may relate to the multiple effects of this drug class. A dose of corticosteroid is known to alter mRNA expression for approximately 25% of the genome(122). In the PICU, intensivists are typically focused on the favorable hemodynamic and anti-inflammatory properties of corticosteroids as an approach to treating “critical illness related corticosteroid insufficiency” (CIRCI)(123-127). However, there has been less appreciation of the protein catabolic and immune-inhibitory actions of this drug class. As a primary mediator of gluconeogenesis, a key side effect of corticosteroids is hyperglycemia(128). Multiple pediatric descriptive investigations have reported associations between hyperglycemia and multiple adverse outcomes including MODS and mortality(129-131). Another consequence of corticosteroid-mediated lean body catabolism is diffuse muscular weakness, including the diaphragm(132). Additionally, sepsis is associated with suppression of most elements of adaptive immunity, and prescription of a corticosteroid to children with septic shock leads to further compromise of this aspect of immunity(133). These molecular biology findings may be considered in context of the known increased risk of hospital-acquired infections among children treated with corticosteroids(134, 135) and the increasingly recognized role of acquired immunosuppression in mediating adverse outcomes among sepsis patients(136). At least five descriptive investigations have concluded either no benefit or potential harm when adjunctive corticosteroids were utilized for treatment of pediatric sepsis(137-141). At this juncture, there exists evidence that corticosteroids utilized as adjunctive treatment for pediatric sepsis may confer benefit or may confer harm(119). Composite evidence published to date argues for both community as well as individual equipoise in terms of examining this key research question (Table).

Mineralocorticoids - Aldosterone

Aldosterone, a mineralocorticoid, exhibits a number of properties that may be beneficial in MODS associated with sepsis. These include actions related to sodium reabsorption and potassium excretion, insulin resistance, blood pressure, NF-KB activation, arginine vasopressin release and hydrogen ion excretion(142). Hyperreninemic hypoaldosteronism has been described in critically ill patients since the 1980s(143). Patients with this condition typically have infection and hypotension with increased plasma cortisol and plasma renin, but low circulating levels of plasma aldosterone and its precursor 18-hydroxycorticosterone. These critically ill patients have increased risk of mortality associated with their infection and are typically unresponsive to adrenocorticotrophic hormone (ACTH) or angiotensin 2 infusions. Among children with meningococemia, plasma aldosterone levels have been reported to be depressed as compared to other non-septic, critically ill children(144). Pro-inflammatory cytokines, for example tumor necrosis factor (TNF) and IL-2, are known to inhibit angiotensin 2-induced aldosterone synthesis in a dose-dependent fashion(145). Accordingly, local or systemically produced pro-inflammatory mediators that are typically present in patients with septic shock may represent important negative modulators of aldosterone synthesis. It is well known that dopamine provides tonic regulation of aldosterone synthesis, and it is possible that exogenous administration of dopamine exacerbates this effect(146). The primary reason for discussing aldosterone as a treatment for sepsis-associated MODS is that the one contemporary clinical trial of adjunctive hydrocortisone therapy for recalcitrant adult septic shock that reported hastened resolution of shock as well as decreased mortality, also included daily administration of fludrocortisone, an aldosterone agonist(120).

Gonadocorticoids - Oxandrolone

As noted above, proteolysis of lean body muscle represents a key feature of the stress response and is particularly important in severe sepsis. This process, driven by endogenous/exogenous corticosteroids, pro-inflammatory cytokines, and immobilization, activates several atrogene protease pathways resulting in the release of amino acids from lean body muscle for gluconeogenesis, synthesis of acute phase proteins and expansion of the immune system(147). Although an essential aspect of the acute stress response, if exaggerated or prolonged, stress-mediated proteolysis may become maladaptive. Stress proteolysis is clinically relevant in terms of diffuse muscle weakness that corresponds to actual dissolution of the myocyte A band due to loss of myosin thick filaments as viewed by electron microscopy(148). Multiple interventions have been proposed for this catabolic state including the use of anabolic steroids. Significant experience with this approach has been documented for burn patients. Oxandrolone, for example, promotes improved nitrogen balance post-burn injury, an effect that is closely aligned with enhanced protein synthesis(149, 150). Although multiple investigations, particularly those emanating from the Shriners' Hospital for Children in Galveston, TX, have ascertained the biochemical and clinical benefits of adjunctive oxandrolone treatment for burns, similar potential effectiveness has not been investigated in pediatric sepsis(151-154).

Gonadocorticoids—Estrogens

Lastly, the advantage of female gender has been noted in multiple descriptive studies of critical illness including sepsis-associated MODS. Accordingly, it was not surprising that investigators, employing a murine cecal ligation model of sepsis, reported a marked survival benefit among animals treated with a synthetic estrogen(155). Multiple effects of therapeutic estrogen may be relevant in sepsis-associated MODS, several of which address the concept of cytopathic hypoxia and mitochondrial dysfunction. Estrogen is known to affect aerobic glycolysis, respiratory efficiency, adenosine triphosphate (ATP) generation, calcium load tolerance, antioxidant defenses, as well as mitochondrial function in general(156). Estrogen would seem a logical intervention for MODS associated with diffuse energy failure.

In summary, all of the subclasses of steroids have potential utility in terms of the treatment of sepsis-associated MODS, but none have been adequately investigated in the clinical setting. Significant pediatric data ascertain low aldosterone levels in children with septic shock. In addition, burn surgeons have demonstrated the value of oxandrolone in terms of improved nitrogen balance and clinical outcomes in children with severe thermal burns, but this experience has not extended to children with sepsis-associated MODS. Pre-clinical data regarding the potential benefit of estrogens in improving mitochondrial function are equally intriguing as mitochondrial dysfunction is currently in vogue as a potential overriding mechanism of MODS. Accordingly, phase I trials in the PICU are probably justified for all of these steroid classes. However, a RCT of adjunctive hydrocortisone for refractory pediatric septic shock would appear to be a rational first choice. Cumulative descriptive data clearly argues for community equipoise for the research question, and the pediatric critical care community now has significant experience with multi-institutional interventional trials. If hydrocortisone is truly beneficial in terms of improving long-term outcomes following pediatric sepsis-associated MODS, this is an inexpensive drug that could be more widely employed early in sepsis resuscitation bundles. On the other hand, if hydrocortisone is augmenting immunosuppression and perhaps immunoparalysis and adverse outcomes, then clinicians should not be utilizing this intervention except for those patients who are truly adrenal insufficient. Conducting the study will require intellectual honesty by pediatric intensivists, and ultimately will generate evidence for our practice.

Glycemic Control

Critical illness hyperglycemia (CIH), transient hyperglycemia during severe physiologic stress, is common in both critically ill children and adults, unrelated to diabetes status. It is the result of activation of the hypothalamic-pituitary-adrenal (HPA) axis, sympatho-adrenal system and pro-inflammatory cytokines, in response to a physiologically stressful stimulus such as MODS. Stress hormones such as cortisol, epinephrine and norepinephrine are released in high proportions resulting in metabolic, cardiovascular and immune effects. In particular, there is excessive gluconeogenesis, glycogenolysis and insulin resistance(157, 158). These result in a complex interaction between increased hepatic output of glucose and inhibition of glucose uptake by peripheral tissues such as the skeletal muscles. Inflammatory mediators such as TNF- α , IL-1, IL-6 and C-reactive protein also increase peripheral insulin resistance(157). The CIH incidence (blood glucose level >126 mg/dL [7.0 mmol/L]) after

cardiac surgery in infants and young children, for example, has been reported in some series to be as high as 90%(159, 160).

Retrospective data in pediatrics have revealed that CIH is associated with higher mortality(161) and significant morbidity such as lactic acidosis, cardiac arrest, vasopressor use, ventilation time, and longer intensive care unit and hospital stays(130, 160). However, it has not been found to worsen neurodevelopmental outcomes(159). A key question that remains is the extent to which hyperglycemia is a marker, as opposed to a cause of adverse outcomes. Studies that do find an association between hyperglycemia and adverse outcomes in the pediatric cardiac population suggest that the incremental contribution of hyperglycemia to these adverse outcomes is likely to be mitigated by other factors including age. Specifically, Moga and colleagues found that there was no incremental risk attributable to hyperglycemia in neonates until 54 hours of sustained hyperglycemia for glucose levels < 180 mg/dL (10 mmol/L), although the increase in risk occurred at 12-18 hours for those with worse CIH(160).

Despite the high prevalence of CIH in children undergoing cardiac surgery, and its association with adverse outcomes, the benefits of “tight glucose control (TGC)” achieved in adult cardiac patients have not been replicated in the pediatric cardiac population. Four large RCTs of TGC in critically ill children have been conducted to date(162-166). Three of these trials included children following cardiac surgery(163, 165, 166), and one with severely burned patients; only the trial conducted by Vlasselaers(166) demonstrated possible benefit from TGC. Vlasselaers conducted a single-center RCT of TGC in a pediatric intensive care unit(166). Seventy-five percent of the patients were recruited following cardiac surgery. The study concluded that TGC was of benefit in the study population, with evidence of reduced inflammation, shortened length of stay and fewer deaths in the TGC arm. The incidence of severe hypoglycemia was high, at 24.9% in the TGC cohort, and 44% of those below one year of age.

The Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial included only patients that underwent cardiac surgery with cardiopulmonary bypass (CPB) up to 3 years of age(163). It assessed the ability of TGC in the cardiac ICU to prevent health-care associated infections and found that TGC did not change the rate of health care-associated infections, mortality or the length of stay in the cardiac ICU. A *post hoc* analysis raised the possibility of a differential age-based effect of TGC, with those over 60 days of age demonstrating substantial benefit from TGC. However, this has not yet been validated in other TGC populations(162).

The Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial also randomized critically ill children to TGC (72-126 mg/dL range) or conventional glycemetic control (target level below 216 mg/dL)(165). Sixty percent of the children in the trial had been admitted to the ICU after cardiac surgery. Overall, no benefit of TGC was noted in terms of survival, ventilator-free days, or ICU length of stay. Moreover, increased severe hypoglycemia was noted in the TGC cohort. In the non-cardiac surgery cohort, a decrease in 12-month health care costs was noted, and further elucidative follow-up studies are currently underway to better understand that finding.

Overall, these three studies represent the existing body of knowledge of TGC applied in the pediatric critically ill population. An important feature of all three trials is that none required hyperglycemia as an inclusion criterion, and as a result, roughly one-third of Vlasselaers and CHiP patients and one-twelfth of SPECS patients were never significantly hyperglycemic. Therefore, the total number of pediatric cardiac hyperglycemic patients studied in an RCT to date is approximately 2,300, while only 500 non-cardiac hyperglycemic patients have been studied. The current HALF-PINT trial (NCT01565941) is in the process of randomizing 1,880 hyperglycemic non-cardiac, critically ill children with MODS.

Neurodevelopmental follow-up of two trials has been reported to date. The Vlasselaers trial found no IQ differences between those who had TGC-induced hypoglycemia and usual care propensity score matched comparators(167). SPECS follow-up at one-year of age, however, found significantly reduced scores among those who were exposed even to one episode of moderate or severe hypoglycemia(168). Reconciliation of these two differing sets of findings needs to take into account the performance of the overall study cohort. This variability, combined with the known lethality of prolonged severe hypoglycemia, highlight neurodevelopmental follow-up as a key parameter to be incorporated in future study design.

In summary, despite circumstantial evidence that CIH is associated with poor outcomes, the clinical trial evidence regarding the benefit of TGC in critically ill children with MODS is essentially negative except for one trial in a predominantly cardiac surgical population. Conducting these trials has revealed that severe hypoglycemia should be avoided, and increasingly with emerging technology, it largely can be avoided. While at the present time, a preponderance of the evidence would lean against the performance of TGC in cardiac patients, equipoise remains the appropriate stance for the non-cardiac critically ill population with MODS. Although TGC is unlikely to be the therapeutic intervention that definitively ensures survival, it remains promising as one important component of the best multi-faceted clinical care provided in the pediatric ICU. Further research will define how important it is, and in which populations it is most helpful.

Anti-Oxidant Therapies

Redox chemistry (electron transfer), once thought to be a relatively non-specific, unregulated and toxic disease mechanism, is now commonly appreciated to play a precise, highly regulated and central role in nearly all major cellular processes (replication, gene regulation, protein synthesis/catabolism, etc.). It is essential in vital organ physiology as well as in 'non-structural' physiologic systems (e.g. coagulation and immune systems), in regulation of oxygen supply, and in regulation of mitochondrial and glycolytic pathways, all of which are highly relevant to critical illness and multiple organ failure syndromes(169, 170). Classically, redox reactions were considered to contribute to disease through oxidant excess that simply overwhelmed anti-oxidant defenses and thereby damaged key molecules/structures; this physiologic state was termed 'oxidative stress'. Therapeutic attempts to pharmacologically 'quench' oxidative stress (in a broad range of pathologies) have been largely unsuccessful, prompting deeper investigation of this pathophysiology(171-173). Current perspectives now favor restoring disturbed redox balance (e.g. poise between reductive and oxidative pathways or between oxidized/reduced 'pairs' of key residues/

molecules) and regaining lost compartmentalization/containment of normal redox processes(174). Before further discussion, it will be useful to clarify a few terms unique to this area of study: Reduction potential (also known as redox potential, oxidation/reduction potential, ORP, pE, E, or E_h - quantified in volts (V), or millivolts (mV)) is a measure of the tendency of a chemical species to acquire electrons and thereby be reduced. Each molecule (group of molecules, or cell) has its own intrinsic reduction potential; a solution/compound with a high (more positive) reduction potential will have a tendency to gain electrons (i.e. to be reduced or conversely, to oxidize another compound/solution) and a solution with a lower (more negative) reduction potential will have a tendency to lose electrons to the new species (i.e. to be oxidized or conversely, to reduce another compound/solution). As such, an electrical exchange affords appropriate analogy, with 'current' moving from reducing sources to oxidizing sinks; the E_h for 'oxidants' is 'low' (positive, or 'less-negative' voltage), while the E_h for 'reductants' (also known as 'anti-oxidants') is 'high' (less-positive or more-negative voltage); this analogy has led to the classification of 'anti-oxidants' by their reducing 'power' (e.g. E_h , in mV).

From the above, it should be apparent that all electron transfers (redox reactions) necessarily involve both oxidation and reduction; of note, these reactions are fundamental to normal metabolism (energy production arises from oxidation of glucose (and other substrates), and respiration involves transfer of electrons from donor species to oxygen). Thus, redox gradients are essential to signaling and physiology. In fact, energy is utilized to maintain compartmentalization and dis-equilibrium amongst key 'redox pairs' which serve as sensors (e.g. GSH/GSSG, NADH/NAD⁺, and FADH/FAD⁺, or glutathione, nicotinamide, and flavin adenine, respectively) or as electronic 'switches' that directly regulate protein conformation/activity (e.g. change in thiol redox state of cysteine residues in proteins)(170). Such redox pairs and switches are exquisitely responsive to the biochemical 'milieu' that reflects metabolic sufficiency (substrate abundance, pathway efficiency, etc.). It is also important to note that such pairs/switches commonly operate in cascades (both amplifying/dampening signals) and exist with specific enzymatic regulation (as for phosphorylation/dephosphorylation, oxidases/reductases thereby being analogous to kinases/phosphatases) (175, 176). Finally, significant specificity (amongst redox pairs/switches/regulators) exists for specific reactant categories (e.g. reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive lipid species (RLS) and peptide radicals). As such, from a physiologic (or pharmacologic) perspective, an 'anti-oxidant' is a molecule that delays/inhibits/reverses oxidation of other molecules; such molecules may act as 'quenchers' (e.g. tocopherols, carotenoids, ascorbate, glutathione) in which the anti-oxidant, itself, donates the electron to arrest or divert a radical chain (series of self-sustaining, uncontrolled redox reactions). In doing so, the 'ant-oxidant' is consumed and must be recycled by its reductase. Alternatively, this process may be enzymatically facilitated (e.g. superoxide dismutase, catalase, ceruloplasmin, etc.)(177). Additionally, other 'anti-oxidants' act by chelating/sequestering species capable of converting other molecules into oxidants (e.g. transferrin, haptoglobin, hemopexin, albumin, etc.). It is also important to note that a modest degree of 'oxidative stress' is now appreciated to be beneficial (by prompting a robust genetic response that 'reprograms' cells to prospectively manage metabolic stress)(178) and may be the basis for a range of salutary effects including 'ischemic preconditioning', healthy responses to

exercise(179) and delayed senescence.(180) Clearly, anti-oxidant therapies should not interfere with such normal physiologic stress (also known as ‘hormetic’) responses(181).

Oxidative stress is commonly observed in MODS and appears to arise from normal physiologic stress/defense responses that have become un-damped and/or un-contained, and may arise from the immune system (activated neutrophils, eosinophils, macrophages), the endothelium (NADPH oxidase and inducible nitric oxide synthetase (iNOS)) or as a consequence of injury to the kidneys (accumulation of oxidants such as cyanate), red cells (hemolysis releases heme and iron), and/or dysfunctional mitochondria(182-185). Despite endogenous anti-oxidant systems, this state feeds-forward in a self-sustaining fashion, amplifying individual organ failure and immune dysregulation. Of note, the degree of ‘oxidative stress’ (as measured in the plasma compartment) has been reported to influence outcome in critical illness(186, 187). As noted above, attempts to treat oxidative stress (quenchers: Vitamins A, C and E, melatonin, N-acetyl cysteine, glutamine; enzyme inhibitors: allopurinol, various NOS inhibitors; chelators: deferoxamine) have largely failed translation from model systems and case series to clinical trials. Little to no impact has been observed with these therapies in RCTs(188) (including children(189)), even when administered in ‘cocktails’(190, 191). Critical review of these results suggest that successful management of oxidative stress may require a precision approach which targets specific amounts and species in select pathways and locations(177). Consequently, better monitoring of endogenous anti-oxidant systems will be needed before such an approach may be successfully implemented(174). Such monitoring may involve *in vivo* spectroscopy or imaging of reporter probes to track the status of key redox pairs (GSH, NADPH, etc.), measurement of plasma ‘reducing capacity’ (generally, and for specific agents that might direct targeted oxidant source control) as well as monitoring the oxidative injury ‘footprint’ by blood/urine assay (lipid peroxides, amino acid oxidation products) or by reporter-based or functional/metabolic imaging(176, 192).

With anticipated improvements in redox monitoring, key pre-clinical questions have been proposed to enable selection/screening for suitable ‘modern’ approaches to anti-oxidant therapy prior to human trials(177): (1) Does the therapy interfere with endogenous redox signaling systems? (2) Which specific biomolecules/pathways does the therapy ‘protect’, and are these implicated in disease? (3) Can the targeted biomolecule/pathway be monitored, and may the therapy be delivered in a ‘goal directed’ fashion? (4) Is the therapeutic mechanism clearly understood, and what is the degree of selectivity (or, off target activity) for the therapy? (5) Can the therapy be targeted (context, tissue, organelle, reactants)? (6) Can reactant products (from therapy and oxidant) cause damage, and how are such products cleared? While trial results have been disappointing to date, our enhanced understanding of key endogenous redox signaling and defense systems as well as the development of modern systems-biology, precision or goal-directed interventions hold great promise in this important feature of multiple organ failure pathophysiology(193-195).

Conclusion

Effective therapies to prevent and treat MODS are clearly needed to advance care and improve outcomes for children at risk. Although the current standard of care remains

focused on treating the precipitating etiology and providing supportive care, a number of potential therapeutic options are being suggested, developed, and for some therapies, implemented on a selected basis. Some have undergone testing in clinical trials. In this manuscript, a number of potential and promising therapies at varying levels of clinical preparedness have been described. It should in no way be considered an exhaustive list and these are but a few of the many potential therapies being considered. To advance the field, these and other promising therapies must be rigorously assessed to determine their true clinical value. However, given the high mortality associated with MODS, timely implementation of successful therapies is paramount. Therefore, clinicians must balance the implementation of such therapies with appropriate assessment to both attempt to advance care of the individual patient and to foster an accurate and progressive understanding of the true value of these interventions.

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Table 1
Identified Knowledge Gaps and Potential Opportunities for Study in Developing Effective Therapies for Multiple Organ Dysfunction Syndrome in Children

<p>Author Manuscript</p> <p>Author Manuscript</p> <p>Author Manuscript</p> <p>Author Manuscript</p>	<ul style="list-style-type: none"> • Pharmacokinetic and pharmacodynamics modeling tools that incorporate the influence of organ failure, developmental changes in key parameters, and drug-drug interactions commonly encountered in the PICU setting and extracorporeal systems need to be further elucidated. • There is a need for the development of real-time therapeutic drug monitoring tools and scalable measures of organ failure that influence key pharmacokinetic and pharmacodynamics parameters. • The impact of route, dose, or timing of enteral and parenteral nutrition upon intestinal barrier and microbiome and the subsequent initiation or progression of pediatric MODS need to be determined. • The identification of biomarkers that report the effect of nutrition and other PICU care on the intestinal epithelial barrier and microbiome will help advance care. • There is a need for strategies that maintain intestinal barrier function and microbiome diversity and hold the potential to limit progression of MODS. • An understanding of the best approach to prescribed nutrition delivery, the role of immunonutrition and technology to offer precise and titrated nutrient goals are lacking. • An understanding of the correlation between the clinical phenotypes of MODS with their underlying biochemical aberrations is lacking. There would appear to be a need for the development of consensus for structured common data elements, phenotype definitions and procedures for biospecimen repositories to enable multi-center study of rare MODS phenotypes. • The identification of optimal indications (including TAMOF criteria and biomarker use), timing, dosing and duration of CRRT and plasma exchange is needed. Similarly, an optimal approach to transfusion use and anticoagulation therapy and monitoring remains to be identified for all forms of extracorporeal therapy. • The determination of the impact of plasma free hemoglobin generated during ECMO support on oxidant injury, and the optimal approach to clearance of free hemoglobin remains to be established. • A comprehensive approach to the complex inflammatory status in children with MODS that incorporates interactions between host and pathology, host and microbiome, environmental history, genetic and developmental diversity, and temporal evolution of pathology may help advance the field. • Patient selection criteria, including real-time biomarker analysis, that optimize benefit/risk profiles for anti-cytokine therapies are needed. • An enhanced appreciation of bacterial toxin action at the molecular and cellular level may help mitigate against MODS in children. Equally important, predictors of host susceptibility to toxin-induced MODS and the identification of specific patient populations in which anti-toxin therapy may be beneficial may facilitate improved care. • Tools to effectively quantify the degree and cause of CIRCI and to prospectively identify children with MODS most likely to benefit from steroid therapy are lacking. • The optimal approach to goal-directed dosing for corticosteroid therapy for CIRCI and the indications for the use of mineralocorticoids or gonadocorticoids alone or in combination with corticosteroids for CIRCI remain to be established. • An enhanced understanding of the interaction of TGC, insulin therapy, and the overall neuro-humoral stress response is needed. The quantification of benefit from TGC, the identification of patients most likely to benefit and the neurodevelopmental costs of hypoglycemia are also needed. Additionally, an explanation of the benefit arising from TGC at the mechanistic level requires elucidation. • The development of a closed-loop system which maintains blood glucose within a target range in critically ill pediatric MODS patients with little or no risk of hypoglycemia would seem to hold potential to optimize outcomes.
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PICU – Pediatric Intensive Care Unit

MODS – Multiple organ dysfunction syndrome

TAMOF – Thrombocytopenia-associated multiple organ failure

ECMO – Extracorporeal membrane oxygenation

CRRT – Continuous renal replacement therapy

CIRCI – Critical illness relative corticosteroid insufficiency

TGC – Tight glucose control