Multiple Organ Dysfunction Syndrome

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Abstract

Multiple organ dysfunction syndrome (MODS) occurs after a life-threatening primary insult, including severe infection, hypoxic-ischemic injury, or other serious injuries. It represents a continuum of physiological abnormalities rather than a distinct state (present or absent). Young age and chronic health conditions are the most important risk factors for the development of MODS. Increasing number of dysfunctional organs is correlated with mortality, greater use of resources, and prolonged stay in pediatric intensive care units. Severe insults converge towards a common systemic response resulting in organ dysfunctions, yet the underlying mechanism remains ill-defined. Acute illnesses may trigger severe inflammatory response resulting in cytokine liberation, activation of coagulation, development of shock and capillary leak. Most experimental therapies to date have focused on attenuating the initial inflammatory response with little benefits in humans. As the initial inflammatory storm subsides, relative immune suppression becomes a major contributor to the disease process. Consequently, MODS patients are highly vulnerable to nosocomial infections. Metabolic demands and neuroendocrine responses also follow a similar seesaw pattern of over-activation followed by a state of relative suppression. Therefore, MODS may emerge from the cumulative suppression of metabolic, neuroendocrine, and immune functions resembling a state of dormancy, hypothesized to be an evolutionary protective cellular mechanism in response to overwhelming injuries. Diagnosis of MODS should encourage physicians to uncover the underlying etiology that may require a specific therapy. The symptomatic management of organ dysfunctions must be carefully assessed in the context of systemic interactions with other failing organs. Although long term outcome data of critically ill children with MODS is limited, 60 % of survivors are reported to have a normal quality of life with minimal health problems.

Keywords

Systemic inflammatory response syndrome • Sepsis • Multiple organ dysfunction syndrome • Cytokines • Immunoparalysis

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Introduction

Progressive organ dysfunctions were first reported 50 years ago in the surgical literature. In 1963, adult patients with severe peritonitis were found to develop a state of high output shock and respiratory failure requiring mechanical ventilation. Biochemical and mechanical factors were presumed to explain the severe deterioration in these patients [1].

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Table 35.1 Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock

SIRS[a]
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
Core[b] temperature of >38.5 °C or <36 °C
Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5–4-h time period OR for children <1 year old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-h time period
Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10 % immature neutrophils
Infection
A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)
Sepsis
SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis
Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Organ dysfunctions are defined in Table 35.3
Septic shock
Sepsis and cardiovascular organ dysfunction as defined in Table 35.3

Adapted from Goldstein et al. [10]. With permission from Wolter Kluwers Health
[a]See Table 35.2 for age-specific ranges for physiologic and laboratory variables
[b]Core temperature must be measured by rectal, bladder, oral, or central catheter probe

Table 35.2 Age-specific vital signs and laboratory variables [10, 13]

	Heart rate, beats/min				
Age group	Tachycardia (beat/min)	Bradycardia (beat/min)	Respiratory rate, (breaths/min)	Leukocyte count, (10^9/L)	Hypotension (mmHg)
0 days to 1 week	>180	<100	>50	>34	<59
1 week to 1 month	>180	<100	>40	>19.5 or <5	<79
1 month to 1 year	>180	<90	>34	>17.5 or <5	<75
2–5 years	>140	NA	>22	>15.5 or <6	<74
6–12 years	>130	NA	>18	>13.5 or <4.5	<83
13 to <18 year	>110	NA	>14	>11 or <4.5	<90

Lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th and upper values for heart rate, respiration rate, or leukocyte count for the 95th percentile
NA not applicable

A sequential pattern of organ failures was identified during the 1970s among patients with ruptured aortic aneurysms [2]. Improvement in the medical management of shock states began to change disease progression and more reports of multiple organ failures in shock survivors emerged [3, 4]. Several studies uncovered a relationship between an increasing number of failing organs and mortality [5] or the length of stay in the intensive care unit (ICU) [5]. Multiple organ dysfunctions were found to occur with or without any identifiable infectious source [6], changing in severity over time, and being potentially reversible. Faced with this new entity, adult diagnostic criteria for the systemic inflammatory response syndrome (SIRS) [7], sepsis, and organ dysfunctions were proposed in 1992 [6] and were revisited in 2003 [8]. These definitions helped to distinguish the insult (infection, trauma, etc.), from the host response (SIRS) and the subsequent number of organ dysfunctions, while emphasizing the pathophysiological continuum culminating in these organ dysfunctions [9].

Definition of Pediatric Multiple Organ Dysfunction Syndrome (MODS)

Diagnostic criteria currently used to define the infectious insults, the host response (SIRS), and the number of organ dysfunction in children were established in 2002 [10] and are summarized here. *Systemic inflammatory response syndrome* [7] refers to any combination of two or more symptoms including fever or hypothermia; tachycardia or bradycardia in infants (<12 months of age); tachypnea or hypocapnia; leukocytosis or leukopenia (Tables 35.1 and 35.2) [6]. The host response is called "*sepsis*" when these symptoms are suspected to be triggered by an infection.

Multiple organ failure in critically ill children is defined as the simultaneous dysfunction of at least two organ systems [11, 12]. Criteria for organ failures (Table 35.3) were established according to severity of illness scoring systems used in critically ill children [10, 13]. The aim of using a common definition for MODS is to provide a reproducible assessment of organ dysfunction that allows for tracking of changes in organ function. However, the reproducibility and relative strength of these criteria has not been evaluated. MODS can be classified as primary or secondary, depending on the timing of organ dysfunctions. *Primary MODS* develops rapidly after pediatric ICU (PICU) admission [14–16] and is generally the consequence of a well-defined insult. In one study, the maximal number of organ failures was noted within 72 h in the majority of patients [14]. *Secondary MODS* corresponds to children who develop evidence of organ damages after the first week of PICU admission and/or develop a sequential pattern of organ dysfunction [17].

Pediatric MODS Scoring Systems

Two scores were developed to quantify the severity of MODS and follow its evolution over time: *(1)* Leteurtre et al. developed and validated the PELOD score [18, 19], which is derived from six independent physiological variables (Table 35.4) [18]; *(2)* Graciano et al. developed the Pediatric-MODS score, which relies exclusively on laboratory values (lactic acid, PaO_2/FiO_2 ratio, bilirubin, fibrinogen, blood urea nitrogen) and therefore does not take into consideration the neurological function [20]. This may be a serious limitation of the Pediatric-MODS score, since 80 % of the variability in PELOD scores is attributable to cardiovascular and neurologic dysfunctions [18]. Although both scores have good discriminative values and are useful tools to describe the severity of MODS in critically ill children, the calibration of the PELOD score has been recently criticized [21, 22]. Since mortality is low (around 5 %) and incidence of MODS higher (from 6 % to 57 %) in critically ill children (Table 35.5), the PELOD score has been used as a surrogate outcome measure in pediatric clinical trials for risk adjustment [23] or secondary outcome [24]. Daily PELOD scores of critically ill children effectively identified survivors from non survivors [25]. Fifty percent of 115 deaths were associated with an increase in the score from day 1 to day 2 and from day 2 to day 4 [25].

Epidemiology

Pediatric mortality is closely correlated with the number of organ dysfunctions [11, 12]. Conversely, the number of children who die in the PICU without reaching criteria for MODS is low [12, 15, 18]. MODS may stem from pediatric

Table 35.3 Organ dysfunction criteria (2002)

Cardiovascular dysfunction
Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 h
Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age[a]
OR
Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
OR
Two of the following
Unexplained metabolic acidosis: base deficit >5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: urine output <0.5 mL/kg/h
Prolonged capillary refill: >5 s
Core to peripheral temperature gap >3 °C
Respiratory[b]
PaO_2/FIO_2 <300 in absence of cyanotic heart disease or preexisting lung disease
OR
$PaCO_2$ >65 Torr or 20 mmHg over baseline $PaCO_2$
OR
Proven need[c] or >50 % FIO_2 to maintain saturation ≥92 %
OR
Need for nonelective invasive or noninvasive mechanical ventilation[d]
Neurologic
Glasgow coma score ≤11
OR
Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline
Hematologic
Platelet count <80,000/mm^3 or a decline of 50 % in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
OR
International normalized ratio >2
Renal
Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine
Hepatic
Total bilirubin ≥4 mg/dL (not applicable for newborn)
OR
ALT 2 times upper limit of normal for age

Adapted from Goldstein et al. [10]. With permission from Wolter Kluwers Health

BP blood pressure, *ALT* alanine transaminase

[a]See Table 35.1

[b]Acute respiratory distress syndrome must include a PaO_2/FIO_2 ratio ≤200 mmHg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO_2/FIO_2 ratio must be ≤300 mmHg

[c]Proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required

[d]In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated

Table 35.4 The pediatric logistic organ dysfunction score

	Scoring system			
	0	1	10	20
Organ dysfunction and variable				
Neurological[a]				
Glasgow coma score	12–15	7–11	4–6	3
	and		**or**	
Pupillary reactions	Both	NA	Both	NA
	reactive		fixed	
Cardiovascular[b]				
Heart rate (beats/min)				
<12 years	≤195	NA	>195	NA
≥12 years	≤150	NA	>150	NA
	and		**or**	
Systolic blood pressure (mmHg)				
<1 month	>65	NA	35–65	<35
1 month–1 year[c]	>75	NA	35–75	<35
1–12 years[c]	>85	NA	45–85	<45
≥12 years	>95	NA	55–95	<55
Renal				
Creatinine (μmol/L)				
<7 days	<140	NA	≥140	NA
7 days–1 year[c]	<55	NA	≥55	NA
1–12 years[c]	<100	NA	≥100	NA
≥12 years	<140	NA	≥140	NA
Respiratory[d]				
PaO_2 (kPa)/FIO_2 ratio	>9·3	NA	≤9·3	NA
	and		**or**	
$PaCO_2$ (kPa)	≤11·7	NA	>11·7	NA
	and			
Mechanical ventilation[d]	No	Ventilation	NA	NA
	Ventilation			
Haematological				
White blood cell count ($\times 10^9$/L)	≥4·5	1·5–4·4	<1·5	NA
	and	**or**		
Platelets ($\times 10^9$/L)	≥35	<35	NA	NA
Hepatic				
Aspartate transaminase (IU/L)	<950	≥950	NA	NA
	and	**or**		
Prothrombin time[e] (or INR)	>60	≤60	NA	NA
	(<1·40)	(≥1·40)		

Adapted from Leteurtre et al. [18]. With permission from Elsevier
PaO_2 arterial oxygen pressure, *FIO_2* fraction of inspired oxygen, *$PaCO_2$* arterial carbon dioxide pressure, *INR* international normalised ratio
[a]Glasgow coma score: use lowest value. If patient is sedated, record estimated Glasgow coma score before sedation. Assess patient only with known or suspected acute central nervous system disease. Pupillary reactions: non-reactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation
[b]Heart rate and systolic blood pressure: do not assess during crying or iatrogenic agitation.
[c]Strictly less than
[d]PaO_2: use arterial measurement only
[e]Percentage of activity. PaO_2/FIO_2 ratio, which cannot be assessed in patients with intracardiac shunts, is considered as normal in children with cyanotic heart disease. $PaCO_2$ may be measured from arterial, capillary, or venous samples. Mechanical ventilation: the use of mask ventilation is not counted as mechanical ventilation

Table 35.5 Epidemiology of pediatric MODS

	Patients	Incidence[a]	Mortality[b]
General pediatric ICU population			
Wilkinson et al. [12]	831	27 %	26 %
Proulx et al. [170]	777	11 %	51 %
Tan et al. [171]	283	6 %	56 %
Leteurtre et al. [19]	594	45 %	19 %
Tantalean et al. [15]	276	57 %	42 %
Leteurtre et al. [18]	1,806	53 %	12 %
Khilnani et al. [172]	1,722	17 %	26 %
Typpo et al. [33]	44,693	19 %	10 %
Sepsis			
Wilkinson et al. [11]	726	24 %	47 %
Proulx et al. [173]	1,058	18 %	36 %
Goh et al. [16]	495	17 %	57 %
Kutko et al. [48]	80	73 %	19 %
Leclerc et al. [35]	593	45 %	19 %
Congenital heart diseases			
Seghaye et al. [38]	460	4 %	56 %
Trauma			
Calkins et al. [43]	534	3 %	17 %
Liver or bone marrow transplantation			
Feickert et al. [45]	114	27 %	72 %
Keenan et al. [174]	121	55 %	94 %
Lamas et al.[c] [175]	49	90 %	69 %

Adapted from Proulx et al. [176]. With permission from Wolter Kluwers Health
MODS Multiple organ dysfunction syndrome, *ICU* Intensive care unit; Incidence[a] and mortality rate[b] of MODS; [c]MODS was defined as 3 organ dysfunctions

conditions, including sepsis, congenital heart diseases, trauma, and liver or bone marrow transplantations [26]. The incidence and mortality rate of MODS varies between studies in part due to disparities in case-definition and case-mix (see Table 35.5).

Risk factors for MODS in adults include delayed or inadequate resuscitation, persistent infectious or inflammatory focus, advancing age, malnutrition, or cancer [27]. In children, MODS most frequently affects *children under 1 year of age* [28]. The incidence and mortality of MODS is higher in neonates compared to older children [29] and a distinct pattern of organ dysfunctions was noted in the neonatal population [30, 31]. Indeed, important developmental changes occur during the first year of life that govern the maturation of renal, hepatic, gastrointestinal, and central nervous systems, which may predispose infants to MODS [32].

The presence of *comorbid conditions* increases the incidence of MODS and mortality. While one fourth of children with MODS were reported to have chronic condition in the mid-80s [12], now almost two thirds of pediatric ICU patients have an underlying chronic condition [33]. Not surprisingly, the incidence of MODS is twofold greater among children with a comorbid condition, which independently increases the risk of death [33].

Table 35.6 Etiologies of multiple organ dysfunction in children

Severe hypoxia or cardiorespiratory arrest [170]
Shock states: septic[a], cardiogenic[b], hemorrhagic
Severe dehydration[c]
Multiple trauma [44]
Burns [104]
Inhalation pneumonia
Acute liver failure [177–179]
Acute pancreatitis
Intestinal ischemia[d]
Acute leukemia[e]
Solid organ[f] or bone marrow transplantation[g]
Familial or secondary hemophagocytic lymphohystiocytosis[h] [180, 181]
Thrombotic microangiopathy[i]
Sickle cell [182]
Vasculitis [183]
Inborn errors of metabolism[j] [179, 184]
Malignant hyperthermia [185]
Toxic ingestion
Snake bite

[a]Including purpura fulminans, toxic shock syndrome, severe pneumonia, bacterial meningitis, viral meningoencephalitis
[b]Myocarditis, left heart obstructive lesions, prolonged cardiopulmonary bypass, univentricular physiology
[c]May occur in neonates or children with encephalopathy
[d]Intestinal volvulus, intussusception, perforation, necrotizing enterocolitis
[e]Promyelocytic leukemia
[f]May occur with vascular thrombosis, massive bleeding, occult intestinal perforation, post transplant lymphoproliferative disease
[g]Veno-occlusive disease, graft versus host disease
[h]Secondary hemophagocytosis may also occur during MODS itself [186]
[i]Post diarrheal or atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura
[j]Urea cycle defect, congenital lactic acidosis, organic acidemia

Etiology

The initial life-threatening insult leading to MODS also influences mortality. A diagnosis of MODS compels the physician to identify the underlying cause since several diseases with multi-systemic manifestations may require a specific therapy. An overview of common and less usual causes of pediatric MODS are presented in Table 35.6.

Sepsis

Pediatric MODS in sepsis is associated with a poor prognosis compared to non-infectious SIRS [34]. Moreover, severity of organ failures and mortality rates are closely correlated with the severity of the infectious process [15, 16, 35, 36]. A detailed discussion of sepsis is found later in this textbook.

Congenital Heart Diseases

Children with congenital heart diseases sometimes develop organ dysfunction both before and after cardiac surgery requiring cardiopulmonary bypass. Pre-operative imbalances of the pulmonary and systemic circulations may lead to organ dysfunctions. This is the case of children with hypoplastic left heart syndrome and pulmonary overcirculation associated with poor systemic perfusion. Afterload reduction has been reported to improve hepatic, renal, and gastrointestinal functions pre-operatively in these patients [37]. MODS may also occur after cardiac surgery as a consequence of cardiopulmonary bypass and the surgical correction itself. Cardiovascular instability, endothelial damage, platelet and immune activations from cardiopulmonary bypass predispose to MODS [38]. Persistent renal failure, in the context of cardiac surgery has been associated with poor outcome [39, 40]. The surgical repair may sometimes exacerbate organ damage in the presence of low cardiac output syndrome, residual lesions, or a delayed adaptation to the post-operative physiology [37, 41]. Children with congenital heart diseases may be prone to "classical" adult-type MODS characterized by the development of immune paralysis, and susceptibility to a second-hit phenomenon [42]. For example, in the first week after surgery, Ben-Abraham et al. found that 80 % of mortality was due to MODS; thereafter, sepsis was believed to be the main cause of death [42].

Multiple Trauma

Multiple trauma is a cause of MODS in children, albeit less frequent than in adults. In a series of 334 children admitted to the PICU with isolated head injury, not a single patient developed MODS [43]. Only 3 % of children with multiple traumatic injuries acquired MODS 2 days after their admission to the PICU [43]. However, multiple trauma associated with abdominal compartment syndrome and MODS has a worse prognosis, with a reported mortality rate of 20 % in children [44]. Overall, the mortality from multiple trauma is threefold lower in children compared to adults [43], possibly because children have different mechanisms of injury, fewer comorbid conditions, and a different physiological response to traumatic injury.

Solid Organ or Bone Marrow Transplantations

MODS is a major determinant of early mortality after pediatric orthotopic liver transplantation due to vascular thrombosis, sepsis, or as a result of pre-transplant organ dysfunctions [45]. The extent of damage to the engrafted liver is a major contributor to organ dysfunction. In this regard, hepatic vascular thrombosis may lead to severe

hemorrhagic shock and acute renal failure. This may then lead to polymicrobial sepsis due to intestinal perforation and malnutrition. Severe rejection is rare early after liver transplantation. Conversely, patients with rejections are less likely to develop MODS in the postoperative phase [45]. Long term survival depends on the underlying disease, the presence of MODS in the post-operative phase, or late sepsis [45]. The development of chronic graft failure or lymphoproliferative disease are also major determinants of outcome [45], the latter being associated with a 50 % mortality rate [46].

In bone marrow transplantation, pre-transplant conditioning leads to potentially reversible cytotoxicity including pancytopenia, capillary leak syndrome, acute graft versus host disease, and hepatic veno-occlusive disease. If important, this toxicity may create MODS. In one large prospective study, MODS was the only variable that had a negative impact on the outcome [47]. An increased mortality rate has been noted in children who developed septic shock and MODS after bone marrow transplantation, but not among those suffering from neoplasic disorders who did not have transplantation [48]. In the former group, pulmonary or neurological dysfunctions were important determinants of patient survival [49]. Respiratory insufficiency may be secondary to opportunistic infections, bronchiolitis obliterans, pulmonary edema, or toxicity. Combined neurological and renal dysfunctions may occur with cyclosporine or tacrolimus toxicity and the related bone marrow transplant thrombotic microangiopathy.

Pathogenesis

Evolutionary Ties Between Sepsis and Tissue Injury

Despite similar host responses to severe sepsis and post-traumatic SIRS suggestive of a unifying cause, the molecular mechanism has been poorly understood. Due to lower blood pressure and relative splanchnic hypoperfusion in severe trauma, the possibility of bacterial translocation from the gut was initially suggested. However, this hypothesis was later refuted. More recent evidence posits activation of the innate immune system through highly conserved molecules known as the pathogen-associated molecular patterns (PAMPs), expressed by a variety of pathogens. Similarly, host molecules released following tissue injury called damage-associated molecular patterns (DAMPs) also initiate the innate immune response through shared signalling pathways with PAMPs, even in the absence of microbial pathogens [50]. Recent evidence reveals that DAMPs, including the high mobility group protein (HMGB1) produced by nucleated cells, are released in the blood of injured patients and their levels correlate with the development of organ failures.

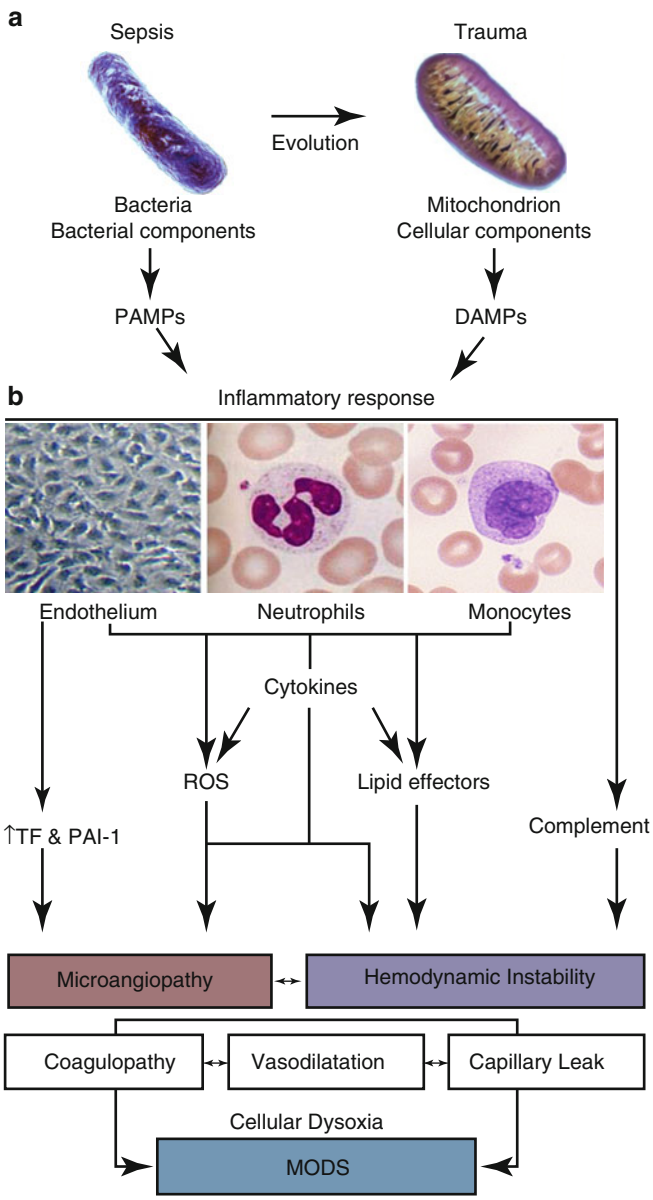

Fig. 35.1 Sepsis, tissue injury and the inflammatory response. (Panel **a**) Release of molecules called pathogen-associated molecular patterns (*PAMPs*) from bacteria and damage-associated molecular patterns (*DAMPs*) from tissue necrosis and mitochondrial fragments trigger the inflammatory response. (Panel **b**) Activation of innate immunity and the complement cascade leads to the release of cytokines, reactive oxygen species (*ROS*) and highly reactive lipid mediators. Hemodynamic instability is the outcome of changes in myocardial contractility, vasodilatation and capillary leak. The endothelium begins to express tissue factor (*TF*) launching the coagulation cascade, while plasminogen activator inhibitor-1 (*PAI-1*) decreases fibrinolysis; this results in microangiopathy and DIC. Together, cellular dysoxia culminate in organ dysfunctions (Adapted from Cohen [187]. With permission from Nature Publishing Group)

Mitochondria provide a plausible explanation for the common infectious and tissue injury triggers of the innate immune response (Fig. 35.1a). Mitochondrial and bacterial DNA share similar structural motifs as an evolutionary consequence of the bacterial origin of these organelles [51].

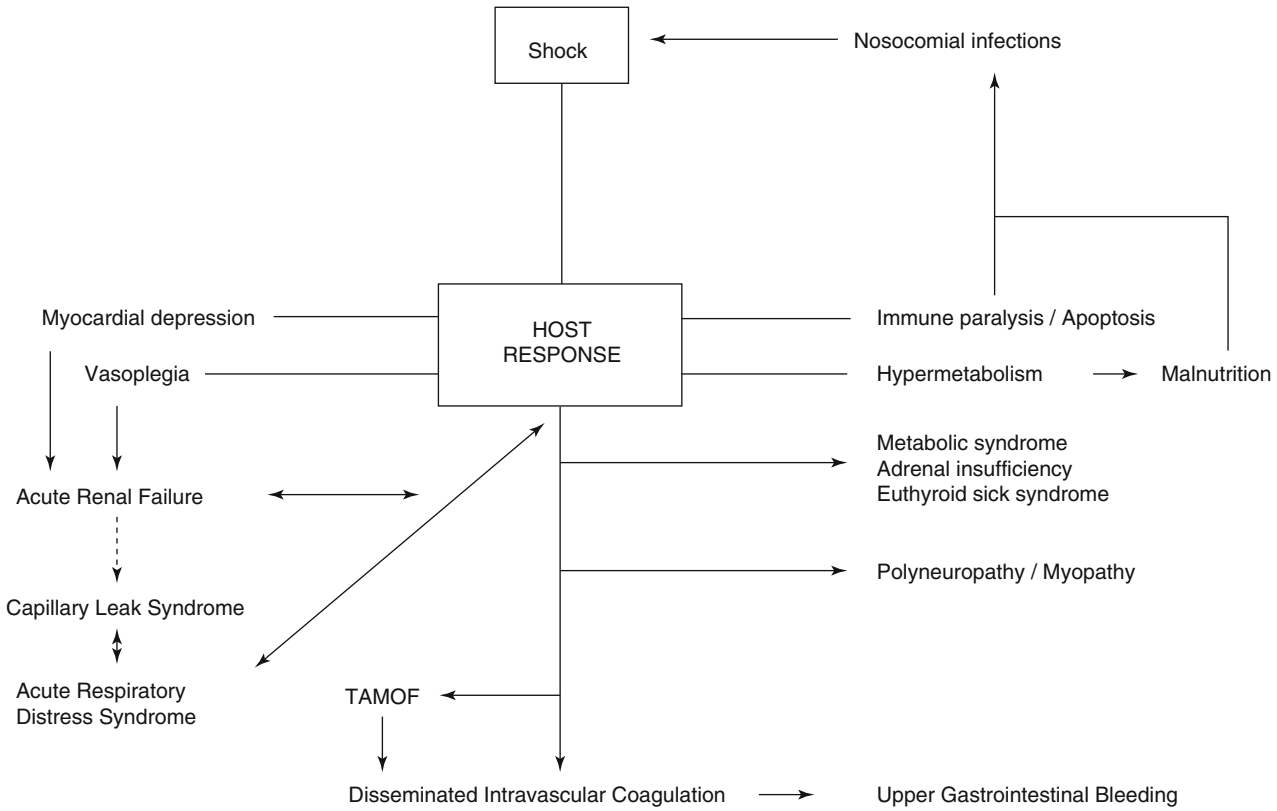

Fig. 35.2 Overview of the pathophysiology of multiple organ dysfunction syndrome. The host response to injury or infection is central to the development of multiple organ dysfunction syndrome (*MODS*). Shock states are characterized by abnormal microcirculatory blood flow, with variable degree of peripheral vasoplegia and myocardial depression that may cause acute renal failure. The latter may aggravate capillary leak syndrome. Renal failure itself may result in worse lung injury or other organ failure. Inflammatory processes, including the cytokine and chemokine response, lead to endothelial cell activation, which is clinically recognized as disseminated intravascular coagulation, capillary leak as well as acute respiratory distress syndrome. Hypermetabolism, also called "septic autocannibalism", may result in a state of severe malnutrition which is associated with secondary immunoparalysis. Overall, impaired mechanisms of tissue repair may lead to the development of nosocomial infections, usually 7–10 days later. The biological significance of other clinical conditions highlighted above remains to be clarified (*TAMOF* Thrombocytopenia associated multiple organ failure)

Zhang et al. therefore postulated that mitochondrial components spilled by necrotic tissue after severe trauma (DAMPs) could mimic PAMPs and activate host response [52]. Administration of mitochondrial DAMPs in rats induced acute lung injury. Severe trauma in humans caused a rapid release of mitochondrial DNA and mitochondrial DAMPs such as formyl peptides, which attracted neutrophils and initiated the immune response through pattern-recognition receptors (PRRs), such as toll-like receptor 4 (TLR-4). Conserved molecular motifs between bacteria and mitochondria may therefore provide an explanation for a shared immune response to injury and infections [52].

Inflammation and Immune System

Sepsis and MODS were traditionally believed to result from over-activation of the immune system and the ensuing inflammatory cascade (Fig. 35.1b). Overwhelming stimulation of innate immune cells expressing PRRs rapidly initiate host defence after tissue damage or microbial infection [53]. TLRs are a subfamily of PRRs crucial to the initiation of the inflammatory response. TLR4-mediated recognition of lipopolysaccharide and DAMPs (such as mitochondrial DNA), rapidly initiates host response and facilitate crosstalk with the complement system [53]. Activated neutrophils and macrophages produce cytokines, chemokines, and complement-activation products, resulting in a markedly imbalanced cytokine response (or 'cytokine storm'). This pro-inflammatory environment triggers the liberation of powerful secondary lipid mediators and reactive oxygen species that further amplify the inflammatory storm, leading to host tissue damage. Children who died from meningococcal sepsis presented higher concentrations of several pro-inflammatory cytokines, as well as increased serum levels of anti-inflammatory mediators (IL-10, soluble TNF receptors) [54, 55]. Hereditary markers of innate immunity influence the outcome of sepsis [56, 57]. However, if most patients die during the initial phase of sepsis and MODS, several succumb later during the second phase characterized by protracted immune suppression (Fig. 35.2).

Adaptive Immunity and Immune Suppression

In contrast to the innate immune system, adaptive immunity develops over several days and provides a more specific line of defence against pathogens. T cells orchestrate the inflammatory response, particularly CD4+ T helper 1 (T_H1) and 2 (T_H2) cells, with distinct cytokine profiles. During sepsis, adaptive immunity shifts from a T_H1 cell mediated inflammatory response (interferon-γL-2 and IL-12), to a T_H2-cell response (IL-4, IL-5, IL-10 and IL-13), which can contribute to immunosuppresion.

Multiple cellular mechanisms underlie the immune suppression in sepsis. Increased levels of apoptosis in lymphocytes and dendritic cells contribute to immune suppression [58]. Moreover, apoptotic cells intensify the process of 'immune paralysis' in remaining immune cells characterized by shut-down of cytokine response and signalling capacity [59, 60], albeit not a generalized phenomenon [61]. In contrast to circulating immune cells, those derived from tissues appear to remain fully responsive, thereby indicating compartmentalization of inflammatory processes [61]. Intracellular reprogramming may be responsible for the hyporeactivity of circulating leukocytes and may represent a physiological adaptation with protective effects. This observation is reminiscent of the phenomenon of endotoxin tolerance well described in sepsis models [62–64].

Autopsies of pediatric and adult patients that died of sepsis and MODS revealed significant lymphoid depletion. An absolute lymphocyte count of less than 1,000 for more than 7 days was only observed in children with MODS [65]. Lymphopenia and lymphoid depletion predispose to anergy, a state of non-responsiveness to antigens. Together, this immune reprogramming (or 'immunoparesis') referred to as the compensatory anti-inflammatory response syndrome (CARS), is an adaptive mechanism to restrain the initial aggressive inflammatory burst. However, relative immune suppression also predisposes critically ill patients to viral reactivation [66], nosocomial infections and death [65].

Coagulation and Fibrinolysis

The sepsis triad refers to the activation of coagulation and inhibition of fibrinolysis triggered by inflammation [67] (see again Fig. 35.1b). The extent of pro-thrombotic and anti-fibrinolytic plasma activation is correlated with the severity of pediatric MODS and mortality [68–75]. Tissue factor (TF) is pivotal to the initiation of the coagulation cascade. In sepsis, inflammation results in the expression of TF on endothelial cells, the activation of coagulation and ensuing disseminated intravascular coagulation (DIC). Tissue factor binds and activates factor VII, X and V, thereby increasing thrombin activation, fibrin deposition, and microthrombi formation [76]. Inflammation also elevates the levels of plasminogen-activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) which impair fibrin removal [77]. The general consumption of factors that regulate thrombin formation, such as antithrombin III, protein C and tissue-factor pathway inhibitor (TFPI) further exacerbates DIC [78].

Thrombocytopenia-associated multiple organ failure (TAMOF) is a clinical entity associated with sepsis. It comprises a spectrum of similar conditions including disseminated intravascular coagulation (DIC) and secondary thrombotic microangiopathy (TMA) [79]. Autopsies of children with TAMOF revealed a predominance of von Willebrand factor-rich (vWF) thrombi in the microvasculature of their brain, lung and kidney [80]. Recent evidence also suggests that as many as 30 % of children with severe sepsis have moderately decreased (20 % activity) ADAMTS-13 protease activity [81], which may increase the risk of thrombosis and organ dysfunction in this population.

Capillary Leak Syndrome

MODS has been associated with abnormal systemic vascular permeability resulting in the development of the capillary leak syndrome [82, 83]. In meningococcemia, the amount of circulating endotoxin and complement activation determines the severity of capillary leakage [84]. Susceptibility to the development of edema after cardiopulmonary bypass [85, 86] or bone marrow transplantation [87] is also related to activation of the complement system. More importantly, a positive fluid balance is associated with prolonged mechanical ventilation and increased mortality [88, 89]. PICU survivors had less fluid overload and were more likely to attain their target dry weight during continuous renal replacement therapy [90–92]. However, it is unclear whether endothelial dysfunction and the ensuing edema is simply an epiphenomena or contributes to the disease process. Recent work explored the role of adherens junctions that binds endothelial cells together to prevent vascular leak. Slit proteins and its receptor Robo4 are important to neuronal and vascular development. London and colleagues recently demonstrated that Slit and Robo4 proteins can stabilize VE-cadherin on endothelial adherens junction thereby decreasing vascular permeability [93]. In three different mouse model of infection, intravenous injection of Slit prevented vascular leakage and reduced mortality [93]. The role of the microvascular barrier in severe infections is now considered a therapeutic target [94]. Although confirmation in human is required, this may

suggest a critical role of the endothelium and the capillary leak syndrome in sepsis.

Neuroendocrine Response

The initial phase of MODS results in a massive release of stress hormones, including adrenocorticotropic hormone (ACTH) and cortisol, catecholamines, vasopressin, glucagon, and growth hormone [95]. These hormones help supply the increased demand by maintaining circulation and the liberation of energy substrate, namely glucose, fatty acids and amino acids. Insulin resistance is a common manifestation of this overwhelming neuroendocrine response, although the mechanism remains ill-defined [95]. Intracellular metabolism, energy expenditure and tissue oxygen consumption doubles during that initial period. Concurrently, less vital systems are shut down and anabolism is halted.

In the second phase of MODS, the hormonal response recedes. Vasopressin levels are often insufficient, the adrenals become less responsive to ACTH, and sick euthyroid syndrome begins to appear [95]. Suppression of the hypothalamus-pituitary-adrenal axis is presumed to be a consequence of hypoperfusion, cytokine, and nitric oxide signalling in situ [96]. The transition between the first and second phase of the hormonal response may result from the abnormal pulsatile secretion of growth hormone, thyrotropin, and prolactin [95]. The later endocrine changes may also in part be the consequence of inhibitory feedbacks from the initial burst of hormonal activation. As such, high cortisol levels prevent the secretion of growth hormone, and together with prolactin repress the secretion of gonadotropins. Cortisol may also modulate thyroid metabolism by promoting the generation of metabolically inactive reverse T3, contributing to the development of the sick euthyroid syndrome.

In children, non-survivors from meningococcal sepsis had variable aldosterone levels [97, 98], lower serum cortisol, and severely decreased cortisol to ACTH ratio, indicating a state of adrenal insufficiency [97, 99, 100]. They also had acquired sick euthyroid syndrome (decreased total T_3 and T_4, increased reverse T_3, normal free T_4 and TSH) [96, 101, 102]. In newborns, dopamine curbs the secretion of growth hormone, thyrotropin and prolactin, which could aggravate partial hypopituitarism and sick euthyroid syndrome [103].

Hyper and Hypometabolism

At the onset of severe infections or thermal injury, a decreased metabolic rate with hypothermia and stimulation of the neuroendocrine response has been referred to as the ebb phase [104]. Hypermetabolism has then been noted during the flow phase, usually about 24 h after injury [105]. Normal metabolic requirements were noted in children with SIRS or sepsis without any organ dysfunction [106]. Briassoulis et al. noted a predominance of a hypermetabolic pattern which declined within 1 week of an acute stress [107]. In adults, hypermetabolism occurs as a result of an increased oxidation of glucose and fatty acids [108], as well as an increased rate of neoglucogenesis through the use of lactate, glycerol or amino acids (alanine, glutamine, serine, glycine).

Humoral factors released by the wound have been shown to trigger skeletal muscle proteolysis. TNF-α, also known as "cachectin", plays a major role along with IL-1 in the development of "septic autocannibalism" [108]. Decreased lipoprotein lipase activity induced by TNF-α leads to increased serum levels of triglycerides, cholesterol and hyperglycemia, a clinical condition known as the "metabolic syndrome". Glucose-lactate metabolism between skeletal muscle and liver is known as the Cori cycle. Under hypoxic conditions of tissue injury or infection, glucose is transformed into lactate which is further converted within liver into glucose, before returning to the injured area. This process resulted in a net loss of 4 mol of adenosine triphosphate per cycle which may explain in part the drainage of energetic reserve. In the most severely ill patients, muscle protein breakdown with consumption of branched amino acids and increased nitrogen urinary losses, may lead to muscular cachexia, atrophy of intestinal epithelium, abnormal wound healing and secondary immune dysfunction.

Cellular Dysoxia

Compromised oxygen delivery in shock is a major determinant of organ failures. Inducible nitric oxide synthase (iNOS) triggered by the inflammatory response liberates large concentrations of nitric oxide (NO), far exceeding the regional production [109]. This may lead to abnormal regional vascular blood flow and would contribute to inadequate oxygen delivery [109]. The severity of arterial hypotension in pediatric sepsis is correlated with serum concentrations of nitrites and nitrates [74]. Neuroendocrine and inflammatory factors can exacerbate hypoperfusion as discussed. Although organ failure is classically believed to result from hypoxia and cellular damage, histological inspection of dysfunctional organs is often normal [110]. This would suggest a functional rather than a structural deficit.

Cytopathic dysoxia is therefore potentially important to the pathogenesis of MODS. Mitochondrial respiration generally increases in the acute phase of critical illness, but tends to fall with prolonged inflammation [111]. The presence of glucocorticoids and thyroid receptors on mitochondria

[112] suggests the integration of neurohormonal demands with corresponding energy supply at the cellular level. However, NO and cytokines have been shown to inhibit enzymes of the mitochondrial respiratory chain, which curtails energy production [113]. Markers of oxidative and nitrosative stress also correlate with decreased mitochondrial respiratory chain activity (mainly Complex I) [114]. Despite reduced ATP production from cytopathic dysoxia, ATP levels are largely maintained in surviving septic patients, thereby implying a state of diminished cellular energy consumption [115]. Based on these observations, Singer et al. have argued that multiorgan failure is a survival mechanism instating a dormant state analogous to hibernation that may increase the chances of survival when faced with a potentially overwhelming insult [116].

Organ Dysfunctions in Critically Ill Children

Cardiovascular Dysfunction and Septic Shock

Hemodynamic profiles noted in critically ill children with septic shock are more unpredictable than initially recognized [117–119]. Indeed, only 20 % of children with fluid refractory septic shock presented the classical picture of high cardiac index and low systemic vascular resistance [120]. Nearly 60 % of patients showed low cardiac index with high systemic vascular resistance, and both parameters might even be decreased [120]. During shock, sympathetic stimulation preferentially directs blood flow toward the brain and myocardium, diverting it from the splanchnic circulation (the so-called "dive reflex"). This may lead to increased serum lactate concentrations [121, 122]. In contrast to adults, most studies performed in critically ill children did not find the gastric pH to be predictive of developing MODS or death [121, 123–126]. However, decreased intestinal pH in very low birth weight infants was associated with a higher risk of developing necrotizing enterocolitis [127].

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Pulmonary congestion with protein-rich pulmonary edema is a cardinal feature of the acute respiratory distress syndrome (ARDS) [26, 128], which has been associated with a 20 % mortality rate in children [129]. This can be due to a direct pulmonary insult such as infection (so-called "direct ARDS") or secondary to systemic inflammation (so-called "indirect ARDS"). Abnormally increased vascular pulmonary permeability has been associated with platelet activation, neutrophils and macrophage infiltration [128], as well as with fibrin exudate resulting in hyaline membrane formation [128]. During the early phase of pulmonary injury, a restrictive pattern is noted with a decrease in respiratory system compliance and forced vital capacity [130]. The natural course of ARDS has been characterized by inadequate gas exchanges requiring more aggressive mechanical ventilation. This leads to the production of inflammatory mediators that would further increase pulmonary capillary permeability and generates deleterious mechanical forces that leads to further damage of the alveolar-capillary membrane [131].

Gut Mucosal Barrier Dysfunction

Gut injury and inflammation have been proposed as the "motor of MODS" [132]. The mechanism was thought to be related to intestinal bacteria and/or endotoxin translocating to the systemic circulation via the portal vein. However, neither clinical studies nor animal studies demonstrated bacterial translocation via the portal vein [133]. Instead it appears that mesenteric lymph translocates factors which activate neutrophils and injure endothelial cells [133]. In neonates, the development of necrotizing enterocolitis resulted in increased plasma endotoxin levels [134]. Endotoxemia was more severe at the onset of illness among infants with necrotizing enterocolitis and play a critical role in the development of MODS [134]. Theorically, measures to improve gut epithelial barrier may improve or prevent MODS.

MODS is a significant risk factor to develop upper gastrointestinal bleeding [135–137]. Clinically significant upper gastrointestinal bleeding occurs in 2 % of PICU admissions [137]. It is most frequently observed among mechanically ventilated patients with a PRISM score higher than 10, and with evidence of systemic coagulopathy [137].

Neuromuscular Syndromes

Neuromuscular syndromes, including critical illness polyneuropathy, pure motor polyneuropathy, thick-filament myopathy, and necrotizing myopathy have been described [138–141]. Prolonged weakness has been identified in 2 % of critically ill children studied prospectively, of whom 63 % had MODS and 57 % had transplantation [142]. SIRS has been proposed as a common underlying pathogenic process, which may have been potentiated by the use of corticosteroids or neuromuscular blocking agents [138]. Patients showed flaccid quadriplegia with the inability to wean from ventilatory support [138]. In most severe cases, deep tendon reflexes were abolished. Electrophysiological abnormalities usually showed a pattern of axonal polyneuropathy or abnormalities of neuromuscular transmission [138]. Recovery in strength most frequently occurred over a period of weeks to months.

Outcome of Pediatric MODS

Development of MODS is associated with greater resource use and an increased length of stay in the PICU [28]. A normal quality of life with minimal health problems is reported in 60 % of children with MODS, while 32 % indicated a fair quality of life with ongoing health, emotional, social, physical or cognitive problems that required some intervention or hospitalization; 2 % had a poor quality of life [143]. The return of organ function in children who developed MODS has not been examined in a systematic manner. There are few small case series in children with ARDS or those with MODS after cardiac surgery [144, 145]. In one study, 78 % of children who left the hospital after acute renal failure in the ICU survived beyond 24 months [146].

Treatment of Pediatric MODS

The care of children with MODS is best performed by a multidisciplinary team that carefully balances multiple therapeutic modalities. These modalities include general supportive care and organ specific therapeutics. The patient clinical condition should be reassessed periodically as for the need to perform complementary exams or invasive procedures in order to distinguish between possible, probable or definitive diagnosis.

General Supportive Care

Control of the infectious focus is of major importance. *Antibiotic therapy* should be started early with appropriate resection of infected or necrotic tissue. However, the prolonged use of large spectrum antibiotic therapy should be avoided when cultures are negative, and the risk-benefit of invasive catheters must be re-evaluated periodically. The use of recombinant human activated protein C reduced mortality and improved organ dysfunction among adults with severe sepsis [147]. However, in the RESOLVE trial, a pediatric trial in which children with sepsis-induced cardiovascular and respiratory failure were randomly assigned to receive placebo or recombinant human activated protein, there was no difference between treatment groups in either organ failure resolution or mortality [148]. While overall bleeding events were not different between groups, there was an increased incidence of central nervous system bleeding in the treated group among children younger than 2 months. Based upon follow-up trials in adults showing no benefit, the manufacturer removed activated protein C from the market and it is no longer available for clinical use [149]. Results of the CORTICUS trial in adults suggest that although shock reversal may occur more rapidly with corticsteroids, overall survival is not improved, apparently due to an increased rate of infections [150]. In the case of a transplanted patient with active systemic infection, *immunosuppressive therapy should be minimized*. Lymphopenia may occur with the prolonged use of dopamine or steroids, and prolonged lymphopenia has been associated with secondary infection and MODS [65].

A large-scale multicenter clinical trial in PICU patients who were hemodynamically stable, the TRIPICU study, showed that a *restrictive transfusion strategy* based on an hemoglobin transfusion threshold of 70 g/L, was not inferior to a liberal approach (threshold: 95 g/L) with regard to the number of patients with "new or progressive MODS or death" [151]. The incidence rate of "new and/or progressive MODS" in the TRIPICU study was 12 %, while the death rate was, as expected, only 4 %.

Critically ill children should receive *appropriate sedation and analgesia*. Vet et al. have recently shown that increased disease severity resulted in lower clearance of midazolam (decreased cytochrome 3A activity), without decreasing midazolam dose requirements [152]. Several drugs used in critical care have a narrow therapeutic index. Caution should be applied when using nephrotoxic or hepatotoxic drugs, with a special emphasis on timely drug dosages, metabolic clearance and drug interaction. Iatrogenic complications may typically occur due to difficult vascular catheterization, or overactive cardio-respiratory support usually based on a blind treatment of numbers.

While inadequate oxygen delivery to tissues results in organ dysfunction initially, MODS itself may well occur as a result of mitochondrial dysfunction [153]. As children with septic shock have better outcomes than adults, it is suggestive that their mitochondrial functions are relatively preserved compared to that of adults. This is a new area of research as therapies are being developed to affect mitochondrial function in sepsis [154]. There is some evidence that *blood glucose control* can improve mitochondrial dysfunction in patients with sepsis [155]. What remains unclear at this point is whether therapy aimed at reversing the metabolic response is helpful in critically ill patients [156]. In medical or surgical adult ICUs, tight glycemic control with intensive insulin therapy has been reported to decrease morbidity or mortality; other studies suggested no benefit or potential harm due to hypoglycemia [157–159].

Organ Therapeutic Management

In this section, only some specificities of organ dysfunction management are reported. For more details in the management, readers should refer to the appropriate and relevant chapters later in this textbook.

Hemodynamic Management

Early goal-directed therapy has been shown to decrease mortality and the severity of MODS in adults with sepsis [160]. Guidelines developed in 2002 proposed a time-dependent flow diagram in the hemodynamic support of children with sepsis [161].

Lung Protective Ventilation

There is no clear data in children. Expert opinions recommend to keep positive inspiratory pressures below 30 cmH_2O and consider small tidal volume ventilation (physiologic tidal volumes in a normal subject are in the range of 6–8 ml/kg). The other therapies such as endotracheal surfactant, high-frequency oscillatory ventilation, prone positioning, bronchodilators or corticosteroids for lung inflammation and fibrosis need further research before they can be recommended in clinical practice [162].

Renal Failure Management

Renal replacement therapy can be continuous or intermittent according to team experience and patient tolerance. High dialysis dose did not demonstrate any benefits in adults [163, 164] and no data are available in children. Although, fluid overload is a risk factor of death in adults [165, 166] and children [90, 167, 168], no data are available on the impact of negative fluid balance on critically ill children outcome [169]. Such aggressive ultrafiltration needs to be balanced with the risk of hypovolemia.

Nutritional Support

Nutritional support may allow sufficient protein-calorie intake. Early enteric feeding has been proposed to prevent intestinal disuse with secondary mucosal atrophy, decreasing the susceptibility to bacterial translocation and systemic inflammation. Indeed, the capacity to tolerate enteral feedings, as for the mobilization of third space and peripheral edema, usually represent a trend for clinical improvement.

Withdrawal of Curative Care

Despite the willingness to provide as good as possible intensive care to children with MODS, several patients simply persistently fail to improve or spontaneously further deteriorate, presenting several complications, that may ultimately be viewed as an inexorable pathway to death. Therefore, the issue of medical futility and palliative care is frequently encountered in children with MODS. The pro's and con's of not escalating the level of care, the withdrawal of cardiopulmonary resuscitation (CPR), or discontinuing some of the therapeutic modalities, are usually evaluated by the members of the multidisciplinary team. With the aim of reaching a consensus between the medical team and family, honest clinical information should be provided at least daily to the family, including when standard of medical care fails to lead to recovery.

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