CHAPTER 52  ■  GENE THERAPY IN CRITICAL ILLNESS: PAST APPLICATIONS AND FUTURE POTENTIAL
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INTRODUCTION
Gene therapy refers to the transfer or delivery of nucleic acids to somatic cells, resulting in a therapeutic effect through the correction of a genetic defect, the production of a therapeutically useful protein, or the attenuation of endogenous mRNA (1). While traditional medical and surgical treatment modalities are often effective in the treatment of disease processes, most small-molecule approaches are nonspecific, carrying with them the risks of adverse side effects and the possibility of harm to the patient (2). Even protein-based therapies, such as monoclonal antibodies or receptor antagonists, frequently have associated untoward side effects related to antigen recognition and activation of acquired immunity. Additionally, in disease processes such as inborn errors of metabolism, or chronic inflammatory or autoimmune diseases such as diabetes mellitus or rheumatoid arthritis, medication is frequently temporizing, and not curative, and must be taken indefinitely. In theory, gene therapy is a more tailored approach to disease, with results that are not only therapeutically successful, but also specific to a disease process, often lacking in significant side effects, and potentially curative in chronic disease states.

Unfortunately, while gene therapy offers these potential opportunities, in most cases, they remain only theoretical and unrealized, and have not yet been applied to practice. A number of significant practical hurdles exist to the use of gene therapy in the clinical arena, and, despite some 20 years of experimental work, few clinical successes have resulted. However, the prognosis for gene therapy is, in general, quite bright, and there have been a number of impressive results demonstrating the potential utility of this approach. This chapter will briefly review these research areas and summarize the essential aspects of human gene therapy, including the mechanism, possible risks, disease states amenable to gene therapy, and clinical use now and in the future. Our emphasis in the latter sections of this review will focus on the clinical application of gene therapy to acute inflammatory conditions in critical illness, such as sepsis, traumatic injury, and adult respiratory distress syndromes.

OVERVIEW
While the concept of gene therapy is a relatively simple one, the practice is complex and requires the following:

- The identification of a gene target in a disease of interest
- Creation of a DNA sequence that will generate a therapeutically active product
- Selection and incorporation of the sequence into an appropriately selected vector with an appropriate promoter sequence
- Delivery of the vector into the cells of interest
- The successful incorporation of the sequence into the host’s cellular machinery for expression

A good deal of groundwork has been laid for the identification of gene targets and the creation of DNA sequences through efforts such as the recently completed Human Genome Project. Utilizing the information obtained through this and other undertakings, the number of areas for potential intervention has continued to multiply.

VECTORS
While targets identified, the first step toward the integration of the gene sequence into the cells of interest is the selection of a vector. In this context, we use the term vector to refer to the delivery system for exogenous genetic material, and it can be as simple as a bacterial plasmid (Fig. 52.1) or as complicated as a recombinant virus. In general, we are not referring to the direct administration of nucleic acids with catalytic or other activities, such as ribozymes or small inhibitory RNA (siRNA) sequences. Rather, we are discussing expression systems where the host synthetic machinery is required to express either the induced protein or RNA sequences. Immediate goals for the creation and use of a vector are the delivery of genetic material to the correct site and expression of that material at a meaningful (therapeutic) level, all in a controlled fashion (3). No vector currently in use is completely successful at achieving this end. What follows is a discussion of a few of the more commonly considered vectors utilized at present, with a brief summary evaluation of some of their positive and negative features in critical illness.

Viral Vectors
Viral vectors represented the first vehicle utilized in gene therapy, and their use is still commonplace today. In general, viral vectors offer the advantages of intrinsic delivery methods combined with an inherent means for incorporating genetic material into the host cells (either episomal or with integration into the host genome). This takes advantage of the evolutionary
success that viruses have attained in inserting their genetic material into eukaryotic cells and manipulating their expression machinery. Their overall disadvantages include generation of an immune response to varying degrees, as well as variable assimilation of genetic material into the host and its expression.

In fact, the major challenge today with the use of viral vectors is controlling the host immune and other cellular processes that have evolved to control and ultimately eliminate viral infections.

Viral vectors can also be divided based on whether they integrate their genetic information into the host genome (such as retroviruses and adeno-associated viruses (AAVs) or remain primarily episomal (such as adenovirus). While the former generally results in prolonged expression, often in excess of several months, the latter generally results in transient expression, lasting several days to a few weeks. While multiple different viruses have been proposed and are occasionally used as vectors, three primary viral vectors are in common use today, and will be presently discussed: adenoviruses, retroviruses, and AAVs.

**Adenoviruses**

Adenoviruses are the most commonly utilized vector in human gene therapy, accounting for 26% of all vectors currently being utilized in gene therapy clinical trials (4). Adenoviruses have a number of characteristics that account for their popularity in this field (Table 52.1):

1. They are easily grown in high viral titers.
2. They have a large capacity for transgene insertion.
3. They are efficiently transduced into both dividing and non-dividing cells.
4. Only under very rare conditions do they incorporate into the host genome.

**TABLE 52.1**

<table>
<thead>
<tr>
<th>Viral vector</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Adenovirus** | 1. Generation of high viral titers  
2. Rapidly transfects dividing and nondividing cells  
3. Rapid onset of expression (within hours)  
4. Transient high-level expression  
5. Large genome available for expressed transgene  
6. Incorporation into host genome is rare  
7. Many existing methods for manipulating genome | 1. Significant inflammatory response and activation of innate immunity  
2. Pre-existing exposure to and humoral immunity in human population  
3. Transient expression precludes use in chronic conditions |
| **AAV** | 1. Nonpathogenic  
2. Mild immunogenicity  
3. Stable integration into host with long-term expression  
4. Many variants  
5. Many existing methods for manipulating genome  
6. Many existing production and purification methods | 1. Small size of vector limits ability to package larger genes  
2. Long lag time between administration and maximal expression  
3. Stable integration precludes use in acute inflammation |
| **Retro- or lentivirus** | 1. Membrane coat protects genetic material  
2. Target receptors allow uptake by specific cells  
3. “Self-contained” mechanisms for incorporation of genetic material into host genome  
4. Generates both gene product and mRNA for stable integration into genome | 1. Low titer  
2. Limited cellular targets  
3. Targets dividing cells only  
4. Stable integration precludes use in acute inflammation |
5. There are a variety of different serotypes with varying affinities for different cell types. Many methods have been developed for manipulation of the adenoviral genome, allowing for tailored approaches to individual clinical scenarios and the potential for overcoming obstacles associated with immune responses and the duration of therapeutic activity (5).

The primary disadvantage of using adenovirus as a therapeutic vector is its intense activation of innate and both humoral and cellular immune responses. We and others have previously shown that administration of adenovirus into an immunocompetent host produces an often unwanted and dose-dependent induction of a number of proinflammatory cytokines, including tumor necrosis factor (TNF)-α (6,7). This activation of innate immunity and inflammation was most dramatically presented in the case of a subject who died from a "cytokine storm" and multisystem organ failure following the intravenous injection of adenovirus (8). In less dramatic but more frequent cases, adenovirus may activate inflammatory and immune processes, with the potential to prove harmful to the patient and undoubtedly limit expression of the therapeutic gene, and can prevent the effectiveness with repeated administration of the vector (9). Because of the ubiquitous nature of adenoviruses and because most patients have some existing acquired immunity to adenovirus infections, adenoviral vectors are often neutralized quickly in the setting of previous exposure. Furthermore, adenovirus receptors are present on many different types of cells, making targeting of specific cell types difficult, although this latter concern can be remedied to some degree with tissue-specific promoters (5,9). As a result, there are considerable ongoing research efforts to modify the adenoviral delivery system, in some cases by removing the adenoviral genes that, when expressed, are recognized by the host immune system. These “gutless” adenoviral recombinants reduce, but do not eliminate, their recognition by host immune tissues (10). Even with all of these limitations well known, the advantages of adenovirus still make it the most popular vector, in large part because of the high degree of, but transient, expression that is achieved. For the critically ill patient, adenovirus remains a potentially effective tool for the short-term delivery and expression of therapeutic proteins. As we will see, many of the hurdles associated with its immunogenicity and immune processes can still be managed, even in the setting of acute inflammation.

Retroviruses

Retroviruses are second among the commonly utilized vectors (4) and are attractive for use in gene therapy, owing to the presence of three features:

- Membrane-coated viral particles are taken up through a receptor-mediated mechanism into target cells.
- A plus-stranded RNA genome is then incorporated into a double-stranded DNA within cellular chromosomes via reverse transcriptase.
- Particles are assembled in the cytoplasm with incorporation of the full-length retroviral mRNA as the mobile form of genetic information (11).

Clearly, these features could be beneficial, as the retrovirus offers a protective environment for delivery, an inherent mechanism for incorporation of genetic material into the host genome and the generation of both therapeutic product as well as mRNA for delivery to subsequent cells. As such, retroviruses can lead to a stable integration of genetic material into the host genome for long-lasting effects (1). Unfortunately, unlike the adenovirus, retroviruses cannot be generated in high titer. An additional complicating factor is that the cellular targets for retroviruses are quite limited, and retroviruses are unable to incorporate genetic material into cells that are not dividing. This is a significant limitation because adult mature cell populations are often not amenable to transduction. Finally, there is a small, but proven, risk of mutagenesis resulting from insertion of material into the host genome (12). This has been most dramatically demonstrated by the occurrence of leukemia in two patients with primary combined immunodeficiency treated with retrovirus-based gene therapy (13).

Adeno-associated Vectors

Adeno-associated viral vectors are less commonly employed in clinical trials than adenoviruses or retroviruses; however, their promise as a delivery method that can produce prolonged expression in the absence of a host inflammatory response has led to a recent increase in enthusiasm for their use. Adenovirus-associated virus is a replication-deficient parovirus found in humans as well as nonhuman primates, and exists in over 100 distinct variants (14). The advantageous features of AAV are many, including its nonpathogenicity, long duration of infection, large number of variants, generally mild immunogenicity, ease of genomic modification, and the fact that a number of recombinant production and purification methods have been developed for it (15). A number of experimental studies have demonstrated long-term expression of a variety of genetic materials following transfection of recombinant AAV vectors into a number of tissues, including muscle, lung, liver, gut, the central nervous system, and eye (16). The primary limitation to the use of AAV is its small size, which limits the amount of material that may be packaged into the vector. A second potential drawback is the presence of a significant lag time between the administration of the AAV and maximal gene expression, which may limit its efficacy in conditions where a rapid response is desirable, as in the acute inflammatory conditions to be discussed later. Additionally, since the expression of genetic material is so durable when AAV is utilized, improved regulatory mechanisms are necessary to control expression in disease states where constitutive expression would be deleterious (16). Again, this is potentially problematic in acute inflammation, where long-term immune suppression or enhancement could be undesirable.

Nonviral Vectors

With the intrinsic problems associated with the use of viral vectors, it is not surprising that significant research has been directed toward the development of synthetic vectors that do not rely on viral delivery systems. Interestingly, the exploration of nonviral delivery systems goes back to the early 1970s when it was first shown that exogenous nucleic acids could be readily taken up into cells (17). Initially, it was believed in the mid-1990s that these nonviral vectors would have the potential to overcome the previously discussed issues of generated immune responses, nonspecificity, and potential mutagenesis associated with viral delivery systems. Additionally, the perfect nonviral
vector would be incorporated efficiently into dividing and non-dividing cells, and have a large DNA capacity (18). As with viral vectors, these ideals have not been fully realized. In fact, a number of significant hurdles remain that have limited the usefulness of current nonviral approaches. The primary difficulties with nonviral approaches are the recognition of plasmid DNA by components of the innate immune system and generation of an inflammatory response; at the same time, the incorporation of DNA tends to be poor, and their expression is limited. At present, the most commonly utilized nonviral vector is plasmid DNA, administered either as naked DNA or incorporated into liposomal delivery systems. An overview of these vectors follows.

**Naked DNA**

Naked DNA is appealing for use in human gene therapy because its introduction into a patient generally does not stimulate an acquired immune response. Unfortunately, plasmid DNA, generally composed of bacterial sequences, is often recognized by the innate immune system, and can generate a potentially limiting inflammatory response. Bacterial DNA generally has a methylation pattern distinct from eukaryotic DNA and, as such, is recognized by toll-like receptors, specifically TLR9. Activation of TLR9 by CpG sequences in plasmid DNA can induce a proinflammatory cytokine response via nuclear factor-κB-dependent signaling pathways (19). We have shown that the administration of plasmid DNA can exacerbate existing inflammation and increase mortality during acute inflammatory processes (20).

In addition, the administration of naked DNA is not target specific; it does not discriminate against host defenses. Under normal conditions, greater than 99% of administered DNA is destroyed by circulating, lysosomal, and cytosolic endonucleases (21). Thus, the use of naked DNA generally relies upon the administration of relatively large amounts of DNA and novel approaches that can circumvent these limitations. A variety of methods have been introduced in an attempt to prevent naked DNA from being destroyed. High-pressure delivery systems have been among the most studied and utilized (18). The process is a conceptually simple one, placing DNA onto a metallic microparticle and then using a “gene gun” to deliver the particles into target cells utilizing electromagnetic force (22). There is some evidence to suggest that uptake and incorporation of DNA is increased in injured or damaged cells, and these high-pressure delivery systems may inadvertently injure cell populations and reduce cell recovery mechanisms. Unfortunately, though, while these mechanical delivery systems such as the gene gun deliver the DNA to cells of interest, they do so over a very limited area and have primarily been demonstrated to be effective only in superficial tissues; thus, different high-pressure methods, such as hydroprotrusion (intravenous injection of a large volume of DNA in solution) and jet injection (intravenous injection of a small volume of DNA in solution), have been proposed to overcome these obstacles for the systemic delivery of DNA, and have each shown success in different animal and human models (23,24).

Electroporation is a technique that uses electrodes implanted in the tissue of interest to generate an electric field, with a resultant increase in permeability for the subsequently introduced DNA. While gene transfer is increased substantially through this technique, it is limited by the need for surgery to place electrodes and the tissue damage generated by the electric field (18); additionally, the exact mechanism for the success of electroporation has been called into question (25). More recently described techniques include laser beam gene transduction, ultrasonic gene delivery, magnetofection (using magnetic nanoparticles to carry DNA to target tissues via direction by a magnetic field), and photochemical internalization (using light-sensitized endosomal vesicles to deliver DNA, and then lysing these vesicles with wavelength-appropriate light). Each of these methods has been shown to either increase the efficiency of gene transfer or increase expression in target tissues (reviewed in reference 18).

**Liposomal Delivery**

Liposomal delivery methods are the most common traditional approaches to nonviral DNA delivery, and have been utilized extensively since their introduction as one of the initial gene delivery methods (26). The concept is that the cationic lipid forms an electrostatic association with the DNA, leading to collapse of the anionic polymer, forming what is known as a lipoplex (18). These lipoplexes may be modified by the addition of ligands, antibodies, or other lipids in an attempt to improve target specificity, improve their stability, or decrease their toxicity. The lipoplexes fuse with the cellular membrane and are incorporated into endosomes. While liposomes do not trigger cellular immunity per se, they can activate the innate immune system, and their toxicity is the major limitation to their widespread use as a vector. Recent efforts have focused on diminishing the toxicity of these vectors, and two recent efforts have proven effective at lessening the immune response. The first, a simple staged procedure involving injection of liposomemediated transfection has proven effective at lessening the immune response. The second method involves the creation of a “saftoplex” containing anti-inflammatory entities such as glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or NF-κB inhibitors (28). The authors demonstrated significant suppression of inflammatory cytokine production via this method to go along with efficient gene delivery and expression.

**SEPSIS AND ACUTE INFLAMMATION**

Inflammation, in a general sense, a principal component of innate immunity and is the body’s first reaction to an infectious or injurious agent (29). Under normal circumstances, this response is a well-orchestrated series of events designed to promote the isolation or destruction of a bacterial or viral invader, or healing from a traumatic insult. However, when unchecked, the activation of the innate immune system may trigger additional inflammatory responses in distant organ systems in what has been termed the systemic inflammatory response syndrome (SIRS) (29). When SIRS occurs in the setting of a microbial infection, it is defined as sepsis. Patients who develop SIRS may recover from this condition or progress to multiple organ dysfunction syndrome (MODS), in which they develop signs and
symptoms of failure in multiple organ systems. These conditions take a heavy toll on affected patients, with significant morbidity and, in the case of sepsis, a mortality rate ranging from 25% to 80% (reviewed in reference 30).

Despite significant advances in both our understanding of the mechanisms underlying inflammation and in the resuscitation of critically ill patients with SIRS and sepsis, mortality rates from these conditions have not changed significantly over the past three decades. Current modalities utilized in the treatment of patients suffering from these disease states remain largely supportive or carry with them potentially dangerous side effects. Immune modulation through gene therapy carries a great deal of promise and would appear to be well suited for treatment of patients with these conditions; however, barriers still exist to the use of gene therapy clinically.

Endotoxemia

Most studies involving gene therapy for acute endotoxemia have focused on the immunomodulatory roles of interleukin-10 (IL-10). Our laboratory was the first to explore the possibility of gene therapy in endotoxemia, demonstrating the beneficial effect of expressing either a soluble TNF-α receptor or human IL-10 gene on mortality (31). In a subsequent study by Dräzen et al., the authors also achieved inhibition of TNF-α and IL-1β by using an adenoviral vector to express viral IL-10 in the livers of neonatal mice; interestingly, though, they did not note significant modulation of IL-6 production (32). Xing et al. likewise used an adenoviral vector given intramuscularly to express murine IL-10, finding that they achieved expression not only at the site, but also in distant tissues; further, they showed a decrease in the levels of TNF-α as well as IL-6 (33).

IL-10 gene transfer has also been shown to decrease endotoxin-induced pulmonary inflammation when given intratracheally (34). Finally, it has been demonstrated that pretreatment with an AAV expressing IL-10 also confers a survival advantage in mice undergoing an endotoxemic challenge, suggesting that it may be possible to pretreat susceptible individuals (35).

While IL-10 has received the most attention with gene therapy for the treatment of endotoxosus, other targets have been explored. Among the first to utilize a different approach, Baumhofer et al. performed gene transfer of other anti-inflammatory cytokines, IL-4 and IL-13, using cationic liposomes, finding a decreased TNF-α response to a lethal endotoxin challenge and showing a survival advantage in experimental mice when compared with controls (36). Alexander et al. showed similar results utilizing an adenoviral vector expressing bacterial permeability increasing protein (BPI) to lethal endotoxosus (37).

Given the beneficial effects of IL-10-based gene therapy, there has been increasing interest in therapeutic approaches aimed at interfering directly with inflammation signaling pathways. One such approach has been to target nuclear factor-κB (NF-κB) activation during inflammation. For example, Matsuura et al. evaluated the effect of transfecting an NF-κB decoy into lung tissue and demonstrated decreased expression of inflammatory mediators in lung tissue, decreased pulmonary vascular permeability, and improved blood gas parameters when compared to control (38). A similar approach has been to overexpress another group of targeted proteins, the suppressor of cytokine signaling (SOCS) family, which has been determined to be a group of feedback inhibitors of cytokine receptor signaling. Fang et al. used a liposomal delivery system to express SOCS3 and IL-10 into mice that were subsequently given an endotoxic challenge. The authors reported that delivery of SOCS3 in addition to IL-10 led to the greatest improvement in survival, but that administration of either independently improved the survival of mice at 48 hours (39). Finally, Nakamura et al. found that they could diminish the degree of renal dysfunction typically seen in endotoxosus by using adenoviral-mediated delivery of β2-adrenoceptor to rat kidneys (40).

While these approaches have yielded generally positive results in animal models, concerns have been raised regarding the safety of administering a potentially immunogenic vector in the setting of acute inflammation. Our laboratory evaluated this possibility, showing that there is TNF-α-mediated hepatic injury when first-generation adenoviral vectors were administered in the setting of endotoxosus (7); however, we also demonstrated that utilizing lower doses and incorporating an IL-10 construct into the vector abrogated this injury. These data were later supported by findings by Fejer et al., who demonstrated dramatic increases in TNF-α and nitric oxide levels in the kidney, liver, lung, and spleen. They further showed that these findings correlated with a diminished survival in animals treated with adenovirus and lipopolysaccharide (LPS) (41).

Sepsis

Sepsis is a particularly challenging disorder for treatment by gene therapy because sepsis is a systemic disease (29), and targeting therapy to a single tissue or organ is generally ineffective. In addition, the failure of most monotherapies for the treatment of sepsis has convincingly shown that the pathologic basis for
sepsis is multifactorial, and treatment against a single compo-
ment of sepsis is unlikely to be dramatically successful.

With that said, however, the primary effort of using gene
therapy in sepsis has been directed against the exuberant in-
flammatory response; as in endotoxicosis, by far the most com-
monly used approach has been the forced expression of the
anti-inflammatory protein, IL-10. IL-10 is a particularly attrac-
tive transgene in sepsis for a number of reasons (42,43). IL-10 is
a profoundly anti-inflammatory cytokine and is known to sup-
press the expression of early proinflammatory genes like TNF-
α and IL-1 by preventing NF-κB translocation. As previously
discussed, IL-10 gene therapy has been frequently successful in
reversing the expression of early proinflammatory genes seen in
lethal endotoxicosis. Importantly, IL-10 works through what is
known as a “bystander effect,” meaning that transfection does
not need to occur in every cell, since expression and secretion
of IL-10 by a few transfected cells can produce biologic effects
in adjacent, but not transfected, cells or tissues. Unfortunately,
treatment of septic animals with the systemic administration of
IL-10 protein has produced variable results, with most investi-
gators unable to show any therapeutic benefit (44).

Because of the need for rapid but transient expression of
the transgene, most transfection schemes have used either ade-
novirus or plasmid-based nonviral approaches for sepsis and
acute inflammatory injury. Although it is difficult to com-
pare results from different investigators with different vectors
and delivery systems, the results have generally been positive
with IL-10-based gene therapies in severe sepsis. Probably the
most convincing data with systemic IL-10-based gene therapy
has come from the recent studies of Kabay et al. in Turkey
(45,46). These investigators used a plasmid-based approach
which contained liposomes, and IL-10 was coexpressed with the
intraperitoneal injection of plasmids expressing human IL-10
could improve survival and reduce end-organ injury in a cecal
ligation and puncture model of sepsis. The authors were able
to demonstrate—using immunohistochemistry—human IL-10
expression in the liver, kidney, and lung following gene therapy.

We used plasmid-based IL-10 gene therapy for the treatment
of experimental pancreatitis and were also able to show tran-
sient expression and improved outcomes (20,47,48). However,
the data were complicated by the fact that the administration of
cationic liposomes and the plasmid DNA without the trans-
gene alone actually exacerbated the inflammatory response to
pancreatitis and worsened outcome (20). In this case, expres-
sion of the IL-10 was required to dampen the inflammatory
response not only to the experimental pancreatitis, but also to the
administered plasmid and cationic liposomes.

During the initial studies with nonviral approaches and IL-
10, we were disappointed by the low level of expression and its
concentration in the lung injury and multiorgan failure (51). Interestingly, better ef-
fects were seen with viral IL-10 expression, which appeared
to be more tissue-associated than in the systemic circulation
(50), and the beneficial effects of human IL-10 expression were
strongly dose dependent (51,53). Actually, higher doses of ade-
novirus administered intratracheally and producing systemic
concentrations of protein were frequently less effective than
lower doses producing only local expression (53). Interestingly, the ade-
novirus also had to be administered prior to the inflam-
matory stimulus; once the process was ongoing, gene therapy
was ineffective (51).

Also exciting was the observation that when very small
quantities of adenovirus were administered ex vivo into the
lung, outcome from a cecal ligation and puncture-induced
sepsis was markedly improved (54). Subsequent studies revealed that this compartimentalized administration of
the adenoviral vector resulted in the transfection and expres-
sion of IL-10 by primarily dendritic cells (54,55). In the case of
footpad injections, these IL-10 expressing dendritic cells then
migrated to the draining lymph nodes where they expressed
the protein in the context of class II expression and antigen
presentation (Fig. 52.2). In these studies, we learned that au-
tocrine production of IL-10 created a novel dendritic cell that
had a phenotype consistent with an immature, tolerant, regula-
tory dendritic cell (56). Surprisingly, we subsequently showed
that we could ex vivo transfect myeloid dendritic cells with this
adenoviral recombinant expressing IL-10, and when they were
reintroduced into a mouse prior to sepsis, could also improve
outcome (56). Although the mechanism of protection is still
unknown, it is speculated that this novel dendritic cell pop-
ulation expressing IL-10 may have fostered the expansion of
regulatory T cells with the capacity of reducing the magnitude
of the inflammatory response.

Although IL-10 has been the primary transgene used
in models of sepsis as an anti-inflammatory agent, other
approaches have been considered. As previously discussed,
blocking NF-κB activation in endotoxicosis is an alternate
approach aimed at preventing an exuberant inflammatory re-
response (38); however, other approaches targeting more spe-
cific components of the injury response have been consid-
ered. For example, Weiss et al. used an adenoviral vector
to delivery HSP70 into the lungs of mice following a cecal
ligation and puncture (57). These investigators observed a
Transfection efficiency following adenoviral gene transfer.

A: An empty adenoviral vector or one expressing the green fluorescent protein (gfp) was injected directly into the footpad of mice. Twenty-four hours later the popliteal lymph node was removed and gfp fluorescence determined by microscopy. Cells transfected with the adenovirus expressing gfp could be detected in accessory cells, predominantly dendritic cells. (Reprinted from Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock. 2001;16:83, with permission.)

B: The same adenoviral vectors were injected into the thymus of mice, and 24 hours later, the thymi were removed, and gfp fluorescence determined in CD11c+ dendritic cells. Approximately 27% of the CD11c+ dendritic cells were expressing the gfp. (Reprinted with permission from Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock. 2001;16:83.)

C: Twenty-four hours later, the thymi were removed, and gfp fluorescence determined by microscopy. Cells transfected with the gfp expression in the accessory cells of thymi injected with recombinant adenovirus expressing gfp. (Reprinted with permission from Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock. 2001;16:83.)

FIGURE 52.2. Transfection efficiency following adenoviral gene transfer.

The future of gene therapy for critical illness remains a elusive target in the future. There has been considerable progress made using gene therapy for the correction of inherited genetic disorders, and the possibility of cures for primary combined immunodeficiency, cystic fibrosis, α1-antitrypsin deficiency, Pompe disease, and other genetic diseases are on the horizon (Table 52.2). In contrast, progress as a drug (protein) delivery system for acute illnesses remains a considerable challenge. Limitations are primarily centered on optimizing the vector and promoter, which must still undergo further refinements to yield a delivery system that is rapid, transient, tissue specific, and safe, and one that does not exacerbate activated inflammatory and innate immune systems. Although adenovirus and plasmid-based delivery systems are most frequently used today, both have significant limitations in their current iterations.

In addition, there is little consensus about the optimal gene target to express, as critical illness, sepsis, trauma, and shock simultaneously affect a large number of immune and somatic cell systems, including innate and acquired immunity, thrombosis, fibrinolysis, acute phase, and neuron–endocrine, endocrine, and renal systems. Most approaches to date have been focused on either the global inflammatory response, the interaction between innate and acquired immunity, or specific lung functions. Whether a global approach will be superior to targeting specific components of the response in critical illness is still unproven.
### TABLE 52.2

**ANNOTATED SUMMARY OF STUDIES USING GENE THERAPY IN MODELS OF CRITICAL ILLNESS**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Vector and mode of delivery</th>
<th>Experimental model</th>
<th>General results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogy et al., 1995</td>
<td>Plasmid-based human IL-10, IP injection</td>
<td>Endotoxicosis</td>
<td>Improved survival, reduced TNF-α</td>
</tr>
<tr>
<td>Drazan et al., 1996</td>
<td>Adenoviral viral IL-10, IP injection</td>
<td>Endotoxicosis</td>
<td>Reduced TNF-α and IL-1β, no impact on IL-6</td>
</tr>
<tr>
<td>Xing et al., 1996</td>
<td>Adenoviral murine IL-10, IM injection</td>
<td>Endotoxicosis</td>
<td>Reduced TNF-α and IL-6</td>
</tr>
<tr>
<td>Baumhofer et al., 1998</td>
<td>Plasmid-based human IL-4 and IL-13, IP injection</td>
<td>Endotoxicosis</td>
<td>Improved survival, reduced TNF-α, decreased peritoneal macrophage function</td>
</tr>
<tr>
<td>Denham et al., 1998</td>
<td>Plasmid-based human IL-10, IP injection</td>
<td>Endotoxicosis</td>
<td>Reduced TNF-α and IL-6</td>
</tr>
<tr>
<td>Chen et al., 2000</td>
<td>Adenoviral TNF-α, IT injection</td>
<td>Endotoxicosis</td>
<td>Improved survival, reduced TNF-α, improved survival</td>
</tr>
<tr>
<td>Doldka et al., 2000</td>
<td>Cytomegaloviral murine IL-10, IT injection</td>
<td>Endotoxicosis</td>
<td>Reduced lung inflammation</td>
</tr>
<tr>
<td>Minter et al., 2000</td>
<td>Adenoviral human IL-10, IT, IV injection</td>
<td>Endotoxicosis</td>
<td>Attenuated inflammatory response, improved survival in multisystem organ failure when given IV</td>
</tr>
<tr>
<td>Norman et al., 2000</td>
<td>Cationic liposomal plasmid DNA, IP injection</td>
<td>Endotoxicosis</td>
<td>Increased severity and mortality in pancreatitis</td>
</tr>
<tr>
<td>Oberholzer et al., 2001</td>
<td>Adenoviral human IL-10, intrathymic and IV injection</td>
<td>Pancreatitis</td>
<td>Decreased inflammation, improved survival</td>
</tr>
<tr>
<td>Dreeschug et al., 2002</td>
<td>First- and second-generation adenoviral vectors, IV injection</td>
<td>Endotoxicosis</td>
<td>Decreased survival when first-generation vectors used</td>
</tr>
<tr>
<td>Oberholzer et al., 2002</td>
<td>Adenoviral human IL-10, SQ injection</td>
<td>Endotoxicosis</td>
<td>Dose-dependent improvement in survival</td>
</tr>
<tr>
<td>Weis et al., 2002</td>
<td>Adenoviral heat shock protein, IT injection</td>
<td>Endotoxicosis</td>
<td>Dose-dependent improvement in survival</td>
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<td>Chen et al., 1999</td>
<td>Plasmid-based TFPL-CD4–P-selectin and hirudin–CD4–P-selectin, IV injection</td>
<td>Endotoxicosis</td>
<td>Improved survival, improvement in pulmonary function</td>
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<td>Alexander et al., 2004</td>
<td>Cytomegaloviral murine BPI, IP injection</td>
<td>Endotoxicosis</td>
<td>Reduced TNF-α and MP-2, improved survival</td>
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<tr>
<td>Matsuda et al., 2004</td>
<td>NF-κB decoy oligonucleotide, IV injection</td>
<td>Endotoxicosis</td>
<td>Reduced lung inflammation, blood gas improvement</td>
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<td>Fang et al., 2005</td>
<td>Cationic liposomal SOCS3, IP injection</td>
<td>Endotoxicosis</td>
<td>Reduced TNF-α, improved survival</td>
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<td>Fejer et al., 2005</td>
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<td>Endotoxicosis</td>
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<td>Endotoxicosis</td>
<td>Diminished reduction in renal function</td>
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<td>Plasmid-based human IL-10, IP injection</td>
<td>Endotoxicosis</td>
<td>Improved survival</td>
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<td>McAuliffe et al., 2006</td>
<td>Adenoviral human and viral IL-10, inhalation</td>
<td>Endotoxicosis</td>
<td>Dose-dependent worsening of inflammation and survival</td>
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(Continued)
**TABLE 52.2**

(Continued)

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<th>Experimental model</th>
<th>General results</th>
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<tr>
<td>Shu et al., 2006*</td>
<td>Adenoviral β-defense-2, intranasal injection</td>
<td>Pseudomonic acute lung injury</td>
<td>Improvement in pulmonary function, delayed mortality</td>
</tr>
<tr>
<td>Zhou et al., 2006*</td>
<td>Adenoviral CTP, phosphatidylcholine cytididylyltransferase, IT injection</td>
<td>Pseudomonic acute lung injury</td>
<td>Improvement in pulmonary function, delayed mortality</td>
</tr>
</tbody>
</table>

**References**

13. Marshall E. Gene therapy progress and prospects: vectorology: de-
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. 53.3). When not altered by intervention or complications, the stress response is initiated by coexisting disease or interrupted by adverse events such as intervention, these changes 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 a chronic disease. The organism then may enter a state of persistent hypermetabolism. This continued 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.

Chapter 53: The Host Response to Injury and Critical Illness

JAMIE TAYLOR • CLIFFORD S. DEUTSCHMAN

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. 53.3). When not altered by intervention or complications, the stress response is initiated by coexisting disease or interrupted by adverse events such as intervention, these changes 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 a chronic disease. The organism then may enter a state of persistent hypermetabolism. This continued 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 a chronic disease. The organism then may enter a state of persistent hypermetabolism. This continued 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.
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 (3,5–8). 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...
capillary dilatation to increase flow and improve delivery. Un-
fortunately, due to thrombosis in damaged tissue, most injured areas are avascular. 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 glyceral through gluconeogene-
sis; 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 insulinlike 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, angiotensin 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 glucocorticoids and mineralocorticoids. Glucocorticoids and glucagon promote glucagenolysis 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 hemorraghe 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-
munocyte 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 will fuse and consist of vascularized granulation tissue 
with phagocytosis of foreign or damaged material and 
fibroblasts upon antigen introduction. Macrophages respond to stimula-
tion by macrophages, APCs, and lymphocytes. Macrophages 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-
lcular dendritic cells have a similar function except that they present antigens to B cells and therefore initiate humoral im-
nunity. Lymphocytes are the prime components of the adaptive
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 “institute 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 
release 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 compartments. In a normal stress response, catabolism is ac-
companied by an increase in the vascular space (reaccumulation); expansion of the extravascular, extracellular space; and a de-
crease in the intracellular space. This process ends 4 to 5 days after injury with a shift to anabolism (11). The extracellu-
ture contracts, fluid is removed from the extracellular 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 osmolality move back, leading to de-
creases in serum electrolytes and, therefore, diuresis and salt 
creases in serum electrolytes are the hallmarks of resolution of the stress response.

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 an-
gens and chemoattractant molecules (chemokines) released by endothelial cells and 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-
lcular dendritic cells have a similar function except that they present antigens to B cells and therefore initiate humoral im-
nunity. 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 APCs 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, the switch 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 an- drogens, which are secreted in great quantities in catabolism, may be hormonally mediated. It is known that cortisol and andro gens, which are secreted in great quantities in catabolism, stimulate Th2 cell production. 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, malnutri tion, 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. These result in a recurrence of shock, with vasoconstric tion, 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 hyperme tabolism. Persistence of a hyperdynamic circulation and secretion of immunologic markers; elevations of serum potassium, magnesium, and phosphate; and/or marginal urine output indi cate 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 TABLE 53.1

DIAGNOSTIC CRITERIA FOR SEPSIS IN ADULTS

<table>
<thead>
<tr>
<th>SUSPECTED OR DOCUMENTED INFECTION</th>
<th>General variables</th>
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<tbody>
<tr>
<td>Fever (T &gt;38.3°C)</td>
<td></td>
</tr>
<tr>
<td>Hypothermia (T &lt;36°C)</td>
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</tr>
<tr>
<td>Heart rate (&gt;90 bpm or &gt;2 SDs above normal for age)</td>
<td></td>
</tr>
<tr>
<td>Tachypnea</td>
<td></td>
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<tr>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td>Edema or positive fluid balance</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;120 mg/dL or 7.7 mmol/L) without DM</td>
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<tr>
<td>Leukopenia (WBC &lt;4,000/μL)</td>
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<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SDs above the normal value</td>
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<tr>
<td>Plasma procalcitonin &gt;2 SDs above the normal value</td>
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</tr>
<tr>
<td>Tachycardia (HR &gt;90 mm Hg or &lt;2 SDs below normal)</td>
</tr>
<tr>
<td>SvO2 &gt;70%</td>
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<tr>
<td>Cardiac index &gt;3.5 L/min/m²</td>
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<tr>
<td>Organ dysfunction variables</td>
</tr>
<tr>
<td>Arterial hypoxemia (PaO2/FiO2 &lt;300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/h for at least 2 h)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 s)</td>
</tr>
<tr>
<td>Lactosuria (plasma total bilirubin &gt;4 mg/dL or 70 mmol/L)</td>
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<table>
<thead>
<tr>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia (&gt;1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

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/Sepsis/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 cate-
cholamines (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 leaving 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-
mmatory failure (36–39). More specifically, sepsis is associated with an alteration in the adaptive immune response (40). The early phase of sepsis resembles normal stress in that there is a hormonal milieu that stimulates Th2 responses and these responses are observed. Indeed, studies have shown that pa-
tients with sepsis have increased Th2 cells and IL-10 and that these levels predict mortality (41,42). However, as sepsis pro-
gresses, there is 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-
fect 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 50% 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-Caucasians 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 39% 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 immuno suppression 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 analgesia 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 outcome in a single-centre 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) or in a previously unpublished multicenter European trial (GLUCOMON, confirmed by personal communication). The benefit of insulin appeared to be confined to patients in the ICU for less than 7 to 8 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 offset 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**


CHAPTER 54  
MULTIPLE ORGAN DYSFUNCTION SYNDROME

J. MATTHIAS WALZ  ·  STEPHEN O. HEARD

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.

MOHs 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 increases, in a process 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 (DO_{2}). Therefore, diagnosis and therapy focus, whenever possible, on preventive measures. Changes in the cellular oxygen (O_{2}) 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 O_{2} 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 blood pressure while addressing life-threatening derangements in acid-base balance and gas exchange. Prompt correction of hemodynamic instability to defined end points that correlate with resolution of tissue O_{2} debt minimizes ischemia-related organ damage. The element of time is a critical factor. Delays in completing initial resuscitation, eliminating foci of infection or devitalized tissue, or treating de novo organ-specific problems such as oliguria all worsen outcome. Late-phase (e.g., over 72 hours) problems involve acquired immunosuppression, predisposition to secondary infection, and hypermetabolism, which impairs wound healing and host defense.

Initial Essential Diagnostic Tests and Procedures

Hemodynamic and Metabolic Monitoring

1. Begin assessing the adequacy of initial resuscitation efforts by noninvasive measures including skin color and temperature, arterial blood pressure, pulse rate, respiratory rate, mental status, and urine output; determine if metabolic acidosis is present from arterial blood gas and plasma bicarbonate (NaHCO_{3}) determinations. If acidosis is present, establish whether the anion gap and plasma lactate concentrations are increased.


2. Consider invasive hemodynamic monitoring by arterial and central vascular catheterization. Central venous pressure estimates (right heart filling) but may not accurately gauge left ventricular preload with tricuspid insufficiency, pre-existing heart disease, pulmonary hypertension, or acute respiratory distress syndrome (ARDS). Exclude myocardial infarction as a cause of hemodynamic instability by electrocardiography, creatine kinase isoenzyme, and troponin I levels.

3. Targeted hemodynamic management can be accomplished by invasive or noninvasive means (e.g., pulmonary artery catheterization, pulse contour analysis, or esophageal Doppler monitoring). Mixed or central venous O₂ saturation and lactate concentrations—if the latter are initially elevated—should be monitored to determine adequacy of resuscitation and assist in the titration of therapy.

4. Hemodynamic instability despite adequate fluid resuscitation in patients with severe sepsis should be treated with inotropes as indicated, and the hemoglobin level should be raised to 10 mg/dL in the early stages of resuscitation according to the principles of early goal-directed therapy (EGDT).

**Evaluation for Infection**

1. For suspected sepsis upon ICU admission, blood cultures—including fungal cultures where appropriate—should be immediately obtained, as should Gram stains and cultures of urine, an adequate sputum specimen (where "adequate is defined by 25 or more leukocytes per low-power field") or transtracheal washings, and wound discharges before antimicrobial therapy. Suspicious skin lesions should undergo culture by aspiration and biopsy. On discovery of fluid collections, perform thoracentesis and paracentesis within 12 hours or less; determine pH; and perform a Gram stain, culture, cell count, cytologic studies, glucose level, and other chemistries.

2. Evaluate the patient thoroughly for all infectious and potential noninfectious etiologies of MODS.

3. For suspected nosocomial sepsis, reculture blood, urine, and sputum; evaluate all sites of vascular cannulation and remove catheters, if possible; and consider fiberoptic bronchoscopy to obtain protected brush specimen or bronchialvalear lavage (BAL) samples in patients with pneumonia. Exclude infective endocarditis or endovascular infection by echocardiography and scintigraphic scanning for high-grade or recurrent bacteremia.

4. Serially monitor renal, pancreatic, and hepatic function; exclude acalculous cholecystitis or pancreatitis by abdominal ultrasound. Perform computed tomography of the sinuses, chest, abdomen, and pelvis when appropriate to define fluid collections.

5. Maintain a high index of suspicion for opportunistic fungal infection with Candida sp. despite negative results on blood culture.

**Initial Therapy**

1. Resuscitation of hemodynamic instability should be rapidly initiated with crystalloid or colloid infusions, followed by replenishment of the red cell mass.

2. Vasopressors—dopamine, norepinephrine, vasopressin—are titrated to a systolic pressure of 90 to 100 mm Hg or a mean arterial pressure of 70 mm Hg, or higher.

3. In patients with septic shock and hypotension despite adequate fluid resuscitation, evaluate the patient for evidence of adrenal insufficiency and initiate therapy with low-dose corticosteroids if indicated.

4. Evaluate and treat ionized hypocalcemia and severe metabolic acidosis if the response to catecholamine therapy is inadequate.

5. If shock persists despite rapid and aggressive fluid resuscitation, consider endotracheal intubation and mechanical ventilation, irrespective of arterial blood gas values. Proper titration of ventilatory therapy averts respiratory muscle fatigue and arrest by reducing shock-related increases in the O₂ cost of breathing.

6. Evaluate and treat oliguria. Differentiate prerenal causes by obtaining serum and urine Na⁺, creatinine, and urea nitrogen to calculate the fractional excretion of sodium (FeNa) or urea nitrogen.

7. Stabilize long bone fractures early.

8. Initiate broad-spectrum antimicrobial therapy, including coverage against methicillin-resistant Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa. Add coverage for suspected anaerobic intra-abdominal sepsis.

9. Begin antifungal therapy in patients at high risk for fungal sepsis despite negative results on blood culture when clinical findings are suggestive (e.g., extensive colonization by Candida, noninterfering skin rash, myositis, or retinitis).

10. Perform prompt re-exploration for suspected intra-abdominal sepsis and abscess formation.

**Epidemiology of Multiple Organ Dysfunction Syndrome**

Significant advances have been made in critical care medicine over the last 30 years, particularly in the last decade. Nonetheless, many critically ill patients often suffer the progressive deterioration in the function of one or more organs, a phenomenon that has been termed multiple organ dysfunction syndrome (1). MODS is the leading cause of death for patients in the intensive care unit. Furthermore, the death rate remains high for patients who survive their ICU admission. In addition, the financial costs are significant, with more than 60% of ICU resources consumed by these patients (2).

Individual organ dysfunction may result from a direct insult, such as pulmonary aspiration of gastric contents (primary MODS), or it can be associated with a systemic process such as shock or pancreatitis (secondary MODS) (1). Alterations in organ function seen during MODS are a continuum rather than a discrete, dichotomous event indicating the failure of an organ. A number of organ dysfunction scores have been developed to predict the clinical outcome of these patients (Table 54.1). These scores not only serve to establish the baseline degree of organ dysfunction, but also enable the clinician to evaluate the progression or resolution of organ dysfunction over time. In general, an increase in the number of dysfunctional organs increases the risk of death. Examples of early scores of organ failure include those published by Goris et al. (3) and Knaus et al. (4). Refinement of these scores led to the development
Chapter 54: Multiple Organ Dysfunction Syndrome

Table 54.1

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Sequential Organ Failure Assessment (SOFA) (6)</th>
<th>Multiple Organ Dysfunction Score (MOD) (5)</th>
<th>Logistic Organ Dysfunction (LOD) (184)</th>
<th>Brussels (185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Blood pressure and vasopressor use</td>
<td>Blood pressure and adjusted heart rate</td>
<td>Blood pressure, fluid responsiveness, and acidosis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;/FiO&lt;sub&gt;2&lt;/sub&gt; and mechanical ventilation</td>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;/FiO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;/FiO&lt;sub&gt;2&lt;/sub&gt; and mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Bilirubin</td>
<td>Bilirubin</td>
<td>Bilirubin and prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Platelets</td>
<td>Platelets</td>
<td>Platelets and white blood cell count</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine and urine output</td>
<td>Creatinine</td>
<td>Creatinine, blood urea nitrogen, or urine output</td>
<td></td>
</tr>
<tr>
<td>Central Nervous</td>
<td>Glasgow Coma Score (GCS)</td>
<td>GCS</td>
<td>GCS</td>
<td></td>
</tr>
</tbody>
</table>


of the multiple organ dysfunction (MOD) score (5) and the sequential organ failure assessment (SOFA) score (6). In principle, these scores are based on parameters for six organ systems: Cardiovascular, respiratory, hematologic, renal, central nervous system (CNS), and hepatic (7). The difference in these scores lies in the parameter to describe cardiovascular dysfunction. The MOD score describes the degree of cardiovascular dysfunction as a composite of heart rate, central venous pressure, and mean arterial pressure (pressure-adjusted heart rate), whereas the SOFA score describes cardiovascular dysfunction by the dose of vasoactive agents administered.

Several trials have evaluated the performance of these scores as descriptors of multiple organ dysfunction and failure, and to assess the incidence of MODS in the intensive care unit. Moreno et al., in a prospective, international multicenter trial composed of 1,449 patients, were able to demonstrate that total maximum SOFA score and change in SOFA score over time (8) can be used to quantify the degree of organ dysfunction present on ICU admission, the degree of dysfunction or failure that appears during the ICU stay, and the cumulative insult suffered by the patient (7). These findings were subsequently confirmed by Ferreira et al. (8), who demonstrated that changes in the SOFA score were a good indicator of prognosis. In their study of 352 consecutive patients, an increase in SOFA score during the first 48 hours of intensive care predicted a mortality rate of at least 50% (8). In a group of patients with ARDS, the Toronto ARDS Outcomes Group found a significant relationship between the change in MOD score over time of the ICU stay and the distance walked in 6 minutes up to 1 year following discharge from the ICU (9). The recent European Sepsis Occurrence in Acutely Ill Patients (SOAP) multicenter trial analyzed data from 3,147 adult ICU admissions to determine the incidence of MODS and its associated mortality in mixed medical and surgical ICU populations (10). The overall rate of MODS, defined as severe acquired dysfunction in two or more organ systems, was 43% for patients without a diagnosis of sepsis and 73% of those with a diagnosis of severe sepsis, which represents a substantially higher incidence than in some previously published reports (4). Like other investigators, they found a direct relationship between the number of organs failing and the ICU mortality (Fig. 54.1). Single organ failure carried an ICU mortality rate of 6%, whereas patients with four or more failing organs had mortality rates of 65%. While earlier reports have suggested that the increase in mortality associated with an increased number of failed organs is independent of the identity of dysfunctional organ systems

![Mortality](image)

(11–13), the SOAP investigators found different results. Organ failure in patients with severe sepsis generally carried a higher mortality than in those patients without a diagnosis of severe sepsis. As for individual organ systems in the group of patients with severe sepsis, failure of the coagulation system carried the highest mortality (52.9%), followed by the hepatic (45.1%), CNS (43.9%), cardiovascular (42.3%), and renal system (41.2%). Respiratory failure in this analysis was associated with a mortality risk of 34.5%. Certain subsets of patients admitted to the ICU appear to be at greater risk of MODS: patients older than 65 years (older than 55 years in trauma patients [13]), increased severity of illness as assessed by APACHE II scores (20 or more), and diagnosis of sepsis or acute lung injury (ALI) on admission. Among the patients with severe sepsis, the SOAP investigators found as independent predictors of mortality the following: “Medical” admissions, Pseudomonas species infection, SAPS II score on admission, SOFA score at the onset of sepsis, bloodstream infection, cirrhosis, and cumulative fluid balance within the first 72 hours of the onset of sepsis. The latter variable has not previously been identified as an independent predictor of mortality; further investigations will be necessary to distinguish whether a positive fluid balance in the ICU is simply a marker of severity of illness or is harmful, per se.

### PATHOPHYSIOLOGY

MODS usually occurs in patients who exhibit signs of a generalized inflammatory response system (SIRS), Table 54.2 (1). Although SIRS is often the result of infection, other conditions such as necrotizing pancreatitis or trauma can also lead to systemic manifestations of inflammation; SIRS due to infection has been defined as sepsis. Recent guidelines (14) have broadened the diagnostic criteria for sepsis that were originally proposed in 1992. For those patients who present with SIRS only, a significant number will progress to sepsis, septic shock, and, ultimately, MODS (15). Although suspected or documented infection is not required for the development of MODS, the syndromes of SIRS, sepsis, and MODS are closely related. Consequently, the review of the pathophysiology of MODS will also include discussions of SIRS and MODS.

#### Derangements in Oxygen Delivery and Consumption

In most tissues, oxygen consumption (VO2) is determined by metabolic demand and is independent of DO2. When DO2 is

### TABLE 54.2

<table>
<thead>
<tr>
<th>A</th>
<th>Infection</th>
<th>Microbial phenomenon characterized by an inflammatory response to the presence of the micro-organism or the invasion of normally sterile host tissue by those organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bacteremia</td>
<td>The presence of viable bacteria in the blood</td>
</tr>
<tr>
<td>C</td>
<td>Systemic inflammatory response syndrome (SIRS)</td>
<td>The systemic inflammatory response to a variety of severe clinical insults, manifested by two or more of the following conditions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1) Temperature greater than 38°C or less than 36°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Heart rate greater than 90 beats/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Respiratory rate more than 20 breaths/min or PaCO2 less than 32 mm Hg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4) WBC more than 12,000 cells/μL, less than 4,000 cells/μL, or more than 10% immature (band) forms</td>
</tr>
<tr>
<td>D</td>
<td>Sepsis</td>
<td>The systemic response to infection. The manifestations are the same as those enumerated for SIRS.</td>
</tr>
<tr>
<td>E</td>
<td>Severe sepsis</td>
<td>Sepsis associated with organ dysfunction, hypoperfusion, or hypotension</td>
</tr>
<tr>
<td>F</td>
<td>Septic shock</td>
<td>Sepsis with hypotension, despite adequate fluid resuscitation, and perfusion abnormalities, including but not limited to the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1) Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Oliguria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Acute alteration in mental status</td>
</tr>
<tr>
<td>G</td>
<td>Hypotension</td>
<td>A sustained BP less than 90 mm Hg or a reduction of more than 4 mm Hg from baseline in the absence of other causes for hypotension</td>
</tr>
<tr>
<td>H</td>
<td>Multiple organ dysfunction syndrome</td>
<td>Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention</td>
</tr>
</tbody>
</table>

WBC, white blood cell; BP, blood pressure.


reduced, VO$_2$ is maintained by increased oxygen extraction by the tissues. If DO$_2$ is reduced to the point where the metabolic need cannot be met, then VO$_2$ becomes “supply dependent” (Fig. 54.2). The point at which VO$_2$ decreases is called the critical DO$_2$. Although one study (16) suggested that the critical DO$_2$ in anesthetized humans is 330 mL/minute/m$^2$, another investigation where life support was withdrawn in critically ill patients demonstrated that the value is substantially lower (17).

A number of studies from the 1970s, 1980s, and early 1990s seemed to suggest that systemic VO$_2$ was supply dependent over a wide range of DO$_2$ in patients with sepsis or ARDS. Since VO$_2$ and DO$_2$ are independent of each other, the linking of these two variables in patients with ARDS or sepsis was coined pathologic supply dependency. This concept is important, as it implies that inadequate oxygen is being delivered to the tissues and anaerobic metabolism is occurring despite “normal” global perfusion. As a consequence, inadequate production of adenosine triphosphate (ATP) and other high-energy phosphates may contribute to the development of MODS in these patients.

The validity of the concept of pathologic supply dependency was subsequently challenged. Mathematical coupling of data (e.g., VO$_2$ and DO$_2$ both determined by use of a pulmonary artery catheter), pooling of data, and spontaneous changes in metabolic demand (which would increase DO$_2$) can explain many of the results of the studies purporting to show pathologic supply dependency. Clinical investigations that utilized independent means to measure both DO$_2$ and VO$_2$ failed to demonstrate pathologic supply dependency in patients with ARDS or sepsis. Furthermore, critical DO$_2$ in these patients was no higher than in other critically ill patients.

More recently, there has been a recognition that supply dependency may be occurring in patients, but not at the global level. There is an increasing appreciation that the regional circulation and microcirculation—arterioles, capillary bed, and postcapillary venules—play a crucial role in the pathogenesis of organ dysfunction in shock. Heterogeneous microcirculatory abnormalities occur due to changes in the activation state and shape of endothelial cells, alterations in vascular smooth muscle tone, activation of the clotting system, and changes in red and white blood cell deformability (discussed later). The surface receptors and mediators associated with these changes are now being identified, and include oxidants, lectins, proteases, vasoactive products of inducible nitric oxide synthase (iNOS), and altered adrenergic receptor sensitivity. Alterations in microvascular circulation have been demonstrated in congestive heart failure, cardiogenic shock, hemorrhage, and sepsis. Microcirculatory changes of conges-
Section V: Modulating the Response to Injury

ROLE OF INFLAMMATORY AND VASOACTIVE MEDIATORS

Although early clinical series emphasized the implication of uncontrolled infection in the development of MODS, it is clear that MODS can occur with either extensive tissue injury such as that seen with trauma, pancreatitis, or sepsis. A large amount of evidence is available that implicates the release of inflammatory mediators in the pathogenesis of MODS (Table 54.3).

**Complement, Neutrophils, and Reactive Oxygen Metabolites**

The complement cascade is activated via three pathways (Fig. 54.4). The classical pathway is triggered by antibody-coated targets or antigen-antibody complexes. The alternative pathway is activated by aggregated immunoglobulins, products of tissue trauma, lipopolysaccharide (LPS), and other complex polysaccharides. The lectin-ficolin pathway is initiated by the binding of organisms to mannose binding lectin (MBL), a protein important in innate immunity (34). Once MBL is bound to a pathogen, an MBL-associated serine protease is produced, which forms a C3 convertase by cleavage of C4 and C2. Products of the complement pathway activate neutrophils, which can obstruct capillaries and release oxygen radicals and lysosomal enzymes—among other mediators, thereby damaging the endothelium. Furthermore, adhesion molecules, which are expressed on both polymorphonuclear leukocytes (PMNs) and vascular endothelium in response to LPS and other inflammatory mediators, facilitate the adherence and diapedesis of PMNs through the endothelium.

A significant amount of evidence exists, suggesting that complement activation is important in the pathophysiology of MODS. In an animal model of generalized inflammation (e.g., with zymosan treatment), C5-deficient mice had a lower mortality compared to wild-type mice; however, late organ

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**TABLE 54.3**

| INFLAMMATORY MEDIATORS IMPORTANT IN THE PATHOGENESIS OF SEPSIS AND THE MULTIPLE ORGAN DYSFUNCTION SYNDROME |
| Complement (C3a, C5a) |
| Neutrophil products |
| Proteases |
| Neutral proteases |
| Elastase |
| Cathepsin G |
| Collagenase |
| Acid hydrolase |
| Cathepsins B and D |
| β-glucuronidase |
| Glucosaminase |
| Oxygen radicals |
| Superoxide anion |
| Hydroxyl radical |
| Hydrogen peroxide |
| Peroxynitrite |
| Bradykinin |
| Lipid mediators |
| Prostaglandins |
| Thromboxane A2 |
| Prostaglandin E2 |
| Platelet-activating factor (PAF) |
| Leukotrienes (LTB4, LTC4, LTD4, LTE4) |
| Cytokines |
| Tumor necrosis factor-α (TNF-α) |
| Interleukins (IL-1, IL-6, IL-8) |
| High-mobility group 1 (HMGC-1) |
| Macrophage migration inhibition factor (MIF) |
| Nitric oxide |

Classical Pathway

Lectin Pathway

Alternative Pathway

C₁ + C₂ + C₃

C₄

C₅

C₆ + C₇ + C₈ + C₉

Terminal Membrane Attack Complex (MAC, C₅b-₇b-₉b)

C₁q

C₁r C₁s

C₄

C₃a

C₅a

C₄b₂a

C₄b₂a₃b

C₄bC₂

Microbial surfaces (mannose) and others (e.g., IgA)

Spontaneously occurring and after contact with foreign surfaces, (e.g., LPS)

Immune (IgG + IgM) complexes and others (e.g., CRP)

C₁-INH

C₂b

C₃b

Activation Anaphylatoxin

Macrophage Endothelial Cell

Chemotoxic factors Vascular Permeability Mediators

C₂b

Factor D

Factor I

Factor H

MCP

CR1

FIGURE 54.4. The three complement activation pathways (classic, alternative, and lectin). IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; CRP, C-reactive protein; MBL, mannose-binding lectin protein; MASP, MBL-associated proteases; C₁-INH, C₁-inhibitor; LPS, lipopolysaccharide; CAM, cell adhesion molecules; MAC, membrane attack complex; PSN, polymorphonuclear leukocytes; MCP, monocyte chemoattractant protein; CR1, complement component receptor 1. (Reproduced from Goldfarb RD, Parrillo JE. Complement. Crit Care Med. 2005;33:S482–S484, with permission.)

failure was not different between the groups (35). An inhibitor of complement, bisbenzyloxyquinoline alkaloid, will decrease mortality and the percentage of animals with organ injury in zymosan-treated mice (36). In a rodent model of abdominal aortic aneurysm rupture, a complement C₅a receptor antagonist attenuated lung and intestinal permeability indices and lung myeloperoxidase activity compared to controls (37). Clinically, activation of both complement and neutrophils occurs in patients with ARDS or burns (38,39), and circulating plasma levels of C₃a correlate with severity of injury and outcome in patients with multiple trauma (40). Evidence of complement and neutrophil activation has also been found in bronchoalveolar lavage (BAL) from patients with ARDS (41). Administration of a C₁-inhibitor in patients with severe sepsis and septic shock reduces neutrophil activation (42) and improves renal function and SOFA scores compared to untreated control patients (43).

Reactive oxygen species—superoxide anion, hydrogen peroxide, and the hydroxyl radical—are released by activated PMNs and can injure tissues by damaging DNA, cross-linking cellular proteins, and causing peroxidation of membrane lipids (44,45). Lipid peroxidation diminishes membrane fluidity and increases membrane permeability, thereby impairing cellular function. The conclusion that toxic oxygen radicals are important in the pathophysiology of respiratory dysfunction comes from clinical studies of patients with ARDS where plasma levels of lipid peroxides are elevated, levels of hydrogen peroxide are increased in the expiratory condensate (46), and oxidative damage to proteins in BAL fluid is found (47). In addition, patients with ARDS have reduced levels of oxygen radical scavengers (e.g., α-tocopherol, ubiquinone, and glutathione), a sign of “oxidant stress” (48,49). Despite these data, antioxidant therapies have not translated into improved outcome for patients with ARDS or MODS, although such interventions may increase the number of days “free” of acute lung injury (50) or mechanical ventilation (51), decrease the incidence of new organ failures (51), and reduce the oxidative stress during septic shock (52).

The Kallikrein-Kinin System

The kallikrein-kinin system is part of the contact system, and is composed of complement, coagulation, and kallikrein-kinins. Bradykinin, the end product of this cascade, is a potent vasodilator and increases vascular permeability. Some of these effects are mediated by the release of secondary mediators, such as nitric oxide and eicosanoids. Although some experimental and clinical data suggest that the kallikrein-kinin system is important in the pathogenesis of sepsis and MODS, a clinical trial of a bradykinin receptor antagonist (CP-0127) for the adjunctive therapy of sepsis failed to alter the 28-day mortality (53).
Section V: Modulating the Response to Injury

The Coagulation System

LPS and many proinflammatory mediators will activate the coagulation system (Fig. 54.5). Coagulation in sepsis or inflammatory states is initiated primarily by the extrinsic tissue factor–dependent pathway, as these mediators induce the expression of tissue factor (TF) on monocytes and endothelial cells (54). Although these same mediators activate the fibrinolytic system, subsequent increases in plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) effectively suppress fibrinolysis. Important inhibitors of coagulation such as antithrombin, tissue factor pathway inhibitor (TFPI), protein C, protein S, and endothelial-bound modulators—heparan sulfate and thrombomodulin—may be down-regulated (34). Consequently, there is a net procoagulant tendency with the potential for the development of disseminated intravascular coagulation (DIC). DIC can cause microvascular thrombosis and organ failure, and/or bleeding from consumption of platelets and clotting factors (55,56). Recombinant human activated protein C has been shown to reduce the relative risk of death in patients with severe sepsis by over 19%, at least in part by its inhibition of the coagulation cascade (37).

Prostaglandins, Leukotrienes, and Platelet-Activating Factor

Prostaglandins (PGs), leukotrienes (LTs), and platelet-activating factor (PAF) are potent lipid mediators formed by the stimulation of a membrane-bound enzyme, phospholipase A2 (PLA2), via a variety of mediators including norepinephrine, adenosine, bradykinin, PAF, tumor necrosis factor (TNF), and interleukin (IL)-1β (58). PLA2 catalyzes membrane phospholipids to lyso-PAF and arachidonic acid (Fig. 54.6). Both experimental and clinical studies support the notion that these mediators play a role in the pathophysiology of sepsis and MODS. Elevated plasma levels of thromboxane B2 (TXB2), the metabolite of the prostaglandin thromboxane A2 (TXA2), are observed in animal models of sepsis and are correlated with organ injury and outcome. Inhibitors of cyclo-oxygenase and thromboxane synthase abrogate the organ injury and improve survival. Clinically, elevated plasma levels of TXB2 and PGI2 have been measured in patients with Gram-negative septic
shock and correlate with the severity of organ failure and survival. However, clinical trials of nonselective inhibitors of cyclooxygenase (ibuprofen) have failed to show any effect on survival (59), and a recent trial evaluating the effectiveness of a selective inhibitor of a group IBA secretry phospholipase in patients with suspected sepsis and organ failure showed no survival benefit nor effect on organ dysfunction (60). The anti-fungal agent, ketocanazole, is an imidazole derivative that inhibits thornbomocyte synthase. Use of ketocanazole in patients at risk for ARDS prevents the development of ARDS (61,62); however, once ARDS is established, this agent is ineffective at reversing the syndrome or improving survival (63). Other clinical trials evaluating inhibitors of prostaglandin production have been underpowered to show any effect.

A significant role of leukotrienes in the pathobiology of the cardiovascular dysfunction observed in sepsis is unlikely, since the administration of leukotrienes (LTc4 and LTD4) to primates and sheep results in increased systemic vascular resistance and depressed cardiac output. However, intratracheal administration of these leukotrienes in animals results in a significant increase in capillary permeability, leading to a pattern of pulmonary edema not consistent with ARDS. Furthermore, elevated concentrations of LTB4, LTC4, and LTD4 have been measured in the BAL fluid recovered from patients with ARDS. Although leukotriene receptor antagonists have improved pulmonary hemodynamics and oxygenation in experimental sepsis studies, no clinical trials using these agents for sepsis or ARDS have been performed.

A large amount of data exists supporting the role of PAF in the pathogenesis of sepsis and MODS. In vitro, incubation of macrophages with PAF will lead to an exaggerated release of TNF and tissue factor by these cells following exposure to LPS. Conversely, LPS-induced release of TNF by macrophages is inhibited by PAF receptor antagonists. PAF expression on the surface of endothelial cells will result in PMN adherence and activation. In addition, stimulation of PAF receptors on the endothelium results in changes in cell shape and cytoskeletal structure. In animal models of endotoxemia, elevated plasma levels of PAF have been measured and are associated with many of the physiologic abnormalities seen in sepsis: myocardial dysfunction, vasodilation, and microvascular permeability. Infusion of PAF into animals reproduces many of the findings observed in endotoxins or sepsis. In animal models of sepsis, PAF receptor antagonists have had variable effects on outcome; however, most studies have demonstrated an improvement in organ function (58). Clinically, depressed plasma levels of PAF are associated with a better outcome in patients with sepsis, and plasma levels of PAF have been observed in critically ill patients and correlate inversely with organ dysfunction. However, a phase II trial of recombinant PAF-AH failed to improve outcome or prevent organ dysfunction (64). A subsequent study of critically ill patients revealed that plasma levels of PAF-AH were variable over time and with severity of illness (65). Such a finding provides a partial explanation for the lack of efficacy of recombinant PAF-AH.

**Cytokines**

Cytokines are small proteins that are secreted by nearly all nucleated cells and exhibit autocrine, paracrine, or endocrine activity (66,67); they are generally classified as proinflammatory or anti-inflammatory molecules. This classification, however, is somewhat arbitrary as an individual cytokine may act in either a proinflammatory or anti-inflammatory fashion depending on the underlying biologic process. Proinflammatory cytokines such as TNF and IL-1 can stimulate the release of other mediators: PAF, nitric oxide, LTs, and PGs.

TNF assumes an important role in the pathogenesis of human sepsis, septic shock, and MODS. TNF is directly cytotoxic to some cell types and will induce the expression of adhesion molecules on neutrophils and endothelial cells to promote the recruitment of these white cells to the site of injury or infection. Furthermore, endothelial permeability is increased. Metabolic effects attributable to TNF include activation of the acute-phase response, fever (along with IL-1), skeletal muscle catabolism, and increased peripheral lipolysis and hepatic lipogenesis (67). When injected into normal volunteers, small doses of LPS or recombinant TNF will reproduce many of the metabolic and hemodynamic changes observed in sepsis (68,69). Similar findings are observed in animal studies, and treatment with anti-TNF antibodies will prevent many of the adverse consequences of endotoxic or live Gram-negative bacterial shock (70). However, in studies of critically ill patients, the correlation of plasma TNF levels and outcome is variable (71,72). Such disparate results may be due to timing and method of the TNF assay, as well as to the acuity, etiology, or treatment of the patient’s illness, or genetic differences in patients. Results from multicenter studies of adjunctive therapy with either anti-TNF antibodies or soluble TNF receptors have demonstrated that neither passive immunization nor the soluble receptors reduce mortality from sepsis. However, in one recent trial where patients were treated according to the initial plasma levels of IL-6 (as a marker of severity of illness), outcome was improved, and organ dysfunction was ameliorated with the administration of an monoclonal antibody to TNF (73).

Like TNF, IL-1 has a wide variety of biologic actions and has been implicated in the pathogenesis of sepsis and MODS (74). In addition, TNF and IL-1 will often act in a synergistic fashion. IL-1 induces the expression of cyclooxygenase (COX)-2 and iNOS expression (75). Furthermore, IL-1 increases the expression of other cytokines—most notably TNF and IL-6—chemokines, adhesion molecules, and a number of tissue proteases and matrix metalloproteases (75). IL-1 also stimulates the release of myeloid progenitor cells, resulting in neutrophilia (75). Animal models suggest a role for IL-1 in the pathogenesis of sepsis and MODS, and the use of IL-1 receptor antagonist (IL-1RA) is beneficial in several human inflammatory diseases (e.g., rheumatoid arthritis). However, use of IL-1RA in patients with sepsis does not reduce mortality nor reverse organ failure (76–78). Interleukin 6 (IL-6) is another cytokine that has been identified to be important in the response to infection and development of MODS. Small doses of endotoxin administered to normal volunteers will stimulate the release of IL-6 (79). IL-6 will persist for longer periods of time in the blood than other cytokines and may serve as an important marker for the outcome of patients with sepsis or septic shock. Both the IL-6 receptor and the signaling receptor gp130 are required for the biologic activity of IL-6 to be realized (79). Murine models of hemorrhagic shock indicate that IL-6 is important in the development of gut barrier dysfunction (see below) (79). In addition, IL-6 may be important in promoting thrombosis during sepsis. Passive immunization with an anti-IL-6 antibody reduces activation of the coagulation cascade in a primate model of
Modulating the Response to Injury

Endotoxins but has no effect on the coagulation abnormalities associated with low-dose LPS in humans (80). IL-8 is a chemotactic cytokine (chemokine) and is expressed principally by monocytes and macrophages by stimulation with LPS, bacteria, TNF, and IL-1 (81). IL-8 induces chemotaxis of inflammatory cells, and its presence at sites of inflammation may persist for long periods of time (81). That IL-8 is important in the development of MODS is demonstrated by the observation of high IL-8 levels in BAL fluid from patients with ARDS or pneumonia (82). Although neutralizing IL-8 may reduce cardiac ischemia/reperfusion injury in dogs, a reduction in chemokines increases mortality in animal models of pneumonia (81).

High-mobility group box 1 (HMGB1) is a cytokine that was discovered over 30 years ago, but its importance as an inflammatory mediator was appreciated only recently (Fig. 54.7) (83). HMGB1 is released from a variety of cells in response to LPS or bacteria, and the response is delayed (84). Exposure of the lung to HMGB1 increases neutrophil accumulation, edema, and other proinflammatory cytokines, whereas gastrointestinal exposure results in increased gut permeability and translocation of bacteria to mesenteric lymph nodes (84). Administration of this cytokine to animals causes death as a result of epithelial barrier disruption. Treatment of experimental endotoxicosis or sepsis with antibodies to HMGB1 or HMGB1 antagonists improves survival (83,85). There have been no clinical studies to evaluate the efficacy of anti-HMGB1 therapies in sepsis or other inflammatory conditions.

Nitric Oxide

Nitric oxide (NO) is an inorganic free-radical gas, produced by catalysis of one of the terminal guanidine nitrogens of L-arginine by the NO synthase (NOS) group of enzymes (89). Two general classes of NOS have been described: Constitutive (calcium-dependent) NOS (neuronal and endothelial) and inducible (calcium-independent) NOS (90). The production of the latter enzyme is induced by LPS, TNF, and a variety of other inflammatory mediators. A variety of cells and tissues release NO, including endothelium, vascular smooth muscle, neutrophils, and mononuclear, glial, mast, hepatic, and adrenal medullary cells (90). Vasorelaxation, neurotransmission, and microbicidal activity are some of the important functions that NO possesses. The role that NO plays in the host is a function of the rate and timing of its production and the surrounding

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**Figure 54.7**: Inflammatory responses in various areas of the host that are mediated by high-mobility group box 1 (HMGB1). tPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor. (Reproduced from Wang H, Yang H, Tracey KJ. Extracellular role of HMGB1 in inflammation and sepsis. J Intern Med. 2004;255:320-331, with permission.)
environment. Normally, NO acts as a direct signaling molecule (e.g., vasorelaxation and neurotransmission), and low levels of NO (produced by constitutive NOS and at times by inducible NOS) have protective effects (Fig. 54.8) (90). Alternatively, it may function as an indirect cytotoxic agent and induce intestinal barrier dysfunction.

A significant amount of experimental and clinical evidence suggests that NO plays an important role in the pathophysiology of sepsis and MODS. Inducible NOS and NO production increase in animals during both endotoxic and hemorrhagic shock. iNOS-deficient mice are protected from LPS-induced hypotension, and have a higher survival following endotoxemia (91). NO contributes to TNF-induced cardiac dysfunction in a concentration-dependent fashion (92). Increased urinary excretion of NO metabolites (nitrite and nitrate) has been reported in septic patients and correlates inversely with systemic vascular resistance (SVR) (91).

Excess NO in the presence of superoxide anion results in the formation of peroxynitrite (ONOO⁻), a reactive oxidant that causes lipid peroxidation, inhibits mitochondrial respiration, inactivates glycolaldehyde-3-phosphate dehydrogenase, inhibits membrane sodium/potassium ATP activity, and triggers DNA single-strand breakage. As mentioned previously, DNA damage activates the nuclear enzyme, PARP, which can lead to cellular energy depletion and death (93). Furthermore, excessive amounts of NO and peroxynitrite can activate the transcription factor, NFκB, and amplify the inflammatory response (94).

The efficacy of inhibitors of NOS in the treatment of sepsis and MODS is unclear, and the use of some inhibitors may actually be detrimental. Although hypotension, vascular leak, and vasopressor requirements can be reduced with the use of non-specific NOS inhibitors, microcirculatory blood flow can be altered, resulting in organ injury. Indeed, a large randomized, prospective trial evaluating the efficacy of the nonselective NOS inhibitor, L-N⁵-monomethylarginine, in patients with septic shock was stopped early because the death rate was higher in the intervention group (95).

THE ENDOTHELium

The role of the vascular endothelium is to control the flow of nutrients, blood cells, and a broad array of biologically active molecules to the tissues; this is achieved via membrane-bound receptors for a plethora of molecules and through tight junction relationships (96). Endothelial cell injury may well impair the delivery of nutrients to tissues and allow the extravasation of proinflammatory mediators into the interstitial space.

There is a large amount of data supporting the role of an impaired endothelium in the development of MODS. Endothelial cell exposure to LPS will cause anatomic changes including nuclear vacuolization, cytoplasmic swelling and fragmentation, and detachment from the internal elastic lamina (97). In humans with septic shock, elevated levels of circulating endothelial cells can be detected and correlate with outcome. High plasma levels of molecules that are expressed on the surface of endothelial cells (i.e., thrombomodulin [TM], intercellular adhesion molecule [ICAM]-1, and E-selectin) are observed during sepsis and acute lung injury, and are an indirect indication of endothelial damage (98). Furthermore, this injury appears to be sustained, as injection of small doses of LPS into human volunteers will result in high plasma levels of TM that peak at 24 hours and of TF that are still increasing at 48 hours (96).

In the uninjured state, the endothelial cell has important antioxidants properties. Several heparin-like molecules are expressed on the surface of the cells to accelerate the inactivation of serine proteases of coagulation by antithrombin (96). Thrombomodulin binds thrombin and forms a complex that activates protein C. However, exposure of the endothelial cells to inflammatory or septic mediators will shift the endothelial cells to a procoagulant state by increasing expression of TF and internalization of TM. Furthermore, the endothelial cell will have impaired release of tissue plasminogen activator and an increased release of PAI-1. This procoagulant/antifibrinolytic state is associated with fibrin deposition, platelet consumption,
microthrombi, tissue ischemia and necrosis, and an increased risk of death (99).

Leukocytes and monocytes can migrate into tissues, they must adhere to the endothelium. This process is accomplished by the local synthesis of PAF and cytokines (IL-1, IL-8, and TNF), which stimulates the expression of surface molecules called selectins on leukocytes (L-selectin) and endothelial cells (E-selectin). The interplay between these selectins allows loose binding of the leukocyte to the endothelium. Leukocytes are bound more strongly to the endothelium by the interaction between the CD11/CD18 complex, which is expressed on the leukocyte, and the ICAM-1, which is expressed on the endothelial cell membrane. The role of leukocyte adhesion in the development of MODS is suggested by several lines of evidence. In animal models of sepsis, endotoxosis, or ischemia/reperfusion, monoclonal antibodies to the CD11/CD18 integrin or to L-selectin will improve organ dysfunction (100). Knockout animals lacking either ICAM-1 or E-selectin have improved survival during experimental sepsis (101). Clinically, plasma ICAM-1 levels are higher in patients with septic shock than in healthy controls or patients with SIRS (98), and the levels correlate with the severity of shock.

Endothelial-derived relaxation is also impaired in sepsis, and such alteration may contribute to MODS. Acetylcholine-induced relaxation of aortic rings obtained from septic animals is attenuated. In animals with chronically overexpressed endothelial cell nitric oxide synthase (eNOS), resistance to LPS-induced hypotension, lung injury, and death are observed (96). In normal volunteers, small doses of LPS will also impair endothelium-dependent relaxation for days (102). These data help explain the observations that reactive forearm hyperemia is attenuated in patients with sepsis. In addition, the importance of intact eNOS in these patients is supported by the observation that treatment of patients with septic shock by nonselective NOS inhibitors is associated with no change or an increase in mortality compared to untreated patients (95).

**Derangements in Gut Barrier Function**

Although epithelial barrier function in the intestine may be altered during sepsis and other inflammatory states, thereby allowing bacterial translocation to occur, there are other components of the gut barrier that will prevent the bacteria or bacterial products from gaining access to systemic organs (107). In addition to alterations in the epithelial barrier described previously, other clinical conditions that can contribute to altered gut barrier function include antibiotics, stress ulcer prevention, hypoaalbuminemia, vasoactive agents, and use of hypersmolar feeding preparations. The clinical importance of the disrupted gut barrier function in the pathogenesis of MODS remains ill defined at this point.

**APOTOPSIS**

Apoptosis (programmed cell death) is the term used to describe a specific method by which cells die. The event is a well-defined, active, and energy-dependent process. There are two primary pathways involved in apoptosis. The intrinsic (mitochondrial and endoplasmic reticulum) pathway and the extrinsic (“death receptor”) pathway (108). The latter pathway is activated by receptors such as Fas, with the subsequent activation of two enzymes, caspase-8 or -10. The intrinsic pathway stimulates caspase-9 by loss of the mitochondrial membrane potential and movement of cytochrome c into the cytosol. These initiator caspases cleave effector caspases (e.g., caspase-3 and -7), which results in the cleavage of cellular proteins and DNA and, ultimately, apoptosis (109).

The exact role of apoptosis in the development of MODS is unclear. In animal models of infection, lymphocyte, endothelial cell, kidney, lung, and skeletal muscle, apoptosis is increased (110). Data from clinical studies show that up-regulation of apoptotic pathways is increased in patients with ARDS (111). Furthermore, widespread apoptosis occurs in splenic and colonic lymphoid populations in patients who die from sepsis and MODS (112,113). The effect of apoptosis on the immune function includes loss of various immune cells and impairment of immunity by apoptosis-induced immunosuppression of the remaining immune cells (114). Therapies directed against these programmed pathways are under intense investigation and include inhibition of cytochrome c release, use of RNA interference for gene silencing, and caspase inhibitors (114).
Chapter 54: Multiple Organ Dysfunction Syndrome

**COMPLEX NONLINEAR SYSTEMS**

The body may be considered a biologic network that is complex, highly coupled, and nonlinear (115). The host response to trauma, shock, or sepsis—invoking metabolic, neural, endocrine, inflammatory, and immune components—is such an example (116). The behavior of such a system cannot be predicted with great reliability; however, the system is “attracted” to specific states or stable configurations: “organized variability” (116,117). A large enough perturbation to an organ or mediator network may have unexpected and significant results elsewhere in the host and ultimately lead to MODS (118). In the healthy individual, there is a high degree of heart rate (beat-to-beat) variability. Several studies have shown a relationship between loss of heart rate variability and increased mortality in critically ill patients (119). In fact, normal volunteers injected with small doses of LPS exhibit loss of heart rate variability (120). Other examples of increased regularity of rhythms associated with disease include Cheyne-Stokes respiration, parkinsonian gait, neutrophil count in chronic myelogenous leukemia, and fever in Hodgkin disease (117). However, several diseases—acromegaly and Cushing disease—are associated with increased complexity (117). These data suggest that health is determined by “distance” from thermodynamic equilibrium: too much or too little variation (low or high entropy) represents pathologic conditions (117). A causal link between perturbations in complex systems and outcome remains elusive. However, following variability over time might allow greater accuracy in patient prognostication or may suggest a medical intervention (121). For example, a low level of complexity in the temperature curve of critically ill patients with MODS portends a poor prognosis (122). More research is needed into nonlinear dynamics to determine its importance and role in the development of MODS.

**GENETIC SUSCEPTIBILITY**

Single base variations in DNA—single nucleotide polymorphisms (SNPs)—are commonly used to discern genetic differences among patient populations (123). Approximately 1 in every 1,000 bases in the human genome is different between two unrelated individuals (123). Although more than 10 million SNPs have been mapped, only 4% of these occur in genes. By comparing healthy individuals to patients, SNPs involved in disease can be identified. Indeed, some—but not all—clinical studies have documented an increased risk of death and organ dysfunction in patients suffering from sepsis or ARDS and who are homozygotes for SNPs (124–128). In the future, patients may be identified in advance as to who should be monitored more closely or who might be benefit from certain interventions (e.g., anticytokine therapies) (123).

**PREVENTION AND TREATMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME**

Although much progress has been made in our understanding of the pathogenesis of MODS, our knowledge remains incomplete. Consequently, the prevention and treatment of MODS are nonspecific and include the goals of maintaining adequate tissue oxygenation, finding and treating infection, providing adequate nutrition support, minimizing iatrogenic complications, and when necessary, providing artificial support (e.g., dialysis or mechanical ventilation) for individual dysfunctional organs.

### Resuscitation

An episode of circulatory shock is probably the most common event that occurs before the development of MODS. As a result, timely restoration of intravascular volume and oxygen delivery is important in preventing or abrogating MODS in high-risk patients.

Controversy continues regarding the correct fluid for resuscitation and the optimal circulating hemoglobin concentration. Crystallloid solutions are efficacious and cheaper than colloid solutions. In a prospective study of a diverse population of critically ill patients comparing the efficacy of normal saline to albumin for fluid resuscitation, there was no overall difference in outcome—death, length of stay, or organ dysfunction—between the two groups (129). Subgroup analysis demonstrated an increased relative risk of death for trauma patients who received albumin, whereas the relative risk of death for severe sepsis patients was higher if saline was used (129). Colloids or hypertonic crystallloid solutions—or colloid/hypertonic crystallloid mixtures—may have beneficial effects on the inflammatory response or the development of edema, and may allow for faster resuscitation (130), but these effects have not been proven to be of overall value when these solutions are used clinically.

Assessing the adequacy of tissue oxygenation can often be difficult. The clinical parameters used most often, including arterial blood pressure, skin color, temperature, urine flow, mixed venous oxygen saturation, and blood-lactate concentrations, may be unreliable. Since observational studies have shown that “supranormal” levels of DO2 (660 mL/minute/m2), VO2 (170 mL/minute/m2), and cardiac index (4.5 L/minute/m2) are associated with higher survival rates, some clinicians have advocated resuscitation to such end points in critically ill patients. Although some studies of patients undergoing high-risk surgery or suffering from trauma suggest that such an approach may be of benefit, the majority of studies over the past 15 years clearly show that resuscitation to these end points in critically ill patients is of no benefit, or actually worsens outcome. Likewise, the use of the pulmonary artery catheter to guide therapy has not been shown to be of benefit in a large number of studies (131–133) and pulmonary capillary wedge pressure does not accurately reflect ventricular volume, even in normal volunteers (134). Less invasive and probably safer monitors have been developed for monitoring cardiac output that compare favorably with the accuracy of the thermodilution method. Use of systolic blood pressure variation, pulse pressure variation, stroke volume variation, or left ventricular end-diastolic area (as assessed by transesophageal echocardiography) may be of greater benefit to guide volume resuscitation than the use of pulmonary capillary wedge pressure. More recent data suggest that such aggressive resuscitation in the ICU may be too late. Early (i.e., in the emergency department before hospital admission), goal-directed therapy can reduce mortality and organ dysfunction in patients with severe sepsis and septic...
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Mechanical Ventilation

The method by which patients are mechanically ventilated can contribute to organ dysfunction. A plethora of experimental and clinical data indicate that overdistension of the lung through the use of large tidal volumes will cause lung injury, stimulate the release of inflammatory mediators, and effect derangements in organs other than the lung (143–145). Use of small tidal volumes (6 mL/kg) in the care of patients with ALI and ARDS will decrease mortality and increase ventilator-free and organ failure–free days (146). It is crucial to note that oxygenation cannot be used as a proxy for efficacy of therapy since patients who are ventilated with small tidal volumes require a longer period of time before PaO$_2$ improves.

Cyclic “opening” and “closing” of collapsed airways during tidal ventilation is also thought to cause lung injury (147). A recent small study of patients with ARDS suggests that the use of positive end-expiratory pressure (PEEP) above the lower inflection point of the respiratory system compliance curve reduces mortality and the number of failed organs compared to control patients (148). However, this concept has been called into question by data demonstrating that efforts to improve recruitment of collapsed lung units with high levels of PEEP do not reduce mortality or duration of mechanical ventilation (149) and a computed tomography (CT) scan investigation of patients with ARDS showing that ventilator-induced hyperinflation rather than cyclic recruitment/derecruitment is associated with a greater release of pulmonary inflammatory mediators (150).

Other methods of improving oxygenation in the patient with ARDS or ALI, such as the recruitment maneuver and the prone position, have been attempted. However, prospective randomized studies (151,152) have failed to demonstrate an outcome benefit to these approaches.

Fluid management is also an important component in the care of the patient with ARDS or ALI. Recent data show that a restrictive fluid strategy where cumulative fluid balance is kept close to zero in these patients improves the oxygenation index and increases the number of ventilator-free days without increasing the number of other organ failures (153).

Acute Renal Failure

Acute tubular necrosis (ATN) accounts for over 75% of the cases of acute renal failure (ARF) in the ICU (154), with a mortality rate ranging from 40% to 80%. The most common insult that predisposes ICU patients to ATN is persistent prerenal azotemia (154). Furthermore, in the critically ill patient, there is often more than one insult to the kidney: sepsis; exposure to aminoglycosides, amphotericin B, or radiographic contrast agents; and the administration of nonsteroidal anti-inflammatory agents. Efforts to minimize these insults to the kidneys should be maximized. Timely resuscitation as mentioned previously is very important to prevent renal ischemia (155,156). If aminoglycosides must be used to treat infection, once-daily dosing (156) or the use of drug levels to discern pharmacokinetics (157) appears to reduce the risk of nephrotoxicity. Use of liposomal preparations of amphotericin B reduces the risk of renal damage (156). If patients are to receive contrast agents, hydration with sodium bicarbonate solutions have been shown to reduce the risk of subsequent renal dysfunction (158). Although N-acetylcysteine has been purported to reduce the risk of contrast-induced ARF (139), the observed results may be a reflection of the activation of creatinine kinase or an increase in the tubular secretion of creatinine (156). Medications such as “low-dose” dopamine or fenoldopam, which increase renal blood flow or loop diuretics, have no impact on preserving renal function in high-risk patients and should be avoided (156).

The various methods of renal replacement therapy for patients with established renal failure are beyond the scope of this chapter; the reader is referred to Chapter 161.

Debridement of Necrotic Tissue and Fracture Stabilization

The presence of dead or devitalized tissue appears to predispose patients to the development of MODS; timely debridement of dead tissue is an important component in the prevention of the syndrome. Early surgical fixation of major lower extremity fractures will result in a lower incidence of ARDS and pneumonia. However, “damage control” orthopedics has recently gained popularity and is a concept whereby fractures are initially treated with external fixation. Definitive therapy occurs later when the patient is more stable. The inflammatory response appears to be attenuated in these patients, and the incidence of organ dysfunction is no higher compared to patients with established renal failure are beyond the scope of this chapter.

Infection

Sepsis is an important cause (or correlate) of MODS. It is important that the presence of infection is excluded in critically ill patients with signs of deteriorating organ function.
Empiric administration of broad-spectrum antibiotics is often necessary in the patient with suspected infection. Failure to administer adequate antibiotics (163) in a timely fashion (162) can increase the risk of death for the patient.

**Intra-abdominal Sepsis**

Early and adequate drainage of intra-abdominal sepsis is important to prevent the development of MODS. Some surgeons have advocated multiple planned reoperations or open packing for severe cases of intra-abdominal sepsis or necrotizing pancreatitis. However, recent retrospective studies have questioned the utility of the open abdomen for intra-abdominal sepsis therapy because ICU and hospital length of stay and hospital rates appear higher than in matched controls (163). Randomized, prospective trials will be needed to determine when the open approach is optimal; one such trial is under way for patients with pancreatitis (164). Without clinical or radiologic evidence of intra-abdominal infection, “blind” laparotomy in the patient with worsening MODS is unlikely to be fruitful.

**Pulmonary Sepsis**

Ventilator-associated pneumonia (VAP) can play a role in the development and course of MODS; this is discussed in more detail in Chapter 111. Proven preventive measures include non-invasive positive pressure ventilation, elevation of the head of the bed (165), continuous subglottic suctioning, weaning protocols, optimization of sedation with daily “wake-ups” for the patient (166), and chlorhexidine oral rinse.

Selective digestive decontamination (SDD) is a technique by which topical nonabsorbable antibacterial and antifungal agents (usually with a concomitant 3- to 5-day course of systemic antibiotic therapy) are applied to the oropharynx and proximal bowel in mechanically ventilated patients to reduce the incidence of nosocomial infections, organ dysfunction, and mortality. A meta-analysis of 57 randomized controlled trials demonstrated a favorable effect on bloodstream infections and mortality (167). Fears concerning the emergence of resistance organisms do not appear to be well founded. SDD may very well reduce the incidence and prevalence of colonization with resistant Gram-negative aerobic bacteria (168). However, the use of SDD in the United States does not enjoy widespread popularity for reasons that are unclear.

**Catheter-related Sepsis**

Catheter-related bloodstream infections (CRBSIs) may contribute to the development and propagation of MODS. Proven strategies to reduce the risk of CRBSIs include handwashing prior to catheter insertion, use of maximum barrier precautions (cap, mask, sterile gloves and gown, and a large sterile drape that covers the patient), use of an aseptic cholangitis skin preparation solution, avoiding the femoral site for catheter insertion, and removing catheters when no longer needed (169). If these measures are ineffective in reducing the risk of infection, catheters with antiseptic surfaces (170,171) or impregnated with antibiotics (172) or the use of chlorhexidine dressing sponges can reduce the risk of infection.

**Other Sources of Sepsis**

Many other sources of infection in critically ill patients may contribute to the development of MODS. These infections are not always readily apparent, and the practitioner caring for the patient should remain alert to their presence. Some of these sources of infection include purulent sinusitis, suppurative rhomboiditis, otitis media, perirectal abscess, epididymitis, prostatitis, and calcific cholecystitis (173), meningitis or brain abscess (particularly after instrumentation of the central nervous system), prosthetic intravascular graft infection, lower or upper urinary tract infection, and endocarditis. Physical examination and appropriate laboratory and radiographic studies should exclude these conditions.

**Nutrition Support**

Malnutrition can contribute to the morbidity and mortality of sepsis and MODS (see Chapter 64). Prooxidation is a prominent finding in sepsis and, although it cannot be suppressed by infusing amino acids, protein anabolism can be achieved by appropriate nutritional support. Furthermore, cathelalbumin is mediated by endogenous cathelalbumin, and administration of d-adrenergic blocking agents can reverse the hypermetabolic response and protein catabolism (174). Early nutritional support may be beneficial in patients at risk for developing MODS (175). The consensus among experts is that if nutritional support is started, enteral feeding is preferable to the parenteral route in a variety of critically ill patients (176).

Regardless of the route of feeding, overfeeding should be avoided. The excessive administration of carbohydrates can alter the respiratory quotient with adverse effects on weaning from mechanical ventilation and affect hepatic metabolic function, thereby altering drug clearance and inducing hyperglycemia. Current guidelines for the use of hypermetabolic patients with sepsis or MODS include a total caloric intake (exclusive of protein) of 20 to 25 kcal/kg/day to 5 g/kg/day of glucose, plus 0.5 to 1.0 g/kg/day of fat, and 1.2 to 1.5 g/kg/day of protein. The number of calories needed for a given patient can be estimated using the Harris-Benedict equation or refined using indirect calorimetry.

Hyperglycemia can be a difficult problem, even when patients are not being fed. A strategy using a continuous infusion of insulin to maintain a range of serum glucose of 80 to 110 mg/dl in surgical patients can reduce mortality and organ dysfunction (e.g., renal failure and critical illness polyneuropathy) (177). In medical ICU patients, morbidity, but not mortality, is reduced with such an intensive insulin regimen (178). Such a strategy is cost effective, with average savings of over $1,500 per patient (179). Maintenance of normal serum glucose levels appears to be the factor associated with the favorable outcome rather than the insulin dose (180).

**Specialty Formulas**

A number of enteral nutritional formulas are available that provide specific nutrients: glutamine, peptides, arginine, omega-3 fatty acids, nucleic acids, and antioxidants (e.g., vitamin E and β-carotene). Arginine is the substrate for NO synthase and is important in lymphocyte proliferation and wound healing (181). Omega-3 fatty acids change membrane lipid composition and can alter the inflammatory response (182). Nucleic acids assist in the proliferation of lymphocytes and intestinal crypt cells, as well as DNA and RNA synthesis (183). Several enteral nutrition formulas are available that include combinations of these additives. The Canadian Critical Care Clinical Practice Guideline Committee (183) recommends that arginine...
## Table 54.4  
### SUGGESTED STRATEGIES FOR THE PREVENTION OF MULTIPLE ORGAN DYSFUNCTION SYNDROME

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>1. Prevention of hospital-acquired infection</strong></td>
<td></td>
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</tbody>
</table>
  a. Prevention of catheter-related bloodstream infections  
  - Implementation of educational initiatives  
  - Use of chlorhexidine solution for skin preparation  
  - Use of maximum barrier precautions  
  - Avoidance of the femoral insertion site  
  - Removing catheter as soon as possible when no longer needed  
  b. Strict infection control measures and hand hygiene |
| **2. Metabolic control and support** |  
  a. Strict glucose control  
  b. Early enteral nutrition |
| **3. Early and appropriate treatment of infection and trauma** |  
  a. Early goal-directed therapy for severe sepsis  
  b. Early and aggressive resuscitation of trauma victims  
  c. Prompt eradication of documented sources/foci of infection  
  d. Early fracture stabilization in multiple trauma  
  e. Appropriate empiric antibiotic therapy according to consensus guidelines where available with earliest possible de-escalation of therapy according to culture results |
| **4. Prevention of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and ventilator-associated and aspiration pneumonia** |  
  a. Elevation of the head of bed to 30 degrees in all patients without spine precautions  
  b. Stress gastritis prophylaxis according to consensus guidelines  
  c. Lung protective ventilation strategies in patients with ALI/ARDS  
  d. Implementation of weaning protocols  
  e. Daily sedation holidays  
  f. Chlorhexidine oral rinse  
  g. Selective decontamination of the digestive tract |
| **5. Prevention of acute renal failure** |  
  a. Normal saline administration to prevent contrast-induced nephropathy with the addition of sodium bicarbonate or N-acetylcysteine as indicated  
  b. Discontinuation of nephrotoxic drugs whenever possible; consider once-daily dosing regimens for aminoglycoside antibiotics |

and other “select” nutrients not be used for enteral nutrition. However, in patients with ARDS, a formula supplemented with fish oil, borage oil, and antioxidants should be used (183). Although routine use of glutamine is discouraged, in patients with trauma and burns, enteral glutamine should be considered (183).

### Summary

Standard therapy for patients with MODS includes adequate cardiovascular resuscitation, identification and timely treatment of infection, early enteral nutrition, “tight” glucose control, individualized support for dysfunctional organs, and minimizing iatrogenic complications by following clinical practice guidelines based on evidence-based medicine for mechanical ventilation and prevention of ventilator-associated pneumonia and catheter-related bloodstream infections (Table 54.4) (184,185). Development of well-functioning ICU teams helps facilitate these paradigms of care. Improved outcome may be realized if patients at high risk for developing the syndrome can be identified earlier so that preventive measures can be instituted when appropriate. Because the pathogenesis of MODS involves numerous mediators, it is doubtful that all patients can be treated with a single agent or mode of therapy.

### Pearls

- MODS develops in up to 40% of critically ill patients without a diagnosis of sepsis and up to 70% of those with a diagnosis of severe sepsis. Mortality attributable to MODS rises as the number of failing organ systems increases; mortality rates in patients with one, two, or three failing organs average 30%, 50%, and greater than 70%, respectively, depending on the etiology of MODS and the organ systems involved.
- Population-based, but not individual, risks of mortality can be predicted with high degrees of precision by several severity-of-illness scoring systems and models.
- MODS may result from “single-hit” insults such as severe infection or trauma, or may evolve through several stages, each having characteristic clinical features.
- An uncontrolled focus of infection, ongoing perfusion deficits resulting in diminished tissue DO₂, injured or de-vitalized tissue, and persistent inflammation commonly initiate and sustain MODS.
- Fever or hypothermia and leukocytosis are not always the manifestations of sepsis but may represent systemic inflammation.
- TNF-α, IL-1, IL-6, IL-8, platelet-activating factor, ROS, and NO are pivotal early mediators in the host response to
infection and have multiple pathophysiologic effects relevant to MODS.

- Inappropriate regulation of the production of cytokines, eicosanoids, ROS, and NO is thought to be of causal significance in MODS, as are pathologic neutrophil-endothelial interactions and cross-talk among elements of the coagulation, complement, and kinin cascades.

- Alterations in microvascular blood flow play an important role in the pathogenesis of organ dysfunction in shock. The surface receptors and mediators associated with these alterations include oxidants, lectins, prostates, vasoactive products of iNOS, and altered adrenergic receptor sensitivity.

- Clinically occult dysfunction of the gastrointestinal (GI) mucosal barrier in the ICU is common because of splanchic ischemia from shock, and may result in endogenous endotoxemia and bacterial translocation.

- Neutrophil- and ROS-mediated intestinal I/R injury in the postresuscitation period is a potential mechanism of remote organ damage. This may lead to a domino-like sequence of organ failures.

- The liver plays a pivotal but clinically inapparent role in systemic host defense through four mechanisms. First, mononuclear phagocytes (Kupffer) cell uptake processes control the magnitude and circulating half-life of endotoxin, bacteria, and vasoactive by-products. Second, production and export of TNF-α with other mediators directly modulate lung function and cardiovascular stability. Third, hepatobiliary clearance is important in the metabolic inactivation and detoxification of such mediators. Fourth, the synthesis of acute-phase reactants regulates several key aspects of tissue metabolism and inflammation.

- Reductions in total hepatic blood flow (QL) and DO₂, or its partitioning between portal venous and hepatic arterial flows, may alter the aforementioned mechanisms, thereby influencing systemic immunoenegulation.

- Signs of established MODS are manifested differently in each organ (e.g., ARDS, ARF), yet such changes often reflect generalized endothelial injury and inflammation.

- Diverse medical conditions may mimic sepismatic-related MODS and should be excluded when appropriate. These include connective tissue diseases, intoxications, and neoplasms.

- Typical metabolic responses in MODS include hyperglycemia from insulin resistance, accelerated Cori cycle activity, and hepatic glucose release from gluconeogenesis and glycogenolysis. Hypertriglyceridemia results from TNF-α-related reductions in lipoprotein lipase activity. Hepatic lipogenesis is enhanced, increasing the respiratory quotient and minute ventilation. Marked protein catabolism from cytokine-mediated muscle proteolysis and urinary nitrogen wasting is typical.

- Early rapid resuscitation from shock, irrespective of its etiology, attenuates injury to regional organs and may decrease the incidence of MODS.

- Goal-oriented hemodynamic therapy should be initiated early (within 6 hours) after presentation and target values achieved within 12 to 24 hours.

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Section V: Modulating the Response to Injury


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