SECTION 10

Clinical Syndromes and Acute Kidney Injury

CHAPTER 37

Multiple Organ Dysfunction

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OBJECTIVES

This chapter will:

1. Explain that multiple organ dysfunction syndrome is the complex interaction between cellular hypoxia, dysoxia, and a dysregulated host inflammatory and metabolic response.
2. Describe that the spectrum of the inflammatory response extends from the adaptive (beneficial) phase to the maladaptive phase in multiple organ dysfunction syndrome.

Multiple organ dysfunction (MOD) is characterized by a profound disturbance in global hemodynamics and organ perfusion and a marked and dysregulated inflammatory response. Clinical scenarios typically associated with multiorgan dysfunction syndrome (MODS) include sepsis, major surgery, major trauma, severe and prolonged hypotension, acute pancreatitis, and burn injury. The clinical syndrome encompasses a broad spectrum of clinical phenotypes ranging from a mild degree of organ dysfunction to a complete loss of organ function. The severity and duration of organ dysfunction usually correlates with illness severity and the probability of death.

Various illness severity scores have been developed based on population data to correlate organ dysfunction to the probability of mortality. Sequential measurements of organ dysfunction scores allow patient progress to be tracked. Commonly assessed organ systems include cardiovascular, respiratory, renal, liver, hematologic, and the central nervous system. The Sequential Organ Failure Assessment score (SOFA) score and Multi-Organ Dysfunction score are examples of such scores.[1–3] Organ dysfunction scores allow risk-adjusted mortality comparisons between different ICU populations. Irrespective of the underlying cause of MODS, the associated mortality remains high. Mechanisms leading to MODS are described broadly, although poorly defined. This reflects the complex interplay between different overlapping biologic pathways. Central to the underlying pathophysiology are cellular hypoxia (lack of oxygen delivery resulting from impaired perfusion), dysoxia (impaired cellular oxygen use because of mitochondrial dysfunction), and a dysregulated host inflammatory and metabolic response.

MECHANISMS

Cellular Hypoxia

The hemodynamic instability associated with various critical illness states has led to the dogma that MODS is primarily a consequence of organ ischemia and ensuing cell death. However, experimental data have demonstrated that oxygen delivery varies markedly between individual organs and to any particular organ over the clinical course of sepsis.[4] Significant heterogeneity also exists in the degree of acidemia, lactatemia, and tissue O_2 responses between organs in different causes of shock states.[5] Local changes in O_2 supply and utilization is likely to underlie these differences in response. It is not possible to extrapolate organ perfusion from global oxygen delivery as "uncoupling" of regional oxygen delivery from global oxygen delivery occurs even in early sepsis.[6] Despite relatively preserved global hemodynamic variables, microvascular blood flow, using the sublingual microcirculation as a "window," often is impaired in patients with sepsis.[7] Early studies using indwelling renal vein catheters to measure renal blood flow in septic patients with acute kidney injury (AKI) revealed preserved or even elevated renal blood flow (RBF).[8–10] Recent experimental work has confirmed this. RBF may change over time, with an early rise in response to an infusion of *E. coli*.[11] A threefold increase in cardiac output and RBF occurred in an ovine sepsis model,[12] with the decrease in renal vascular resistance being proportional to the increase in RBF. Despite an increase in renal blood flow, renal function may be impaired.

Experimental models of sepsis demonstrate that creatinine clearance and RBF may not correlate[11,13] and that oliguria

may occur with a fall in creatinine clearance despite an increase in RBF.[14] Changes in intrarenal circulation subsequent to modification in efferent arteriolar function and intrarenal shunting are more likely than a global reduction in RBF to be responsible for septic AKI.[11] A key paradigm of MODS in sepsis is the finding of relatively preserved organ histology despite significant functional perturbations. Sepsis-induced cardiac dysfunction is clinically evident despite the lack of histologic evidence of cell death.[15] Similarly, despite significant functional impairment, histologic evidence of tubular cell injury is relatively minimal.[15–18] Although renal tubular cell injury is focal and common, most renal tubular cells appear normal.[15] Cellular hypoxia leading to cell death does not appear to be causal in the loss of cellular and organ function, particularly in sepsis. This discordance between preserved structural integrity and impaired function raises important questions about the underlying pathophysiologic mechanisms. Alternatives such as inflammation and mitochondrial dysfunction are implicated.

Mitochondrial Dysfunction and Cellular Dysoxia

In health, "mitochondrial function" typically is associated with oxidative phosphorylation and adenosine triphosphate (ATP) production as an energy substrate to fuel metabolic processes. However, mitochondria also have multiple other homeostatic, biosynthetic, and immunologic functions, including calcium regulation and cell signaling, primarily via reactive oxygen species (ROS). Many of these functions are central to the host response to infection. These include the regulation of hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF), regulation of the NOD-like receptor protein-3 (NLRP3) inflammasome, signaling intermediates for cytokines and Toll-like receptors (TLRs), and autophagy. These initial responses may have an adaptive, protective function. However, if prolonged or excessive, collateral damage (including ROS-induced oxidative stress and cell death) may be inevitable.

In resuscitated septic patients skeletal muscle oxygen tension is elevated, suggesting availability of oxygen but a decrease in consumption.[19,20] Decreased oxygen consumption (VO_2) may represent, at least in part, an adaptive mechanism.[21] Mitochondria, the primary consumer of O_2 within the body, can regulate metabolism by determining the availability of energy substrate (i.e., ATP). A prolonged inflammatory result can result in decreased mitochondrial activity through several mechanisms including (1) inhibition of mitochondrial respiration by increased production of nitric oxide and other mediators such as carbon monoxide and hydrogen sulfide, (2) damage from an excess of nitric oxide and other ROS, overwhelming intrinsic mitochondrial antioxidant defenses, and (3) downregulation of transcription of respiratory protein subunits.[22,23] The subsequent reduction in energy availability may divert the body from its normal activities and direct its efforts toward dealing with the acute stressor of infection. However, with overwhelming inflammation, this response may become exaggerated, resulting in decompensation with organ dysfunction and, ultimately, death in many cases. A clear association has been reported between the degree of mitochondrial dysfunction, organ failure, and mortality.[22] Understanding the time course of changes in mitochondrial function in sepsis and how these changes relate to recovery is important when considering any potential therapeutic intervention. Alterations to respiratory protein subunits and transcripts occur within the first 24 hours of admission to the ICU and correlate with eventual outcome.[22] Skeletal muscle antioxidant reserves are reduced within 48 hours of admission to critical care and are associated with mortality risk.[23] At present, monitoring of mitochondrial function is limited to experimental work. Promising real-time in vivo techniques include tissue oxygen monitoring, reduced Nicotinamide adenine dinucleotide (NADH) fluorometry, magnetic resonance spectroscopy (MRS), and near-infrared spectroscopy.[24] Such techniques have shown promise in animal models of different shock states and warrant further investigations in sepsis.

Inflammation

Although the precise mechanism of MODS is unclear, various related mechanisms are implicated. The host immune system is activated nonspecifically by pathogen-associated molecular patterns (PAMPs), as well as damage-associated molecular patterns (DAMPs) arising from the host. Well-characterized DAMPs include intracellular proteins and nucleic acids that are released into the extracellular space. Examples of DAMPs include proteins (heat shock proteins and HMGB1), nucleic acids (nuclear and mitochondrial deoxyribonucleic acid [DNA]), purines (ATP and adenosine), and hyaluronan fragments. PAMPs and DAMPs trigger a cascade of events culminating in systemic inflammation, altered cellular and organ function, and, eventually, organ dysfunction. Inflammatory mediators produce a cascade of events, including enhanced neutrophil chemotaxis and phagocytic activity, increased capillary leak, complement activation, cellular stress, and activated coagulation factors. These are associated with organ dysfunction in sepsis, although direct cause-and-effect remains uncertain.[25] DAMPs and PAMPs activate a series of pattern recognition receptors (PRRs) that can discriminate "self" from "non-self" antigens. Several classes of PRRs have been identified, including transmembrane Toll-like receptors (TLR), C-type lectin receptors (CLRs), retinoic acid inducible gene-I (RIG-I) receptors, intracellular NOD-like receptors (NLRs), and HIN-200 receptors.[26–28] Extracellular PAMPs and DAMPs are recognized by TLRs and CLRs, whereas NLRs and RIGs recognize intracellular molecular patterns.

PRRs are expressed primarily by innate immune cells but also by endothelial and epithelial cells. The innate immune system is "primed" by activation of PRRs by PAMPs and/or DAMPs, leading to activation of proinflammatory transcription factors; the best characterized is nuclear factor kappa-B (NF-κB). There is a consequent increase in transcription of genes encoding multiple mediators (e.g., cytokines and chemokines) and receptors. An excessively dysregulated host response results in detriment to the host (critical illness). In many circumstances it remains unclear why some patients develop such a response to infection. Some bacterial toxins, including *Staphylococcus aureus* enterotoxin A, may result in a life-threatening toxic shock syndrome secondary to nonspecific polyclonal T cell activation.[29] However, in the vast majority of septic patients, there is no single identifiable cause. Within the kidney, intrinsic renal cells, especially tubular epithelial cells, express components of the inflammasome pathway, including TLRs,[30,31] which are upregulated in sepsis. Renal tubular epithelial cells produce various proinflammatory cytokines and chemokines (e.g. IL-6, IL-18, and monocyte chemotactic protein [MCP-1]).[32] The kidney also contains resident antigen-presenting cells (dendritic cells and macrophages) that modulate the local immune response to DAMPs and PAMPs filtered from the circulation.[33] The expression and activity of channels responsible for solute reabsorption are

downregulated during inflammation. Tumor necrosis factor-alpha (TNF-α) downregulates the renal Na^+-K^+ pump and the Na^+-K^+-$2Cl^-$ cotransporter in vivo,[34] while interleukin-1β (IL-1β) inhibited, in a dose-dependent manner, Na^+/K^+-ATPase activity in medullary and cortical renal cells.[35] Lipopolysaccharide (LPS) significantly downregulated ion transporters, including the Na^+/H^+ exchanger 3 (NHE3), Na^+/K^+-ATPase, renal outer medullary K^+ channel (ROMK), epithelial Na^+ channel (ENaC), Na^+–K^+,$2Cl^-$-cotransporter 2 (NKCC2), Na^+–Cl^--cotransporter (NCC), and kidney-specific chloride channels -1 and -2 (CLCK-1 and -2).[36,37] This effect also was seen in mice given lower doses of LPS where blood pressure was maintained. Similar effects were seen with injection of proinflammatory cytokines (IL-1β, TNF-α, Interferon gamma INF-γ) and ischemia-reperfusion injury, but not with hypoperfusion.[36] Alteration of renal sodium transporters during LPS-induced AKI thus appears mediated by cytokines rather than ischemia. Studies using knockout mice for TNF-α, IL-1β, and INF-γ show that, even in the absence of these cytokines, renal tubular epithelial cells still can downregulate ion transport channels in response to LPS. This suggests that multiple pathways are present.[36]

AN ADAPTIVE STATE?

It has been proposed that MODS may represent an adaptive and protective response during critical illness.[21] During extreme stress, including critical illness, it may be advantageous to reprioritize energy expenditure in an attempt to improve chances of survival, especially when oxygen delivery is compromised by cardiac and macro- and microvascular perturbations and the local milieu is heavily proinflammatory. Metabolism is dependent upon an adequate supply of substrate. If metabolism continues normally in the face of an insufficient availability of energy, ATP levels fall and cell death pathways are activated. The cell can increase its glycolytic activity to partially offset this fall in aerobic respiration as well as decreasing its metabolic rate and reducing oxygen consumption. Although this hibernation-type process will protect the cell, it occurs at the expense of reduced organ functionality, which is recognized as biochemical and/or physiologic "organ failure."[21] As mitochondria are the primary source of O_2 use, predominantly for ATP generation, this strongly implicates mitochondrial dysfunction in the pathophysiology of MODS. However, this response may become maladaptive with inadequate cellular functionality to sustain life. There is a clear association between the degree of mitochondrial dysfunction, organ failure, and mortality.[22] Whole-body VO_2 is elevated in mild sepsis in patients but falls with increasing severity.[38] During recovery, there is a rebound increase in VO_2. However, attempted augmentation of VO_2 by increasing global O_2 delivery (DO_2) in the established phase of septic shock was associated with an increase in mortality.[39] Eventual nonsurvivors have reduced cardiac reserve and fail to increase VO_2 after resuscitation; when DO_2 is enhanced with inotropic support, oxygen extraction falls.[40] This iatrogenic harm offers further evidence, albeit indirect, that the natural reduction in VO_2 may in fact be adaptive.

Functionally, a reduction in organ function may confer a survival benefit. For instance, in hypovolemic states, a reduction in urine output helps to conserve circulating blood volume.[41] In this context, oliguria is adaptive. "Physiologic oliguria" may be achieved by a decrease in glomerular filtration, with a net reduction in the need for tubular resorption and therefore energy conservation. Changes in intrarenal circulation subsequent to modification in efferent arteriolar function and intrarenal shunting allow a reduction in GFR can be achieved without a reduction in global renal blood flow.[11] However, if prolonged, the effects of oliguria itself may become detrimental to the host.

REVERSAL OF MULTIORGAN DYSFUNCTION SYNDROME AND RECOVERY

After a period of MODS, recovery often is identified by improving organ functional parameters toward "normal" physiologic ranges. Underlying this improvement is a restoration of global and regional oxygen delivery, recovery of mitochondrial function, increased oxygen consumption and cellular metabolism,[38] and a transition from an overall proinflammatory immune phenotype to one that is predominantly antiinflammatory. However, this immunosuppression may increase the risk of secondary infection, particularly because the patient is far less mobile, has multiple drains, tubes, and catheters breaching body barriers, and is receiving drugs such as sedatives, corticosteroids, catecholamines, and antibiotics that may accentuate this immunosuppressive effect.

The recovery phase, with an increased requirement for ATP availability requires the generation of new, healthy and active mitochondria (biogenesis) to meet cellular metabolic energy demands and to fulfill other roles, including calcium homeostasis, maintenance of cellular redox state, and cell signaling. The onset of mitochondrial biogenesis in sepsis corresponds with the restoration of normal mitochondrial oxidative respiration.[42] The course of sepsis and recovery is characterized by an increment in markers of mitochondrial biogenesis with increased mitochondrial number and density.[43] The roles of resident immune cells include cell recruitment, regeneration and repair, and fibrosis. Resident renal macrophages assume a proinflammatory M1 phenotype (classically activated) or an antiinflammatory M2 phenotype (alternatively activated),[44] depending on the local environment. In the early stages of sepsis, resident macrophages and dendritic cells may have important proinflammatory roles in antigen presentation and phagocytosis. During the resolution phase of MODS, renal macrophages may play a role in repair and regeneration. Similarly, in trauma, the balance between ratios of Th1/Th2 and Th17/Treg is altered from initial presentation to recovery to reflect a transition from a pro- to an antiinflammatory phase.[45]

FUTURE THERAPIES

Understanding the natural history of MODS in critical illness is a fundamental part of designing trials to evaluate potential therapeutic agents. Evolution has ensured that we can adapt to adverse situations, such as mounting an appropriate immunologic and physiologic response to survive. However, if the insult is prolonged and severe, the same host response, albeit exaggerated, may have a detrimental effect. There is likely to be a complex interplay between the multiple interventions required for immediate lifesaving treatment and intrinsic adaptive changes. Because medical interventions have evolved far quicker than biology, critical illness is no longer an adaptive state determined by evolution alone. This makes it very challenging to extrapolate findings

from a simplistic preclinical model to the complex clinical setting. Most research on pharmacologic interventions in sepsis has focused on attenuating the proinflammatory phase. This includes the use of monoclonal antibodies against IL-1[46] and TNF-α,[47] TLR4 antagonists,[48] inducible nitric oxide synthase (iNOS) inhibitors,[49,50] antioxidants,[51] and modulation of the coagulation system.[52] Despite initial promise in preclinical studies and early clinical studies, no immunomodulatory therapy has yet demonstrated conclusively any benefit in sepsis. The assumption that sepsis simply represents a proinflammatory state has been laid bare. Many patients, even on admission to intensive care, are in a state of immunosuppression. Thus the addition of an immunosuppressive therapy may compromise further the host response, increasing the risk of secondary infection and a poor outcome.[53,54] Some small studies have shown that immunostimulatory therapies may be beneficial in the right patient subset.[55] A personalized medicine approach in which patients can be targeted individually by relevant biomarkers to receive appropriate therapies given at optimal dose and duration will lead to better patient selection and, hopefully, improved outcomes.

Emerging nonpharmacologic therapies to limit and potentially reverse MODS include the use of mesenchymal stem cells and bone marrow–derived stromal cells. Preclinical studies have demonstrated the potential role of mesenchymal stem cell therapy in experimental sepsis.[56–58] Apoptotic adipose-derived mesenchymal stem cell therapy (A-ADMSC) was superior to healthy ADMSC (H-ADMSC) therapy in preventing acute lung injury and AKI in rats with CLP-induced sepsis.[59] Animals treated with H-ADMSC had higher levels of cellular antioxidants and significantly greater mitochondrial integrity (as measured by cytochrome C) compared with untreated animals or animals treated with H-ADMSC. This may relate to the immunosuppressive effect of apoptotic cells.[60] Further data are required regarding the long-term effects of mesenchymal stem cell therapy, the potential of delayed treatment, the optimal dose, and potential side effects.

Another exciting area of research is the use of bone marrow-derived stromal cells (BMSCs) as a means of transferring healthy mitochondria to damaged cells. BMSCs are able to form connexin 43 (Cx43)–containing gap junctional channels with alveolar epithelia, releasing mitochondria-containing microvesicles that epithelia engulf. A mouse model so treated was protective in the treatment of LPS-induced lung injury in mice.[61]

SUMMARY

Organ failure is a hallmark of critical illness. Yet little is understood about the evolutionary drive behind organ failure in critical illness. Clinical trials in various shock states have been highly disappointing: multiple drug and interventional strategies all fail to show consistent outcome benefit in large randomized controlled trials. These repeated failures highlight the major complexities presented by critical illness in which multiple pathways are simultaneously affected and marked fluctuations occur over time. Many of the biologic and physiologic alterations previously viewed as pathologic actually may be adaptive and protective, and our well-meaning but misguided attempts to normalize or overcorrect perceived abnormality actually may be injurious.

Key Points

1. An excessively dysregulated immune response results in detriment to the host (multiorgan dysfunction syndrome [MODS] and critical illness).
2. Central to the underlying pathophysiology of MODS are cellular hypoxia, dysoxia, and a dysregulated host inflammatory and metabolic response.
3. Cellular hypoxia leading to cell death does not appear to be causal in the loss of cellular and organ function, particularly in sepsis. A prolonged inflammatory result can result in decreased mitochondrial activity through several mechanisms.
4. Critical illness represents a dynamic process in which multiple pathways are affected simultaneously, and marked fluctuations occur over time.

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A complete reference list can be found online at ExpertConsult.com.

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