Multiple Organ Dysfunction Syndrome

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Contents

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Learning Objectives

- To recognize the clinical scenarios that may lead to the development of multiple organ dysfunction syndrome
- To describe the proposed cellular mechanisms that lead to multiple organ dysfunction syndrome in response to a pathologic stimulus and attendant organ pathology
- To understand the attendant organ pathophysiology in a patient experiencing multiple organ dysfunction syndrome
- To plan a course of therapy for a patient with multiple organ dysfunction syndrome
- To review reported outcomes, and the criteria used to predict them, among patients with multiple organ dysfunction syndrome

36.1 Introduction

All organs are not created equal – in terms of the effect of their dysfunction on patient outcome.

Multiple organ dysfunction syndrome (MODS) is the final common pathway that results from a variety of insults resulting in widespread endothelial dysfunction and organ injury. Although first described in the literature over four decades ago, it still can only be described as a syndrome, a constellation of signs and symptoms that consistently occur together, have a common pathophysiologic mechanism, and have a predictable outcome. In pediatrics, MODS is most commonly related to sepsis and the resultant inflammation. However, it also frequently occurs in a number of other conditions including massive hemorrhage and/or multiple trauma. Upward of 75% of patients admitted to surgical intensive care units who die have their cause of death listed as "multiple organ system failure." The terminology describing multiple organ dysfunction syndrome and failure has evolved over time. In 1992, the American College of Chest Physicians/Society of Critical Care Medicine Consensus statement described the "multiple organ dysfunction syndrome" as a continuum of organ compromise. In 2005, an international pediatric sepsis consensus conference reviewed and revised the diagnostic criteria. In 2015, the National Institutes of Health convened a Pediatric Multiple Organ Dysfunction Syndrome Workshop consisting of experts in the field with the goal to identify knowledge gaps and research priorities. Although multiple terms have been used throughout the published literature to describe this condition including "multiple organ failure" and "multiple organ system failure," multiple organ dysfunction syndrome appears to be the most commonly accepted term at this time.

This chapter will outline the epidemiology and clinical presentation of pediatric patients with MODS. Since the basic pathophysiologic mechanisms leading to MODS are those described amply in the chapters on inflammation, the endothelium, sepsis, and acute respiratory distress syndrome, the reader is referred to those chapters for more detail. The methods of characterizing organ dysfunction in pediatric MODS will be reviewed along with elements of treatment and supportive care. The prevention of MODS relies on early recognition of risk factors and triggering conditions with aggressive treatment of these underlying conditions *before* organ injury develops. The care of patients with MODS is primarily supportive. Subtypes of sepsis-induced multiple organ failure have been characterized, and therapeutic considerations for each will be outlined.

36.2 Epidemiology

Dr. Arthur Baue, a surgeon, first proposed the concept of multiple, progressive, or sequential organ system failure as a syndrome in the mid-1970s. It was a decade later before the first set of diagnostic criteria were reported

Table 36.1 Diagnostic criteria of multiple organ dysfunction syndrome

Organ system	Criteria
Cardiovascular	*If after 40 ml/kg intravenous fluid bolus over one hour* Hypotension (<5% for age) or SBP < 2 SD below normal for age *OR* the need for any vasoactive infusion to maintain normal blood pressure *OR* two of the following:
	Unexplained metabolic acidosis (base deficit >5.0 mEq/L)
	Increased lactate level (>2 times upper limit of normal)
	Oliguria or anuria (<0.5 mL/kg/hour)
	Prolonged capillary refill (>5 seconds)
	Core to peripheral temperature difference (>3°)
Respiratory	PaO_2/FiO_2 < 300 Torr (without cyanotic heart disease or pre-existing lung disease)
	$PaCO_2$ > 65 Torr or 20 mm Hg above baseline
	Need for >50% FiO_2 to maintain oxygen saturations ≥92%
	Need for nonelective invasive or noninvasive ventilation
Neurologic	Glasgow Coma Scale (GCS) ≤ 11
	Acute change in mental status (decrease in GCS ≥ 3 points from abnormal baseline)
Hematologic	Platelet count <80,000/cubic mL (or 50% reduction in chronic patient)
	International normalized ratio (INR) <2
Renal	Serum creatinine ≥2 times the upper limit of normal for age or doubling of baseline creatinine
Hepatic	Total serum bilirubin >4 mg/dL (excluding newborns)
	Alanine transaminase (ALT) 2× upper limit of normal for age

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by Wilkinson in 1987, and Proulx adjusted the definitions in 1996. In 2005, Goldstein revised the diagnostic criteria (Table 36.1). In 2015, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a Multiple Organ Dysfunction Syndrome Workshop. Robust diagnostic criteria are important in accurately establishing both the incidence and prevalence of MODS and in identifying progressive organ dysfunction.

The incidence of MODS in children admitted to the pediatric intensive care unit (PICU) across all diagnoses is reported to range between 6% and 57% in published studies over the last three decades, encompassing the varied sets of diagnostic criteria. Sepsis is the dominant cause of MODS in children, with the incidence ranging between 17 and 73% in published reports. Other causes

of MODS include burns, trauma, congenital heart disease, and hematopoietic cell transplantation. The wide range of reported incidence rates of MODS is likely influenced by the varied definitions used over time.

36.3 Clinical Presentation

MODS is considered to represent the end result, or the most severe end of a spectrum, that is characterized by a systemic inflammatory process (e.g., sepsis in the presence of an infection) or simply the systemic inflammatory response syndrome (SIRS) in the absence of infection. However, many patients meet the criteria of primary MODS on presentation to the PICU, either due to direct organ injury or pre-hospitalization manifestations of progressive organ dysfunction. Primary MODS is defined as two simultaneous dysfunctional organs within a week of PICU admission and without subsequent additional organ dysfunction. The patient who develops failure of more than one organ may have experienced a variety of insults, either overwhelming infection, hemorrhage (with or without a traumatic injury), or other conditions associated with systemic inflammation.

The clinical presentation of MODS can vary tremendously depending upon the underlying cause. Five inflammatory phenotypes have been described in the setting of sepsis, inflammation, and multiple organ failure. These include:

- *Thrombocytopenia-associated multiple organ failure (TAMOF)* which is characterized by reduced ADAMTS13 activity (< 57% of controls) which results in platelet clots, endothelial dysfunction, and a thrombotic microangiopathy. It is clinically manifested by new-onset thrombocytopenia, elevated lactate dehydrogenase levels, and acute kidney injury.
- *Immunoparalysis-associated multiple organ failure* can impact innate and adaptive immune function and is characterized by lymphopenia, a decreased *ex vivo* whole blood tumor necrosis factor-alpha response to endotoxin, decreased monocyte HLA-DR expression, and increased expression of inhibitory cell surface molecules such as PD-1. In addition to organ failure, it may be clinically manifested by an inability to clear bacterial or fungal infections.
- *Sequential multiple organ failure* is characterized by dysfunction of natural killer cells and cytotoxic T-lymphocytes resulting in disrupted destruction of viruses, cancer cells, and activated immune cells leading to unchecked viremia, lymphoproliferation, release of soluble Fas ligand (sFasL), hemophagocytosis, and sFasL-mediated liver injury. Uncontrolled inflammation occurs secondary to the inability to eliminate viruses or to induce apoptosis of activated immune cells. Clinically, it manifests with respiratory failure followed days later by new-onset liver dysfunction.
- *Critical pertussis-associated multiple organ failure (hyperleukocytosis and pulmonary hypertension-associated multiple organ failure)* is characterized by margination of neutrophils and lymphocytes leading to endothelial injury and cellular plugging of pulmonary arterioles, resulting in cardiopulmonary collapse.
- *Macrophage activation syndrome* is proposed to represent a final common pathway of uncontrolled inflammation. It is associated with endothelial disruption, macrophage production, disseminated intravascular coagulation, hepatobiliary dysfunction, and hyperferritinemia.

Shock with its attendant compromise in effective substrate delivery appears to occur commonly in association with these various perturbations. Thus, early aggressive resuscitation to restore oxygen delivery to the tissues in a timely manner is crucial as this has been well documented to improve outcomes and decrease the likelihood of progressing to MODS. Such an approach is now integral to evidence-based guidelines for the treatment of septic shock. However, in the patients who progress to multiple organ failure, the resuscitation phase is followed by a period of metabolic derangement characterized by temperature dysregulation, tachycardia, encephalopathy, acute kidney injury, and coagulation abnormalities. Despite aggressive support, many of these patients succumb to progressive organ dysfunction; the survivors often require prolonged recovery. The clinical presentation by individual organ system is described in the following section.

The clinical presentation of MODS can vary tremendously depending upon the underlying cause with multiple inflammatory phenotypes described in the setting of sepsis.

36.3.1 Cardiovascular

Cardiovascular dysfunction is a common component of MODS. This may occur as a result of one or more of several mechanisms. First, the heart may suffer primary dysfunction in the presence of myocardial depressant factors (e.g., interleukin-6 (IL-6) in the setting of meningococcal sepsis). Second, the increased metabolic demands of systemic inflammation with widespread endothelial injury, attendant interstitial edema, and reduced effective circulating volume can result in an inadequate oxygen delivery to meet the metabolic demands of the body characterized clinically by tachycardia. Interleukins and other vasoactive substances may cause vasodilatation and compensatory responses to maintain perfusion to vital organs. Additionally, the concomitant need for mechanical ventilation has competing effects on the heart. Although the positive intrathoracic pressure may decrease systemic afterload, the positive end-expiratory pressure may impede venous return, resulting in decreased preload and a decrease in cardiac output. Dysrhythmias may result from ischemic injury or from metabolic derangements related to potassium and calcium. The balance between the sympathetic and parasympathetic systems may be altered in the setting of multiple organ dysfunction. This is mediated by several pathways, including the pulmonary stretch receptors, central and peripheral chemoreceptors, and arterial baroreceptors. Decreased heart rate variability predicts a higher severity of MODS, subsequent deterioration, and death. Predictive modeling of heart rate variability is an emerging area of study in the field.

36.3.2 Respiratory

The paramount finding in patients with respiratory compromise is the failure of normal gas exchange that occurs in the presence of multiple pathogenic mechanisms. Acute lung injury (ALI) is associated with interstitial and alveolar edema, promoting atelectasis and ventilation-perfusion inequality, and hypoxemia. Acute respiratory distress syndrome (ARDS) represents progression of the lung injury. The features of pediatric ARDS are discussed fully in another chapter in this text (► Chap. 11).

36.3.3 Neurologic

The first manifestation of neurologic injury in patients with MODS is an alteration in the level of consciousness. Although the exact pathogenesis is not defined, it is likely due in part to impairment of cerebral perfusion, inflammation, and associated metabolic abnormalities. Additionally, the

The first manifestation of neurologic injury in the population of patients with MODS is an alteration in the level of consciousness.

neurologic assessment in pediatric MODS is complicated by the common need for sedatives, analgesics, and, at times, neuromuscular blockade. The brain architecture is usually found to be preserved on autopsy in those dying with MODS, and computerized tomography may reveal the presence of cerebral atrophy in those with prolonged illness. Patients remain at risk for secondary insults including ischemic/hemorrhagic complications associated with abnormal coagulation parameters and hemodynamic perturbations as well as prolonged sedation in the presence of hepatic dysfunction. Depletion of vital nutrients can predispose patients to demyelination syndromes. A well-described phenomenon in later stages is the entity of *critical illness polyneuropathy*, manifest clinically as weakness and inability to wean from mechanical ventilatory support, and electromyography revealing decreased sensory action potential amplitude.

36.3.4 Gastrointestinal

The release of toxic gut-derived substances into the mesenteric lymph, intestinal permeability to bacterial and/or endotoxin translocation, and alterations in the intestinal microbiome may all contribute to MODS.

Pediatric MODS may also be associated with several aberrations of gastrointestinal function. In fact, all components of the gut – the epithelium, the immune system, and the microbiome – may be impacted by critical illness, triggering a pathologic host response leading to MODS. For example, preclinical work has suggested that the release of toxic gut-derived substances into the mesenteric lymph may produce distant organ injury. In addition, intestinal permeability to bacterial and/or endotoxin translocation from mucosal ischemia in shock states has long been hypothesized to be a primary mechanism for systemic disease. Further, recent evidence supports the concept that the intestinal microbiome is also a contributor of pathology. Microbiome diversity was associated with improved outcomes in adults following hematopoietic cell transplantation. Fecal microbiota transplants have a higher cure rate of *Clostridium difficile* infections compared to oral vancomycin. The methods by which the microbiome is optimized remain a focus of ongoing investigation.

Hepatic dysfunction in MODS is usually characterized by elevated serum bilirubin levels.

Hepatic dysfunction, usually characterized by elevated serum bilirubin levels, represents an aberration of the gastrointestinal system frequently encountered in MODS. A period of hypotension can result in hepatocellular injury followed by significant elevations in transaminases. Moreover, the gallbladder may also be affected by hypotensive states and, in rare cases, become necrotic. Gallstones or sludge may be found on ultrasound evaluation.

An ileus may result from a variety of factors including infection, electrolyte disturbances, and narcotic infusions. Pancreatitis can either be the cause of multiple organ failure or complicated by its presence. Amylase and lipase levels should be screened for in the setting of MODS. Gastrointestinal bleeding may result from or be potentiated by stress ulceration, prolonged nasogastric tube placement, and/or existing coagulopathy.

Diarrhea may result from bacterial overgrowth states, infection with commensal or opportunistic organisms, or the vigorous use of cathartic agents. Fluid losses can be severe and may require volume replacement especially in the younger child. Voluminous stool output may also predispose a patient to skin breakdown near the anus and buttocks, providing a portal of entry for organisms that may result in an additional insult to an already debilitated patient. Alternatively, the use of narcotic infusions may result in constipation, sometimes requiring cathartic agents or manual decompression.

36.3.5 Hematologic

Coagulopathy is a common finding in the patient with MODS. This may result from liver injury, dilutional states, overwhelming infection, and/or disseminated intravascular coagulation.

The presence of multiple organ failure can promote a full spectrum of hematologic aberrations, as can be inferred from the multiple criteria in ◘ Table 36.1. Complete marrow failure may accompany overwhelming bacterial or viral infections. The leukocyte count may be either elevated or depressed. Anemia may be present; aggressive blood drawing practice, particularly in small patients, should be monitored and is a common cause of iatrogenic anemia. Thrombocytopenia may be the presenting feature of infection and/or a component of a consumptive coagulopathy. Coagulopathy is a common finding in the patient with multiple organ failure. This may result from liver injury, dilutional states, or overwhelming infection. Clotting factors may be depleted in patients who have received large-volume fluid resuscitation or blood product replacement. In addition, there is accumulating evidence that the coagulation cascades play integral roles in the initiation and propagation of the inflammatory response. Disseminated intravascular coagulation is also common in patients with MODS and is described in detail in ▶ Chap. 38.

36.3.6 Renal

Acute kidney injury and renal failure are frequently observed in the patient with MODS. Renal failure ensues when the kidney is unable to excrete nitrogenous wastes and maintain fluid and electrolyte balance. Oliguria and azotemia result, requiring administration of diuretics or continuous renal replacement therapy. Fluid resuscitation that occurs in the setting of shock may result in volume overload. This may be problematic as the amount of fluid overload has been found to be an independent risk factor for death; as little as 10% fluid overload has been associated with an increased risk of mortality. In survivors, greater than 20% overload is associated with six times greater length of mechanical ventilation than those with less volume overload. The time to initiation of continuous renal replacement therapy (CRRT) has similarly been found to be an independent predictor of mortality with some data suggesting that every hour delay is associated with a 1% increase in mortality.

36.3.7 Other Systems

Many patients with MODS will experience hyperglycemia.

Although typically not considered as "organs" to meet criteria for MODS, other critical regulatory systems are often affected. Patients with MODS may experience dramatic alterations in blood glucose levels. The neonate with suboptimal glycogen stores may present with hypoglycemia. Many patients with MODS will experience hyperglycemia; up to 50% of previously healthy patients and almost all diabetic patients experience this complication. Proposed mechanisms include insulin resistance, relative insulin deficiency, and increased levels of counter-regulatory hormones. There is some concern that hyperglycemia may be related to a worse outcome in patients with sepsis and MODS. Patients with a history of steroid use, as well as others, may be at risk for adrenal insufficiency. Therefore, random cortisol sampling or ACTH-stimulation testing may be useful in this setting.

The skin is the largest organ of the body; it is important in both temperature regulation and as a barrier to infection. The skin dissipates heat quickly. In the infant or patient who has sustained trauma, burns, or an operative procedure, resultant hypothermia can promote coagulopathy and suboptimal

perfusion. Prolonged recumbency may facilitate the development of decubitus ulcers. The incidence of this complication is reported to be as high as 10% in some critically ill populations. Despite aggressive intervention, these wounds can become infected, possibly leading to systemic bacteremia, cellulitis, and/or osteomyelitis, all poorly tolerated in the already severely compromised patient. Meticulous attention to skin care may decrease these preventable complications.

The musculoskeletal system is affected in patients with multiple organ failure. Trauma and burn victims may develop rhabdomyolysis, which may quickly result in pigment nephropathy and acute kidney injury. Critical illness myopathy is another musculoskeletal condition associated with MODS. Prolonged bedrest, inadequate nutrition, neuromuscular blockade, and steroid use may all place a patient at risk for critical illness myopathy. The diagnosis may be confirmed by electromyography or muscle biopsy, which may reveal low compound muscle action potentials or Type II atrophy, respectively. Patients experiencing MODS are likely to benefit from early mobility as part of a comprehensive bundle to optimize recovery.

36.4 Outcomes and Predictors of Outcome

The PELOD score is a valid method of quantifying pediatric MODS.

The earliest descriptions of pediatric MODS highlighted the increased mortality risk that roughly correlated with the number of failed organs. The science of predictive modeling has been applied in developing the Pediatric Logistic Organ Dysfunction (PELOD) score, by assigning weighted scores based on degrees of different organ dysfunction. This score has been validated and offers clinicians and researchers a meaningful method of quantifying the degree of organ dysfunction. This score was further assessed in an unselected multicenter PICU population, in conjunction with the diagnostic categories of SIRS, sepsis, severe sepsis, and septic shock. The study not only validated the predictive value of the PELOD score but also demonstrated that the presence or absence – and severity – of the septic state dramatically alters mortality risk. For example, an increase of the PELOD score by 10 points in children without SIRS was associated with a hazard ratio of death of 2.5. In contrast, an increase of the PELOD score by 10 points in children with septic shock was associated with a hazard ratio of death of 81.5 (◘ Fig. 36.1). An updated PELOD score (PELOD-2) has been developed, validated, and published in 2013. It differs from the original PELOD in that mean arterial blood pressure and lactatemia have replaced heart rate and systolic blood pressure in the cardiovascular section, hepatic dysfunction has been excluded, and it now represents a continuous scale. The PELOD-2 score is in the public domain to be used for clinical research and is reproduced in ◘ Table 36.2.

The PELOD (PELOD-2) score utilizes the most abnormal values during the entire PICU stay; the daily PELOD (*d*PELOD) uses the most abnormal value for a 24-h period. For the dPELOD, when a variable is not measured, it is assumed to be either identical to the last measurement (if the physician considers that the value of the variable did not change) or normal (if the physician considers that the value of the variable is normal).

Given the difficulty of achieving adequate sample size to demonstrate differences in mortality in PICU clinical trials, organ dysfunction scores are often used as proxy outcome measures in lieu of mortality for these studies. The concept of *new and progressive MODS* (NPMODS) is commonly used as an

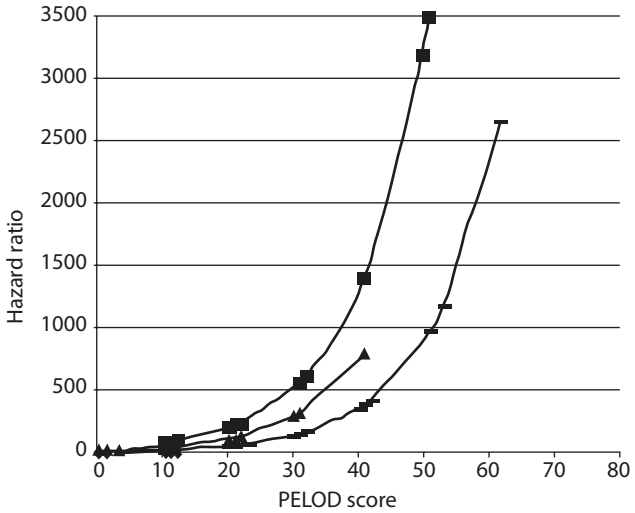

Fig. 36.1 Observed cumulative hazard ratios (HR) of death of the PELOD score and the diagnostic category of septic state. The figure depicts the observed cumulative hazard ratios (HR) of death of the PELOD score (which may range from 0 to 71) and the diagnostic category of septic state in the study population of 593 children consecutively admitted to a participating PICU. The HR of death is calculated by multiplying HR of the Pediatric Logistic Organ Dysfunction (PELOD) score ($1.096^{\text{PELOD score}}$) by HR of diagnostic category: no systemic inflammatory response syndrome (SIRS) (*diamond*); SIRS, sepsis (*dash*); severe sepsis (*triangle*); and septic shock (*square*). The subset of patients without SIRS depicted by the diamonds had low PELOD scores and low HR of death. Thus, they are depicted in the lower left side of the graph. (Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society (Leclerc et al. 2005))

outcome variable in pediatric critical care clinical studies. NPMODS is defined as the proportion of patients who die within a study period or who develop new or progressive MODS. *New MODS* is a term used to describe patients who have no or only single organ dysfunction at the start of analysis (e.g., PICU admission or study randomization) and who develop two or more concurrent organ dysfunctions at any time during the study period (e.g., PICU discharge or study termination). Patients with MODS at the start of analysis (e.g., PICU admission or study randomization) can develop *progressive MODS* which is defined as death or the development of at least one additional concurrent organ dysfunction at any point during the study period.

In addition to PELOD, there are other scores that are used to identify organ system failure and severity. The Pediatric Multiple Organ Dysfunction Score (P-MODS), the Pediatric Sequential Organ Failure Assessment (P-SOFA), the Organ Failure Index (OFI), and the organ failure-free days represent but just a few of those that have been used. In addition, efforts to link circulating cytokine levels to predict organ injury and outcome in sepsis have been evaluated. Higher admission procalcitonin and tumor necrosis factor-alpha levels have been demonstrated among nonsurvivors of septic shock. Similarly, the lack of a decline in procalcitonin levels portends a significantly higher mortality rate. At this time, PELOD and other MODS scores serve as a measure of morbidity and severity of illness and not as a predictor of mortality. As such, they are not intended as replacement for the prognostic scoring systems designed and validated to predict the risk of death upon patient admission such as the Pediatric Risk of Mortality III (PRISM III) or Pediatric Index of Mortality-2 (PIM-2).

Table 36.2 Pediatric Logistic Organ Dysfunction-2 score

Organ dysfunctions and variables[a]	Points by severity levels						
	0	1	2	3	4	5	6
Neurologic[b]							
Glasgow Coma Score	≥11	5–10			3–4		
Pupillary reaction	Both reactive					Both fixed	
Cardiovascular							
Lactatemia (mmol/L)	<5.0	5.0–10.9			≥11.0		
Mean arterial pressure (mm Hg)							
0 to <1 month	≥46		31–45	17–30			≤16
1–11 months	≥55		39–54	25–38			≤24
12–23 months	≥60		44–59	31–43			≤30
24–59 months	≥62		46–61	32–44			≤31
60–143 months	≥65		49–64	36–48			≤35
≥ 144 months	≥67		52–66	38–51			≤37
Renal							
Creatinine (μmol/L)*							
0 to <1 month	≤69		≥70				
1–11 months	≤22		≥23				
12–23 months	≤34		≥35				
24–59 months	≤50		≥51				
60–143 months	≤58		≥59				
≥ 144 months	≤92		≥93				
Respiratory[d]							
PaO_2 (mm Hg)/FiO_2	≥ 61		≤60				
$PaCO_2$ (mm Hg)	≤ 58	59–94		≥95			
Invasive ventilation	No			Yes			
Hematologic							
WBC count (×109/L)	>2		≤2				
Platelets (×109/L)	≥142	77–141	≤76				

Logit (mortality) = −6.61 + 0.47 × PELOD-2 score
Probability of death = 1/(1 + exp. [−logit(mortality)])
Adapted from Leteurtre et al. (2013)

[a]All variables must be collected, but measurements can be done only if justified by the patient's clinical status. If a variable is not measured, it should be considered normal. If a variable is measured more than once in a 24-h period, the worst value is used in calculating the score. *PaO_2* arterial partial pressure of oxygen; *FiO_2* fraction of inspired oxygen; *$PaCO_2$* arterial partial pressure of carbon dioxide

[b]Neurologic dysfunction: Glasgow Coma Score: use the lowest value. If the patient is sedated, record the estimated Glasgow Coma Score before sedation

Assess only patients with known or suspected acute central nervous system disease. Pupillary reactions: nonreactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation

[c]Cardiovascular: Do not assess the mean arterial pressure during crying or iatrogenic agitation

[d]Respiratory dysfunction: PaO_2: use arterial measurement only. PaO_2/FiO_2 ratio is considered normal in children with cyanotic heart disease. $PaCO_2$ can be measured from arterial, capillary, or venous samples. Invasive ventilation: the use of mask ventilation is not considered invasive ventilation

To convert μmol/L to mg/dL, multiply by 0.0113

36.5 Cellular Mechanisms and Pathology

Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis.

MODS can be viewed as the end-organ injury from the systemic inflammation that is initiated in SIRS or sepsis. In brief, a variety of stimuli can trigger an inflammatory cascade, initiated by cytokines (tumor necrosis factor-alpha, interleukin-1 (IL-1), etc.) from neutrophils and activated macrophages. The process is propagated by additional components such as platelet-activating factor and interferon gamma triggering the release of secondary mediators, arachidonic acid metabolites, and nitric oxide, by endothelial cells. Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis. Organ involvement in MODS is characterized by edema, neutrophil infiltration, and microvascular thrombosis. Additionally, increased evidence of programmed cell death, apoptosis, has been noted in splenic lymphocytes and colonic epithelium.

36.6 Therapy

Meticulous supportive care remains the mainstay of treatment for pediatric MODS patients.

The mainstay of therapy in MODS is treatment of the inciting event that led to systemic compromise. Prevention of further insults by meticulous supportive care is paramount in promoting recovery of the affected systems.

36.6.1 Supportive Care in Multiple Organ Dysfunction Syndrome (MODS)

Once a patient has developed MODS, supportive care of affected organ systems is essential. The anticipation and prevention of additional complications improves the likelihood of survival and optimal outcome. Examples of such prevention techniques are summarized in ◘ Table 36.3 and described below.

The neurologic sequelae that MODS patients experience may be in part due to therapeutic measures designed to promote comfort and facilitate care, such as deep sedation, analgesia, and neuromuscular blockade. Critical illness myopathy may occur as a consequence of prolonged infusion of neuromuscular blocking agents, especially when coupled with corticosteroids or aminoglycoside antibiotics. Although titration may not prevent this complication, patients receiving neuromuscular blockade should be assessed frequently for the degree of blockade utilizing train-of-four monitoring (► Chap. 23) or intermittent medication cessation to reduce the risk of excessive dosage. In addition, many patients develop tolerance to sedative and analgesic infusions; abrupt withdrawal of these medications may predispose a patient to withdrawal symptoms of diarrhea, agitation, and, occasionally, seizures. Anticipation and initiation of a scheduled taper may mitigate these undesirable events. Any abrupt change in neurologic status warrants full evaluation, including brain imaging and, if safe and feasible, lumbar puncture. Patients who receive prolonged benzodiazepine infusions are at risk for the development of delirium. Patients who survive their initial insult are likely to benefit from measures to improve sleep and awareness. Long-term cognitive follow-up is an important area of study in patients who survive prolonged intensive care unit stays. A recent publication demonstrated that nearly one-quarter of children surviving community-acquired sepsis experience a clinically significant deterioration in health-related quality of life.

Cardiovascular manifestations of multiple organ failure result from both the disease process itself and therapeutic measures and procedures used during the hospitalization. Many patients with MODS require inotropic and/or vaso-

Table 36.3 Supportive care strategies in pediatric multiple organ dysfunction syndrome (MODS)

System	Treatment
Neurologic	Interruption of sedative and neuromuscular blockade infusions
Cardiovascular	Titration to optimize oxygen delivery
Respiratory	Adequate gas exchange, minimize risk of oxygen toxicity and baro-/volutrauma, prevention of ventilator-associated conditions
Gastrointestinal	Prevention of stress ulceration, early feeding when appropriate
Renal	Consideration of renal replacement therapy to treat/prevent fluid overload and allow for administration of adequate caloric intake
Endocrine	Maintain euglycemia, high index of suspicion for adrenal insufficiency
Immune	Adjustment of immunosuppressive agents
Infectious	Appropriate antimicrobials/anti-infectives, strict handwashing by caregivers, meticulous attention to aseptic technique in insertion/maintenance of intravascular catheters
Hematologic	Judicious use of blood products, consideration of granulocyte macrophage colony-stimulating factor
Musculoskeletal/ integumentary	Prevention of skin breakdown, aggressive therapy of decubitus ulcers, physical therapy to prevent muscle wasting, early mobility

active infusions. These should be initiated after adequate volume resuscitation has occurred. Central venous pressure monitoring may assist in optimizing intravascular volume. Maintaining superior vena cava oxygen saturations ($ScvO_2$) > 70% has been associated with improved outcomes in pediatric patients with septic shock. As with all invasive maneuvers, the risks and benefits must be carefully balanced. Dysrhythmias may result from the presence of a catheter in or near the right atrium or from electrolyte disturbances; this complication may be preventable with close attention to catheter position and serum levels of potassium, magnesium, and calcium.

Respiratory failure connotes the lack of adequate gas exchange which, in the past, prompted aggressive attempts to normalize pH, partial pressure of carbon dioxide, and arterial oxygen tension. Such strategies employed the use of supraphysiologic tidal volumes, resulting in excessive distention injury to the lung. As highlighted in other chapters (► Chap. 11), not only can the lung architecture be damaged, but this can also perpetuate the systemic release of inflammatory mediators, thus adding further to the cascade underlying the process of MODS. In addition to reducing further lung injury by mechanical ventilation, special attention must be given to reduce the risk of ventilator-associated infection (VAI), which can occur in up to 5% of mechanically ventilated PICU patients.

The degree of fluid overload may carry prognostic significance; poor outcomes are associated with higher percentages of total body fluid overload.

Acute kidney injury frequently requires aggressive supportive measures. This begins with vigorous fluid administration. The fluid restriction that is often needed in a patient with established, intrinsic, oliguric/anuric renal disease to maintain euvolemia may not be warranted in the patient with multiple organ failure and ongoing capillary leak as maintenance of adequate circulating volume is essential. With the endothelial injury that these patients incur, they frequently develop total body fluid overload. As described above, there is

increasing evidence that the degree of fluid overload has important prognostic significance. When examining the use of CRRT in MODS patients with ≥3 organ failures, the percent fluid overload prior to initiation of CRRT is significantly higher among nonsurvivors than survivors, and it is independently associated with survival. When children with MODS were treated aggressively with CRRT, their survival rates compared favorably to historical controls. Early CRRT use is emphasized to mitigate the deleterious effects of volume overload and to allow for advancement of nutrition.

Endocrine issues may also play an important role in the care of patients with MODS. Early trials in adult surgical patients found that intensive insulin therapy (blood glucose concentrations maintained between 80 and 110 mg/dL) reduced mortality, bloodstream infections, the number of red blood cell transfusions, and the incidence of both renal failure and critical illness polyneuropathy. However, more recent studies have not confirmed these findings suggesting that tight glucose control may not influence outcomes, even in adult ICU patients. Hyperglycemia was identified as an independent correlate of mortality among patients receiving either mechanical ventilation or vasoactive infusions. Additionally, organ dysfunction (≥3 organs failed) is significantly associated with hyperglycemia. However, a multicenter randomized controlled trial in pediatric patients failed to demonstrate that tight glucose control had any impact on major clinical outcomes including days alive and ventilator-free days. Thyroxine infusions have been employed in a small series of patients with cardiogenic shock with improvements in cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure. Further, the measurement of cortisol levels has been suggested as a means to guide the administration of hydrocortisone in the setting of shock. In sum, it is clear that further studies are necessary to best inform interventions aimed at altering the endocrine system in children with MODS.

Antimicrobials should be administered in a timely manner when a suspected or documented infection exists. Empiric coverage should be initiated as soon as possible with reproducible data suggesting that the timely initiation of antimicrobials is associated with improved outcomes among patients with sepsis. The timely initiation of antibiotics should be based on local protocols and should incorporate the institution's patterns of expected pathogens and resistant organisms, as well as the patient's known colonizing flora. Broad-spectrum antimicrobials should be tailored as soon as speciation and sensitivities are available to prevent the emergence of resistant pathogens. Strict handwashing by caregivers is essential in the prevention of hospital-acquired infection. Attention to sterile technique during intravascular catheter placement and care is of utmost importance. Furthermore, prompt removal of catheters prevents colonization and the continued breach of skin integrity, which should further decrease infectious risk.

Additionally, attention should be focused on the anticipation and correction of abnormal hematologic findings. The administration of packed red blood cells may improve oxygen delivery in anemic patients. Although not specific for MODS patients, a multicenter, randomized trial among PICU patients found no difference in outcome between threshold hemoglobin values of 9.5 g/dL and 7 g/dL. Platelets should be administered to bleeding patients with thrombocytopenia. Vitamin K and plasma should be used to attempt to correct clinically significant coagulation defects. The use of granulocyte macrophage colony-stimulating factor (Gm-CSF) in neonates with sepsis and neutropenia has been found to improve outcomes. Similarly, there are emerging data to suggest that the use of Gm-CSF in pediatric patients with sepsis may improve survival.

Nutritional support should be provided as early as possible in the care of critically ill patients. A lower risk of intestinal permeability defects and multiple organ failure have been demonstrated in patients fed enterally early (within 6 h of admission) compared to those fed late (>24 h after admission). Among enterally fed critically ill children receiving mechanical ventilation, energy repletion is independently associated with survival.

36.7 Specific Therapeutic Consideration in MODS

Specific therapeutic considerations in MODS are centered around specific pathobiologic phenotypes (Table 36.4). Thrombocytopenia-associated multiple organ failure is manifest by endothelial dysfunction, impaired ADAMTS13 activity, and production of von Willebrand factor ultralarge multimers. This results in a consumptive coagulopathy with microvascular and organ injury. Therapeutic plasma exchange may restore ADAMTS13 activity, and eculizumab may be considered in the setting of atypical hemolytic uremic syndrome.

Immunoparalysis-associated multiple organ failure may be associated with both decreased innate and adaptive immune function. Treatment is directed toward the underlying condition; however, Gm-CSF may prevent secondary infection. Reducing or discontinuing immunosuppressive agents may be indicated.

Critical pertussis-associated multiple organ failure is manifest by hyperleukocytosis and pulmonary hypertension. Margination of neutrophils and lymphocytes lead to endothelial injury and cellular plugging of pulmonary arterioles, resulting in cardiopulmonary collapse. Leukoreduction may be indicated along with the appropriate antimicrobials. Extracorporeal support may be useful in some cases.

Sequential multiple organ failure is characterized by lymphoproliferation in the setting of disrupted activation-induced cell death, leading to unchecked viremia. This is most commonly found in patients with Epstein-Barr virus, resulting in posttransplant lymphoproliferative disorder. The mainstay of therapy is the reduction of immunosuppressant agents or the use of an anti-CD20 monoclonal antibody (rituximab).

Table 36.4 Inflammatory phenotypes and adjunctive therapeutic modalities

Phenotype	Therapy
Thrombocytopenia-associated multiple organ failure	Plasmapheresis, eculizumab
Immunoparalysis-associated multiple organ failure	Gm-CSF, decreased immunosuppression
Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure	Extracorporeal leukoreduction Appropriate antimicrobials
Sequential multiple organ failure with liver failure	Cessation of immunosuppression Rituximab
Macrophage activation syndrome	IVIG, anakinra, tocilizumab

Notes: *Gm-CSF* granulocyte macrophage colony-stimulating factor, *IVIG* intravenous immunoglobulin

Macrophage activation syndrome represents a hyper-inflammatory state characterized by endothelial disruption, macrophage production, disseminated intravascular coagulation, hepatobiliary dysfunction, and hyperferritinemia. Anti-cytokine therapy may be indicated in this phenotype with the IL-1 receptor antagonist (anakinra) or IL-6 blockade with tocilizumab. Hemophagocytic lymphohistiocytosis (HLH) is classified into primary and secondary forms. In primary (familial) HLH, inherited genetic mutations result in reduced cytotoxic T-cell and NK-cell function and/or other functional immunologic abnormalities. Secondary HLH results from both malignant and nonmalignant conditions, resulting in reduced function of these cells, excessive macrophage activation, and excessive cytokine production. Treatment may include steroids, plasma exchange, and intravenous immunoglobulin. Hematopoietic cell transplantation may be required for the treatment of primary HLH.

36.8 Summary

Multiple organ dysfunction syndrome (MODS) results from a variety of insults, most commonly sepsis and trauma. It often follows a common pathway once systemic inflammation cascades are triggered, and endothelial injury results in sequential organ dysfunction. Mortality remains high, roughly correlating with the number of organs involved, and survival is dependent upon treatment of the inciting process and optimizing supportive care. The validated PELOD score offers a reliable method of quantifying the severity of pediatric MODS. These critically ill infants and children are at risk for the development of progression of organ dysfunction and comorbid complications. Anticipation and prevention of these events with meticulous supportive care is currently the best available approach to improving outcomes. There are ongoing trials evaluating both targeted and nonspecific strategies to modulate the inflammatory process responsible for ongoing organ injury.

Review Questions

1. A 10-year-old male is admitted to the pediatric intensive care unit on postoperative Day 2 after undergoing exploratory laparotomy and drainage of abscesses secondary to a ruptured appendix. He develops altered mental status and hypotension. Vital signs are temperature 40 °C; heart rate 150 beats per minute, sinus rhythm; blood pressure 70/30 mmHg; respiratory rate 30 breaths per minute; and oxygen saturation 92% while receiving 15LPM of oxygen via a non-rebreather mask. Measurement of central venous pressure via a subclavian catheter is 1 mmHg. On examination, he is drowsy, but arousable, with nasal flaring and intercostal retractions. His abdomen is slightly distended with two closed-suction bulb drains draining serosanguinous fluid. His extremities are cool with a capillary refill of 3 s. After receiving 80 mL/kg of isotonic crystalloid solution, his blood pressure is 90/40 mmHg, the central venous pressure measurement is 4 mmHg, and he has had no urine output. He has become more somnolent and is beginning to grunt, while his oxygen saturation has dropped to 84% while on bilevel positive airway pressure of 20/10 cmH_2O.

   What is the next best intervention?

   A. Administer 40 mL/kg of 5% albumin.
   B. Administer 1 mg/kg intravenous furosemide.
   C. Begin an infusion of milrinone at 0.5 mcg/kg/min.
   D. Endotracheally intubate the child.
   E. Obtain computerized tomography of the head.

2. Which of the following scoring systems are used to quantify the severity of pediatric multiple organ dysfunction syndrome?
   A. Pediatric Risk of Mortality III (PRISM III)
   B. Injury Severity Score (ISS)
   C. Pediatric Index of Mortality-2 (PIM-2)
   D. Pediatric Logistic Organ Dysfunction (PELOD)
   E. Functional Status Scale

3. A 17-year-old female with a history of spina bifida and neurogenic bladder presents with a 2-day history of fever. In the emergency department, she is febrile to 39.4 °C, her heart rate is 140 beats per minute in sinus rhythm, blood pressure is 80/30 mmHg, respiratory rate is 30 breaths per minute, and oxygen saturation is 97% in room air. She has a clear sensorium, bounding pulses, and no organomegaly, and her skin is flushed with brisk capillary refill. There is a scant amount of urine in an indwelling catheter. A fluid bolus (20 mL/kg isotonic crystalloid) and antibiotics are administered, and she is admitted to the pediatric intensive care unit. *Which of the following statement is true regarding her care?*
   A. Acute kidney injury is the most likely explanation for her clinical condition.
   B. Additional crystalloid fluids should be administered prior to vasoactive infusions.
   C. Further fluid resuscitation should be restricted in order to prevent pulmonary edema.
   D. Parenteral nutrition is superior to enteral nutrition in this setting.
   E. The focus of infection is most likely pneumonia given her tachypnea.

4. Pathologic specimens of organs involved in MODS typically reveal infiltration with which of the following?
   A. Histiocytes
   B. Macrophages
   C. Monocytes
   D. Neutrophils
   E. Red blood cells

5. Anti-cytokine therapy using the IL-1 receptor antagonist (anakinra) has been suggested to be of benefit in treating this sepsis-induced MODS phenotype.
   A. Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure
   B. Immunoparalysis-associated multiple organ failure
   C. Macrophage activation syndrome
   D. Sequential multiple organ failure with liver failure
   E. Thrombocytopenia-associated multiple organ failure

6. The use of granulocyte macrophage colony-stimulating factor (Gm-CSF) has been suggested to be of benefit in this MODS phenotype.
   A. Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure
   B. Immunoparalysis-associated multiple organ failure
   C. Macrophage activation syndrome
   D. Sequential multiple organ failure with liver failure
   E. Thrombocytopenia-associated multiple organ failure

7. A 14-year-old male admitted to the pediatric intensive care unit with septic shock is somnolent but easily awakened. When prompted, he is following commands and conversing appropriately. His pupils are equal and reactive. He is receiving respiratory support via a CPAP mask set at 8 cmH_2O and 40% oxygen. He is found to have the following vital signs over the course of the 24-h period:
   Temperature: 36.7–40.1 °C
   Heart rate: 125–165 bpm
   Respiratory rate: 18–32 breaths per minute
   Mean arterial blood pressure: 50–68 mmHg
   His only laboratory results during that 24-h time period are as follows:
   Sodium: 132–139 mmol/L
   Potassium: 3.2–3.9 mmol/L
   Creatinine: 1.2–1.5 mg/dL (106–133 μmol/L)
   Lactate: 5.8 mmol/L
   WBC: 27,700 cells/μL
   Hemoglobin: 8.5 g/dL
   Platelet count: 105,000 cells/μL
   Aspartate transaminase: 75 U/L
   INR: 1.2–1.9
   pH: 7.33–7.39
   PaO_2: 65–93 mmHg
   $PaCO_2$: 31–43 mmHg
   Based on these values, his daily PELOD-2 score is which of the following?
   A. 1
   B. 3
   C. 6
   D. 7
   E. 10

Answers

1. D
2. D
3. B
4. D
5. C
6. B
7. D

Suggested Readings

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