Multiple Organ Failure

7

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Introduction

While traumatic brain injury and uncontrolled hemorrhage remain the leading causes of death after trauma, sepsis followed by multiple organ failure (MOF) are leading contributors to mortality in critically ill surgical and trauma patients. MOF is the leading cause of morbidity in the intensive care unit (ICU) following trauma and represents the endpoint of the spectrum of SIRS and sepsis [1]. Despite the identification of this disease process in the early 1970s, our understanding of the pathophysiology and the ensuing treatment of this syndrome remains a perplexing entity to which entire books have been dedicated. This chapter provides a brief overview of the evolution of the disease, the clinical presentation, and discusses the epidemiology and salient pathophysiology, as well as current treatment options and future considerations of this disease.

Historical Perspective

Military conflicts have historically been the impetus for knowledge advancement in the arena of care of the critically injured patient. The evolution of the medical communities' knowledge of morbidity and mortality from a single organ injury to MOF is an example of such a process. In World War I, death of the injured was primarily due to hemorrhagic shock and infections. During World War II (WWII) the lessons learned from prior conflicts, including control of hemorrhagic shock and expeditious evacuation to a surgical treatment facility, greatly reduced the immediate death rate to half of what it had been for the US Army in early WWII [2–4]. Transfusions in WWII aided resuscitation in stabilizing hemodynamic parameters but delayed renal failure was a significant morbidity. In the Korean War, delayed deaths in resuscitated patients were most often as a result of acute renal failure [5]. The increased resuscitation with crystalloid improved the renal failure but resulted in acute lung injury. This emerging constellation of symptoms is now known as Acute Respiratory Distress Syndrome (ARDS) [6]. These serial improvements were beneficial in the understanding of resuscitation of severely injured patients. However, the survival of these patients revealed the damage that multiple end organs had sustained as manifested in a new syndrome now known as MOF. MOF is at the severe end of the severity of illness spectrum of both systemic inflammatory response syndrome (SIRS) and sepsis.

The term "multiple organ failure" (MOF), was used by Shoemaker in a 1973 editorial to describe the circulatory, respiratory, renal, cerebral and cardiac complications that ensued after the initial resuscitation of a trauma patient [7]. Around the same time, Tilney described a similar syndrome of sequential organ failure in 18 patients following surgical repair of their abdominal aortic aneurysms [8]. In 1975, Baue expanded on the organ systems affected and recognized that when more than one organ system failed, the knowledge and ability to care for the patient was stretched. Additionally, Baue offered suggestions (Table 7.1) to prevent further damage as well as potential therapeutic options which included prevention of respiratory failure, volume resuscitation, early vasopressor use, source control, and early nutrition. It is salient to point out that these principles are still very central to the treatment of this disease process. Currently, the terms multiple organ dysfunction syndrome (MODS) and MOF are often used interchangeably [9]. The nuances of the two words effectively describe the syndrome of organ impairment at the point where expeditious treatment might prevent overt organ failure (MODS) versus established coexisting MOF as described in numerous organ failure scores [10]. Effectively, MOF is the end of a continuum that ranges from SIRS to severe organ dysfunction.

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Table 7.1 Goals to prevent MOF identified in 1975

Goals to prevent MOF
• Prevent ventilatory failure by early support, not allowing the lungs to fail and produce hypoxemia.
• Avoid fluid overload, maintaining a urine output of 25–50 ml/h and no more.
• Avoid excess sodium and sodium bicarbonate.
• Filter blood before transfusion.
• Insist on sighing and deep breathing during operation, during resuscitation, and afterward.
• Maintain adequate cardiac output by circulatory support using inotropic agents early such as isoproterenol, dopamine, and epinephrine.
• Empty the stomach, keep it empty and instill antacids after operation or injury.
• Continue controlled ventilation after operation if ventilatory problems are anticipated.
• Follow a sigh-suction-sit treatment program for ventilation.
• Prevent renal failure by maintaining renal blood flow and urine output.
• Use diuretics or dialysis early.
• Provide for early nutritional support of such patients.
• With tissue injury, use antibiotics before operation to reduce invasive sepsis.
• Drain septic foci and eliminate continuing peritoneal contamination.

Table 7.2 Definitions of SIRS, sepsis, severe sepsis, and multiple organ dysfunction

SIRS
• Two or more of the following conditions and can result from infectious or noninfectious causes:
• Temperature >38°C or <36°C
• Heart rate > than 90 beats per minute
• Respiratory rate > than 20 breaths per minute or $paCO_2$ < than 32 mmHg
• White blood cell count >12,000 or <4,000, or >10% bands
Sepsis
• SIRS in conjunction with an infection is termed sepsis
Severe sepsis
• Sepsis associated with organ dysfunction
• May include hypotension, elevated lactate, acute renal failure, liver failure, altered mental status, and/or hematologic abnormality
Septic shock
• Subset of severe sepsis with the addition of hypotension manifested by
• Systolic blood pressure (SBP) <90 mmHg
• Mean arterial pressure (MAP) <70 mmHg
• Decrease in systolic blood pressure (SBP) >40 mmHg from baseline
Multiple organ dysfunction (MODS)
• Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

Definitions

In the mid 1980s, after the recognition of sequential organ failure as a syndrome was recognized, multiple terms were used inconsistently by the medical community [11]. These disparate definitions attempting to describe the same physiologic phenomena led to the 1991 consensus conference. The societies of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) were present. The goal of this conference was to establish a definition to describe what is now known as the spectrum of physiologic response to infection and/or inflammation. The term "systemic inflammatory response syndrome" (SIRS) was introduced at this conference. Additionally the terms sepsis, severe sepsis, septic shock and multiple organ dysfunction were defined as a result of this meeting (Table 7.2). The term "SIRS" was established to differentiate sepsis from a noninfectious, inflammatory state [12]. SIRS was defined as two or more of the following conditions:

- Core body temperature >38°C or <36°C
- Heart rate > than 90 beats per minute
- Respiratory rate > than 20 breaths per minute
- $paCO_2$ <32 mmHg
- White blood cell count >12,000 or <4,000, or >10% bands.

SIRS could represent the symptoms from an infectious or noninfectious source. Infection was described as the invasion of normally sterile tissue by organisms. The term "sepsis" was defined as SIRS in conjunction with a confirmed infection. "Severe sepsis" was defined as sepsis associated with organ dysfunction, hypotension or hypoperfusion as evidenced by: elevated lactate, acute renal failure, liver failure, altered mental status and/or hematalogic abnormalities. "Septic shock" was the term established as a subset of severe sepsis with the added additional clinical information of persistent hypotension, despite adequate fluid resuscitation. Hypotension was defined as systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <70 mmHg, or a decrease in SBP >40 mmHg from baseline.

MODS was defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention and is the culmination of septic shock and multiple end-organ failure [13]. The 2001 Consensus Conference further expanded on these definitions [14]. A problem similar to the disparate use of the word "sepsis" in the early 1980s remains a problem in regard to the definition of MOF. This is evidenced by a lack of consensus with regard to the innumerable scoring systems available to assess mortality.

Epidemiology

Sepsis, severe sepsis, septic shock, and MOF are commonplace in intensive care units and afflict 1.1 million people annually. Moreover, MOF results in 215,000 deaths in the

United States alone. Mortality from the spectrum of sepsis is estimated to be 9.3% of all deaths in the United States [15]. The individual costs of treating a single patient with MOF can be upwards of $150,000 per patient [16]. In the United States alone the costs of treating sepsis and its related sequelae is approximately $24 billion annually [17]. Additionally, the cost of critical care can account for as much as 1% of the gross national product of some countries. The resultant morbidity from this disease and consequent loss of wages and quality of life are difficult to quantify. These costs illustrate the substantial financial and societal burden this disease process inflicts. The irony of MOF is that it emerged as a result of improvements in critical care but that it has remained a substantial encumbrance in terms of morbidity, mortality, and cost despite numerous improvements made in critical care in regard to resuscitation and supportive measures.

The overall mortality ranges between 40 and 60% for MOF in all patients and this mortality increases as more organ systems are affected [18, 19]. The incidence of any organ failure in all ICUs ranges from 30 to 60% [20]. In a 1985 study of intensive care patients by Knaus, single organ failure occurred in approximately one-third of all patients at some point during their ICU stay and MOF occurred in 15% of these patients [21]. MOF following septic shock remains the leading contributor to mortality in ICU patients. In a study by Mayr that looked at causes of death in 3,700 ICU patients, the most common cause of death in a single ICU was MOF (47%) [20]. Specifically regarding trauma patients, traumatic brain injury and uncontrolled hemorrhage remain the leading causes of early death after trauma. MOF is, however, the number one cause of late deaths in trauma patients [22]. Despite our improved understanding of the pathophysiology of this disease, the use of antibiotic agents, and more innovative therapies, there continues to be a high mortality rate for MOF.

Regarding the demographics of sepsis and organ failure, a study by Martin et al. in 2003 elucidated some important differences. This study revealed that men are more likely to have sepsis and are more frequently enrolled in clinical trials despite the predominance of women in the population of the United States. Additionally, African-American men had the youngest age of onset in this study as well as the highest mortality. The reason for these demographic differences is not known; however, genetic differences and socioeconomic factors most likely contribute to these disparities [23]. Recently, research has confirmed a lower overall incidence of MOF [24]. The incidence of early single organ dysfunction has not changed but there has been a decrease in early MOF from 22 to 7%. The incidence of MOF in 1992 was 1.8 times the incidence in 2002 [25, 26]. A similar study of trauma patients by Durham also revealed a lower overall mortality for single organ failure as well as a decrease in the overall incidence of MOF [27].

Risk Factors for the Development of Organ Failure

MOF resides at the most severe end of a spectrum of illness that includes SIRS, sepsis, severe sepsis and septic shock. Any point along this constellation of criteria puts the patient at risk for MOF. The risks of organ failure are multiple and due to lack of consensus regarding a scoring system, it is difficult to ascertain which risk factors are most specific. MOF was originally thought to be catalyzed by an infectious process. While the majority of patients with MOF will have an infectious source, it is also known that MOF occurs without an infection, per se, and can be solely due to unregulated inflammation, as occurs with severe pancreatitis, trauma or burns [28]. Immunosuppression, pneumonia, blood transfusions and bacteremia are all associated with increased risk for developing sepsis, severe sepsis, or septic shock and therefore also increases a patient's risk for MOF [29, 30].

A demographic risk factor for MOF includes advanced age. Advanced age, defined as greater than 65, has likewise been associated with worse quality of life indicators in survivors of sepsis. These patients more often require extensive rehabilitation as well as skilled nursing facility admission upon their hospital discharge from their acute septic event [31]. In a multivariate analysis, adjusted for age, sex, and severe head injury, patients with MOF had four times greater odds of requiring assistance from others in activities of daily living more than 2 years after trauma as compared to trauma patients without organ failure. There was no statistically significant difference regarding self-care between patients who did not have a history of organ failure when compared with those patients who had a history of a single organ failure [32]. Obese patients, in general, have been found to have higher post-traumatic morbidity and mortality. Obesity is defined as body mass index (BMI) >30 kg/m and as the BMI goes up, the incidence of MOF increases as well [33]. Moreover, when age, injury severity score (ISS), and transfusions are adjusted for, obesity is associated with an 80% increased risk of MOF [22, 34]. This is likely associated to the pro-inflammatory state that obesity confers to patients [35]. Additionally, patients with nonoperative diagnoses—for example, patients admitted postacute myocardial infarction—have also been found to have a higher likelihood of developing MOF [21].

In trauma patients, Balk and colleagues aptly identified several major risk factors for the development of postinjury MOF. These included prolonged periods of hypotension, trauma, bowel infarction, hepatic insufficiency, advanced age, and alcohol abuse [36]. Additionally, ISS, number of units of packed red blood cells transfused, base deficit, and lactate levels are all associated with an increased risk of developing MOF [37, 38]

Table 7.3 MOF risk factors

Risk factors for MOF
• Hypotension
• Trauma
• Ischemic bowel
• Pancreatitis
• Advanced age >65
• Shock
• Infection
• Obesity
• Alcohol abuse
• Transfusion of blood products
• Injury severity score ISS >25
• Immunosuppression
• Base deficit >8
• Genetic factors
• Lactate >2.5

(Table 7.3). Blood transfusions have independently been shown to be predictors of SIRS, MODS and mortality [39]. Furthermore, Durham et al. also validated that total blood products infused in the first 24 h after injury in addition to higher Acute Physiology and Chronic Health Evaluation (APACHE) III scores, amplified the risk for MOF occurrence [27].

Genetic factors also play a role in determining the severity and progression of organ failure. Genetic variants, particularly single-nucleotide polymorphisms (SNPs), are critical determinants for individual differences in both inflammatory responses as well as clinical outcomes in trauma patients [40]. Individuals who possess specific genetic polymorphisms in genes controlling the synthesis of cytokines or toll like receptors (TLR) may be predisposed to excessive inflammatory response to sepsis which increases their risk for the development of MODS [41]. For example, toll-like receptor 9 (TLR9) signaling plays an important role in the innate immune response. Trauma patients with SNPs of TLR9 have been found to have a greater responsiveness of their peripheral blood leukocytes as well as a higher risk of sepsis and multiple organ dysfunction [42]. Henckaerts and colleagues furthermore showed that these functional polymorphisms involved in innate immunity predispose patients to severe infections and death. Further study and elucidation could contribute to formation of a risk model where patients could be stratified as to who could benefit from specific preventative or therapeutic options [43].

Scoring Systems

MOF does not have a consensus definition and there are a variety of scoring systems used to categorize the severity of organ dysfunction. Trending these scores during a patient's hospital course enables physicians to prognosticate the patient's risk of mortality [44]. There is also a direct relationship between the number of organ failures and ICU mortality. Moreover, improvements in cardiovascular, respiratory and renal function during an ICU course can predict a better survival [45].

Scoring systems like the Acute Physiology and Chronic Health Evaluation (APACHE) score are based on measured laboratory values that enable staging of the severity of organ dysfunction. One of the most commonly used scoring systems is the Sequential Organ Failure Assessment Score (SOFA) (Table 7.4). Clinical and laboratory variables in six organ systems (respiratory, hematologic, liver, cardiovascular, central nervous system, renal) are utilized to calculate a total score [46]. Patients with no organ failure defined by a SOFA score below or equal to two for each organ at admission have an ICU mortality rate of 6% compared to 65–100% for those with four or more organ failures [34]. The Denver MOF score is also a frequently used and well validated score. It is defined as two or more organ systems failing greater than 48 h after injury. The Denver score looks at dysfunction in the cardiac, respiratory, renal and hepatic systems [47] (Table 7.5). When comparing the Denver postinjury MOF score with the SOFA score, the SOFA score is very sensitive but not as specific as the Denver MOF score, whereas the Denver postinjury MOF score is more specific and less sensitive than the SOFA score when dealing with the trauma population. This distinction is important when analyzing epidemiologic data as more sensitive scores will have a higher incidence of MOF, while a more specific score will have a higher mortality rate [48–50]. Regardless of what score is used to evaluate the various physiologic and clinical parameters, it is an underlying theme in all organ failure scores, that as the number of organ systems that are affected increase, so does the mortality [51, 52]. Moreover, these scoring systems were developed to quantify the severity of illness and the risk of mortality in ICU patients. These prognostic scores will not tell how a patient will respond to therapy and are best utilized to predict outcomes in certain homogenous groups of patients. Additionally, these scores are unable to provide details regarding how a patient will respond to treatment. However, they can be repeatedly assessed to evaluate a patient's progress and used to identify patients for enrollment and to assess morbidity in clinical trials [53].

Clinical Presentation, Evaluation, and Diagnosis

The common clinical manifestations leading to multiple organ dysfunction are included in the ACCP-SCCM guidelines and can fall anywhere within the continuum of SIRS to MOF. These most commonly include alterations in body temperature (hyper or hypothermia), tachypnea or hypocarbia, tachycardia, leukocytosis, leukopenia or bandemia, hypotension, thrombocytopenia or coagulopathy, and

Table 7.4 SOFA score. MOF is defined as a score ≥4 with involvement of ≥2 organ systems

SOFA score					
System	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory PaO2/FiO2	>400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation platelets (Ã-103/mm^3)	>150	<150	<100	<50	<20
Liver bilirubin (mol/l)	<20	20–32	33–101	102–204	>204
Cardiovascular	No hypotension	MAP <70 mmHg	Dopamine >5 or any dobutamine dose	Dopamine >5 or epi_0.1	Dopamine >15 or epi >0.1
Renal creatinine (mol/l)	<110	110–170	171–299	300–440	>440
Central nervous system Glasgow Coma Scale	15	13–14	10–12	6–9	<6

Table 7.5 Denver postinjury multiple organ failure score

Denver postinjury multiple organ failure score				
Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary PaO2/FiO2 ratio	>250	250–200	200–100	<100
Renal creatinine (mol/l)	<159	160–210	211–420	>420
Hepatic total bilirubin (mol/l)	<34	34–68	68–137	>137
Cardiac	No inotropes	Only 1 ionotrope at small dose	Any ionotrope at moderate dose or >1 agent at small dose	Any ionotrope at large dose or >2 agents at moderate doses

The MOF score is the addition of the worst value for the day for each organ system. MOF is defined as score >3

alterations in mental status [54]. Fever is the most common presenting symptom of sepsis and should be an impetus for further evaluation the patient as well as identification of a source. Elderly patients with sepsis or those that are immunosuppressed may not mount a febrile response or conversely may be hypothermic [55]. In sepsis, common sites of infection are the pulmonary, gastrointestinal, and urinary tract systems. Other nosocomial causes of sepsis are intravenous catheter infections, ventilator-associated pneumonia, and sinusitis. As approximately 20% of patients will not have an identifiable source, noninfectious etiologies for SIRS should be considered [56]. These may include surgery, trauma, hematoma, subarachnoid hemorrhage, venous thrombosis, pancreatitis, myocardial infarction, transplant rejection, thyroid storm, acute renal or adrenal insufficiency, lymphoma, tumor lysis syndrome, transfusion reaction, opiates, benzodiazepines, anesthetic related malignant hyperpyrexia, and neuroleptic malignant syndrome [57].

A thorough physical examination should include a head-to-toe exam as well as inspection of indwelling catheters, a rectal exam, and examination of all wounds, including those under casts/fixation devices. Potential atypical causes of sepsis should be given consideration when an obvious source is identified. These potential causes of sepsis include sinusitis, meningitis, septic joint, acalculous cholecystitis, septic thrombophlebitis, deep muscular abscess, or a viral infection. Corresponding laboratory values based on the suspected differential diagnoses should be obtained.

Infections leading to sepsis can also arise in surgical sites from the skin to the deep muscle layers. Physical examination should be repeated if no source is identified. An investigation of all organ systems should be thorough and systematic. Subtle findings of end organ hypoperfusion such as altered mental status, tachypnea, hypoxia, hypotension, oliguria may be missed if the physician does not have a high index of suspicion and an incomplete exam is performed; i.e., failure to remove a dressing to inspect a wound. Failure to investigate thoroughly can lead to a delay in diagnosis and increased morbidity and mortality. Physical examination should include a rapid review of the patient's hemodynamic condition and should include continuous monitoring. Patients in shock should have arterial catheters placed for blood pressure monitoring. Persistent clinical signs of SIRS may suggest ongoing inflammation or infection. In addition to the patient's hemodynamic status, clinical signs of poor end organ perfusion, such as change in mental status, low urine output, mottling, and poor capillary refill, should be taken into consideration and used to guide resuscitation [58]. Initiation of resuscitation should take place immediately upon recognition of SIRS or sepsis symptoms and should not wait for transport to the next level of care.

Laboratory Evaluation

While no laboratory value will diagnose sepsis or MOF, they may assist in narrowing the differential diagnosis, localizing

the source and guiding appropriate antibiotic therapy. Laboratory studies should include a complete blood count with differential, chemistry profile, arterial blood gas with lactic acid, prothrombin time and partial thromboplastin time, fibrinogen, and urinalysis [59]. Utilizing lactic acid level trends to guide resuscitation has been shown to be helpful in septic patients. For prognostication purposes, resolution of lactic acidosis with resuscitation efforts is associated with improved outcomes [60].

Pan cultures of the urine, blood, and sputum should be collected. The SCCM guidelines recommend that one pair of blood cultures be obtained at the onset of symptoms and another set obtained again at 24 h [12]. When taking blood cultures, two sets of blood cultures should be drawn from peripheral sites. If this is not possible, then one set should be drawn peripherally and the other from a recently inserted central catheter after careful cleansing of the port site. Every effort must be made to draw the first cultures before the initiation of antimicrobial therapy. They can be drawn consecutively or simultaneously, unless there is suspicion of an endovascular infection, in which case separate peripheral blood draws separated by timed intervals can be drawn to demonstrate continuous bacteremia [61].

Based on physical exam, additional body fluids may be sampled if the patient exhibits localized symptoms of infection. For example, cerebrospinal fluid, pleural fluid, joint aspiration, and ascites can all be sampled to localize the source of infection and help guide antibiotic therapy. Radiographic images should be tailored to the most likely source. If plain films are nondiagnostic, CT scans can assist in elucidating a suspected source and used to guide therapy, for example abscess drainage.

Pathophysiology

The pathophysiology of MOF is at best a nebulous interaction of multiple inflammatory mediators. Our understanding of this process and the innumerable interactions is in its infancy. A complete discussion of the immunology of this process is beyond the scope of this chapter as entire books have been dedicated to this task [62–64]. This section highlights some salient points regarding the pathophysiology of MOF.

Initially, SIRS was thought to be an overwhelming, uncontrolled response to infection. While MOF frequently is the end point of the spectrum of SIRS and severe sepsis, severe inflammation is also a mitigating factor and can result in the same endpoint of organ failure. This indicates overlap in the pathophysiology between inflammation and infection. The progression to MOF from SIRS from either cause is likely the result of an unbalanced interaction between the pro and anti inflammatory mediators. In most patients, the initial SIRS response is physiologically followed by a compensatory anti-inflammatory response syndrome (CARS). This acts to limit the SIRS response so that it is not counterproductive. The subsequent balance between the pro-inflammatory (SIRS) and anti-inflammatory (CARS) response has been referred to as the mixed antagonistic response syndrome or MARS [36]. If the balance of these two systems is disturbed the inflammatory response becomes systemic and deregulated. The result is whole-body activation of the inflammatory response, with resultant disruption of normal cellular metabolism and microcirculatory perfusion. Both of these responses, if unchecked can result in complications, the former leading to MOF and the later secondary infections. At the site of injury, endothelial cells and leukocytes coordinate the local release of mediators of the inflammatory response, including cytokines interleukins, interferons, leukotrienes, prostaglandins, nitric oxide, reactive oxygen species, and products of the classic inflammation pathway. It is this usually functional biologic response that becomes unregulated and leads to MOF [65].

Table 7.6 Risk factors for early and late MODS

Risk factors for early MODS <72 h of injury	Risk factors late MODS >72 h after injury
• ISS > 24	• Age > 55
• SBP < 90	• >6 units of blood transfused within 12 h of injury
• >6 units of blood transfused within 12 h of injury	• Base deficit >8 mEq/l within first 12 h of injury
• Lactate > 2.5	• Lactate > 2.5 mmol/l within 12–24 h of injury

In 1996, Moore and colleagues recognized MOF is not necessarily related to an infectious process and follows a bimodal distribution. Early MOF is now defined as organ failure that develops within 72 h of the initial diagnosis of sepsis (Table 7.6). Late MOF was defined as organ failure that develops after 72 h after the initial diagnosis of sepsis [66]. When compared to the late MOF group, patients with early organ failure died sooner, had more cardiac dysfunction and had greater evidence of hyper inflammation. In contrast, patients with late MOF were older, had greater evidence of hepatic failure, and were more likely to have an infection as a "second hit" [67].

Multiple theories exist regarding the cause for MOF and it is likely that these pathways overlap to cause initially organ insufficiency that, unless reverses, ultimately leads to failure. Four overlapping categories have been proposed to the complex pathophysiology of MOF. These are the cytokine hypothesis, the microcirculatory hypotheses, the gut hypothesis and the two-hit hypothesis [63].

The Cytokine Hypothesis of MOF

In the cytokine hypothesis, the immune response to infection or inflammation results in excessive or prolonged activation or stimulation of mediators. These include interactions between polymorphonuclear neutrophils (PMNs), endothelial cells, and macrophages. PMN stimulation results in "priming" of the neutrophil and can lead to overzealous production, surface expression, and liberation of cytokines [68]. These mediators often have an exaggerated response and the products of these cascades exert damaging local and systemic effects. A temporal relationship between cytokine production and time of injury was recognized. Cytokines predictive of MOF in trauma patients include inducible protein (IP)-10, macrophage inflammatory protein (MIP)—1B, interleukin (IL) IL-10, IL-6, IL-1Ra, and eotaxin [69]. Several lines of evidence support the central role of inflammatory cells in the pathogenesis of lung and systemic organ injury. Tumor necrosis factor (TNF) has been considered one of the most potent pro-inflammatory cytokines identified in SIRS and sepsis. Administration of TNF to experimental animals creates the hemodynamic and metabolic observations consistent with SIRS. Analysis of cytokine serum biomarkers has shown that patients with MOF show a biphasic elevation of IL-6 and significantly higher soluble TNF receptor (sTNF-R) concentrations [70]. Activation of leucocytes and their subsequent inappropriate sequestration in organs appears to additionally be one of the key events in the development of early MOF. Once activated, leukocytes have the capacity to release their cytotoxic factors including nitric oxide and lysosomal granules, which aid in polymicrobial killing. These factors can cause necrosis and inflammation of organs such as the lung despite a lack of an infectious stimulus [71]. Additionally, PMN stimulation provokes endothelial and epithelial injury through up-regulation of adhesion molecules on these cells. This prompts changes in the cell wall, increased permeability cell swelling and culminates in cellular dysfunction. Neutrophil elastase is a key marker of severity of injury and has also been found to be a prognostic marker [72].

The Microcirculatory Hypothesis of MOF

The microcirculatory hypothesis proposes that organ injury is related to ischemia or vascular endothelial injury [73]. Some authors have speculated that even though adequate blood flow may reach the various tissue beds, there may be an inability of the mitochondria or cells to take up or use the delivered oxygen and substrate. Although prolonged tissue hypoperfusion and hypoxia leads to inadequate adenosine triphosphate (ATP) generation and potentially irreversible cell damage, this shock period is not long enough in most clinical conditions for that to occur. This damage is relieved by reperfusion and thus pro-inflammatory factors and oxygen radicals are introduced and lead to injury [74]. In vitro studies have found that nitric oxide (NO) up-regulates the production of pro-inflammatory cytokines (TNF-alpha, IL-8 and prostaglandins) and can lead injury of the lung, and intestine. Additionally, the superoxide anion and hydrogen peroxide can interact with NO and form peroxynitrite, which is toxic to cells [72]. During shock, these mediators, such as reactive oxygen species, are released to destroy the offending bacteria and to inactivate toxins. The unintended effects are that when unregulated, they also result in damaging the patient's organ systems [75].

Gut Hypothesis of MOF

The gut is considered an immunologically active organ and a main in the burden of infection-induced systemic inflammation [76]. Gut barrier dysfunction can occur for a variety of reasons including trauma, shock, infection, and malnutrition. It is proposed that, as a result of the loss of the gut barrier function, intestinal bacteria and endotoxin cross the mucosal barrier and lead to exposure of the intestinal immune cells. The production of gut-derived toxins and inflammatory products reach the systemic circulation through the intestinal lymphatics, leading to SIRS, ARDS, and MOF [68]. These translocating bacteria are phagocytosed by intestinal immune cells and contribute to the intestinal inflammatory response. Some of these translocating bacteria or their toxic products are trapped in the intestinal lymph nodes, causing inflammatory reaction [72]. This hypothesis is supported by the demonstration of circulating levels of endotoxin in the peripheral blood of critically ill patients with sepsis and SIRS. Reports of endotoxemia in these critically ill patients, even without clinical or microbiologic evidence of infection with gram-negative organisms supports the potential role of translocation in the production of MODS/MOF [36]. The phenomenon of bacterial translocation, however, is not sufficient to explain the development of MODS in ICU patients. The development of MODS in these high-risk patients is likely due to intestinal injury and the resultant inflammatory cascade that reaches the systemic circulation via the intestinal lymphatics [77].

Two-Hit Phenomenon in MOF

The phrase "two-hit phenomenon in MOF" is used to describe the biologic phenomenon in which an initial insult primes the host such that on a second or subsequent insults, the host's response is greatly amplified. Primers to the subsequent insult can be infection, shock, inflammation, or trauma.

Despite the decreasing incidence of MOF, the rate of PMN priming has not changed. PMN priming increases elastase release, IL-8 production, L-selectin expression, and CD-18 expression, and delays apoptosis. This is evident by a lack of change in the incidence of early lung dysfunction postinjury, which is a surrogate marker of PMN priming [78]. The timing of the second hit phenomenon was shown in laboratory experiments evaluating abdominal compartment syndrome (ACS). If subjects had early decompressive laparotomy (<2 h) or late (>18 h), they had a lower mortality than those having a decompressive laparotomy at 8 h. This correlates with the clinically identified time frame of the development of postinjury ACS, which manifests 8–12 h window after trauma. Severely injured patients who develop ACS have a fourfold increase in their chance of developing MOF compared to the non-ACS patients with similar demographics, shock parameters and injury severity [24]. These insults prime the immune system to mount an exaggerated response when exposed to a second physiologic insult. Botha described the observation that the first hit primes and activates PMNs within 3–6 h after injury. This primer creates a vulnerable window during which a second insult activates excessive cytokine release. This second hit results in an elevated risk of developing MOF [79]. This exaggerated immune response then results in end organ injury [80]. In summary, MOF results from an excessive host response to an infectious or inflammatory stimulus. Any or all of the aforementioned hypotheses can coexist and each overlaps with the other. The cytokine, endovascular, and systemic storm that ensues thereafter, predisposes to additional infections and can lead to organ failure [45].

The temporal series of events in MOF is usually predictable and is independent of the etiology. Multiple studies have demonstrated that the respiratory system is usually the first to fail and is the most commonly affected [15]. This is typically followed by hepatic, intestinal, and renal failure, in that order. As the number of organ systems affected increases from 1 to 4, the mortality increased from 21 to 100% [81]. Hematologic and myocardial failures are usually later manifestations of MOF, whereas the onset of central nervous system alterations can occur either early or late [24]. Physiologically, these patients are hyper metabolic and they have a hyper dynamic circulation, which is characterized by an increased cardiac output and a decreased systemic vascular resistance. This classical sequential pattern of organ failure may be modified, however, by the presence of preexistent disease or by the nature of the precipitating clinical event. For example, renal failure may precede hepatic or even pulmonary failure in patients with intrinsic renal disease or in patients who have sustained prolonged periods of shock, whereas hepatic or myocardial failure may be an early or even the initial manifestation of this syndrome in the patient with cirrhosis or myocardial damage [82]. The exact sequence of organ failure, however, is not always predictable and can be influenced by the patient's preexisting morbidities as well as their acute process. However, as the number of organs that fails increases from one to four, the mortality rate progressively increases from 30 to 100% [27].

Multiple Organ Failure by System

Pulmonary Dysfunction

The sequence of organ dysfunction is predictable and the lung is usually the first organ to show signs of failure. Initial pulmonary insufficiency and renal impairment are followed by circulatory failure and then metabolic dysfunction and liver failure. Respiratory failure can range from mild hypoxia and tachypnea to ARDS [83]. ARDS is defined as a P_aO_2/F_IO_2 ratio lower than 200 mmHg in association with bilateral fluffy pulmonary infiltrates and a pulmonary capillary wedge pressure lower than 18 mmHg [84]. Increased capillary permeability and neutrophil influx are the earliest pathologic events in ARDS. As the acute inflammatory process resolves, further lung injury results both from the process of repair, which involves fibrosis and the deposition of hyaline material, and from further lung trauma, resulting from positive pressure mechanical ventilation [85]. ARDS may occur within a few days of admission or after the development of SIRS and sepsis. Sepsis-induced ARDS is associated with the highest mortality rates. Additionally, the data suggests that approximately 40% of patients with severe sepsis develop ARDS. Historically, 10–12 ml/kg tidal volumes were commonplace and resulted in alveolar damage due to over distention. Parenchymal injury appears to be due primarily to oxidative damage from the activated neutrophils in the lung. Endotracheal intubation and a controlled mode of ventilation are the mainstays of support for respiratory failure. Lung protection ventilation strategies, with low tidal volumes (4–6 ml/kg) for patients with ARDS, are recommended and showed a decreased mortality from 40 to 31%. Due to the smaller tidal volumes, patients typically will have a rise in carbon dioxide [86]. This permissive hypercapnia has been shown to have a protective effect in critically ill patients [87]. Some patients with refractory hypoxemia may require alternative therapies such as extracorporeal membrane oxygenation (ECMO), high-frequency oscillation, or inhaled nitrous oxide.

Gastrointestinal and Hepatic Dysfunction

The gastrointestinal tract is a crucial component of the SIRS response. Shock is associated with obligatory gut ischemia

due to vasoconstriction. With resuscitation efforts, reperfusion results in a local inflammatory response that can set the stage for ACS. ACS is a syndrome that occurs either primarily or secondarily [88]. Primary ACS occurs in patients undergoing damage control laparotomy. The presence of laparotomy pads, blood products and resuscitation fluid increases the pressure in the abdomen to a tipping point, usually 25 mmHg. Secondary ACS occurs after a non-abdominal injury that requires massive transfusion. The products of resuscitation result in edematous bowel and fluid sequestration and the same impaired end-organ perfusion [89]. This pressure elevation is higher than the mesenteric and splanchnic arterial beds resulting in ischemia. Respiratory physiology is impaired due to elevated peak pressures and vena cava compression results in impaired cardiac filling. This constellation of symptoms requires an investigative clinician. Once the diagnosis is made, the abdominal pressure is usually relieved by emergent laparotomy. Clinical studies have clearly documented the poor outcome of patients developing ACS and the frequent association of ACS and MOF [90].

Risk factors for hepatic insufficiency include perfusion deficits, persistent foci of dead or injured tissue, an uncontrolled focus of infection, the presence of the respiratory distress syndrome, and preexisting fibrotic liver disease [91]. In patients with septic shock, transaminitis is a common laboratory finding in patients. The catecholamine, norepinephrine induces injury to hepatocytes by activating adrenergic receptors on Kupffer cells. In turn, norepinephrine enhances chemokine and NO production, resulting in mitochondrial damage [50]. This process is usually transient and limited to a laboratory abnormality that corrects once the patient is resuscitated. However, if hemodynamics are not restored, a secondary hepatic dysfunction may occur and can lead to bacterial product spillover, amplified inflammation and may lead to MOF and death [92].

Renal Dysfunction

Acute renal failure is a common dysfunction in patients with sepsis. It confers its own mortality risk and when it develops in association with MOF [93]. In a recent review by Wohlauer et al. early acute kidney injury was present in 2.13% of severely injured patients and was associated with a 78% MOF incidence and 27% mortality. Both rates were higher than those associated with early heart, lung, or liver failure [94]. The causes of renal dysfunction are multifactorial and can be due to inadequate perfusion, nephrotoxic medications, acute tubular necrosis, contrast induced nephropathy, ACS, and obstruction. Activation of the renin–angiotensin system may contribute to reduced perfusion as vasoconstriction exacerbates ischemia. This is clinically manifested as oliguria (<30 ml/h) or anuria and as an increased serum concentration of creatinine and urea [83]. The vasoconstrictive shunting due to compensatory mechanisms or concomitant vasopressors agents can exacerbate the injury and results in further nephron ischemia. Additionally, TNF has been shown to be directly injurious to nephrons by inducing apoptosis [50]. Treatment is aimed at identifying the source and provision of supportive care. Moreover, up to 70% of patients with severe sepsis require some form of renal replacement therapy [57]. While intermittent and continuous hemodialyses are equivalent, continuous dialysis avoids the hemodynamic instability often seen with intermittent dialysis [95]. The typical indications for dialysis are volume overload, refractory acidosis, uremia, and electrolyte derangements.

Cardiovascular Dysfunction

Myocardial depression is a well-recognized manifestation of organ dysfunction in sepsis. Due to the lack of a generally accepted definition and the absence of large epidemiologic studies, its frequency is uncertain. Cardiac dysfunction in sepsis is characterized by decreased contractility, impaired ventricular response to fluid therapy, and ventricular dilatation. Cardiac echocardiograms suggest that 40–50% of patients with prolonged septic shock develop myocardial depression, as defined by a reduced systolic and diastolic ejection fraction. Additionally, peroxynitrite has a direct damaging effect on myocyte mitochondria and causes reduced contractility [96]. Troponin elevation is also seen and correlates to the severity of illness and dysfunction [50]. Sepsis-related changes in circulating volume and vessel tone inevitably affect cardiac performance. The principle hemodynamic profile shows elevated cardiac output, but substantially reduced systemic vascular resistance [97]. Mitochondrial dysfunction, another feature of sepsis-induced organ dysfunction, will also place the cardiac myocytes at risk of ATP depletion. However, clinical studies have demonstrated that myocardial cell death is rare and that cardiac function is fully reversible in survivors. Hence, functional rather than structural changes seem to be responsible for intrinsic myocardial depression during sepsis [98]. Current studies support that myocardial depression is due to a complex underlying physiopathology with a multiple overlapping pathways. Cytokine release and circulation such as TNF-alpha, IL-1, and endothelin-1 directly inhibit myocyte contractility contributing to the overall cardiac dysfunction [99]. Nitric oxide production additionally has a complex role in sepsis-induced cardiac dysfunction and may have a deleterious as well as a beneficial role [100].

Endocrine Dysfunction

Endocrine abnormalities are common during sepsis and MOF and include hyperglycemia and insulin resistance. Hyperglycemia is common in critically ill patients, with approximately 90% of patients treated in an ICU developing blood glucose concentrations >110 mg/dl [101]. Historically, hyperglycemia was not treated until the blood glucose level rose above 200 g/dl. In a randomized controlled study, Van den Berge and colleagues used insulin infusions to maintain tight control of blood sugars in critically ill surgical patients. The strictly controlled group had their blood glucose maintained between 80 and 110 g/dl. The more liberal threshold was only treated at >180 g/dl. A mortality benefit, from 8 to 4.6%, was identified in the surgical patients that had strict control of their blood sugar. This survival benefit was largely related to a reduction in deaths due to MOF [102]. Due to tighter control utilizing insulin drips, patients were noted to more episodes of hypoglycemia requiring treatment. Subsequently, follow-up studies have shown that hypoglycemia is an increased risk factor for mortality [103]. Conversely, the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study reported increased mortality with a tight blood sugar control approach [104]. Recent meta-analyses do not support intensive glucose control for critically ill patients and more moderate recommendations to target a blood glucose concentration between 144 and 180 mg/dl (8–10 mmol/l) are now in effect [105].

In addition to hyperglycemia, a relative state of adrenal insufficiency is common in critically ill patients [50]. This is defined as an abnormally low level of the patient's endogenous cortisol at the time of physiologic stress. In response to hypotension and following trauma or surgery, circulating cortisol concentrations should exceed 25 μ(mu)g/dl. Marik et al. discovered that 70% of ICU patients had inappropriately low levels of cortisol. This low level of cortisol can result in a blunted response to hypoglycemia and hypotension [106]. The Surviving Sepsis Campaign suggests giving intravenous hydrocortisone to adult septic shock patients after their hypotension is identified to be poorly responsive to fluid resuscitation and vasopressor therapy. If one suspects adrenal insufficiency, corticosteroids should be administered without waiting on results of a cosyntropin stimulation test [107].

Hematalogic Dysfunction

Thrombocytopenia is the most common hematalogic dysfunction and is present in 20% of patients and is associated with an increased mortality [108]. The causes are multifactorial but include bone marrow suppression from sepsis, sequestration, consumption and heparin induced thrombocytopenia (HIT). As critically ill patients are often immobilized and mechanically ventilated, they are at elevated risk for deep vein thromboses. If no contraindication exists, critically ill patients should be on daily chemical thromboprophylaxis. This chemical prophylaxis can lead to HIT by production of antibodies against the heparin-platelet factor 4 complex. The antibody-platelet complex is then removed prematurely from the circulation leading to thrombocytopenia [109].

Anemia is also a common finding in patients who are critically ill. The etiology is usually multifactorial and can result from direct inhibition by cytokines, deficiency of erythropoietin, blunted erythropoietic response, acute blood loss, nutritional deficiencies, as well as renal insufficiency [110]. Leukocytosis is also common within hours after injury or the onset of sepsis. Typically, the number of leukocytes markedly increases and the number of lymphocytes and monocytes decreases. This post injury leukocytosis is primarily due to increased PMN numbers, and several studies have shown a link between high number of PMNs during the first hours after injury and an increased risk of organ failure and mortality [79].

Neurologic Dysfunction

Central nervous system (CNS) dysfunction occurs in as many as 70% of critically ill patients. The brain plays a pivotal role in sepsis, acting as both a mediator of the immune response and a target for the pathologic process. Sepsis-associated encephalopathy is associated with increased mortality and morbidity [111]. Its pathophysiology remains insufficiently elucidated, although there is evidence for a neuroinflammatory process sequentially involving endothelial activation, blood–brain barrier alteration and cellular dysfunction and alteration in neurotransmission [112]. Increased permeability to cytokines, neuroamines, and endotoxemia have all been implicated in septic encephalopathy [113]. It is difficult to quantify neurologic impairment as there are no specific biomarkers of neuronal injury and bedside evaluation of cognitive performance is difficult in an ICU [114]. The Glasgow Coma Scale is frequently utilized by organ failure scoring systems to evaluate the severity of a patient's neurologic failure but sedatives and analgesics can make this score unreliable. New delirium in a critically ill patient should raise the suspicion of the physician to the possibility that this is the first presentation of infection.

Treatment

Initial Resuscitation

Current strategies are aimed at preventing organ failures and supporting failing organ systems in critically ill patients. Once MOF has developed, therapies are aimed at supporting

failed organ systems and preventing secondary example infection. Currently there is no specific pharmacotherapy for ARDS or MOF.

A crucial component in preventing the progression of septic shock to MOF is early recognition and expeditious implementation of goals of therapy. Initial resuscitation should include establishing intravenous access and prompt initiation of fluid resuscitation. Rivers et al. in a study of patients with severe sepsis and septic shock found that early goal-directed therapy, directed toward attaining a SvO_2 >70%, conferred a substantial reduction in mortality from 46.5 to 30.5%. This study also demonstrated the importance of the urgency of resuscitation and that it should be started as soon as it is recognized, whether it is in the emergency department or the hospital ward. Studies in which aggressive resuscitation was delayed until after transfer to the ICU failed to show improved outcome or a reduction in MODS [115]. Patients should be admitted to an ICU that is conducive for invasive hemodynamic monitoring and frequent reassessment.

Vascular access with two large bore intravenous (IV) catheters is adequate for initiating resuscitation but if hemodynamic compromise is present, central venous access should be established. The optimal type of fluid is an ongoing controversy in the critical care literature, but crystalloid should be given at an initial bolus of 20 ml/kg of ideal body weight. Fluids should be bolused to attain a goal central venous pressure (CVP) of 8–12 mmHg, MAP >65 mmHg, urine output >0.5 ml/kg/h, and a SvO_2 >70% (Table 7.7). Recognition of the sequelae of each IV fluid should be recognized and tailored to the patient's specific pathophysiology, i.e., resultant hyperchloremic acidosis with normal saline administration [50]. If hypotension is still present after the CVP goals are attained, vasopressor assistance should also be initiated.

The Surviving Sepsis Campaign established resuscitation and management bundles that emphasize the prompt initiation of therapy for sepsis. The resuscitation bundle describes tasks that should begin immediately, and must be accomplished within the first 6 h of presentation for patients with severe sepsis or septic shock (Table 7.8).

Some items may not be completed if the clinical conditions described in the bundle do not apply, but clinicians should assess their patients for them. The goal is to perform all of the indicated tasks 100% of the time within the first 6 h of identification of severe sepsis. The management bundle provides evidence-based goals that similarly must be completed within 24 h for patients with severe sepsis, septic shock and/or lactate >4 mmol/l (36 mg/dl) (Table 7.9). For patients with severe sepsis, as many as four bundle elements must be accomplished within the first 24 h of presentation. Again, some items may not be completed if the clinical conditions described in the bundle do not apply but a high index of suspicious by physicians should exist to rule them out. The goal is to perform all indicated management tasks, 100% of the time, within the first 24 h of presentation [12].

Table 7.7 Endpoints of resuscitation

Endpoints of resuscitation
• Central venous pressure (CVP) of 8–12 mmHg
• Mean arterial pressure (MAP) >65 mmHg
• Urine output >0.5 ml/kg/h
• SvO2 >70%

Table 7.8 Sepsis resuscitation bundle: must be completed within the first 6 h of presentation

Sepsis resuscitation bundle
• Measure serum lactate
• Obtain blood cultures prior to antibiotic administration
• Administer broad-spectrum antibiotic within 3 h of ED admission and within 1 h of non-ED admission
• Treat hypotension and/or elevated lactate with fluids
• In the event of hypotension and/or serum lactate >4 mmol/l:
– Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
– Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mmHg
• In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/l:
– Achieve a central venous pressure (CVP) of >8 mmHg
– Achieve a central venous oxygen saturation (ScvO2) >70% or mixed venous oxygen saturation (SvO2) >65%

Table 7.9 Sepsis management bundle: must be completed within 24 h

Sepsis management bundle
• Administer low-dose steroids for septic shock in accordance with a standardized ICU policy.
• The prior Drotrcogin alfa (rhAPC) recommendation is discontinued
• Maintain glucose control lower limit of normal, but <180 mg/dl (10 mmol/l)
• Maintain a median inspiratory plateau pressure (IPP) <30 cm H_2O for mechanically ventilated patients

Along with the aforementioned endpoints of resuscitation, measurement of blood lactate has also been used as a means to assess prognosis and is inversely proportional to survival [116]. As the lactate concentration increased from 2.1 to 8 mM/l, the estimated probability of survival decreased from 90 to 10% [117]. Abramson et al. also revealed the importance of lactate clearance and survival following traumatic injury. If a patient's lactate normalized (lactate <2 mmol/l) within 24 h their survival rate was 75% versus 14% if the lactate level did not return to normal by 48 h [118].

Vasopressors

Once fluid resuscitation has been initiated and hemodynamic monitoring established, if the patient's MAP remains <65 mmHg, vasopressor therapy should be initiated. The Surviving Sepsis Campaign Guidelines (SSCG) recommends norepinephrine or dopamine as the first line vasopressor agents. Due to a relative deficiency of vasopressin in septic shock, consideration should be given to adding a low dose vasopressin drip (0.04 units/min), which may assist in correcting refractory hypotension [119]. Additionally, the SSCG guidelines regarding vasopressors also recommend using epinephrine as an alternative if blood pressure is poorly responsive but it should not be used as a first line agent. Volume resuscitation should be occurring simultaneously but if hypotension is refractory, vasopressors should be initiated to maintain MAP > 65.

Source Control and Antibiotic Therapy

Once the suspicion for SIRS or sepsis is present, a thorough physical exam, laboratory studies and radiographic evaluation of the patient should ensue to identify the causative agent. Ongoing sources of infection are known to "prime" the host immune system so that a second insult can cause an exaggerated systemic inflammation ultimately culminating in MOF [53]. Laboratory values that should be sent were mentioned earlier. Indwelling catheters should be inspected for signs of infection or outright removed if the clinical suspicion is high. A positive blood culture from a centrally placed catheter is considered infected if the culture becomes positive at least 2 h before the peripherally obtained culture does [120]. Antibiotics should be administered within 1 h of suspicion of sepsis and the urgency should be conveyed to the ICU pharmacist to assist in expediting the administration of the antibiotics to the patient. A study by Kumar et al. demonstrated that patients had a survival rate of 79% if antibiotics were given within 1 h of the development of hypotension. Conversely, the same study showed a decrease in survival of 7.6% for every hour antibiotic administration was delayed [121]. This illustrates the importance of having a high index of suspicion and initiating antimicrobial therapy. According to the SSCG antibiotics should be broad spectrum and active against bacterial/fungal pathogens. Therapy should be limited to 7–10 days unless a mitigating circumstance is present and once susceptibilities return, de-escalation of therapy is appropriate.

Should a surgical source of infection be identified, utilization of damage control techniques is appropriate to prevent further injury. Originally described in trauma patients as an abbreviated laparotomy, this involves making a decision, to address only the critical issues at the first surgery and to return the patient to the ICU for further resuscitation [122]. Depending on the intracavitary findings, a conscious decision to leave bowel in discontinuity or to leave the abdominal wall open may be made with a planned returned once the patient is further resuscitated. This technique has been used in trauma and emergency general surgery and should be considered for any surgical patient with ongoing resuscitation needs or who has preexisting or is at risk for, acidosis, coagulopathy and hypothermia.

Corticosteroids

Relative adrenal insufficiency is often seen in septic shock due to what is hypothesized as suppression of the hypothalamic-pituitary-adrenal axis. The debate regarding the benefit of giving corticosteroids is ongoing and multiple studies have had conflicting results. Annane et al. performed a multicenter, double-blind, placebo-controlled trial study that administered hydrocortisone plus fludrocortisone to patients with septic shock [123]. This landmark study showed improved survival in patients and decreased vasopressor requirements. In contrast, the Corticosteroid Therapy of Septic Shock (CORITCUS) trial was a multicenter, randomized, double-blind, placebo-controlled trail that also evaluated the use of hydrocortisone in patients with septic shock. This study failed to show a mortality benefit but did show a statistically significant benefit of faster shock reversal [124]. Despite the ongoing controversy and presence of multiple conflicting studies, the current Surviving Sepsis Guidelines recommendations include administering corticosteroids to septic patients if hypotension is refractory to fluid resuscitation and vasopressor initiation. Cosyntropin (ACTH) stimulation test is not required and clinical suspicion of adrenal insufficiency should be the impetus to start steroids rather than waiting on the stimulation test to be resulted. Once the patient's vasopressor requirements have subsided, the steroid therapy may be weaned [105].

Activated Protein C

Activated protein C (APC) directly inhibits clotting factors Va and VIIIa and restores the fibrinolytic system by blocking plasminogen activator inhibitor. In sepsis, there is decreased production of APC resulting in a procoagulant state [125]. APC also has anti-inflammatory effects that include limiting leukocyte chemotaxis and reducing thrombin production. However, the levels of endogenous APC are depleted during sepsis [50, 126]. In 2001, the protein c worldwide evaluation in severe sepsis (PROWESS) study found that when patients with APACHE scores >25 received activated protein C for sepsis; they had a relative and absolute risk reduction of 19.4 and 6.1%, respectively [127]. The PROWESS study also demonstrated that patients that received APC had a statistically significant increase in serious bleeding events. (3.5%

vs. 2.0%) In 2004, the first SSCG included the use of dretrecogin alfa on patients at high risk of death, APACHE II ≥25, sepsis-induced MOF, septic shock, or sepsis-induced ARDS and no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit of activated protein C [128]. The 2008 guidelines suggested that consider its use in the patients that met the previous criteria but that it should not be used on patients with a low risk of death. Of note in 2011, a Cochrane review in 2011 and 2012 found no evidence to suggest that APC reduced the risk of death in any patient [129]. Moreover, heightened risk of bleeding precluded its use and the drug was pulled from the market [130].

Nutrition

The past few decades have led to considerable interest regarding nutritional support of critically ill patients. Sepsis and organ failure are hypermetabolic states and increase the patient's metabolic demand. If the caloric needs are not met by supplemental nutrition, muscle breakdown and weakness can ensue. The intestinal tract is now recognized as an immune organ and the intact intestinal wall acts as a barrier. It has been recognized that loss of this barrier can potentially lead to bacterial translocation, progressive shock and ultimately organ failure. The use of enteral nutrition is known to reduce infectious complications in subpopulations of patients with trauma and burns [131]. No single formula matches every patient's needs thus formulas should be tailored to match the pathophysiology of the individual patient. Formulas containing linoleic acid, antioxidants, and omega-3 fatty acids may reduce the incidence of organ failure in patients with acute lung injury and may reduce mortality rates in mechanically ventilated patients [132, 133]. Arginine and glutamine containing formulas have shown benefit in trauma and burn patients [134, 135]. Arginine containing formulas, however, may be detrimental to patients with septic shock [136].

Current guidelines strongly recommend early use of enteral nutrition, with parenteral nutrition being reserved for patients in whom enteral nutrition fails to provide sufficient nutrition [137]. While enteral feeding is preferred, ileus due to ongoing infection or inflammation may prohibit enteral feeding. In these patients, parenteral nutrition is the preferred option.

Innovative Therapies

The overlap of inflammatory cells, cytokines, endothelial cells, and organ systems offers numerous potential locations to intervene by enhancing or blocking specific receptors and halt the damaging effects of the deregulated immune system. Potential targets for therapy have been anti-endotoxin antibodies, anti-tumor necrosis factor monoclonal antibodies, interleukin-1 receptor antagonists, antioxidants, dialysis, and activated protein C [82]. A better understanding of the dynamic of interactions at the cellular level is needed to direct therapy and more research is ongoing. Thus far, supportive care is the mainstay once sepsis has progressed to MOF.

Conclusion

MOF remains a major cause of morbidity and mortality in the trauma and surgical ICUs. Due to improvements in recognition of sepsis and early institution of therapy, the incidence of MOF has decreased. Further research is needed to obtain a better understanding of the pathophysiology of this disease and how the inciting event progresses to organ failure. This understanding will afford more potential targets for therapy. Thus far there is not one "magic bullet" therapy and the mainstay of critical care should be prompt recognition of SIRS and the sequelae of sepsis, expeditious treatment, and prevention of end organ damage.

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