Chapter 24

THE SYNDROMES OF SYSTEMIC INFLAMMATORY RESPONSE AND MULTIPLE ORGAN DYSFUNCTION

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INTRODUCTION

Sepsis is a systemic response to an infectious process. An infection, usually caused by Gram-negative enteric bacilli, initially provokes a localized beneficial inflammatory response. However, if bacteria invade the surrounding tissue (thus gaining access to the bloodstream) and elicit an acute systemic inflammatory response by the host, myriad organ and systemic dysfunctions, possibly culminating in death, can ensue. Gram-positive organisms usually associated with suppuration, viruses, fungi, rickettsiae, and protozoa can also cause this systemic response. It is the systemic response—especially when it is manifested by cardiovascular shock and progressive, sequential dysfunction of multiple organs—that differentiates bacteremia or localized infection from sepsis. Diagnosis of an infection, however, may not be easy, as fever, leukocytosis, and a hyperdynamic "septic" state may naturally occur soon after injury.[1] Furthermore, everyday clinical use of words such as "infection" and "sepsis" does not always make this distinction.

Compounding this semantic imprecision is the confusion that the signs and symptoms themselves introduce. The signs and symptoms seen when sepsis is associated with bacterial infection are indistinguishable from those seen with noninfectious inflammatory states. Clinical conditions that mimic sepsis include pulmonary atelectasis, pulmonary emboli, hematomas, tissue necrosis, transfusion reactions, myocardial infarction, hypotension or hypovolemia from an ongoing occult hemorrhage, spinal shock, central fever, or drug fever.[1] Although infection often occurs in patients with these conditions, the conditions themselves must be considered as possible causes for a patient's deteriorating condition. Therefore, paradoxically, some patients seem to have sepsis but no microorganisms can be cultured.

In an attempt to both address the paradox and clarify the meaning of the constellation of terms revolving around "sepsis," the American College of Chest Physicians and the Society of Critical Care Medicine held a joint consensus conference in August 1991. The *Textbook of Military Medicine* uses their recommended definitions and guidelines (Exhibit 24-1).[2] The Consensus Conference introduced a new term that provides an overall conceptual and practical rubric: the systemic inflammatory response syndrome (SIRS).

The relationship of SIRS to sepsis can be demonstrated in a Venn diagram that comprises three overlapping populations (Figure 24-1): (*a*) infection, in which most of the population has neither sepsis nor SIRS; (*b*) sepsis, which is a subgroup of the infection population that by definition also has SIRS; and (*c*) SIRS, which comprises both those with sepsis and those in whom there is no apparent infectious process. The Consensus Conference recommended that sepsis be defined as the clinical condition that exists when the systemic inflammatory response state is due to *infection*, the most common cause for SIRS. For this reason, the term sepsis/SIRS will be used in this chapter.

The two most severe pathophysiological consequences of SIRS are septic shock (the most severe circulatory derangement caused by sepsis) and multiple organ dysfunction syndrome (MODS, the sequential and progressive failure of two or more organ systems). Although the terms "multiple system organ failure" and "multiorgan failure" are also to be found in the literature, this chapter uses MODS, the terminology adopted by the Consensus Conference.[2] The term SIRS/MODS, which reflects the intense relation of SIRS and MODS, will also be used.[3] MODS is most often associated with sepsis (any diffuse inflammatory stimulus may act as the initiating event), with a temporal relation to septic shock (Exhibit 24-2 and Figure 24-2).

This definition and description of MODS should not be applied to the casualty with multiple trauma who has concomitant injuries to more than one organ system. Such *primary* MODS should be distinguished from MODS that is *secondary* to sepsis/SIRS with the concomitant release of endogenous vasoactive mediator substances and is associated with such systemic manifestations of sepsis as hypotension and hypermetabolism.

EPIDEMIOLOGY

To understand the etiology and treatment of SIRS/MODS, it is first necessary to understand the circumstances in which it arises (ie, its epidemiology). The most extensive experience with this syndrome has been in civilian medicine, for not only is that patient population much larger than the population encountered by military medicine, but the conditions for providing care are much more suitable for making clinical observations. Furthermore, the military experience with SIRS/MODS is epi-

EXHIBIT 24-1

DEFINITIONS OF TERMS

Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion or normally sterile host tissue by those organisms.
Bacteremia	The presence of viable bacteria in the blood.
SIRS	*Systemic inflammatory response syndrome*; the systemic inflammatory response to a *variety* of severe clinical insults. The response is manifested by two or more of the following conditions: (1) temperature > 38°C or < 36°C, (2) heart rate > 90 beats per minute, (3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg, or (4) leukocyte count > 12,000 mm^3, < 4,000/mm^3, or > 10% immature (band) forms.
Sepsis	The systemic response to infection; manifested by two or more of the following conditions as a result of *infection*: (1) temperature > 38°C or < 36°C, (2) heart rate 90 beats per minute, (3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg, or (4) leukocyte count > 12,000 mm^3, < 4,000/mm^3, or > 10% immature (band) forms.
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
Septic Shock	Sepsis-induced, with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Sepsis-Induced Hypotension	A systolic blood pressure < 90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes for hypotension.
MODS	*Multiple organ dysfunction syndrome*; the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Data source: Bone RC, Balk RA, Cerra FB, et al. The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101:1644–1655.

sodic, depending on the random occurrence of wars. Nevertheless, the military experience with sepsis/SIRS has been of disproportionately great importance to understanding this syndrome: observations made by military physicians led to the initial concepts of the renal and pulmonary components of MODS.[4,5]

The Civilian Experience

Sepsis/SIRS and the related pathological conditions of septic shock and MODS occur in 5 to 10 of every 1,000 hospitalized patients; the rate for patients admitted to intensive care units (ICUs) is increased by 10-fold.[6,7] This equates to 100,000 to 500,000 new cases per year in the United States, with 70,000 to 300,000 cases per year arising from Gram-negative infections alone.[6,8] Of these, approximately 200,000 will develop septic shock with a mortality rate of about 50%.[8] The prevalence of SIRS/MODS appears to be increasing as a consequence of (*a*) the population of patients now receiving treatment and (*b*) advances in medicine; for example,[6]

- the care being given to an ever-increasing aged population with their associated chronic diseases;

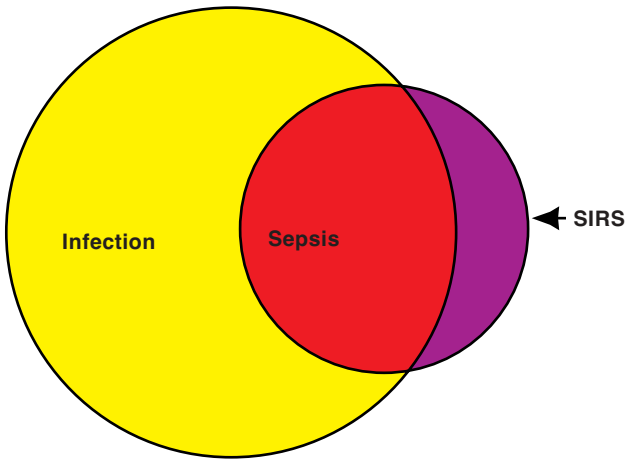

Fig. 24-1. In this Venn diagram showing the interrelation of infection, sepsis, and the systemic inflammatory response syndrome (SIRS), the large circle represents the population with infection and the small circle represents the population with SIRS. The intercept—sepsis—represents the subpopulation who have both infection and SIRS. Note that some patients with SIRS do not have sepsis. Data source: Bone RC, Balk RA, Cerra FB, et al. The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101:1645.

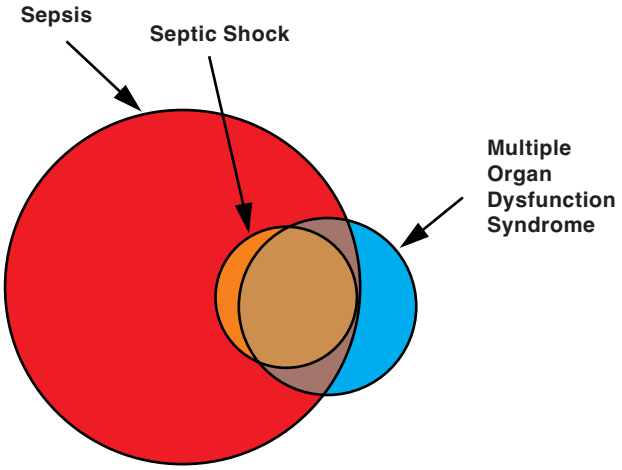

Fig. 24-2. This Venn diagram represents the interrelation of sepsis, septic shock, and multiple organ dysfunction syndrome (MODS). By definition, all patients with septic shock have sepsis, but not all patients who develop MODS have sepsis as the etiology.

EXHIBIT 24-2

KNOWN ETIOLOGY OF SEPSIS/SIRS

Microbial Agents
- Bacteria
- Viruses
- Fungi, protozoa, rickettsiae, etc

Gram-Negative Bacterial Component
- Endotoxin

Tissue Inflammation Caused by
- Multiple trauma
- Pancreatitis
- Long-bone or pelvic fractures
- Aspiration pneumonitis
- Adult respiratory distress syndrome

Tissue Hypoperfusion
- Distributive shock

- the numbers of immunocompromised patients (steroidal or chemotherapy, transplantation, human immunodeficiency virus [HIV] disease) now receiving care;
- the widespread use of antibiotics with subsequent development of resistant bacterial strains,
- an increased number of patients surviving severe trauma; and perhaps
- the sophistication, increased invasiveness, and aggressive use of current medical diagnostic procedures, interventions, and treatments.

The Military Experience

During peacetime, the epidemiology of sepsis and its related conditions is the same in the civilian and military healthcare systems with the important distinction that the military population consists of young, healthy individuals who are less likely to become ill compared to the civilian population as a whole. During wartime, injuries and diseases that may predispose to the development of sepsis have a high prevalence. In U.S. Army, attrition (as assessed by hospital admissions) has been due predominantly to disease and nonbattle injury and not due to injury that resulted from combat. The ratio of admissions to admissions for combat-related injuries ranged from 16:1 during World War I to 88:1 during World War II.[9] Most of these admissions were for relatively minor illnesses and injuries that

occurred outside the combat zone and rarely progressed to a septic state.

In contrast to the 18th and 19th centuries, death due to septic consequences of disease and nonbattle injuries has been less common during the 20th century. However, given special circumstances such as the influenza pandemic of 1917 to 1919, sepsis can be the leading cause of mortality. For example, of the 3,264,694 enlisted personnel who were admitted to the hospital for disease from April 1917 through December 1919 in the United States and Europe, 51,447 died of disease compared with 50,385 deaths caused by combat.[10–12] The most common sepsis-related disorders causing death during this period (1917–1919) included general septicemia, broncho- and lobar pneumonia, and suppurative pleurisy.[11] Although disease-related death rates have decreased in subsequent wars, diseases accounted for a large proportion of all U.S. Army hospital admissions during the Vietnam War (1965–1970): from a high of 74% in 1965 (when diseases accounted for 5,697 of 7,682 hospitalizations) to a low of 56% in 1968 (when diseases accounted for 51,082 of 91,417 hospitalizations).[12,13]

Traumatic Injury

Traumatic battle injuries pose a major threat to combat forces—vastly greater than anything seen in the civilian experience. Severe injuries often result in death. On the basis of the civilian experience with trauma, it is possible to categorize deaths from injury into three categories, based on the time of death in relation to the time of injury. *Immediate* deaths are caused by massive trauma, aortic rupture, decapitation, and so forth. These can only be prevented by measures designed to prevent trauma (eg, public safety measures, safer cars and airplanes). *Early* deaths occur during the first hour following injury and are caused by posttraumatic conditions such as hypovolemic shock or tension pneumothorax. These conditions can be effectively managed only by individuals or institutions capable of providing early interventions and therapy. (It is this category of deaths that has been the focus of the Advanced Trauma Life Support Course sponsored by the American College of Surgeons.) *Late* deaths occur during the first week after traumatic injury. Two major causes are irreversible brain injury and sepsis.[14,15] The civilian experience has been that from one third to one half of all trauma deaths fall in the *late* category. SIRS/MODS progressing to organ failure is important for anesthesiologists and critical care specialists to understand because

- the syndrome is a major cause of death from civilian trauma,
- the potential for live-saving intervention is real, and
- the need to develop effective means of prevention and treatment cannot be overemphasized.

The potential that combat-related deaths can be reduced through improved prevention and management of SIRS/MODS is less favorable. In contrast to the civilian experience, most combat-related deaths (70%–80%) are early (this is the category called *killed in action*) and only about 10% of the total fatalities occur during treatment in a hospital (*died of wounds*). By far most combat deaths are due to hemorrhage or mutilating brain injury.[16] This population does not live long enough to develop sepsis. SIRS/MODS is the cause of death in about one third of those who die while being treated (or perhaps 5% of all fatally wounded soldiers).

Trauma-Related Sepsis and Septic Shock

The traumatized combat victim is at great risk for developing sepsis. A civilian study of 437 trauma patients who sustained both blunt and penetrating injuries revealed that more than three fourths of deaths that occurred after 7 days resulted from sepsis and MODS.[15] In another study, almost 90% of deaths after 7 days in patients sustaining blunt trauma were shown to be related to sepsis.[17] And in patients sustaining thermal injury or trauma, at least 75% of deaths may, in part, be due to sepsis.[18]

Military data on posttraumatic sepsis are best delineated in statistics describing the U.S. Army's experience in World War II and the Korean and Vietnam Wars. The decrease in the died-of-wounds rate—from 8% in World War I to the overall 4.5% recorded in World War II—has been attributed to the prevention of sepsis in extremity wounds by earlier and more extensive surgery. As expected, shock and hemorrhage were the major causes of death among the hospitalized wounded, followed by infection (especially in the peritoneal cavity). Other cases of unrecognized sepsis may well have occurred in those patients whose cause of death was described as myocardial failure, anuria, pulmonary edema, or atelectasis.[19]

The incidence of true septic shock was not described outside these categories. However, in 1944 in the Fifth U.S. Army, the deaths of 1,273 hospitalized soldiers were attributed to shock. Of these, 34% resulted from trauma and hemorrhage in asso-

ciation with documented sepsis. An additional 22% might appropriately be included: those patients without recognized sepsis but who had, in addition to trauma and hemorrhage, what was then called cardiorespiratory embarrassment.[19] The severity and complexity of combat-related wounds, then, portends a particularly significant risk for the development of infection and sepsis. MODS and eventual death are common among those who sustain severe war wounds and who survive long enough to reach a medical treatment facility. The U.S. Army's most recent extensive experience was during the Vietnam War. Data on the causes of hospital deaths show that sepsis and its complications probably caused about one third of the deaths (Figure 24-3).[20]

Most individuals deployed for possible combat are relatively young and healthy. Thus, soldiers generally do not have the medical illnesses that predispose to the development of sepsis (eg, diabetes mellitus, hepatic cirrhosis, chronic renal insufficiency, underlying malignancies, and inherited or acquired immunological defects).[21,22] But larger mobilizations that employ personnel not on active duty will most certainly include individuals whose underlying illnesses will become manifest. Illnesses acquired during military operations, principally infectious diseases such as malaria, will alter the host's immunoregulatory function in such a way that bacterial sepsis may be likely to occur. The fatigue, stress, and loss of sleep associated with combat maneuvers may also be associated with an increased incidence of infection.[23]

As trauma management continues to improve, more patients remain alive 2 or 3 days after injury. Infection during these first several days is rare, but increases in prevalence thereafter. Most cases of SIRS/MODS in the military will occur in casualties with multiple injuries whose infectious complications are caused by some or any of the following predisposing factors:

1. contaminated, open injuries (ie, penetrating thoracic or abdominal wounds, open fractures, or burns), which have a high propensity for infection and the subsequent systemic responses; for example, penetrating abdominal trauma results in an infection rate of 14% in patients without hemorrhagic shock (among patients with hemorrhagic shock, the infection rate increases 2- to 2.5-fold)[24];
2. depression of both the humoral and the cell-mediated immune systems, which traumatic injury causes[1];
3. compromised host defenses, which can be caused by medications such as steroids and the use of parenteral nutrition[1]; and
4. transfused blood products, which can spread such viral infections as hepatitis B and C, as well as HIV.[1]

Prolonged stay in an ICU increases the incidence of nosocomial infections as a consequence of the use of endotracheal tubes, intravascular and in-dwelling urinary catheters, and other monitoring and support systems. Therapies including hyperalimentation, antibiotics, and dialysis also contribute to the development of infection because normal

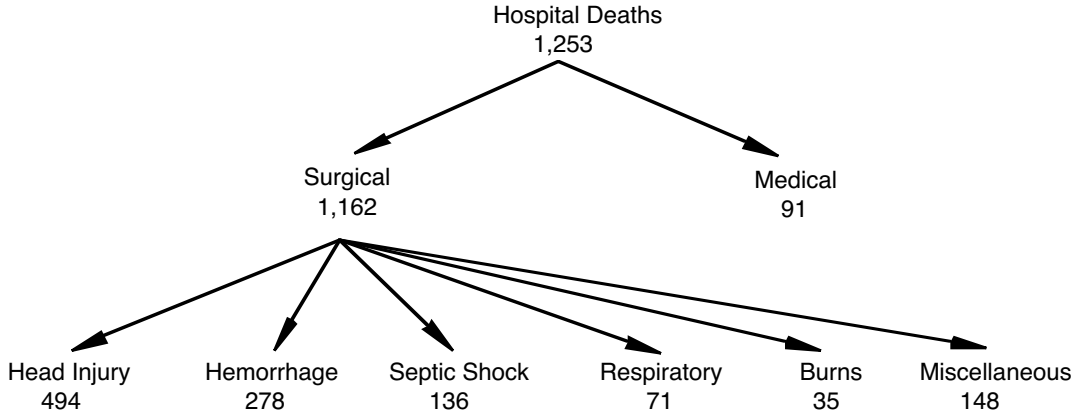

Fig. 24-3. The causes of death for 1,253 casualties who were hospitalized in Vietnam in 1969. The "miscellaneous" category includes entries such as fat embolism, 24; acute renal failure, 15; quadriplegia, 15. Data source: Arnold K, Cutting RT. Causes of death in United States military personnel hospitalized in Vietnam. *Milit Med*. 1978;143:161–164.

skin and mucosal physical barriers to infection are broken by these devices. Contamination of these devices during insertion or use can also result in superinfection.[25]

As a consequence, after 3 days in a surgical ICU, 50% of patients become colonized with potentially pathogenic bacteria, and by 10 days, 95% of patients acquire new flora.[26] In a study done between 1977 and 1984 at the Shock Trauma Center, Maryland Institute for Emergency Medical Services Systems (MIEMSS) in Baltimore, Maryland, 1,407 patients (14% of total admissions) developed 2,310 documented infections.[1] Among trauma patients who survived their initial injury, 22% to 63% developed one or more infections, with a 41% to 65% mortality. Once the patient contracted an infection, the duration of stay in the ICU increased from 7.4 to 13.5 days. The five leading infections in this study were, in order of frequency, urinary tract infections, pneumonia, surgical-wound infections, phlebitis, and intraabdominal infections. Patients with pneumonia or intraabdominal infection had mortality rates of 29% and 25%, respectively.[1] Most nosocomial infections in surgical patients occur in the urinary tract, the surgical wound and skin, and the respiratory tract.[27] Tabulated data from 82 hospitals show the frequencies of these infections to be 39%, 32%, and 16%, respectively.[28] The causative organisms vary somewhat with the location. Across all services (medical and surgical), *Escherichia coli* is the most prevalent pathogen and *Staphylococcus aureus* the second most common. The second most prevalent pathogen on medical and general surgical services alone is *Pseudomonas aeruginosa*. (*Enterococcus* is the second most common on gynecological and obstetrical services.[25])

Infections in trauma patients were well described in the MIEMSS study. The most frequent pathogens were *S aureus* (25%), *E coli* (13%), *P aeruginosa* (10%), *Enterobacter* species (10%), and *Klebsiella* species (9%). Gram-positive cocci were causative alone or partially involved in 43.9% of the infections, Gram-negative bacilli in 66.8%, anaerobic bacteria in 9.3%, and yeast in 1.5%. Nationwide, the pathogen most frequently found in the traumatized patient is *S aureus*.[1]

The true incidence of sepsis resulting from trauma is difficult to glean from the literature. At MIEMSS, of the more than 10,000 patients admitted during the study period, 1,407 developed 2,310 infections, 900 (39%) of which were documented cases of bacteremia.[1] The mortality rate of patients with bacteremia was 21%. Additional studies reported an 8.3% incidence of sepsis with bacteremia in 300 trauma patients,[29] and a 17% incidence in 200 patients.[30] Thus among trauma patients, the incidence of bacteremia with subsequent sepsis is 10% to 20%.[1]

Other sources of bacteremia in trauma patients in the MIEMSS study include vascular infections (22%), pneumonias (14%), intraabdominal infections (10%), empyemas (9%), and wound infections (8%). The vascular infection rate may have been underestimated, as it is only a recent practice to culture the tips of intravenous lines. An additional 21% of cases were without a definite source.[1]

The organisms resulting in bacteremia were similar to those causing all diagnosed infections. *Staphylococcus aureus* was the most common, resulting in 35% of the cases of bacteremia. Others were *Klebsiella* (12%), *Enterobacter* (10%), *Pseudomonas aeruginosa* (8%), and *Escherichia coli* (9%).[1]

Microbes in the bloodstream are the consequence of, or perhaps lead to the development of, overwhelming infection. Two separate complications arise from the systemic circulation of microorganisms[31]:

1. Organisms are seeded throughout the body, with subsequent formation of microscopic or even macroscopic abscesses.
2. A systemic effect occurs as a consequence of the mere presence of the organism or organism components (eg, the cell wall) in the bloodstream. This activates a cascade of inflammatory and endocrinological events that produce the systemic deterioration seen in sepsis, the final stage of which is septic shock.

Cellular and Subcellular Mechanisms Leading to SIRS/MODS

SIRS/MODS is now believed to result from the patient's systemic response to the growth of microorganisms at what is initially a localized site of infection (the *nidus*). Various components of microorganisms (eg, the cell wall), or substances elaborated by microorganisms (eg, toxins) are now thought to provoke the cellular components of blood (eg, monocytes and neutrophils) that are responsible for the normal immune response. The normal immune response results in the formation of endogenous mediators, which, if overproduced, have many deleterious pathophysiological effects (eg, myocardial depression and peripheral vascular vasodilation). Shock, MODS, and possible death then ensue.[32] Figure 24-4 is a schematic representation of this sequence of events.

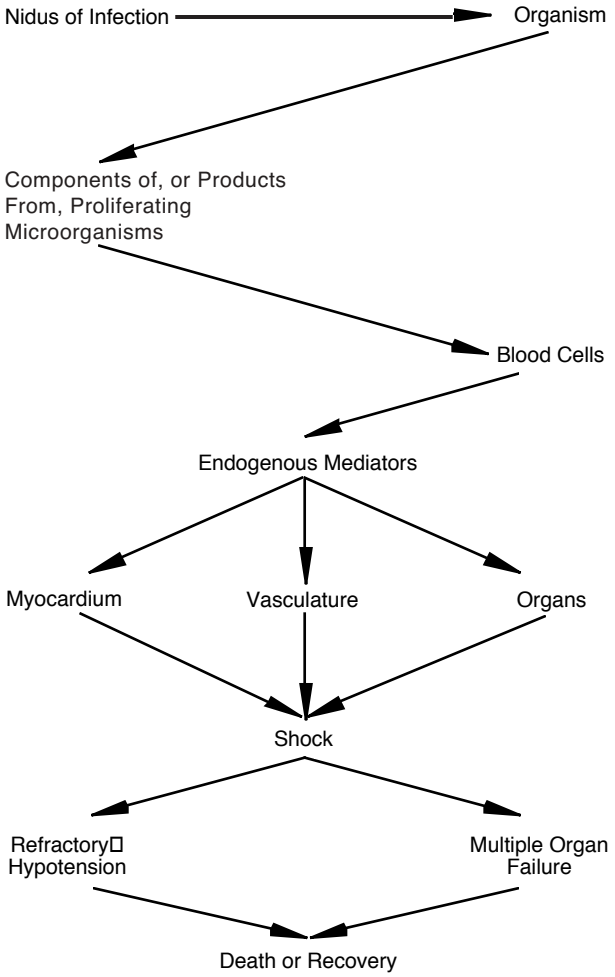

Fig. 24-4. Schematic showing important steps by which infection can cause shock, multiple organ failure, and death. Endogenous mediators released from normal cellular constituents of the blood play a crucial role. Adapted with permission from Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med*. 1993;328:1472.

By emphasizing the primacy of the host response, this paradigm advances our understanding of the origins of the deleterious consequences of sepsis. The immune system, which normally protects the host, releases endogenous mediators as part of its "normal" inflammatory response to infection. Such detrimental phenomena as cell and organ damage and death seem to result from the immune system's hyperresponsiveness to the insult.

Components and Products From Microorganisms Giving Rise to SIRS/MODS

The most notorious toxins produced by microorganisms include the neurotoxin of food-borne botulism, the neurotoxin that causes tetanus, the cardiotoxin of diphtheria, and the various histotoxins produced by species of *Clostridium*. These toxins, which are secreted by Gram-positive bacteria, are polypeptides with specific tissue targets. In contrast, *endotoxins* (literally, toxins from within) are normal constituents of the cell wall of Gram-negative bacteria; they are injurious to humans in the clinical setting that we now recognize as sepsis/SIRS. In fact, the most widely studied triggering event for sepsis/SIRS is the presence of endotoxin.

Endotoxin, from inside to outside the cell wall, comprises Lipid A, the core polysaccharide, and the O Antigen (Figure 24-5). In addition, endotoxin has one chemically unique constituent, the strange sugar molecule *Kdo* (3-deoxy-D-manno-2-octulosonic acid), which is found in all endotoxins and links the core polysaccharide to lipid A.[33] It is important to recognize that the peptidoglycan/teichoic acid complex of the cell wall of Gram-positive organisms, as well as the polysaccharide constituents of certain yeasts, have toxicity similar to that of endotoxin. As Lewis Thomas described in 1974, endotoxin is not only a strange substance chemically, it also provokes a violent and frequently self-destructive response in humans and other animals:

> Our arsenals for fighting off bacteria are so powerful, and involve so many different defense mechanisms, that we are in more danger from them than from invaders. We live in the midst of explosive devices; we are mined.
>
> It is the information carried by the bacteria that we cannot abide.
>
> The gram-negative bacteria are the best examples of this. They display lipopolysaccharide endotoxin in their walls, and these macromolecules are read by our tissues as the very worst of bad news. When we sense lipopolysaccharides, we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all tissues in the area. Leukocytes become more actively phagocytic, release lysosomal enzymes, turn sticky, and aggregate together in dense masses, occluding capillaries and shutting off the blood supply. Complement is switched on at the right point in its sequence to release chemotactic signals, calling in leukocytes from everywhere. Vessels become hyperreactive to epinephrine so that physiologic concentrations suddenly possess necrotizing properties. Pyrogen is released from leukocytes, adding fever to hemorrhage, necrosis, and shock. It is a shambles.
>
> All of this seems unnecessary, panic-driven. There is nothing intrinsically poisonous about endotoxin, but it must look awful, or feel awful, when sensed by cells. Cells believe that it signifies the presence of gram-negative bacteria, and they will stop at nothing to avoid this threat.[34(p92)]

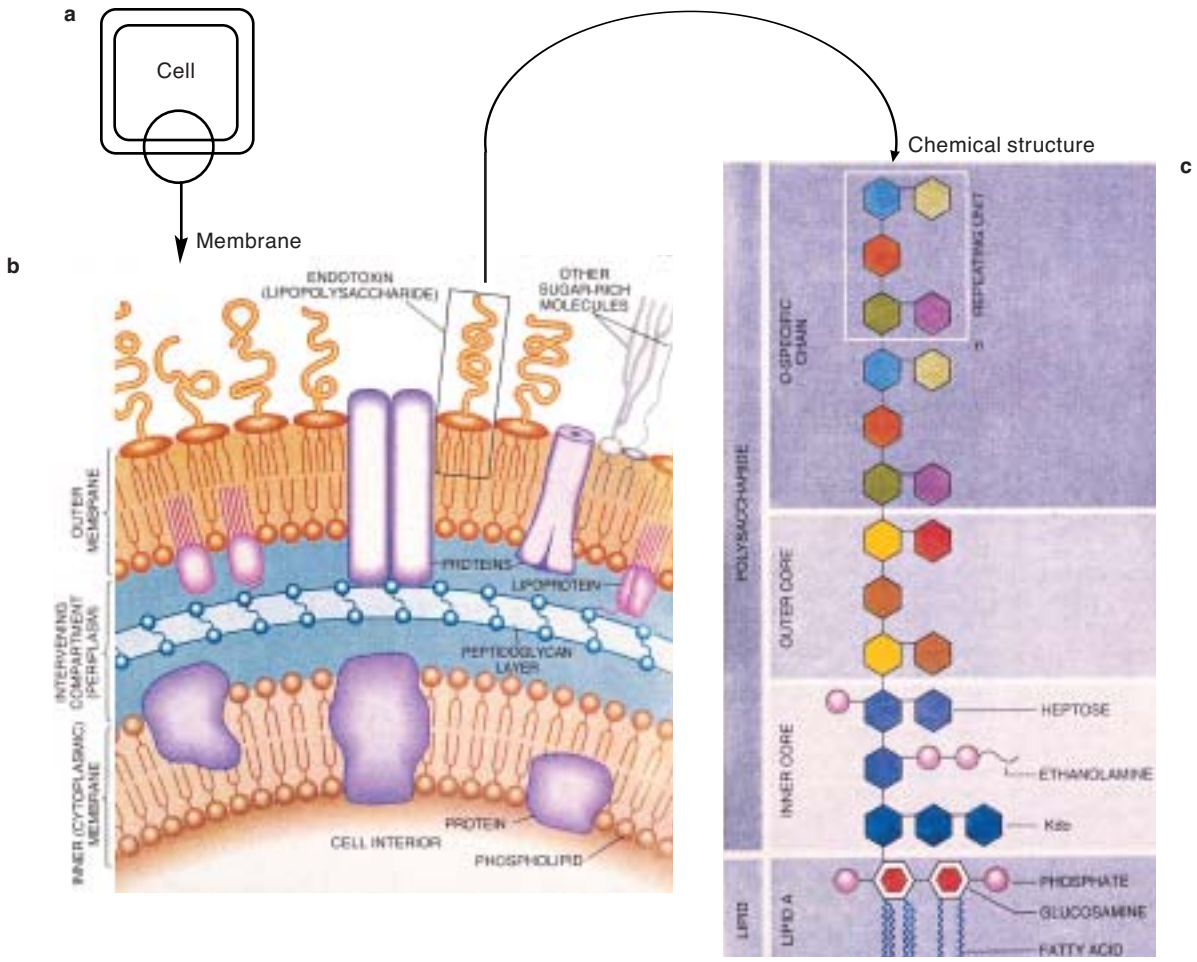

Fig. 24-5. The cell membrane of a Gram-negative bacterium, diagrammed at successively higher magnifications. (**a**) The cell wall, composed of two layers of lipids. (**b**) Endotoxin in its normal position in the outer membrane. (**c**) The chemical composition of the endotoxin. There are two important moieties: (1) a polysaccharide known as the O-chain and (2) a fat called lipid A. Several sugar molecules of unusual composition are found at the polysaccharide–lipid A junction. Lipid A, together with the sugar 3-deoxy-D-manno-2-octulosonic acid, is the portion of the endotoxin molecule that is responsible for its pathophysiological effects. Reprinted with permission from Rietschel ET, Brade H. Bacterial endotoxins. *Sci Am*. 1992;August:56, 57.

Until recently, data had been accumulated only from animal studies, but prospective assays reported in 110 patients with shock show a 43% incidence of endotoxemia in septic shock, compared with a 10% incidence in shock from other causes.[35] Patients who had endotoxemia developed organ failure 10-fold more frequently than other patients, indicating that the damaging role of this compound is significant.

Cellular Components Contributing to SIRS/MODS

It is now generally agreed that endotoxin by itself is not the direct cause of the pathophysiology of sepsis/SIRS. Rather, its effect is mediated through a variety of cells both in the blood and in tissue.

Mononuclear Cells

The mononuclear phagocyte system is composed of (*a*) bone marrow–derived monocytes that circulate in the blood stream and (*b*) tissue macrophages such as the hepatic Kupffer cells and pulmonary alveolar macrophages.[36,37] These blood and tissue macrophages appear to be the essential cellular components required for the development of sepsis and SIRS/MODS. As part of the inflammatory process, resting macrophages exposed to stimuli such as T cell–produced interferon gamma (IFN-γ)

or lipopolysaccharide (endotoxin) from Gram-negative–organism cell walls are activated into larger, more metabolically active cells. These activated macrophages secrete lysozyme, proteases (collagenase and elastase), plasminogen activator, interleukin-1 (IL-1), various leukotrienes, and cytokines such as tumor necrosis factor (TNF).[34]

Polymorphonuclear Cells

An interaction occurs between activated macrophages and polymorphonuclear leukocytes (PMNs). Human alveolar macrophages, and perhaps others, secrete a neutrophil activating factor that appears to enhance the PMNs' bactericidal activity by causing a greater release of superoxide. This interaction likely contributes to further host-tissue damage and inflammation.[36]

Protection of the host against many infections depends greatly on both the absolute number and the functions of PMNs, including chemotaxis, adherence, phagocytosis, and the eventual destruction of the ingested microorganism.[36] It is during the killing of the phagocytized organisms that the neutrophil may release substances that are toxic to the host, resulting in injury to the host (the patient).

Polymorphonuclear adherence to vascular endothelial sites (leukostasis) contributes to vascular injury in inflammation, particularly in the lung, and may also explain the initial neutropenia noted in some patients with sepsis.[36,38–40] To be effective, the PMNs must act at the site of microbial invasion. Chemotaxis or directed migration to the inflammatory nidus occurs in response to many agents, including oligopeptides produced by the invading organism, complement factor C5a induced by both the organism and the accumulated neutrophils, and leukotriene B_4 produced by on-site neutrophils.[37] After the neutrophil's phagocytosis, a respiratory burst within the PMN contributes to the inflammatory response in the following three ways:

1. The increased oxygen consumption of this respiratory burst is associated with the increased production of lethal oxidants (superoxide anion, hydrogen peroxide, hypochlorous acid, the hydroxyl radical, and the hydroxyl anion).
2. Lipid metabolism results in the production of thromboxane, leukotrienes, platelet activating factor, and leukotoxin.
3. The PMN degranulates.

The inflammatory process in the host is activated and propagated by these mechanisms. The various mediators released by the neutrophil, in particular the oxygen radicals, are not specific for foreign antigens. Thus the host tissues are susceptible to the toxic effects of these substances. This is a major factor in the adverse response to infection.

In the adult respiratory distress syndrome (ARDS), the abundance of neutrophils retrieved from a bronchoalveolar-lavage sample is evidence for the central role that neutrophils play.[41] In contrast, few neutrophils are recovered from bronchoalveolar lavage in patients with non-ARDS respiratory failure. Abundant neutrophils are a component of syndromes other than ARDS, however: ARDS can also occur in neutropenic patients. Neutrophils in the pulmonary circulation have been shown to release several harmful byproducts (eg, collagenase, myeloperoxidase, and elastase) that may cause systemic injury.

Lymphocytes

Specifying the host's immunological response to invading pathogens is the role of the lymphocyte. The full response requires an extensive interaction between these lymphocytes and macrophages. Lymphocytes are subdivided into T lymphocytes, which make up 70% of all mononuclear cells, and B lymphocytes, which, along with natural killer cells and monocytes, comprise the remaining 30%.[42]

T lymphocytes direct cell-mediated immunity in the host and exist in two forms:

1. helper/inducer or cluster of differentiation (CD) 4+ cells, which enhance the host's immunological response by supporting T-T cell, T-B cell, and lymphocyte–macrophage interactions; and
2. suppressor or CD8+ cells, which inhibit B cell–antibody production and, hence, diminish immunological function.

Antibody-mediated (humoral) immunity is governed by the differentiation of B lymphocytes into plasma cells that are capable of secreting antibodies. Antigens processed by the macrophage are presented to B cells specific for that particular antigen, based on the antigen binding site (Fab segment) on the B lymphocyte's membrane-bound immunoglobulin. The degree of B cell and plasma-cell clonal expansion is controlled by helper and suppressor T cells.[43]

Macrophages are known to interact with both T and B cells at inflammatory sites. An interaction between T cells and the macrophage causes the T cell to secrete lymphokines (eg, IFN-γ, macrophage inhibitory factor, monocyte chemotactic factor, IL-2) and the macrophage to release monokines (including IL-1 and TNF).[37] These lymphokines also modulate the host's immunological response by their effects on other lymphocytes, macrophages, neutrophils, and invading organisms.[43]

Endogenous Mediators

Much of the current experimental and clinical research is directed toward finding the endogenous mediators produced by cells that link such pathophysiological derangements as septic shock and MODS to microorganisms and their endotoxins. The two leading candidates at present are a group of small-molecular-weight proteins known as cytokines and the eicosanoid metabolites of arachidonic acid.

Cytokines: Tumor Necrosis Factor and the Interleukins

TNF (also called *cachectin*)—a small polypeptide protein with a molecular weight about 17,000—is released when endotoxin stimulates blood or tissue macrophages, endothelial cells, and lymphocytes. Its effects include

- enhancement of the immune system,
- hypotension due to a decrease in peripheral vascular resistance,
- loss of fluid from the vascular bed (caused by an increase in both the systemic and pulmonary capillary permeability),
- a variety of metabolic changes (eg, lipolysis and increased amino acid loss from skeletal muscle), and
- the long-term acceleration of wound healing.

Many of these changes are virtually identical to those observed with endotoxin, including fever, shock, and lactic acidosis. Several studies have identified a prime role for TNF in clinical sepsis or MODS:

- Intravenous injection of human recombinant TNF into laboratory rats[44] and dogs[45] results in hypotension, shock, metabolic acidosis, and death due to respiratory arrest within hours. Autopsy showed many of the same findings seen in patients who had died of MODS.[46]
- The administration of monoclonal antibodies to TNF almost completely prevents obvious organ injury in most animal models of septic shock including those in which endotoxin is also administered.[47]
- TNF produces myocardial cell dysfunction in an animal model[48] and may be the substance responsible for myocardial depression in human sepsis/SIRS.[49]

Studies on humans with sepsis have begun to provide support for the paradigm that views TNF as the proximate cause of SIRS:

- Serum levels of TNF are significantly higher in patients with sepsis who ultimately developed septic shock, compared with patients who did not develop shock.[50]
- Patients who died of sepsis within 25 hours of starting treatment for septic shock had TNF levels nearly 20-fold greater than those who die later.[50]
- TNF production from monocytes taken from trauma victims correlated with septic episodes.[51]

Interleukin-1 and Interleukin-2

IL-1, which can be thought of as an endogenous pyrogen, is classified as a *monokine*, which is produced when a macrophage is stimulated by bacteria. The effects of this mediator include hypothalamic stimulation, producing fever, leukocytosis, an increase in the hepatic acute-phase reactants (eg, C-reactive protein), and an increase in muscle proteolysis. An intravenous infusion of IL-1 in laboratory animals results in the hemodynamic appearance of septic shock. The exact contribution of IL-1 in the pathophysiology of MODS is unknown.

IL-2 is a macrophage product that has been administered to patients with metastatic cancer as part of immunotherapy. Administration of IL-2 causes hemodynamic changes that mimic the sepsis syndrome. Furthermore, case reports have described patients who developed organ failure during immunotherapy with IL-2.[52,53]

Eicosanoids: The Arachidonic Acid Metabolites

Eicosanoid is the generic term for the leukotriene, prostaglandin, and thromboxane metabolites of

arachidonic acid (a polyunsaturated fatty acid). For the most part, they are potent but short-lived molecules produced by all nucleated cells anywhere in the body. Endothelial cells, macrophages, and platelets produce eicosanoids in areas where microorganisms have invaded tissue, a feature that is of special importance to the study of sepsis.

Given any number of stimuli such as hypoxia, damaged vascular endothelium, and especially the liberation of cytokines, free arachidonic acid is liberated from the phospholipid component of the cell membrane, from which it diffuses into the cytosol. Depending on the cell type, arachidonic acid becomes the substrate for one of two enzymes: lipoxygenase or cyclooxygenase (Figure 24-6). Lipoxygenase catalyses the formation of the leukotriene eicosanoids, while cyclooxygenase forms multiple eicosanoids, of which the most important are thromboxane A_2, prostacyclin (prostaglandin I_2), and prostaglandin E_2.

Of the myriad biological effects associated with eicosanoids, the effects most likely to be relevant to our understanding of sepsis/SIRS are those caused by

- the leukotrienes, which cause alterations of neutrophil function leading to increased chemotaxis, synthesis of the superoxide anion radical, increased microvascular permeability, vasoconstriction, and bronchoconstriction;

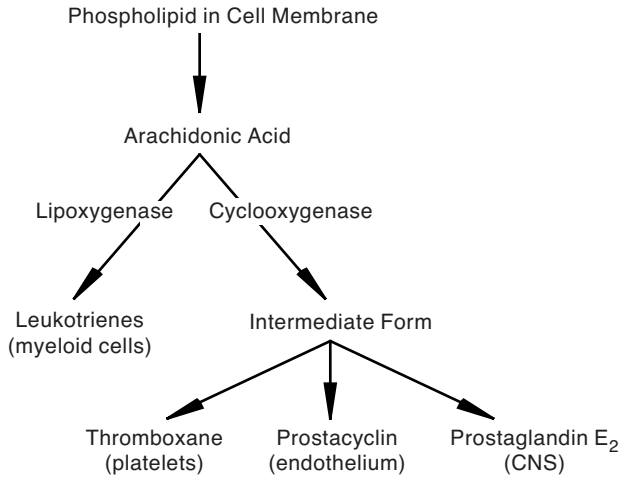

Fig. 24-6. The origin and partition of several biologically important eicosanoids. Note that arachidonic acid can be acted on by two enzymes: (1) lipoxygenase, which gives rise to the leukotrienes, and (2) cyclooxygenase, which gives rise to thromboxane, prostacyclin, and prostaglandin E_2, which have markedly different physiological effects.

- thromboxane, which causes platelet aggregation and vasoconstriction;
- prostacyclin, which causes platelet disaggregation and vasodilation; and
- prostaglandin E_2, which causes intensive pulmonary and systemic vasodilation, hyperalgesia, and fever.

The leukotrienes have the ability to cause many of the pathophysiological changes that are seen in sepsis/SIRS. However, there are two reasons why the eicosanoids produced by the lipoxygenase pathway are less likely to be important than those produced by cyclooxygenase:

1. The enzyme lipoxygenase is present only in myeloid cells, whereas cyclooxygenase is present in all cells.
2. Lipoxygenase, in contrast to cyclooxygenase, is normally inactive and needs to be "turned on" before any eicosanoids are produced.

Several lines of evidence support the role of the cyclooxygenase metabolic products of arachadonic acid in the development of sepsis/SIRS. Putative reasons for the involvement of phospholipids as endogenous mediators of sepsis/SIRS have been the subject of considerable research.[54] Many of the signs and symptoms of sepsis/SIRS such as fever and shock can be replicated by eicosanoids. For example, elevated levels of thromboxane B_2 have been measured in patients with sepsis, but whether a cause-and-effect relationship exists is unclear at present. Some of these findings include the following:

- There is less hemodynamic compromise and increased survival when thromboxane is inhibited.[55]
- In human volunteers, ibuprofen lessens the signs and symptoms associated with endotoxin administration.[56]
- Ibuprofen normalizes hemodynamic indices in dogs with experimental sepsis.[57]
- Pulmonary permeability edema decreases in a large-animal sepsis model using ibuprofen to inhibit the cyclooxygenase pathway.[58]

Prostacyclin, because of its strong vasodilator properties, may be the mediator of the peripheral vasodilation seen in most cases of human septic shock—although why its effect should predomi-

nate over that of its antagonist, thromboxane, is unclear.

The ability of prostaglandin E_2 to cause hyperpyrexia relates to its direct effect on the thermoregulatory center in the hypothalamus. The activity of the enzyme cyclooxygenase is decreased by drugs that contain or are metabolized to salicylic acid (eg, aspirin). The antipyretic action of aspirin depends on its ability to decrease the formation of prostaglandin E_2. The same mechanism—inhibition of cyclooxygenase—explains the analgesic effects of aspirin: prostaglandin E_2, which is known to sensitize nerve endings to noxious stimuli, is not produced.

Unfortunately, the most recent and methodologically valid study of the role of eicosanoids in humans with severe sepsis failed to show a clear-cut advantage from pharmacologically blocking the formation of eicosanoids with the nonsteroidal antiinflammatory drug ibuprofen. Although fever, blood pressure, heart rate, and oxygen transport were at least partially normalized in the treated patients, the researchers found no decrease in mortality compared with control patients.[59] These negative findings suggest that the cascade of mediators causing systemic response and sepsis is so complex that blockade of only one component will not result in improved patient survival.

Endorphins

A role in the pathogenesis of sepsis/SIRS for endogenous opioids, of which β endorphin is the best known, was first proposed in 1977 by researchers at Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. Naloxone, an antagonist of β endorphin, was shown in a rat model to reverse the hypotension that was caused by endotoxin.[60] Significant species differences exist; in baboons, for example, hypotension from endotoxin is not reversed by naloxone.[61] Studies in which naloxone is given to humans with septic shock have shown transient reversal of hypotension but no effect on survival.[62,63] Even though β endorphin levels rise with trauma,[64] the attention paid to endogenous opioids in the pathogenesis of septic shock should probably be minimized, because these substances do not give rise to the hyperdynamic and vasodilated state that characterizes human septic shock.

Free Radicals

Free radicals are chemical entities that contain one or more unpaired electrons in their outermost molecular orbitals. Their chemical activity is markedly heightened compared with molecules with paired outermost electrons. Most free radicals are derived from oxygen (a not-unsurprising situation given the prominence of oxygen in our environment and our dependence on oxygen for the energy-producing processes necessary for life). Nearly all the oxygen that enters into the normal mitochondrial production of adenosine triphosphate is converted to water by the near-simultaneous addition of four electrons. However, in a process known as the *univalent leak*, about 1% of the oxygen molecules normally undergo a four-step reduction that involves the addition of one electron at a time. Each time an electron is added, a different type of oxygen-derived free radical is formed. These are, in order of their generation: the superoxide anion radical ($O_2\bar{\bullet}$), the hydroperoxyl radical ($HO_2\bullet$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH\bullet$). Although hydrogen peroxide itself is not a free radical, it is rapidly converted into the hydroperoxyl and hydroxyl radicals.

Mammalian cells normally contain substances with strong antioxidant properties, of which the enzymes *superoxide dismutase* and *catalase* are best known; these enzymes prevent the intracellular accumulation of the toxic free radicals. Superoxide dismutase catalyzes the conversion of the superoxide anion radical to hydrogen peroxide, while catalase catalyzes the conversion of hydrogen peroxide to water. When these antioxidants function properly, they prevent the generation of the hydroperoxyl and hydroxyl radicals and thereby minimize the potential for oxygen-derived free-radical injury.

Superoxide dismutase and catalase effectively minimize oxygen-derived free-radical injury except in two circumstances: the first is during the reperfusion phase, when blood flow is normalized following shock, ischemia, or hypoxia; the second, paradoxically, is when neutrophils are activated as part of their normal function (ie, they display their respiratory burst). The generation of free radicals presumably evolved for a beneficial purpose: the destruction of foreign objects such as bacteria by phagocytic cells. Neutrophils and macrophages have on their cell membranes a liberal amount of the enzyme *nicotinic acid diphosphohydrogen oxidase*, which, when activated by any of several endogenous mediators such as TNF, generates superoxide anion radicals and hydrogen peroxide. At the same time, the enzyme *myeloperoxidase* is released by the cell and catalyses the formation of hypochlorous acid from hydrogen peroxide and chloride

ions in the cell's neighborhood. Hypochlorous acid kills bacteria. The effect is twofold: not only does the neutrophil's respiratory burst produce lethal oxidants, but it also contributes to the inflammatory response by generating thromboxane, leukotrienes, platelet activating factor, and leukotoxin.

Increasingly, the generation of oxygen-derived free radicals in shock, ischemia, and hypoxia is believed to be a major source of the injury that characterizes these conditions. Although all constituents of a cell are at risk, the lipid-containing membranes appear to be especially sensitive to destruction because of the self-propagating nature of free-radical attack on the polyunsaturated fatty acid portion of the cell wall. Reaction of a free radical with a polyunsaturated fatty acid not only chemically alters the fatty acid but also generates new free radicals—lipid peroxides—that incorporate into parts of the original fatty acid. Two different free-radical attacks are possible. First, the *hydroperoxide* pathway generates two free radicals for every lipid molecule destroyed. Second, the *endoperoxide* pathway generates three free radicals. Thus, rapid dissolution of cell membranes occurs in a process reminiscent of the chain reaction that characterizes atomic fission.

Nonoxygen-derived free radicals may also play a role in the pathophysiology of sepsis/SIRS. One of the most significant recent advances in vascular physiology is the recognition that normal vascular endothelium produces a potent vasodilator. This was subsequently shown to be nitrogen monoxide in one or more of its three forms: the free radical nitric oxide (NO•), the nitrosonium cation (NO^+) or the nitroxyl anion (NO^-).[65] The vasodilator property of TNF has been shown to be dependent on the presence of normal vascular endothelial cells, suggesting that nitric oxide may be the proximate cause of the hypotension associated with sepsis.[66] In fact, high concentrations of the metabolites of nitric oxide have been described in patients with clinically apparent sepsis, but not in trauma patients or controls who did not have sepsis. Furthermore, the concentrations of these metabolites was inversely related to the peripheral vascular resistance.[67] These data suggest that increased production of nitric oxide may be a causative factor in the development of septic shock. Specific blockers of the generation of nitric oxide have been tried in patients in septic shock.[68] Although the patients' hypotension was ameliorated, their survival was not enhanced (which is not too surprising given that hypotension by itself is one of the several derangements that occur in septic shock).

Additional Mediators

Complement. The alternate pathway of complement is known to be activated by endotoxin and other bacterial products. The resultant release of C3a and C5a leads to neutrophil stimulation and the following adverse effects, which are seen in patients with sepsis/SIRS:

- increased vascular permeability,
- histamine release,
- release of tissue proteases leading to autocatabolism, and
- development of oxygen free radicals.

Fibronectin. Fibronectin is an endogenous compound that functions like an opsonin (ie, it enhances phagocytosis). In concert with the reticuloendothelial system, fibronectin helps to clear particulate matter from the circulation. Many studies have shown that depletion of fibronectin occurs in a state of multiple trauma, shock, or sepsis. Fibronectin, in the form of cryoprecipitate, has been administered to patients who then demonstrate a slight improvement in their hemodynamic status. Because cryoprecipitate is a multidonor product, carrying with it a significant risk for the transmission of infectious agents, great skepticism surrounds the advisability of using it in the treatment of SIRS/MODS.

Platelet Activating Factor. Platelet activating factor can be released from leukocytes, macrophages, or the vascular endothelium. The two effects of this agent are (1) the induction of platelet and neutrophil aggregation and (2) stimulation of the arachidonic acid pathway, causing the release of eicosanoid compounds.

Stress Hormones. Several hormones are released during a state of physical stress, which characterizes the "fight or flight" survival response. These include glucagon, hydrocortisone, epinephrine, growth hormone, and thyroid hormone. One hypothesis concerning this neuroendocrine secretion is that vascular or organ damage may occur when states of hypermetabolism and negative nitrogen balance are created.

Cascade of Events Leading to SIRS/MODS

For SIRS to become fully developed, multiple endogenous mediators and several different types of cells interact in ways that result in a continuous amplification of the original stimulus provided by

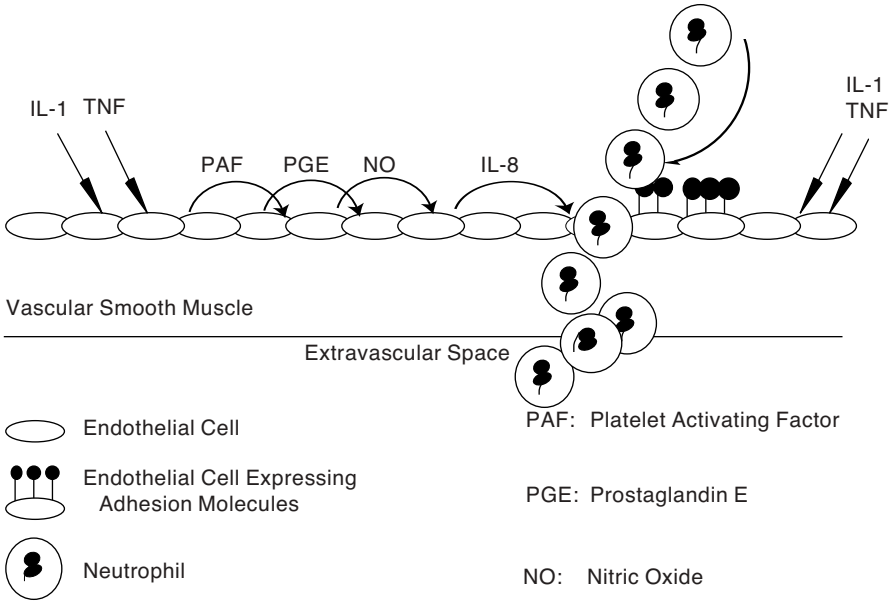

Fig. 24-7. Schematic showing the putative interaction of several endogenous mediators (interleukin-1 [IL-1] and tumor necrosis factor [TNF]) and the vascular endothelium. The mediators cause the endothelium to generate the potent vasodilators nitric oxide (NO) and prostaglandin E (PGE), as well as platelet activating factors (PAF). The mediators also cause a substance (endothelial adhesion molecule) to be formed that attracts circulating neutrophils. The neutrophils become activated and generate oxygen-derived free radicals and other substances that damage the microcirculation and contiguious cells. Reprinted with permission from Dinarello CA, Gefland JA, Wolff, SM. Anticytokine strategies in the treatment of the systemic inflammatory response syndrome. *JAMA*. 1993;269(14):1830.

endotoxin. This cascade of events (Figure 24-7) appears to follow this sequence[69]:

- TNF and IL-1 stimulate endothelial cells to produce nitric oxide, prostaglandin E_2, IL-8, and the platelet activating factor.
- Nitric oxide and prostaglandin E_2 produce vasodilation and hypotension.
- IL-8 and the platelet activating factor cause neutrophils to adhere to the endothelial cells and then to migrate to the extravascular space.
- Cells are damaged by the release of oxygen-derived free radical from the extravascular neutrophils. If the cellular damage is sufficiently extensive, organ dysfunction will occur.

ORGAN-SPECIFIC RESPONSES

If the effects of this cascade are confined to the local area of microorganism growth and tissue invasion, it is probably advantageous to the patient. However, if the endogenous mediators and their effects become systemic, as may occur in human bacteremia and sepsis/SIRS, then functional impairment of one or more organs can be expected, a process that may culminate in a perpetuating organ injury.

Cardiovascular Response

Cardiovascular and hemodynamic dysfunction in septic shock have been the subjects of much interest and debate since the 1950s. Two subsets of patients were initially described in the setting of Gram-negative bacteremia. The differentiating factor was postulated to be their *cardiac index* (the amount of blood ejected by the heart in a unit of time, divided by the body surface area, and usually expressed in liters per minute per square meter). Patients presumed to have a low cardiac index had cold, clammy skin with weak and thready pulses, while warm, dry skin and bounding pulses were attributed to a high cardiac index.[70] In 1956, an animal model of intravenously administered endotoxin elicited a syndrome similar to that ascribed to low cardiac index (hypotension with a depressed

cardiac index). Most early studies with animals and humans reported a characteristic hemodynamic profile of septic shock, particularly in those cases with a poor prognosis: one of depressed cardiac output with associated increased systemic vascular resistance.[71]

By the mid-1960s, however, the usual hemodynamic pattern seen in septic shock in humans was reported to be one of normal or increased cardiac index with an associated low systemic vascular resistance.[72] Subsequent studies have confirmed that this pattern is the usual cardiac profile seen early in patients in septic shock.

In retrospect, the occurrence of these two hemodynamic patterns is probably iatrogenic; specifically, the therapy affected ventricular preload. Therapy during the early 1960s was likely to be associated with an inadequate restoration of ventricular preload, which therefore led to an inadequate cardiac index. It was thought then that fluid therapy in septic shock had to be judicious, for vigorous fluid resuscitation resulted in pulmonary edema. In reality, much of the lung fluid may have been related to ARDS, a phenomenon of increased pulmonary capillary leakage that is most often a consequence of sepsis. With greater understanding of ARDS and with the introduction of the pulmonary artery catheter (also called the Swan-Ganz catheter), patients with depressed cardiac indices were found to have low left ventricular preload, as estimated by pulmonary capillary wedge pressure (PCWP). Thus, in attempting to prevent the development of pulmonary edema, too little volume or preload was utilized, thereby depressing the cardiac index.[73,74] With the PCWP as a guide to left ventricular preload, infusion of large amounts of fluids to compensate for the septic shock–induced vasodilation and capillary leakage results in a pattern of elevated cardiac index in more than 90% of patients in septic shock.[73]

Hemodynamic Data Derived From Clinical Investigation

Despite the hemodynamic pattern described above, patients who die in septic shock were thought by many to manifest a falling cardiac index and progressive acidosis before they die.[71] Although this mechanism of death appears plausible, whether systemic hypoperfusion was the cause or the effect remained to be proven.[73]

To more thoroughly investigate serial cardiovascular variables, 48 consecutive patients with hypotension and blood cultures positive for bacteria were evaluated.[75] With a pulmonary artery catheter in place, hypotension was managed with fluids, then dopamine, and finally levarterenol (norepinephrine) as needed to maintain a mean arterial pressure of at least 60 mm Hg. Hemodynamic variables were recorded for any change within the first 24 hours, and at least daily until the patient either recovered or died. Of the 60% of patients who died, three fourths had irreversible hypotension. Eighty percent of this hypotensive group died with a persistently elevated cardiac index and decreased systemic vascular resistance. The remaining patients died of continued worsening cardiac index and heart failure. All these hypotensive patients died within 7 days of the onset of shock. The remaining patient (who died after the 7th d), died as a consequence of MODS. Thus, death from refractory hypotension due primarily to a low cardiac index is not common. The more likely cause of early death in patients with sepsis is refractory hypotension associated with a low systemic vascular resistance.

Early studies that predicted the outcome of patients in septic shock were conflicting, with some showing a progressive fall in cardiac index and worsening of a metabolic acidosis prior to death, others showing no difference from the initial hemodynamic profile between survivors and nonsurvivors. One study[71] showed that patients with an extreme elevation in cardiac index (> 7.0 L/min/m^2) had a very poor prognosis. Another[75] revealed that an initial heart rate less than 106 beats per minute, and a rate at 24 hours of less than 95 beats per minute predicted survival. An initial hyperdynamic response was found in both survivors and nonsurvivors, although survivors tended to return toward a more normal hemodynamic state over the first 24 hours, with a decrease in heart rate of at least 18 beats per minute or a decrease in cardiac index of at least 0.5 L/min/m^2. Nonsurvivors tended to have a persistently low systemic vascular resistance and an elevated cardiac index and heart rate.[75] Persistent vasodilation may be the result of systemic absorption of previously mentioned mediators.

Myocardial Dysfunction

Early studies of myocardial dysfunction correlated a low cardiac index, particularly in the setting of an elevated central venous pressure, with myocardial depression. More sophisticated monitoring has added other means of evaluating ventricular function (ie, left ventricular stroke work index

[LVSWI] in response to volume infusion). Further calculation of oxygen delivery and consumption data has been proposed by some as a more accurate reflection of the adequacy of cardiac function.[71]

Radionuclide cineangiography was first introduced in the evaluation of patients with sepsis in 1981.[76] This technique was used in patients with septic shock and was reported in 1984.[77] Of the 20 patients evaluated, 13 survived. Survivors and nonsurvivors alike were found to have the characteristic hemodynamic profile seen in septic shock: an elevated cardiac index with a decreased systemic vascular resistance. The left ventricular end diastolic volume index (LVEDVI) was also evaluated (stroke volume index determined from thermodilution cardiac index divided by the radionuclide-determined ejection fraction); this is a more accurate indicator of left ventricular preload than is PCWP, because the real determinant of left ventricular ejection is *volume* (myocyte stretch) not intraventricular *pressure*. Survivors were noted initially to have a depressed ejection fraction, which returned to normal in 7 to 10 days. This reduced ejection fraction was associated with an increased end diastolic volume index, which also returned to normal in 7 to 10 days. Thus, in survivors, the initial decrease in ejection fraction was associated with left ventricular dilation. This pattern of depressed ejection fraction with increased LVEDVI has been subsequently confirmed in other studies using two-dimensional echocardiography.[73] Thus, the increased cardiac index that occurs despite myocardial depression is the result of both an increased heart rate and a normal or slightly elevated stroke volume. Gross dilation of the left ventricle, which is usually considered to be a pathological process, can be considered to be a compensatory mechanism in septic shock, for it allows the maintenance of a more normal stroke volume and, hence, cardiac output. Interestingly, nonsurvivors maintained a normal ejection fraction and left ventricular end diastolic indices because the left ventricle ejects against the pathologically low afterload of a dilated systemic vascular bed.

An increased cardiac index in sepsis requires adequate preload. In 1977, researchers demonstrated that compared with survivors of septic shock, nonsurvivors of septic shock had significantly depressed ventricular performance curves. That is, LVSWI in nonsurvivors was depressed in response to volume infusion as monitored by the PCWP.[78] More recently, ventricular performance curves using LVEDVI, rather than PCWP, as a measure of preload were studied in three groups of patients—controls, hemodynamically stable patients with sepsis, and patients in septic shock.[79] In response to volume infusion, both groups of patients with sepsis had decreased LVSWIs compared with controls, and demonstrated no further increase in ventricular performance when the PCWP exceeded 18 mm Hg. Volume administration with PCWP as a guideline may not achieve the expected improvement in left ventricular performance because left ventricular end diastolic pressure (LVEDP) is not related to LVEDVI by a simple linear relation.

Left ventricular diastolic dysfunction also appears in sepsis. Compared with normal controls, patients with sepsis, both with and without shock, were shown to have abnormal diastolic filling (Figure 24-8).[80] Echocardiographic and pulsed-wave Doppler studies were characterized by an increase in peak atrial velocity, increased atrial filling fraction, and prolongation of the atrial filling period as a function of the diastolic filling period. Septic patients may have an increased dependence on atrial systole for diastolic filling.

Right ventricular dysfunction also occurs in patients with sepsis and appears to be independent of right ventricular afterload. In a study of right ventricular function in 25 patients in septic shock, utilizing radionuclide ventriculography as well as catheterization of the right side of the heart, 13 had a depressed right ventricular ejection fraction.[81] As expected, right ventricular dysfunction occurred in patients with respiratory failure or increased pul-

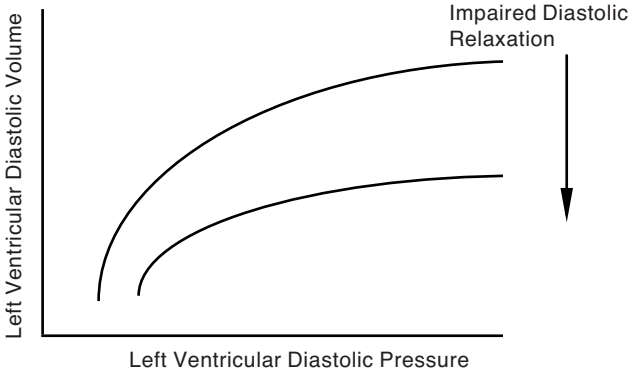

Fig. 24-8. This schematic drawing shows the relation between left ventricular diastolic pressure and volume for two different states of left ventricular compliance. The upper curve represents normal diastolic relaxation, while the lower curve represents impaired diastolic relaxation. Note that for any given filling pressure, the ventricle with impaired relaxation has a smaller filling volume. The arrow shows the direction of increasing impaired relaxation.

monary arterial pressures. However, in many of the patients, the degree of dysfunction was out of proportion to right ventricular afterload. While 8 of the 13 patients had concomitant decreases in left ventricular performance, the ejection fraction was normal in 5 patients.

In one study,[82] significant right ventricular systolic dysfunction, as defined by decreased ejection fraction and right ventricular dilation, was seen in all patients in septic shock. Nonsurvivors appeared to have depressed right ventricular performance because of a decrease in contractility, as manifested by a marked increase in end-systolic volume without significant change in right ventricular afterload. Apparent diastolic dysfunction of the right ventricle was also suggested by the downward displacement of the pressure–volume curves.

Depressed biventricular function and biventricular dilation was noted in another study[83] of 38 patients in septic shock; these abnormalities returned to normal within 7 to 14 days. In this study, 31 patients (82%) with depressed right ventricular function had simultaneous left ventricular dysfunction. Thus, the myocardial depression seen in septic shock is a biventricular phenomenon.[71]

The mechanism of myocardial dysfunction has been attributed to either ischemia secondary to inadequate coronary perfusion or the presence of a circulating humoral factor that depresses myocardial contractility.[84] Studies that evaluate coronary sinus blood flow and myocardial metabolism have demonstrated neither decreased coronary blood flow nor increased myocardial lactate production. High coronary sinus oxygen saturation with a low myocardial oxygen extraction is similar to the arteriovenous shunting seen peripherally in septic shock. Thus, septic shock does not appear to cause myocardial dysfunction by decreasing cardiac perfusion.[71]

Myocardial Depressant Factor

A circulating humoral substance that results in myocardial depression has been proposed for many years. This myocardial depressant factor has been reported in animal models and in a number of bioassays that utilize plasma or serum from patients in septic shock. In 1985, using a bioassay of beating newborn rat heart-cell cultures, researchers[85] described a circulating myocardial depressant substance or factor in patients with septic shock. To accomplish this, the researchers imaged and analyzed the leading edge of the beating rat myocardial cells, and recorded the extent and velocity of shortening. The cells were bathed in sera from 20 patients with septic shock. The sera were then assayed for evidence of a depressant factor. In a comparison study[71] with sera from three different groups of patients, sera from the patients in the acute phase of septic shock caused the least myocardial cell shortening. Of note, there was a significant correlation between this decrement in vitro and the measured left ventricular ejection fraction in vivo. This temporal and quantitative association between the in vitro results and the clinical myocardial depression noted in vivo appears to validate the presence of a circulating myocardial depressant factor in patients with septic shock.[71] Revisions in this assay and subsequent studies have confirmed the association between myocardial depression in these patients and a circulating substance that decreases myocardial contraction in vitro.[84]

A plethora of septic shock mediators has been evaluated for myocardial depressant activity, of which TNF and endotoxin have been found to be the most potent.[35,48] Other mediators that may contribute, determined from both animal models and humans, include prostaglandins, histamine, IL-1 and IL-2, and platelet activating factor. No one substance appears to be the universal myocardial depressant substance. Rather, myocardial depression probably occurs as a consequence of many mediators that may work synergistically.[71]

Regardless of the actual etiology, survival of septic shock appears improved when the patient's left ventricle dilates sufficient to maintain cardiac output in the presence of decreased contractility, due to the circulating myocardial depressant substance. Presumably, the ventricles of nonsurvivors could not dilate sufficiently to compensate for the decrease in contractility caused by the circulating myocardial depressant substance.

Pulmonary Response

The best known clinical manifestations of sepsis / SIRS are arterial hypoxemia and respiratory failure. As the lung is probably the first organ to manifest physiological derangement from sepsis, the astute clinician will be alerted early to the onset of sepsis, ideally *before* shock occurs. Why should the lung be injured so frequently during sepsis? The following statements are among the possible explanations[86]:

- The lung is a source of marginated polymorphonuclear leukocytes.

- All of the body's venous return passes through the lung.
- The lung is exposed to blood-borne mediators and endotoxin.

Clinical Features

The association between lung injury and sepsis is perhaps best typified by ARDS, a frequently fatal pulmonary condition. This association has been known since 1967, when this constellation of clinical signs resulting from a variety of pulmonary insults was first described.[87] In the proper clinical setting, the presence of ARDS can be inferred from tachypnea and dyspnea, a decrease in pulmonary compliance, and refractory hypoxemia and diffuse alveolar radiological densities. The full-blown syndrome does not always develop; lesser degrees of impairment of pulmonary function can occur. Hypoxemia during sepsis is frequent and occurs prior to the onset of pulmonary edema or other changes characteristic of ARDS. Minimally, most patients will manifest both an increased intrapulmonary shunt, resulting in mild-to-moderate hypoxemia, and an increased physiological deadspace, resulting in an elevated minute ventilation.

Pathophysiology

Most of the data presented here are the results of experiments on animals. Studies on humans are difficult or impossible to conduct for the following reasons:

- Pulmonary dysfunction in patients is frequently not recognized early.
- There are no laboratory markers to chart the course of impending pulmonary injury during sepsis.
- When ARDS does develop, it frequently occurs quickly following the onset of sepsis.
- Histological examination of the lung in the early phases of sepsis is only possible in the animal model.

Although the exact incidence of pulmonary dysfunction during sepsis in humans is unknown, the incidence is probably higher than was reported previously.[86] As is true for other conditions in the critically ill patient, the reported incidence depends on the diagnostic criteria. This is particularly important because the terms "sepsis," "sepsis syndrome," "septic shock," and "hypermetabolism" have been used imprecisely and have been confusing to many clinicians.

The clinical situation of sepsis-induced pulmonary dysfunction is complex and is not due simply to the presence of a single endogenous mediator or an inflammatory response. Many factors may contribute to the development of hypoxemia during sepsis (Exhibit 24-3).

Perhaps the earliest demonstration of pulmonary dysfunction in the septic animal model is an increase in airway resistance.[88] Decreased dynamic compliance occurs within hours and precedes both radiographic and clinical evidence of pulmonary parenchymal disease. Increases in airway reactivity have been demonstrated in humans even during the recovery phase of ARDS. Bronchoconstriction is likely the result of release, either locally or systemically, of endogenous mediator substances in response to endotoxin (in the Gram-negative sepsis models).

Prominent among these mediators are the byproducts of arachidonic acid metabolism, including the well-described vasoconstrictor thromboxane A_2 and the leukotrienes. Other mediators include complement and the proteolytic enzymes and superoxide radicals generated locally by pulmonary neutrophilic sequestration. This leukocytic sequestration occurs within minutes of an endotoxin infusion.[88] Supporting evidence for the role of these compounds in the development of increased airway reactivity is (*a*) the presence of eicosanoids in lung lymph flow and (*b*) the partial attenuation of abnormal mechanics when prostaglandin antagonists, or nonsteroidal antiinflammatory drugs are administered. The polymorphonuclear leukocyte is not, however, an absolute prerequisite for the development of ARDS; this syndrome has also been described in neutropenic oncology patients.[89]

In animal models, pulmonary hypertension also occurs early after endotoxin infusion.[88] Clinical experience in patients with existing pulmonary artery catheters at the time sepsis develops supports the frequency with which this physiological alteration also occurs in humans. Once again, the most likely etiology for pulmonary vasoconstriction is the arachidonic acid metabolites. Increased amounts of thromboxane has been recovered from animals' pulmonary lymph flow following endotoxin administration. The origin of the release of thromboxane is unclear as the depletion of both neutrophils and platelets does not prevent the onset of pulmonary hypertension.

An increase in the pulmonary capillary permeability is probably the most widely recognized pul-

EXHIBIT 24-3

CAUSES OF HYPOXEMIA DURING SEPSIS

Endogenous mediator-induced bronchoconstriction[1]

Ventilation–perfusion mismatch due to maldistribution of ventilation, exacerbated by positive-pressure ventilation[2]

Increased shunting due to loss of regional hypoxic pulmonary vasoconstriction[3]

Increased pulmonary vascular permeability leading to interstitial and alveolar pulmonary edema[3]

Pulmonary hypertension and increased cardiac output leading to an increased gas exchange surface area in the presence of poor ventilation[3]

Increased oxygen consumption, both systemically and in respiratory muscles[4]

Respiratory muscle fatigue[5]

Alveolar collapse due to decreased surfactant[6,7]

Sources: (1) Esbenshade AM, Newman JH, Lams PM. Respiratory failure after endotoxin infusion in sleep: Lung mechanics and lung fluid balance. *J Appl Physiol*. 1982;54:967–976. (2) Norwood S. Physiologic principles of conventional mechanical ventilation. In: Kirby RK, Banner MJ, Downs JB, eds. *Clinical Applications of Ventilatory Support*. New York, NY: Churchill Livingston; 1990: 145–171. (3) Brighman KL. Specific organ function/dysfunction in sepsis: Pulmonary. In: Sibbald WJ, Spung CL, eds. *Perspective and Sepsis and Septic Shock*. Fullerton, Calif: The Society of Critical Care Medicine; 1986: 147–156. (4) Griffel MI, Asiz ME, Rackow EC, Weil MH. Effect of mechanical ventilation on systemic oxygen extraction and lactic acidosis during early septic shock in rats. *Crit Care Med*. 1990;18(1):72–76. (5) Hussain SN. Respiratory muscle fatigue: A cause of ventilatory failure in septic shock. *J Appl Physiol*. 1985;58:2031–2033. (6) Pison V, Obertacke U, Brand M, et al. Altered pulmonary surfactant in uncomplicated and septicemia-complicated courses of acute respiratory failure. *J Trauma*. 1990;30(1):19–26. (7) Oldham KT, Guice KS, Stetson PS, Wolfe RR. Bacteremia-induced suppression of alveolar surfactant production. *J Surg Res*. 1989;47(5):397–402.

monary injury that occurs during sepsis. Lymph-flow analysis that demonstrates increases in both volume and protein content supports the existence of increased capillary permeability in many septic animal models. The pathophysiology of this capillary "leak" appears to be largely the result of leukocytic-directed injury to the endothelial lining (ie, production of superoxide radicals and elastase); perhaps endothelial gaps are a direct cytotoxic effect of endotoxin.

Although pulmonary edema clearly may worsen gas exchange, this is not the only cause of hypoxia during sepsis. Both animal and human measurements have shown a lack of correlation between calculated variables of the efficiency of oxygenation, (eg, the alveolar-to-arterial oxygen difference, $AD_{O_2} - aD_{O_2}$) and the amount of extravascular lung water.[88] Despite the development of pulmonary hypertension, experimental evidence shows that within hours of an endotoxin infusion the regional ability of the lung for hypoxic vasoconstriction is lost.[86] Thus, blood flow continues to areas of the lung that are poorly ventilated; the result is poor gas exchange and hypoxemia.

Renal Dysfunction

The incidence and significance of acute renal failure in hospitalized patients were documented in 1983, when 2,216 consecutive hospital admissions were analyzed, revealing 129 episodes, in 109 patients (4.9%) of newly developed renal insufficiency.[90] (Impairment in renal function was defined as an increase of the serum creatinine of 0.5 mg/dL when the admission serum creatinine was less than 1.9 mg/dL, or an increase of 1.0 mg/dL for patients with a baseline serum creatinine of 2.0 to 4.9 mg/dL). This study concluded that decreased renal perfusion caused new-onset renal insufficiency in 54 episodes (42%), and 10 episodes (19%) were associated with septic shock. An important finding was the marked increase in patient mortality, 16 of 25 (64%) when the increase in serum creatinine exceeded 3.0 mg/dL, compared with 6 of 104 (6.5%) mortality when the rise in serum creatinine was less than 3.0 mg/dL.

Consecutive admissions to medical and surgical ICUs in 13 different medical institutions were evaluated in 1985.[91] Definitions for clinically significant

renal failure were drafted and validated by the observed rate for survival. In this study, renal failure was identified by the occurrence of any of the following measures:

- urinary output < 480 mL/24 h or <160 mL/8 h,
- serum creatinine > 3.5 mg/dL, or
- serum blood urea nitrogen (BUN) >100 mg/dL.

Another study[92] (N = 315) used a stricter definition: a rise in serum creatinine of 20% above the hospital admission level. Twenty-nine of 47 (62%) patients who developed acute renal insufficiency died.

Two studies[93,94] addressed the significance of renal failure occurring during sepsis. The first, published in 1980, studied 612 patients with Gram-negative bacteremia and found that the development of azotemia increased the fatality rate and the subsequent incidence of shock.[93] The second, published in 1987, studied 250 consecutive cases of severe, acute renal failure (defined as a serum creatinine > 5.5 mg/dL) that occurred at a single hospital.[94] Of the new cases, 125 (50%) occurred in medical patients, and 118 (47%) in surgical patients. Within the surgical group, major vascular surgery was the most common association (42 of 118). Renal failure associated with sepsis resulted in a greater need for dialysis (23 of 24), compared with renal failure following vascular surgery (33 of 42). Recovery of renal function occurred more frequently following vascular surgery (22 of 42), compared with sepsis (5 of 24). In the group of medical patients, the most common cause of renal failure was sepsis (29 of 65 patients), which was also associated with a nearly uniform requirement for dialysis (24 of 29) and a low recovery rate (11 of 29). The mortality rate for sepsis-induced renal failure was significantly higher than the overall group mortality (62%–78% compared with 44.4%).

Literature revealing the pathophysiological mechanisms of sepsis-induced renal failure is sparse. Because sepsis and septic shock cause clinical events that may be injurious to the kidney, the pathophysiology is certain to be multifactorial (Exhibit 24-4).

EXHIBIT 24-4

PATHOPHYSIOLOGICAL MECHANISMS IN SEPSIS-INDUCED ACUTE RENAL FAILURE

Decreased effective intravascular volume

Decreased cardiac output

Decreased renal blood flow secondary to decreased renal perfusion pressure

Positive pressure ventilation,[1] resulting in decreased cardiac output

Alterations in renal afferent and efferent arterial vasodilation from sympathetic or neurohumoral effects[2,3]

Tubular obstruction and renal tubular cellular swelling

Concomitant trauma or extremity ischemia resulting in the release of heme pigment

Sepsis-induced disseminated intravascular coagulation

Reperfusion injury (no reflow phenomenon and the release of oxygen free radicals)

Direct effect of substances such as endotoxin[4]

Nephrotoxic antibiotics used to treat a focus of infection

Intrarenal redistribution of blood flow away from the cortical nephrons[5]

Sources: (1) Rosenthal MH. Hemodynamic effects of pulmonary insufficiency. *Int Anesthesiol Clin*. 1986;24:145–148. (2) Turnquest PE, Rosenthal MH. Acute renal failure in trauma and critically ill patients. *Sem Anesth.* 1989;8(4)338–346. (3) Cumming AD, Kline R, Linton AL. Association between renal and sympathetic responses to nonhypotensive systemic sepsis. *Crit Care Med.* 1988;16(11):1132–1137. (4) Wardle N. Acute renal failure in the 1980s: The importance of septic shock and of endotoxemia. *Nephron*. 1982;30:193. (5) Lucas CE. The renal response to acute injury and sepsis. *Surg Clin North Am.* 1976;56:953–975.

Neurological Manifestations

Dysfunction of the nervous system, particularly the central nervous system, is of paramount importance, for the degree of recovery determines the functional status of the patient who leaves the ICU or hospital. Brain dysfunction may appear early in sepsis without an infectious agent present in the central nervous system. Acutely altered mental status due to sepsis alone has been reported to occur in approximately 23% of patients with sepsis.[95]

Clinical Features

Encephalopathy associated with sepsis is usually nonfocal, with mental-status changes ranging from mild disorientation and confusion through lethargy, agitation, and confusion, to deep coma.[96] Elderly patients appear to be at particularly high risk; agitation or subtle mental-status changes may be the only clinical signs of early sepsis in this group. Metabolic or septic encephalopathy typically presents with a constellation of signs, including normal pupils and eye movements, tremor, asterixis, and multifocal myoclonus.[97] Also, generalized seizures, focal seizures, and other focal signs such as hemiparesis and gaze paresis have been seen.[98] Thus, the presence of focal findings does not exclude the clinical presentation of sepsis.

Patients with sepsis may have a multitude of physiological derangements that may contribute to encephalopathy. These include not only hypotension, hypoxia, and uremia, but also electrolyte, endocrinological, or metabolic abnormalities. Nevertheless, sepsis-associated central nervous system depression can occur in the absence of these factors. Direct microbial invasion or their products such as endotoxin have been implicated, and diffuse microabscesses appear to be common in patients with sepsis.[97,98] Patients in septic shock may develop vascular lesions that include cerebral purpura or microinfarctions.[98] Decreases in cerebral blood flow in these patients may not correlate with mean arterial blood pressure or perfusion pressure.[99] Lastly, administered therapies can also cause encephalopathy. Common causes include sedative medications and hyperosmolality or other metabolic derangements from total parenteral nutrition.

Diagnosis and Prognosis

Diagnosis of septic encephalopathy is based initially on diagnosing a central nervous system infection. Computerized tomography scan will show a mass lesion such as an abscess, hemorrhage, or infarction, but not cerebral microabscesses, hemorrhages, or microinfarctions. Further resolution may be sought with magnetic resonance imaging. Cerebrospinal fluid examination is also necessary to rule out meningitis. Clearly, etiologies for encephalopathies other than meningitis must be entertained, for the majority of patients with sepsis do not have a central nervous system infection.[96]

Although many electroencephalogram changes occur in septic encephalopathy, they are not specific and may be seen in many toxic and metabolic encephalopathies. Electroencephalogram changes include diffuse slow-wave abnormalities, generalized suppression, burst suppression, triphasic waves, and focal or generalized seizures.[97]

Prognosis varies with the course of sepsis, failures of other organ systems, associated central nervous system trauma, and the initial Glasgow coma score. Of patients with nontraumatic coma, 68% of those whose coma was caused by metabolic disease or sepsis were either dead or comatose when reevaluated at 2 weeks.[100] Patients with acutely altered mental status due to sepsis have a higher mortality than those who have no mental-status changes.[95]

Peripheral Neuropathy

Peripheral nerve dysfunction also appears in patients with sepsis. This critical-illness polyneuropathy occurs in at least 50% of patients who remain septic or critically ill for longer than 2 weeks.[97] In a study[101] of patients with sepsis/SIRS who were admitted to an ICU for longer than 5 days, electrophysiological studies revealed that 70% developed some form of polyneuropathy; 30% developed primary axonal degeneration of both motor and sensory fibers. This disorder may present as difficulty in weaning from the ventilator, with severely ill patients showing no diaphragmatic responses to phrenic nerve stimulation.[97] Limb weakness and depressed or absent deep-tendon reflexes occur in mild cases. In severe cases, the absence of any voluntary or reflex-induced movement in all four limbs has been reported.[101]

This polyneuropathy occurred primarily in older patients (mean age 64 y) and affected males and females equally.[101] The etiology of this polyneuropathy remains unclear. The factors that most closely correlated with the development of polyneuropathy were

- the number of invasive procedures performed,

- elevated glucose,
- low serum albumin, and
- the duration of stay in the ICU (mean onset was 28 d).

All patients had concomitant evidence of septic encephalopathy. Complete recovery occurred only in patients whose illness was mild to moderately severe. Patients with a severe peripheral nerve dysfunction, in which diaphragmatic and limb paralysis occurred, failed to improve and eventually died. Thus, critical-illness polyneuropathy can have a significant impact on the course or the eventual recovery of the patient with sepsis.

Metabolic and Endocrinological Responses

Acute illness or injury results in a hypermetabolic state that is characterized by increased gluconeogenesis, mobilization of fat stores, and rapid nitrogen metabolism. Oxygen consumption increases and epinephrine, cortisol, and glucagon levels are increased.[93] Newly manifested hyperglycemia in a critically ill patient should always raise the differential diagnosis of early sepsis. The severity of this increased metabolic demand relates in part to the severity of the illness or injury, with the resting energy expenditure increasing by 10% to 20% with multiple fractures, 12.9% with respiratory failure, and 40% to 100% with extensive thermal injury.[102]

Immunological Aberrations

Cellular and subcellular interactions, the mediators that are released by these cells, and the response to infection and sepsis were discussed previously in this chapter. The immunological changes and defects related to trauma, infection, and critical illness are the focus of this section. Inadequacy or decrements in immune function predispose the patient to overwhelming sepsis, MODS, and death.

Immunosuppression and Critical Illness

Serious injury or illness primarily affects T cell function, as reflected by anergy on skin testing. B cell dysfunction is less common but can appear in individuals who are ill for a prolonged time period, are inadequately nourished, or are subjected to severe burns.[43] B cell function is generally assessed by measuring total serum immunoglobulin levels or the amounts of the individual immunoglobulin subclasses. Tetanus toxoid in vivo and pokeweed mitogen in vitro test the B cell's recall or secondary immune function.

Infections. Primary infectious disease processes often predispose individuals to further infection. Bacterial pneumonia following viral infection or bacterial sepsis associated with malaria are common examples. Much of the predisposition may relate to the breakdown of natural host defenses from the primary infection. One example is the tracheobronchial mucous membrane derangements secondary to the local effects of viral infections. Infectious diseases that depress cell-mediated immunity can potentially complicate the course of an already compromised host. Several infections that have been associated with depressed cell-mediated immunity in humans include influenza, measles, infectious mononucleosis, herpes simplex virus, cytomegalovirus, tuberculosis, histoplasmosis, leprosy, syphilis, pertussis, and streptococcal infections. Malaria has been shown to depress the humoral immune system as well.[103] These common infections, particularly among deployed forces (soldiers are stressed because they have been removed from their normal immunological milieu), then may compromise the individual's immunological response to other insults, such as wound infections or trauma.

Trauma. Major trauma has a profound effect on the patient's immunological function. Total T cell counts and T cell function are markedly depressed in response to injury. The T cell count decreases within hours of injury and may remain depressed for up to 10 days.[1,43] The percentage of T cells in the peripheral blood remains normal, although it may decrease to less than 40% of normal 6 to 8 days following severe burns.[1,43,104] The suppressor/helper T cell ratio increases from 0.55 to 1.04 after trauma.[1]

Testing of cell-mediated immunity with delayed cutaneous hypersensitivity testing has found patients to be anergic following major trauma, a condition that usually persists 4 to 7 days.[104,105] Persistent anergy is associated with an increase in septic complications. Up to 59% of trauma victims with complete anergy to delayed cutaneous hypersensitivity testing develop a significant infectious or septic process.[104,106] Anergy early in a patient's course may predict infectious complications, although later anergy may result from a septic focus.[43]

B cell counts also fall after trauma, although their percentage of the total lymphocyte count remains unchanged.[1] Total immunoglobulin levels fall. Immunoglobulin (Ig) G levels have been shown to be severely depressed for 1 to 2 months after thermal injury.[1,104] However, most of the decrease in the

levels of IgG and other immunoglobulins appears to be dilutional.[104]

B cell dysfunction does not appear to be a major factor leading toward increased infection. A study of burn patients who were immunized with a polyvalent *Pseudomonas* vaccine reported effective humoral immune responsiveness; the incidence of *Pseudomonas* bacteremia decreased from 16% to 6%.[107]

Trauma activates the complement pathways, affecting primarily the alternate pathway. The classic pathway becomes active prior to and during the appearance of sepsis.[1] As a result, serum levels of complement as well as fibronectin are depressed, with C3 levels inversely related to the severity of injury.[1,104,108] Fibronectin levels, falling within 4 hours of injury, return to normal within 3 days barring complications.[104]

Malnutrition. Most soldiers injured in combat should be relatively well nourished when injured, unless they have been involved in an arduous or protracted campaign. Without adequate nutrition, immunological dysfunction occurs within days. T cell numbers decrease and the function of T-helper cells is impaired. Evaluations of cell-mediated immunity have revealed a relationship between malnutrition, anergy, and humoral immunological impairment. In response to new antigens, these patients' immunoglobulin generation is impaired, leading to an increased infection rate.[43,109]

Surgery in the Immunocompromised Patient With Sepsis/SIRS

Wounded casualties frequently require surgery, and anesthetic agents can contribute to significant perioperative immunological aberrations. Halothane, nitrous oxide, and pentothal decrease total lymphocytic counts and the number of antibody-forming cells in the spleen.[110] Polymorphonuclear leukocyte chemotaxis and phagocytosis is also impaired.[109]

The immunological abnormalities that occur in accidental trauma also appear in patients who undergo the more controlled traumatic injury performed in the operative suite. For example, the phagocytic capacity of reticuloendothelial cells is depressed following surgery and trauma in proportion to the severity of the insult. Opsonization of bacteria, which enhances these cells' function, is depressed, perhaps as a result of decreased levels of the major opsonic protein, fibronectin.[109] Administering cryoprecipitate that contains high levels of fibronectin to surgical and traumatized patients with sepsis has been shown to improve physiological variables (cardiac index, oxygen consumption, oxygen delivery, and pulmonary shunt fraction); however, improved survival has yet to be shown definitively.[111]

Cell-mediated immunity is the immunological function most affected in the postoperative patient. T cell changes parallel those described above in the traumatized patient. In 46 otherwise healthy, nontraumatized patients who were studied, minor surgical procedures under general anesthesia did not appear to alter skin test results significantly (ie, these patients did not become anergic).[112] However, of patients who underwent major cardiovascular procedures (such as coronary artery bypass grafting or abdominal aortic aneurysm repair), 42% became anergic by postoperative day 3. Compared with patients who retained their immunocompetence, these anergic patients had more infectious complications and were hospitalized longer. Restoration to normal, reactive skin tests may take as long as 28 days.

Perioperative hemorrhage that requires the transfusion of 10 or more units of blood in 24 hours has a mortality rate of approximately 50%. Young, otherwise-healthy trauma victims who require 25 or more units of blood have a 71% mortality rate.[104] Transfusion of blood appears to contribute to the immunological depression seen in trauma victims, even allowing the prediction of subsequent infection.[113] Only 10% of patients who received no transfusion developed an infectious complication, whereas 80% of patients who required more than 15 units of blood did.

Persistent anergy has been seen in postoperative patients with sepsis. The prompt return of normal skin tests follows surgical drainage of an intraperitoneal abscess, an infected common bile duct, or another inflammatory process.[114]

Immunological depression in the battlefield casualty may occur in response to many factors. The severity of these defects clearly dictates the patient's eventual outcome and survival. As no specific therapy has yet been proven to correct these immunological defects, meticulous patient care is important to prevent compounding immunological depression.[43]

Hematological and Coagulation Defects

Sepsis adversely affects the hematopoietic system, resulting in a variety of clinical maladies that can complicate an already seriously ill patient's course. Pancytopenia, which may occur in a variety of medical illnesses, clearly predisposes a patient to

develop significant infections. On the other hand, pancytopenia has also been *caused* by infections such as *Mycobacterium tuberculosis*, atypical mycobacteria—especially *Mycobacterium kansasii*, *Histoplasma capsulatum*, *Salmonella typhi*, *Mucor* species, and *Brucella* species.[115] Isolated infections (eg, localized pulmonary infections) do not typically cause this significant hematological insult. Rather, overwhelming infection (during which these organisms are frequently recovered on bone marrow culture) is the typical clinical scenario leading to pancytopenia.

Leukocyte Interactions

Neutrophilia. The degree of neutrophilia varies among patients and the severity of their infections. Mild, localized infections may be associated with neutrophil cell counts of 12,000 to 14,000/mm^3, while severe, pyogenic infections may have cell counts reaching 50,000 to 75,000/mm^3. Leukemoid reactions with cell counts of 50,000 to 100,000/mm^3 are exaggerated responses to these phenomena and, although uncommon, they do occur in a substantial number of infections (eg, pneumonia, meningitis, diphtheria, and tuberculosis).[115]

Neutrophil-releasing factor is stimulated by endotoxin and may, in fact, be the activated complement component C3a.[96] IL-1 also plays a role in the release of neutrophils from the bone marrow.[115] Neutrophilia that persists with chronic infection is probably mediated by colony-stimulating factors, which increase the cell division and turnover of granulocyte precursors.

Although most bacterial infections result in a leukocytosis, this is not universal. In a study of medical patients with sepsis whose blood cultures were positive for bacteria, only 69% had leukocytosis on the first day of septicemia.[116] Neutrophilia is uncommonly seen in infections caused by *Chlamydia* species, *Mycoplasma* species, *Rickettsia*, *Mycobacteria*, and fungal infections.[115]

Neutropenia. Neutropenia is characteristically seen in infections such as typhoid fever, brucellosis, salmonellosis, pertussis, rickettsial infections, disseminated histoplasmosis, and disseminated tuberculosis. However, development of neutropenia in a patient with sepsis may portend a bad prognosis and may result from splenic sequestration, altered immunity, complement-induced neutrophil aggregation,[96] or increased neutrophil consumption in the setting of depleted bone marrow. This condition can be seen in infants, the elderly, and patients with alcoholism, diabetes, malnutrition, or shock.

Neutrophil Morphology. In a study[116] of medical patients with sepsis, 38% had toxic granulations noted on the initial day of sepsis and over one half developed them at some time during their septic course. Another study[117] of patients with bacteremia and fungemia found toxic granulations in 75%. Döhle bodies, Pelger-Huët anomaly (bilobed neutrophils), and vacuolation were also found, the latter being touted as a sensitive and specific marker for bacteremia.[96] However, although they are suggestive, none of these findings are pathognomonic for infection.

Eosinophils. Eosinophilia is rare in bacterial and fungal infections, though in adults it is common in bronchopulmonary aspergillosis and coccidioidomycosis.[115] It classically occurs in invasive helminth infections. Eosinopenia (50 cells/mm^3), on the other hand, commonly heralds the onset of severe bacterial infections. Causes include margination or migration of these cells from the vascular space, inhibition of bone marrow release, and lastly, a decrease in bone marrow production.[96] The absence of eosinopenia when a febrile patient is evaluated is thought by some to question the diagnosis of severe infection.[118] Counts greater than 5% may suggest a nonbacterial etiology such as drug fever, Addison's disease, myeloproliferative disease, or a parasitic infection.[96] Although without defined sensitivity and specificity, eosinopenia is commonly associated with the acute onset of sepsis.

Monocytes and Lymphocytes. Monocytosis (> 800 cells/mm^3) has been associated with a variety of infections, though usually in those of a subacute or chronic course. It is found in approximately 15% to 20% of patients with disseminated tuberculosis, and similarly in those with subacute bacterial endocarditis.[115] Because there is no bone marrow reserve of monocytes, an increased turnover in association with exudates may result in a monocytopenia.[118]

Lymphocytosis (> 4,000 cells/mm^3) is not usually seen in traumatized patients with sepsis. Lymphocytosis occurs commonly in pertussis, rarely with other bacterial or fungal infections, and occasionally in tuberculosis, syphilis, brucellosis, rickettsial, and viral infections. More commonly, however, lymphocytopenia (< 1,000 cells/mm^3) is associated with acute bacterial infections.

The Effect of Sepsis on Erythrocytes

The principal erythrocytic response to infection is anemia, which can arise after several days in an acute, severe infection but is more typically associ-

ated with chronic bacterial or fungal infections. The rapid appearance of anemia in an acute infection is the result of one of four processes[118]:

1. hemorrhage,
2. erythrocyte destruction secondary to the infection itself (eg, malaria),
3. microangiopathic hemolysis in association with disseminated intravascular coagulation (DIC), or
4. activation of an underlying, preexisting hemolytic process.

Although most patients are anemic when they are admitted to a medical ICU, 85% demonstrate a further drop in hematocrit in association with sepsis.[116] A reticulocytopenia as well as a shortened erythrocyte survival time persist for approximately 2 weeks in these patients. Occasionally, hypochromic and microcytic indices occur when iron metabolism is disturbed, resulting in low values for serum iron and transferrin. Two possible causative factors are IL-l and TNF. Of particular significance is IL-1's ability to induce the release and activation of lactoferrin from neutrophils and to decrease hepatic transferrin synthesis, both of which contribute to the decrease in serum iron. Decrease in serum iron levels may, in part, be a host-defense mechanism, for free iron contributes to microbial virulence. Chronic anemia that develops during the first month of an illness is typically normochromic and normocytic. Anemia may result from chronic, suppurative infections such as meningitis, empyema, cavitary pulmonary disease, endocarditis, or occult intraabdominal abscesses. Although a variety of bacterial and fungal agents have been reported to cause hemolytic anemia, it actually occurs only rarely. Although three fourths of patients infected with *Mycoplasma pneumoniae* develop cold agglutinins, Coombs-positive hemolytic anemia is exceedingly rare.[115]

Sepsis-Induced Platelet Dyscrasia

Thrombocytopenia (platelet counts < 150,000/mm^3) is present in 33% of medical patients with sepsis and blood cultures that are positive for bacteria.[116] In 65% of these patients, the thrombocytopenia is recognized prior to the onset of sepsis. Most of these patients experience further declines in their platelet counts. The incidence of thrombocytopenia in patients with sepsis ranges from 30% to 100%.[115,119] Approximately two thirds of patients with bacteremia have platelet counts lower than 150,000/mm^3, while one third have platelet counts lower than 50,000/mm^3.[120] Thus, thrombocytopenia is a common finding in patients with sepsis, particularly when associated with DIC (88%–100% incidence).[115]

Thrombocytopenia may occur in critically ill patients prior to the onset of severe infections. Many etiologies for depressed platelet counts are present in this patient population and have been reviewed elsewhere.[119] Briefly, low platelet counts can be due to clumping and therefore spurious, thus warranting close evaluation of the peripheral blood smear. Platelet production can be depressed from the use of alcohol or drugs, toxins, infection-induced aplastic anemia, and nutritional deficiencies, particularly vitamin B_{12} or folate. Distribution and dilution problems also result in thrombocytopenia, as occurs in hypersplenism, hypothermia, and massive transfusion or fluid therapy.

Another category of causes of thrombocytopenia is platelet consumption or destruction. This is the most common reason for thrombocytopenia found in the critically ill patient, and it occurs via two mechanisms: *nonimmune* (mediated by thrombin or surface interactions) and *immune-mediated*. Either mechanism—alone, or in concert with the other—contributes to thrombocytopenia in many settings, only one of which is infection. The most common means of increased platelet destruction during bacterial infections is consumption during DIC. The organisms most commonly implicated are *Neisseria meningitidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.[119]

Bacterial, viral, fungal, rickettsial, and protozoal infections all may cause thrombocytopenia. Although usually associated with blood-borne organisms, thrombocytopenia can develop in severe infections with blood cultures that are negative for bacteria (eg, pneumonia, peritonitis, or abscesses).[115]

Platelet aggregation, particularly as induced by *Staphylococcus aureus* or endotoxemia, is a major cause of increased platelet turnover. An immunologically mediated destruction is also seen, particularly in Gram-negative infections. Platelet-associated IgG has been found to be elevated in almost three fourths of patients with Gram-negative sepsis and thrombocytopenia, and in 80% of patients with Gram-positive sepsis.[121] Damage to vascular endothelial cells by *Rickettsia* species and perhaps *Neisseria meningitidis* may result in increased platelet adherence.[119,120]

Viral-induced thrombocytopenia is probably as common as that associated with bacterial infections.[119] Viral infections commonly implicated in-

clude mumps, varicella, disseminated herpes simplex, cytomegalovirus, infectious mononucleosis, rubeola, and rubella.[120] Thrombocytopenia is also common in HIV infections, whether it be based solely on serologic evidence or in association with acquired immunodeficiency syndrome (AIDS).[120] Although usually mild, the thrombocytopenia seen in these infections can at times be life threatening.[119]

Finally, protozoal infections that can be seen in deploying forces can cause thrombocytopenia. A chronic disorder is seen with toxoplasmosis, whereas more-acute thrombocytopenia, often in conjunction with DIC, is seen in malaria or trypanosomiasis.[120]

Disseminated Intravascular Coagulation

The development of DIC in patients with sepsis, particularly sepsis from Gram-negative organisms, has been well described.[118,122] Endothelial cells become damaged, activated, or are shed as a consequence of the onset of sepsis. Contributory factors include endotoxin, cellular hormones such as TNF, and tissue hypoxia. Tissue thromboplastin is released and, with exposed collagen, causes platelet adhesion and activation. Diffuse coagulation ensues and overwhelms normal compensatory mechanisms. Fibrinogen, platelets, and coagulation factors are consumed. The formation of fibrin and fibrin monomers activate the fibrinolytic system, which then produces fibrin degradation products. These products then inhibit coagulation, impair platelet function, and can cause pulmonary vascular constriction.[118] The predominant clinical findings in DIC, whether they may be thrombosis or hemorrhage, depend upon the balance of pathological processes or the competing compensatory mechanisms.

Dermatological and Ophthalmological Manifestations

Outward cutaneous manifestations of sepsis are often present and may be overlooked in the evaluation of the patient with sepsis. Three patterns of cutaneous lesions appear in these patients.[96] The first is a consequence of bacterial invasion directly into the skin or subcutaneous tissues. Both the nature of the invading organism and the host's response determine the appearance of the lesion. The second occurs as a result of the septic picture, such as hypotension or DIC, without direct cutaneous involvement of the infection. And third, signs of immune-mediated vasculitis or microinfarctions from infective endocarditis may appear.

Gram-negative sepsis from *Campylobacter fetus*, *Vibrio* species, *Aeromonas hydrophila*, *Bacteroides* species, *Yersinia enterocolitica*, and *Serratia marcescens* cause cellulitis, erysipelas, and fasciitis.[96] The lower extremities are at particular risk, with *C fetus* causing lesions that may appear similar to deep venous thrombosis.[123]

Bacterial involvement of the skin and subcutaneous tissues can occur without much associated inflammation and can therefore appear in the granulocytopenic host. The invading organisms are usually Gram negative, particularly *Pseudomonas aeruginosa*, and initially form vesicles or erythema multiforme. These later progress to necrotizing bullous lesions, termed ecthyma gangrenosum.[124]

In sepsis, DIC is associated with acrocyanosis of peripheral tissues such as the fingertips, toes, ears, and nose.[96] Subsequent necrosis may occur and is termed *symmetrical peripheral gangrene*. Although typically associated with Gram-negative infections, these findings can also occur in sepsis associated with Gram-positive organisms.

In patients who have ophthalmological complications of sepsis/SIRS, fundoscopic examination can often aid in the diagnosis of the causative organism. Common, nonspecific retinal changes include retinal hemorrhages, cotton wool spots, and subconjunctival hemorrhages. Roth's spots secondary to infective endocarditis can also appear. Other nonbacterial organisms can present with retinal findings. These include viruses such as cytomegalovirus, parasites such as toxoplasmosis, and fungi such as *Candida* species.[71] Ophthalmological consultation for diagnosis and management is usually necessary for many of these disorders.

DIAGNOSIS AND MONITORING

The physician's senses of vision, hearing, and touch, accompanied by a high index of suspicion, remain the most valuable monitors for the early detection of sepsis. No other diagnostic tool can replace the clinical acumen of an experienced physician. However, regardless of the physician's clinical experience, various laboratory analyses should be made to confirm the diagnosis. The microbiologic diagnosis of the potential cause of sepsis in a patient requires proper submission and handling of the specimens. Close coordination between the clinician and the microbiology laboratory is indicated.

Hematological Evaluation

The clinical and laboratory diagnosis of sepsis and septic shock were reviewed earlier in this chapter. Typical findings include: leukocytosis with a left shift or leukopenia, thrombocytopenia, and prolonged prothrombin time or activated partial thromboplastin time.[125] Most hematological and chemistry studies are routinely performed on critically ill patients, based on a thorough history and physical examination. The patient's clinical condition and course should then dictate the diagnostic laboratory studies to be performed.

Microbiologic Evaluation

Diagnosis of the infection responsible for the septic picture in the critically ill patient requires that adequate, appropriate, and representative samples be collected for laboratory and microbiologic processing. Specimens of blood and respiratory-tract exudates are the most frequent submissions for evaluation. Urine samples obtained from clean-catch, mid-stream, catheter, or suprapubic specimens are also usually submitted for evaluation. Significant values are more than 10^6 organisms per milliliter, although any growth in newly catheterized or suprapubic specimens is significant. Other specimens from body fluids, exudates, pus, and mucous membranes also require submission for study.

Ideally, specimens should be collected from normally sterile body sites and not be contaminated by the usual skin or mucous-membrane flora. Whenever possible, tissue specimens are preferred over specimens obtained via swabs. Specimens also require prompt transport to the laboratory for proper processing to ensure optimal recovery of the causative organisms. If possible, the specimens should be obtained before antimicrobial therapy is initiated.[125]

Specimens should initially be examined directly. The test that should be performed most commonly is the Gram's stain, to evaluate the bacterial population in the specimen. Wet mounts are useful in demonstrating protozoa; india ink or potassium hydroxide is added to look for *Cryptococcus neoformans* or fungi, respectively. Acid-fast stains identify *Mycobacteria* species and fluorescent stains can identify *Legionella*. Silver stains are useful for fungi and *Pneumocystis,* and malarial parasites can be seen with a Giemsa stain.[126]

Cultures are performed on all suitably submitted specimens. Different isolation techniques are required for the wide variety of bacteria, fungi, viruses, and protozoa. Once an organism is identified, the susceptibility of the isolated pathogen to various antimicrobial agents is performed. Susceptibility or resistance to the agent is expressed as the minimal inhibitory concentration of the antimicrobial agent required to prevent the growth of a specific inoculum of organisms. The therapeutic goal in choosing an antimicrobial agent is to achieve a mean drug concentration in the affected tissue that is 2- to 4-fold greater than the minimal inhibitory concentration.[126]

Blood Cultures

Bacteremia, particularly with Gram-negative organisms, is the prototypical infection that causes sepsis and septic shock. Blood cultures obtained from sterile venipunctures are the primary means of detecting bacteremia. In untreated patients who eventually develop bacteremia, a single blood culture will be positive approximately 75% of the time; if three blood cultures are drawn, this rate increases to 98%. Most of these cultures turn positive during incubation within 72 hours. Thus, three sets of blood cultures observed for 3 days will detect Gram-negative bacteremia in more than 90% of patients who will eventually become bacteremic.[127]

Respiratory-Tract Cultures

Specimens from the respiratory tract are usually obtained from sputum samples taken via an endotracheal tube. (Obtaining pulmonary specimens is complicated by the inevitable contamination by upper-airway flora. Gram-negative organisms that colonize the upper airways of patients in the ICU may or may not be pathogenic.) Examination of the sputum is necessary to ensure an adequate sample. In the nonintubated patient, finding a single dominant type of organism in the presence of polymorphonuclear cells is useful in determining the pathogenic organism of a lower-respiratory-tract infection. The reliability of these criteria is less well known in intubated patients.[126] Potential complications and the lack of clinically useful data have caused the use of transtracheal aspiration to decline.

Specimens obtained via bronchoscopy may be useful for microbiologic study of the respiratory tract. Simple bronchial washings for bacterial flora are difficult to interpret; the reliability of these specimens to diagnose lower-tract infections is similar to that of sputum cultures. Protected brush

specimens may improve the diagnostic yield; the sensitivity and specificity for properly diagnosing the etiologic bacteria normally ranges from 59% to 70%, although some report 90%.[126]

Bronchoalveolar lavage has also proven to be a beneficial means of obtaining specimens and is particularly efficacious in patients with AIDS. Yields of nearly 100% for *Pneumocystis carinii* have been reported, with yields for other pathogens ranging from 60% to 85%.[126] Bronchoalveolar lavage makes it possible to diagnose infections by means of both rapid-staining techniques and cultures. Rapid stains for *Pneumocystis*, viral inclusions, *Legionella*, fungi, *Mycobacteria*, and bacteria have been beneficial in aiding early, appropriate antimicrobial therapy.

Additional Tests

Diagnostic tests other than culturing can be performed to determine the potential cause of sepsis in a patient. Capsular polysaccharide antigens can be detected for *Hemophilus influenza*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Cryptococcus neoformans*. Enzyme-linked immunosorbent assays (ELISAs) to detect bacterial antigens have been useful in diagnosing infections by *N gonorrhea* and *Legionella* species. And lastly, serologic evidence for antibody detection has been used to diagnose typhoid fever, brucellosis, tularemia, Legionnaires' disease, acute viral diseases, histoplasmosis, rickettsial typhus and spotted fevers, toxoplasmosis, and amebiasis.[126] Other organisms are being detected and other diagnostic measures are continually being developed.

Sophisticated Bedside Monitors

Because significant cardiovascular dysfunction occurs in sepsis / SIRS, accurate assessment of hemodynamic function is imperative to successfully manage these critically ill patients. Clinical assessment and observation often fail to accurately determine the hemodynamic status, and, hence, the optimal therapy for these patients. Hemodynamic monitoring can be invasive and noninvasive.

Pulmonary Artery Catheter

The development of the flow-directed pulmonary artery catheter has enabled us to more accurately assess the hemodynamic status of patients with sepsis. Newer catheters now allow the physician to measure and calculate intracardiac and pulmonary arterial pressures, cardiac output and cardiac index, intracardiac and mixed venous oxygen saturation, right ventricular ejection fraction, right ventricular end diastolic and end systolic volumes, and "continuous" cardiac output.[128] With this information at hand, the clinician can obtain a more accurate assessment of the patient's intravascular volume status and ventricular performance, calculate hemodynamic and respiratory indices to aid management, and determine oxygen delivery and tissue oxygen consumption.

Many indications for the use of the pulmonary artery catheter have evolved since its introduction.[129,130] If ARDS develops in the patient with sepsis, it can be more readily diagnosed and managed with a pulmonary artery catheter that distinguishes cardiogenic from noncardiogenic pulmonary edema. Particularly in the traumatized or postoperative patient, intravascular volume status can be more accurately assessed.

Insertion techniques have been described in detail elsewhere.[131] Catheterization of the pulmonary circulation can be performed by inserting the pulmonary artery catheter into the internal jugular, subclavian, femoral, or antecubital veins. Minor and major complications can occur with the placement and use of these catheters, however.[128,132] Insertion complications include bleeding, vessel perforation, pneumothorax or hemothorax, and ventricular dysrhythmias. Maintaining the catheter in the pulmonary artery has complications, as well. These include local vascular thrombosis, pulmonary arterial rupture, pulmonary infarction, or catheter-related sepsis. So, although a pulmonary artery catheter is beneficial in the management of patients with sepsis, further injury is possible and warrants consideration before the catheter is inserted.

Two major assumptions must be made before the data obtained from the pulmonary artery catheter can be interpreted correctly:

1. The equipment must be properly functioning and calibrated, and the transducer zeroed at the mid-left atrial level. The function of the pulmonary artery catheter is to obtain an estimate of left ventricular preload, which is determined by left ventricular end diastolic volume.
2. A direct relationship is assumed between the left ventricular end diastolic volume, which is difficult to measure, and the more easily obtained left ventricular end diastolic pressure. Changes in left ventricular compliance, however, alter this volume-to-pressure relationship.

Under conditions of a normal pulmonary vascular bed, mitral valve, and left ventricular function or compliance, PCWP measured at end expiration in pulmonary zone III is equal to both the mean left atrial pressure and left ventricular end diastolic pressure. The second major assumption is altered by changes in any of these factors or catheter placement.[129] Other factors, such as the application of positive end-expiratory pressure to mechanical ventilation, also alter this assumption.

Pulmonary artery catheters also provide a means of obtaining an estimate of cardiac output by thermodilution. Using the proper volume and temperature of injectate required by the specific catheter and cardiac computer is of utmost importance in obtaining an accurate estimate. Timing the injections for cardiac output measurement within the same period in the respiratory cycle may improve the reproducibility of the results. However, indiscriminate timing of injections for cardiac output throughout the respiratory cycle more accurately determines the clinical status of the patient. Cardiac output divided by body surface area yields cardiac index, a figure that can then easily be compared between individuals. Obtaining these figures is necessary to determine systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), stroke work index (SWI), and oxygen delivery (Do_2).

One measurement that can be obtained only from a pulmonary artery catheter is a mixed venous blood gas. This measurement can be (*a*) obtained intermittently or, via a specially designed catheter that uses reflectance oximetry, (*b*) monitored continuously. The measurement of venous oxygen saturation (Svo_2) is necessary to determine oxygen consumption (Vo_2).

Svo_2 varies directly with cardiac output, hemoglobin, and arterial oxygen saturation. Decreasing Svo_2 may result from increased metabolic rate, with concomitant tissue extraction of oxygen or decreased oxygen delivery as a result of cardiac dysfunction, anemia, or arterial hypoxemia. Increases in Svo_2 occur where less oxygen is either utilized or extracted, as in arterial-venous fistulae, cirrhosis, left-to-right cardiac shunts, peripheral shunts, cyanide poisoning, hypothermia, inadvertent sampling of blood from the pulmonary artery (taken when the catheter is improperly inflated or wedged), and sepsis.[128]

Sepsis causes an increase in measured Svo_2 as a result of decreased tissue oxygen extraction when

1. a disproportionately high percentage of cardiac output is distributed to the skin, where oxygen consumption is minimal, and
2. microvascular occlusion occurs from leukocyte aggregates, microthrombi, vasoconstriction, and platelet aggregates.

Additional findings that typically occur in patients with sepsis with a pulmonary artery catheter in place include

3. a moderate-to-high cardiac output in the presence of
4. a low systemic vascular resistance.

These findings are necessarily contingent on other determining factors such as adequate hemoglobin, arterial oxygen saturation, and intravascular volume. Any reduction in these determining factors could lead to misinterpretation of the data. Using a pulmonary artery catheter has aided the diagnosis of unsuspected sepsis. One study revealed that unsuspected septic shock was diagnosed in 38% of patients only after a pulmonary artery catheter was inserted.[133] Whether the use of pulmonary artery catheters improves outcome from septic shock remains to be definitively determined. Proponents have advocated its use to optimize oxygen delivery to tissues in an attempt to maintain adequate tissue oxygen consumption and hence, improve survivability.

Echocardiography

The major noninvasive means of evaluating cardiac performance is the echocardiogram. Through the use of the traditional M-mode echocardiograph, two-dimensional echocardiography, and the recently developed Doppler color-flow mapping, echocardiography can be used to assess left ventricular function both quantitatively and qualitatively, diagnose ischemic heart disease, to include infarction, evaluate pathological lesions in and around the heart in the great vessels, and observe intracardiac blood flow through the valves and intracardiac shunts.[134] The effectiveness of these studies has been further improved through the development of transesophageal imaging. Placing the transducer within the chest cavity can eliminate many of the artifacts of chest-wall deformities, subcutaneous tissue, emphysematous lungs, or even surgical bandages, and thus provide a more accurate, detailed study.

In addition to these diagnostic capabilities, echocardiography can now be used as a noninvasive monitor of cardiac output via a continuous-wave

Doppler cardiac-output computer. This technique depends on measuring blood flow velocity through the aortic valve and accurately measuring the cross-sectional area of the valve.[134] Two transducers are used, one in the suprasternal notch and the other on an esophageal stethoscope. Cardiac output is determined by the formula:

$$C.O. = SVI \bullet Ao\ area \bullet HR$$

where *C.O.* represents cardiac output, *SVI* (systolic velocity integral) represents the integral of the area under the velocity curve measured by the transducer aimed at the aortic valve, *Ao area* represents the cross-sectional area of the aortic valve (usually measured by M-mode or two-dimensional echocardiography), and *HR* represents heart rate.

The accuracy of Doppler-measured cardiac output depends on both the patient and the operator. Comparisons with standard thermodilution techniques have been in conflict, although a correlation between r = 0.88 and 0.97 has been reported.[134]

Echocardiography has proven useful in the evaluation of patients with sepsis. Two-dimensional echocardiography has been used to monitor myocardial failure and ventricular dilation, as well as the recovery from septic shock.[135] Segmental myocardial dysfunction in septic shock can be seen by echocardiography. Typically associated with ischemic heart disease, this abnormality has also been seen in patients with sepsis who have no evidence of either coronary artery disease or myocardial injury.[136]

Echocardiography may not at this stage replace invasive pulmonary arterial catheterization in the evaluation and management of patients with sepsis. It is, however, complementary, as it is able to monitor chamber size in sepsis and during therapeutic interventions.[137] Improvements in equipment and the development of other noninvasive techniques such as bioimpedance cardiography will further increase our ability to obtain information about the hemodynamic status of patients with sepsis.[138]

Radiological Procedures

Many radiological procedures may be beneficial in the diagnosis and management of patients with sepsis. All procedures and tests must be performed while keeping in mind the potential complications inherent in preparing and transporting the patient, and weighing these potential complications against the potential benefit from obtaining useful information. Suboptimal patient preparation, such as the inability to administer oral contrast solution prior to an abdominal computed tomography (CT) scan, impairs the adequacy of the results and may warrant delaying the study.

Chest Radiography

The principal radiographic study utilized in the evaluation and management of the critically ill patient with sepsis is a chest roentgenogram made by a portable X-ray apparatus. The roentgenogram must be reviewed in a systematic fashion, examining from the peripheral soft tissues to the mediastinum and including all structures, including those iatrogenically placed.

Evaluation of the pulmonary parenchyma is usually the focus of attention in the patient with sepsis. In these patients, loss of alveolar space is commonly in the form of atelectasis (loss of lung volume), which appears rapidly and occurs commonly in the postoperative setting.

Pneumonia can present as a wide variety of radiographic appearances. It can be interstitial and diffuse or localized with dense, airspace consolidation. Combinations and variations are common. The definitive diagnosis requires information other than that obtained on the roentgenogram, as atelectasis or pulmonary edema may be indistinguishable from pneumonia.[139]

Patients with ARDS usually present with a diffuse interstitial and alveolar infiltrate, which many diffuse pulmonic processes can mimic. These other processes include pulmonary edema, fat embolism syndrome, diffuse pneumonia, or massive aspiration pneumonitis.[139] The definitive diagnosis requires further clinical and hemodynamic data and cannot be made solely on the basis of its radiographic appearance.

Pleural-based disease must also be evaluated. Pleural fluid is not specific and can occur in a wide variety of disorders in the septic patient, including congestive heart failure, empyema or parapneumonic inflammation, and pancreatitis. The pleural space must also be evaluated for evidence of barotrauma, as pneumothorax is common in mechanically ventilated patients (with an incidence of approximately 10%). Pleural air is usually seen without difficulty in an upright film. However, in the supine patient, air may collect in the anteromedial portion of the hemithorax, producing a medial pneumothorax, or dissect over the hemidiaphragm, producing an abnormally deep costophrenic sulcus (the *deep sulcus* sign).[139]

Sinus Evaluation

Critically ill patients frequently require nasotracheal intubation, nasogastric suctioning, or nasogastric feeding, all of which may cause iatrogenic sinusitis. Sinusitis should be considered in the differential diagnosis in the seriously ill, febrile patient. Physical exam and bedside routine sinus roentgenograms frequently miss the diagnosis. CT is useful in making the diagnosis of occult sinusitis-induced sepsis.[140]

Ultrasonography

Ultrasonography has proven beneficial in the diagnosis of clinical dilemmas in critically ill patients with sepsis. Improved imaging and portability have made bedside evaluations possible. The bedside procedure is safer for the patient as well, as it obviates the need to transport the patient to the radiology department (which, for critically ill patients, is potentially complicated and dangerous).

Ultrasound can now be used in the initial evaluation of acute renal failure to screen for obstruction, with a 93% to 98% sensitivity in the detection of hydronephrosis.[141] Intrinsic renal disease and renovascular disease can also be evaluated, the latter aided by Doppler analysis. Acute pancreatitis, which can accompany or mimic sepsis, can also be evaluated by ultrasound. Diagnosis of the complications of pancreatitis, such as hemorrhage, pseudocysts, or biliary tract obstruction can all be confirmed by sonography.

Biliary tract evaluation can help determine the etiology of jaundice that may appear in the septic patient. By identifying and measuring the common hepatic duct, obstructive jaundice can be diagnosed with 90% accuracy.[141] Hepatocellular disease is evaluated with much less sensitivity. Using ultrasonography to exclude intraabdominal fluid collection is particularly useful. Those areas most amenable for study are the right upper quadrant (liver, subhepatic space, subphrenic space, and right kidney), abdominal wall, pelvis, and left upper quadrant for splenic pathology. Abscesses can be seen in these areas, including within the liver, spleen, and kidney, with a 90% to 98% accuracy.[141] Ultrasonographic signs of acalculus cholecystitis in a patient with sepsis/SIRS include pericholecystic fluid, gall bladder distension and wall thickening, and intrahepatic duct dilation and the absence of stones.[142]

Other abdominal areas are less well seen because of bowel gas and surgical dressings; other patient variables such as obesity can also limit the study. Depending on accessibility, ultrasound-guided percutaneous drainage of a fluid collection can be performed to determine its composition, or can at times be used as an alternative to surgical drainage of an abscess.

Computerized Tomography

Imaging of the patient with sepsis, particularly if the patient also has had trauma, is probably best performed with CT. Inherent in this study is the need to transport the patient with all accompanying life support equipment to the machine in other areas of the hospital. Transporting for elective procedures—to the CT scanner in particular—have a high incidence of mishaps.[143]

In a study[144] of 20 patients in the ICU who received routine, portable chest roentgenograms, researchers found that in 15 (75%) of them, a thoracic CT scan was helpful in determining treatment plans. Another study[145] found clinically significant lesions such as pneumothorax and pulmonary or mediastinal abscesses. The overall accuracy of radiographic studies in diagnosing intraabdominal pathology has been shown to be about 76%. The most accurate diagnostic study appears to be the CT scan, with sensitivity and specificity in diagnosing an abdominal source of infection reported at approximately 90%.[145] The accuracy of diagnosis by ultrasound and radioactive gallium scan is lower than with CT scanning.[146] Diagnostic accuracy with CT scanning improves with the addition of oral and perhaps intravenous contrast.

Abdominal examinations should include the pelvis because fluid collects in the cul-de-sac or the retrovesicular spaces. CT scans have proven beneficial in diagnosing empyema and abdominal abscesses, postoperative pancreatitis, bile leakage, or delayed hemorrhage from trauma or surgical procedures.[139] The CT has been used in a similar—and at times, more successful—fashion than ultrasound in guiding needle aspiration or percutaneous drainage of fluid collections. With the exception of case reports, there is no literature indicating that magnetic resonance imaging (MRI) is a useful diagnostic tool in the patient with sepsis/SIRS.

Surgical Reexploration

Abdominal injuries are frequent in combat casualties. Thus, abdominal infections are a significant possibility during the recovery phase following the initial laparotomy. Reoperation or intervention

after abdominal surgery during the same hospitalization may be the only therapeutic intervention that can successfully treat a patient with sepsis whose condition is deteriorating. The indications for reoperation have changed little over the past 60 years and include the need to eliminate or remove the source of infection, remove infectious exudative material, perform intraperitoneal lavage to attempt to reduce the infective organism load, and drain an abscess sufficiently. Most reoperations are performed for peritonitis (45%), mechanical ileus (29%), postoperative bleeding (17%), and miscellaneous causes (9%), including a second acute process such as gangrenous cholecystitis, wound dehiscence, or acute bowel ischemia.[147] The mortality of patients undergoing reexploration is approximately 43%: the lowest mortality in one series[146] was found in trauma patients; the highest, in the patients undergoing evaluation for MODS who did not have a treatable finding at the time of laparotomy.

Evaluation of the patient prior to reoperation requires a thorough physical examination. More than 85% of patients who prove to have an abnormality at laparotomy have tenderness, fever, and absent bowel sounds.[146] These findings can be misleading in the sedated patient or the patient with mental status changes. The decision to reexplore can be made in most patients solely on clinical grounds. In addition to the clinical examination, radiographic studies can be beneficial when deciding whether to reexplore a patient with sepsis. A 1985 review[148] of the indications and results of reoperation for sepsis found that no patient without organ failure died, and that the risk associated with a normal exploration was outweighed by the potential of finding drainable intraperitoneal pus.

The etiology of postoperative peritonitis is most commonly (54%) secondary to an abdominal abscess.[146] The second most frequent cause (16%–39%) is a suture leak.[146,147] Other causes include necrotic bowel and technical error at the first operation.

The need for reexploration depends largely on the patient's clinical examination and hospital course. Additional beneficial information can be gleaned from radiographic evaluation, principally the CT scan. Although mortality rates from reexploration have not dropped significantly, current critical-care management has allowed more patients to tolerate such a procedure.[146,147] Early intervention in a surgically reparable disease process will perhaps lead to lower reoperative morbidity and mortality.

THERAPEUTIC MODALITIES

The primary issue in resuscitation for shock of any type, including septic shock, is to preserve adequate oxygen delivery to the tissues. Simple fluid administration may accomplish this in the volume-depleted patient as a result of increasing venous preload and thus optimizing the cardiac stroke volume.

Although the patient's clinical condition should be monitored (eg, mental status, mucous membranes, and urinary output), a more accurate means, particularly with a pulmonary artery catheter, may be desirable. However, the limitations of both the use and the interpretation of these data must be considered.

Fluid Resuscitation

Intravascular volume is decreased in patients with septic shock for the many reasons previously discussed. Increased vascular permeability markedly increases fluid and protein transport into the interstitium.[149] This absolute intravascular fluid loss, coupled with any additional loss from trauma or surgery, is aggravated by a redistributive loss due to the systemic vasodilation of septic shock.

Volume resuscitation, ideally with the aid of hemodynamic monitoring, should be the initial therapeutic intervention in the unstable patient in septic shock. However, the following facts must be kept in mind:

- Sepsis alters the normal response to volume infusion.
- Myocardial function is depressed in septic shock.

In these patients, volume infusion has been shown to result in only a minor increase in left ventricular end diastolic volume and stroke work when compared to other critically ill patients who do not have sepsis.[79] Thus, many patients with sepsis have a blunted ability to either dilate or increase ventricular contractility in response to volume infusion. One therapeutic strategy is to increase the PCWP, using 250-mL fluid boluses, until the cardiac index fails to increase further. In patients with septic shock, the PCWP associated with this maximal preload is approximately 10 to 14 mm Hg.[150] It is the choice of resuscitation fluid in the bolus—crystalloid or colloid—that remains controversial (Table 24-1).

TABLE 24-1

FACTORS IN FLUID SELECTION

Factor	Crystalloid	Colloid
Cost	Inexpensive	Expensive
Peripheral edema	Significant	Minimal
Anaphlyactoid reaction	Absent	Small risk (< 2%)
Colloid osmotic pressure	Decreases	Increases
Amount needed to maintain intravascular volume	Large	Small

Crystalloid Solutions

Crystalloid solutions can pass through a semipermeable membrane; colloid solutions cannot. The cheapest and most commonly used crystalloid resuscitation fluids are isotonic saline solutions, principally normal saline (0.9% sodium chloride) and Ringer's lactate (Table 24-2). These fluids distribute throughout the extracellular space. In normal, healthy adults, only 25% of the volume infused remains in the intravascular space after 1 hour. In the critically ill patient, however, less than 20% remains intravascular.[150] (Because 5% dextrose in water distributes throughout the total body water space, it is not effective in increasing intravascular volume.)

Isotonic saline and Ringer's lactate can be used interchangeably if the electrolyte differences are kept in mind. The theoretical concern of a hyperchloremic acidosis from the administration of large volumes of normal saline is not of clinical significance except in patients with severe renal insufficiency. Also, the administration of lactate in Ringer's solution does not potentiate an existing lactic acidosis or alter blood lactate measurements.[151,152] The rare exception is a patient with severe hepatic insufficiency who cannot metabolize lactate.

Colloid Solutions

Albumin. Albumin is the primary colloid used in the volume resuscitation of patients with sepsis. It is a natural protein of 584 amino acids synthesized in the liver at a rate of 130 to 200 mg/kg/d in healthy adults.[151] Albumin synthesis is regulated in part by colloid osmoreceptors located in the interstitial spaces near the sites of hepatic synthesis.[152] This may be of therapeutic significance when exogenous albumin or other colloids are administered. Its molecular mass ranges from 66,000 to 69,000 daltons and has a strong negative charge at physiological pH levels. Albumin is a major transport protein for metals, drugs, hormones, enzymes, fatty acids, amino acids, and bilirubin.[151,152]

Albumin is the major oncotically active protein in plasma, providing approximately 80% of the colloid osmotic pressure. The normal serum albumin is approximately 3.5 to 5.0 g/dL, with 40% of the body's albumin located in the intravascular space.[152] Extravascular stores are largest in the skin, but are also located in muscle and viscera. Only free, non-tissue-bound, interstitial-space albumin is able to return to the intravascular compartment via the lymphatic system in response to hypovolemia.[151]

In response to hemorrhage, albumin synthesis increases and its degradation or metabolism decreases. Mobilization of extravascular stores helps to minimize the loss in oncotic pressure. However, under severe stress, as in sepsis, albumin synthesis falls and the colloid osmotic pressure subsequently follows.

Exogenous albumin can be administered as either a 5% or a 25% solution. The 5% solution contains 50 g of albumin per liter of physiological saline and is isooncotic. The 25% solution contains 12.5 g of albumin in 50 mL of a buffered diluent that contains 130 to 160 mEq of sodium per liter.[152] When 100 mL of the hyperoncotic 25% solution is administered, the intravascular volume increases during the next 30 to 60 minutes to a maximum of 450 mL through the translocation of 350 mL of interstitial fluids. Hence the use of the hyperoncotic solution may be most beneficial in the intravascularly de-

TABLE 24-2

COMPOSITION OF CRYSTALLOID SOLUTIONS

Component	Normal Saline	Lactated Ringer's
Sodium	154 mEq/L	130 mEq/L
Chloride	154 mEq/L	109 mEq/L
Potassium	0	4 mEq/L
Calcium	0	3 mEq/L
Lactate	0	28 mEq/L
Osmolality	308 mOsm/L	275 mOsm/L
pH	6.0	5.1

pleted patient with elevated total body water or edema. The 5% solution is often used in initial volume resuscitation of the hypovolemic patient without edema.

Albumin is safe when used properly. Albumin-induced anaphylaxis occurs at a rate of only 0.47% to 1.53%; the reactions are generally mild, consisting of fever, chills, and urticaria. No infectious risk of hepatitis or human immunodeficiency virus is associated with its use secondary to prolonged heat-killing processing.[151] One major drawback to the use of albumin is its cost, which is approximately 30-fold greater than that of crystalloid fluids.

Hetastarch. Hydroxyethyl starch (hetastarch) is another colloid commonly used to treat hemorrhagic shock. This compound is a synthetic colloid composed of amylopectin that resembles glycogen. It is available in 500-mL containers of a 6% solution with an average molecular mass of 69,000 daltons (range 10,000–1,000,000) and an osmolarity of 310 mOsm/L.[151] After administration, smaller-molecular-weight molecules are cleared rapidly in the urine, whereas larger molecules require amylase hydrolysis before they can be excreted in the urine or bile.[152] Delayed excretion occurs because of (*a*) the necessary breakdown of the larger molecules and (*b*) tissue absorption, most notably in the reticuloendothelial system. In normal volunteers, approximately one half the hetastarch is eliminated in the urine within 2 days.[151]

The plasma-volume expansion that occurs with hetastarch is roughly equivalent to that of 5% albumin.[151] Hetastarch is not immunogenic and does not cause a histamine release, although minor anaphylactic reactions can occur with an incidence of less than 0.085%.[151,152] Minor alterations in coagulation studies appear to be dose dependent and are not associated with clinical bleeding, in patients without a bleeding diathesis, in a dose less than 1,500 mL/d. Transient thrombocytopenia and prolonged prothrombin and activated partial thromboplastin times are the three abnormalities that have been noted.[151]

Because its major route of elimination is via the kidney, patients with renal impairment are at increased risk of volume overload and tissue accumulation if hetastarch is used for volume resuscitation. Amylase levels will rise, commonly to 2-fold higher than normal values, after its administration. These raised levels may persist for 5 days, although no change in pancreatic function occurs.[151]

Despite these few side effects, hetastarch remains a safe and viable option for colloid volume resuscitation in the patient with sepsis. Its major advantage over albumin is that it costs approximately one fourth as much as an equivalent amount of 5% albumin (Table 24-3).

TABLE 24-3

COMPARISON OF COMMERCIAL COLLOID SOLUTIONS

Factor	Albumin 5%/25%	Hetastarch
Cost	Expensive	¼ cost
Infectious risk	None	None
Anaphylactoid reaction	0.5%–1.5%	< 0.08%*
Half-life	< 24 h	2 d (assuming normal renal function)

*Source for this value: Rainey TG, English JF. Pharmacology of colloids and crystalloids. In: Chernow B, ed. *The Pharmacologic Approach to the Critically Ill Patient*. Baltimore, Md: Williams & Wilkins; 1988: 235.

Selection of Resuscitation Fluid

Which of the two classes of fluid should be used for volume resuscitation remains controversial. However, proponents of either agree on several points[153]:

- Colloid solutions more efficiently replace blood volume than crystalloids.
- Colloid solutions are more expensive.
- Crystalloid solutions cause no anaphylactoid reactions.
- Both types of fluid are more readily available than blood, and should be used initially in the management of hemorrhagic shock as the patient will tolerate anemia better than hypovolemia.
- Colloid therapy provides a more effective maintenance of colloid osmotic pressure.
- Regardless of the fluid selected, fluid overload is to be avoided.

It seems quite clear that patients with septic shock have a heightened potential for extracellular fluid sequestration, compared with trauma patients who are not septic. No doubt this is caused by the capillary membrane damage that results from the sequential interaction of endogenous mediators and cells in SIRS.[154] The circumstances under which

these pathophysiological differences may become clinically relevant are not the only factors that need to be considered when the choice of fluid is discussed. Additional areas of debate in the use of these two fluids are whether there is a significant difference in their effects on the patient's coagulation, renal function, pulmonary interstitial water, development of ARDS, length of stay in the hospital or ICU, and survival.[153] The answers to these clinical questions should determine whether continued use of colloid fluids is warranted in light of the cost and potential side effects.

The main reason for using colloids is to prevent pulmonary edema. The amount of pulmonary edema that forms depends on (*a*) microvascular hydrostatic pressure (estimated by the PCWP), (*b*) colloid osmotic pressure, and (*c*) permeability of the alveolar-capillary membranes. The role played by hydrostatic pressure is more important than that of colloid osmotic pressure. The low colloid osmotic pressure seen with hypoalbuminemia does not, in and of itself, lead to pulmonary edema. The development of pulmonary edema is encouraged when capillary permeability is altered, for increased hydrostatic pressure results in increased transudation of fluid into the interstitial space. One concern with colloid infusions in this setting is that increasing protein, and hence oncotic pressure in the interstitium, will worsen edema. This hypothesis, however, remains to be definitively confirmed.[155]

Most studies comparing colloids and crystalloids have occurred in the setting of surgery, thermal burns, or trauma. One study compared the cardiorespiratory effects of treating patients in circulatory shock with 5% albumin, 6% hetastarch, or 0.9% saline.[156] Over two thirds of the patients studied were in septic shock; the remainder were in hypovolemic shock. Their median age was 79 years. All three solutions were found to provide the same cardiac function and hemodynamic stability. Neither albumin nor hetastarch depressed myocardial function. Hetastarch and albumin were of equivalent efficacy in treating circulatory shock. To attain the same physiological end points, 2- to 4-fold more crystalloid solution was required. Saline administration decreased the colloid osmotic pressure as expected. When the patients were resuscitated to the same physiological end points, the crystalloid solution caused an increased incidence of pulmonary edema compared with the two colloids.[155]

These results were, however, a summation of the effects seen in patients with sepsis and patients in hypovolemic shock. In studies of patients who do not have sepsis, alterations in capillary, microvascular membrane permeability are relatively minor, an aberration that occurs early in sepsis.[155] Nevertheless, a study that used the technique of meta-analysis concluded that, in the trauma patient with sepsis, better survival and better resuscitation are achieved with crystalloid solution.[157]

Which fluid is to be used varies with the clinical setting. Those clinical conditions associated with both intravascular hypovolemia and extracellular fluid deficit are best replenished with crystalloids. These fluids are more plentiful, less expensive, and without anaphylactoid side effects. More volume must be administered when compared with colloids, a condition easily tolerated in patients with trauma and perhaps surgical patients, particularly if they are young. Older individuals, and possibly patients with sepsis, are at greater risk of developing pulmonary edema. However, inadvertent volume overload with crystalloid solutions is relatively short lived, due to equilibration with the extravascular space.

A lesser volume of colloid solution is needed to obtain the same hemodynamic parameters as crystalloids; a greater percentage remains in the intravascular space for a longer time period.

Hetastarch is cheaper than albumin and increases colloid osmotic pressure over 3-fold that of an equivalent volume of albumin,[158] although its use has other potential effects (discussed above). The concern that colloid molecules pass through membranes of increased permeability, as is seen in sepsis, thereby increasing interstitial oncotic pressure and edema, remains speculative. Some authorities[151,159] recommend using only crystalloid solutions in this setting until the "leak" has sealed. The following are general guidelines for the use of crystalloid and colloid solutions:

- Colloids may be used for prompt volume expansion, and should be used in conjunction with crystalloids when more than 30% of the intravascular volume requires replacement.
- The total volume of crystalloid used and perhaps the subsequent development of interstitial edema may be minimized by concomitant administration of albumin or hetastarch to maintain colloid oncotic pressure.
- In the setting of increased total body water or edema, 25% albumin should be used.
- Volume overload must be monitored because colloids remain for a prolonged time within the intravascular space.

- Little additional benefit is gained in intravascular colloid osmotic pressure when the pressure is greater than or equal to 20 mm Hg, the serum albumin is greater than or equal to 2.5 g/dL, or the total serum protein is greater than or equal to 5.0 g/dL.

Tissue Oxygen Delivery and Consumption

Tissue oxygen delivery (Do_2) is a function of cardiac output (C.O.) and arterial oxygen content (Cao_2):

$$Do_2 = C.O. \bullet Cao_2$$

Arterial oxygen content is a function of hemoglobin (Hb) concentration and the degree of oxygen saturation of the blood (Sao_2), the latter being determined by the partial pressure of oxygen (Po_2):

$$Cao_2 = 1.34 \bullet \text{grams of Hb} \bullet Sao_2 + 0.003 \bullet Po_2$$

Tissue oxygen consumption (Vo_2) can be calculated as the difference between the arterial (Cao_2) and venous (Cvo_2) oxygen contents multiplied by the cardiac output (C.O.):

$$Vo_2 = C.O. \bullet (Cao_2 - Cvo_2)$$

If tissue oxygen delivery is inadequate or if tissue oxygen extraction is abnormal, all three factors—cardiac output, hemoglobin, and oxygen saturation—must be optimized.

Cardiac Index

Optimal left ventricular preload has been described previously in this chapter. Less is known concerning the optimal cardiac index for patients with sepsis or septic shock. Most patients with sepsis or septic shock manifest an elevated cardiac index as the principal compensatory mechanism by which tissue oxygen delivery is increased to meet demand.

Increased survival in patients with sepsis whose cardiac outputs are higher than normal has been demonstrated.[160–162] In a study[160] comparing critically ill patients after surgery, the variables that showed the greatest statistical discrimination between survivors and nonsurvivors were left ventricular stroke work, oxygen delivery, and oxygen consumption.

Hemoglobin

Hemoglobin is the major determinant of the oxygen content of arterial blood. One gram of hemoglobin increases arterial oxygen as much as increasing the partial pressure of arterial oxygen (Pao_2) from 100 to 400 torr. This is because hemoglobin oxygen saturation is close to 100% at a Po_2 of 100 torr. A higher Po_2 increases oxygen content only slightly because the added oxygen is carried dissolved in the plasma and constitutes only about 2% of the total oxygen being carried. The optimal hematocrit for patients with sepsis is not known. The conventional wisdom has been than a hematocrit between 0.30 and 0.40 provides the maximum oxygen delivery if all other factors are held constant. This is based on clinical studies that show increased viscosity, decreased cerebral blood flow, and increased incidence of vascular occlusive episodes when the hematocrit exceeds 0.45. Despite a calculated increase in the arterial oxygen content that would result from transfusion of packed erythrocytes, in patients with septic shock, significant increases in systemic oxygen consumption are not apparent.[162] The explanation may be a reflexive decrease in cardiac output.

A clinical study that was published in 1993 also showed that transfusion of packed red cells did not cause an increase in systemic oxygen consumption, even though cardiac index did not change.[163] As part of this study, gastric intramucosal pH was also measured. The pH fell after the transfusion, and the magnitude of the decrease was directly related to the age of the blood. The researchers suggest that (*a*) the ability of erythrocytes to *deform* (ie, to fold, which enables them to pass more easily through capillaries—a capacity that is known to be decreased in aged blood) was reduced in aged blood, and (*b*) this factor depressed tissue oxygen availability.

Arterial Saturation

Arterial oxygen saturation depends on the partial pressure of dissolved oxygen and the position of the oxyhemoglobin dissociation curve; specifically, the point on the dissociation curve where the hemoglobin is 50% saturated (P_{50}). Fresh red blood cells have a higher P_{50} than bank blood that has been stored for several weeks, and therefore might be expected to display more-favorable oxygen-unloading characteristics.[164] Nevertheless, although shifts of the hemoglobin saturation curve occur under many clinical situations (eg, P_{50} is decreased by hypothermia or alkalosis but is increased by hyperthermia or acidosis), there is virtually no evidence in the literature that this results in a clinically significant change in tissue oxygen delivery.

Critical Oxygen Delivery

In well individuals, a biphasic relation exists such that when oxygen delivery is decreased to a critical point (approximately 8–10 mL/kg/min), oxygen consumption falls. Above this critical level, oxygen consumption remains constant and independent of oxygen delivery. However, this relation may not be true for patients with sepsis/SIRS or MODS. Many studies[150,165–167] indicate that in these patients, either the critical level of oxygen delivery is much higher or a definable critical level is lost (Figure 24-9). As a result of this change in physiology, tissue oxygen utilization may become "supply dependent" and, although the utilization is greater than normal, it may actually be associated with cellular hypoxia. This is suggested by the frequent presence of elevated plasma lactate levels. A number of explanations have been proposed for the paradoxical coexistence of elevated oxygen delivery and apparent hypoxia (Exhibit 24-5). These explanations fall into two categories: (1) abnormalities in blood flow at the level of the microcirculation and (2) deranged cellular metabolism.

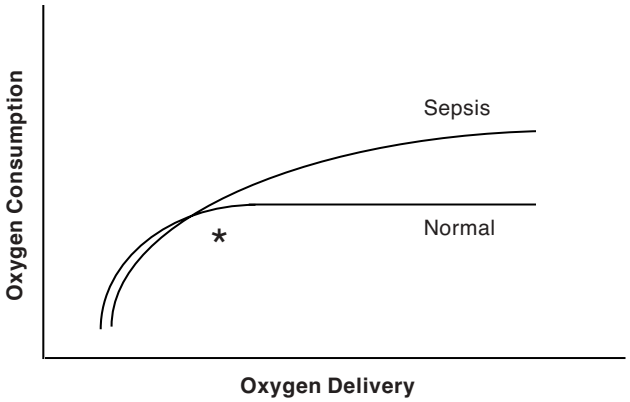

Fig. 24-9. This schematic drawing shows the relation between oxygen consumption and oxygen delivery in normal humans and in patients with sepsis. In normal humans, oxygen consumption does not increase once a certain level of delivery is reached; it remains essentially constant and independent of delivery. This phenomenon is indicated by (*). In patients with sepsis, however, a similar phenomenon is not seen: oxygen consumption continues to increase as oxygen delivery increases.

EXHIBIT 24-5

FACTORS CONTRIBUTING TO SUPPLY-DEPENDENT TISSUE OXYGEN UTILIZATION

1. Mitochondrial cellular respiration is inhibited (there are no clinical human data).
2. Decreased V_{O_2} is a protective mechanism to prevent organ damage (this has been disproved in cerebral ischemia model).
3. The phenomenon is simply the result of mathematical coupling (this is probably not true because the correlation between V_{O_2}, as measured directly by gas analysis, is well correlated with the value calculated by the Fick equation, and the V_{O_2}–D_{O_2} correlation appears "linked" in septic patients but not in control groups).
4. A disproportionate percentage of the cardiac output may be delivered to organs with low metabolic demands and oxygen extraction (eg, skin and muscle).
5. Arteriovenous shunts may occur in the precapillary tissue beds.
6. There is a maldistribution of microcirculatory flow as a result of the following factors:
   - microembolization or microthrombi blocking the peripheral vascular bed,
   - endothelial injury and tissue edema increasing the membrane thickness through which oxygen must diffuse,
   - leukocyte aggregation blocking the peripheral vascular bed,
   - altered erythrocyte deformability,[1] and
   - endogenous mediator-induced vasoconstriction reducing flow of the tissue vascular beds.

[1]Hud TC, Dasmahapatia KS, Rush BF, Machiodo GW. Red blood cells deformability in human and experimental sepsis. *Arch Surg*. 1988;123:217–220.

Most animal studies support the concept that shunting blood flow past tissue beds is frequently secondary to the factors listed in Exhibit 24-5. Shunting of blood from the visceral organs to the skin is evident in patients with sepsis, who have vasodilated and warm skin in the presence of oliguria. Because the skin has very little metabolic need and thus extracts little oxygen, the saturation of venous blood returning to the heart (mixed venous oxygen saturation) remains higher than normal.

Many important questions remain unanswered. What causes shunts to open in the skin? Why is the increased cardiac index that characterizes septic shock in humans not adequate to simultaneously perfuse *both* the skin and the visceral organs? Furthermore, although open shunts at the microcirculatory level in viscera would allow blood to bypass nutrient pathways at the cellular level, there is little evidence that such shunts open. However, it is possible that blood flow at the microcirculatory level in a given organ might be maldistributed in a manner similar to that seen when ventilation and perfusion are mismatched in the lung.

The metabolic abnormalities that occur in sepsis/SIRS may arise at the cellular level. Perhaps endogenous mediators impair metabolic pathways in the Krebs cycle, leading to the need for augmented formation of adenosine triphosphate through glycolysis. Experimental and clinical evidence does not provide convincing support for this explanation, for neither the cellular high-energy phosphate levels nor the ratio of the concentrations of pyruvate and lactate are consistently abnormal in either humans or experimental animals with severe sepsis.[168]

A number of studies (some of which confirm, others which do not) demonstrate the presence of abnormal oxygen-supply dependency during septic shock. The reason for the conflict in results is not known; however, this difference may be the result of the heterogeneous population of patients who develop septic shock and the great variety of metabolic demands that may be associated with the septic shock syndrome. If a defect in oxygen utilization does exist, it probably results from tissue hypoperfusion secondary to microcirculatory flow abnormalities.

Lactic Acidosis

The usual cellular response to hypoperfusion is anaerobic metabolism; lactic acidosis may develop as a consequence. However, it is important to recognize that lactate, not lactic acid, is the product of anaerobic glycolysis, and it is the breakdown of adenosine triphosphate, not its formation, that generates hydrogen ions.

Lactate levels are most accurately assessed through an arterial sample so that focal limb hypoperfusion does not affect the sample. Frequent monitoring of the lactate level in the patient with sepsis may yield information regarding the severity of disease,[169] the possible presence of oxygen-supply dependency, the response to therapy (particularly volume administration),[170] and the patient's prognosis.[170,171] Decreased survival has been documented in critically ill patients who have arterial lactate levels greater than 2.0 mmol/L.[172] Both the initial and the subsequent degree of reduction of the lactate levels have been used as prognostic indicators: a study[170] published in 1991 of 48 patients in septic shock documented the superiority of blood lactate levels over oxygen-derived variables in estimating the patient's prognosis.

The monitored variables discussed above (DO_2, VO_2, and lactate level) are probably best used in complement to aid the physician's decision making regarding therapeutic responses and ultimate prognosis.

Inotropic and Vasopressor Drugs

Not infrequently, the profound vasodilation that occurs in sepsis causes refractory hypotension despite adequate volume resuscitation. Inadequate tissue perfusion that occurs as a result of hypotension will exacerbate organ damage and thus must be corrected. Although inotropic and vasopressor medications are commonly used, few studies compare the efficacy of these agents in the treatment of septic shock. In contrast to cardiogenic shock, for which the selection of a drug with α-agonist properties is undesirable, sepsis-induced vasodilation often demands the use of a drug with significant effect on vascular tone. For example, amrinone lactate causes vasodilation predominantly, making this agent a poor choice for sepsis-induced hypotension unless the patient also has myocardial depression. Table 24-4 lists the characteristics of several commonly used vasopressor/inotropic drugs.

At one time, the use of norepinephrine was shunned because physicians feared that peripheral vasoconstriction, digital ischemia, and renal insufficiency would ensue. Using a canine septic model, researchers demonstrated that the addition of low-dose dopamine (4 μg/kg/min) caused an increased level of renal blood flow whenever norepinephrine was used.[173] The use of norepinephrine has recently been reappraised, particularly in patients with shock refractory to dopamine. One study[174] reported a

TABLE 24-4

CHARACTERISTICS OF USEFUL INTROPES AND VASOPRESSORS

	DOP	DOB	EPI	NOR	AMI
Alpha selectivity	++	–	+++	++++	–
Renal vasodilation	++	–	–	–	–
Tachycardia	++	+	+++	–	+
Dysrhythmias	++	+	+++	–	+
Dosage (μg/kg/min)*	2–20	4–20	0.01–1.0	0.01–1.0	5–20

*Dosages listed are the standard range for patient treatment, and do not infer a maximum safe dosage
DOP: dopamine in moderate dose range (5–10 μg/kg/min); DOB: dobutamine; EPI: epinephrine; NOR: norepinephrine; AMI: amrinone

40% incidence of dopamine resistance in 29 patients in septic shock. The addition of norepinephrine infusion reversed the shock in 10 of 12 (83%) patients. Another study[175] reported a 100% success rate in reversing hypotension in 10 patients with intractable septic shock.

The fear that potential renal insufficiency and decreased tissue blood flow will result from using norepinephrine has been shown to be unfounded. Five studies[175–179] evaluating renal function following the use of norepinephrine for refractory hypotension and oliguria in septic shock are reviewed in Table 24-5. One notable study[179] indicates that patients with a persistent perfusion deficit, as evidenced by lactic acidemia, did not demonstrate an improvement in renal function following the administration of norepinephrine.

Support of the Respiratory System

As discussed earlier in this chapter, respiratory insufficiency is common in patients with sepsis. Although the patient may be able to maintain an adequate level of arterial oxygenation, the increased

TABLE 24-5

NOREPINEPHRINE IN REFRACTORY SEPTIC SHOCK

No. of Patients	Success Rate	Urinary Output*	Creatine Clearance*	Survival
25[1]	100%	I (100%)	I (100%)	16⁄25 (64%)
5[2]	100%	I (100%)	N/A	2⁄5 (40%)
6[3] (elevated lactate)	100%	NC	D (100%)	0
9[3] (normal lactate)	100%	I (100%)	NC	4⁄9 (44%)
24[4]	100%	I (83%)	I (83%)	16⁄24 (67%)
10[5]	100%	I (100%)	N/A	4⁄10 (40%)

*The incidence in which the target blood pressure was achieved with norepinephrine
NC: no change; N/A: not measured; I: increased; D: decreased
Data sources: (1) Desjars P, Pinaud M, Bugnon D, Tasseau F. Norepinephrine therapy has no deleterious renal effects in human septic shock. *Crit Care Med.* 1989;17(5):426–429. (2) Hesselvik JF, Brodin B. Low-dose norepinephrine in patients with septic shock and oliguria: Effects on afterload, urine flow, and oxygen transport. *Crit Care Med.* 1989;17(2):179–180. (3) Fukuoka T, Nishimura M, Imanaka H, Taenaka N, Yoshiya I, Takezawa J. Effects of norepinephrine on renal function in septic patients with normal and elevated serum lactate levels. *Crit Care Med.* 1989;17(11):1104–1107. (4) Martin C, Eon B, Saux P, Aknin P, Gouin F. Renal effects of norepinephrine used to treat septic shock patients. *Crit Care Med.* 1990;18(3):282–285. (5) Meadows D, Edwards JD, Wilkins RG, Nightingale P. Reversal of intractable septic shock with norepinephrine therapy. *Crit Care Med.* 1988;16(7):663–666.

work of breathing and the corresponding increased oxygen consumption may be harmful. Earlier studies have shown that during respiratory failure, blood flow to the diaphragm may approach 20% of the total cardiac output, compared with the normal 3% to 5%, potentially depriving other tissues of necessary oxygen delivery. Additionally, oxygen utilization of the respiratory muscles alone may account for up to 25% of the total oxygen consumption.[180] Although it remains unproven, the institution of mechanical ventilation may reduce systemic oxygen consumption and thus aid in clearing lactic acidosis. The clinician must ensure that hypovolemia has been treated because the institution of positive pressure ventilation may cause a decrease in both venous return and cardiac output.

Antimicrobial Therapy

Although the diagnosis of sepsis may be elusive, once considered, therapy must begin early and decisively. This treatment includes excision, debridement and drainage of abscesses or focal sites of infection, and the restoration of a volume deficit. Adequate tissue oxygen delivery, support of organ dysfunction, and the initiation of antimicrobials[181] are the primary therapeutic goals.

The most common category of wound sustained in combat involves only the soft tissue of the body (skin, fat, and skeletal muscle)—wounds that are infrequent sources of fatal sepsis when treated following the established principles of military surgery. However, wounds that involve deeper structures such as bones and especially intraabdominal viscera, even given state-of-the-art surgical care, have a high likelihood becoming infected, with the possibility of inducing sepsis (45% of open comminuted fractures of the femur become infected,[182] as did 45% of open comminuted fractures of the tibia,[183] and 50% of colonic wounds[184]).

Nosocomial infections, though, are common in traumatized patients and are significant potential causes of sepsis.[181] In these instances, antimicrobial therapy can be directed at the identified or presumed pathogens. However, in those cases of generalized sepsis without an identified source, or those with several possible sources, antimicrobials—particularly antibiotics—must be initiated early and broadly enough to cover a variety of potential pathogens.

Selection of Antimicrobial Therapy

Ideally, the infecting pathogen should be identified before antibiotic therapy is started. This requires identification through culture, a process that delays initiating therapy. Specific clues as to the organisms may be gleaned from the physical examination and Gram's stain of material from potential pathogenic sites. Examination of the skin may be of significant benefit, as it allows infections in surgical wounds, venipuncture sites, or intravenous catheter sites to be identified. Pathognomonic lesions from meningococcemia, toxic shock syndrome, or infectious endocarditis may also be identified.[185] All potentially infected materials such as blood, urine, sputum, wound exudate, and cerebrospinal fluid should be examined and cultured based on the patient's condition.[186] Cultures and Gram's stains require proper handling to prevent contamination and potential misinterpretation. Additional diagnostic studies such as CT scan may help identify a potential source of infection. Not uncommonly, though, critically ill patients cannot undergo the optimal diagnostic procedure. They may be too hypoxic for a bronchoscopy, too thrombocytopenic for a tissue biopsy, or too unstable for transport to the radiology department or operating room.[187]

After all diagnostic measures have been completed, specific treatment aimed at the isolated pathogen should begin. Often, however, the initial therapy is nonspecific, pending identification of the responsible pathogen. When selecting an antibiotic, some of the many factors that must be considered include the following[185,186]:

- onset of infection (traumatic, community-acquired, or nosocomial),
- assumed infective focus,
- immunological status of the patient,
- underlying diseases,
- accompanying organ failure,
- previous antibiotic treatment,
- pharmacokinetics and toxicities of the antibiotics, and
- epidemiology of isolated organisms at the institution, including patterns of resistance.

Ideally, the chosen antibiotic regimen is well tolerated by the patient, is bactericidal, has minimal side effects, and covers all potential pathogens for the particular patient. Antibiotics must be given early, in sufficient dosages, and usually parenterally[186] in the critically ill patient.

Bacterial Infections. Although Gram-negative infections are well known for producing sepsis/SIRS, Gram-positive organisms can also cause it. Immunocompetent patients are often infected with a single pathogen. Immunocompromised patients,

however, are frequently infected with many different organisms; hence, they require broad antibiotic coverage. Broad, initial antibiotic coverage is ideally narrowed to more-specific, less-toxic antibiotics after culture results are obtained. Such measures minimize drug toxicity, lower costs, reduce the incidence of superinfection, and lower the development of antibiotic resistance.[185]

After a thorough diagnostic evaluation, empirical treatment is usually based on the presumed site of infection. Nosocomial pneumonias are usually caused by resistant, aerobic, Gram-negative rods, particularly *Pseudomonas* species. Treatment includes an antipseudomonal penicillin (mezlocillin, ticarcillin, or piperacillin) or an effective cephalosporin (ceftazidime) in combination with an aminoglycoside. Cephalosporins with activity against Enterobacteriaceae from the lung and other sites include cefotaxime, ceftizoxime, and ceftriaxone.[151] Other bacterial causes of nosocomial pneumonia are *Legionella,* which is treated with erythromycin; *Staphylococcus aureus*, which, depending on whether the microorganism is methicillin-resistant or penicillinase-producing, can be treated with methicillin, vancomycin, or a cephalosporin such as cephalothin or cefazolin; and the anaerobic organisms, which are treated with clindamycin or metronidazole. However, imipenem/cilastatin, a combination of a carbapenem and a metabolic inhibitor (Primaxin, manufactured by Merck, Sharp and Dohme, West Point, Pa.), is a more recent and possibly a better choice.

Urosepsis is usually caused by Gram-negative rods or enterococci and can be treated with ampicillin (or vancomycin in the penicillin-allergic patient) and an aminoglycoside. Enterobacteriaceae can be treated as above.

Peritonitis or intraabdominal infections are polymicrobial and include enteric Gram-negative rods and anaerobes. Initial treatment includes an aminoglycoside and metronidazole or clindamycin, with the addition of ampicillin or vancomycin for enterococci.

Cellulitis is caused by streptococci or staphylococci and can be treated with a first-generation cephalosporin (such as cefazolin), oxacillin, or vancomycin. Sepsis associated with an intravenous catheter is caused by *Staphylococcus aureus*, *Staphylococcus epidermidis* or Gram-negative rods and will respond to treatment with vancomycin, an appropriate cephalosporin or, in the case of Gram-negative rods, an aminoglycoside.

Outpatient meningitis, which is often seen in troop populations that are in close confines (eg, in barracks), is caused by *Streptococcus pneumoniae* or *Neisseria meningitidis*, and can be effectively treated with high-dose penicillin. Meningitis seen after trauma requires treatment for (*a*) Gram-negative infections, with a third-generation cephalosporin such as cefotaxime or ceftriaxone, or (*b*) *Staphylococcus aureus*, with vancomycin.

Usually the initial therapy of sepsis consists of a β-lactam antibiotic and an aminoglycoside. The β-lactams include the penicillins and cephalosporins as well as the newer carbapenems and monobactams. These agents may be combined with β-lactamase inhibitors such as clavulanic acid or sulbactam.[186] Quinolones are also potentially beneficial. The antibiotics with the broadest aerobic Gram-negative, Gram-positive, and some anaerobic coverage are imipenem/cilastatin and ticarcillin/clavulanate (Timentin, manufactured by SmithKline Beecham, Pittsburgh, Pa.). These are often held in reserve for severe septic infections or in those cases where the etiologic septic focus is unclear and a simplified, less-toxic antibiotic regimen is required. Aztreonam is a monobactam active only against Gram-negative strains and at times may provide an alternative to aminoglycosides.

Lastly, the quinolones are emerging as a potential complement to the regimen in treating patients with sepsis, particularly as resistance to other antibiotics appears. Ciprofloxacin from this group has displayed activity against Enterobacteriaceae, *Legionella* species, *Campylobacter* species, *Yersinia* species, *Staphylococcus aureus*, *Hemophilus* species, and *Pseudomonas aeruginosa*.[186]

Appropriately chosen antibiotics should be expected to result in patient improvement within approximately 48 hours. The patient's failure to improve may suggest one or more of the following problems[185]:

- inappropriate antibiotic selection, due either to inactivity against the pathogen or to poor penetration into the infected site,
- inadequate dosing,
- an antibiotic-induced toxicity such as drug fever,
- an undrained focus of infection,
- an infection such as infective endocarditis that requires a longer time to show a clinical response, or
- infection with another pathogen not covered by the chosen antibiotic.

Nonbacterial Infections. Nonbacterial infections can occur in the immunocompromised, septic pa-

tient, particularly those on antibiotics. Fungal infections are becoming more prevalent in the compromised host. The most common pathogenic fungus is *Candida*, particularly *C albicans*. Superficial mucosal infections are common as normal bacterial flora are inhibited by antibiotics. Local visceral involvement of the kidneys, lung, and central nervous system can also occur. Finally, disseminated candidiasis with candidemia, *Candida* endophthalmitis, or multiorgan involvement can occur in the seriously ill patient who is being treated with antibiotics.

The source of *Candida* is usually the patient's own gastrointestinal tract. Overgrowth occurs when bacterial flora are reduced, and invasion occurs via surgery, intravenous devices, or translocation across the gastrointestinal wall.[188] Disseminated disease is notoriously difficult to diagnose, with less than one half the patients having documented candidemia or candiduria. Treatment of disseminated candidiasis is with high-dose amphotericin B. Empirical amphotericin B may become justified when adequate antibacterial therapy fails to elicit an appropriate clinical response and candidiasis is suspected.[189]

Infections with viruses such as herpes simplex, varicella-zoster, and cytomegalovirus are common in medical patients with primary or secondary immunodeficiencies, although these may also appear in patients with sepsis or other severe illnesses. For example, reactivation of latent herpes infections may appear in many patients, particularly those with burns or skin breakdown.[189] Lastly, occult tropical or parasitic diseases endemic to the theater of operations may complicate a seriously ill patient's course (eg, by causing persistent fever).

Proposed Therapies

Although the high mortality for sepsis/SIRS and septic shock is widely recognized, the disparate definitions for sepsis and septic shock that were used prior to the American College of Chest Physicians–Society of Critical Care Medicine Consensus Conference contribute to the difficulty of scientific analysis of therapeutic trials. Fluid therapy, optimization of oxygen delivery and consumption, inotropic support, and antimicrobial therapy are the mainstay treatments for sepsis/SIRS. As we learn more about the derangements of this syndrome and the consequences of the disease state itself, and its treatments, newer therapies are being discovered. Investigational therapies have suggested evidence of success, but their validity is not yet established; therefore, this chapter will treat these as proposed therapies.

Prevention of Nosocomial Pneumonia

Nosocomial pneumonia is a significant cause of morbidity and mortality in hospitalized patients and is particularly prevalent in mechanically ventilated patients. In the past, four causes of pneumonia have been theorized[190]:

1. bacterial inoculation by hematogenous spread,
2. direct extension into the lung from a contiguous site,
3. contamination of hospital equipment, and
4. aspiration of bacteria from the stomach and oropharynx.

Of these, the first two are thought to be rare, the third has been implicated, and the fourth appears to be the most common.

Bacterial overgrowth of Gram-negative organisms occurs in the stomach when the pH is increased (> 3.5–4.0).[191] This occurs in patients treated with antacids or histamine type 2 (H_2) blocking agents that are used as prophylaxis against stress-induced gastrointestinal bleeding. With this bacterial overgrowth, reflux of bacteria with subsequent aspiration predisposes to the development of Gram-negative pneumonia.[190]

Sucralfate is a nonabsorbable, cytoprotective agent that minimally neutralizes stomach acid, although it is as protective as antacids and H_2 blocking agents in preventing stress ulceration.[191] In 1987, researchers reported that, when compared with gastrointestinal prophylaxis with sucralfate, the use of antacids or H_2 blocking agents or both resulted in a 2-fold increase in the incidence of pneumonia and a 6-fold increase in the mortality.[192] These data suggest, then, that elevating gastric pH increases the risk of nosocomial pneumonias through increased bacterial overgrowth.

This information, however, remains controversial. Further review of these data suggest that other factors may play a role in the development of nosocomial pneumonias. When the use of antacids was separated from the use of H_2 blocking agents, only the groups using antacids had the high incidence of pneumonias, whereas the patients who received H_2 blocking agents alone did not. One suggestion is that antacids increase gastric volume, leading to more reflux, whereas H_2 blocking agents reduce gastric volume.[190] Differences in the kinds of

organisms found colonizing the stomach and the lung have also been reported. One study[193] reported that different pathogens were found in these two locations 28% of the time, and 22% of the time the organisms appeared in the trachea before they appeared in the stomach. These data throw the pathophysiological mechanism previously reported into question. Thus, prophylactic gastric protection, and its relationship to nosocomial pneumonias, remains controversial.

Selective Gut Decontamination

After 1 week in an ICU, 70% to 90% of mechanically ventilated patients become colonized with hospital-acquired bacteria in the oropharynx, with subsequent infection occurring in more than 60%.[194] Most infections are endogenous, in the sense that they are caused by potentially pathogenic organisms that are normal constituents of the oral or intestinal flora at the time of the patient's admission to the ICU (primary endogenous infections); others are acquired from the environment while in the ICU (exogenous infections).[195] The organisms primarily involved in the colonization and subsequent infection are the Enterobacteriaceae, *Pseudomonas* species, *Acinetobacter* species, and *Candida* species.[194,195]

Infection occurs when normal host defenses break down. Normal colonization defenses include mucous membrane integrity, normal physiology and motility (swallowing, peristalsis, and salivation), secretions (saliva, mucous, gastric acid, and bile), secretory IgA, normal mucosal-cell turnover, and indigenous anaerobic flora. The causes of the breakdown in critically ill patients include instrumentation, anesthetics and muscle relaxants, antacids and H_2 blocking agents, and antibiotics.[195]

Attempts to prevent infection from colonizing organisms were first introduced in the ICU following a 1981 study involving patients undergoing colorectal surgery, and patients who were immunocompromised, granulocytopenic, or victims of a burn injury.[196] The antimicrobial regimen most commonly used covers all potential pathogens, avoids indigenous (mostly anaerobic) flora, is nonabsorbable, has minimal bactericidal concentrations for most potential pathogens, and is not degraded by food or enzymes within the gut lumen.[195] One example of selective gut decontamination by antibiotics is the following[194,195,197]:

- a 10-mL suspension of 100 to 200 mg of polymyxin E, 80 mg of tobramycin, and 500 mg of amphotericin B is administered through a gastric tube four times daily;
- a paste containing 2% each of polymyxin E, tobramycin, and amphotericin B is applied to the oral mucosa every 6 hours; then
- an intravenous antibiotic is usually given as prophylaxis for 4 days after the patient is admitted to the ICU until most colonizing potential pathogens are eliminated, to prevent early pulmonary infections caused by community-acquired pathogens (the antibiotic is usually cefotaxime, 1 g administered intravenously every 6 h).

The reported results are varied. Most studies have been performed in Europe and their results have been reviewed and summarized recently.[195] Many studies included patients who were already infected when they were admitted, although some studies included noninfected, traumatized patients. Nevertheless, all studies confirmed a significant reduction in secondary colonization and infection of the respiratory tract. Among the general surgical patients, although selective gut decontamination significantly reduced the incidence of acquired infections, it did not reduce mortality. The mortality of trauma patients was reduced, particularly among those who were severely injured. In this population, mortality from sepsis or MODS was almost completely prevented. The emergence of organisms resistant to the antimicrobials used did not occur.

The enteric flora controlled by this regimen may be responsible for much of the sepsis seen in the control population (ie, those who did not receive the gut decontamination). Potential enteric pathogens may, theoretically, contribute to the patient's illness (known as "gut-origin sepsis") through one of three mechanisms[195]:

1. direct spread to contiguous organs or through aspiration of oral or stomach flora;
2. absorption of endotoxin from enteric, aerobic Gram-negative organisms; and,
3. as demonstrated in animal studies, translocation of potential pathogens through a permeable gut mucosa that has been impaired as a result of ischemia, shock, burns, trauma, or endotoxin.

Although the results published to date appear to support these theories, many questions remain to be answered. In a study of patients with combined acute renal and respiratory failure who received selective gut decontamination, 10 of 12 (83%) con-

trol patients developed defined infections, compared with 5 of 15 (33%) patients who received the regimen. However, no significant difference in survival between the groups was seen.[197] Infections appear to be controlled with this technique, although further evaluation is necessary to determine its indications.

Immunotherapy

As noted throughout this chapter, conventional therapy with antimicrobials and supportive measures in the treatment of sepsis/SIRS has not appreciably reduced morbidity and mortality, particularly in the case of Gram-negative sepsis. Immunotherapy directed at causative organisms has been evaluated as a means to improve survival. Specific immunotherapy directed at causative organisms is not simple, for the three common Gram-negative organisms often implicated in sepsis have many serotypes: *Escherichia coli*, approximately 150; *Klebsiella* species, approximately 80; and *Pseudomonas aeruginosa*, approximately 17.[198] Thus, less-complicated schemes have been devised and are being investigated. It is the invasion of Gram-negative organisms that usually initiates the series of events that ultimately produces the sepsis/SIRS syndrome. Immunomodulation of several of these steps has been evaluated in an attempt to abate the septic process at whatever stage it has reached. The areas studied have been therapies directed against the common pathogens; endotoxin; and the cytokines, the end products of the sepsis process.

The use of intravenous IgG in patients with sepsis remains controversial. Generally, in the absence of a functional hypogammaglobulinemia, intravenous IgG does not significantly mitigate the infectious process.[198] Some studies in patients with impaired defense mechanisms (such as occurs in multiple trauma or major surgery) suggest a possible therapeutic role for the use of intravenous IgG in combination with antibiotics.[191,199,200] More specific anti-*Pseudomonas* immunoglobulins are being prepared and tested.

Sepsis caused by *Pseudomonas*, *Klebsiella*, and *Escherichia coli* has been found to be caused by relatively few of their many serotypes. With this information, in an attempt to target Gram-negative pathogens more specifically, vaccines against these predominant serotypes have been developed and are being tested both as active vaccines and for use in the induction of type-specific antibodies that could then be used to prepare a hyperimmune intravenous immunoglobulin for passive immunotherapy. Some progress has been made with these vaccines and they may, at some future time, be given prophylactically to patients at risk for infection (eg, prior to elective bowel surgery) or to populations at risk for trauma (eg, soldiers).[198]

The most intriguing data on immunotherapy published during the 1980s is that directed against the lipopolysaccharide moiety of endotoxin. In 1982, researchers prepared an antiserum to endotoxin by vaccinating healthy men with the J5 mutant *Escherichia coli*.[201] Lacking the oligosaccharide side chain, the lipopolysaccharide core—known as lipid A—of this mutant, which is nearly identical to that of most other Gram-negative bacteria, was exposed to promote antibody formation. In a controlled trial, patients with bacteremia and those in profound shock had improved survival when treated with the J5 antiserum, when compared with controls. Whether the factor responsible for these patients' improvement was an immunoglobulin has not been validated. One study that used intravenous immunoglobulin from donors immunized with a J5 vaccine failed to replicate these results.[202]

More recently, a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin (HA-1A) has been produced, alleviating the need to further pursue the active factor in the J5 antiserum.[203] In a study of 197 patients with documented Gram-negative bacteremia, treatment with HA-1A resulted in a lower mortality in 32 of 105 patients (30%), compared with 45 of 92 patients (49%) in the control group. A similar benefit was seen in those patients who were admitted to the hospital with a diagnosis of Gram-negative bacteremia and shock (33% mortality with treatment, compared with 57% in the control group). Although mortality was lowered as a whole for patients who received the antibody, the 63% of study patients who did not have documented Gram-negative bacteremia showed no significant improvement in survival with the treatment.

Despite the apparent improvement that occurred in the group of treated patients in this study, a significant number of the patients with sepsis died, including approximately one third of patients with demonstrated Gram-negative bacteremia. The final common pathway in the septic process is the release of cytokines from macrophages in response to infections. These compounds may be the source of many of the adverse effects seen in those patients in this study with documented Gram-negative bacteremia who died, as well as in that group of patients who had sepsis/SIRS but did not have a Gram-negative infection. If the septic process has

progressed beyond the endotoxin interaction with macrophages, or if it is caused by a non-Gram-negative organism, treatment with the HA-1A antibody would not be expected to cause significant improvement.

Immunological or pharmacological modulation of the cytokine release may be of additional benefit in patients with sepsis. Antibodies directed at TNF have proven beneficial in animal studies and are now beginning to be investigated in human studies. Antagonists against platelet activating factor and the use of pentoxifylline against TNF and IL-1 are also being studied.[191,198]

Hence, immunotherapy directed at different steps in the septic process is being developed. Combination therapy with antibiotics, other pharmacological agents, and immunomodulation of sequential stages of sepsis is being investigated intensively and may prove to be the most effective. This combined approach may be beneficial because the stage in the sepsis continuum in which a given patient lies is not easily determined.[198]

Immunoglobulins cannot, however, be administered with impunity. An upper limit may exist beyond which host-defense mechanisms, such as decreased production of immunoglobulin, are impaired.[204] One researcher states this concern regarding immunotherapy:

> A word of caution is warranted regarding the use of inhibitors of the mediators of septic shock. The pathogenetic mechanisms of septic shock are complex and interdependent, and many of them represent the body's compensatory response to sepsis and therefore have salutary effects.[32(p1476)]

Also of practical concern is the enormous costs involved in immunotherapy.[198] Nevertheless, the promise of an effective management tool against sepsis makes this form of therapy worth ongoing evaluation.

Corticosteroids

The use of glucocorticoids in sepsis/SIRS has been theorized to be beneficial by preventing the release of mediators of tissue damage and hemodynamic instability, improving cardiac performance, inhibiting inflammation and complement activation, stabilizing cell membranes, and preventing lysosomal release.[191] Impaired immune responses such as leukocyte chemotaxis that occurs with their use may, however, be harmful. Animal studies done in 1976 suggested some benefit, although usually only when administered before or soon after experimentally induced sepsis. In 1976, a prospective, randomized, controlled study[205] of patients with sepsis who were treated with infusions of high-dose glucocorticoids reported a reduction in mortality with treatment (10% vs 38%). The results of this study have not been replicated, but have prompted several evaluations of the possible role of glucocorticoids in both sepsis and septic shock as well as in the treatment and prevention of ARDS.

Studies of Adult Respiratory Distress Syndrome

At least two studies have failed to demonstrate a significant benefit when corticosteroids were used in the management of ARDS. In one study[206] of 99 patients with established ARDS from several causes, treatment with methylprednisolone (30 mg per kg body weight given every 6 h for 24 h) was evaluated. The study reported no difference in mortality or in the reversal of ARDS with treatment. A similar study[207] of patients admitted to an ICU with fever and hypotension, using methylprednisolone in an identical fashion, failed to demonstrate any reduction in the subsequent development of ARDS or of mortality. One recent uncontrolled study[208] of patients with established ARDS reported that a sustained course of steroids resulted in improvement of ARDS; however, these results have yet to be verified in a controlled fashion.

Studies of Human Sepsis

Other studies have attempted to confirm the previously reported benefits of steroids in the treatment of sepsis. In one study[209] investigating the effects of high-dose corticosteroids in patients with septic shock, patients were treated an average of 18 hours after the onset of sepsis with methylprednisolone (30 mg/kg), dexamethasone (6 mg/kg), or no therapy. A one-time second dose was administered 4 hours later if shock persisted. Patients who received steroids within 4 hours after the onset of shock had a higher incidence of shock reversal. Similarly at 24 hours after drug administration, more patients who received treatment had reversal of shock than those who did not. However, over the course of the study, the reversal of shock disappeared and no improvement in survival was apparent. These researchers concluded that steroids were not beneficial, although they may be helpful early in the septic course in a select group of patients.

Two other controlled studies that followed reached similar conclusions. In 1987, the Veterans

Administration Systemic Sepsis Cooperative Group[210] reported a study of patients with sepsis who received a high-dose corticosteroid bolus (30 mg/kg methylprednisolone) followed by an infusion (5 mg/kg/h for 9 h) within an average of 2.8 hours after the diagnosis of sepsis had been made. Again, no statistical improvement in survival was noted at 14 days. Also in 1987, another group[211] published the results of their controlled multicenter study, in which patients received 30 mg/kg of methylprednisolone every 6 hours for four doses beginning within 2 hours of the diagnosis of sepsis or septic shock. They found no significant improvement in the treatment group with regard to the prevention of shock, reversal of shock, or overall mortality; however, the incidence of secondary infections was increased.

So despite the improvement noted in a 1976 animal study,[205] the conclusions of more-recent studies in sepsis are that high-dose corticosteroids have no place in the management of sepsis. And also, despite the recent, uncontrolled report[208] of the use of a sustained course of corticosteroids in established ARDS, most controlled data suggest that steroids neither prevent nor reverse ARDS.

Naloxone

Endogenous opioid peptides have been reported to be involved in the pathophysiology of septic shock. Animal studies that utilize the opioid antagonist naloxone have demonstrated some improvement in the treated animals' conditions.[191] Clinical responses in humans have been varied, however. Most often cited is a 1981 study[212] in which blood pressure increased in 8 of 13 patients with hypotension and shock following the infusion of 0.4 to 1.2 mg of naloxone, although only 3 of the 13 treated patients survived. Most of the nonresponders in this study were adrenally insufficient; hence, it has been postulated that naloxone therapy requires intact adrenocortical function. Prolonged infusions of naloxone have been shown to reduce inotropic and vasopressor requirements and improve stroke volume and heart rate.[213] One uncontrolled study[214] reported an increase in systolic and mean arterial pressure in patients with sepsis with a naloxone bolus followed by an infusion, although no overall effect on mortality was observed. Naloxone may provide a temporizing means to improve the hemodynamics or cardiovascular status of a patient in septic shock. But without a randomized, prospective, controlled study, its use to improve survival remains unproven.

Cyclooxygenase Inhibitors

Cyclooxygenase inhibitors and thromboxane synthetase inhibitors have also been shown to have some benefit in animal models of sepsis.[191] Many of the mediators of sepsis activate enzymes that release fatty acids, such as arachidonic acid, from cell membranes. Cyclooxygenase inhibitors such as indomethacin may help ameliorate some of the hypotension and organ damage reported to be associated with arachidonic acid metabolites. Administration of ibuprofen decreases extravascular lung water in septic animals.[58]

Metabolic Manipulations

Bacterial translocation from the bowel has been discussed as a potential endogenous source of enteric, Gram-negative sepsis. Total parenteral nutrition and the absence of enteral feeding have been associated with gut mucosal atrophy, bacterial and fungal invasion, and increased mortality.[191] As demonstrated in animal models, bacterial translocation from the gut is increased in animals fed parenterally versus those receiving enteral feeding.[215] Early enteral feeding stimulates gut function and protects the gut barrier. The early institution of enteral feeding may prove to be a major therapeutic modality in the prevention of sepsis. This was the case in trauma victims who had fewer infections and lower mortality when fed enterally.[216]

Calcium abnormalities are common in the septic state. The hypocalcemia seen appears to result from aberrations in the parathyroid hormone–vitamin D axis, perhaps aggravated by endotoxin.[217] Although hypocalcemia is usually mild, it can be severe. Only ionized calcium levels can accurately reflect true hypocalcemia. Replacement, though, is not always indicated, for intracellular calcium overload results in activation of protease and other digestive enzymes and the uncoupling of oxidative phosphorylation, with the end result being cellular death.[218] Sepsis itself may increase intracellular calcium by diminishing adenosine 5'-triphosphate (ATP), by interfering with calcium transport systems, or increasing calcium entry into the cell, or both.[191] In this regard, the calcium channel–blocking agents have been shown to improve hemodynamics, cardiovascular function, and survival in a dog model of sepsis.[219] Further study is warranted before widespread use of calcium channel–blocking agents in sepsis is recommended.

Other investigational therapies for sepsis are also being explored.[191] Toxic oxygen radicals have been

implicated in many clinical disorders including sepsis/SIRS. Enzymes such as superoxide dismutase, catalase, and peroxidase are being evaluated for their ability to remove free radicals. Xanthine oxidase, which is involved in free-radical formation, is inhibited by allopurinol; iron chelators such as desferrioxamine limit the availability of iron and therefore also limit the subsequent free-radical formation. Many other theoretical modes of therapy are being investigated. Most of these require more animal testing before clinical trials can be initiated. As is the case with the corticosteroids, widespread acceptance or rejection of a new therapy requires proven clinical efficacy through a well-designed, randomized, controlled, and preferably double-blind study.

ESTABLISHED MULTIPLE ORGAN FAILURE

Multiple, sequential, progressive organ failure as a syndrome is relatively newly described. Other nomenclature used in the literature of the past include the syndromes of hypermetabolism[220] and malignant intravascular inflammation.[221] The initial descriptions of an organ-failure syndrome were written near the end of the Vietnam War.[4,5] Since then, the United States has been involved in no major conflict or war resulting in a large number of casualties, and most of the military medical experience in recognizing and treating the syndrome results from the peacetime care of military members, their dependents, and retirees.

Sequential or progressive organ failure following an initial injury or illness was described in 1973.[222] The syndrome was defined in 1975.[52] In 1980, Fry and associates[223] reported the principal predisposing factors for the development of MODS: (*a*) resuscitation with a large volume of fluid or (*b*) the presence of infection. This paper was also the first to report the mortality rate for multiple, sequential organ failure. The development of multiple organ failure became an accepted indication for an exploratory laparotomy to search for an unrecognized source of sepsis. Also in 1980, infection was observed to be not the only preceding factor for the development of multiple organ failure, as only 50% of patients were found to have positive blood cultures.[224] The term "non-bacteremic sepsis" was coined to describe this phenomenon. By 1985, other researchers[225] wrote that multiple organ failure could be produced by any process initiating an inflammatory response.

Multiple organ failure is now the major cause of death in patients surviving longer than 48 hours following severe trauma, and is also the most common cause of death in patients in surgical ICUs.[220]

Before we can discuss the importance or prevalence of this medical condition, we must clearly define the syndrome. Much of the earlier research regarding this condition was hampered by the lack of a uniform description or definition. Again, Fry and associates[223] were the first to carefully define organ-system dysfunction in the postoperative patient. The frequency of multiple-system organ failure was retrospectively examined in 1,200 patients. The criteria used for sepsis were the most strict; thus, these patients were quite seriously ill.

In 1985, using a large database, the Critical Care Medicine group at George Washington University Hospital, Washington, D. C., developed a uniform set of definitions of organ system failure (Exhibit 24-6).[91] Their goal—to use criteria that were not only objective but also independent of therapy—was intended to facilitate an analysis of patient therapy and outcome. The definition for respiratory failure was the exception to these stringent criteria; respiratory failure is increasingly difficult to define when the clinical signs are masked by mechanical ventilatory support.

Prevalence

The George Washington University team used the definitions in Exhibit 24-6 to evaluate more than 2,800 patients admitted to ICUs in 13 medical centers within the United States and more than 2,400 patients admitted to ICUs in hospitals in France. The resultant combined database contained 5,248 randomly selected admissions to ICUs. The prevalence of organ-system failure on admission was not published in the 1985 study, but, "49% [of the patients met] at least one of the definitions prior to discharge from the ICU or death."[226(p224)] Furthermore, if multiple organ failure is literally the presence of more than one failed organ system, then this occurred in approximately 15%, or one of every seven patients. Three principal factors that would aid in predicting subsequent development of multiple-system organ failure in patients cared for in combined medical–surgical ICUs were identified[226]:

- the severity-of-disease score (as measured by the Apache II test),
- the admission diagnosis, and
- age greater than 65 years.

EXHIBIT 24-6

DEFINITIONS OF ORGAN SYSTEM FAILURE

One of the following criteria needs to be met during a 24-hour period:

Cardiovascular Failure[1]
- Heart rate ≤ 54/min
- Mean blood pressure ≤ 49 mm Hg
- Ventricular tachycardia or fibrillation
- Serum pH ≤ 7.24 with a $Paco_2$ of ≤ 49 mm Hg

Respiratory Failure[1]
- Respiratory rate ≤ 5/min or ≥ 49/min
- $Paco_2$ ≥ 50 mm Hg
- $A–aDo_2$ ≥ 350 mm Hg, with $A–aDo_2$ calculated as (713 • Fio_2) – $Paco_2$ – Pao_2
- Dependent on ventilator on the 4th d of organ system failure

Renal Failure[1]
- Urinary output < 480 mL/24 h or < 20 mL/h/8 h
- Serum blood urea nitrogen ≥ 100 mg/dL
- Serum creatinine ≥ 3.5 mg/dL

Hematological Failure[1]
- White blood cells ≤ 1,000 mm^3
- Platelets ≤ 20,000 mm^3
- Hematocrit ≤ 0.20

Neurological Failure[1]
- Glasgow coma score ≤ 6 in the absence of sedative drugs

Hepatic Failure[2]
- The patient must have *both*:
  - Bilirubin > 6 mg/dL
  - Prothrombin time > 4 s over control, in the absence of systemic coagulation defect or anticoagulant medication

$A–aDo_2$: alveolar – arterial difference in partial pressure of oxygen; Fio_2: fraction of inspired oxygen; $Paco_2$: arterial partial pressure of carbon dioxide; Pao_2: arterial partial pressure of oxygen

Data sources: (1) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Ann Surg*. 1985;202:685–693. (2) Knaus WA, Wagner DP. Multiple systems organ failure: Epidemiology and prognosis. *Crit Care Clin*. 1989;5(2):221–232.

Additional authorities have reported the subsequent development of multiple organ failure in surgical patients (Table 24-6).

Prognosis

Several researchers have investigated the risk of death from MODS (Tables 24-7 and 24-8).[91,223,227,228] Their data demonstrate two main points regarding the prognosis following the onset of organ failure. First, patient age greater than 65 years increases the risk of death by 10% to 20%. The outcome for elderly patients is also affected to a greater degree by the length of time during which organ failure continued. Second, the mortality rate is so high for patients with three or more organ-system failures that youthful age is no longer a protective factor. By the second day of failure of three or more organ systems, the mortality rate exceeds 90%.

It appears that not all organ-system failures affect mortality equally. In particular, neurological

TABLE 24-6

INCIDENCE OF MULTIPLE SYSTEM ORGAN FAILURE

Date	Patient Characteristic	Prevalance (%)
1985	Medical/surgical intensive care unit[1]	15
1986	Multiple trauma[2]	5–12
1986	Emergency surgery[3]	7–22
1986	Intraabdominal abscess[3]	30–50
1988	Emergency surgery[2]	7

Data sources: (1) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Ann Surg*. 1985;202:685–693. (2) Fry DE. Multiple system organ failure. *Surg Clin N Am*. 1988;68(10):107–122. (3) Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-organ-failure syndrome. *Arch Surg*. 1986;121:196–208.

TABLE 24-7

PROGNOSIS FOLLOWING THE ONSET OF MULTIPLE ORGAN FAILURE

Patient Characteristics	Mortality (%)	Patient Characteristics	Mortality (%)
ARDS alone (n = 13)[1]	31	Emergency surgery / MOF[3]	74
ARDS with MOF (n = 38)[1]	74	Medical-surgical ICU / MOF admissions[4]	64–98
ARDS with MOF[2]	50		

ARDS: adult respiratory distress syndrome
ICU: intensive care unit
MOF: multiple organ failure (≥ two organ failures)
Data sources: (1) Richardson JD. Adult respiratory distress syndrome. *Surg Profiles.* 1988;10–15. (2) Bell R, Coalsu J, Smith J. Multiple organ system failure and infection and the adult respiratory distress syndrome. *Ann Intern Med.* 1983;99:293–298. (3) Fry DE, Pearlstein L, Fulton RL, Polk HC. Multiple system organ failure. *Arch Surg.* 1980;115:136–140. (4) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Ann Surg.* 1985;202:685–693.

TABLE 24-8

AGE-RELATED RISK OF DEATH FROM MULTIPLE SYSTEM ORGAN FAILURE

Day of Failure	No. of Failed Organ Systems	64 Years Old and Younger			65 Years Old and Older			All Ages		
		Deaths	Patients	%	Deaths	Patients	%	Deaths	Patients	%
1	1	440	2,297	19	488	1,323	37			
	2	313	718	44	267	419	64			
	3 or more							404	491	82
2	1	294	1,291	23	347	842	41			
	2	262	561	47	221	302	73			
	3 or more							302	322	94
3	1	248	1,036	24	309	672	46			
	2	219	415	53	153	214	71			
	3 or more							208	223	93
4	1	221	846	26	264	561	47			
	2	185	350	53	139	191	73			
	3 or more							152	159	95
5	1	198	729	27	235	491	48			
	2	160	311	51	128	178	72			
	3 or more							127	131	97
6	1	170	615	28	222	441	50			
	2	146	270	54	111	138	80			
	3 or more							103	105	98
7	1	145	542	27	179	353	51			
	2	126	217	58	87	105	83			
	3 or more							103	105	98

Adapted with permission from Knaus WA, Wagner DP. Multiple systems organ failure: Epidemiology and prognosis. *Crit Care Clin.* 1989;5(2):228.

failure has been associated with an independent mortality rate of nearly 40%. All other organ-system failures are accompanied by approximately a 30% risk of death. However, the researchers at George Washington University Hospital concluded in 1989:

> Indeed it can be argued that virtually all patients who die in intensive care units, unless they have sudden death, die with some degree of multiple system organ failure.[226(p224)]

Etiology and Pathophysiology

A brief review of the medical literature published only during the 1980s will help the reader understand the pathophysiology of this condition. (In view of the still-evolving descriptions of this syndrome and our incomplete understanding of it, hereinafter we will use the term MODS when discussing this syndrome in its historical context, regardless of the extant terminology.) During 1980, MODS was believed to be the result of either an inadequate circulatory state or unresolved sepsis. Fry's research revealed four pathological conditions, each of which was associated with a 24% to 28% incidence of MODS: (1) oligemic shock, (2) septicemia, (3) massive crystalloid therapy (> 6 L) and (4) massive blood therapy(> 6 units).[223] The latter two conditions were associated with the development of MODS independent of the initial disease state.

In further support of the role of infection during this syndrome, Fry demonstrated that 34 of 38 (89%) emergency surgery patients with two or more organ-system failures had sepsis. Furthermore, 100% of patients with three or more organ-system failures had sepsis, and infection was considered to be the cause of death in 58% of all fatalities.[223]

Fry believed that abnormal oxygen utilization secondary to infection was common and in 1980 supported that view with the following observation:

> The failure of organ function in tissues anatomically and functionally different suggests that a common cellular insult may be the fundamental pathophysiologic event in patients with uncontrolled systemic infection.[223(p139)]

By 1982, while reviewing enterococcal bacteremia, Garrison and Fry[229] reported that 48 of 114 patients (42%) had no identifiable primary focus of infection and did not respond to the usual antibiotic regimen. They believed that these bacteremic episodes were the result of bacteria translocated across the gastrointestinal tract. In order for this event to occur, the authors postulated that there must be a break in the gastrointestinal tract mucosal barrier, which is followed by either perihepatic shunting or an overwhelming of the hepatic reticuloendothelial system, as previously demonstrated in states of starvation, excessive alcohol use, or use of corticosteroids. Many studies have been published since that support the translocation of bacteria across the gastrointestinal lumen (Table 24-9).

In 1985, the interaction of endotoxin (also called lipopolysaccharide) with hepatic Kupffer cells was reported in an animal model.[230] The result was a marked decrease in hepatic protein synthesis and subsequent liver failure. Endotoxin that was administered systemically did not have the same effect. Much of the adverse effects appeared to be mediated through the macrophage (Kupffer cell), and its secretory products including complement, IL-1, the prostaglandins, and oxygen free radicals. The report suggests that

> [because lipopolysaccharide] is known to activate Kupffer cells and other macrophages, and [lipopolysaccharide] had no effect on isolated hepatocytes, all combine to support the idea that endotoxin may stimulate Kupffer cells to release mediators, which impair hepatocyte function.[230(p93)]

Thus, new information revealed that bacteria alone may not be responsible for all of the effects on organ systems, and that the presence of live bacteria are not necessary to initiate the cascade. This observation further supports the existence of "culture-negative" sepsis.

In 1985, a retrospective review[225] comparing patient groups of multiple trauma to those with intraabdominal infections and sepsis was published. The incidence of patients with a blood culture positive for bacteria was 40% in the trauma group compared with 73% in patients with intraabdominal sepsis. However, the sequence and severity of organ failure were the same in both groups. Pulmonary failure occurred within 3 days, followed by hepatic, and finally, cardiovascular. Of patients with MODS, 34% had negative blood cultures. The theoretical pathophysiological explanation is that complement is activated, which stimulates polymorphonuclear cells to aggregate, which, in turn, releases prostaglandins and oxygen free radicals, setting in motion a vicious circle:

TABLE 24-9

EVIDENCE OF BACTERIAL TRANSLOCATION IN THE GASTROINTESTINAL TRACT

Date	Model	Significant Findings
1969[1]	Human shock	Histological changes in the gastrointestinal tract were observed after shock
1974[2]	Animal	*Candida* organisms were found to cross from the gastrointestinal tract to the portal venous system
1982[3]	Human sepsis	Description of focus enterococcal bacteremia
1988[4]	Animal	Translocation of bacteria into the mesenteric nodes was proven at autopsy, yet fewer than one third had positive blood cultures
1988[5]	Animal, nontraumatized and on total parenteral nutrition	Higher incidence of bacteria in mesenteric lymph nodes was seen in the group receiving nothing by mouth
1989[6]	Animal, in hemorrhagic shock	Mesenteric lymph nodes, liver, and blood were all positive for bacteria

Data sources: (1) Sorenson FH, Vetner M. Hemorrhagic mucosal necrosis of the gastrointestinal tract without vascular occlusion. *Acta Chir Scan.* 1969;135:439–448. (2) Stone HH, Kolb LD, Currie CA. *Candida* sepsis: Pathogenesis and principles of treatment. *Ann Surg.* 1974;179:697–711. (3) Garrison RN, Fry DE. Enterococcal bacteremial clinical implications and determinants of death. *Ann Surg.* 1982;196:43–47. (4) Baker JW, Deitch EA, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *J Trauma.* 1988;28(7):896–906. (5) Alverdy JC, Aoys E, Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery.* 1988;104:185–190. (6) Deitch EA, Bridges W, Ma L, Berg R, Specian RD, Granger DN. Hemorrhagic shock-induced bacterial translocation: The role of neutrophils and hydroxy radicals. *J Trauma.* 1990;30(8):942–951.

> [I]t should be realized that after appropriate surgery the vicious circle of activated complement, permeability edema, and tissue anoxia is in itself able to perpetuate severe generalized inflammation and has the potential to kill the patient.[225(pp1114–1115)]

Clinical Manifestations

One of the features that distinguishes MODS is the usual *sequential* failure of organ systems, as opposed to the immediate failure of many organs that is seen with trauma. An inciting injury or event is followed initially by successful resuscitation. This may be followed by a period of 2 to 3 days of relative stability. Following this is a period of hypermetabolism (manifested by a near doubling of the patient's metabolic rate and carbon dioxide production). The mortality during this phase alone is approximately 25% to 40%.[21] If the patient's metabolic needs are not abated by resolution of infection, inflammation, or circulatory compromise, then progressive organ failure will develop in approximately 7 to 21 days. This occurs in approximately 40% of patients who develop the hypermetabolic state.[220]

Thus, although the an initiating injury may have been localized to a single organ (eg, the lung), the physiological response can be thought of as a "global circulatory injury."[231(p888)] While established MODS is nearly always manifested by hepatic failure, one study reveals two separate clinical courses for the development of this condition[220]:

- One subset of patients has lung injury as the predominant clinical feature with other organ failure developing shortly before death.
- A second, more-common clinical course is early lung injury followed by a stable period of 10 to 14 days, after which progressive organ failure occurs.

Metabolic Changes

In addition to a greatly increased metabolic rate and oxygen requirement, the body's handling of cellular substrate changes. The metabolic mechanism that normally promotes the entry of pyruvate into the Krebs cycle decreases. Despite the fact that glucose cannot be utilized properly, a relative insulin deficiency exists, which results in hyperglycemia as a result of increased glucagon, increased hepatic gluconeogenesis, and increased glycolysis. Increased lactate production is an additional result of the changed metabolism of pyruvate. The body's tissues must

receive their substrate needs from other sources (eg, fat and protein). This results in increased lipolysis and decreased peripheral lipoprotein lipase activity, and leads to hypertriglyceridemia. Administration of excess lipid via nutrients can lead to hypoxemia and immunosuppression.[220]

Perhaps the most injurious metabolic feature of this syndrome is the extreme catabolism resulting from muscle breakdown: urinary nitrogen excretion exceeds 20 g/d.[220] A marked decrease in the normal hepatic synthesis of albumin and other proteins compounds this protein loss.

Pulmonary Failure

The lung is usually the first organ to fail in the sequence of MODS.[223] Pulmonary injury may occur directly (eg, via aspiration or infectious pneumonia) or secondarily (eg, via sepsis). Why does the lung so frequently become injured in patients who have distant foci of infection or injury? The answer probably can be found in two pathophysiological mechanisms:

1. Inflammatory mediators and toxic by-products are released.
2. Cellular aggregates comprising leukocytes, platelets, and fibrin may block pulmonary capillaries leading to an elevation of the pulmonary vascular resistance and ventilation–perfusion abnormalities. (This mechanism is inherent to the normal function of the lung as a component of the reticuloendothelial system.)

Patients in an early state of MODS may present with "soft" clinical signs and symptoms of distress (ie, a slight increase in respiratory rate and a subjective feeling of dyspnea at rest). This frequently progresses rapidly to respiratory failure accompanied by marked tachypnea, the use of accessory muscles of respiration, and hypoxemia. Patients in early MODS require mechanical ventilatory support for hypoxemia, which requires that supplemental oxygen be administered to an elevated concentration, and to provide relief from the work of breathing. In models of respiratory failure, blood flow to the diaphragmatic musculature alone may use up to 30% to 40% of the entire cardiac output.[232]

The pathophysiological changes include decreases in both (*a*) pulmonary compliance associated with interstitial fluid accumulation and (*b*) the functional residual capacity (ie, the volume that ensures normal oxygenation of the continuous blood flow adjacent to the alveoli). Positive end-expiratory pressure functions mainly to increase this volume, which, in turn, generally decreases the shunted fraction.

Despite the problem that hypoxemia presents, these patients generally do not die of hypoxia. Maintaining a Po_2 greater than 60 mm Hg is usually not difficult. The clinical situation is more complicated; Po_2 represents only the dissolved oxygen carried in the blood. In ARDS and MODS, it appears that some tissue beds do not utilize oxygen. Much of the current literature supports the contention that this is caused by the shunting of blood flow past tissue or organ beds, particularly in the splanchnic circulation.[150,233]

Once mechanical ventilatory support is required, additional risks include a significant incidence of nosocomial pneumonia, oxygen toxicity, and a state of lung inflammation that acts as a self-perpetuating cause of further organ damage.

The lung also functions as a metabolic organ, clearing vasoactive substances such as the prostanoids and bradykinin from the circulation. When this lung function fails, elevated plasma levels of certain mediator substances may also play a role in the hemodynamics of sepsis, manifesting as refractory vasodilation.

Cardiovascular Failure

The hemodynamic responses are the best-studied clinical signs in patients with either sepsis/SIRS or MODS. Most clinicians are aware that high cardiac output and low systemic vascular resistance measurements are characteristic. However, not all patients who demonstrate these values, as measured by the pulmonary artery catheter, should be labeled septic, for the following reasons:

1. Systemic vascular resistance is a *calculated* variable, so if an elevated cardiac output occurs, the systemic vascular resistance value will be calculated as low. This may not match the patient's actual physical state.
2. High cardiac output and decreased systemic vascular resistance have other causes, including severe anemia, cirrhosis, excessive volume resuscitation, thryotoxicosis, and arteriovenous malformation or shunt.

Despite the consistent measurements of high cardiac output, there is still considerable myocardial

dysfunction observed in sepsis or MODS.[77] Myocardial depression, as evidenced by a global cardiomyopathy or dilation of the left ventricle, has been documented. Patients who are unable to develop this dilation, usually viewed as an abnormal state, have a higher mortality than patients who do. In patients with ARDS, improved survival has been observed to be associated with an elevated left ventricular end diastolic volume. This compensatory response allows for the development of an increased stroke volume, cardiac index, and oxygen delivery. Increasing evidence has demonstrated dysfunction of the right ventricle as well, particularly if there are high pulmonary arterial pressures.[82,83]

The most obvious hemodynamic change is the profound degree of vasodilation, which results in hypotension. This low perfusion pressure at the time of increased metabolic needs may further contribute to organ damage. Despite a high cardiac output, blood flow does not appear to be properly distributed among tissues, leading to an inappropriately high, mixed venous-oxygen content, reflecting a decreased tissue-organ oxygen uptake.[234]

The degree of oxygen debt may reflect the elevated arterial lactate level and is correlated with decreased survival.[235,236] A low cardiac output is observed only in the final stages of sepsis or MODS, with this caveat: some patients with a previous history of myocardial infarction, particularly the elderly, are unable to mount a hyperdynamic response. This compensatory response—hyperdynamic circulation—appears to increase the probability of survival.[160]

Other possible explanations for an abnormal relationship between oxygen delivery and consumption include the following:

- The tissues may not be able to extract oxygen.
- There may be areas of underperfused capillary beds (unrecruited).
- A disproportionate percentage of the cardiac output may be delivered to organs with low metabolic demands and oxygen extraction (eg, skin and muscle).
- Arteriovenous shunts may occur in the precapillary tissue beds.
- Endothelial injury may result in tissue edema, thereby increasing the distance across which oxygen must diffuse.
- Microthrombi may block the peripheral vascular bed.
- Mediator-induced vasoconstriction may reduce flow through tissue vascular beds.

Hepatic and Gastrointestinal Failure

The liver and other components of the gastrointestinal tract comprise another organ system that fails in MODS. This organ system's role in the pathophysiology and clinical features of MODS was ignored for many years, but interest has been renewed. Some authorities view the gastrointestinal tract as a target organ, while others see it as the motor that drives the entire MODS process.[220,237,238] Primary among the clinical signs seen are those involving hepatic injury. The liver is directly downstream from the gastrointestinal tract, and thus may be exposed to a large number of bacteria translocated into the portal venous system.[239] Functioning as a component of the reticuloendothelial system, the liver filters out bacteria and particulate matter. Hepatic Kupffer cells comprise nearly 70% of the body's entire macrophage population.

The gastrointestinal tract appears to play a significant role in the perpetuation of MODS, usually manifesting injury concomitantly with the lungs:

> [T]he important role played by the reticuloendothelial system is suggested by the fact that the liver and lungs, two large reticuloendothelial organs, are in series and can, therefore, filter particulate matter from blood draining from the [gastrointestinal] tract, preventing their passage to the systemic circulation.[240(p199)]

Thus the liver may become injured, mechanically blocked, or it may completely fail.[241] The clinical signs are jaundice, altered protein handling, and immunosuppression from a decreased secretion of IgA antibodies.

The stomach is also known to be affected in these syndromes. Endotoxin decreases mucosal blood flow, increases mucosal permeability, and increases total acid production.[242] The result may be stress ulceration or gastritis and gastrointestinal hemorrhage. This is much less frequent than it was even as recently as the 1980s, as antacids, histamine blocking agents, or sucralfate (Carafate, manufactured by Marion Merrell Dow, Kansas City, Mo.) are now routinely administered to seriously ill patients. This may come with a price, though, as bacterial overgrowth in the stomach occurs when the normal acidic environment is changed to alkaline. The same bacteria were found in the stomach and upper airway in 52 of 60 (87%) surgical ICU patients.[243]

Small-bowel dysfunction frequently occurs, presenting as abdominal distention, ileus, or intolerance to enteral feeding.[240] This occurs secondary to edema of the small-bowel wall and a decrease of the

villous absorptive area. Animal models of shock show that these changes may occur within hours of the inciting injury.[191]

The gallbladder is not infrequently involved, with a pattern of cholecystitis different than usual. Patients who are critically ill as a result of trauma, burn injury, or medical illness may not tolerate enteral feeding. The lack of enteral nutrition or the use of total parenteral nutrition has been associated with acalculus cholecystitis. The importance of this condition is the high incidence of gallbladder gangrene (approximately 50%), and perforation (10%).[244] Thus, despite their degree of illness, these patients must have drainage. Recent practice has been to drain these abscesses percutaneously at the bedside under ultrasound guidance, rather than to perform an open cholecystotomy in the operating room.

Renal Failure

Renal failure occurs frequently as a component of MODS (45%–65% incidence).[225] Anecdotally, the kidneys appear to be injured more from uncontrolled sepsis than they are from the use of relatively toxic antibiotics (eg, gentamicin or tobramycin). Renal failure is discussed as a consequence of sepsis earlier in this chapter, and is the subject of Chapter 26, Acute Renal Failure; therefore, it will not be discussed further here.

Coagulation Failure

The most controversial issue regarding DIC is the therapy for it. Clearly, the most effective management tool is effective treatment of the underlying or precipitating infection or disorder and associated factors such as shock. The use of heparin in an attempt to block enhanced clotting activity has not proven to be efficacious in treating DIC that is associated with sepsis/SIRS.[118] Heparin should be reserved for use in patients exhibiting thrombotic complications.[122] Replacement therapy with platelets and fibrinogen is likewise controversial but may be prudent in the patient who is hemorrhaging.[96] Antifibrinolytic agents such as ε-aminocaproic acid are probably contraindicated due to an increased incidence of significant thrombotic events.[118]

Current Treatment Modalities

The current treatment of MODS centers around four modalities. First and foremost is the prevention, control, or elimination of any known inciting or promoting condition. This includes the drainage of abscesses, excision of a burn wound, control of hemorrhage, and aggressive hemodynamic support during shock.

The second approach is additional circulatory resuscitation, the proper end point of which has not yet been elucidated. The parameters that have been considered normal are not normal for the critically ill patient with sepsis.[245,246] Previously, conventional wisdom had recommended increasing the patient's hemodynamic state only if it fell below the individual's baseline preoperative value. More recently, researchers have recommended increasing oxygen delivery until a supranormal level has been reached, or until the consumption no longer increases and the arterial lactate level decreases.[160,244,247,248] General criteria to ensure optimal tissue perfusion include the following:

- minimal or absent acidosis and an *arterial* lactate level less than 2 mmol/L, and
- urinary output maintained above 0.5 mL/kg/h (polyuria may sometimes occur in sepsis as a result of a concentration defect).

In states of oxygen-supply dependency, use Shoemaker's therapeutic goals:

- cardiac index > 4.5 L/min/m^2,
- oxygen delivery > 650 mL/min/m^2, and
- oxygen consumption > 160 to 170 mL/min/m^2.

An alteration in cardiac function and ventricular dilation results in right atrial pressure and PCWP, which do not accurately reflect the intracardiac volumes. This has been recently confirmed in patients with ARDS.[248] The PCWP may help in guiding fluid therapy to avoid further increases in the extravascular lung water and subsequent pulmonary edema.

The third modality in therapeutic support for MODS is nutritional or metabolic modification. The subject, particularly as it applies to combat casualties, is well described in Chapter 23, Metabolic Derangements and Nutritional Support, and therefore will be mentioned only briefly here. As previously discussed, these patients become markedly catabolic. Malnutrition results in a decreased function of both humoral and cellular immunity. Specifically, achieving a positive nitrogen balance appears to improve survival. Nutritional formulae with higher concentrations of the branched-chain amino acids appear to better increase hepatic synthesis of protein and result in lower urea produc-

tion. However, use of high-branched-chain amino acid formulae does not appear to lessen mortality.[246] Most authorities recommend between 1.5 and 2.0 grams of protein per kilogram of body weight per day. The total caloric supplement should not exceed 30 to 35 nonprotein kilocalories per kilogram of body weight per day to avoid the development of fatty liver. The calorie-to-nitrogen ratio should be low, as near 100 as possible.[220]

A controversy has arisen recently regarding whether enteral nutrition is superior to parenteral nutrition for critically ill patients. A prospective randomized trial[248] of enteral versus parenteral nutrition, beginning within 6 days after the onset of sepsis, demonstrated no difference in the overall incidence of MODS or mortality. A retrospective study[249] published in 1987 found that patients given total parenteral nutrition developed higher septic-severity scores than patients fed enterally.

In a prospective study[250] done in 1988 that evaluated early enteral feeding following laparotomy for trauma, patients who received enteral feeding within 12 to 18 hours of admission to the ICU had fewer infections and improved survival. Animal models of *Escherichia coli* peritonitis[251] or hemorrhagic shock[252] have demonstrated a marked decrease in the mortality in groups fed enterally. Specifically, the peptide-based diets, compared with total parenteral nutrition for metabolic support, led to increased survival. Other nutritional therapies are also being studied:

- Tailored nutritional therapy, including the administration of fish oil high in omega 3 polyunsaturated fatty acids. These fatty acids are incorporated into cellular membranes and competitively inhibit the cyclooxygenase and lipoxygenase pathways. This has been shown to decreases the production of prostaglandins and leukotrienes (such as TNF and IL-1) by hepatic macrophages.
- Increased glutamine diet. Glutamine is a trophic factor and increases the small-bowel villous absorptive area. Glutamine is also thought to be involved in maintaining the mucosal-barrier function of the gastrointestinal tract.

The fourth modality in treating renal failure in patients with sepsis/SIRS or MODS is hemodialysis. Because supporting renal failure with hemodialysis is the subject of Chapter 26, Acute Renal Failure, it will not be discussed in this chapter.

SUMMARY

Although the etiologies of the syndromes of systemic inflammatory response and multiple organ dysfunction are varied, the pathophysiological mechanisms leading to their clinical manifestations are remarkably similar. The current state of our understanding reveals this to be the result of the activation of the patient's endogenous cellular and humoral defense systems with the subsequent release, activation, or synergistic stimulation of endogenous mediator substances. The multiplicity of these mediator-induced cell-to-cell and tissue interactions reveals the extreme complexity of the human response to foreign material (ie, endotoxin released from Gram-negative bacteria). Good medical supportive care remains a cornerstone of therapy for patients with sepsis/SIRS to prevent progression to MODS. Early recognition and aggressive treatment of (*a*) persistent foci of infection or inflammation and (*b*) residual microcirculatory shock cannot be overemphasized: appropriate treatment by the vigilant clinician can alter the outcome of these patients before the abnormalities of these syndromes become irreversible.

The body's initial, local, tissue response to infection or inflammation is beneficial. If, however, the response becomes generalized, the body becomes flooded with a multitude of complex mediators; this initiates an unrestrained, perpetuating, systemic response. The nature of some of the mediators (ie, the endotoxin moiety) and the subsequent antigen–antibody formation suggest that immunotherapy might be useful in obviating the effects. Immunotherapy may become an effective treatment in the future.

Sepsis/SIRS and MODS have particular relevance for medical officers. Although the actual number of soldiers who die of these syndromes is small, the potential that this population may benefit from lifesaving intervention is great.

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