Published in final edited form as:

Pediatr Crit Care Med. 2017 March ; 18(3 Suppl 1): S24–S31. doi:10.1097/PCC.0000000000001050.

Monitoring Severity of Multiple Organ Dysfunction Syndrome: New Technologies

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Abstract

Objective—To describe new technologies (biomarkers and tests) used to assess and monitor the severity and progression of multiple organ dysfunction syndrome (MODS) in children as discussed as part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development MODS Workshop (March 26–27, 2015).

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

Study Selection—Not applicable

Data Extraction—Moderated by an experienced expert from the field, investigators developing and assessing new technologies to improve the care and understanding of critical illness presented their research and the relevant literature.

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

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Conflict of interest

Andrew Seely has patents related to continuous multiorgan variability analysis, and is Founder and Chief Science Officer of Therapeutic Monitoring Systems, a company created to help bring variability-derived clinical decision support to the bedside to improve care. The other authors did not have any conflict to declare.

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Conclusions—There are many innovative tools and techniques with the potential application for the assessment and monitoring of severity of MODS. If the reliability and added value of these candidate technologies can be established, they hold promise to enhance the understanding, monitoring, and perhaps, treatment of MODS in children.

Keywords

biomarkers; monitoring; multiple organ failure; multiple organ dysfunction syndrome; pediatric; variability

Introduction

There are a variety of approaches and techniques being used to better understand and assess disease processes. In some cases, these techniques are beginning to be applied to the assessment of multiple organ dysfunction syndrome (MODS). In others, the technique has not been applied to the study of MODS, but holds promise as a potentially useful tool for the assessment of this life-threatening condition. In this manuscript, a number of these techniques are briefly reviewed and their potential applicability in the assessment and monitoring of pediatric MODS are considered.

Serum Biomarkers for Stratification of Septic Shock, Organ Failure Burden, and Identification of Endotypes

Biomarkers are currently being used to assess a host of pathophysiological conditions including sepsis and septic shock. Given that septic shock is a major cause of pediatric MODS, it is plausible that the use of serum biomarkers may play an important role in the assessment of MODS in children. Over the last decade, Wong has developed a multi-institutional, clinical and biological database of children with septic shock (1). The database includes a biological repository of whole blood-derived ribo-nucleic acid (RNA), which has been leveraged for genome-wide transcriptomic studies enabling the discovery and development of biomarkers to stratify patients with septic shock, identify patients at risk for the development of septic acute kidney injury (AKI), and identify endotypes of pediatric septic shock.

Stratification Biomarkers

Understanding baseline mortality risk is fundamental to effective clinical practice and research. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) assigns a reliable mortality probability for children with septic shock (2, 3). PERSEVERE is based on Classification and Regression Tree methodology and a panel of stratification biomarkers objectively selected through discovery oriented transcriptomic studies (4). Using serum samples obtained during the first 24 hours of presentation with septic shock, PERSEVERE assigns a range of clinically meaningful mortality probabilities. The model was validated in a separate cohort, demonstrating excellent performance (5). Patients with a high risk of PERSEVERE-based mortality who actually survive, have a higher burden and duration of organ failure compared to those with a low PERSEVERE-based risk of mortality.

There are several applications for PERSEVERE. These include prognostic enrichment for interventional clinical trials, serving as a metric for quality improvement efforts, improving decision making for individual patients, and providing a tool to conduct risk stratified analyses of clinical data.

Biomarkers to Estimate the Risk of Septic AKI

The development of acute AKI is associated with increased mortality in patients with sepsis. Identifying those at greatest risk of developing septic AKI could provide an opportunity to mitigate the development of AKI or to intervene sooner to support kidney function. Using discovery oriented transcriptomics, a gene signature associated with the development of septic AKI was identified (6). From this list of candidate genes, a multi-plex protein assay was developed to estimate the risk of septic AKI using a panel of serum protein biomarkers and Classification and Regression Tree methodology (7). The derived model performed well in validation, thus potentially providing a tool to estimate the risk of a specific form of organ failure associated with sepsis.

Septic Shock Endotypes

An endotype is defined as a subclass of disease or syndrome, as defined by function or biology. Wong has described and validated the existence of septic shock endotypes based on the expression pattern of over 8,000 genes (8–10). Recently, the subclassification method was refined for clinical application by distilling the endotype-defining gene signature to the top 100 class-predictor genes, measuring gene expression using a multi-plex digital RNA quantification platform, and depicting the gene expression patterns using visually intuitive gene expression mosaics. Using separate derivation and validation cohorts, the existence of two septic shock endotypes were described; allocation to one of the two endotypes appears to be associated with increased organ failure burden and mortality (11). Importantly, the endotype-defining genes correspond to the adaptive immune system and the glucocorticoid receptor signaling pathway, thus opening the possibility to apply precision medicine for children with septic shock. Indeed, *post hoc* analyses demonstrated that the prescription of adjunctive corticosteroids was independently associated with four times the risk of mortality in one of the two septic shock endotypes (11).

In summary, discovery oriented transcriptomics has been employed to identify potential biomarker signatures that can be used to identify high risk patients with sepsis. These biomarkers are able to stratify severity of illness and to identify patients at risk for subsequent organ injury. They may even be utilized to identify endotypes associated with an increased risk of organ failure and death. Given these findings and the close association of MODS with sepsis and septic shock, it is likely that such technology will be applicable and valuable in the assessment and monitoring of pediatric MODS; however, this remains to be proven (Table 1).

Applying Mechanistic Mathematical Modeling to Investigate the Severity of MODS: Lessons from Cancer

Computational Models Enable a Broader Understanding of Biological Processes

Biological processes are complex. They involve multiple time- and spatial-scales and numerous cell types, molecular species and signaling pathways. Pathological conditions add to the complexity of normal biological processes, where communication between organs, cells, and molecules is distorted or abolished. In the case of MODS, uncoupling or isolation of damaged organs is hypothesized to be indicative of disease severity (12).

The complexity of biological processes, especially under pathological conditions, necessitates the use of systems biology approaches. Systems biology studies how individual components of biological systems give rise to the function and behavior of the system and aim to predict this behavior by combining quantitative experimental techniques and computational models (13). Computational systems biology, in particular, offers powerful tools with which to study complex biological processes. These tools can account for and predict the behavior of a large number of species, signaling networks, cells, and tissues, and even capture whole-body and population dynamics.

MODS is an inherently systemic disease, one in which a reductionist approach of investigating individual organs is not able to fully capture the pathology. Understanding the progression and severity of pediatric MODS is a particular area of interest that may benefit from systems biology modeling. Here, results from modeling tumor angiogenesis are presented to demonstrate the utility of computational systems biology approaches and provide suggestions for how a similar approach can be applied to study pediatric MODS.

Computational Models of Angiogenesis Provide Insight into Cancer Therapeutics

Angiogenesis is the formation of new blood capillaries from pre-existing vessels. Quantitative models of angiogenesis have provided insight into the fundamental mechanisms of neovascularization (14). Researchers have sought to apply computational systems biology models to understand the effects of angiogenesis-inhibiting drugs (“anti-angiogenic” therapeutics), to optimize the ability of drugs to specifically target tumor vessels rather than healthy ones, and to identify prognostic biomarkers that can be used to identify patients that will respond to a particular therapy (15).

Finley and colleagues have worked to develop a physiologically-based computational framework to study vascular endothelial growth factor (VEGF, a potent regulator of angiogenesis) kinetics and transport in humans (16, 17) and in mice (18, 19) to complement pre-clinical and clinical studies. The model was applied to determine how various drug-specific characteristics and properties of the tumor microenvironment influence the response to VEGF-targeted drug treatment (16). The model has been extensively compared to clinical measurements, which validate the predictions (20). A particularly interesting prediction is that anti-VEGF treatment can increase unbound VEGF in the tumor, depending on the tumor microenvironment, pointing to the importance of personalized medicine. This hypothesis is currently being validated experimentally. In summary, this research demonstrates the

clinically relevant insight provided by computational models and provides a template for applying mechanistic systems biology approaches to investigate MODS.

Existing Computational Models of MODS Can Benefit from Greater Molecular Detail

Computational models have been used to study MODS, with a focus on: 1) correlative models of heart rate variability (HRV) and 2) multiscale models of tissue damage, as described below.

- Multiscale models provide insight into tissue and organ dysfunction using a) phenomenological modeling, which focuses on mediators, or b) agent-based modeling, which focuses on cell-cell interactions. Two representative examples of computational studies in conditions related to MODS are described below.
 - Chow and colleagues used an ordinary differential equation phenomenological model to predict the acute inflammatory response in shock (21). The model predicts how cytokines mediate macrophage transition from a resting state to an activated state. The kinetics of the transition occurs in response to the various “physiologic processes” of shock including endotoxin and trauma. Although this model tracks the concentrations of specific molecular species, the particular interactions leading to activation of macrophages are neglected.
 - An and colleagues applied agent-based modeling to study the epithelial barrier (22, 23). Their models simulate crosstalk between the gut and the lung. The models also linked hypotheses for sepsis and multiple organ failure by examining epithelial barrier failure and diffuse endothelial activation. The models focus on cells, rather than the underlying signaling networks that drive cell-cell and ultimately, tissue function.
- Godin and Buchman hypothesized that healthy organs behave like coupled biological oscillators (12). They found in the context of MODS that systemic loss of HRV is associated with a less “healthy” state in critically ill patients. This is discussed in more detail in the following section.

These existing models of MODS focus on multiple organ dysfunction at the tissue and organ level, without examining the molecular mechanisms that drive the pathology. However, without molecular-detailed, mechanistic models of MODS, it is difficult to predict the effects of molecular-targeted treatment strategies. Thus, to advance the field, it may be useful to develop mechanistic models of signaling networks involved in potential starting point for the development of such models as the “tumor necrosis factor- α (TNF- α)/nuclear factor κ light-chain enhancer of activated B cells (NF- κ B)/matrix metalloproteinase-9 (MMP-9)” (TNF- α /NF- κ B/MMP-9) axis. It has been demonstrated that MMP-9 is increased in MODS (24) and is correlated with changes in TNF- α in ischemia reperfusion injury (25, 26). The work already conducted in modeling TNF- α and NF- κ B in cancer and other pathological conditions (27) may help inform such study. Moreover, to construct the proposed mechanistic model of MODS signaling high-throughput, quantitative data with which molecular mechanisms can be interrogated will be needed. Consequently, gene

expression studies such as those performed by Wong and colleagues (28) may be particularly useful. The proposed models can be applied to provide quantitative, mechanistic insight into MODS signaling networks, how signaling in the tissues and organs is disrupted as the syndrome progresses, and the effects of treatments that target particular signaling molecules.

In summary, existing models of MODS focus on multiple organ dysfunction at the tissue and organ level, without examining the molecular mechanisms that drive the pathology. Without molecular-detailed, mechanistic models of MODS, it is difficult to predict the effects of molecular-targeted treatment strategies.

Heart and Respiratory Variability

Chaos and Fractals

As described above, heart and respiratory rates are driven and autoregulated by coupled biological oscillators. When monitored over hours, these rates show highly complex and “chaotic” patterns. There is evidence that the chaotic autoregulation rooted in nonlinear dynamics of the cardiac and respiratory systems is disturbed in patients with MODS. A better elucidation of this process may result in an enhanced understanding of and ability to track MODS, and ultimately, improved outcomes.

The concept of chaos (i.e. irreducible uncertainty) originated in the challenge of predicting the orbit of three interdependent celestial bodies. Henri Poincaré found that it is impossible to predict exactly the forthcoming orbit of any of these celestial bodies; however, he was able to predict that the forthcoming orbit will fit within a range of possible orbits that can be predicted by a mathematical equation typical of a chaotic pattern.

Mathematical chaos is characterized by repetitive patterns that are driven and limited by a ‘strange attractor’. Chaotic patterns are ubiquitous in biology. Heart rate typically follows highly complex and chaotic patterns in healthy humans. When the degree and complexity of the HRV is reduced (hypothesized to be due to organ uncoupling), there is an increased risk of cardiac arrest. Reappearance of the chaotic pattern of heart rate (recoupling) in severely ill patients is associated with better outcomes (29–31). A similar trend is observed with respiratory rate.

Biological Chaotic Variability

Variability is produced through highly interconnected non-linear coupled biological oscillatory patterns. Variability can be defined as the degree and character of variation over intervals-in-time. A high degree of variation and a high degree of complexity of variation are both observed in healthy subjects; on the other hand, a reduced degree and complexity of variation correlate with illness severity. At the onset of septic shock, sympathetic drive is disturbed (32). Heart rate variation is decreased in experiments where endotoxin is injected to animals or human beings (33). There is a clear association between the alteration in HRV and outcomes of patients with sepsis and septic shock (34). In addition to signalling increased severity of illness, the loss of variability also appears to signify loss of the capacity

to adapt, associated with adverse outcomes. Maintaining a normally highly complex pattern of biological oscillatory regulators is essential for life.

The respiratory rate also varies naturally. Although humans on the average breathe every five seconds, it is nearly impossible to actually breathe precisely every five seconds, and it is contrary to physiology. However, a set rhythm is enforced with ventilators particularly in the setting of neuromuscular blockade or heavy sedation; some experts believe that this is not optimal, and that a biologically variable pattern should be integrated into ventilators.

Monitoring Heart and Respiratory Rate Variability: Feasibility

Many methods derived from nonlinear dynamics can be used to monitor and analyze biological variability (35, 36). Bradley (37) demonstrated that monitoring heart rate and respiratory rate variability is feasible in adult critical care patients undergoing routine care (Table 2). Cardiac and respiratory variability were derived from continuous electrocardiography and capnography (end-tidal CO₂) in 34 critically ill adults aged 56.5 ± 15.9 years with an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 22.8 ± 6.7 . The average length of monitoring was 11.0 ± 3.6 days. Analysis processing of HRV was possible $81.2\% \pm 25.0\%$ of the time, respiratory variability, in $87.5\% \pm 11.9\%$ of the time. Problems were primarily related to disconnection and data cleaning.

Monitoring Heart and Respiratory Rate Variability: Clinical Impact

Other studies have examined the usefulness of heart rate and respiratory rate variability monitoring at the bedside. For example, monitoring breathing variability may be used to predict extubation failure in critically ill patients. Wysocki (38) reported that breathing variability was greater in patients who were successfully separated from the tracheal tube than those who were not. Additionally, Seely (39) enrolled 721 patients in a multicenter, prospective, observational study, evaluating clinical estimates of the risk of extubation failure using continuous monitoring of heart and respiratory rate variability during spontaneous breathing tests. They developed a score based on the respiratory rate variability that produced a mean receiver operating characteristic (ROC) area under the curve (AUC) of 0.69, which was higher than that of the heart rate (0.51), rapid shallow breathing index (0.61) and respiratory rate (0.63).

There are also data suggesting that continuous monitoring of HRV can save lives of neonates if translated into a clinically intelligible measure, namely a risk of subsequent deterioration. Moorman (31) enrolled 3,003 very-low-birth weight neonates in a multicenter RCT of continuous HRV monitoring versus controls without such monitoring. For the babies whose heart rate characteristics were monitored continuously, a bedside monitor would provide a clinician with a risk of subsequent deterioration (most likely due to sepsis), and the doctors were then permitted to modulate their therapeutic plan or to ignore the signal accordingly. Despite the lack of a structured and protocolized response, the mortality rate was 20% lower in the monitored group than in the controls (8.1% vs. 10.2% , $p = 0.02$).

Monitoring HRV can also be useful to predict the onset of infection, and thus, may be able to prevent septic shock. Seely reported that decreased HRV heralded the onset of sepsis in adults up to 18 hours before septic shock developed (37, 40, 41). Additionally, decreased

HRV is associated with endotoxemia (33, 42). It is also associated with both the presence and severity of infection in adults (34, 43) as well as in children and neonates (30, 44–46).

There are also data to suggest that the monitoring of heart and/or respiratory rate variability may be useful with respect to MODS. Decreased HRV predicts subsequent deterioration, organ failure and death (47, 48). Bradley (37) reported that a reduction in variability was correlated with higher severity of MODS in 34 critically ill adults. When a population of patients was analyzed, a loss in variability was significantly associated with the progression of MODS; however, when analyzing individual patients, this variability proved very challenging to track due to the multiple HRV metrics that vary markedly over time in individual patients. The innumerable therapies that are delivered in a variable manner particularly complicate this analysis. Thus, monitoring illness severity or response to an intervention in an individual patient still requires further investigation.

Heart/Respiratory Rate Variability: Conclusion

Infinite knowledge of component parts cannot explain the whole system: evaluation of the system as a whole is required. Infinite knowledge of the present, or of populations, cannot predict the future: continuous monitoring over time is required. It is hypothesized that continuous evaluation of multiorgan variability can provide evaluation of a whole system over time (49, 50), and that such continuous evaluation can be performed by continuous monitoring of heart and/or respiratory rate variability.

In order to improve the quality and efficiency of care utilizing the monitoring of variability, it is helpful to translate the data into novel clinical decision support utilizing predictive modelling. Although reduced heart rate and/or respiratory rate variability are associated on average with increased severity of MODS, this does not necessarily indicate that monitoring changes in variability would help predict the onset or resolution of organ failure in individual patients. Realizing the importance of understanding how such monitoring could impact clinical decision making, it would appear important that variability needs to be translated into clinically relevant probabilistic information that provides more intelligible clinical decision support. However, further study in this area may help to better elucidate the mechanisms responsible for multiple organ dysfunction, mechanisms for altered heart and respiratory rate variability, and to improve outcomes.

Redox Monitoring in MODS – Strategies and Sensing Techniques

Oxidation-reduction (redox) reactions, including those involving oxygen free radicals and reactive oxygen species (ROS), lie at the heart of nearly every physiologic response occurring in illness and injury, including those playing a central role in multiple organ dysfunction. While metabolically active biologic systems rely on orderly conduction of electrons through interconnected redox reactions, alterations in redox balance have been linked to the generation of injurious free radicals (51), cellular apoptotic signaling (52), and the disruption of extracellular redox balance (51, 53), subsequently producing systemic redox shifts and oxidative stress. These redox shifts and oxidative stress are not merely a secondary phenomenon, but also play a central role in driving the systemic inflammatory response leading to multiple organ dysfunction (54, 55). In fact, mitochondrial ROS have

been found to have the ability to drive the initiation of the inflammatory cascade via inflammasome-dependent and independent pathways, as well as through their interaction with Damage Associated- and Pathogen Associated-Molecular Pattern Molecules (DAMPs and PAMPs) (56). There is mounting evidence that restoring redox balance is of vital importance to improving the metabolic derangements in shock as well (57, 58). Further, the concept of a “sepsis redox cycle” has been suggested as a state in which redox balance may be chronically altered and/or dysfunctional during sepsis, producing ongoing cellular dysfunction that requires restoration of a baseline redox state (51). In addition, a strong association has been demonstrated between individual markers of cellular redox balance and the onset of organ failure after injury, and these measurements are able to differentiate survivors from non-survivors during critical illness (59).

Because redox measurements reflect the balance between oxidants and reductants present, these measurements provide *direct* and *primary* measurements of the oxidative stress occurring in critical illness, including those central to the derangements leading to MODS. Yet, while it is well recognized that MODS can be present despite normal appearing *secondary* measures of oxidative stress such as the mixed venous oxygen saturation, and while many physicians recognize the importance of ROS and redox balance in the pathophysiology of disease and progression to MODS, redox monitoring is not currently performed in the clinical setting. This is due to both 1) a lack of understanding of the complex biochemistry involving redox species throughout the body and in MODS, and 2) the inability to make real-time, reliable measurements of redox balance in biologic media, such as whole blood. Given the potential benefit that redox monitoring may bring to clinical practice, overcoming these obstacles would appear to be an important goal.

To this end, while many investigators have focused on individual markers of oxidative stress, isolated redox species, and/or redox pairs in relation to shock and organ dysfunction (55, 59), few have investigated systemic, or organ-specific redox balance. This is understandable given the vast complexity of ROS pathways and the numerous redox pairs that are active in the systemic management of oxidative stress. However, given this complexity, overall systemic or organ-specific redox balance is unlikely to be defined appropriately by measuring isolated redox pairs and single ROS pathways. While these ROS pathways must continue to be studied, including the redox state in the mitochondria, we must also utilize a more global measure of redox balance, such as the whole blood redox potential, that accounts for each of these pathways and species. The determination of a whole blood redox potential may more appropriately reflect the progressive redox imbalance that leads to organ injury and MODS.

Obtaining redox measurements is relatively simple in concept. It only requires a reference electrode and a working electrode through which the balance of oxidants and reductants in any media can be measured via voltage (mV). However, there has been no proven reliable method to measure redox in whole blood or any other biologic fluids due to biofouling (blockage of the electrode surface by proteins and other factors in biologic media). Consequently, there is no rapid, direct and reliable method for evaluating redox species and redox balance in the metabolic and oxidative stress occurring in MODS. However, while continued development of electrode technology is needed, there have been improvements in

this area, including promising sensor technology that is currently being developed to enable direct redox testing in biologic media (60). In addition to improvements in electrode technology, further advancements are required in order to evaluate changes in redox balance in real time, and under experimentally controlled conditions, in order to gain greater insight into the association between redox states and the physiologic derangements that occur in shock, critical illness/injury, and MODS.

In the end, redox monitoring has great potential for providing a direct, real-time measure of the pathophysiological changes leading to MODS in a broad critical care population. It is well suited for evaluating disease processes and organ injuries that are highly affected by ROS and changes in oxidative stress, such as acute lung injury xxxxx (ALI).

Redox measures may not only provide guidance in diagnostic decision making, but may also inform the use of therapeutic interventions in the future. Although there is much debate regarding anti-oxidant therapies in critical illness, there have been multiple studies demonstrating the potential benefits of this treatment. The use of ascorbic acid to both attenuate the development of organ injury (61) and MODS (62), as well as to reduce the proinflammatory and procoagulant states that induce lung vascular injury in sepsis (63) is but one example. The use of resuscitation fluids with targeted anti-oxidant therapy, including mitochondrial anti-oxidants and ROS scavengers such as MitoQ and others, has been reported to improve organ function, recovery, and survival times in experimental models of sepsis and to protect against multiple organ dysfunction (64, 65). The use of such therapies might be optimized by redox balance monitoring. Clearly, organ systems operate optimally within a narrow range of systemic pH; it is plausible that the same is true within an optimal range of redox balance.

With sensor technology and measuring techniques steadily improving, there are a number of potential opportunities for the study of redox in critical illness and MODS (Table 1). These include not only the investigation of whole blood redox as it relates to critical illness/injury and MODS, but also organ-specific evaluation such as the assessment of redox in exhaled breath condensate (EBC) in acute lung injury, the evaluation of continuous renal replacement therapy (CRRT)/dialysis effluent and urinary redox in AKI, and the evaluation of cerebrospinal fluid redox in traumatic/anoxic brain injury. Redox may be found to be useful as a biomarker for evolving organ injury, an early warning signal for future injury, and/or to guide future therapeutic interventions in a variety of clinical conditions including MODS.

Conclusion

There is room for enhanced and more precise monitoring of MODS. Several candidate markers can be proposed to serve in this role. Various biomarkers are examples of promising candidates, like the PERSEVERE panel, redox, and monitoring heart and/or respiratory rate variability as well as computational modeling, which are discussed in this paper. Other candidates merit some attention, like biomarkers measured in sweat, and many physiological markers like global O₂ delivery (DO₂) and/or O₂ consumption (VO₂), intermittent or continuous central venous oxygen saturation (ScvO₂), near-infrared spectroscopy (NIRS),

blood lactate, global or peripheral O₂ extraction rate (O₂EXT, pO₂EXT), plethysmographic variability, gastric tonometry, etc. If the reliability and added value of these candidate technologies can be established, they hold promise to enhance the understanding, monitoring, and perhaps, treatment of MODS in children.

Acknowledgments

We thank the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and their Office of Science Policy, Analysis and Communications for their support of this Workshop. The research program of Dr Wong is supported by grants R01GM099773 and R01GM108025 from the NICHD.

Abbreviations

AKI	acute kidney injury
HRV	heart rate variability
ICU	intensive care unit
IL	interleukin
MMP	matrix metalloproteinase
MODS	multiple organ dysfunction syndrome
NF-κB	nuclear factor κ light-chain enhancer of activated B cells
PELOD	pediatric logistic organ dysfunction
PERSEVERE	Pediatric Sepsis Biomarker Risk Model
PICU	pediatric ICU
PRISM	pediatric risk of mortality
RCT	randomized controlled trial
RNA	ribo-nucleic acid
ROS	reactive oxygen species
RRV	respiratory rate variability
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor

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Table 1
Identified Knowledge Gaps and Potential Opportunities for Study Regarding the Ability and Use of New Technologies to Monitor the Severity of the Multiple Organ Dysfunction Syndrome (MODS)

<ul style="list-style-type: none"> Given the close association of MODS with sepsis and septic shock, it is important to understand if a panel of stratification biomarkers, selected through discovery oriented transcriptomic studies, can reliably estimate mortality probability for children with MODS. The ability of such biomarkers to provide biological information regarding the pathophysiology of MODS needs to be elucidated. A better understanding of the use of biomarkers to identify potential therapeutic targets to mitigate the development and progression of MODS may improve outcomes. The development of mechanistic models of signaling networks involved in MODS may also be useful in advancing the field. To do so, gene expression studies may be particularly helpful in informing such work. The assessment of heart and respiratory rate variability in the early detection and monitoring of MODS in children would appear to require further investigation. To begin, the feasibility of monitoring heart/respiratory rate variability in critically ill children needs to be established. For example, a monitor for neonates has been developed that calculates heart rate variability and issues a continuous score. The development of such technology for non-neonatal, critically ill children may help advance the field. The degree to which the variability of heart/respiratory rate vary independently of their frequency per minute and how that variability correlates with increased stress, decreased adaptability, and/or increased severity of illness is not clearly established. The etiology for the loss of variability in heart/respiratory rate and its potential to be used as a modifiable biomarker are not understood. It remains to be determined if there are specific high risk pediatric patients in whom continuous heart/respiratory rate variability monitoring could predict impending deterioration. The potential clinical utility of direct measurements of redox balance in the setting of MODS is not known. This is the result of a lack of understanding of the complex biochemistry involving redox species throughout the body and in MODS, and the inability to make real-time, reliable measurements of redox balance in biologic media, such as whole blood. The potential for measurements of redox balance to provide a gauge by which anti-oxidant/anti-reductant therapies, including those targeting the mitochondria, may be monitored for efficacy and clinical improvement has not been ascertained. The optimal range of redox balance within each organ system to assure the most efficient and effective level of functioning is not established; securing such data may be of clinical relevance. Further work is required in order to evaluate changes in redox balance in real time, and under experimentally controlled conditions, in order to gain greater insight into the association between redox states and the physiologic derangements that occur in shock, critical illness/injury, and MODS.

Table 2

Monitoring Heart and Respiratory Rate Variability in 36 Critically Ill Adults: Feasibility (37)

Problem	Heart rate variability ^a	Respiratory rate variability ^a
Disconnection	1.3% (1.0% – 2.1%)	7.3% (2.9% – 11.6%) ^b
Data cleaning	6.6% (1.4% – 17.9%)	5.5% (2.9% – 8.4%)
Atrial fibrillation	0.6% (0.1% – 3.9%)	

^aRepresent percent of 5 minutes and 15 minutes windows measured continuously that were not eligible for subsequent heart rate variability and respiratory rate variability analysis.

^bDisconnection and apnea.