Pathophysiology of Pediatric Multiple Organ Dysfunction Syndrome

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Objective: To describe the pathophysiology associated with multiple organ dysfunction syndrome in children.

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

Study Selection: Not applicable.

Data Extraction: Moderated by an experienced expert from the field, pathophysiologic processes associated with multiple organ dysfunction syndrome in children were described, 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: Experiment modeling suggests that persistent macrophage activation may be a pathophysiologic basis for multiple organ dysfunction syndrome. Children with multiple organ dysfunction syndrome have 1) reduced cytochrome P450 metabolism inversely proportional to inflammation; 2) increased circulating damage-associated molecular pattern molecules from injured tissues; 3) increased circulating pathogen-associated molecular pattern molecules from infection or endogenous microbiome; and 4) cytokine-driven epithelial, endothelial, mitochondrial, and immune cell dysfunction. Cytochrome P450s metabolize endogenous compounds and xenobiotics, many of which ameliorate inflammation, whereas damage-associated molecular pattern molecules and pathogen-associated molecular pattern molecules alone and together amplify the cytokine production leading to the inflammatory multiple organ dysfunction syndrome response. Genetic and environmental factors can impede inflammation resolution in children with a spectrum of multiple organ dysfunction syndrome pathobiology phenotypes. Thrombocytopenia-associated multiple organ dysfunction syndrome patients have extensive endothelial activation and thrombotic microangiopathy with associated oligogenic deficiencies in inhibitory complement and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. Sequential multiple organ dysfunction syndrome patients have soluble Fas ligand-Fas–mediated hepatic failure with associated oligogenic deficiencies in perforin and granzyme signaling. Immunoparalysis-associated multiple organ dysfunction syndrome patients have impaired ability to resolve infection and have associated environmental causes of lymphocyte apoptosis. These inflammation phenotypes can lead to macrophage activation syndrome. Resolution of multiple organ dysfunction syndrome requires elimination of the source of inflammation. Full recovery of organ functions is noted 6–18 weeks later when epithelial, endothelial, mitochondrial, and immune cell regeneration and reprogramming is completed. (*Pediatr Crit Care Med* 2017; 18:S32–S45)

Key Words: cytochrome P450 metabolism; immunoparalysis; macrophage activation syndrome; sequential multiple organ failure; thrombocytopenia-associated multiple organ failure

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STATE OF THE SCIENCE

Overview

Baue et al (1–6) first described multiple system organ failure (MSOF) in a case series of general surgery patients who died

after 3 days in the ICU with sequential respiratory and then hepatorenal organ failures (rather than from shock in the first 3 d of critical illness). At autopsy, these patients had a persistent nidus of inflammation which Baue et al (1) hypothesized was the catalyst of MSOF. Steinberg et al (7) subsequently developed an experimental model of MSOF with the pre hoc intention that it be a sterile inflammation model rather than an infection model, and that it induce MSOF with both late survivors as well as late deaths. They discovered that only a combined injection of mineral oil plus zymosan (a component of the Saccharomyces A cell wall) induced MSOF, whereas single injections of either zymosan or mineral oil induced little illness. Importantly, this "gold standard" MSOF model exhibits a zymosan dose response effect on degree of organ dysfunction and mortality. Mineral oil provides irritation and zymosan provides pathogen-associated molecular patterns (PAMPs), which together cause persistent peritoneal macrophage activation that leads to cytokine-mediated epithelial, endothelial, mitochondrial, immune cell, and systemic organ dysfunction. The endogenous cytochrome P450 (CYP450) system, which ameliorates inflammation, is protective in this model (8), as is pretreatment with etoposide (9, 10). When studying this model, it is important to note that the term "MSOF" has evolved to be interchangeable with the term "multiple organ failure" (MOF) and "multiple organ dysfunction syndrome" (MODS). Importantly for our purposes, the experimental sterile inflammation intraperitoneal mineral oil and zymosan model has been validated in both "adult" and "pediatric" rodents (11–13).

In children, the pathophysiology of MODS has been evaluated in vivo and ex vivo in cohort studies using clinical definitions of persistent (14), progressive, or secondary (15) MOF/MODS described as three or more organ failures at 3 days, or increasing organs failing or development of MOF at 7 days, respectively. In these clinical studies of children with MODS, the findings are similar to the experimental model. Decreased CYP450 activity has been found to be inversely correlated with degree of cytokinemia and organ dysfunctions, supporting a role of altered metabolism in allowing pathologic inflammation (16). The "danger hypothesis" (17) posits that injury to endogenous cells releases damage-associated molecular patterns (DAMPs) that alter antigen-presenting cell responses to exogenous antigens or PAMPs in a way that amplifies the cytokine response. This hypothesis is supported by pediatric MODS studies (18–27). Children with MODS have been found to have higher circulating biomarkers of DAMPs, PAMPs, and cytokines that correlate with the degree of organ dysfunctions. The combination of decreased CYP450 metabolism, tissue injury–related DAMPs, and circulating PAMPs leading to self-injurious cytokinemia in pediatric MODS can be caused by cardiopulmonary bypass, trauma, cancer, liver failure, burns, pancreatitis, ischemia-reperfusion, inborn errors of metabolism, sepsis, rejection, graft versus host disease, overwhelming hemolysis, or autoimmune disease (**Fig. 1**). Cytokinemia in these children can lead to 1) epithelial cell dysfunction and apoptosis manifested as acute respiratory distress syndrome (ARDS), hepatobiliary dysfunction, and/or acute kidney tubular dysfunction; 2) endothelial cell dysfunction and apoptosis manifested as thrombotic microangiopathy with loss of microvascular homeostasis; 3) mitochondrial autophagy (mitophagy) and dysfunction manifested as catabolism, hibernation, and dysautonomia; and 4) immune cell dysfunction and apoptosis manifested as lymphoid organ depletion with ineffective microbe removal and tissue repair.

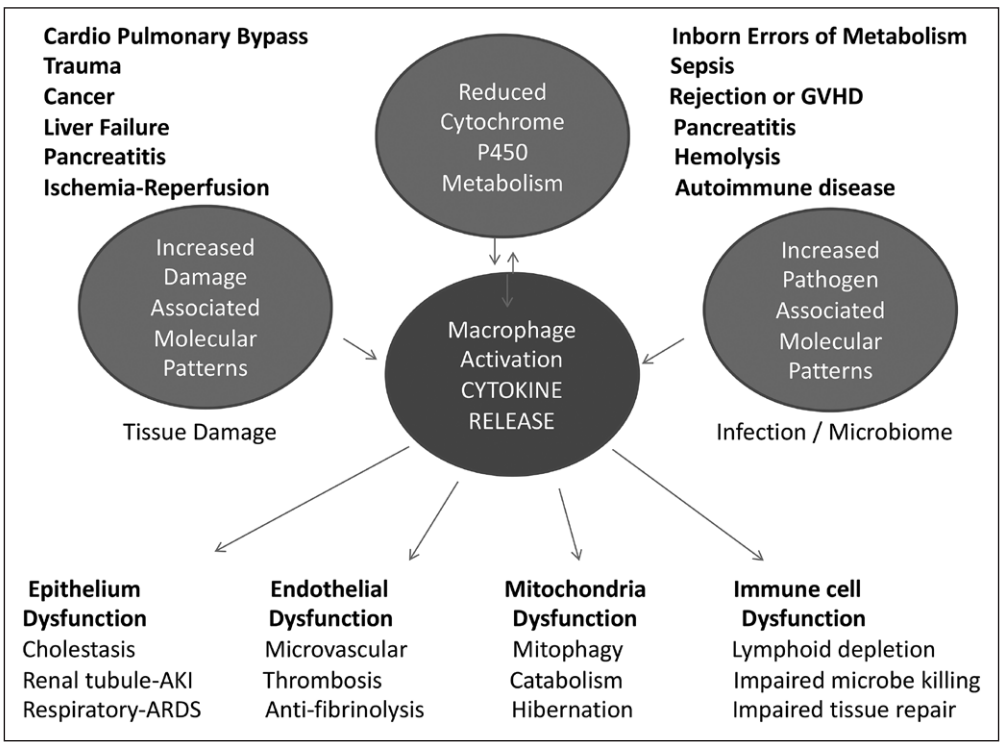

Figure 1. Four conditions are observed in pediatric MODS: 1) reduced cytochrome P450 activity, 2) increased circulating damage-associated molecular pattern molecules (DAMPs), 3) increased circulating pathogen-associated molecular pattern molecules (PAMPs), and 4) macrophage activation driven cytokine release associated with epithelial, endothelial, mitochondrial, and immune cell dysfunction and apoptosis. AKI = acute kidney injury, ARDS = acute respiratory distress syndrome, GVHD = graft versus host disease.

Experimental and clinical studies demonstrate that genetic and environmental factors can impede resolution of systemic inflammation in pediatric MODS. A spectrum of three inflammation pathobiology phenotypes has been described (**Figs. 2** and **3**). The first phenotype, thrombocytopenia-associated MODS, has low a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity (formerly known as

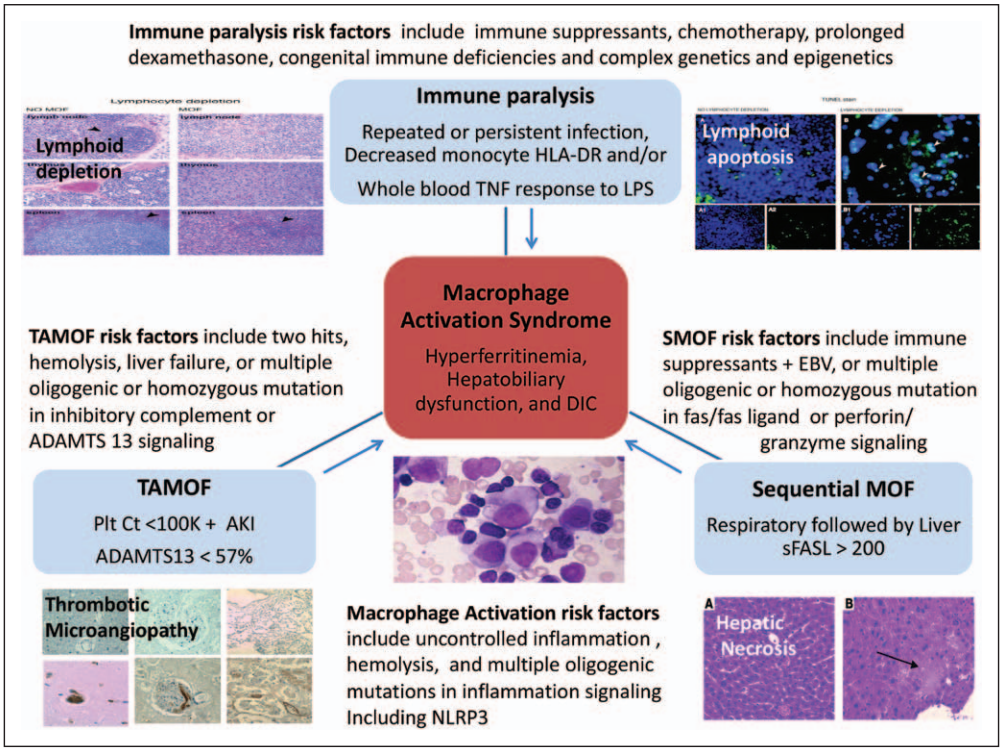

Figure 2. Environmental and genetic factors can impair the ability of the child with multiple organ dysfunction syndrome (MODS) to resolve inflammation: 1) Immunoparalysis is a condition in which antigen-presenting cells are unable to present and remove microbes and dead tissue; 2) Thrombocytopenia-associated multiple organ failure (TAMOF) is a condition in which complement activation is unopposed by inhibitory complement and von Willebrand factor (vWF) microvascular thrombosis is unopposed by ADAMTS13 (vWF cleaving protease); and 3) Sequential MODS is a condition in which cytotoxic T lymphocyte and natural killer cells cannot induce virus, cancer, or activated immune cell death and sFasL-Fas interactions cause liver failure. The common end pathway of uncontrolled inflammation is macrophage activation syndrome which can be associated with one or more of these phenotypes, or an inability to remove the source of inflammation for other reasons, or the presence of other pediatric hyperinflammatory syndromes including the cryopyrin-associated autoinflammatory periodic syndromes spectrum.
AKI = acute kidney injury, DIC = disseminated intravascular coagulation, EBV = Epstein-Barr virus, HLA = human leukocyte antigen, IL = interleukin, LPS = lipopolysaccharide, NLRP3 = Nod-like receptor-P3, Plt Ct = platelet count, SMOF = sequential multiple organ failure, sFASL = soluble Fas ligand, TNF = tumor necrosis factor.

"von Willebrand factor" [vWF] cleaving protease), acute kidney injury with extensive endothelial activation, and systemic vWF multimer thrombotic microangiopathy in brain, kidneys, and lungs (28–30). This has been related to oligogenic deficiencies in genes which produce inhibitory complement as well as ADAMTS13 that can lead to complement and thrombosis overactivation (31–41). This form of MODS has been successfully treated with the combination of eculizumab (C5a monoclonal antibody) and plasma exchange (restores ADAMTS13 activity) (42–50). Hemolysis-derived free hemoglobin also drives this phenotype related to both ADAMTS13 inhibition and macrophage activation (51–54). This endothelial activation phenotype can be experimentally produced with monoclonal antibodies to ADAMTS13 or with hemorrhage (DAMP stimulation) and subsequent endotoxin (PAMP stimulation) (55, 56).

The second phenotype, sequential MODS, develops soluble Fas ligand (sFasL)-Fas–mediated liver failure with associated oligogenic deficiencies in genes related to perforin and granzyme signaling that lead to slow resolution of lymphocyte and macrophage activation and proliferation (57). This can be reproduced experimentally in perforin/granzyme signaling knockout mice, which develop MODS when exposed to an otherwise innocuous viral antigen challenge (58–60). Patients with the homozygous mutant form of the disease are treated with chemotherapy including etoposide to target lymphoproliferation and then eventually bone marrow transplantation to restore cytotoxic T lymphocyte (CTL)/natural killer (NK) cell function (61). Patients with the oligogenic (heterozygous) form are treated with solumedrol, IV immunoglobulin (IVIG), and biologics including interleukin-1 receptor antagonist protein (IRAP) (61, 62). The third phenotype, immunoparalysis-associated MODS, has impaired ability to kill infection which can be related in part to environmental factors that induce lymphoid depletion such as chemotherapy, prolonged use of dexamethasone, and overuse of immunosuppressants (63–65). Treatments may include immunosuppressant tapering and the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) (64–67).

Hyperinflammation among these three phenotypes, whether associated with hypercomplementemia, lack of CTL and NK cell function, or inability to kill infection and mount tissue repair can all result in the macrophage activation syndrome (MAS) manifested clinically as hyperferritinemia (> 500 ng/mL), hepatobiliary dysfunction, and disseminated intravascular coagulation. Oligogenic mutations in interleukin (IL)-1, interferon (INF)-γ, nod-like receptor-P (NLRP), and CTL/NK signaling (67, 68) have been attributed to macrophage activation–associated MODS in newborns and children, and IRAP has been given U.S. Food and Drug Administration (FDA) orphan designation for the treatment of cryopyrin-associated autoinflammatory periodic syndromes spectrum of diseases which include familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease/chronic inflammatory neurologic cutaneous articular syndrome. Pediatric MAS-induced MODS has been successfully reversed with methylprednisolone, IVIG, and plasma exchange therapy as well as with IRAP (69, 70). Cytokine releasing syndrome–induced MODS in pediatric cancer patients treated with antineoplastic therapies has been successfully treated with monoclonal antibodies to tumor necrosis factor (TNF), as well as to IL-6 (71, 72).

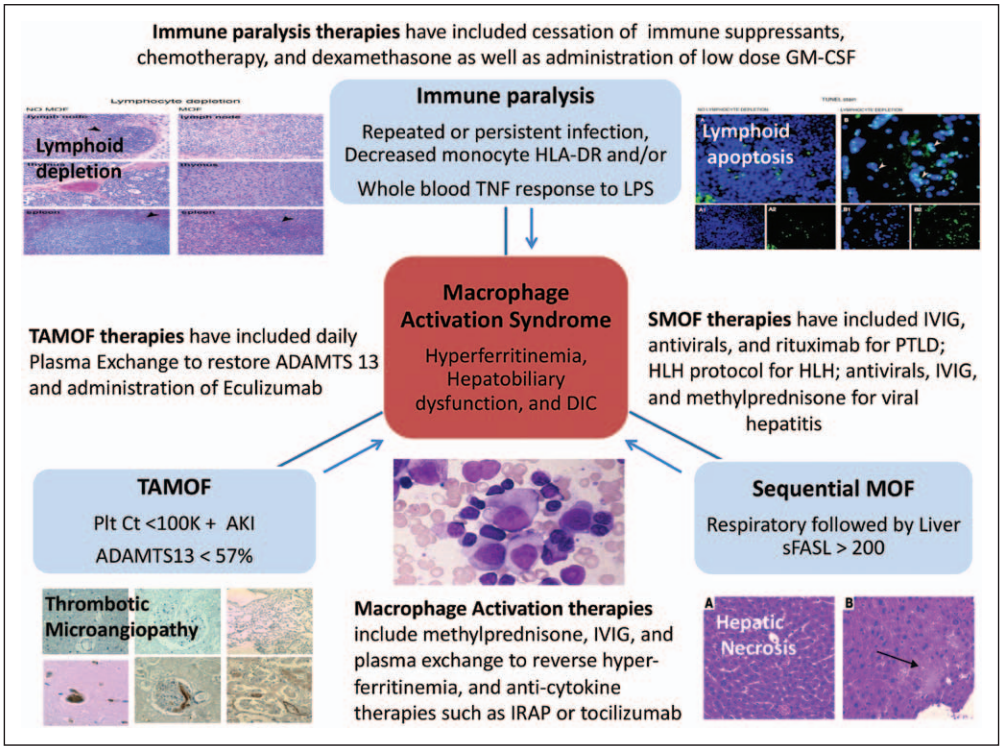

Figure 3. Phenotype-specific therapies reported as effective in resolving inflammation and facilitating multiple organ dysfunction syndrome recovery. AKI = acute kidney injury, ADAMTS13, DIC = disseminated intravascular coagulation, GM-CSF = granulocyte-macrophage colony-stimulating factor, HLH = hemophagocytic lymphohistiocytosis, HLA = human leukocyte antigen, IRAP = interleukin-1 receptor antagonist protein, IVIG = IV immunoglobulin, LPS = lipopolysaccharide, MOF = multiple organ failure, Plt Ct = platelet count, PTLD = post-transplant lymphoproliferative disorder, sFASL = soluble Fas ligand, TAMOF = thrombocytopenia-associated multiple organ failure, TNF = tumor necrosis factor.

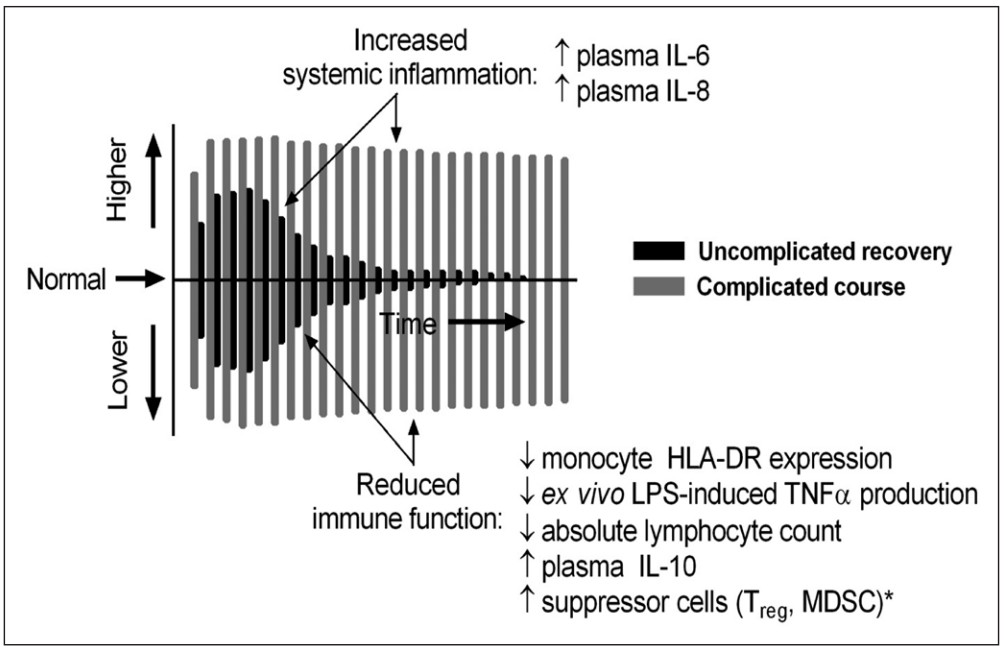

Figure 4. The dynamic immunoresponse in multiple organ dysfunction syndrome. Children who experience an uncomplicated recovery (*black bars*) frequently demonstrate prompt resolution of systemic inflammation with mild and transient reduction in immune function. Children with complicated courses (*gray bars*) often have persistently high levels of systemic inflammation concomitant with markedly reduced immune function. *Elevations in levels of suppressor cells have been demonstrated in critically ill adults but have not yet been found in children. HLA-DR = human leukocyte antigen, IL = interleukin, LPS = lipopolysaccharide, MDSC = myeloid-derived suppressor cell, T_{reg} = regulatory T cell, TNF = tumor necrosis factor.

The key to clinical success in preventing and reversing pediatric MODS is removal of the source of inflammation. For patients who have genetic or environmental factors impeding resolution of inflammation, clinicians can consider immune phenotype-specific strategies as well. Once inflammation resolves, the clinician can expect that full organ function recovery will take 6–18 weeks, which is the time needed for epidermal growth factor, hepatocyte growth factor, vascular endothelial growth factor, stem cell factor, endothelial progenitor cells, hematopoietic stem cells, mesenchymal stem cells, and various resident stem cells to orchestrate epithelial and endothelial cell regeneration, mitochondrial biogenesis, and immune cell reconstitution and reprogramming.

PAMPs and DAMPs

Pathogens express a diverse group of molecular motifs known as "PAMPs" that activate the inflammatory cascade. These motifs are recognized by a limited number of highly conserved pattern recognition receptors (PRRs), which include the toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors (73, 74). These PRRs also recognize the endogenous danger signals (75) or DAMPs. DAMPs are molecules (of many classes, e.g., DNA, RNA, proteins/peptides, lipids, carbohydrates) that are actively secreted or passively released into the extracellular environment from endogenous cells in response to tissue damage, regardless of cause. Since the first description of the cytokine-like properties of high-mobility group box 1 (HMGB1), it has been established as a prototype for

DAMPs (76–83). The delayed kinetics of HMGB1 release parallels the onset of lethality in animal models of sepsis. Treatment with neutralizing anti-HMGB1 antibodies can rescue mice from lipopolysaccharide (LPS) or sepsis-induced lethality (80), thereby solidifying its role as a potential therapeutic target. Elevated serum HMGB1 levels have been demonstrated in pediatric patients with MOF (81). Elevated serum HMGB1 concentrations are also present in adult septic patients with MOF. However, circulating HMGB1 levels were not different between survivors and nonsurvivors and failed to predict hospital mortality (82–84). Despite this lack of variation in serum HMGB1 levels between survivors and nonsurvivors, the currently held opinion is that HMGB1 is a critical late mediator of sepsis and a potential therapeutic target for MODS.

There is growing appreciation that both PAMPs and DAMPs contribute to organ failure and death although the precise mechanisms are unclear. PAMPs and DAMPs activate immune cells via TLRs leading to the production of reactive oxygen species (ROS) that promote endothelial dysfunction by the oxidation of crucial cellular signaling proteins (73). Although ROS are important in killing pathogens, excessive or unchecked ROS lead to tissue injury (85). In particular, cytokine- and hypoxia-induced production of ROS lead to mitochondrial dysfunction with subsequent development of cellular dysfunction and organ failure (86). Brealey et al (87) reported depressed adenosine triphosphate (ATP) levels in muscle biopsies taken from critically ill patients who went on to die, in contrast to eventual survivors who demonstrated elevated ATP levels in muscle biopsies. Similarly, elevated tissue oxygen tensions have led Fink et al (88, 89) to propose that septic organ failure represents cytopathic hypoxia, that is, cellular inability to use oxygen rather than a lack of its availability. Hypercytokinemia activates glycogenolysis and hepatic gluconeogenesis that leads to elevated glucose concentrations; therefore, systemic inflammation can alter ATP production rate and efficiency by altering the substrate availability. ATP depletion accompanied by an inhibited Na^+/K^+ pump leads to an increase in the cellular Na^+ concentration, resulting in cellular gain of electrolytes and water, causing early reversible cellular swelling (90). Inability of the organ to meet the ATP demand with diminished mitochondrial reserve capacity can activate cell death pathways that could lead to organ failure. Thus, key effectors in the pathogenesis of MODS include the inflammatory response that mediates ROS with subsequent reduction in mitochondrial function.

Mitochondria

Mitochondria play a central role in cellular metabolism in all organ systems (except for RBCs) and are responsible for more than 90% of cellular energy production through oxidative phosphorylation (91). In addition to generate ATP, mitochondria also play an integral role in other cellular pathways, including gene expression, inflammation, immune function, oxidative stress, calcium homeostasis, cell motility, heat production, hormone synthesis, and regulated cell death (91). Mitochondrial function varies in response to both intra- and extracellular factors that stress cellular bioenergetic homeostasis.

Perturbations in mitochondrial structure and function have been recognized for decades in animal models and, more recently, in critically ill patients with MODS (92). Under normal conditions, oxygen consumption through the mitochondrial electron transport system is tightly coupled to ATP production and is closely regulated by metabolic demand. In critical illness, acquired deficits in ATP production and other mitochondrial functions as a consequence of hypoxemia, ischemia, and inflammation can impair cellular bioenergetics, accelerate oxidant stress, and disrupt key metabolic pathways (92). Thus, mitochondrial dysfunction has been implicated as a "final common pathway" in the pathogenesis of organ dysfunction in sepsis, trauma, cardiac arrest, and other life-threatening illnesses.

Several lines of evidence support a role for mitochondrial dysfunction in the pathogenesis of MODS. In animal models of sepsis and trauma, mitochondrial abnormalities have been reported across vital organ systems (87, 93, 94). In humans, decreased mitochondrial oxygen consumption, low ATP, and mitochondrial gene repression have been linked to illness severity and death (87, 95–97). Metabolomic studies further suggest that energetic substrates related to fatty acid oxidation and the citric acid cycle are less efficiently used through mitochondrial aerobic respiration in sepsis nonsurvivors than in survivors (98). Finally, both spontaneous and pharmacologic restoration of mitochondrial function have been associated with recovery from MODS and improved survival. In particular, enhancement of mitochondrial biogenesis to produce new mitochondria and mitophagy to remove defective mitochondria has been found to restore organ function and promote survival (99).

Mitochondria also play a propagative role that fuels the systemic inflammatory response and contributes to distant organ injury. Mitochondrial DNA (mtDNA) fragmented by oxidative stress can be exported to the cytosol or the extracellular space. In the cytosol, mtDNA promotes the formation of the NLRP3 inflammasome, a supramolecular platform that up-regulates proinflammatory cytokines (100). In the circulation, mtDNA is recognized by the innate immune system as a DAMP and can trigger a systemic inflammatory response (101). Clinical studies have demonstrated an association of circulating levels of mtDNA with adverse outcomes (102, 103), and mtDNA has been proposed as a potential biomarker linked to mitochondrial dysfunction (103).

Notably, the term "mitochondrial dysfunction," although commonly used, may be somewhat of a misnomer. Experimental evidence suggests that purposive down-regulation of mitochondrial activity likely represents an adaptive response when oxygen and substrate availability are low, as is common in the acute phase of critical illness (92, 104). Although this hypometabolic state may manifest clinically as organ dysfunction, it is akin to mammalian hibernation and may help protect cells from a bioenergetic crisis and exposure to high levels of oxidative stress that can precipitate cell death. The observation that organ function rapidly recovers in MODS survivors, even in organs that are poorly regenerative, supports the notion that

a coordinated decrease in mitochondrial activity may be both adaptive—at least initially—and reversible (105). The factors coordinating the restoration of mitochondrial respiratory capacity, including mitochondrial biogenesis, fission/fusion, and mitophagy, are an active area of research (99).

Immunoparalysis

In the current era of critical care, many children survive the acute stages of critical illness from a myriad of triggers (e.g., sepsis, trauma, cardiopulmonary bypass), only to experience progressive organ dysfunction and delayed death. Most initial critical insults are characterized by the proinflammatory host response. It is increasingly evident, however, that the subacute course of critical illness is associated with an attenuated response of the host immune system, so-called, "immunoparalysis" (**Fig. 4**). Investigators have identified infections from opportunistic pathogens, unresolved sources of infection at autopsy, and reactivation of latent viruses all consistent with a functional alteration of host immunity following the acute insult (106).

It is now recognized that the host immune response in critical illness is highly dynamic, with systemic inflammation often concomitant with suppression of leukocyte numbers and function. The latter phenomenon represents the compensatory anti-inflammatory response syndrome (CARS) which, if transient, serves to prevent runaway inflammation (107). If persistent or severe, however, the CARS response represents an important form of acquired immune deficiency which can greatly complicate recovery from MODS. The development of impaired innate (e.g., monocyte, macrophage, dendritic cell) and adaptive (e.g., lymphocyte) immunity has been described in the aftermath of sepsis, critical viral infections, trauma, and cardiopulmonary bypass in children (108–112). Severe or persistent immune impairment has been associated with increased risk for secondary infection, MODS, and death in these settings.

The simultaneous elaboration of pro- and anti-inflammatory mediators in the storm of critical illness has been termed "immunologic dissonance" (107). This is a result of complex interactions of signal transduction pathways triggered by host exposure to PAMPs and endogenous DAMPs. These molecules bind to leukocytes as well as other tissues and use a variety of pathways to transmit their signals to the nucleus. The propagation of signals in these pathways relies on interconnected networks of multifunctional, signaling molecules which ultimately elicit a gene expression response that impacts cellular functions. For each of these signaling pathways, there exist negative regulatory mechanisms, including decoy molecules and inhibitory proteins, which can repolarize the cell to an anti-inflammatory phenotype. The literature suggests that in settings such as sepsis and critical trauma, down-regulation of leukocyte gene expression does occur, with the degree of suppression associated with mortality risk (113, 114). There are host-specific factors which can predispose patients to immunoparalysis. Family studies have demonstrated heritable tendencies toward increased anti-inflammatory cytokine production (115) although specific polymorphisms have not been identified. Epigenetics also likely plays a role, with an anti-inflammatory "gene on" histone methylation signature demonstrated in immunoparalysis following pediatric cardiopulmonary bypass (112). Disease or pathogen-specific factors are also important determinants of the risk for immunoparalysis. In addition to diseases that overtly affect immune function (e.g., primary immunodeficiency, leukemia), some forms of pediatric critical illness appear to be particularly immunosuppressive. These include severe traumatic brain injury (110) and infection with *Staphylococcus aureus* (109).

Finally, treatment-related factors can contribute to the development of immunoparalysis. The use of immunosuppressive medications such as glucocorticoids, antirejection drugs, and chemotherapy impair immune function. Many of the medications and therapies that are routinely used in the PICU, including sedatives and RBC transfusions, can negatively modulate the immune response as well (116). In this complicated setting, it is therefore crucial to have immune function tests that can identify the patient's place on the spectrum of immunosuppression or immunocompetence. This is particularly important because evidence suggests that immunoparalysis can be reversible through the use of medications such as GM-CSF or INF-γ with beneficial effects on outcomes in properly selected patients (66, 106, 117).

Innate immune function in critical illness has been measured through the quantitation of monocyte antigen-presenting capacity and/or cytokine production capacity. Expression of human leukocyte antigen (HLA)-antigen D-related (DR), an important antigen-presenting molecule, on the surface of monocytes can be quantified by flow cytometry. Data from critically ill adults and children suggest that risks for adverse outcomes increase if less than 30% of monocytes strongly express HLA-DR (118). Studies using a newer quantitative flow cytometry methodology suggest a similar threshold at less than 8,000 HLA-DR molecules per monocyte (119). Whole blood from patients with immunoparalysis will not respond robustly to ex vivo LPS stimulation, with reduced TNF-α production capacity being similarly associated with secondary infection, and mortality risk in pediatric MODS (66). Although TNF-α production in the laboratory will vary depending on the volume of blood used, the type of LPS, and the incubation duration, standardized protocols have been developed that permit single- and multicenter immune monitoring studies (109, 120). New microfluidic technology promises to reduce the blood volumes and times required for cytokine production capacity to be determined. At present, similar to HLA-DR measurement, no assay for TNF-α quantitation is currently FDA approved for clinical use in the United States.

Adaptive immune function has also been found to be reduced in critical illness, both in terms of lymphocyte function and numbers. Prolonged lymphopenia, with absolute lymphocyte counts less than 1,000 cells/mm^3, has been reported to independently predict secondary infection and mortality risks in pediatric MODS (65). Autopsy studies have demonstrated marked lymphocyte apoptosis in lymphoid organs from

TABLE 1. Identified Knowledge Gaps and Potential Opportunities for Study

There is a need to develop a better understanding of the role of cytochrome P450 as a protective system against MODS.
A more clear understanding of the molecular mechanisms involved in PAMP/DAMP-mediated cytokine release in MODS; such insight may result in the ultimate development of DAMP and PAMP modulators to prevent and ameliorate MODS.
The evolution and mechanisms of mitochondrial dysfunction and recovery in MODS are not completely established; deficits in mitochondrial metabolic pathways including electron transport system, citric acid cycle, and β oxidation of fatty acids require more evaluation. The ability to assess and monitor relatively rapid changes in mitochondrial function in a clinically relevant time frame is needed such that commonly used drugs which can inhibit/damage mitochondria during MODS may be assessed.
A clear understanding of the molecular mechanisms of macrophage activation in MODS is lacking.
The influence of genetic, epigenetic, and environmental factors in determining the risk for immunoparalysis, TAMOF, SMOF, and MAS is not completely understood. Additionally, the impact of intensive care interventions such as medications, transfusions, and mechanical support on the development of immunoparalysis, TAMOF, SMOF, and MAS also requires further elucidation.
The development of standardized immune function testing (e.g., human leukocyte antigen-DR expression, ex vivo lipopolysaccharide-stimulated TNF-α production capacity) that can be performed in the clinical laboratory in a clinically relevant time frame is needed.
There is a need to identify strategies for restoring immunologic balance in MODS, potentially including immunomodulation medications that target innate and/or adaptive immune function.
The role of FasL and defective activated immune cell death in MODS including liver injury and lymphoproliferation is not completely understood.
Further definition of the role of natural killer and CD8 cytolytic pathways in normal immune down-regulation and in hyperferritinemic MODS with MAS may help advance the field.
The genetic overlap in perforin and granzyme signaling (multiple oligogenic heterozygotes vs homozygous mutants) in pediatric MODS is not clearly elucidated.
There is a need for targeted therapies which control persistent hyperferritinemic hyperinflammatory states without inducing immunosuppression.
There is also a need for the development of a rapid and feasible biomarker assay for the identification of TAMOF such as a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, von Willebrand factor, and complement activities.
The therapeutic value of plasma exchange in the treatment of TAMOF needs to be better elucidated.
A better understanding of the common mechanistic pathways among various MODS phenotypes is needed.
The role of growth factors and regenerative response in reprogramming after MODS is not well elucidated.

DAMP = damage-associated molecular pattern; MAS = macrophage activation syndrome, MODS = multiple organ dysfunction syndrome, MOF = multiple organ failure, PAMP = pathogen-associated molecular pattern; SMOF = sequential multiple organ failure; TAMOF = thrombocytopenia-associated multiple organ failure.

nonsurvivors of sepsis-induced MODS (121, 122). Reduced capacity of lymphocytes to produce proinflammatory cytokines such as INF-γ and IL-2 has been associated with increased risk of infectious complications in septic children (123). Although cell counts should be a part of the routine clinical assessment of immunocompetence, it is unclear which markers of lymphocyte function are best for use in the ICU. It is possible that measurement of the negative costimulatory cell surface molecule, programmed death (PD)-1 or its ligands, PD-L1 and PD-L2, on lymphocytes and antigen-presenting cells, respectively, may have a role in ICU immune monitoring. High levels of PD-1, PD-L1, and PD-L2 expressions have been associated with immunoparalysis, and murine data suggest that they may be good therapeutic targets in future clinical trials (122, 124), potentially in combination with IL-7 therapy (125).

Hyperinflammatory Immune Mechanisms in MODS

Over the last decade, it has been convincingly demonstrated that immune responsiveness is down-regulated during MODS induced by sepsis, trauma (including traumatic brain injury), and other entities; however, there are notable patients who have "hyperinflammatory" conditions. Persistent inflammation can occur related to failure to achieve activated immune cell death (AICD). Two signal transduction systems which mediate AICD are particularly important, the Fas-Fas-ligand signaling pathway and the CTL/NK cell signaling pathway. The Fas-Fas ligand (Fas and FasL) molecules are among the key regulators of apoptosis of activated immune cells (126). Fas is a type 1 transmembrane protein of the TNF-receptor family. It is widely expressed constitutively and can be induced during the inflammatory response. Ligation of Fas by the FasL triggers a signaling pathway that leads to AICD (127). Fas can be cleaved from the cell surface into a soluble form (soluble Fas [sFas]) much like the TNF receptor and may serve as a decoy binding FasL and preventing its interaction with Fas (127). The expression of FasL is mostly restricted to T and NK cells (127). Its production is induced during inflammation, and it has its own proinflammatory properties including induction of IL-8, IL-1β, monocyte chemotactic protein-1, TNF-α, and others, and it has chemotactic properties bringing neutrophils and macrophages into inflamed areas (128).

TABLE 2. Reported Therapies for Multiple Organ Dysfunction Syndrome Subtypes

Subtype	Treatment	Study Population	Design	Study	Outcome
Immunoparalysis	Immunosuppressant withdrawal			Case reports	Infection and MODS resolution
	GM-CSF (66, 117, 119)	Children with ≥ 3 organ failure and ex vivo to tumor necrosis factor response < 168 pg/mL, $n = 14$; GM-CSF, $n = 7$; standard, $n = 7$	Randomized controlled trial	Prospective single center (66)	GM-CSF reversed immunoparalysis and reduced the onset of nosocomial infection from eight infections in seven patients with placebo to zero infections in seven patients with GM-CSF ($p < 0.05$)
		Adults with septic shock/severe sepsis/MODS and immunoparalysis defined by low monocyte HLA-DR expression, $n = 38$; GM-CSF, $n = 19$; placebo, $n = 19$	Randomized placebo controlled trial	Prospective multiple center study (115)	GM-CSF reversed immunoparalysis, increased ventilator free days, and improved physiologic severity/MODS score ($p < 0.05$)
	INF-γ (153)	Intubated adults with severe multiple trauma and immunoparalysis, $n = 21$; inhaled INF-γ, $n = 11$; inhaled placebo, $n = 10$	Randomized placebo controlled trial	Prospective single center study (153)	Inhaled INF-γ reduced ventilator-associated pneumonia ($p < 0.5$) and restored alveolar macrophage HLA-DR expression
TAMOF	Plasma exchange (30, 31, 48, 49, 152)	Pediatric TAMOF, $n = 42$; 15 plasma exchange; 27 standard care	Cohort study plasma exchange vs standard therapy	Prospective multiple center analysis (49)	28-d mortality decreased from 70.4% to 26.7%; multivariate analysis found improved survival controlling for Pediatric Risk of Mortality, organ failure index, Pediatric Logistic Organ Dysfunction score, and neurologic failure ($p = 0.048$)
		Pediatric TAMOF, $n = 10$; plasma exchange, $n = 5$; standard therapy, $n = 5$	Randomized controlled trial plasma exchange vs standard therapy	Prospective single center (30)	Plasma exchange restored organ function, improved a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 levels, and reduced 28-d mortality from 80% to 0% ($p < 0.05$)
		Adult TAMOF, $n = 37$; plasma infusion, $n = 22$; plasma exchange, $n = 15$	Randomized trial plasma infusion vs plasma exchange	Prospective single center (152)	Plasma exchange reduced hospital mortality from 32% to 0% ($p < 0.001$)
		Adult TAMOF, $n = 102$; plasma infusion, $n = 51$; plasma exchange, $n = 51$	Randomized trial plasma infusion vs plasma exchange	Prospective multiple center (31)	Plasma exchange reduced hospital mortality from 16% to 4% ($p = 0.035$) and 6 mo mortality from 37% to 22% ($p = 0.035$)
	Complement component 5a antibody (Eculizumab) (42–47)	Two small phase II trials; age > 12 yr with atypical hemolytic uremic syndrome	Open label single arm; year long treatment	Prospective multiple center (42)	Improved renal function over time and loss of plasma exchange dependence led to Food and Drug Administration approval as orphan drug

(Continued)

TABLE 2. *(Continued).* Reported Therapies for Multiple Organ Dysfunction Syndrome Subtypes

Subtype	Treatment	Study Population	Design	Study	Outcome
		Case series, $n = 3$, of children with hemolytic uremic syndrome-Shiga toxin producing *Escherichia coli*-related MODS treated with plasma exchange/Eculizumab rescue	Open label single arm 2-wk treatment	Retro-spective Single Center Case Series (47)	Improved MODS resolution and renal function thought to be temporally related to Eculizumab
Sequential MOF	Rituximab (154, 155)	Phase II trial of $n = 43$ adults with PTLD unresponsive to holding immunosuppression subsequently treated with rituximab	Open label single arm	Prospective Multiple center study (154)	86% survival at 80 d; 62% survival at 1 yr
		Phase II trial of adding rituximab to low dose chemotherapy, $n = 55$, in children with PTLD already receiving low dose cytoxan and prednisone	Open label single arm	Prospective multiple center study (155)	83% survival at 4.8 yr
	Antivirals/IV immunoglobulin/methyl-prednisolone			Case reports	Infection and MODS resolution
	HLH protocol (156)	Case series treated with HLH-94 protocol	Registry, open label single arm	Retro-spective, multiple center (156)	5-yr probability of survival is 54%
Macrophage activation syndrome	Methylprednisolone /IV immuno-globulin/plasma exchange (69)	Pediatric secondary hemophagocytic lymphohistiocytosis/sepsis/MODS/macrophage activation syndrome, $n = 23$; HLH chemotherapy protocol, $n = 6$, IV immunoglobulin/methylprednisolone, $n = 17$	Cluster randomized trial comparing HLH protocol with plasma exchange to IV immunoglobulin/methylprednisolone with plasma exchange	Prospective multiple center analysis (69)	Plasma exchange and treatment with IV immunoglobulin/methylprednisolone reduced hospital mortality from 50% to 0% ($p = 0.002$)
	IRAP (70, 157)	Adult MODS with disseminated intravascular coagulation and hepatobiliary dysfunction	Randomized double blinded placebo controlled trial	Post hoc multiple center analysis (157)	28-d mortality decreased from 64.7% to 34.6% hazard ratio, 0.28 [95% CI l, 0.11–0.0071]; $p = 0.007$
		Pediatric secondary hemophagocytic lymphohistiocytosis/sepsis/MODS/macrophage activation syndrome treated with IRAP, $n = 8$	Case series	Post hoc single center (70)	Considered to be temporally related to improvement of MODS. Hospital survival 100%
	Tocilizumab (71, 156)	Pediatric patients with cytokine releasing syndrome after chimeric antigen receptor T-cell therapy treated with tocilizumab, $n = 13$	Case series	Post hoc single center (158)	Considered to be temporally related to improvement of MODS

GM-CSF = granulocyte-macrophage colony-stimulating factor, HLH = hemophagocytic lymphohistiocytosis, HLA-DR = human leukocyte antigen DR, INF = interferon, IRAP = interleukin-1 receptor antagonist protein, IVIG = IV immunoglobulin, MODS = multiple organ dysfunction syndrome, *n* = number of patients, PTLD = posttransplant lympho proliferative disease, TAMOF = thrombocytopenia-associated multiple organ failure.

Impairment of AICD by defective Fas-FasL function can lead to autoimmunity, and in the autoimmune lymphoproliferative syndrome, Fas and FasL mutations are thought to be responsible (129). In children with sepsis-induced MODS (57), sFas levels were found to be highest in children with persistent (> 3 d) or sequential MODS (respiratory failure followed by hepatorenal failure), whereas sFasL levels were only elevated in sequential MODS. sFasL was associated with viral infection-related lymphoproliferative disease and the development of hepatic failure (57). Autopsy findings revealed hepatic lymphocytic infiltration, Epstein-Barr virus (EBV) infection, and lymphoproliferative disease in children with sFasL levels greater than 200 ng/mL, and hepatic necrosis in children with sFasL levels greater than 500 ng/mL. In hepatocyte cell culture experiments, incubation with exogenous sFasL greater than 500 ng/mL results in hepatocyte necrosis. These data support a role for lymphoproliferation-generated sFasL inducing hepatic injury in sequential MOF patients (57). Other investigators have also reported the presence of hepatocytes expressing Fas with FasL positively stained lymphocytic infiltration at the site of tissue injury in acute hepatitis/liver failure patients (130). Up-regulation of the sFas-FasL system has been observed in MODS related to ARDS (131, 132), inflammatory bowel disease (133), graft versus host disease (134), trauma (135), thrombotic thrombocytopenic purpura and disseminated intravascular coagulation (136), burns (137), MAS (138), and hemophagocytic lymphohistiocytosis (HLH) (139). All of these entities have a hyperinflammatory response. It is unclear whether Fas-FasL has an important role in these syndromes related to failed AICD or to sFasL being directly injurious to tissues.

Another important mechanism to achieve AICD is CTL and NK cell cytolysis of target cells (140). HLH and MAS (also known as "secondary" or "reactive HLH") share many features and are characterized by persistent hyperinflammation with hypercytokinemia. In familial HLH, there are mutations of genes involved with NK cell degranulation of perforin and granzyme (cytolytic mechanisms) (141). MAS can occur with oligogenic mutations most often observed in children with autoinflammatory conditions such as systemic juvenile idiopathic arthritis (SJIA) and its adult equivalent adult-onset Still's disease, numerous autoimmune diseases, malignancy, viral infections, and Kawasaki disease (142–144). Both HLH and MAS are characterized by low NK cell activity per cell, high levels of the CTL activation marker soluble CD25 (IL-2 receptor), and accumulation of $CD8^+$ CTLs and macrophages (143). Despite defective cytolytic activity, proliferation and cytokine production of these cells are robust leading to a prolonged and exaggerated inflammatory response (140, 141). Experimental and clinical studies have demonstrated that INF-γ is a key mediator in this process (58, 145, 146). The precise mechanisms leading to defective NK and CD8 cytolytic functions are unknown; however, one model of MAS in a genetically normal rodent demonstrates that it can be induced by repeated TLR-9 stimulation using cytosine-phosphate guanine (a microbial DNA, or PAMP mimicker) (147). Autoimmune disease, malignancy, and some persistent viral infections result in TLR-9 stimulation and can provoke these syndromes. Most viral infections induce robust INF-γ production which sensitizes macrophages to TLR ligand stimulation. It is plausible that viral infections trigger HLH/MAS because of INF-γ induction in the setting of genetic susceptibility or other unknown predispositions. Recently, whole exome sequencing of patients with SJIA and MAS revealed several (oligogenic) heterozygous protein–altering rare variants within some of the homozygous genetic mutations in the cytolytic pathway present in familial HLH. These findings were more common in SJIA positive MAS compared with SJIA without MAS (36% vs 14%, respectively) (148).

Currently, treatment of HLH includes high dose steroids, cyclosporine, and etoposide, all of which have substantial toxicities (149). Other biologic therapies being explored for MAS are anticytokine in nature including anti-IL-1, anti-TNF, and anti-IL-6 with some case reports of paradoxical MAS (with anti-IL-1 or anti-IL-6) during treatment for SJIA (150). In EBV-induced lymphoproliferation, anti-CD20 (rituximab) has been found to be successful (151). Because of the compelling experimental and clinical data implicating INF-γ, clinical trials using INF-γ blocking strategies are currently being conducted (146).

SUMMARY

MODS pathophysiology occurs when damaged tissue molecules (DAMPs), infection or bacterial toxin molecules (PAMPs), and reduced protective CYP450/mitochondrial metabolism lead to uncontrolled inflammation that perturbs endothelial, epithelial, immune, and mitochondrial cell homeostasis resulting in multiple organ system failures/dysfunctions. Altered coagulation with bleeding and thrombosis, and immunodysregulation with immunodepression and macrophage activation, are associated with several MODS phenotypes related to environmental exposures and host genetics. In addition to organ support, pathophysiology-based MODS therapies may include 1) removal of damaged and necrotic tissues (e.g., surgery), 2) removal of infection and toxin sources (e.g., timely administration of appropriate antimicrobials and antitoxins), and 3) MODS phenotype-specific therapies (e.g., immunomodulation for immunoparalysis; eculizumab and/or plasma exchange for thrombocytopenia-associated MOF; IVIG and/or rituximab for lymphoproliferative sequential MOF; and IVIG, methylprednisolone, and/or anti-inflammatory biologics for MAS). It is hoped that with further study, important knowledge gaps may be bridged that will enhance the understanding of the pathophysiology of this life-threatening condition and result in improved outcomes (**Tables 1** and **2**).

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