CHAPTER 53  THE HOST RESPONSE TO INJURY AND CRITICAL ILLNESS

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In 1794 John Hunter wrote, “There is a circumstance attending accidental injury which does not belong to disease—namely, that the injury has in all cases a tendency to produce both the disposition and the means of a cure.” This first described the stress response, a biphasic physiologic response that, when uninterrupted by complications, has predictable characteristics and lasts 7 to 10 days (Fig. 53.1). When not altered by intervention or complications, the stress response is initiated by a global depression of energy expenditure and metabolism. This 24-hour phase that occurs immediately after occurring injury is followed by a period of hypermetabolism that characteristically persists for 5 to 7 days. The driving force for this second phase appears to lie with the need to mount an immune or inflammatory response to combat infection and facilitate repair of damaged tissues. Most markers for ongoing inflammation and metabolism peak on postinjury day 2 and return to baseline around day 7. Although the intensity of the response may change or the time course may be altered by intervention, these events must take place or the organism will not survive.

It is possible for the normal stress response to be altered by coexisting disease or interrupted by adverse events such as recurrent bleeding, systemic inflammatory response syndrome (SIRS), or progression of SIRS into sepsis. When the stress response is altered, the organism then may enter a state of persistent hypermetabolism. This continued inflammation has been postulated to lead to organ dysfunction and immune incompetence (Fig. 53.2). The onset of

immune incompetence marks a transition from a hyperfunctional to a hypofunctional state in which patients are at higher risks for nosocomial infections and demonstrate a pervasive endocrinopathy (Fig. 53.3). It is from this state that most intensive care unit (ICU) deaths occur (1).

THE NORMAL STRESS RESPONSE

David P. Cuthbertson was perhaps the first to study the host response to injury. In 1929, while working at Glasgow University, Cuthbertson was charged with the duty of investigating why fractures of the distal femur were slow to heal. He discovered that if prolonged immobilization occurred postinjury, the urinary excretion of sulphur, nitrogen, phosphorus, and calcium was elevated. As an aside to these studies, Cuthbertson noted that body temperature followed a characteristic pattern (Fig. 53.1). In the first 24 hours following the fracture, temperature decreased. Following this period, temperature rose, peaking on postinjury day 3 and returning to baseline by postinjury day 7. He correlated this change in temperature with alterations in oxygen consumption and carbon dioxide production. Further, he noted that the sulphur : nitrogen ratio closely matched that of muscle. This led to Cuthbertson’s proposal of a paradigm by which the body responded to injury. If the damage to the patient is not immediately fatal, there is a compensatory reaction in which vasoconstriction shunts blood away from the periphery and to the central organs, most notably the heart and brain. This promotes short-term survival. Hypothermia and oliguria are associated with a global decrease in oxygen consumption and energy expenditure. In an effort to expand plasma volume and avoid failed oxygen delivery, the body conserves salt and water by increasing aldosterone secretion (2). These effects are seen throughout the body in the first 24 hours after injury. Cuthbertson termed this sequence of events the “ebb” phase or traumatic shock. When it becomes clear that death is not imminent, a second aspect of the response emerges. The key to these reactions is an attempt to repair tissue damage, a process that is accomplished via the activity of white blood cells (WBCs). Slowed circulation in the ebb phase allows WBCs to move toward the periphery and adhere to the endothelium. Neutrophils react first, with macrophages following. With restoration of the circulation, the process becomes active. It is characterized by phagocytosis and lysis of bacterial, viral, or fungal invaders and removal of cellular debris. In addition, macrophages, lymphocytes, and antigen-presenting cells (APCs) secrete proteins called cytokines. To a great extent, these are growth factors that facilitate repair of damaged tissue. This process requires enormous amounts of energy, with a 2- to 20-fold increase in oxygen consumption and resting energy expenditure (REE). Body temperature rises and oxygen consumption and carbon dioxide production increase (2,3). Monk et al. showed an increase in REE of up to 55% above predicted in trauma patients (4). Some studies suggest that survival is dependent on this ability to maintain hypermetabolism and adequate oxygen utilization (3,3–8). Because WBCs are more or less obligate glucose users, there is an associated increase in glucose requirements (9). After the first 24 hours, hepatic glycogen stores are depleted and a source of de novo glucose is required. This is generated by hepatic gluconeogenesis. Cuthbertson proposed that the body was able to provide its own source of nutrients by breaking down protein, a theory that has since been validated. This provides substrate for gluconeogenesis and constituent amino acids for synthesis of hepatic proteins and repair in the area of injury. However, adequate mobilization is not enough to ensure substrate delivery. Therefore, the response includes

CHRONIC CRITICAL ILLNESS

The normal stress response


![FIGURE 53.2. Continued inflammation, which has been postulated to lead to organ dysfunction and immune incompetence. SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome.](image2)

![FIGURE 53.3. The onset of immune incompetence marks a transition from a hyperfunctional to a hypofunctional state in which patients are at higher risks for nosocomial infections and demonstrate a pervasive endocrinopathy. SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome.](image3)
capillary dilation to increase flow and improve delivery. Un-
fortunately, due to thrombosis in damaged tissue, most injured areas become necrotic. To allow substrate delivery to these regions, capillary tight junctions separate, allowing fluid and substrate to “leak” from the vasculature. Increased vascular permeabil-
ity results in redistribution of extracellular fluid and plasma proteins to form edema and exudate (10). Glucose and other nutrients move down their concentration gradients across the extracellular matrix to areas of damage. Removal of waste re-
quires an increase in renal blood flow and glomerular filtration to enable excretion of amino acid degradation products. The liver detoxifies nitrogenous wastes by the production of urea; metabolizes alanine, lactate, and glycerol through gluconeogen-
esis; and produces acute-phase proteins that bind metabolic by-products and limit the activity of proteolytic enzymes se-
creted by activated WBCs (1). Because this process increases delivery to nearly every part of the body, Cuthbertson termed this part of the response the “flow” phase.

Work by Cuthbertson and Francis C. Moore demonstrated that initiation of the flow phase is in part hormonally modu-
lated. An initial dramatic release of endogenous catecholamines (13) is supplemented by alterations in the somatotropic sys-
tem (growth hormone and insulinklike growth factor) such that anabolism is postponed and energy substrates are redi-
rected to vital organs. Both the thyroid and the gonadal axes are suppressed. Adrenocorticotropic hormone (ACTH) secretion is heightened by increased corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), catecholamines, angiotropin II, serotonin, and some inflammatory cytokines (in-
terleukin [IL]-1, IL-2, IL-6, and tumor necrosis factor [TNF]). ACTH stimulates the adrenal glands to produce glucocorti-
coids and mineralocorticoids. Glucocorticoids and glucagon promote gluconeogenesis and induce peripheral insulin resistance, leading to increased glucose production (12). This in turn increases insulin secretion, producing an “insulin-
resistant” state.

Tissue repair is initiated by these activities. Traumatized tis-
sue and hemorhage initiate platelet accumulation and activa-
tion. The coagulation cascade is triggered by both the intrinsic and extrinsic pathways. This serves to sustain and enhance im-
mune cell migration and activation. In addition, fibroblasts at the edge of the wound divide, migrate toward the center, and produce collagen. Surviving capillaries bud, and these new cap-
illaries also migrate toward the center. Eventually the wound edges will fuse and consist of vascularized granulation tissue (13). This process is thought to be mediated by an increase in fibroblast growth factors, epidermal growth factor, platelet-
derived growth factor, and vascular endothelial growth factor
(14).

This massive mobilization of defense mechanisms may also affect normal tissue. Therefore, one of the most important char-
acteristics of the normal stress response is that it is a balance between the inflammatory and the anti-inflammatory systems. This involves the proinflammatory cytokine TNF, released by the activated macrophage. When TNF “spills over” from the interstitium into the bloodstream, it stimulates the mediatory reticular formation and the hypothalamus in the brain. This ac-
tivation of the hypothalamic-pituitary-adrenal axis ultimately causes increased anti-inflammatory activity. For example, glu-
corticoids released as a result of this process limit the negative biologic consequences caused by inflammation (15). TNF also stimulates the dorsal vagal complex and alters the effenter vagal output. This is in part responsible for “sickness” behavior (i.e., anorexia and fever) (16–18). More importantly, however, is neuroimmunomodulation of the immune response. The “inflammatory reflex” or the cholinergic anti-inflammatory pathway occurs when proinflammatory cytokines such as IL-1 and TNF stimu-
late the parasympathetic nervous system through receptors on the vagus nerve. The afferent input travels to the nucleus soli-
tarius and is relayed to the dorsal motor nucleus, resulting in an increase in acetylcholine release at cholinergic nerve termi-
nals in the areas of inflammation. Activated macrophages have acetylcholine receptors that, when stimulated, decrease the re-
lease of proinflammatory cytokines (19,20). This balance of the systems is crucial in limiting the stress response.

Moore et al. also observed changes in the size of body fluid compartiments. In a normal stress response, catabolism is ac-
panied by an increase in the vascular space (recipient); expansion of the extravascular, extracellular space; and a de-
crease in the intracellular compartment. This process ends 4 to 5 days after injury with a shift to anabolism (11). The extrava-
scular space expands, fluid is removed from the extravascular space and either moves back into cells or is excreted by the kidneys, and the intracellular shift is accompanied by an influx of protein and electrolytes. While the physiologic “signal” that initiates this transition is still unknown, it is telling that the transition occurs at the completion of the first wave of angiogenesis. The generation of a new vascular highway obviates the need for nu-
trient concentration gradients, increased vascular permeability, and water and electrolyte conservation. Conservation of salt and water is no longer a priority and a brisk diuresis results. In addition, as the intracellular space expands, increases in in-
tracellular anions and cations (12) are of key importance in innate immunity, a process that is directed to vital organs. Both the thyroid and the gonadal axes are suppressed. Adrenocorticotropic hormone (ACTH) secretion is heightened by increased corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), catecholamines, angiotropin II, serotonin, and some inflammatory cytokines (in-
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The cellular immune response to normal inflammatory stim-
uli involves neutrophils, monocytes (macrophages), lympho-
cytes, and APCs. Neutrophils are recruited to areas of injury early in the process. This is stimulated in part by protein ant-
gens and chemokine molecules (chemokines) that induce VCAM and ICAM cell adhesion molecules that fixed tissue macrophages. Their function is removal of cellular debris by phagocytosis and secretion of lytic molecules such as digestive enzymes and free radicals. While the influx of neutrophils is self-limited, lasting about 48 hours, the rest of the response, which starts within hours of neutrophil influx, may be more persistent. It consists of utiliza-
tion by macrophages, APCs, and lymphocytes. Macrophages are of key importance in innate immunity, a process that is nonspecific and involves natural barriers such as skin, natural killer cells, and chemicals in the blood that act immediately upon antigen introduction. Macrophages respond to stimula-
tion with phagocytosis of foreign or damaged material and secretion of cytokines that stimulate inflammation and also function as growth factors. In addition, they contribute to adaptive immunity by presenting antigens, a function that also is served by APCs. Antigen-presenting cells such as dendritic cells capture antigens, transport them to lymph nodes, and present them to T cells, initiating cell-mediated immunity. Fol-
locular dendritic cells have a similar function except that they present antigens to B cells and therefore initiate humoral im-
munity. Lymphocytes are the prime components of the adaptive
immune response. They have specific receptors for antigens. B cells produce antibodies and are mediators of humoral immunity. T cells recognize peptide fragments of protein antigens bound to MHCs and are involved in cell-mediated immunity. T cells can be further divided into CD4 cells, which enhance or inhibit the immune response; CD8 cells, which lyse other cells with intracellular pathogens; and natural killer (NK) cells, which do not express antigen receptors and contribute to innate immunity.

Adaptive immunity is antigen specific and can be divided into five phases. The first phase is presentation of the antigen to a B or T cell by an APC. In the second phase, B and T cells are activated, undergoing clonal expansion, differentiation, and antibody production. Antigens are eliminated in the third or effector phase. Decline is the fourth phase: The stimulus has been removed and there is apoptosis of immune cells and phagocytosis of cellular debris. The last phase involves the surviving immune cells acquiring memory (21). As the process proceeds, there is a change in the phenotype of CD4 T cells that is profoundly important. The catabolic phase of inflammation is characterized by an abundance of CD4 cells of the type 1 helper T cell (Th1) phenotype. This results in secretion of proinflammatory cytokines such as IL-2, TNF-α, and interferon-γ.

The switch to anabolism is accompanied by a predominance of type 2 helper T cells (Th2), which secrete anti-inflammatory cytokines such as IL-4 and IL-10. In a normal stress response, immune function declines and the transition from Th1 to Th2 occurs by the fourth or fifth day. The switch from Th1 to Th2 may be hormonally mediated. It is known that cortisol and other anti-inflammatory cytokines such as IL-4 and IL-10. In a normal stress response, immune function declines and the transition from Th1 to Th2 occurs by the fourth or fifth day. The switch from Th1 to Th2 may be hormonally mediated. It is known that cortisol and other anti-inflammatory cytokines such as IL-4 and IL-10.

One clinical manifestation of this is in the blood. That is, early in the response there is a mixed leukocytosis with neutrophil predominance. This gives way to a macrophage/lymphocyte-rich pattern and is followed by an overall decline in the white blood cell count.

### DEVIATION FROM THE NORMAL STRESS RESPONSE

The stress response is considered to be adaptive and vital in order to survive an injury. However, many aspects of the process may become excessive or unbalanced. This converts an adaptive response into a pathologic one. Risk factors that predispose to the development of an abnormal response include inadequate or delayed resuscitation, persistent inflammatory or infectious sources, baseline organ dysfunction, age older than 65 years, immunosuppression, alcohol abuse, malnutrition, and invasive instrumentation (22). There are two such common occurrences in the surgical or trauma population. The first is hemorrhage, uncorrected fluid loss, or underresuscitation. This results in a recurrence of shock, with vasconstriction, decreased perfusion and cardiac output, and impaired tissue substrate delivery. The treatment is identification and treatment of the underlying cause accompanied by correction of the fluid imbalance.

The second common abnormality is prolonged hypermetabolism. Persistence of a hyperdynamic circulation and secretion of immunologic markers; elevations of serum potassium, magnesium, and phosphate; and/or marginal urine output indicate a prolonged or renewed stress response and warn of a new or recurrent abnormality. This state commonly is referred to as systemic inflammatory response syndrome. If SIRS is suspected to be from an infectious cause, then the condition is referred to as sepsis or the sepsis syndrome. Initially, the normal stress response—SIRS, and sepsis may mimic each other. Differentiation lies in the time course and in the etiology of the metabolic perturbations. The definitions of SIRS, sepsis, and severe sepsis, as formulated in 2001, are detailed in Table 53.1. Sepsis is the most common cause of death in noncardiac intensive care units. The increasing use of broad-spectrum antibiotics, immunosuppression therapy, and invasive technology may be responsible (23). Recent studies estimate the incidence of sepsis in the United States as 240 to 300 cases of severe sepsis per 100,000 people, an increase from 74 cases per 100,000 people in 1979. The mortality rate ranges from 17.9% for sepsis, 28.6% for severe sepsis, and up to 50% in those with septic shock.

### TABLE 53.1

**DIAGNOSTIC CRITERIA FOR SEPSIS IN ADULTS**

<table>
<thead>
<tr>
<th>SUSPECTED OR DOCUMENTED INFECTION</th>
<th>General variables</th>
<th>Inflammatory variables</th>
<th>Hemodynamic variables</th>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (T &gt;38.3°C)</td>
<td>Hypothermia (T &lt;36°C)</td>
<td>Heart rate (&gt;90 bpm or &gt;2 SDs above normal for age)</td>
<td>Tachycardia</td>
<td>Arterial hypotension (SBP &lt;90 mm Hg, MAP &lt;70 or SBP, or &gt;80 mm Hg or &lt;2 SDs below normal)</td>
</tr>
<tr>
<td>Hypotension (SBP &lt;90 mm Hg, MAP &lt;70 or SBP, or &gt;80 mm Hg or &lt;2 SDs below normal)</td>
<td>Leukocytosis (WBC &gt;12,000/μL)</td>
<td>Plasma C-reactive protein &gt;2 SDs above the normal value</td>
<td>Plasma procalcitonin &gt;2 SDs above the normal value</td>
<td>Hyperlactatemia (plasma total bilirubin &gt;4 mg/dL or &gt;70 mmol/L)</td>
</tr>
<tr>
<td>Leukopenia (WBC &lt;4,000/μL)</td>
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<td>Plasma procalcitonin &gt;2 SDs above the normal value</td>
<td>Hyperlactatemia (plasma total bilirubin &gt;4 mg/dL or &gt;70 mmol/L)</td>
<td>Tissue perfusion variables</td>
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Chapter 53: The Host Response to Injury and Critical Illness

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The Host Response to Injury and Critical Illness

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shock and comorbid conditions. The etiology of sepsis has also changed over time. In the 1970s and 1980s, Gram-negative bacteria were the predominant cause of sepsis. Gram-positive organisms are now the leading pathogens, with fungal organ-

isms on the rise (24). Sepsis likely predisposes to organ dysfunction. When this dysfunction is overt, the process is referred to as multiple or-

gan dysfunction syndrome (MODS). However, abnormalities in MODS seem to be confined to cellular and organ dysfunction as histology and infrastructure are preserved. The most proxi-

mal defect that has been identified to date in SIRS/Severe/MODS is an abnormality of oxygen utilization at the subcellular level. Two theories to explain this have been advanced. The first is that there is an impairment of microcirculatory autoregulation. Vasodilation of some vascular beds coexists with vasoconstric-

tion of others, causing a maldistribution of flow and, therefore, oxygen (25). The second theory assumes adequate perfusion but an alteration in cellular metabolism with an inability to extract and use oxygen (26). This is supported by recent stud-

ies demonstrating a defect in mitochondrial function (27–29). In either case, the result is a block in cellular metabolism. As a result, the ability of cells and organs to respond to external stimuli may be lost. For example, there is a progressive loss of hormonal responsiveness. The liver becomes unresponsive to insulin and glucagon and the cardiovascular system to catecholamines (30–32). As such, the hyperfunctional state cannot be maintained. It has been proposed that cells enter a “preserva-

tion mode” in which viability is maintained but the capacity to communicate with each other is lost. Cellular interaction is lost and thus organ function is compromised (33–35). Acute lung injury (ALI) progresses to acute respiratory distress syndrome (ARDS) and hypotension from vasoplegia is compounded by cardiac dysfunction that requires vasopressors and isotropic and chronotropic support. Renal function decreases to a point that renal replacement therapy must be considered and hepatic dysfunction results in severe ascites and coagulopathy, both having the potential to lead to a profound encephalopathy. The immune system is one of the most important systems to be affected. The development of immune incompetence coupled with a pervasive endocrinopathy places the patient at a higher risk for nosocomial infections, and it is in this state that most deaths from sepsis occur.

The issue of immune incompetence requires further discus-

sion. Historically, sepsis has been viewed as a condition ruled by uncontrolled inflammation. However, an increasing num-

ber of studies indicate that sepsis is in fact a state of inflam-

matory failure (36–39). More specifically, sepsis is associated with a profound endocrinopathy and progressive anergy (12). That is, chronic critical illness is associated with a loss of T-cell responsiveness on any level (43). This may re-

flect enhanced lymphocyte apoptosis (44–46). Hotchkiss et al. also demonstrated that there were decreased levels of follicular dendritic cells, B cells, and CD4 T cells at the time of death of septic patients, resulting in impaired antigen presentation, antibody production, and B-cell and macrophage stimulation (44–46). The ultimate result of immunosuppression is the de-

velopment of sequential infections, often invoking the decision to withdraw therapy.

One major contributor to the development of complications from inflammation is the presence of comorbidities. Chronic comorbid conditions are present in over 30% of patients with sepsis and are associated with an increase in mortality (47–

49). Diseases reported to increase the risk of the normal stress response developing into sepsis are diabetes mellitus (DM), hu-

man immunodeficiency virus (HIV), chronic liver disease, and cancer (47). Esper et al. conducted a historical cohort study that reviewed patients with the diagnosis of sepsis in U.S. acute care hospitals from 1979 to 2003, characterising the type and source of infections and comorbid diseases. They found that men were more likely than women and African Americans were more likely than Caucasians to develop sepsis. Non-Caucasian patients who were septic were more likely to have concomitant DM, HIV, chronic renal failure, and alcohol abuse. Caucasians had higher incidences of cancer and chronic obstructive pul-

monary disease (COPD). The presence of one comorbidity in-

creased the risk of developing at least one organ system failure by 30%. Those with two comorbidities had a 35% chance and those with three or more had a 45% chance of developing acute organ failure (50).

It is not difficult to imagine how baseline insufficiencies af-

fect the stress response. For example, the ability to maintain a circulatory system capable of providing oxygen and nutrients to areas of injury is paramount to survival. In the setting of underlying coronary artery disease (CAD), this ability may be impaired. Kern et al. (51) found that patients with CAD have a significantly decreased cardiac index and oxygen delivery and, not surprisingly, an increased oxygen extraction ratio during sepsis. They also showed that these patients had increased en-

dothelial adhesion molecule expression, which may correlate with the severity of sepsis, shock, and organ failure and predict poor outcome (52,53). Chronic pulmonary disease, regardless of the etiology, increases the chance of intubation and the re-

quirement for prolonged ventilatory support. Intubation places the patient at risk for ventilator-associated pneumonia, aspira-

tion, and respiratory muscle atrophy. A patient with chronic renal or liver failure is at risk for anemia, coagulopathies, and immunosuppression prior to being injured. With an impaired functional reserve in vital organs and responses, the stress re-

sponse to injury has a high likelihood of progressing to a state of prolonged critical illness.

TREATMENT OR PREVENTION

It is logical that treatment of pre-existing disorders and co-

morbidities will alter the stress response. Indeed, a number of studies have examined the role of perioperative β-blockade and concluded that, in appropriate patients, outcome is im-

proved. More problematic are attempts to alter the course of the prolonged state that constitutes SIRS, sepsis, MODS, and chronic critical illness. Despite promising animal data, most approaches have failed in patients. The successes are no-

table. Herndon et al. showed that in the pediatric burn pop-

ulation, resting energy expenditure decreased and net muscle protein balance increased with administration of prazosin. However, there have been several experiments conducted with mice in septic or hemorrhagic shock showing an increase in mortality from immunosuppression after β-blockade (54,55).
Adequate allogasias via epidural and intravenous use of agents such as opiates, α-blockers, nonsteroidal anti-inflammatory drugs, and local anesthetics have been shown to both decrease inflammation and improve immune function (56–59). Early goal-directed resuscitation has been shown to improve outcomes in a single-center trial (60). A multicenter trial in the United States is beginning. Similarly, a protocol using insulin infusions to maintain serum glucose levels between 80 and 110 mg/dL has been shown to reduce mortality and complications in a surgical ICU in a single institution (61). However, similar results were not observed in the medical ICU in the same institution (62). These results, as yet unpublished multicenter European trial (GLICUNTR, confirmed by personal communication). The benefit of insulin appeared to be confined to patients in the ICU for more than 3 to 5 days. This would suggest that insulin is one of many hormones that become ineffective in chronic critical illness.

**SUMMARY**

Injury is present in the form of elective surgery, trauma, infection, and medical illnesses such as pancreatitis. It is crucial for the clinician to understand the underlying course of events that comprise the stress response. This enables the detection of deviations from normal physiology. Although intervention may be useful in reducing the extremes of the stress response and limiting the untoward impact of comorbidities, balance is the hallmark of a normal response. Pre-existing disease and persistent hypermetabolism offsets this balance and pathologic conditions prevail. Both anti-inflammatory and inflammatory strategies may offer therapeutic benefit to attenuating the abnormalities, but most therapy has proved disappointing.

**References**

IMMEDIATE CONCERNS

Major Problems

Progressive dysfunction of multiple organ systems, culminating in the syndrome of multiple organ dysfunction syndrome (MODS), has become a leading cause of death in critically ill and injured patients. MODS is a disease of medical progress. Broader use of intensive care unit (ICU) resources, combined with improvements in single organ-directed therapy, such as mechanical ventilation and renal replacement therapy, has reduced early mortality after major physiologic insults. The result is a longer ICU stay for an increasing number of patients after severe sepsis and trauma, during which inflammation and tissue injury may result in MODS. MODS represents a systemic disorder of immunoregulation, endothelial dysfunction, and hypermetabolism, with varying manifestations in individual organs. The mortality of MODS will increase as the number of failing organs in increases, suggesting that changes in the function of all organs have equal significance in outcome. However, organs differ in their host defense functions and sensitivity to host-derived inflammatory mediators or reductions in oxygen delivery (DO₂). Therefore, diagnosis and therapy focus, whenever possible, on preventing measures. Changes in the cellular oxygen (O₂) supply and metabolism may cause and complicate MODS. Consequences can include direct hypoxic organ damage, secondary ischemia/reperfusion (IR) injury mediated by neutrophils and reactive O₂ species (ROS), and enhanced injury by activation of cytokines, including tumor necrosis factor-α (TNF-α). Initial and subsequent therapy follows a two-tiered approach, targeting systemic factors that contribute to ongoing inflammation and single organ–related problems. Efforts are first directed at stabilizing hemodynamic and immune implications in critical illness. J Crit Care Med. 2004;28(2):108–122.

DO

Chest.


Crit Care Med.

Multiple Organ Dysfunction Syndrome

CHAPTER 54

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Resuscitation.

Multiple Organ Dysfunction Syndrome

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