The Multiple Organ Dysfunction Syndrome: Syndrome, Metaphor, and Unsolved Clinical Challenge

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The origins of intensive care date back to the 19th century, and the recognition by Florence Nightingale that the most seriously ill or injured patients benefit from more intensive monitoring and nursing care (1). Contemporary approaches can be traced to the early 1950s (2). The Danish anesthetist, Bjørn Ibsen, suggested that polio victims who had previously died of respiratory failure might survive if they received external respiratory support (**Fig. 1**). He showed that a strategy of early tracheostomy and positive pressure ventilation lowered the mortality rate of respiratory failure from 87% to 40% and, in the process, gave birth to the contemporary discipline of *Critical Care Medicine* (3).

The development of techniques of positive pressure ventilation (4) coincided with other advances that enabled the support of severely ill patients who might otherwise have died—hemodialysis (5), effective antibiotics (6), fluid resuscitation, and hemodynamic monitoring (7) to name a few. Prolonged, if not ultimate survival following life-threatening illness became possible, and led to the creation of the ICU as an area in the hospital system where life-sustaining care could be provided (8), and to a new clinical discipline—*Critical Care Medicine*. Supporting acute organ dysfunction was the raison d'être of the ICU. However, the ICU also gave rise to previously unknown medical disorders—those that only arose in the survivors of life-threatening acute illness, whose lives were prolonged by intensive care support.

MULTIPLE ORGAN FAILURE: THE DEFINING SYNDROME OF CRITICAL CARE

The first ICUs appeared during the decade of the 1950s; by the end of the 1960s, ICUs had become a fixture of the contemporary healthcare system, and the discipline of critical care medicine was born. Half a century ago, the first professional organizations took shape, and journals dedicated to a fledgling specialty appeared. This year, we celebrate those developments, even as we practice a discipline that is still learning about its possibilities and its consequences.

An ability to support primary organ system insufficiency brought with it an awareness that new organ system failure could be a complication of those successes. Burke et al (9), for example, drew attention in 1963 to "high-output respiratory failure" in patients with life-threatening intraabdominal infection, a phenomenon that Ashbaugh et al (10) called adult (more recently acute) respiratory distress syndrome (ARDS). Other reports from that era drew attention

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Figure 1. Contemporary intensive care has its origins in the 1952 polio epidemic in Denmark, with the recognition by Ibsen that lethal respiratory failure could be supported by external positive pressure ventilation, performed not by machines, but by medical students. Used with permission from the Medical Museion, University of Copenhagen.

to the failure of organ systems that were not directly involved in the disease process that triggered ICU admission. MacLean et al (11), for example, described the contemporaneous development of derangements in multiple organ systems as a complication of *Escherichia coli* bacteremia following a septic abortion (**Fig. 2**).

Skillman was the first to propose that the phenomenon of organ failure might best be considered a syndrome (12), when he suggested that stress-induced upper gastrointestinal bleeding frequently coexisted with respiratory failure, hypotension, sepsis, and jaundice. Several years later, Tilney et al (13) drew attention to a similar process in patients admitted with ruptured abdominal aortic aneurysms; he termed this, "sequential systems failure." But, the concept that organ failure in the critically ill is best viewed as a syndrome first appeared in an editorial by Baue (14). In describing the evolution of the care of multiply traumatized patients, he wrote,

> it seems that the major limiting factor after injury in patients who do not have brain injury is not so much a system, but rather a combination of events that can best be called multiple systems failure, progressive systems failure, or sequential systems failure (14).

Theories of pathogenesis varied. Some pointed to the common presence of undiagnosed or untreated infection as an inciting factor (15–17), whereas others underlined the role of systemic metabolic derangements (18, 19). Still others pointed to the potential role of translocation of viable bacteria or their products from the gut (20–22), but a common theme to all theories was that organ dysfunction reflected an aberrant response of the host.

Terminology has also evolved. What was first called multiple organ failure (23) or multiple systems organ failure (24) is now more commonly called the multiple organ dysfunction syndrome (MODS) (25). Current terminology reflects three core assumptions about the disorder:

- it involves systemic changes in the function of more than one single system;
- it entails graded degrees of severity and is potentially reversible;
- it arises through a common biologic process or processes and so comprises a syndrome.

MODS is more than a biologic syndrome. It is a metaphor for an approach to care whose methods are exogenous support of failing systems using mechanical ventilation, fluids and vasoactive medication, dialysis, nutritional support, and blood products. And, it is an inherently iatrogenic process, arising only because active intervention has staved off death, but evolving because that same support can produce further organ system injury.

THE EPIDEMIOLOGY OF MODS

MODS is synonymous with the need for physiologic support in an ICU and represents a spectrum of illness severity. As a result, it is challenging to generate sensible estimates of its prevalence and impact. It is

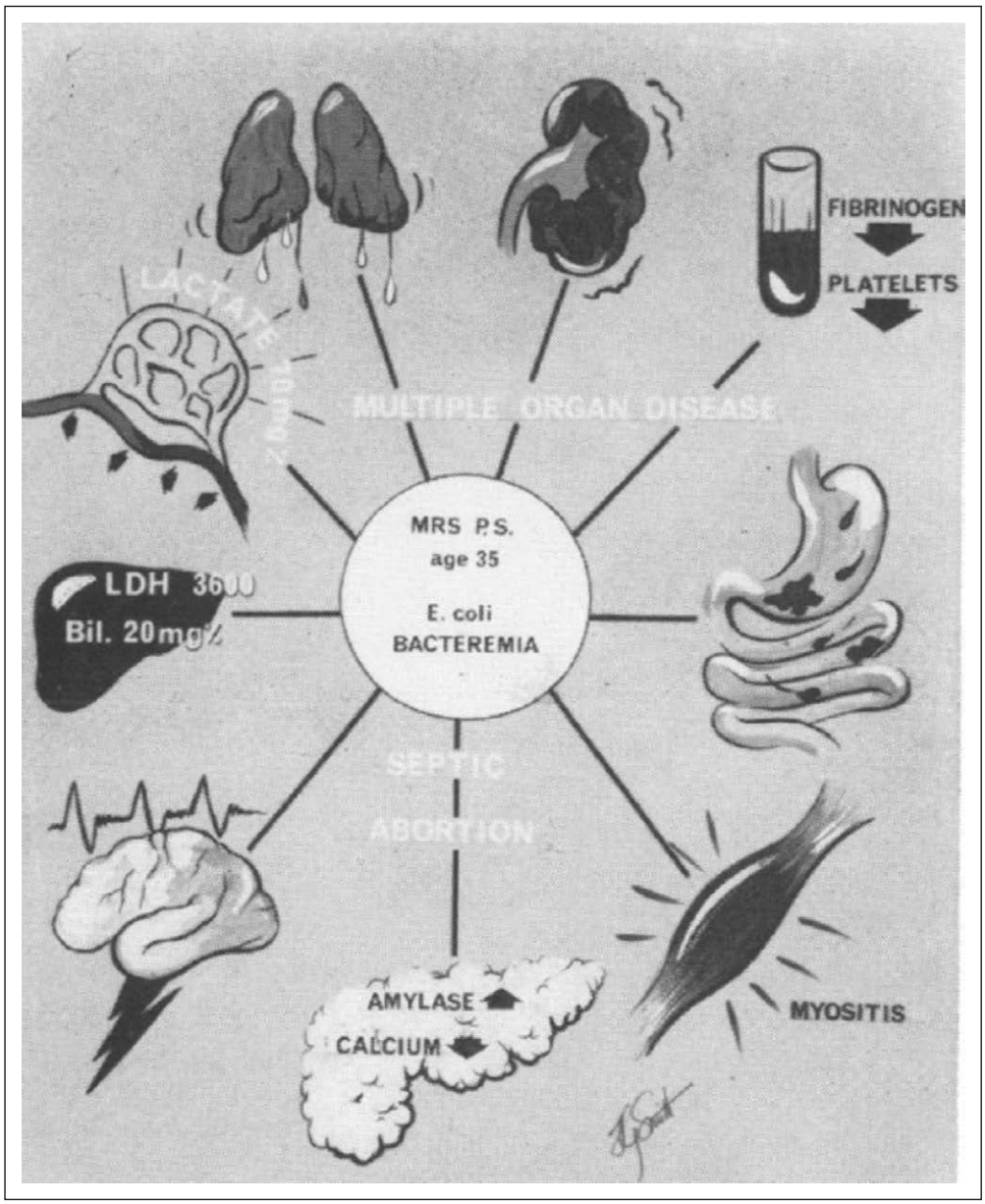

Figure 2. Early descriptions of the sequelae of septic shock, in this case, a young woman with Gram-negative bacteremia following a septic abortion, drew attention to the impact of the infection in causing the physiologic dysfunction or failure of multiple organ systems, and laid the foundations for formulations of the process that we currently know as multiple organ dysfunction syndrome. Used with permission from MacLean et al (11). Bil = bilirubin, Bil = bilirubin, *E. coli.* = *Escherichia coli*, LDH = lactate dehydrogenase.

perhaps easier to describe those patient populations in whom MODS is rarely a prominent aspect of mortality risk—those admitted electively for ventilation and monitoring following major surgery, a drug overdose, isolated head injury, as a potential organ donor, or following a myocardial infarction—although MODS can complicate the course of any of these diagnoses. Chronic comorbidities further confound the description of MODS; they carry an independently increased risk of death and a lower threshold for ICU admission but are neither acute nor reversible.

Recognizing that the most common proximate cause of ICU death is an explicit decision to terminate support in the face of nonresolving acute or chronic need for that support, MODS is the leading cause of death for critically ill patients. The majority of deaths in an ICU are anticipated, and upwards of 90% of those who die, die with, if not because of MODS (26).

MODS is inextricably linked to systemic inflammation and sepsis; it is a core element of contemporary definitions of sepsis (27). Its inciting triggers, however, include any insult that can evoke a systemic inflammatory response—infection, but also injury, ischemia, and autoimmune diseases.

MODS: A CONCEPTUAL MODEL

The framing of a disease shapes its management, implicitly and explicitly. For example, peptic ulcer disease was classically considered a disorder resulting from an imbalance between gastric acidity and the mucosal defenses of the stomach and duodenum. This model placed emphasis on interventions that either reduced gastric acidity (histamine H2 blockers, proton pump inhibitors, or surgical interventions such as vagotomy) or enhanced mucosal defenses (antacids, sucralfate). Only with the recognition of the role of *Helicobacter pylori* in disease pathogenesis did the concept of treating with antibiotics gain plausibility, with striking effects on the epidemiology of the disorder (28).

The diseases of critical illness, including MODS, are emblematic of our limited understanding of their pathogenesis. The biology of health is dynamic and complex. Normal biologic homeostasis can accommodate and adapt to acute changes in physiology, but only within limits. Beyond these, and in the absence of external support, physiology fails, and death ensues rapidly. With support, vital organ function can be sustained; this support and the derangements that made it necessary comprise the syndrome at its onset. MODS is an iterative process. It is initiated by the interplay of a primary severe insult and the initial host response to that insult, but it is modified by a series of further insults resulting from resuscitation and support. The factors that precipitate MODS are a diverse group of insults, including infection (17, 24), trauma (29), and tissue ischemia (30). With adequate early resuscitation, definitive intervention, and support, the immediate threat can be addressed, so that life continues. However, the insult and the response—both physiologic and iatrogenic—can also generate secondary insults. Hypovolemia and impaired gut perfusion result in the absorption of endotoxin from the gut (31); intubation and positive pressure mechanical ventilation can cause further lung injury (32); fluid resuscitation and the resulting edema can impair venous return and produce ischemia (33): each of these can result in a further detrimental host response. MODS is the quintessential iatrogenic disorder: it develops because the doctor has intervened in an otherwise lethal process, but it evolves because of the inadvertent consequences of those interventions.

MODS: THE CLINICAL SYNDROME

Acute dysfunction can impact all organ systems. The conventional focus on six of these—the respiratory, cardiovascular, renal, hematologic, gastrointestinal, and central neurologic systems (34, 35)—is an artifact of habit and convenience: habit because these are the alterations we most readily see and support, and convenience because they are the changes that we can most easily measure (**Table 1**). It would, for example, be entirely reasonable to consider muscular, endocrine, and immunologic dysfunction as elements of the syndrome or even to view changes in the microbiome associated with acute illness as elements of the disorder. MODS is not so much a smorgasbord of isolated physiologic derangements as a systemic state of profoundly altered homeostasis from which no system is spared, although the pattern of derangements, and the severity with in any given system, may vary from one patient to the next.

Within the lung, MODS is characterized by impaired gas exchange across the alveolar-capillary membrane (36); the magnitude of physiologic impairment can be measured as the ratio of Pao_2 to Fio_2. Multiple factors contribute to this process, including collapse of alveolar units, edema of the alveolar wall, infiltration of the alveoli by innate immune cells such as neutrophils and macrophages, thrombosis of small alveolar vessels, destruction of the alveolar architecture, and later, fibrosis of the delicate alveolar-capillary membrane. The causes of these changes are diverse—local activation of inflammation, intravascular coagulation, ventilator-induced trauma, and the subsequent processes of tissue repair.

The cardiovascular derangements of MODS are varied. Prominent among the changes is systemic hypotension, a consequence of disseminated peripheral vasodilatation and increased capillary permeability with the extravasation of protein-containing fluid into the interstitium. Myocardial depression has been documented, although the hemodynamic consequences of these changes are more modest, and the dominant hemodynamic profile is one of increased cardiac output. Atrial dysrhythmias are also described. The quantification of cardiovascular dysfunction is more challenging. The Sequential Organ Failure Assessment (SOFA) score measures it as the dose of vasoactive agents needed to maintain a mean arterial pressure of 65 or higher, whereas the Multiple Organ Dysfunction (MOD) score measures it physiologically as fluid nonresponsive hypotension by analogy to the Po_2/Fio_2 ratio, using the pressure-adjusted heart rate (pressure-adjusted rate = heart rate × central venous pressure/MAP).

The etiology of altered kidney function is also multifactorial and includes ischemia secondary to reduced renal blood low, intravascular thrombosis, local inflammation, and the nephrotoxic effects of medications (37). Histologic injury is mild and nonspecific, and the glomerular filtration rate is decreased despite normal or increased renal blood flow (38). Oliguria and azotemia precede evidence of organ injury (39). Dysfunction is typically measured by the serum creatinine level, urine output, or the use of renal replacement therapies.

TABLE 1.
Measuring Organ Dysfunction as a Physiologic Derangement and as a Clinical Response

Organ Systems	Measures of Dysfunction	Modes of Support
Lung	Po_2/Fio_2 ratio	Invasive/noninvasive ventilation
Cardiovascular	Mean arterial pressure, pressure-adjusted rate, dose of vasoactive agents, lactate	Fluid, vasopressors, inotropes
Renal	Creatinine	Diuretics, renal replacement
Hematologic	Platelet count	Blood products
Gastrointestinal/hepatic	Bilirubin	Extracorporeal liver support
Neurologic	Glasgow Coma Scale score	Sedatives, anxiolytics, analgesics

Early descriptions of MODS emphasized stress-induced upper gastrointestinal bleeding as a cardinal feature of the syndrome. This complication has become much less common in recent years (40), and because other measures of gastrointestinal function are more challenging to quantify, contemporary descriptors of MODS omit consideration of gut function. Altered hepatic function, reflected primarily in increases in the serum bilirubin level, is recognized although the phenomenon has become less common and often reflects preexisting hepatic compromise. Hyperbilirubinemia may be a consequence of hemolysis, and so alterations in hepatic excretory function may be a truer measure of impaired liver function (41).

Elements of the syndrome of disseminated intravascular coagulation comprise the hematologic derangements of MODS; the platelet count is the most common metric used to measure this dysfunction. Neurologic dysfunction is also multifactorial, a function of poorly characterized alterations in cerebral perfusion and function, the effects of sedative medications, subclinical cerebral edema secondary to altered permeability, withdrawal from psychotropic medications, and disruption of normal diurnal sleep wake patterns. It is most commonly manifest as delirium.

In truth, critical illness at its most severe results in global alterations in normal homeostasis, whether it be in the above systems, in the endocrine system (42), the immune system (43), the musculoskeletal system (44), or even the normal microbiome (45) that sustains homeostasis in health.

It is tempting to try to describe the MODS as following a characteristic temporal course or exhibiting distinctive subtypes, but the clinical reality is much less structured. Some aspects of an apparent temporal progression are more likely artifacts of the measures used to describe organ dysfunction. Renal or hepatic dysfunction occurs later in part because it takes time for the serum creatinine or bilirubin level to increase to meet the threshold for more severe dysfunction. Furthermore, the frequency of some types of organ dysfunction has changed over time—gastrointestinal bleeding and new onset jaundice becoming less common for example, as a result of changes in management over time. Since organ dysfunction can be defined by what the clinician "does," the rate, and even the nature of specific organ dysfunctions reflects our capacity, and our proclivity to address abnormal physiology—by initiating mechanical ventilation or targeting a specific blood pressure with vasoactive agents.

Distinctive subtypes of MODS have not been described, and there is no compelling reason to think that the combination of hematologic and cardiovascular dysfunction reflects a different underlying etiology or biologic profile than the combination of respiratory and renal dysfunction. To the extent that there may be prognostic differences, these likely reflect the calibration of the individual variables rather than the impact of the specific organ dysfunction: regardless of how the variables are defined, it is clear that prognosis correlates directly with the aggregate degree of dysfunction (**Fig. 3**).

MECHANISMS OF ORGAN DYSFUNCTION IN MODS

MODS is best understood as a consequence of systemic activation of the complex host response to infection and injury. Just as "rubor, calor, tumor, dolor, and functio laesa" are the cardinal manifestations of localized inflammation, so systemic inflammation yields systemic sequelae, including impairment of function,

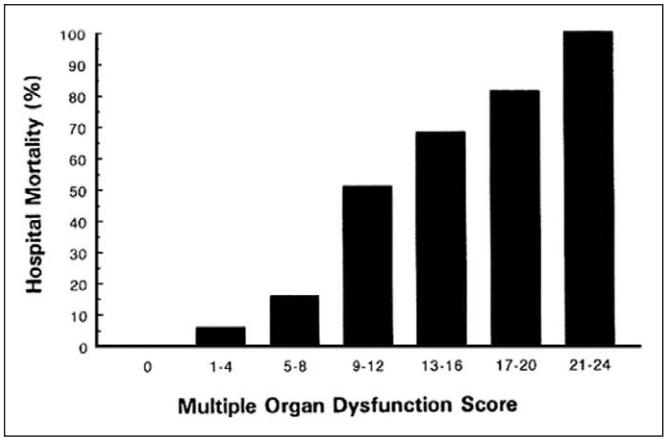

Figure 3. Prognosis for patients with multiple organ dysfunction syndrome is a function of the global burden of physiologic dysfunction and so can be measured using tools that quantify this dysfunction across multiple relevant systems. Organ dysfunction can be measured at the time of ICU admission, or over the course of the ICU stay, pooling the worst data from each system over that stay, as shown here. The difference between values at baseline and those over the ICU stay—the delta score—is a reflection of new and potentially preventable organ dysfunction arising during the process of ICU care. Used with permission from Marshall et al (34).

that are further modified by the consequences of organ support in the ICU (**Fig. 4**). Early reports emphasized the role of occult and untreated infection in the pathogenesis of MODS (15, 24); however, it is now apparent that MODS can evolve following successful treatment of infection and even in patients in whom infection is never diagnosed.

The mechanisms of MODS are incompletely understood and highly redundant. Some explanatory themes have emerged, but these are far from definitive, and their therapeutic implications are speculative.

Tissue Ischemia

Early work on the pathogenesis of MODS focused on tissue ischemia. Gastrointestinal mucosal acidosis (46) and circulating byproducts of anaerobic metabolism such as lactate (47) suggested that a regional or systemic deficit of oxygen delivery resulted in impaired cellular function and so reduced organ function at the tissue level. This hypothesis was the driving force behind clinical strategies to augment oxygen delivery to supranormal levels, typically guided by measurements obtained using a pulmonary artery catheter, and increasing cardiac output by volume resuscitation, vasoactive medications, and transfusion (48).

Although the objective of limiting tissue ischemia was the rationale behind goal-directed resuscitation (49), an approach that has transformed the early hemodynamic support of critically ill patients, efforts to test the hypothesis in the clinical arena have yielded disappointing results. Augmentation of cardiac output by inotropic agents (50) or transfusion (51) has not proven beneficial in clinical trials, and the use of the pulmonary artery catheter to guide management approaches has not been shown to improve outcomes (52, 53). Even the formal approach of early goal-directed resuscitation appears to be no more efficacious than a more pragmatic resuscitative strategy (54).

Tissue ischemia in MODS may be a consequence of impaired oxygen utilization at the mitochondrial level, rather than of impaired delivery to the cell, a process that has been called "cytopathic hypoxia" (55). Although multiple strategies targeting mitochondrial dysfunction have shown success in preclinical models (56), this promise has not been replicated in humans.

Minimization of tissue ischemia has become a cornerstone of the prevention of MODS. Ischemic tissue is a potent trigger of a systemic inflammatory response, and in experimental models, the response upon reperfusion of ischemic tissue is more deleterious to the host than the initial ischemia (57).

Regional Sequelae of Systemic Inflammation

A localized inflammatory response results in the release of multiple host-derived mediators from resident tissue macrophages and other cells and causes local vascular changes and the influx of inflammatory cells, predominantly neutrophils. Local vasodilation induced through the generation of nitric oxide and enhanced vascular permeability results in increased regional blood flow and the leakage of protein-rich fluid into the interstitium. Chemokines—molecules such as interleukin (IL)–8 that attract circulating leukocytes—recruit activated neutrophils to the site. Although these phagocytic cells respond effectively to microorganisms and to injured cells, their defenses are nonspecific, and local tissue injury is an invariable accompaniment. Within the lung, this massive influx of neutrophils can fill the alveoli, impeding gas exchange (**Fig. 5**).

Strategies to blunt the inflammatory response—either nonspecifically using agents such as corticosteroids or specifically with interventions that target key mediator molecules such as tumor necrosis factor or IL-1—have had limited success in altering the course

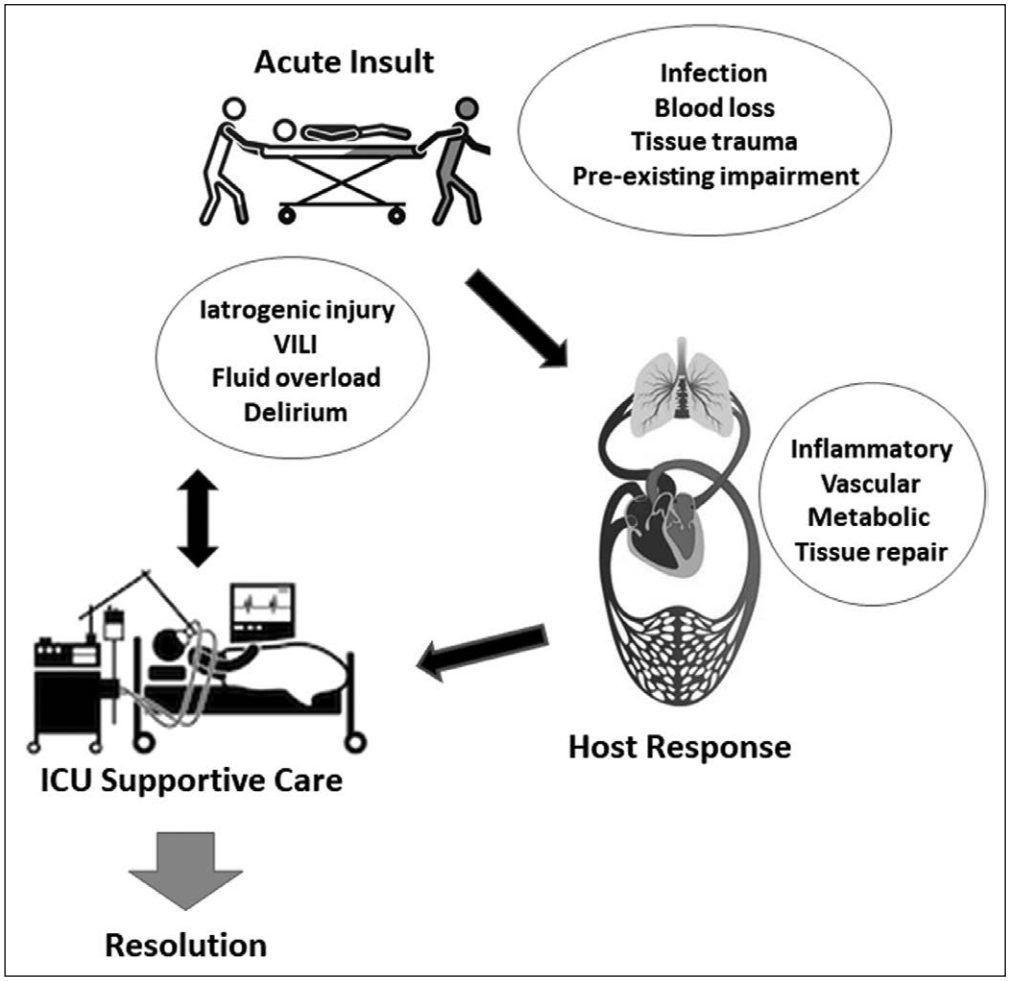

Figure 4. Organ dysfunction is a dynamic and iterative process. It is characteristically initiated by a severe insult to normal homeostasis, for example, multiple trauma, infection, or shock, further modified by preexisting limitations on functional reserve. This disruption activates systemic changes in immune, metabolic, endocrine, and vascular function that evolved to preserve vital function but that serve as a secondary insult through the activation of endogenous host inflammatory responses and the reprioritization of metabolic functions. Although support sustains life, it can further aggravate injury through the inadvertent consequences of the interventions used to support failing physiology; ventilator-induced lung injury (VILI) is the best-studied example of this additional insult.

or severity of MODS (58) although they have shown benefit in subpopulations of patients (59). Whether this is a failure of therapeutic concept or appropriate patient stratification remains an open question (60).

Endothelial Dysfunction and Microvascular Thrombosis

The endothelium is a dynamic structure that can contribute to organ dysfunction in a variety of ways. Alterations in adhesion molecule expression on the endothelial cell favor local trafficking of leukocytes and their passage into the interstitial space (61). Damage to the endothelial glycocalyx facilitates leukocyte adhesion, intravascular thrombosis, and loss of endothelial barrier integrity (62). Up-regulation of tissue factor on damaged endothelial cells and exposure of matrix components can initiate the coagulation cascade, producing microvascular thrombosis (63). Imaging of the microcirculation shows marked changes in flow, more pronounced in those patients with greater degrees of organ dysfunction (64).

Yet, strategies that target the microcirculation have had at best a limited impact on the treatment of MODS. Recombinant activated protein C showed initial promise (65); however this was not sustained in subsequent trials (66), and studies of other anticoagulants have been similarly disappointing (67, 68).

Dysregulated Apoptosis

Apoptosis is a physiologic process through which viable cells are degraded and removed in a noninflammatory manner. Both excessive and impaired apoptosis have been documented in patients with MODS. The apoptosis of epithelial cells and lymphocytes is enhanced (69), whereas the survival of neutrophils is prolonged through the inhibition of a normally constitutive apoptotic program (70). The former may contribute to impaired gut and endothelial barrier function and immune suppression, whereas the latter promotes the persistence of inflammation.

Modulation of the excessive apoptosis of lymphocytes (71) or the impaired apoptosis of neutrophils (72) improves survival in animal models of sepsis; however, this promise has not been translated into effective therapies for critically ill patients.

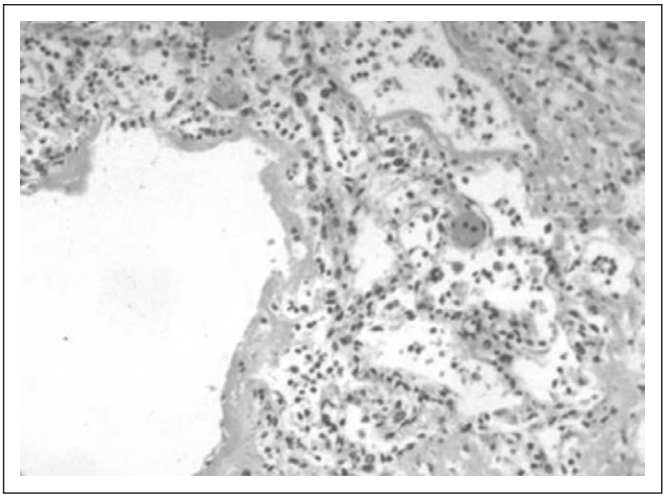

Figure 5. Photomicrograph of the lung from a patient with acute respiratory distress syndrome, showing neutrophilic infiltration, small vessel thrombosis, and fibrin deposition—hallmarks of innate host defense mechanisms, resulting in impaired gas exchange.

Metabolic Reprogramming

Profound abnormalities of immune function accompany critical illness (43, 73); however, it is not clear that these contribute directly to adverse outcome. Although nosocomial infection is common in the patient with MODS, and risk correlates directly with the severity of organ dysfunction (74), the responsible organisms are relatively avirulent, and treatment does not necessarily alter prognosis. An alternate hypothesis suggests that alterations in cellular metabolism associated with an inflammatory response result in impaired cellular function. A shift to aerobic glycolysis—the so-called Warburg effect—describes a shift in cellular function to glycolysis, even in the presence of adequate oxygen supply (75). First described in cancer cells, aerobic glycolysis promotes the synthesis of intermediates—amino acids and fatty acids—necessary for rapid cell growth. The phenomenon has been described in leukocytes in sepsis and may account, at least in part, for increased circulating levels of lactate (76).

Mitochondrial Dysfunction

A global defect in energy production is an alternate explanation for the presence of dysfunction in multiple organ system. Abnormalities in oxidative phosphorylation have been identified in a number of tissues in both humans with MODS and in animal models (77). Decreased oxygen consumption and limited activity in complex I, II-III, and IV have been demonstrated (78). These alterations contrast with adaptive changes in macrophages where disruptions of the Krebs cycle that activate proinflammatory pathways are supported by reversal of oxidative phosphorylation (79). Additional mitochondrial abnormalities include structural damage and decreased membrane potential as a result of proton leak from the transmembrane space into the matrix or opening of the mitochondrial transition pore (80). The encapsulation and elimination of damaged or senescent mitochondria has been reported to be either enhanced, decreasing the number of active mitochondria, or impaired, leading to increased rates of apoptosis (81). Biogenesis, the process of creating new mitochondria, is impaired in the later stages of sepsis (82). These findings seem to be organ dependent. These findings have not been observed in all tissues, and a number have been demonstrated in animal models only. Therapeutic approaches have been tested experimentally, but not clinically.

Altered Microbiome—the Gut in MODS

Disruption of normal host-microbial homeostasis is a cardinal feature of MODS and nowhere is this more evident than within the gastrointestinal tract (20). The diversity of the indigenous flora is reduced (83), and the proximal gut becomes overgrown with the same microorganisms that predominate in nosocomial ICU-acquired infections (22). Both viable microorganisms (84) and bacterial products such as endotoxin (85) can translocate across the normally impermeable gut epithelium. Interactions between an altered flora and host cells in the gut not only facilitate bacterial invasion but also impact multiple other aspects of normal host-microbial symbiosis, resulting in alterations of systemic immune and metabolic function (86).

Interventions that target an altered gut microbiome have shown promise. The best studied of these is selective digestive tract decontamination (SDD), a technique that entails the topical application of a combination of nonabsorbed antibiotics that reduce numbers of aerobic Gram-negative organisms (tobramycin and polymyxin B) and fungi (amphotericin), while leaving the Gram-positive and anerobic flora unaffected. SDD has been evaluated in upwards of 50 randomized trials, and data from these pooled in multiple meta-analyses. These show an aggregate odds ratio for mortality of 0.73 (95% CI, 0.64–0.84) (87) and a

reduction in rates of MODS (88). Systematic reviews of probiotics suggest benefit in reducing rates of ventilator-associated pneumonia and shortening the ICU length of stay (89).

THE IATROGENIC ROOTS OF ORGAN DYSFUNCTION

Organ injury in MODS results from the inciting insult but can be further exacerbated by clinical support in the ICU. This recognition opens new avenues for the prevention or minimization of further injury.

Ventilator-induced lung injury is the best characterized example of iatrogenic organ dysfunction in MODS (90). Excessive distention of the lung during positive pressure mechanical ventilation, particularly in the absence of pressure to maintain the lung open during expiration (positive end-expiratory pressure), can induce a systemic inflammatory response (91) and increase ICU mortality (32). Multiple other interventions initiated in a well-intentioned effort to restore normal physiology and including transfusion of red cells (51), administration of large volumes of crystalloids (92), provision of sedation (93), use of vasoactive agents to maintain a normal blood pressure (94), and the liberal use of broad spectrum antibiotics (95) all exacerbate critical illness and adversely impact clinical outcomes.

The most cogent concept underlying MODS is that the syndrome is inescapably iatrogenic: it only arises in patients whose lives have been saved by resuscitation and support; at the same time, its subsequent evolution is heavily shaped by the inadvertent and often unrecognized consequences of that resuscitation and support.

ORGAN DYSFUNCTION IN CHILDREN

Organ dysfunction also develops in critically ill children (96). Affected organ systems are those seen in adults, and development of the syndrome portends a similar increased mortality risk, although much remains to be clarified about the epidemiology of MODS in pediatric intensive care (97).

MEASURING ORGAN DYSFUNCTION IN CLINICAL PRACTICE

Although preventing or reversing organ dysfunction is arguably the predominant focus of the intensivist, quantification of aggregate organ dysfunction has not proven to be a clinical priority and is of most importance in measuring outcomes in clinical trials or quality improvement initiatives. Multiple tools have been developed to quantify MODS, including the SOFA core (35), the MOD score (34), and the Logistic Organ Dysfunction score (98). These evaluate the same six organ systems but differ in minor respects with regard to the variables used to assess dysfunction and the timing of ascertainment. They have not been updated since they were introduced a quarter of a century ago.

CONCLUSIONS

Critical care is a specialty that is, if not in its infancy, still in its early years. The capacity to support organ function and to prolong life has engendered an array of new clinical challenges that, at present, are framed in the imprecise construct of syndromes—ARDS, MODS, acute kidney injury, disseminated intravascular coagulation. The future holds the promise of discriminating discrete disease states—alterations within a biochemical pathway—and it is likely that these alterations will prove to be not only heterogeneous among patients who meet the criteria for a syndrome but common in patients across syndromes. Our challenge will be to discern these patterns. This challenge is massive, given the complexity of the biochemical processes within the individual patient, and the substantial role played in their pathogenesis by external factors—preexisting comorbidities and the complications of supportive care, the latter related not only to the mechanics of devices but to the wide variability in global capacity to provide needed care. MODS is a metaphor for the model of critical care we have developed over the past 50 years and a framework for the path we will follow over the next half century.

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