Multiple Organ Dysfunction Syndrome

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The multiple organ dysfunction syndrome (MODS), though newly described, has manifested itself in intensive care unit (ICU) patients for several decades. As the name implies, it is a syndrome in which more than one organ system fails. Failure of these multiple organ systems may or may not be related to the initial injury or disease process for which the patient was admitted to the ICU. MODS is the leading cause of morbidity and mortality in current ICU practice.

While the pathophysiology of MODS is not completely known, much evidence indicates that, during the initial injury which precipitates ICU admission, a chain of events is initiated which results in activation of several endogenous metabolic pathways. These pathways release compounds which, in and of themselves, are usually cytoprotective. However, an over exuberant activation of these endogenous systems results in an inflammatory response which can lead to development of failure in distant organs. As these organs fail, they activate and propagate the systemic inflammatory response.

No therapy has proven entirely efficacious at modulating this inflammatory response and the incidence and severity of MODS. In current ICU practice, treatment is focused on prevention and treating individual organ dysfunction as it develops. With increased understanding of the pathophysiology of MODS therapy will come newer modalities which inhibit or interfere with the propagation of the endogenous systemic inflammatory response. These newer therapies hold great promise and already some are undergoing clinical investigation.

MOSF[c] or MODS as it is now commonly known, is a disease we have been aware of for only the last 20 to 25 years. As the name implies, it is a syndrome, not a specific disease entity, manifested by organ dysfunction affecting more than one organ. In current intensive care practice, it is a leading cause of major morbidity and accounts for a significant number of deaths independent of the patient's initial presentation. We will be increasingly confronted with patients with this syndrome. Physicians must, to the extent possible, anticipate and prevent its development, limit the extent of organ dysfunction when the syndrome manifests itself, and aggressively intervene to improve organ function if we are to decrease morbidity and improve mortality rates. Unfortunately, no current therapy has proven entirely efficacious. Any improvement in survival will probably come from a multifactorial approach encompassing several modalities and therapies which in effect delineate modern intensive care practice. In order to better understand the syndrome and how it came to be, we must look back on the early part of this century.

Historical perspective

Major social upheavals of the 20th century have affected medicine, including the development of MODS. During World War I, many wounded soldiers and civilians died

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[c] *Abbreviations used:* MOSF, multiple organ system failure; MODS, multiple organ dysfunction syndrome, ICU, intensive care unit; ARDS, adult respiratory distress syndrome.

Table 1. Definitions of multiorgan system failure.

Neurologic:	- Glasgow Coma Score < 6 (in absence of sedation) (Glasgow Coma Score: Sum of best eye opening, verbal, and motor response)
Cardiovascular:	- Heart rate < 54 beats per min - Mean arterial blood pressure < 49 mm Hg (systolic blood pressure < 60 mm Hg) - Ventricular tachycardia, ventricular fibrillation, or both - Serum pH < 7.24 with a $PaCO_2$ of < 49 mm Hg
Pulmonary:	- $PaCO_2$ > 50 mm Hg (acutely) - $(A-a)DO_2$ > 350 mm {Hg $(A-a)DO_2 = [713 \times FiO_2 - \{PaCO_2/RQ\}] - PaO_2$} - Ventilator or continuous positive airway pressure dependence on the second day of organ dysfunction
Hepatic:	- Jaundice (bilirubin > 6 mg/100 dL) - $(A-a)DO_2 = [713 \times FiO_2 - \{PaCO_2/RQ\}] - PaO_2$} - Coagulopathy (prothrombin time, 4 sec greater than control, in the absence of anticoagulation)
Renal:	- Urine output < 479 mL/24 hr or < 159 mL/8 hr - Serum BUN > 100 mg/100 dL - Serum creatinine > 3.5 mg/100 dL
Hematologic:	- White blood count < 1,000 cells/ mm³ - Platelets < 20,000 platelets/mm³ - Hematocrit < 20%

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from hemorrhagic shock. With the development of, and improvement in, blood banking capabilities and the realization that patients succumbed to the sequelae of hemorrhage, medical personnel, during World War II, transfused the wounded more aggressively, and hemorrhagic shock accounted for less mortality than in World War I. A new cause for morbidity and mortality, however, was identified. Acute renal failure was more commonly seen in World War II than in World War I. Clinicians came to realize that in addition to replacing blood and blood products, they also needed to aggressively volume-resuscitate patients. This realization affected the care of subsequent armed combatants. During the Vietnam Conflict, wounded soldiers received blood products early and had intravascular volume adequately replaced with both crystalloid and colloid-containing fluids. With this aggressive volume resuscitation, though the incidence of renal dysfunction decreased, an entirely new disease entity became apparent. ARDS, which had been almost unheard of in World Wars I and II, became the disease of the Vietnam Conflict; one of the synonyms was "De Nang Lung." Since the end of the Vietnam Conflict, we have been more aggressive and successful in treating patients with ARDS. Now that patients are less likely to die from hypoxia and acute respiratory failure associated with ARDS, we are confronted with patients who have MODS.

In 1973, Tilney [1] reported on several patients in hemorrhagic shock from ruptured aortic aneurysm who subsequently died from failure of organs that were uninvolved in the initial hypotensive event. Whereas he might have anticipated hepatic and renal dysfunction, his patients were dying from pulmonary, cardiac, and neurologic complications. At the same time, Baue [2] discussed a syndrome with multiple progressive, or sequential systems organ failure. It was Eisner, et al. [3], and Frye, et al. [4], who coined the term

"multiple organ failure." More recently, Bone et al. [5] have designated this the "multiple organ dysfunction syndrome."

Epidemiology

Much of our understanding of the epidemiology of MODS comes from the work of William Knaus and colleagues using the APACHE scoring systems at George Washington University [6]. Their work has given rise to a more consistent method of quantifying organ dysfunction and patient outcome associated with MODS. The criteria developed by Knaus et al. define failure for six systems: respiratory, cardiovascular, renal, hematologic, neurologic, and hepatic (*see* Table 1). From an epidemiologic perspective, we now know that risk factors associated with the development of MODS in decreasing order of importance include: 1) severe illness at the time of ICU admission (the essence of the APACHE scoring system), 2) diagnosis of sepsis or infection at the time of ICU admission, and 3) age of the patient.

Based on this work, we now understand that the greater the number of dysfunctional organs, and the greater the duration of this dysfunction, the higher the mortality from MODS. Single organ failure for more than three days is associated with a 30 to 40% mortality; two organ failure for more than three days, 60% mortality; and greater than three organ failure for more than three days, 90% mortality.

Encephalopathy or coma is associated with the highest single-organ mortality rate at about 40%. Patients more than 65 years old have an increased mortality of 10% to 20% compared to those under age 65. The prognostic methods developed by Knaus et al. [6] will become increasingly important as a means to predict both the risk of development of MODS, and to evaluate treatment for patients with MODS and its affect on outcome.

Clinical presentation

Several characteristics of MODS present clinical paradoxes. First, the organs that fail are frequently not initially involved as part of the initial disease or illness for which the patient was admitted to the ICU. Second, a lag period often exists between this initial insult and the development of systemic organ failure. Third, many people believe that MODS is a systemic manifestation of infection that complicates the presenting illness. However, not all patients with clinical sepsis and MODS have documented evidence of microbiologic infection. There is evidence that infection, and in particular endotoxin, does not play a critical role in the pathogenesis of MODS [7]. Even in those individuals with documented infections, early identification and effective treatment of the infection may not lessen the patient's chances of developing organ system failure that, in this scenario, frequently leads to MODS and death. By all accounts, however, sepsis is an important element in the development of the syndrome. Chronic disease and age (in its extremes) also seem to be involved in the development of MODS perhaps by diminishing organ reserve which predisposes patients to MODS [9].

The lung is the most common primary organ of injury, manifested by pulmonary dysfunction and presents before any evidence of other organ dysfunction. Other organ systems that are frequently involved during the early development of MODS include the liver, intestines, and kidneys. Hematologic and myocardial dysfunction are late manifestations of MODS. Neurologic sequelae, most commonly encephalopathy, may present early or late in the syndrome's progress.

PATHOPHYSIOLOGY

A number of theories have been promulgated as to why MODS develops.
Hypoxia. Systemic hypoxia was initially advocated as the precipitating event

accounting for the development of organ dysfunction. Based on the pioneering work of Rackow et al. [9], an attractive hypothesis has developed that patients with sepsis and organ dysfunction (acute lung injury) have inadequate oxygenation. This explanation is intuitively obvious for patients with hemorrhagic shock, cardiac arrest, etc. These conditions are often readily reversible. For example, hemorrhagic shock is treated with transfusion of red blood cells, and cardiopulmonary resuscitation is used for patients with cardiac arrest, thus restoring oxygenation. In patients with sepsis, there is a more subtle oxygenation deficit. In this condition, oxygen utilization often becomes dependent on oxygen supply [11]. Decreased oxygen utilization, though, may be due to more than just an oxygen delivery problem. Cellular processes may be involved [12]; to overcome the cellular deficits, a higher oxygen gradient must be present at the mitochondrial level. Independent of how the deficit develops, there is an increased body of evidence suggesting that increasing oxygen supply by either increasing cardiac output or the oxygen-carrying content of blood improves oxygen utilization and decreases morbidity and mortality.

Though this hypothesis has attracted many proponents, recent evidence suggests that an oxygen deficit is not the only factor in the development of MODS. First, in many of the models used to justify this concept, oxygen consumption is mathematically coupled to oxygen delivery [13]. Since cardiac output is used in both equations to calculate oxygen delivery and oxygen consumption, if cardiac output increases, it will have an effect on both calculations. Second, several articles have called into question whether or not oxygen consumption is truly dependent on oxygen delivery, at least in animal models of acute lung injury [14–16]. Third, three randomized clinical trials have failed to demonstrate that increasing oxygen delivery to super normal values reduces morbidity and mortality in critically ill patients [17–19]. As always, there is the possibility of a beta error in these studies. However, evidence increasingly suggests that hypoxia, while it may be an important variable, is not the only variable in the development of MODS. Furthermore, a number of patients develop MODS without ever having systemic or tissue hypoxia, decreased oxygen delivery, or decreased oxygen consumption.

Infection. Another frequently advocated hypothesis is that MODS develops in response to a systemic insult precipitated by an infectious process. This observation is underscored by the work of Knaus et al. [6] that the development of MODS is frequently associated with the diagnosis of sepsis or infection at the time of ICU admission. In this scenario, bacteria and, in particular, lipopolysaccharide derived from the cell membrane of the bacteria, activates complement and plasmin stimulating the release of kinins [20]. These substances, in turn, activate macrophages that release cytokines; cytokines, in conjunction with kinins, stimulate granulocytes to adhere to the endothelium. In addition, the coagulation cascade is activated, the net result of which is adhesion and microembolization of platelets in organ capillary beds. These processes result in damage to endothelial cells which, in turn, result in increased capillary permeability, interstitial edema, a further decrease in tissue oxygen uptake, and organ dysfunction.

However, many patients develop MODS without any direct or indirect symptoms or signs (leukocytosis, fever, infectious nidus, etc.) of infection ever having been present. Furthermore, the studies of either HA- 1A (human) or E5 (murine) monoclonal antibodies demonstrated benefit from the antibodies in only very discrete groups of patients [21, 22]. Evidence has yet to conclusively demonstrate that these antibodies significantly impact on mortality and morbidity in patients presenting with "septic shock."

Systemic inflammatory response syndrome. We do not mean to say that hypoxia and infection do not cause MODS. Several precipitating factors such as hypoxia, infection, trauma, failure of a transplanted organ, etc., can lead to the development of the syndrome. The syndrome is probably the final common pathway for a number of these events. These

initial insults most likely manifest themselves as the MODS when endogenous mediators are released in excessive amounts or because of a number of other predisposing factors, i.e., immunosuppression in patients with the acquired immunodeficiency syndrome (AIDS) and organ failure from iatrogenic causes (aminoglycoside nephrotoxicity) either of which, in essence, leads to a systemic inflammatory response syndrome [23]. The latter can occur without the presence of documented infection and manifests itself by two or more of the conditions listed in Table 2.

Final common pathway. A specific endogenous mediator probably does not precipitate the development of MODS, though several mediators such as tumor necrosis factor, interleukins, and eicosanoids (prostaglandins, thromboxanes, leukotrienes), among others, have been advocated as playing this critical role. Many of these mediators have opposing effects, at least with respect to vasoactive properties, i.e., norepinephrine is more of a vasoconstrictor, whereas epinephrine is more of a vasodilator. Similarly, thromboxane A_2 is a vasoconstrictor and prostacyclin is a vasodilator. Perhaps some of the organ dysfunction associated with these vasoactive substances results from a relative imbalance in the ratio of one vasoactive compound to another. For example, in the development of acute lung injury, a preponderance of thromboxane versus prostacyclin may result in pulmonary vasoconstriction with inadequate lung perfusion.

In addition, another widely accepted theory holds that these endogenous mediators activate receptors on endothelial cells and stimulate the release of adhesion molecules (intracellular adhesion molecule [ICAM] or endothelial leukocyte adhesion molecule [ELAM]; Figure 1) [24]. These molecules, once they attach to endothelial cells, in turn attract neutrophils, platelets, and macrophages to attach to the endothelium, become activated, and release a variety of immunomodulator, vasoactive, and cytotoxic compounds (Table 3). While considerable evidence suggests that such a series of events does, indeed, occur, a single precipitating factor probably does not underlie the many diverse sequelae that become apparent with the development of MODS.

Independent of the precipitating event, once the cascade of events described above becomes activated, it becomes self-propagating. Any intestinal dysfunction leads to a loss of the impermeable gastrointestinal mucosal barrier. With the loss of this barrier comes translocation of bacteria and endotoxin across the gut wall, propagating the additional release of endogenous mediators [25]. Furthermore, some of these mediators, in and of themselves, are immunosuppressive and have negative vasoactive properties. The combination of endotoxemia and endothelial dysfunction predisposes the patient to additional stresses on the cardiovascular system with secondary hypoperfusion of already compromised organs. The net result is endothelial dysfunction with extravasation of fluid and cellular components into the interstitial space of organs. Additional organ dysfunction occurs along with a predisposition to secondary infection, immunocompromise secondary to the release of a number of immunomodulatory agents and, ultimately, the clinical development of MODS.

Table 2. Systemic inflammatory response syndrome manifested by two or more of the listed conditions.

1.	Temperature > 38° or 36°C
2.	Heart rate > 90 beats per minute
3.	Respiratory rate > 20 or $PaCO_2$ < 32 mm Hg
4.	White blood cell count > 12,000 or <4,000 or >10% bands

Precipitating Event

(Hypoxia, Trauma, Infection, Transplant Rejection)

↓

↑ cytokines (TNF, IL-1)

↓

Release of ICAM, ELAM

↓

Leukocyte adhesion

↓

Release of multiple biochemicals and compounds

↓

Endothelial damage

↓

Perivascular interstitial edema

↓
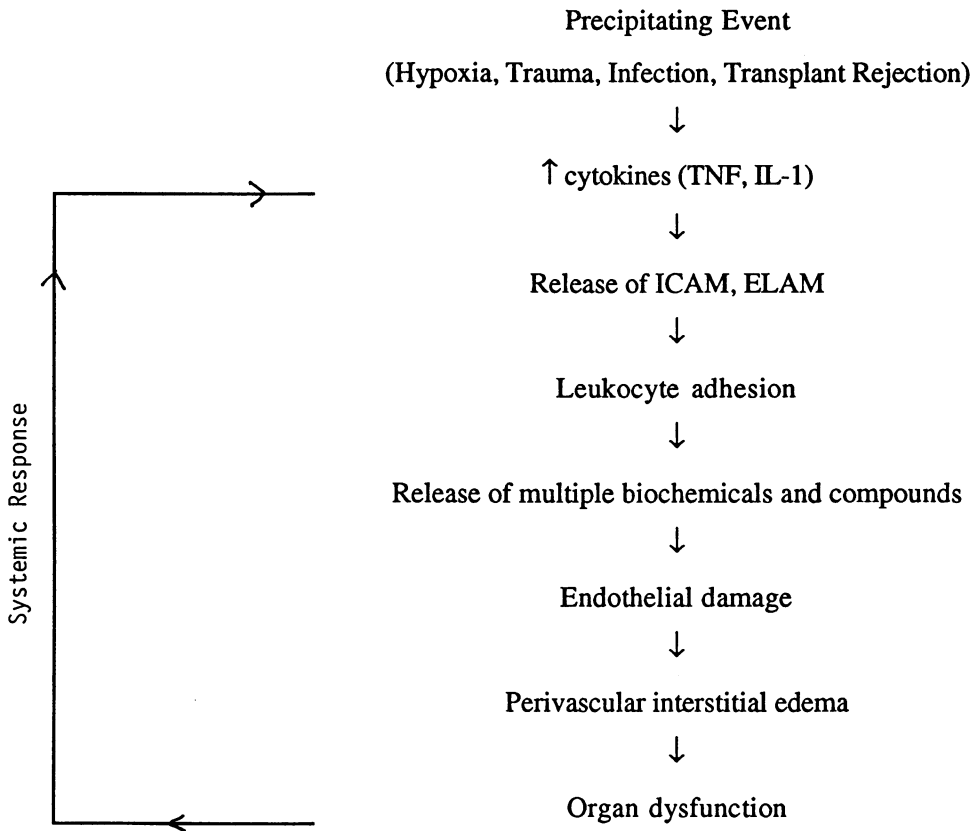
Organ dysfunction

Systemic Response

Figure 1. Schematic diagram outlining the role of various factors in development of systemic inflammatory response and MODS.

TREATMENT

Since the prognosis for MODS is so poor (approximately 90% mortality with dysfunction of three or more organ systems), the most important goal is to prevent its development. The prompt treatment of infection, hemorrhage, trauma, inadequate oxygen delivery, and isolated organ injury is of paramount importance (Table 4).

Because MODS has multiple etiologies, physicians, nurses, and other health care providers must establish a team approach that minimizes nosocomial infections, optimizes any immunotherapy (e.g., steroids for asthma, cyclosporine for transplant patients), controls an overexuberant stress response, either through the use of antagonists or effective analgesia, or anxiolysis, and provides adequate nutritional support and early mobilization when appropriate. Once the syndrome actually develops, care must be taken to rule out and avoid any complicating factors, i.e., secondary pneumonitis in patients with ARDS or acute lung injury, pulmonary embolism in patients who have been inadequately prophylaxed against deep venous thrombosis, myocardial infarction in patients with coro-

Table 3. Proposed mediators of MODS.

Interleukins	Serotonin
Arachidonic acid derivatives	Reactive oxygen species
Leukotrienes	Lysosomal enzymes
Prostaglandins	Fibronectin
Thromboxanes	Tumor necrosis factor
Stress Hormones	Coagulation factors
Catecholamines	Macrophage-derived growth factor
Steroids	Platelet-activating factor
Insulin	Neuropeptides
Thyroxin	Neuropeptide Y
Growth hormone	Vasoactive intestinal polypeptide
Glucagon	Bombesin
Endorphins	Adhesion molecules
Histamine	ICAM
Myocardial depressant factor	ELAM

Table 4. Treatment of MODS.

Predisposing Factor	Therapy
Infection	Incision and drainage of any abscess, antibiotics
Sepsis	Incision and drainage of any abscess, antibiotics, volume resuscitation, inotropes if evidence of inadequate oxygen delivery despite adequate preload
Hemorrhage	Control of bleeding, maintenance of hemoglobin ≥ 6 to 10 gm/dL, volume resuscitation
Trauma	Stabilization of injury, identification and treatment of bleeding sites and of perforated viscera
Isolated organ injury	Specific to individual organs
Inadequate oxygen delivery	Increase oxygen delivery by increasing cardiac output or increasing arterial oxygen content

nary artery disease, acalculous cholecystitis in patients with hepatic or intestinal dysfunction, nephrotoxic agents in patients with renal dysfunction, and factors such as sleep deprivation that worsen the ICU syndrome and drugs that adversely affect mood in patients with encephalopathy.

With MODS, however, much of the care of these patients is supportive, and many will require mechanical ventilatory support. Of paramount importance is minimizing inspired oxygen toxicity (the goal is to maintain fractional inspired concentration [FiO_2 of < 0.5) [26] and minimizing barotrauma by decreasing airway pressure [27] (the goal is to maintain mean airway pressure less than 20 cm H_2O, peak airway pressure less than 30 cm H_2O, and positive end expiratory pressure of less than 10 cm H_2O). Patients with renal dysfunction must be monitored for fluid, electrolyte, and acid-base imbalance and accumulation of toxic compounds, i.e., increased creatinine. Nephrotoxic drugs must be carefully monitored or avoided if possible. After ruling out acalculous cholecystitis, avoid any hepatotoxic drugs in patients with intestinal or hepatic dysfunction. Furthermore, the introduction and maintenance of enteral feedings for patients with

intestinal dysfunction, usually manifested either by ileus or diarrhea, improves the gut mucosal barrier and decreases the incidence of bacterial and endotoxin translocation [28]. Selected bowel decontamination (gentamicin, polymyxin, nystatin) [29] also decreases the incidence of bacterial translocation and decreases the incidence of gram-negative septicemia. Unfortunately, neither therapy has been demonstrated to improve clinical outcome. Nonetheless, as part of the complete care of the patient, they may be cost-effective treatment strategies.

The importance of modulating and improving the stress response cannot be overemphasized in this setting. Uncontrolled stress will augment the release of endogenous mediators with deleterious sequelae. Effective analgesia, through the administration of nonsteroidal anti-inflammatory agents and narcotics, and anxiolysis, through the administration of benzodiazepines or other compounds (e.g., haloperidol) may also play a role [30]. As noted previously, total patient comfort must be continually assessed and assured.

THE FUTURE

Many modalities clearly hold great promise in terms of preventing the development of MODS and treating its consequences once it does develop. These modalities include the use of compounds that block the release of, or prevent the binding to receptors of, endogenous mediators presumed to be partly responsible for the development of MODS. While steroids [31], naloxone [32], and nonsteroidal antiinflammatory drugs [33] have all demonstrated utility in animal studies, none has been conclusively demonstrated to be of benefit in clinical studies. The administration of antibodies to endotoxin has proven equivocal [21, 22]. Ongoing studies are assessing the utility of antibodies to tumor necrosis factor in preventing the development of MODS once patients develop sepsis.

Other promising treatments currently under evaluation include the use of nutrition as immunotherapy to modulate the immune dysfunction or inflammatory process that many researchers feel causes MODS. Several compounds on the market contain agents or biochemicals that may have a role in modulating the immune response. Such biochemicals include the omega-3 fatty acids, arginine, and ribonucleotides [34]. While such nutritional compounds hold great promise, and the preliminary results are encouraging, more work must be performed to better clarify and define the circumstances under which these compounds should be administered to patients. Finally, in the near future, antibodies to tumor necrosis factor or to adhesion molecules such as ICAM or ELAM may likewise demonstrate a role in preventing the development of MODS [24]. This hope for pharmacological tools for MODS does not diminish in any way the previous comments about the use of a multidisciplinary team of physicians, nurses, and other health care providers who coherently and cohesively address the total needs of the patient.

SUMMARY

MODS, a new but relatively common syndrome, is a leading cause of morbidity and mortality in ICU's. Multiple precipitating factors, probably through a common final pathway, result in simultaneous organ failure in several organs, most commonly the lungs, kidneys, gastrointestinal tract, and brain. Treatment goals primarily include preventive and supportive care. New therapies, including nutrition immunotherapy and antibodies to a number of endogenous mediators, hold great promise and are currently under investigation.

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