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Refining the Pediatric Multiple Organ Dysfunction Syndrome

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Abstract

Since its introduction into the medical literature in the 1970s, the term multiple organ dysfunction syndrome (or some variant) has been applied broadly to any patient with >1 concurrent organ dysfunction. However, the epidemiology, mechanisms, time course, and outcomes among children with multiple organ dysfunction vary substantially. We posit that the term pediatric multiple organ dysfunction syndrome (or MODS) should be reserved for patients with a systemic pathologic state resulting from a common mechanism (or mechanisms) that affects numerous organ systems simultaneously. In contrast, children in whom organ injuries are attributable to distinct mechanisms should be considered to have additive organ system dysfunctions but

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not the syndrome of MODS. Although such differentiation may not always be possible with current scientific knowledge, we make the case for how attempts to differentiate multiple organ dysfunction from other states of additive organ dysfunctions can help to evolve clinical and research priorities in diagnosis, monitoring, and therapy from largely organ-specific to more holistic strategies.

Organ dysfunction is the hallmark of critical illness, with a myriad of causes, manifestations, severities, and biological mechanisms.[1,2] Although many illnesses primarily affect a single organ system, and thus present as single organ dysfunction, others affect >1 organ system, with resulting “multiple organ dysfunctions.” This latter state may occur at the onset of illness (eg, with severe trauma) or after some evolution of time (eg, when isolated glomerulonephritis leads to respiratory dysfunction from pulmonary edema or cardiovascular dysfunction from hypertensive cardiomyopathy as kidney injury advances). Numerous studies have revealed an association between the number of dysfunctional organ systems and death in children.[3–11] However, few attempts have been made to differentiate patterns of multiple organ dysfunction in critically ill children, such as (1) a common pathobiology causing dysfunction across >1 organ system, (2) a domino effect whereby primary dysfunction in 1 organ system leads to or induces dysfunction in other organ systems, or (3) unrelated pathobiology, where all organ dysfunctions are independent. As a result, reported mortality rates for children with multiple organ dysfunction vary widely, from <5% to 80%.[2]

We posit that pediatric multiple-organ dysfunction syndrome (MODS) should be considered a systemic pathologic state resulting from a common mechanism (or mechanisms) with varying organ system-specific penetrance. Although this syndrome is likely to be the most common scenario in which acute illness leads to >1 organ dysfunction, children may have additive organ dysfunction for other reasons (Table 1). For example, when a singular organ dysfunction (eg, arrhythmia-induced cardiac insufficiency) induces secondary organ injury (eg, respiratory dysfunction from cardiogenic pulmonary edema) or when concurrent organ dysfunctions are unrelated (eg, antibiotic-induced acute kidney injury [AKI] in a child with pneumonia), the patient should be considered to have additive organ dysfunctions but not the syndrome of MODS. The key advantage to this conceptual framework is that construing MODS as a syndrome caused by a common, systemic pathobiology acknowledges that the approach to diagnosis, monitoring, and therapy may benefit from evolving from isolated organ-specific to more holistic strategies that target a common pathobiology.

We have reviewed the evolution of our understanding of multiple organ dysfunction in pediatric critical illness and discuss the potential advantages and challenges in differentiating MODS from other circumstances in which children exhibit additive organ dysfunctions. We suggest that MODS be selectively applied to children with a specific syndrome rather than as currently used as an indiscriminate descriptor for any patient with >1 organ dysfunction.

HISTORY AND DEFINITIONS OF MULTIPLE ORGAN DYSFUNCTION

The challenge of treating multiple-organ dysfunctions is, in part, the reality of increasingly successful resuscitation and stabilization of acutely ill and injured patients. In the early half

of the 20th century, the major organ dysfunctions that limited survival were cardiovascular leading to shock, respiratory leading to hypoxia, and neurologic leading to herniation. With advances in knowledge and application of improved resuscitation strategies, better source control (for infections, hemorrhage, etc), advanced modes of ventilation, neuroprotective (including decompressive) therapies, and dedicated intensive care services, the natural course and epidemiology of acute illness have been altered over time. By the 1970s, Baue[12] and Tilney et al[13] had each described a condition of diffuse organ system failure among adults who, having survived an initial phase of cardiovascular dysfunction and shock, died after days in the ICU with sequential respiratory, kidney, hepatic, and gastrointestinal organ dysfunctions. Over time, the simultaneous dysfunction of >1 organ system has been designated by numerous terms, including multiple organ failure, multiple organ systems failure, multiple system organ failure, multiple organ dysfunction, and MODS.[2] Although failure is a commonly used term, the ability for many survivors to regain all or partial organ function argues against the notion of irrecovery that this term implies; hence, the term dysfunction is generally preferred in most cases.[14] Yet, the term dysfunction has the inherent problem of suggesting that organs are either functional or dysfunctional when, in reality, a spectrum of function exists from completely normal to completely abnormal. Moreover, what is commonly labeled as dysfunction on the basis of clinical or laboratory measures may not necessarily always be an impairment. A temporary state of altered organ function may, at least initially, provide an adaptive response to outlast ischemic, hypoxic, inflammatory, traumatic, or metabolic stress.[15]

DEFINING MODS AS A SYNDROME

A syndrome is characterized by three criteria: (1) a set of associated symptoms that consistently occur together, (2) a shared mechanism causing those symptoms, and (3) predictable outcomes.[2,16] Multiple organ dysfunction that occurs as a syndrome (ie, MODS) that meets these criteria is conceptually different than an unrelated group of additive organ dysfunctions without a shared mechanism that likely have more disparate outcomes.

The first criterion, ie, a set of associated symptoms that occur together, in MODS is dysfunction in >1 organ system. Although the number, type, and severity of organ system dysfunctions can differ between and within patients over time, this variability does not disqualify MODS as a syndrome. Indeed, many syndromes include variability in the number, type, and severity of symptoms (eg, Down syndrome). In pediatric MODS due to critical illness, the most common symptoms include cardiovascular, respiratory, kidney, hematologic, liver, and neurologic dysfunction. In children, at least 3 sets of criteria are in common use to define organ dysfunction, including criteria published by Wilkinson et al[17] in 1987, Proulx et al[18] in 1996, and Goldstein et al[19] in 2005 (Supplemental Table 1). None of these definitions were data driven; rather, each was established through consensus from a team of experts. Because inconsistencies between definitions compound patient-level heterogeneity in organ dysfunction,[20] a minimum set of associated symptoms to identify pediatric MODS should be established through a data-driven process that tests specific combinations of organ dysfunction type and severity with outcomes. For example, mild AKI concurrent with mild transaminitis, as might occur in a dehydrated child with viral

mononucleosis, need not necessarily meet the threshold for MODS, even though >1 organ system dysfunction is present.

The second criterion to qualify MODS as a syndrome is the presence of an underlying mechanism (or mechanisms) shared across all dysfunctional organ systems. For the majority of pediatric MODS, this criterion includes a severe systemic inflammatory response and/or generalized cellular energy crisis,[18,21,22] although many other mechanisms may be involved.[23–26] The absence of at least 1 shared underlying mechanism should be the key factor to differentiate MODS from other scenarios of additive organ dysfunctions. For example, concurrent acute respiratory distress syndrome with AKI from sepsis is pathobiologically distinct from aminoglycoside-induced kidney injury in a patient with pneumonia-induced respiratory dysfunction, even though both patients have respiratory and kidney dysfunction. Thrombocytopenia likely indicates hematologic dysfunction in a previously healthy child with sepsis but likely has different prognostic implications in a child with chemotherapy-induced bone marrow suppression in whom sepsis develops. However, we recognize that such a clear distinction will not always be evident in practice, especially when both shared and distinct mechanisms of organ injury could be invoked (eg, a child with sepsis treated with aminoglycosides who has both systemic and organ-specific explanations for AKI). Furthermore, we currently lack robust clinical or laboratory markers to reliably characterize most mechanisms of organ injury. Adding to this challenge is the realization that a shared biological mechanism may manifest differently across organ systems such that severe dysfunction may be observed in some organ systems, whereas mild dysfunction is evident in others. Finally, how to best classify sequential organ dysfunctions that are related but pathobiologically distinct is not entirely clear. For example, should encephalopathy after fulminant liver failure be considered a “shared mechanism,” even though the pathobiology directly causing each organ dysfunction is not the same? Even Baue[12] noted in 1975 that “failure of one organ system may contribute to the failure of others in this period of sequential, progressive, or simultaneous deterioration…[although] sometimes all systems seem to go at the same time.” Although we acknowledge that a clear answer is not yet possible, we suggest that conceptualizing MODS with a requirement for a shared mechanism (or mechanisms) will promote research efforts to better tease out these nuances. For example, improved understanding of systemic mechanisms that lead to MODS in sepsis have enabled the identification of biological phenotypes that benefit from specific treatments (see below).

For the third criterion, MODS must portend predictable outcomes that differ from other cases of additive organ dysfunction. Although it is well established that mortality rises sequentially with cumulative number of organ dysfunctions,[3–11] children with the syndrome of multiple organ dysfunction appear to have worse outcomes than those with other scenarios involving additive organ dysfunction. For example, among children with respiratory dysfunction requiring invasive mechanical ventilation, the group who presented with >1 organ dysfunctions (and thus was most likely to have the syndrome of multiple organ dysfunction) exhibited 7% mortality (103 deaths among 1547 patients) compared with 0.8% mortality (2 deaths among 244 patients) in the group with sequential organ dysfunction ($P < .001$).[27] Surgical patients have also been shown to have lower mortality than medical patients when >1 organ dysfunction is present at PICU admission (5.5% vs 11.8%, $P <$

.0001),[7] likely reflecting pathobiological differences in the etiology of concurrent organ dysfunction. However, few researchers have formally sought to distinguish between patients with MODS and those with other scenarios of additive organ dysfunctions; thus, it remains unproven whether having >1 organ dysfunction should not always be viewed as having a similar prognosis. We support that operationalizing some cases as MODS and others as sequential or unrelated additive organ dysfunction is a necessary first step to drive research efforts to address this epidemiological question.

MECHANISMS UNDERLYING MODS: THE EXAMPLE OF SEPSIS

MODS can accompany most critical illnesses.[28,29] Although MODS commonly involves a severe, systemic inflammatory process and/or a generalized cellular energy crisis,[1,12,30] many other mechanisms may be operative. Because sepsis is one of the most common causes of organ dysfunction in children, we will use sepsis to illustrate the benefits of augmenting organ-specific supportive care with systemic therapeutic strategies that also target mechanisms of MODS across organ systems.

In a subset of children with sepsis, a thrombotic microangiopathy referred to as thrombocytopenia-associated multiple organ failure (TAMOF) can be recognized as new-onset thrombocytopenia, hemolysis, evolving multiple organ dysfunction, and a decrease in the activity of disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13).[31,32] TAMOF is one subphenotype of sepsis-induced MODS, as patients have a set of associated symptoms that occur together (ie, cardiovascular and kidney dysfunction [among other organ dysfunctions] associated with hemolysis, thrombocytopenia), a likely shared mechanism underlying those symptoms (ie, diminished ADAMTS-13 activity that results in platelet- and von Willebrand factor–rich microthrombi), and predictable outcomes (ie, higher severity of organ dysfunction, increased mortality compared with children with sepsis without TAMOF). When TAMOF is present, a therapeutic approach that includes plasma exchange has been shown to replace ADAMTS-13, remove ultralarge von Willebrand factor multimers, and improve outcomes compared with organ-specific supportive therapy alone.[32,33]

Mitochondrial and other metabolic alterations are evident across failing organ systems in sepsis and, thus, are implicated in a systemic cellular energy crisis that contributes to organ dysfunction and MODS.[21,22,30,34–43] The inability of mitochondria to efficiently produce adenosine triphosphate through oxidative phosphorylation creates an energy deficit that can impair cellular—and ultimately whole-organ system—function. Such an energy deficit is expected to present first with dysfunction in high-energy–utilizing organ systems, such as the heart, kidney, brain, and gastrointestinal systems. Thus, shock, AKI, encephalopathy, and ileus are common features of sepsis. Although direct measures of mitochondrial dysfunction are challenging, 1 study of children with sepsis revealed persistent mitochondrial dysfunction in peripheral blood mononuclear cells from the subset with prolonged MODS.[44] Similar pathobiology was also reported in the development of MODS after trauma.[45] Although no therapies in common clinical practice target mitochondrial dysfunction, these could one day offer a novel holistic strategy for children with MODS.

INTERCONNECTEDNESS OF DYSFUNCTIONAL ORGAN SYSTEMS

Because organ systems are interconnected, we acknowledge that it can be difficult (even impossible in some circumstances) to tease apart the mechanisms that underlie 1 organ system dysfunction from another. A primary organ dysfunction can induce systemic biological effects through the release of danger- and pathogen-associated molecular patterns, cytokines, chemokines, hormones, and other biological factors. In this way, an initial single organ dysfunction may provoke or exacerbate other organ dysfunctions. Under the framework we describe, if the secondary organ dysfunction occurs via a common systemic pathobiology as the initial organ dysfunction or >1 of the secondary organ dysfunctions share the same mechanism, the patient has MODS. If the mechanism of each secondary organ injury is unique, the patient has additive organ dysfunctions, but not MODS.

The concept of organ integration and codependence is perhaps best illustrated by cardiovascular dysfunction. In shock, a state of sustained low cardiac output results in inadequate oxygen and metabolic substrate delivery to all tissues that can cause a systemic cellular energy crisis and trigger MODS through hypoxic-ischemic injury.[46] The primary therapeutic strategy here is to restore global organ perfusion rather than target kidney, liver, respiratory, or other organ dysfunctions individually (although organ-specific supportive therapies may need to be provided simultaneously). Viewed another way, in this scenario, kidney function is unlikely to improve until the shock state has been addressed.

Synergistic deleterious effects may also contribute to remote organ injuries—and thus MODS—even in the absence of primary organ dysfunction. For example, researchers found that mechanical ventilation in the setting of low-dose endotoxin led to extrapulmonary organ dysfunction in adult mice even without evidence of primary lung injury,[47] suggesting that compartmentalization of inflammation either by the host or by the clinician (eg, lung-protective ventilation strategies) may help to reduce the risk of remote organ dysfunction and the development of MODS. Again, the key message is that the therapeutic focus may need to extend beyond any 1 specific dysfunctional organ system.

The functional relationship within and between organs can also become uncoupled, such that a perturbation in the interconnectedness across organ systems itself promotes MODS. Godin and Buchman[48] proposed this concept in 1996, suggesting that vital organs (and their constituent cells) are “collections of biological oscillators that are coupled to one another and that the stability of the system resides as much in the couplings as in the oscillators themselves.” Examples of dampened biological oscillators that may contribute to MODS include the neuroendocrine, metabolic/endocrine, and autonomic nervous systems. Especially, low levels of vasopressin, sick euthyroid syndrome, reduced adrenal responsiveness, insulin resistance, hyperglycemia, and hyperleptinemia are all common in sepsis[49] and may impair normal oscillatory interorgan cross-talk. Similarly, emerging evidence reveals that the ability of the autonomic nervous system to maintain homeostasis can be altered by stress, severe infection, and sepsis,[50] with downstream effects on neurologic, immunologic, cardiac, endothelial, respiratory, and gastrointestinal function. Recognition that loss of heart rate variability is 1 manifestation of autonomic dysfunction may guide novel ways to monitor risk for and progression of MODS itself that could

augment more traditional organ-specific monitors at the bedside.[51] In addition, appreciation of the role of the neuroendocrine, metabolic/endocrine, and autonomic nervous system (both sympathetic and parasympathetic) in propagating MODS has led researchers to propose several novel therapeutic strategies to target the entire body system rather than individual organs.[52]

IMPLICATIONS OF DISTINGUISHING MODS FROM OTHER SCENARIOS OF ADDITIVE ORGAN DYSFUNCTION

An admitted advantage of treating all scenarios of >1 organ dysfunction as a count lies in ease of application, both in research (often summarized using the organ failure index with 1 point for each organ dysfunction[53]) and in clinical practice. Most researchers who have reported on the epidemiology of pediatric organ dysfunction have relied on retrospective clinical data abstraction in which data informing potential biological mechanisms were not prospectively assessed or reliably documented.[6,7,54] In addition, newer scoring systems that include both count and severity of dysfunction, such as the Pediatric Logistic Organ Dysfunction 2[10] and the pediatric Sequential Organ Failure Assessment[55] scores, still do not account for the temporal or causal relationship between organ system dysfunctions. Thus, as previously noted, it remains unclear whether MODS is more likely to portend a worse prognosis than other scenarios of sequential or unrelated additive organ dysfunction. If, as we hypothesize, outcomes are indeed worse for the syndrome of multiple organ dysfunction compared with other scenarios of additive organ dysfunction, investigators should attend to relevant mechanisms of organ dysfunction rather than simply a count of dysfunctional organ systems to optimize enrollment of critically ill children into future clinical trials.

An example where the distinction between MODS and non-MODS additive organ dysfunction could prove useful is pediatric acute respiratory distress syndrome (PARDS). Previous studies revealed that up to three-quarters of children with PARDS have extrapulmonary organ dysfunction.[27,56,57] In indirect PARDS, respiratory dysfunction occurs secondary to an extrapulmonary source (most often sepsis or trauma) in which lung injury is 1 manifestation of systemic pathobiology, such as inflammation and endotheliopathy. In direct PARDS, however, extrapulmonary organ dysfunction may be mechanistically distinct from the cause of lung injury (eg, hypovolemic prerenal AKI in a dehydrated child with severe respiratory syncytial virus infection) or a consequence of PARDS itself (eg, systemic inflammation induced by pulmonary biotrauma). Thus, although extrapulmonary organ dysfunction is often present in both indirect and direct PARDS, MODS is more likely in indirect PARDS where respiratory and extrapulmonary organ dysfunction share common underlying mechanisms of injury, including a predominance of endothelial rather than epithelial dysfunction.[58,59] Thus, although lung-protective strategies (eg, low tidal volumes, prone positioning) may improve lung function in both direct and indirect PARDS, amelioration of extrapulmonary organ dysfunction by reducing ventilator-induced lung injury may be less evident in indirect PARDS where extrapulmonary organ dysfunction is also driven by other systemic mechanisms. The extent to which additional attention to the syndrome of multiple organ dysfunction in indirect PARDS—and thus

more aggressive extrapulmonary therapies—could close the gap in observed outcomes from patients with direct PARDS is not yet clear.

THERAPEUTIC STRATEGIES FOR MODS

The treatment of patients with organ dysfunction is a fundamental charge of modern-day intensive care. Notably, the care of patients with established organ dysfunction remains largely supportive and organ specific, with a primary goal being to limit new and progressive organ injuries. Some efforts may hasten recovery from organ dysfunction, such as timely resuscitation from shock, infectious and hemorrhagic source control, and lung-protective ventilator management, but there have been surprisingly few additions to the intensivists' therapeutic armamentarium that specifically restore organ function, even despite evidence that cell death rarely underlies organ system dysfunction until the preterminal period. Indeed, most children die with persistent organ dysfunction when supportive care and life-sustaining therapies are withdrawn rather than as a result of progressive organ dysfunction.[60]

Current strategies to treat patients with >1 organ dysfunction can be categorized into (1) organ-specific therapies that primarily seek to support 1 organ system but may have secondary beneficial effects across other organ systems and (2) systemic therapies that address shared mechanisms across multiple organ systems. Both categories may be beneficial to address organ dysfunction, although we suggest that a key benefit of differentiating MODS from other scenarios of additive organ dysfunction is that clinicians and researchers will more directly acknowledge and seek out more holistic strategies.

Organ-Specific Therapies

The majority of current therapies for children with >1 organ dysfunction primarily support 1 organ system, although these often have secondary beneficial effects across other organ systems. Such therapies benefit both children with MODS and children with other types of additive organ dysfunctions. Examples include fluid and vasoactive resuscitation for cardiovascular dysfunction, blood transfusion for hematologic dysfunction, and renal replacement therapy for AKI. Additionally, for PARDS, organ-specific therapies to improve respiratory function include (1) lung-protective ventilation with low tidal volume, plateau pressure limitation, permissive hypoxemia, and hypercapnia; (2) pain and sedation scales to monitor and titrate sedation with a goal-directed protocol; (3) temporary neuromuscular blockade; and (4) consideration of prone positioning, corticosteroids, inhaled nitric oxide, and exogenous surfactant.[61] Such therapies are primarily focused on restoring or protecting lung function, but secondarily, they may limit extrapulmonary organ dysfunction by reducing systemic inflammation originating from lung injury (alveolar biotrauma), mitigating systemic hypoxemia, and minimizing detriments to perfusion pressure caused by high intrathoracic pressure. Another example is continuous veno-venous filtration, which is primarily used to support kidney dysfunction, may also remove cytokines and restore immune reactiveness.[62]

Systemic Therapies

Some therapies are not targeted to a particular organ system but, rather, to the systemic state of critical illness. Examples include early initiation of antibiotic therapy and source control in cases of sepsis; optimal medication dosing, as MODS affects pharmacokinetics and pharmacodynamics of drugs; nutritional support (preference for the enteral route); glycemic control; and fluid management aimed at maintaining intravascular volume while minimizing fluid overload.[63] The majority of these therapeutic strategies are used to limit secondary insults rather than mitigate mechanisms of the underlying MODS state. Therapeutic plasma exchange for TAMOF, for example, is an intervention used to reverse a cause of MODS.[32,33] Other examples may include intravenous immunoglobulins, corticosteroids, anakinra, or rituximab for macrophage activation syndrome/secondary hemophagocytic lymphohistiocytosis[64—66]; tranexamic acid for trauma-induced MODS[67]; eculizumab for transplant-associated thrombotic microangiopathy[68]; and immunomodulatory agents for MODS associated with immune paralysis and secondary hospital-acquired infections.[69,70] Unfortunately, far more examples exist of failed efforts to target biological mechanisms that underlie MODS, most notably in sepsis-induced MODS.[71] A more personalized approach in which therapies are better aligned with underlying mechanisms of MODS is likely to yield better success.[63,72,73]

CONCLUSIONS

Since its formal introduction into the medical literature 50 years ago, the term MODS (or some variant) has been applied broadly to any patient with >1 concurrent organ dysfunction. As the mechanisms underlying organ injury are better understood, we suggest that attempts to differentiate the syndrome of multiple organ dysfunction from other states of additive organ dysfunction— although not always possible—will help to evolve clinical and research priorities in diagnosis, monitoring, and therapy from largely organ-specific to more holistic strategies that target systemic pathobiology. Although we recognize that this proposed conceptual framework for MODS will, with current scientific knowledge, be difficult to apply to all patients, shifting a focus away from counting organ dysfunctions to identifying underlying pathobiological mechanisms will help the field of pediatric intensive care to advance from largely supportive to more precision-targeted, curative medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ADAMTS-13	activity of disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

AKI	acute kidney injury
MODS	multiple organ dysfunction syndrome
PARDS	pediatric acute respiratory distress syndrome
PODIUM	Pediatric Organ Dysfunction Information Update Mandate
TAMOF	thrombocytopenia-associated multiple organ failure

REFERENCES

1. Proulx F, Joyal JS, Mariscalco MM, Leteurtre S, Leclerc F, Lacroix J. The pediatric multiple organ dysfunction syndrome. Pediatr Crit Care Med. 2009; 10(1):12–22 [PubMed: 19057438]
2. Watson RS, Crow SS, Hartman ME, Lacroix J, Odetola FO. Epidemiology and outcomes of pediatric multiple organ dysfunction syndrome. Pediatr Crit Care Med. 2017;18(3 suppl 1):S4–S16 [PubMed: 28248829]
3. Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. Pediatr Crit Care Med. 2003;4(3) :333–337 [PubMed: 12831416]
4. Tantaleán JA, León RJ, Santos AA, Sánchez E. Multiple organ dysfunction syndrome in children. Pediatr Crit Care Med. 2003;4(2):181–185 [PubMed: 12749649]
5. Proulx F, Gauthier M, Nadeau D, Lacroix J, Farrell CA. Timing and predictors of death in pediatric patients with multiple organ system failure. Crit Care Med. 1994;22(6):1025–1031 [PubMed: 8205810]
6. Weiss SL, Fitzgerald JC, Pappachan J, et al. ; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015;191(10):1147–1157 [PubMed: 25734408]
7. Typpo K, Watson RS, Bennett TD, Farris RWD, Spaeder MC, Petersen NJ; Pediatric Existing Data Analysis (PEDAL) Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Outcomes of day 1 multiple organ dysfunction syndrome in the PICU. Pediatr Crit Care Med. 2019;20(10):914–922 [PubMed: 31589198]
8. Mtaweh H, Kochanek PM, Carcillo JA, Bell MJ, Fink EL. Patterns of multiorgan dysfunction after pediatric drowning. Resuscitation. 2015;90:91–96 [PubMed: 25703785]
9. Dowell JC, Parvathaneni K, Thomas NJ, Khemani RG, Yehya N. Epidemiology of cause of death in pediatric acute respiratory distress syndrome. Crit Care Med. 2018;46(11):1811–1819 [PubMed: 30095498]
10. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the Pediatric Logistic Organ Dysfunction score. Crit Care Med. 2013;41 (7):1761–1773 [PubMed: 23685639]
11. Leteurtre S, Martinot A, Duhamel A, et al. Validation of the Paediatric Logistic Organ Dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet. 2003;362(9379):192–197 [PubMed: 12885479]
12. Baue AE. Multiple, progressive, or sequential systems failure. A syndrome of the 1970s. Arch Surg. 1975;110(7): 779–781 [PubMed: 1079720]
13. Tilney NL, Bailey GL, Morgan AP. Sequential system failure after rupture of abdominal aortic aneurysms: an unsolved problem in postoperative care. Ann Surg. 1973;178(2):117–122 [PubMed: 4723419]
14. Marshall JC. The multiple organ dysfunction syndrome. In: Holzheimer RG, Mannick JA, eds. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich, Germany: Zuckschwerdt; 2001
15. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med. 2007;35(9 suppl):S441–S448 [PubMed: 17713391]

16. Typpo KV, Lacroix J. Monitoring severity of multiple organ dysfunction syndrome: new and progressive multile organ dysfunction syndrome, scoring systems. Pediatr Crit Care Med. 2017;18(suppl):S17–S23 [PubMed: 28248830]
17. Wilkinson JD, Pollack MM, Glass NL, Kanter RK, Katz RW, Steinhart CM. Mortality associated with multiple organ system failure and sepsis in pediatric intensive care unit. J Pediatr. 1987; 111 (3):324–328 [PubMed: 3625400]
18. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest. 1996;109(4):1033–1037 [PubMed: 8635327]
19. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2–8 [PubMed: 15636651]
20. Villeneuve A, Joyal JS, Proulx F, Ducruet T, Poitras N, Lacroix J. Multiple organ dysfunction syndrome in critically ill children: clinical value of two lists of diagnostic criteria. Ann Intensive Care. 2016;6(1):40 [PubMed: 27130424]
21. Fink MP. Bench-to-bedside review: cytopathic hypoxia. Crit Care. 2002;6(6):491–499 [PubMed: 12493070]
22. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence. 2014;5(1):66–72 [PubMed: 24185508]
23. Carcillo JA, Podd B, Aneja R, et al. Pathophysiology of pediatric multiple organ dysfunction syndrome. Pediatr Crit Care Med. 2017;18(3 suppl 1):S32–S45 [PubMed: 28248832]
24. Rossaint J, Zarbock A. Pathogenesis of multiple organ failure in sepsis. Crit Rev Immunol. 2015;35(4):277–291 [PubMed: 26757392]
25. Klingensmith NJ, Coopersmith CM. The gut as the motor of multiple organ dysfunction in critical illness. Crit Care Clin. 2016;32(2):203–212 [PubMed: 27016162]
26. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. Immunity. 2014;40(4):463–475 [PubMed: 24745331]
27. Weiss SL, Asaro LA, Flori HR, Allen GL, Wypij D, Curley MA; Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Investigators. Multiple organ dysfunction in children mechanically ventilated for acute respiratory failure. Pediatr Crit Care Med. 2017;18(4):319–329 [PubMed: 28212163]
28. Upperman JS, Bucuvalas JC, Williams FN, et al. Specific etiologies associated with the multiple organ dysfunction syndrome in children: part 2. Pediatr Crit Care Med. 2017;18(3 suppl 1):S58–S66 [PubMed: 28248835]
29. Upperman JS, Lacroix J, Curley MA, et al. Specific etiologies associated with the multiple organ dysfunction syndrome in children: part 1. Pediatr Crit Care Med. 2017;18(3 suppl 1):S50–S57 [PubMed: 28248834]
30. Ruggieri AJ, Levy RJ, Deutschman CS. Mitochondrial dysfunction and resuscitation in sepsis. Crit Care Clin. 2010;26(3):567–575, x–xi [PubMed: 20643307]
31. Carcillo JA, Halstead ES, Hall MW, et al. ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigators. Three hypothetical inflammation pathobiology phenotypes and pediatric sepsis-induced multiple organ failure outcome. Pediatr Crit Care Med. 2017;18(6):513–523 [PubMed: 28410274]
32. Nguyen TC, Han YY Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. Crit Care Med. 2008;36(10):2878–2887 [PubMed: 18828196]
33. Fortenberry JD, Nguyen T, Grunwell JR, et al. ; Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) Network Study Group. Therapeutic plasma exchange in children with thrombocytopenia-associated multiple organ failure: the Thrombocytopenia-Associated Multiple Organ Failure Network prospective experience. Crit Care Med. 2019;47(3):e173–e181 [PubMed: 30531184]

34. Adrie C, Bachelet M, Vayssier-Taussat M, et al. Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. Am J Respir Crit Care Med. 2001; 164(3):389–395 [PubMed: 11500338]
35. Belikova I, Lukaszewicz AC, Faivre V, Damoisel C, Singer M, Payen D. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis. Crit Care Med. 2007;35(12):2702–2708 [PubMed: 18074472]
36. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–223 [PubMed: 12133657]
37. Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion. 2004;4(5-6):729–741 [PubMed: 16120428]
38. Fink MP. Cytopathic hypoxia. Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? Crit Care Clin. 2002;18(1):165–175 [PubMed: 11910729]
39. Garrabou G, Morén C, López S, et al. The effects of sepsis on mitochondria. J Infect Dis. 2012;205(3):392–400 [PubMed: 22180620]
40. Japiassú AM, Santiago AP, d'Avila JC, et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. Crit Care Med. 2011;39(5):1056–1063 [PubMed: 21336129]
41. Levy RJ, Vijayasarathy C, Raj NR, Avadhani NG, Deutschman CS. Competitive and noncompetitive inhibition of myocardial cytochrome C oxidase in sepsis. Shock. 2004;21(2):110–114 [PubMed: 14752282]
42. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. Curr Opin Anaesthesiol. 2009;22(2):143–149 [PubMed: 19390243]
43. Tavakoli H, Mela L. Alterations of mitochondrial metabolism and protein concentrations in subacute septicemia. Infect Immun. 1982;38(2):536–541 [PubMed: 6128308]
44. Weiss SL, Zhang D, Bush J, et al. Persistent mitochondrial dysfunction linked to prolonged organ dysfunction in pediatric sepsis. Crit Care Med. 2019;47(10)1433–1441 [PubMed: 31385882]
45. Cairns CB, Moore FA, Haenel JB, et al. Evidence for early supply independent mitochondrial dysfunction in patients developing multiple organ failure after trauma. J Trauma. 1997;42(3):532–536 [PubMed: 9095123]
46. Brissaud O, Botte A, Cambonie G, et al. Experts' recommendations for the management of cardiogenic shock in children. Ann Intensive Care. 2016;6(1):14 [PubMed: 26879087]
47. O'Mahony DS, Liles WC, Altemeier WA, et al. Mechanical ventilation interacts with endotoxemia to induce extrapulmonary organ dysfunction. Crit Care. 2006;10(5):R136 [PubMed: 16995930]
48. Godin PJ, Buchman TG. Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 1996;24(7):1107–1116 [PubMed: 8674321]
49. Gheorghiţă V, Barbu AE, Gheorghiu ML, Căruntu FA. Endocrine dysfunction in sepsis: a beneficial or deleterious host response? Germs. 2015;5(1):17–25 [PubMed: 25763364]
50. Badke CM, Marsillio LE, Weese-Mayer DE, Sanchez-Pinto LN. Autonomic Nervous System Dysfunction in Pediatric Sepsis. Front Pediatr. 2018;6:280 [PubMed: 30356758]
51. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An interpretable machine learning model for accurate prediction of sepsis in the ICU. Crit Care Med. 2018;46(4):547–553 [PubMed: 29286945]
52. Parrish WR, Gallowitsch-Puerta M, Czura CJ, Tracey KJ. Experimental therapeutic strategies for severe sepsis: mediators and mechanisms. Ann N Y Acad Sci. 2008;1144(1):210–236 [PubMed: 19076379]
53. Doughty L, Carcillo JA, Kaplan S, Janosky J. The compensatory anti-inflammatory cytokine interleukin 10 response in pediatric sepsis-induced multiple organ failure. Chest. 1998;113(6):1625–1631 [PubMed: 9631803]
54. Typpo KV, Lacroix JR. Monitoring severity of multiple organ dysfunction syndrome: new and progressive multiple organ dysfunction syndrome, scoring systems. Pediatr Crit Care Med. 2017;18(3 suppl 1):S17–S23 [PubMed: 28248830]

55. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. JAMA Pediatr. 2017;171(10):e172352 [PubMed: 28783810]
56. Khemani RG, Smith L, Lopez-Fernandez YM, et al. ; Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med. 2019;7(2):115–128 [PubMed: 30361119]
57. Wong JJ, Phan HP, Phumeetham S, et al. ; Pediatric Acute & Critical Care Medicine Asian Network (PACCMAN). Risk stratification in pediatric acute respiratory distress syndrome: a multicenter observational study. Crit Care Med. 2017;45(11):1820–1828 [PubMed: 28749854]
58. Yehya N, Thomas NJ, Meyer NJ, Christie JD, Berg RA, Margulies SS. Circulating markers of endothelial and alveolar epithelial dysfunction are associated with mortality in pediatric acute respiratory distress syndrome. Intensive Care Med. 2016;42(7):1137–1145 [PubMed: 27101828]
59. Calfee CS, Janz DR, Bernard GR, et al. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. Chest. 2015;147(6): 1539–1548 [PubMed: 26033126]
60. Weiss SL, Balamuth F, Hensley J, et al. The epidemiology of hospital death following pediatric severe sepsis: when, why, and how children with sepsis die. Pediatr Crit Care Med. 2017;18(9):823–830 [PubMed: 28549024]
61. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):428–439 [PubMed: 25647235]
62. Peng Z, Pai P, Hong-Bao L, Rong L, Han-Min W, Chen H. The impacts of continuous veno-venous hemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients. Cytokine. 2010;50(2):186–191 [PubMed: 20202859]
63. Doctor A, Zimmerman J, Agus M, et al. Pediatric multiple organ dysfunction syndrome: promising therapies. Pediatr Crit Care Med. 2017;18(3 suppl 1):S67–S82 [PubMed: 28248836]
64. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. Pediatr Crit Care Med. 2009;10(3):387–392 [PubMed: 19325510]
65. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children*. Pediatr Crit Care Med. 2014;15(5):401–408 [PubMed: 24583503]
66. Demirkol D, Yildizdas D, Bayrakci B, et al. ; Turkish Secondary HLH/MAS Critical Care Study Group. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: what is the treatment? Crit Care. 2012;16(2):R52 [PubMed: 22715953]
67. Shakur H, Roberts I, Bautista R, et al. ; CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23–32 [PubMed: 20554319]
68. Jodele S, Fukuda T, Vinks A, et al. Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow Transplant. 2014;20(4):518–525 [PubMed: 24370861]
69. Hall MW, Knatz NL, Vetterly C, et al. Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. Intensive Care Med. 2011;37(3):525–532 [PubMed: 21153402]
70. Payen D, Faivre V, Miatello J, et al. Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series. BMC Infect Dis. 2019;19(1):931 [PubMed: 31690258]
71. Suffredini AF, Munford RS. Novel therapies for septic shock over the past 4 decades. JAMA. 2011;306(2):194–199 [PubMed: 21750297]

72. Cohen J, Vincent JL, Adhikari NK, et al. Sepsis: a roadmap for future research. Lancet Infect Dis. 2015;15(5):581–614 [PubMed: 25932591]

73. Hattori Y, Hattori K, Suzuki T, Matsuda N. Recent advances in the pathophysiology and molecular basis of sepsis-associated organ dysfunction: Novel therapeutic implications and challenges. Pharmacol Ther. 2017;177:56–66 [PubMed: 28232275]

TABLE 1

Clinical Scenarios Involving >1 Organ System Dysfunction

Description	Defining Features	Examples
MODS	More than 1 concurrent organ system dysfunction arising from a common systemic pathobiological mechanism (or mechanisms)	Sepsis-induced cardiovascular, respiratory, and kidney dysfunction from systemic inflammation and mitochondrial energy failure Trauma-induced cardiovascular, neurologic, and hepatic dysfunction from hemorrhage-induced global hypoperfusion Hypertensive emergency leading to cardiac dysfunction and neurologic dysfunction
Sequential organ dysfunction	A primary organ dysfunction induces a secondary organ system dysfunction, but the underlying mechanisms are different	Primary cardiac dysfunction from an arrhythmia leading to secondary respiratory dysfunction from cardiogenic pulmonary edema Primary liver failure from primary biliary cirrhosis leading to secondary neurologic dysfunction from hyperammonemia and cerebral edema Primary kidney dysfunction from glomerulonephritis leading to secondary cardiac dysfunction from hypertension
Unrelated organ dysfunction	More than 1 concurrent organ system dysfunction, with each organ system dysfunction caused by a different mechanism	Respiratory dysfunction from pneumonia and kidney dysfunction from aminoglycoside-induced acute tubular necrosis Cardiovascular dysfunction from sepsis and hematologic dysfunction from chemotherapy-induced bone marrow suppression

Note that each scenario is not mutually exclusive.