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RESEARCH ARTICLE

Multiple organ dysfunction syndrome: Contemporary insights on the clinicopathological spectrum

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ABSTRACT

Multiorgan dysfunction syndrome (MODS) remains a major complication and challenge to treat patients with critical illness in different intensive care unit settings. The exact mechanism and pathophysiology of MODS is complex and remains unexplored. We reviewed the literature from January 2011 to August 2019 to analyze the underlying mechanisms, prognostic factors, MODS scoring systems, organ systems dysfunctions, and the management of MODS. We used the search engines PubMed, MEDLINE, Scopus, and Google Scholar with the keywords "multiple organ dysfunction syndrome," "intensive care units," "multiorgan failure," "MODS scoring system," and "MODS management." The initial search yielded 3550 abstracts, of which 91 articles were relevant to the scope of the present article. A better understanding of a disease course will help differentiate the signs of an intense inflammatory response from the early onset of sepsis and minimize the inappropriate use of medications. This, in turn, will promote organtargeted therapy and prevent occurrence and progression of MODS.

Keywords: Multiorgan dysfunction syndrome, MODS scoring, sepsis, Intensive Care Units, prognostic biomarkers

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) refers to the critical illness characterized by reversible physiological abnormalities with the dysfunction of two or more organs that occurs simultaneously leading to longer stays in the intensive care unit (ICU) and, in severe conditions, results in higher mortality (27%–100%).[1–3] MODS is primarily associated with mor-

bidity and mortality in patients who survive the first few hours after sustaining a traumatic injury.[4] It is recognized as a critical condition that necessitates extensive clinical management and requires huge healthcare resources. Therefore, identifying the potential preventable predisposing factors of multiorgan failure (MOF) in high-risk patients can be favorable for decreasing mortality. The incidence of MODS depends on the criterion used for MOF as there is no consensus on a single definition as the gold standard.[5] The reported incidence of MODS among critically ill trauma patients varies widely from 28% to 88%.[6] MODS is also considered as the frequent cause of mortality in patients admitted to the surgical ICU and the rate of mortality and length of hospital stay correlated with the number of organs involved and the severity of MODS.[7] An earlier study reported 15% mortality among high-risk surgical patients admitted to the ICU; of which more than half the patients died primarily due to MOF.[8] Apart from higher mortality, critically ill patients that developed MODS stayed three times longer in the ICU and necessitated greater mechanical ventilatory support than those without MODS.[9]

To date, various MOF scoring systems have been proposed to assess severity and risk stratification in critically ill patients.[10] Therefore, it is challenging to compare the incidence of heterogeneous populations using various MODS scoring systems. In addition, there is a lack of consistent data for the course of MODS, the mechanisms of organ dysfunction, and the early prediction of MODS in critically ill patients admitted in different ICUs. We reviewed the published literature in the English language with research engines (PubMed, MEDLINE, Scopus, and Google Scholar) from January 2011 to August 2019. The keywords used were "multiple organ dysfunction syndrome," "intensive care units," "multiorgan failure," "MODS scoring system," and "MODS management." The initial search yielded 3550 abstracts, of which 91 articles were relevant to the scope of the present article. A detailed overview of the underlying mechanisms, prognostic factors, MODS scoring systems, organ system dysfunctions, and the management of MODS are the primary focuses of the current narrative review.

Mechanism of multiple organ dysfunction syndrome

The exact pathologic mechanism of MODS is complex and remains unexplored because of the multifactorial involvement of molecular pathways and genetic predisposition.[11] It has been proposed that the pathophysiology of MODS is directly associated with the excessive proinflammatory response after sepsis, injury, burns, and hypoperfusion, which leads to the release of several immune mediators in the bloodstream, representing the *first hit* in the MODS process.[12] While secondary events, such as bacterial infection and surgical intervention, can initiate the *second hit*.[13] The bimodal model of MODS reoriented the prior notion about MODS being an exaggerated, rampant, and reaction to sepsis.[14] The development of MODS post-trauma is thought to be multifactorial depending upon the severity of the injury, the mixed layer of the patient, and the need for surgical intervention. The deregulated immune reaction is paramount in the pathophysiology of traumatic MODS.[15] Unfortunately, a significant proportion of MODS patients sustain persistent inflammation and immunosuppression that results in a state of oxidative stress.[16]

The two primary factors causing MOF include *systemic inflammatory response syndrome* (SIRS), which is characterized by overwhelming immune responses that lead to free radical generation. The other factor is cellular hypoperfusion causing hypoxia, which releases reactive oxygen and nitrogen species. These species collectively result in profound intracellular oxidative stress causing mitochondrial damage.[17]

Sepsis-induced MODS has complex molecular mechanisms, and so the host response to infection primarily includes pro-and anti-inflammatory immune responses, central elements in disease pathophysiology.[18] The proinflammatory cytokines are predominately released during the early phase of MODS. They comprise tumor necrosis factor-α and interleukin (IL)-1β, together with the overexpression of vascular cell adhesion molecule-1 and endothelial leukocyte adhesion molecule-1, and increased adhesion of lymphocytes with endothelial cells.[19] In contrast, in the advanced phase of MODS, damage to the endothelium initiates innate inflammatory responses in the affected end organs that results in parenchymal injury.[20] In addition, several factors are involved in the pathogenesis of MODS. For instance, mitochondrial dysfunction is also associated with organ damage mediated through the production of oxidants and the initiation of apoptosis. An earlier

study suggested that activation of tissue fibrosis is involved in the pathogenic pathway that leads to organ failure.[21] This pathway has been reported to involve various molecules such as mitogen-activated protein kinase, rho-associated protein kinase, and transforming growth factor (TGF)-β. The activation or inhibition of the complement system after an injury may also result in a hyperimmune response that causes multiple organ dysfunctions.[22] Immunomodulatory drugs may have therapeutic potential to improve outcomes in critically ill conditions, including those post-trauma, hemorrhagic shock, sepsis, and multiple organ failure but still require further investigation.

MODS in trauma, medical, and surgical ICU patients

In trauma patients, SIRS is initiated early postinjury in response to bleeding and tissue damage, which are counteracted by a compensatory anti-inflammatory response to help restore the homeostasis. Initially, if the responses of pro- and anti-inflammatory cytokines are balanced, they may lead to the normalization of the immune response and act as a beneficial compensatory mechanism. However, if this inflammatory response remains persistent or exaggerated, it may lead to organ failure and eventually cause MODS. The extent of the tissue damage, the persistence of shock, and the actual severity of the injury are decisive in the inceptive scale of the inflammatory response to the sustained trauma.[15] Around 99% of postinjury MODS patients presented with initial respiratory dysfunction, thereby making it a major contributor to early multiorgan failure. In MODS patients, cardiac, renal, and hepatic dysfunctions are preceded by pulmonary dysfunction.[2,23] Sepsis with uncontrolled infection could be an etiology in two-thirds of MODS cases. Thus, the literature suggested that MODS may occur independently of sepsis. Nosocomial pneumonia is another ICU-related complication which can trigger a secondary insult in critically injured patients. It either presents as late MODS or plays a role in the severity of the disease.[2,14]

There is heterogeneity in reported studies that include both medical and surgical ICU patients who developed organ failure secondary to various reasons.[24] It is now accepted that organ failure occurs due to a series of physiologic derangements causing clinical failure rather than because of an all-or-none phenomenon as once believed.[25] The current understanding of the process of organ failure suggests that MODS is a progressive, dynamic phenomenon with a variable extent of organ failure that necessitates prognostic scoring systems for early detection and risk stratification.[26]

Prognostic factors and MODS scoring systems

Various prognostic factors have been identified in different ICU settings that accounted for the early risk stratification in MODS. The reported independent risk factors for MOF in patients with severe sepsis admitted in medical ICU were shock, resistant bacterial strain, total parenteral nutrition, and high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score.[27] In trauma patients, the common predictors of MOF are age, male gender, high ISS and head abbreviated injury scale scores, severe Glasgow Coma Scale score, massive blood transfusion, elevated base deficit, initial lactate, Sequential Organ Failure Assessment (SOFA) score, obesity, and abdominal compartment syndrome.[28] MOF that has already precipitated during this initial period may, in turn, be unavoidable.[2,27,29] An earlier study on high-risk noncardiac surgery patients reported that age, presence of peritonitis; diabetes mellitus, increased serum lactate and central venous pressure, unplanned surgery, tachycardia, and initial blood pH were significant predictors of MOF-related mortality.[8]

To date, various scoring systems have been proposed for the diagnosis and severity assessment for MODS. There are two components of a scoring system. One is assigned scores/scales for the designated variables. The other is probability modeling for the outcomes of interest, such as mortality, treatment, triage, or comparative analysis, and thus, can be utilized for decision making and risk stratification.[30] The commonly used MODS scoring systems includes the acute physiology and chronic health evaluation the APACHE II/III, SOFA/qSOFA, simplified acute physiology score (SAPS) I/II, Marshall's MODS, Denver MOF score, Mortality Prediction Model (MPM) II, and the Predisposition, Infection, Response, and Organ dysfunction (PIRO) score (Table 1).[31–37] The SOFA and MODS are the most frequently used scoring systems to classify organ dysfunction in critically ill patients. SOFA efficiently describes the degree of dysfunction of an individual organ system and could be reassessed

Table 1. MODS scoring systems

Scoring system	Description	Parameters	Allotted scores to each parameter
SOFA score (Sequential Organ Failure Assessment) [31]	It is derived from the extent of dysfunction of six different organ systems to predict mortality. Evaluation: On admission & reassessed every 24 h until the patient is discharged utilizing the worst parameters computed during the initial 24 hours. Implications: Development of organ dysfunction can be deduced by the individual scores for each organ. Additionally, as the aggregate of scores on one ICU day and through the whole period of ICU stay, as the aggregate of the worst scores.	• Respiratory (PaO2/FIO2 in mmHg) • Coagulation (platelet count x103/μL) • Hepatic (bilirubin in μmol/L) • Cardiovascular mean arterial pressure or administration of vasoactive agents (dopamine, epinephrine and norepinephrine in μg/kg/min) • Renal (creatinine μmol/L) • Neurological (GCS)	0 – 4
qSOFA score [31]	Quick SOFA used in noncritical care setting at the bedside. Patients >18 years of age with suspicion or confirmed infection with increased risk of in-hospital mortality or prolonged ICU stay (>3 days). It is not a diagnostic tool for sepsis. This score is a predictor of mortality (score of 01: low risk of in-hospital mortality; score 23: high risk). Interpretation: a positive score warrants the evaluation of a SOFA score to confirm the presence of sepsis.	• Altered mental status(GCS <15) • Respiratory rate > or equal to 22/min • Systolic blood pressure < or equal to 100 mmHg	0 – 1
APACHE IV (Acute Physiology and Chronic Health Evaluation) [32]	The score is most commonly used for predicting the length of ICU stay and assessing the risk of short-term mortality from actual clinical data obtained on the first day after admission. Additionally, aids in the evaluation of the severity and prognosis of critically ill diseases.	• Age • Glasgow coma scale • vital signs (temp, MAP, heart rate, respiratory rate) • Oxygenation (PaO2, FiO2 arterial pH) • Urine output/biochemistry (sodium, potassium, creatinine, acute renal failure) • Hematology (hematocrit, WBC) • Severe organ system insufficiency or is immunocompromised	–
Marshall's MOD score [33]	Simple physiologic measures of dysfunction in six organ systems, which correlated well with the eventual risk of ICU and hospital mortality.	• Respiratory(PaO2/FIO2 in mmHg) • Renal(creatinine in μmol/L) • Hepatic (bilirubin in μmol/L) • Cardiovascular mean arterial pressure or administration of vasoactive agents required (dopamine, epinephrine, and norepinephrine in μg/kg/min) • Coagulation (platelet count x103/μL) • Neurological (GCS)	0 – 4 OR presence of organ dysfunction/ failure

Table 1 – *continued*

Denver MOF score [34]	Monitor the severity of MODS in patients with traumatic injury with ISS >15 and survived >48 h and are older than 16 years of age.	• Respiratory(PaO2/FIO2 in mmHg) • Hepatic(bilirubin in μmol/L) • Renal(creatinine μmol/L) • Cardiac inotropes (dopamine)	0 – 3
Predisposition, infection, response, and organ dysfunction (PIRO) score [35]	The PIRO system was developed for ED patients with suspected infection for bedside use at clinical presentation. The four components of this system include various known independent factors that may influence the onset, development, and outcome of sepsis.	• Predisposition (age, COPD, liver disease, nursing home resident, malignancy) • Infection (skin/soft tissue infection, any other infection, pneumonia) • Response [respiratory rate (bpm), bands, heart rate (bpm)] • Organ dysfunction [SBP (mmHg), BUN (mmol/l), respiratory failure/hypoxemia, lactate (mmol/l), platelet count (x109/l)]	0 – 4
Mortality Prediction Models (MPM-II) [36]	Four models have been proposed: MPM II at admission and at 24, 48 and 72 h.	• Physiology (coma/deep stupor, heart rate = 150, systolic blood pressure = 90). • Chronic diagnoses (chronic renal failure, cirrhosis, metastatic neoplasm). • Acute diagnoses (acute renal failure, cardiac dysrhythmia, cerebrovascular incident, gastrointestinal bleed, intracranial mass effect). • Other factors (CPR prior to admission, mechanical ventilation within 1 hr of admission, medical/ unscheduled surgical admit)	0 – 1
SAPS II (Simplified Acute Physiology Score) [37]	Within the first 24 h of ICU admission, the worst physiological variables, corresponding to the highest number of points, should be collected. The score gauges the mortality risk for a group of patients, but is not predetermined to describe an individual patient's chance of survival. Within a single ICU setting, the score can be employed for quality improvement and other initiatives.	• Age • Twelve physiological variables (including the cardiovascular, respiratory, renal, neurological, hematological system, hepatic) • Type of admission (scheduled surgical, unscheduled surgical, or medical) • Three underlying disease variables (acquired immunodeficiency syndrome, metastatic cancer, and hematologic malignancy)	0 – 163 points

easily. On the other hand, patients with sepsis had varying degrees of immune responses, which is dynamic in nature. The scoring for sepsis patients is mainly based on the prediction of mortality or severity of the illness, which is primarily performed using the APACHE and SAPS systems. Several reports have identified the utility of the MODS scoring systems for predicting in-hospital mortality among critically ill patients. Most of these scores perform well in predicting outcomes in the selective patient population.[38,39] However, the appropriate selection of the MODS scoring system depends upon the event, ICU setting, and patient population which is crucial to avoid wasting resources, making incorrect predictions, and inaccurate clinical decision-making.[30] Moreover, the identification of novel blood biomarkers, combined with clinical scores, might accurately stratify high-risk MOF patients and estimate the overall severity of the host response.

Cellular response and MODS

SIRS can be the cause underlying a wide variety of critical conditions or insults, such as pathogenic infection, pancreatitis, ischemia, polytrauma, and hemorrhagic shock.[40] SIRS can be diagnosed based on the presence of at least two of the four clinical findings, such as fever $>38.0°C$ or $<36.0°C$, tachycardia >90 bpm, tachypnea >20 breaths/minute, WBC $>12{,}000$ mL or WBC <4000/mL.[41] In critically ill patients, the development of sepsis and/or SIRS might initiate the pathophysiologic process with the massive release of a diverse array of cytokines causing immune-mediated organ injury.[12] Multiple studies have demonstrated the proliferative response of various immune cells, such as white blood cells, antigen-presenting cells (scavenger cells, accessory cells), and the release of inflammatory cytokines, chemokines, cell adhesion molecules, reactive oxygen species and reactive nitrogen species that play a pivotal part in the pathophysiology of MOF.[42] The initial immune reaction as a local and systemic response is meant for the beneficial effect as host defense. However, this may potentially exert harmful effects depending upon the overwhelming release of proinflammatory cytokines secondary to the severity of the injury, surgical interventions, and nosocomial infections.[2,43,44]

The exposure of exogenous and endogenous inflammatory molecules is mainly responsible for vascular endothelial damage, which is considered as a potential trigger for MODS.[45]

There is also a relationship between the severity of microcirculatory dysfunction and the occurrence of MOF that could be attributed to the inflammation-related disruption of the microvascular endothelium.[46] Moreover, the impaired mitochondrial function has been observed in patients with sepsis-related MOF which is possibly due to lower energy production and inefficient cellular oxygen consumption supporting the theory of cytopathic hypoxia-induced MODS.[47]

Past exposure of triggers can stimulate a response of polymorphic mononuclear (PMN) cell proliferation, which, on subsequent stimulation, resulted in an exaggerated response, referred to as *PMN priming*.[26] The early (within two hours post-trauma) subset of lymphocyte activity is characterized by enhanced NK cell production, decreased Gamma delta ($\delta\gamma$)-T cells, and increased IFN-γ concentration associated with the development of MODS and lymphopenia.[48] These findings suggested that lymphocytes may be essential for the rapid cellular response in trauma patients. Therefore, the development of MODS seems to be affected by the early cellular responses immediately after the injury expressed within two days of the event.[49] In severe trauma patients, lymphopenia developed early within the first 24 hours, which remain persistent in patients developed MODS. Moreover, MODS patients with lymphocytopenia are at a higher risk of mortality.[43]

Experimental models of MODS

Based on animal studies, researchers have proposed several mechanisms that lead to end-organ damage and pathogenesis of MODS at various levels.[50] Earlier studies have demonstrated that the initiation of MODS occurs through various pathological events, which probably interrelate in a tissue-specific and time-dependent manner. Firstly, continuous and progressive visceral vasoconstriction leads to hypoperfusion. This results in a comparative reduction in the blood supply to the end organ (ischemia) or deficient oxygen supply to the tissue (hypoxia).[51] Second, the reaction to inflammation spreads to the gastrointestinal system due to gut ischemia.[52] Finally, inexorable fluid shifted to the cellular level due to the loss of ionic equilibrium, and capillary function results in abnormal microvascular perfusion that may subsequently lead to MODS.[53] Some studies have suggested that alterations in the mitochondrial function might play a major role in the process of

MODS development.[54] In particular, sepsis can influence the function of the mitochondria; but, the exact pathogenic mechanism of mitochondrial dysfunction in sepsis-related MOF remains controversial. Experimental studies proposed three possible mechanisms of sepsis-related organ failure secondary to mitochondrial dysfunction that create a cellular energy crisis. Therefore, tissue hypoxia, immune-mediated inflammation that results in reduced oxygen utilization (cytopathic hypoxia), and compromised mitochondrial respiration lead to mitochondrial dysfunction.[47] In line with experimental studies, an earlier study in severe sepsis patients showed an association between sepsis and immunosuppression. The so-called immune-homeostasis is compromised, and organ dysfunction is generally the result of altered blood perfusion (tissue hypoxia) and metabolism at the tissue and cellular levels. Such patients may benefit from short and long-term multiple organ support.[55] Another study demonstrated that ICU patients suffering from sepsis-induced MOF had a two-fold decrease in the mitochondrial content in both leg and intercostal muscle.[56] Therefore, the experimental studies showed some alignment with real-life situations in critically ill patients with sepsis-induced multiple organ failure.

The data obtained from animal studies have certain limitations regarding human pathology, which certainly poses major concerns in translational research. Experimental animal models of sepsis are supposed to mimic but cannot fully elucidate critical illness in humans. Also, the outcomes of experimental studies in response to a given intervention may not be consistent across different models.[57] For instance, despite promising results and benefits in animal models, many trials of immunomodulatory drugs fail to improve survival in patients with severe sepsis and septic shock. In addition, an endotoxemia variation in the gene expression profile tested at different time points showed a weak correlation with the mouse and human genomic profiles. This finding highlighted speculations regarding the implications of murine models in sepsis research. The microcirculatory dysfunction and the molecular mechanisms of MOF are heterogeneous phenomena. Therefore, conventional hemostatic resuscitation to restore microvascular flow remains challenging. To date, there is a lack of readily available devices to assess microcirculation and tissue oxygenation collectively in clinical settings. There is a need to develop robust devices for the accurate assessment of the microcirculation in patients with sepsis.[57] Also, further research is warranted to develop real-time assessment techniques for microcirculation and the effect of therapeutic interventions to achieve optimal management of critically ill patients. In particular, the type and timing of goal-directed therapeutic interventions should be assessed for optimal capillary flow and tissue oxygenation to achieve hemodynamic stabilization.

Gut hypothesis

The gastrointestinal system constitutes a unicellular epithelial layer, localized immune system, and microbial environment, which have long been speculated to act as "the motor" of MODS.[58] All three constituents of the microenvironment of the intestine are crucial for maintaining homeostasis. However, the development of sepsis disrupts this equilibrium. It results in a state of a pathobiome with inappropriate immune responses, which increase the intestinal permeability and facilitate the entry of pathogens into extraluminal spaces and mesenteric lymph nodes.[59,60] Experimental studies have shown that shock or trauma can cause failure of the gut barrier that results in migration of the gut microorganisms to distant sites.[61] Consequently, the tissue injury factors and proinflammatory cytokines carried via mesenteric lymphatic system could cause endothelial cell activation and injury, neutrophil activation, RBC injury, acute pulmonary injury, bone marrow dysfunction, and cardiac failure.[59]

Dysfunction of specific organ systems in MODS

Abnormal immune responses in the form of local or systemic inflammation can trigger single or multiple organ system dysfunctions. These dysfunctions mainly include the cardiovascular system, the respiratory system, renal, hepatic, and neurological involvement, and hematologic alterations.[33]

Cardiac dysfunction

Cardiac dysfunction is frequent among critically ill patients. It is associated with poor outcomes in different ICU settings.[62] Cardiac involvement has been reported in a higher proportion of severe sepsis patients, who had altered contractility, diastolic failure, and reduced ejection fraction.[63] Particularly, higher mortality (up to 70%) among patients with severe sepsis is associated with both systolic and diastolic dysfunction.[64] It has been suggested that even in the presence of normal or high cardiac outputs, systolic dysfunction and ventri-

cular dilatation may occur in 50% of patients with septic shock.[65] The various causative factors of cardiac dysfunction may include primary ischemia/reperfusion injury to the heart, the effect of inflammatory and adrenergic responses of the body to critical illness and the cardiac effects of treatments (Table 2).[66 – 69]

Therefore, cardiac homeostasis might be undermined by critical illness, which is often indicated by a systemic inflammatory response. This response occurs because of the bidirectional interaction between the heart and other organs that might be involved in the pathogenesis of MODS.[70]

Table 2. MODS and cardiac dysfunction

Determinants	Description	Mechanism of myocardial damage
Myocardial ischemia-reperfusion injury [66]	Happens when tissue O_2 supply is unable to meet the cardiac oxygen demand (e.g., acute myocardial infarction, circulatory arrest, hypovolemic shock)	Ischemia results in ATP depletion, lactic acidosis, intracellular sodium overload, and cell edema. Myocardial calcium overload leads to the stimulation of cellular apoptosis pathways, with impaired diastolic relaxation and susceptibility to arrhythmias. Consequent to reperfusion, there is a paradoxical amplification in cardiac injury due to the disparity between reactive oxygen species production and the inability of cells to detoxify.
Systemic inflammation response syndrome (SIRS) [67]	Recurrent among ICU patients. Distinguished by increased oxidative stress and deregulated inflammatory response.	TNF-α, IL-1, and IL-6 myocardial depressants. Nuclear factor κB provokes an inflammatory response within the myocardium. Mitochondrial damage and self-intensifying cycles of reactive oxidative species may be triggered by inflammation-produced oxidative stress.
Catecholamine induced cardiac dysfunction [68]	Stress reaction to critical illness is distinguished by increased catecholamine levels in plasma, autonomic dysfunction, and increased sympathetic initiation.	Catecholamine- mediated myocardial damage occurs through calcium overload, ATP depletion, mitochondrial dysfunction, and reactive oxidative species overproduction.
Effects of treatments given on CVS [69]	*Norepinephrine* – to maintain organ perfusion pressure and sufficient vascular tone.	May combine with the endogenous adrenergic response and contribute to myocardial damage
	Sedative (Propofol)	Direct cardiac decline along with hypotension and vasodilation resulting in an increased requirement of vasopressors.
	Mechanical Ventilation	Positive end expiratory pressure (PEEP) and positive pressure ventilation reduce the venous return and cardiac output. Higher PEEP may cause an overall decrease in the oxygen delivery due to the decline in carbon dioxide in spite of an induced increase in arterial blood oxygenation.
	Dobutamine – ↑cardiac output and myocardial contractility.	May result in cardiac ischemia because of its association with ↑myocardial O_2 demand.

Respiratory dysfunction in MODS

Acute respiratory distress syndrome (ARDS) refers to an acute inflammatory response associated with diffuse lung infiltrates. In ARDS, increased permeability of the alveolar-capillary membrane causes edema and reduced oxygenation that lead to acute *cor pulmonale* and pulmonary hypertension in approximately 25% of patients.[51,71] Pulmonary vascular dysfunction in ARDS may be linked with poor prognosis. The probable importance of ventilator-induced lung injury is that apart from worsening the existing pulmonary damage it has significant systemic effects that might explain why most patients with ARDS succumb to MOF.[72] Usually the activation of SIRS has been initiated within hours before ICU admission, which probably started with intubation, at the beginning of mechanical ventilation, and may lead to MOF.[73] A large multicenter trial reported a 9-10% mortality rate associated with ventilator-induced lung injury.[74] It has been hypothesized that ventilator-induced lung injury may lead to inflammation of the lung due to the release of various cytokines/immune mediators that might result in MOF.[75] The lung is "*primed*" by the initial insult, such as pneumonia, acid aspiration, or contusion, followed by the "*second hit*" by mechanical ventilation, which leads to an immense pulmonary inflammatory response. The possible mechanism is the release of immune mediators from the lung to the systemic circulation due to the loss of lung compartmentalization. Current investigations have illustrated that this phenomenon is associated with programmed cell death (apoptosis) in distal organs (such as kidney, colonic villi) and end-organ dysfunction (kidney), which is likely to cause MODS.[76] The upregulation of cytokines might be caused by changes in alveolar dynamics (i.e., alveolar size and shape) that occur during mechanical ventilation of acutely injured lungs, thereby causing alveolar instability and recruitment/derecruitment.[77] There is evidence that mechanical injury is solely adequate to cause an increase in proinflammatory cytokines at the tissue and bronchoalveolar lavage levels. It remains a critical issue in minimizing pulmonary trauma and the alveolar stabilization.[23,78]

Renal and other organ system dysfunction in MODS

Approximately 30% of patients admitted to the ICU had acute kidney injury that is frequently associated with the development of MODS.[79] The kidneys work together with other vital organs, such as the heart, the lungs, and the liver to maintain homeostasis.[80] The kidneys play a vital function in oxygen metabolism; therefore, organ failure is often manifested by impaired oxygenation to the tissues, thereby affecting cardiac performance.[81] Acute kidney injury also has adverse effects on pulmonary function by disrupting fluid balance, acid-base balance, and vascular tone.[81] Renal effects on vascular tone influence the stroke volume, thereby determining the afterload. The acid-base balance also exerts its effects on enzymatic functions and vascular resistance. The erythropoietin produced primarily by the kidneys plays a vital role in the production of red blood cells, which carry oxygen.[78,82] The bidirectional relationship between the kidneys and other organ systems is shown in Table 3. Apart from maintaining the homeostasis of the body, the kidneys have an endocrine function and also act as immune organs, which can potentially initiate an acute phase inflammatory response that might influence or trigger MODS.[83] A strong relationship has been observed between the level of cytokines (IL-6, IL-10) and macrophage migration inhibitory factor with the occurrence of sepsis-induced acute renal injury.[84] Moreover, the interaction of leukocytes with activated endothelial cells may result in the occlusion of small vessels, The activation of a hypercoagulable state leads to microcirculatory impairment and regional ischemia.[85] Sepsis-induced hepatic dysfunction is an important factor that contributes to disease severity as the liver is involved in the clearance of infectious agents/products. .[86] During sepsis, the liver attempts to maintain host defense activities and support tissue repair mediated through hepatic cell cross-talk.[87] However, when this control is lost, there is the initiation of hepatic dysfunction that leads to the lack of bacterial scavenging, and higher procoagulant and inflammatory responses that ultimately result in MOF.

Management of MODS

The management of MODS requires a multidisciplinary approach that includes antibiotics for sepsis control, microcirculatory and respiratory support for reperfusion, organ-targeted drugs, and the correction of coagulation abnormalities, acid-base imbalance; metabolic issues, and electrolyte imbalance. Unfortunately, the dysfunction of one organ system is usually followed by impairment of other organ

Table 3. Bidirectional relationship between the kidneys and other organs

- Brain and kidneys
  - Increased levels of glial-programmed cell death.
  - Effects on cerebral blood flow
  - Modulation of the neurotransmitters γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA)
- Heart and kidneys
  - Hypotension
  - Decreased cardiac contractility
  - Cardiac arrhythmias
- Immune system and kidneys
  - Refashioned immune reaction
  - Misdirected T-cells
  - Increased likelihood of infection
- Hematological system and kidneys
  'COAGULOPATHY' with reduced platelet adhesion, compromised release of granule proteins, and β-thromboglobulin
- Lungs and kidneys
  - Impaired gaseous exchange
  - Fluid overload
  - Increased inflammatory response

Adopted from ref 70

systems due to significant organ cross-talk, leading to the rapid progression of the disease.[88] To date, the management of severe MODS remains limited despite the technological and pharmacological advancements. Such complex cases may require extracorporeal organ support (ECOS) or even multiple organ support therapy (MOST), which seems achievable in current practice.[55] The ECOS technique in MODS involves extracting the blood from the tissue of failing organs, and allowing the blood to undergo specific treatments in different circuits with specific devices, and then circulating the blood back to the target organ (Table 4).[89]

The common predisposing factors that can potentially trigger MODS and need to be controlled or prevented as early as possible include sepsis/infection, tissue hypoperfusion, microcirculatory failure, and aggravated inflammatory response.[90] Particularly in severely injured patients, "damage control surgery," is a consideration that comprises a staged surgical strategy.[91] It aims to regulate bleeding/coagulopathy, prevent hypothermia, maintain metabolic balance, and

Table 4. Current extracorporeal organ support (ECOS) techniques for MODS

Organ Support	ECOS Techniques
Kidneys	– Continuous Veno-Venous Hemofiltration (CVVH) – Continuous Veno-Venous Hemodialysis (CVVHD) – Continuous Veno-Venous Hemodiafiltration (CVVHDF) – Sustained Low Efficiency Hemodialysis (SLED)
Liver	– Albumin Hemodialysis (AHD) – Continuous Plasma Filtration/Adsorption (CPFA) – Plasma Exchange (PE) – Hemoperfusion (HP)
Heart	– Venous-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) – Slow Continuous Ultrafiltration (SCUF)
Lungs	– Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) – Extracorporeal Carbon dioxide Removal ($ECCO_2R$)

Adopted from ref: 78 & 81

define operative intervention after attaining hemodynamic stability.[92]

An earlier study in a high-risk population of surgical patients showed that MOF was the primary cause of death. It was independently associated with peritonitis, diabetes, unplanned surgery, age, and elevated serum lactate.[8] The authors suggested that previous knowledge of risk factors of mortality secondary to MOF may help in risk stratification and initiating early therapeutic interventions. The early recognition and treatment of organ failure is the primary basis of the successful management of MODS. Moreover, it is crucial to maintain the metabolic and hemodynamic support continuously to ensure tissue reperfusion.[93] Various studies have reported that the use of early goal-directed therapy to maintain cardiorespiratory function and end-organ reperfusion may reduce the hospital course and rate of mortality among high-risk surgery patients.[8]

Systemic shock is the common event preceding MODS; therefore, early correction of hypoperfusion through transfusion of intravenous fluids, vasopressors, inotropes, and blood products can potentially prevent or control MODS, and its associated outcomes.[94] Impaired intestinal barrier function might result in the translocation of gut bacteria and endotoxins to the systemic circulation, which might initiate the aggravated inflammatory response.[95] The resuscitation of an adequate gut mucosa is very important to support the healing process and prevent gut barrier dysfunction. In non-trauma patients, early primary or re-do operative surgery to remove necrotic tissue and drainage of abscess can help to minimize the risk of infection and the surge of inflammatory responses.[96]

Another major cause of MODS is sepsis, which should be identified and managed early, and should not be confused with noninfectious SIRS. The administration of broad-spectrum antibiotics should be considered selectively in patients who present with suspicion of sepsis and/or MODS with properly identified pathogens. However, they should not be used for prophylaxis.[97] Early appropriate antimicrobial therapy is beneficial for improving outcomes, whereas, inappropriate treatment might lead to adverse outcomes.[98] Therefore, the management of the primary source of sepsis should be the key to planning intervention. Other therapeutic approaches include the use of nonsteroidal anti-inflammatory drugs and potent antioxidants to control cellular damage that occurs secondary to exaggerated inflammatory responses and ischemia-reperfusion injury.[93]

CONCLUSIONS

MODS remains a leading cause of morbidity and mortality in ICU settings with an enormous burden on healthcare resources. The pathophysiology of MODS is dynamic and might be directly associated with the excessive proinflammatory responses after sepsis, injury, and burns, which are regarded as the primary insults. Events, such as bacterial infection and surgical intervention, might trigger the secondary phenomenon. The SOFA and MODS are the most frequently used scoring systems to classify organ dysfunction in critically ill patients. Age, presence of peritonitis, diabetes mellitus, elevated serum lactate; central venous pressure, unplanned surgery, tachycardia, and initial blood pH are the major predictors of MOF-related mortality in high-risk noncardiac surgery patients. Therefore, the identification of potential preventable predisposing factors of MOF could assist in better prognosis. Sepsis-induced MODS have complex molecular mechanisms. Therefore, the host response to infection primarily includes pro-and anti-inflammatory immune responses, and the central elements in disease pathophysiology. Experimental studies have proposed several mechanisms that lead to end-organ damage and pathogenesis of MODS. However, these findings have certain limitations regarding human pathology that raises major concern in translational research. Further research is warranted to develop real-time assessment techniques for microcirculation and evaluate the effects of therapeutic interventions to achieve optimal management of critically ill patients. In addition, prospective studies are needed to identify robust molecular targets considering disease heterogeneity. These targets, in combination with novel therapeutic interventions, will guide the accurate diagnosis and management of sepsis, SIRS, and MODS.

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