

Sepsis and Septic Shock

Microorganisms of Special Relevance

Bacteria

Aerobes

Gram positive

S. pneumoniae

S. pyogenes (Gp.A)

S. agalactiae (Gp.B)

Staphylococcus aureus

Gram negative

Neisseria meningitidis

“Enterics”

Escherichia coli

Klebsiella

Proteus

Enterobacter

Serratia

Citrobacter

Salmonella

“Non-enterics”

Pseudomonas aeruginosa

Acinetobacter

Anaerobes

Bacteroides fragilis

Upper Bacteria

Mycobacteria Tuberculosis

Viruses

Flavivirus

Coronaviridae

Fungi

Candida

Histoplasma

Aspergillus

Sepsis and Septic Shock are clinical syndromes that are paradigms for the interplay of the microorganism and its virulence factors with the host and its inflammatory response. Sepsis is a term generally used to describe a complex of fever, tachycardia, and tachypnea in association with local or systemic infection. Severe sepsis is defined as sepsis with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia, or obtundation). Septic shock describes sepsis with concomitant hypotension despite adequate fluid resuscitation and clinical evidence of diminished tissue perfusion. The microorganism may initiate these syndromes, either by direct invasion of the host's blood stream, by the elaboration of exotoxins, or by both. Either of these microbial events, infection or intoxication, can stimulate host cells to initiate a cascade of inflammatory mediators. These mediators effect cellular, microvascular and hormonal events that are recognized clinically as sepsis, severe sepsis or sepsis with the shock state and multiorgan system dysfunction. The determinants of the particular clinical intensity and evolution of the septic syndrome for the individual patient are not well understood. Currently they are thought to include

genetically determined aspects of the host's immune responsiveness and regulation (perhaps when the host responses are inadequate), as well as specific virulence factors of the infecting organism (perhaps when the host cannot contain the infection).

The Microbial Initiation

Microorganisms from many classifications have the capability of establishing sepsis and septic shock. These syndromes have been associated with infections caused by viruses (for example, dengue fever), by rickettsia (for example, Rocky Mountain spotted fever), by fungi, including *Candida* species and *Histoplasma capsulatum*, and by bacteria. Perhaps because bacteria are the most common microorganisms associated with sepsis and septic shock, they have been best studied. Gram negative aerobic bacillary organisms -- particularly *E. coli*, the *Enterobacteriaceae* (like *Klebsiella*, *Serratia*) and the Pseudomonads -- have increased in frequency not only as causes of serious community-acquired infections but also as causes of serious hospital-acquired infections throughout the 1960's, 1970's, 1980's, and 1990's. Scientific and technologic advances have permitted mechanical ventilatory support for patients with acute respiratory failure, the transplantation of organs for patients with failing kidneys, hearts, livers, as well as the regimens of chemotherapy for treatment of malignant diseases. These opportunities have created populations of patients with altered immune systems, many of whom spend time in hospitals. These new patient populations and new support technologies play major roles in the striking increase in Gram negative bacterial infections. The recognition of these organisms as major pathogens and the life-threatening aspects of their infections have led to intensive study of Gram negative bacterial sepsis and septic shock. In the 1980's and early 1990's Gram positive aerobic bacteria became increasingly important as well. Extrapolation from studies of the Gram negative organisms and independent work with the Gram positive organisms have contributed to our current understanding of the pathogenesis of sepsis and septic shock caused by bacteria, both Gram negative and Gram positive.

Direct invasion and the resulting interaction with critical host cells constitute one major mechanism by which bacteria can cause sepsis and septic shock. Integral components of the outer surface of the organisms have the capacity to stimulate host cells to produce a stereotypic inflammatory response.

Lipopolysaccharide is an essential component of the outer membrane of Gram negative bacteria. It is a major part of a lipoprotein structure with a core of polysaccharide that links the lipoprotein -- anchored in the membrane -- to the outer chains of saccharides.

This lipopolysaccharide structure has been chemically characterized. It consists of a lipoidal acylated glucosamine disaccharide and a linking "core" of phosphorylated heptose and keto-deoxyoctonate (KDO). It is highly conserved throughout most species of Gram negative bacteria. Studies in animal models and in human volunteers have documented that this cell wall component is the biologic equivalent of "endotoxin," producing the inflammatory and hemodynamic profiles associated with Gram negative bacterial sepsis and septic shock or what has been referred to in the past as "endotoxin" shock.

It is important to understand that the lipopolysaccharide structure is deep within the intact cell membrane of the Gram negative bacteria. Although the cell

membrane may well be sterically more fluid than depicted, interaction of this structure with host tissue is believed to occur predominantly during growth phases of bacteria, during cell lysis by host clearance mechanisms such as complement fixation, or during cell lysis after antibiotic action. It is postulated that in these circumstances the inner components of the membrane can interact directly with host tissue.

Lipopolysaccharide or “endotoxin” is unique to Gram negative bacteria. However, cell components of Gram positive bacteria have been identified that appear to be biologically equivalent to endotoxin in stimulating the inflammatory response from host cells associated with sepsis and septic shock. The peptidoglycan layer outside the cell membrane of Gram positive bacteria as well as non-peptidoglycan polymers, the teichoic acids, in particular, have been studied. They have been shown to stimulate the release of cytokines, specifically tumor necrosis factor and interleukin-1.

The elaboration of exotoxins that then initiate the inflammatory response appears to be a second major mechanism by which bacteria can cause sepsis and septic shock. Some of the best studied of these exotoxins are the group of toxic shock syndrome toxins which are products of certain strains of *Staphylococcus aureus* as well as certain strains of Group A Streptococcus (*Streptococcus pyogenes*). These toxins display the unique ability to act as superantigens: they appear to be capable of unconventional binding, both to antigen-presenting cells and to T lymphocytes. The toxins can bind “outside” the antigen-presenting groove of the MHC Class II molecule of the macrophage and bind uniquely to a specific family of T lymphocytes characterized by identical V beta regions of the T-cell receptor (for example, V Beta₁). This novel binding permits very small amounts of these toxins to stimulate the proliferation of large populations of T-cells simultaneously, with the resultant production of large quantities of cytokines.

Pathophysiology of Sepsis and Septic Shock

Many constructs have been offered to explain the clinical manifestations of sepsis and septic shock. The mechanisms, however, remain incompletely understood. Gram negative bacterial sepsis and septic shock remain the best studied and therefore have been the paradigm for our current understanding. Investigative work has demonstrated that the core lipopolysaccharide is an initiator of an endogenous cascade of inflammatory events that results in the stereotypic physiologic changes in the host that are recognized clinically as sepsis, severe sepsis and septic shock. The seminal initiating event is complex but appears to include effects of lipopolysaccharide on both the vascular endothelial cell and on the macrophage.

The cell binding and subsequent cell signaling of lipopolysaccharide is being intensively studied. On the surface of the endothelial cell, one receptor for lipopolysaccharide has been identified and appears to accept soluble CD₁₄ (sCD₁₄) complexed to lipopolysaccharide. On the surface of the macrophage a membrane bound CD₁₄ receptor has been identified which can directly bind the lipopolysaccharide/lipopolysaccharide binding protein complex. One path of subsequent transmembrane signaling appears to be through toll-like receptors (particularly, for example, TLR₄ for Gram negative bacteria; TLR₂ for Gram positive bacteria) with activation of intracytoplasmic kinases and ultimately translocation of nuclear factor KB (NF-KB) and transcription of TNF as well as other inflammatory cytokines.

Endotoxin appears to cause mechanical as well as metabolic perturbation of the endothelial cell membrane. One result is activation of the clotting cascade. The extrinsic coagulation pathway may be initiated by release of the lipoprotein tissue factor from the altered endothelial cell with subsequent activation of factor VII, Factor X and the formation of thrombin and resultant fibrin deposition. With interaction of endotoxin and the endothelial cell, collagen is exposed and Factor XII (Hageman factor) is activated, initiating the intrinsic coagulation pathway. This intrinsic component of the clotting network may function as an auxiliary fibrinolytic system. Investigative work has documented a close relationship and "cross talk" between the clotting network -- both the components of the intrinsic and of the extrinsic pathways -- and the inflammatory peptides, for example, TNF. The clinical manifestations vary. Frank disseminated intravascular coagulation may develop, presenting as active bleeding or thrombosis. At the other extreme, only laboratory confirmation of consumption of clotting factors may be demonstrated.

Activated Factor XII also affects the kinin system, resulting in formation of bradykinin, a potent systemic vasodilator. A third effect of Factor XII activation is the triggering of the complement pathway. Complement fragments are produced, including C5a, which has been shown to cause neutrophil aggregation. With neutrophil aggregation, reactive oxygen metabolites are produced. These metabolites cause injury to cell membranes by initiating lipid peroxidation and bringing about DNA strand breaks. Complement activation alone or in the presence of endotoxin can directly activate phospholipase enzymes, resulting in the release of arachidonic acid from the cell membrane phospholipids of neutrophils and platelets, in particular. The metabolites of arachidonic acid include prostaglandins, thromboxanes, and leukotrienes. These cell products have effects on microvascular permeability, vasomotor tone, and cell aggregation.

Endotoxin has been shown to initiate the release of inducible endothelin-derived-relaxing factor or nitric oxide from endothelial cells. Studies support the role of nitric oxide as the key mediator to the sentinel hemodynamic event in sepsis and septic shock -- vasodilatation.

Endotoxin -- the lipopolysaccharide component of the Gram negative cell wall -- can be bound by lipopolysaccharide binding protein (LPS binding protein), which is present in normal serum. The resulting LPS-LPS binding protein complex binds to the CD14 antigen expressed on the surface of macrophages, stimulating the production and release of several mediator peptides -- monokines -- from macrophages. These monokines are now being identified, and their varied functions as "signal" proteins for thermoregulation, metabolic regulation, and endocrine regulation are being defined. Two of these monokines are tumor necrosis factor and interleukin-1. Tumor necrosis factor may be a central mediator of changes in hemostasis and permeability at the microvascular level. It may be a primary trigger for an array of immunologic, metabolic, and hemodynamic events. The interleukin-1 polypeptides appear to be major, though not sole, mediators of fever through increase of prostaglandin E2 release in the anterior hypothalamus. Their actions also include effects on the number and maturity of circulating neutrophils by action on the bone marrow, mobilization of amino acids from skeletal muscle, and the amplification of subsets of T-cells.

Endotoxin also stimulates the macrophage to produce and release platelet-activating factor (which is also produced by platelets and polymorphonuclear

leukocytes). Platelet-activating factor, a phospholipid mediator, stimulates cell adhesion and amplifies the action of cytokines.

This interplay of lipopolysaccharide -- endotoxin -- with vessel endothelium and macrocytic phagocytes results in the striking hemodynamic changes and the organ dysfunction characteristic of sepsis and shock. Initially there is vasodilatation, a decrease in vasomotor tone. The determinants of this sentinel event are not understood. One possible mediator of this vasodilatation may be the nitric oxides, possibly of endothelial cell origin but also of macrophage origin, induced by the interaction of endotoxin on these cells.

The events that determine the deterioration to frank septic shock are not yet clearly defined. At least two factors appear to be important -- changes in intravascular volume and changes in cardiac function. Early in the transition from the septic state to septic shock, the effective circulating volume falls, in part related to early arterial and venous dilatation. As microvascular permeability increases, fluid extravasates from the intravascular space into the interstitium, resulting in a further decrease in the circulating volume. The second characteristic of septic shock, myocardial dysfunction, is quite distinctive. Studies of patients in septic shock with right heart catheters in place demonstrate an elevated cardiac output of 5-12 L/min. Yet bedside myocardial nuclear scanning techniques demonstrate striking biventricular dilatation and a reduced ejection fraction. The vasodilatation and resultant decrease in afterload as well as the tachycardia favor forward flow and dictate the subsequent rise in cardiac output despite the depressed myocardial function as measured by the reduced ejection fraction displayed by nuclear scanning. Although not yet characterized, a myocardial depressant factor (or factors) is released in sepsis and results in alteration of myocardial compliance and contractility. Compliance is increased -- the ventricles become "baggy." Contractility is decreased as defined by the decreased ejection fraction. With these circulatory and myocardial changes the heart becomes preload-dependent. It is in the volume-replete or volume-resuscitated patient in septic shock that the cardiac output measurements are greatest despite the reduced ejection fraction. The "classic" hemodynamic profile in septic shock is that of low or normal pulmonary artery wedge pressure- as a reflection of left atrial (and ultimately left ventricular end diastolic) pressure and the often strikingly high cardiac output.

Studies in animal models as well as correlations clinically have demonstrated areas of ventilation-perfusion mismatch occurring early in the lung in sepsis and septic shock. Agglutination of white cells and platelets occurs in the pulmonary vasculature, mediated at least in part by activation of the complement cascade as well as by the release of eicosanoids -- leukotrienes, thromboxanes, and prostaglandins. These events alter perfusion in the microcirculation. Increases in pulmonary capillary permeability result in an increase in interstitial lung water and can ultimately disrupt alveolar cell barriers resulting in extravasation of fluid into the alveoli. This results in altered ventilation and oxygenation. The increased interstitial lung water may trigger the "J" or stretch receptors in the lung, contributing to an increased respiratory rate and the primary respiratory alkalosis seen frequently in early sepsis. If white cell and platelet agglutination proceed and vessel permeability continues, respiratory failure -- the respiratory distress syndrome -- may complicate septic shock.

There is evidence that the same alterations in endothelial integrity, increases in interstitial water and agglutination of white cells and platelets, occur not only in the lung but in other organs as well. This results in tissue injury with release of reactive

oxygen species, amplification of the cycle of eicosanoid production, and activation of the extrinsic coagulation cascade with formation of microthrombi. The resultant organ system dysfunction and failure represent a recognized complication of septic shock -- multiorgan system failure. Multiorgan system failure is a major cause of the high morbidity and mortality associated with septic shock.

Finally host immunosuppression seems to be a factor in late death in patients with sepsis. When monocytes from patients with sepsis, *ex vivo*, are stimulated with lipopolysaccharide, they express less proinflammatory cytokines than monocytes from healthy subjects- possibly indicating relative immunosuppression. Apoptosis may also play a role in host immunosuppression. Apoptosis is thought to occur when activated T-helper cells evolve to the Th2 from the Th1 phenotype and the subsequent production of anti-inflammatory cytokines, resulting in a loss of circulating and tissue lymphocytes as well as lung and intestinal epithelial cells (due to increased levels of TNF- α and LPS).

Clinical Manifestations

The clinical features of sepsis and septic shock appear remarkably similar whether caused by infection (either Gram negative or Gram positive bacteria, for example) or by intoxication (as in *Staphylococcus aureus* toxic shock, for example).

Classically the individual with sepsis presents with fever and often shaking chills or rigors. Nausea, emesis, and diarrhea may occur. Occasionally these symptoms may have their onset 1-2 hours after manipulation -- for example, the insertion or removal of a bladder catheter, or after exploration of an infected wound.

On physical examination of the patient with sepsis, the blood pressure is found to be maintained in the patient's normal or near-normal range. The patient may have a high fever or a normal temperature. Occasionally the patient may be hypothermic with temperature in the 94-96°C range. The patient is tachycardic with a rapid "bounding" pulse. The respiratory rate is usually elevated. The skin may be warm and "flushed." The patient may be agitated or confused. Laboratory data obtained in sepsis are often distinctive for an arterial blood gas analysis that reveals a primary respiratory alkalosis and occasionally a modestly reduced pO₂. The white cell count may be elevated or may be strikingly low. Measurement of clotting parameters may show prolongation of the prothrombin time and a decrease in platelets. The blood lactate may be measurably elevated but usually is at low levels (Table 1).

If the diagnosis of sepsis is not made and appropriate treatment is not instituted early (and sometimes even if it is) some patients may progress to septic shock. The clinical findings are initially those of sepsis, but at this clinical stage the patient will now be measurably hypotensive.

Table 1: Sepsis Syndrome: Early Clinical Presentation

Physical Exam

Vital Signs

Pulse Rate – rapid, “bounding”

Blood Pressure – may be normal/low normal

Temperature - \uparrow / normal / \downarrow

Respiratory Rate – rapid

Mental Status

may be confused, agitated

Skin

warm, “flushed”

Urine volumes \downarrow

Laboratory Data

ABG pH \uparrow - pCO₂ \downarrow - pO₂ – modestly \downarrow

blood lactate

WBC \uparrow / \downarrow

Protome may be prolonged / platelets may be \downarrow

In adults, hypotension accepted as compatible with the shock syndrome is defined as systolic blood pressure < 90 mm Hg or a 40 mm Hg decrease below the patient’s baseline systolic blood pressure. The patient’s pulse will be rapid and though initially “bounding” now may become “thready” to palpation. The patient is often tachypneic, but at this stage arterial blood gas analysis may reveal a primary metabolic acidosis as well as hypoxemia. The patient may be confused or somnolent. The skin may still be flushed or may feel cold and “clammy.” Hourly urine volumes, as might be measured in the immediate period after surgery, for example, will be reduced. A white blood cell count may be elevated with many immature neutrophils, or the white cell count may be strikingly low. The measurement of clotting factors is often compatible with disseminated intravascular coagulation. The platelet count is often decreased. The blood lactate level is elevated. Some patients in septic shock may be clinically indistinguishable from those with shock of any cause. Studies suggest that this “later” stage of the septic shock state with cool skin, “thready pulse” and now measurably low cardiac output may be the result of a critical decrease in circulating intravascular volume secondary to arterial and venous dilatation, altered microvascular permeability with a decrease in right heart filling in the setting of the increased compliance of the ventricles. If volume resuscitation is instituted before this stage, or instituted after it has developed the patient will manifest the “early”, hyperdynamic stage that is more typical of the septic state.

Table 2: Septic Shock: Late Clinical Presentation

Physical Exam

Vital Signs

Pulse Rate – rapid, “thready”

Blood Pressure – systolic <90mm Hg (adults)

Temperature - ↑ / normal / ↓

Mental Status

may be confused, agitated

Skin – cool, “clammy”, mottled

Urine volumes ↓↓↓

Laboratory Data

ABG pH ↓ - pCO₂ nl or ↑ - pO₂ ↓

Blood lactate ↑

WBC ↑ / ↓

Protome prolonged / platelets ↓

There is rarely an orderly evolution from sepsis to septic shock. Often the clinical syndromes combine features of both stages. In some situations the manifestations are not clinically obvious. Fever may be absent in the elderly, those with uremia, and patients on corticosteroids. Hypothermia occurs more commonly in the newborn with sepsis than in the adult. Tachypnea and a primary respiratory alkalosis may signal a pulmonary embolism or may be an early sign of sepsis.

Bacterial Organisms

Sepsis and septic shock have been produced by all species of aerobic and anaerobic bacteria. Aerobic Gram negative bacilli are commonly isolated, particularly the members of the families *Enterobacteriaceae* and the Pseudomonads. Aerobic Gram positive cocci are now the most common causes of sepsis and septic shock, both as the result of direct infection (*Streptococcus pneumoniae*, for example) and as the result of toxin production, or both (e.g., *Staphylococcus aureus*, *Streptococcus pyogenes* (Group A)). Hospitalized patients are at particular risk for the development of sepsis and septic shock as a result of the patients’ altered immune defenses as well as the instrumentation and procedures necessary for their care. Each institution will have its own profile of pathogens related to the pattern of antibiotic use as well as to the nature of the patient population. Institutions with leukemia services or with burn units often have a large proportion of *Pseudomonas aeruginosa* and *Enterobacter* organisms isolated. Surgical and gynecologic units have a greater proportion of *Klebsiella* as well as of the anaerobic Gram negative bacillus *Bacteroides fragilis*. There may be local outbreaks of a particular organism, for example, *Serratia marcescens* on a urological service. Polymicrobial sepsis occurs most often from sites in the gastrointestinal tract or occasionally from skin wounds.

Diagnosis and Treatment

The diagnosis of sepsis is considered when the patients have two or more of the SIRS (Systemic Inflammatory Response Syndrome [Bone and colleagues, Chest 1992;101:1644-55]) criteria: 1. Increased heart rate (>90 beats/min) 2. Increased respiratory rate (>20 breaths/min) or $\text{PaCO}_2 <32$ mmHg. 3. Increased temperature ($>38^\circ\text{C}$ or 100.4°F) or decreased temperature ($<36^\circ\text{C}$ or 96.8°F) 4. Increased white-cell count ($>12,000/\text{mm}^3$) or decreased white-cell count ($<4,000/\text{mm}^3$) and suspected or confirmed source of infection. Severe sepsis include one organ dysfunction or more and septic shock occurs when the systolic blood pressure is <90 mmHg or >40 mmHg drop in blood pressure from baseline despite adequate fluid resuscitation. Once sepsis, severe sepsis or septic shock is suspected, the patient should be examined to determine a possible origin of the infection. Cultures of blood, urine, and sputum, as well as other sites as clinically indicated -- CSF, pleural fluid, ascites fluid, joint fluid, wound, for example -- should be obtained. After performing the cultures, antibiotic therapy should be initiated immediately and before the culture results are available. Sepsis and septic shock evolve in rapid tempo, and prompt administration of appropriate antibiotics is life saving. Identification of a likely site (or sites) of infection as well as a knowledge of the specific epidemiology (antibiotic resistance patterns also know as an antibiogram) of the bacteria in the particular hospital environment will permit an educated selection of empiric antibiotics. This initial antibiotic regimen should be modified when culture results become available. Observational studies indicate that outcomes in sepsis and septic shock are significantly worse if the causative microorganisms are not sensitive to the initial antibiotic regimen and when appropriate antibiotics are delayed.

Table 3: Etiologic Agents in Bacteremia

| <i>Site of origin</i> | <i>Etiologic agents</i> | <i>frequent precipitating events</i> |
|--|---|--------------------------------------|
| Skin | <i>Staph. aureus</i> <i>Staph. coagulase negative</i> <i>Corynebacterium jeikeium</i> <i>Pseudomonas aeruginosa</i> <i>Acinetobacter</i> | Intravenous catheter |
| Respiratory tract | Out of hospital: <i>Strep. pneumoniae</i> <i>Strep. pyogenes</i> In hospital: <i>Pseudomonas aeruginosa</i> <i>Serratia</i> <i>Enterobacter</i> <i>Acinetobacter</i> | Aspiration |
| Genitourinary tract Bladder catheter, | <i>E. coli</i> <i>Klebsiella</i> <i>Enterobacter</i> <i>Proteus sp.</i> <i>Pseudomonas aeruginosa</i> | ureteral obstruction, cystoscopy |
| Gastrointestinal tract Biliary tract | <i>E. coli</i> <i>Klebsiella</i> <i>Enterobacte</i> | Cholangitis, biliary stent |
| Bowel abscess | <i>E. coli</i> <i>Klebsiella</i> <i>Enterobacter</i> <i>Serratia</i> <i>Salmonella</i> <i>Bacteroides</i> | Perforation |
| Reproductive system | <i>Streptococcus</i> <i>E. coli</i> <i>Bacteroides</i> | Postpartum, instrumentation |

Use of antibiotics is only part of the therapeutic approach. Source control is also vitally important. This includes treatment of the local site of infection by removal of possibly contaminated catheters, drainage of collections of pus, or excision of necrotic tissue may be required before sepsis, severe sepsis and septic shock can be reversed.

Management of sepsis, severe sepsis and septic shock also must include appropriate support of circulation and ventilation. Efforts to restore the circulating volume may require the monitoring of central venous pressures. Routine invasive monitoring includes the measurement of the central venous pressure from a catheter inserted into the superior or inferior vena cava or other central veins and occasionally by a pulmonary artery catheter. Pulmonary artery catheterization is performed with a

catheter that is constructed with a balloon at the tip. The catheter is placed into the pulmonary artery. When the balloon is inflated, it floats distally into a small pulmonary artery, reflecting left atrial pressure (an estimate of left ventricular end-diastolic volume). At present, it affords the closest assessment of left ventricular pressure and volume available at the bedside. The catheter has a thermistor that allows measurement of cardiac output by the thermodilution technique. Placement of a pulmonary artery catheter, measurement of the pulmonary artery occlusion (or wedge) pressure, and cardiac output may be necessary to permit intelligent fluid resuscitation. Recent studies in medical and surgical patients however indicate that the *routine* use of pulmonary artery catheters have *not improved outcomes* and their use has declined significantly over the past twenty years (JAMA 2007;298(4):423-429). It must be stated that in selected patients with cardiac, pulmonary, and renal disease, the information obtained from the pulmonary artery catheter can be invaluable in the management of patients in shock.

The most important study addressing the early treatment of patients in severe sepsis and shock was conducted by Dr. Rivers and colleagues (NEJM 2001;345:1368-77). Their study was a randomized, controlled trial in which patients with SIRS and shock received early, goal directed, protocolized therapy in the first 6 hours of the diagnosis of shock in the emergency room. The outcome of a series of systematic interventions (the early goal directed therapy group [EGDT] used a continuous central venous saturation monitor developed by Edward Life Sciences) from their protocol resulted in a mortality reduction from 46% to 30% at 28 days—an absolute reduction of 16% (a number need to treat of 6). Patients in the standard therapy group were treated in the first 6 hours with crystalloids to maintain central venous pressure at 8-12 mmHg and if necessary, vasopressors were used to maintain a target mean arterial blood pressure of >65 mmHg. The EGDT group used the continuous central venous saturation (a surrogate for cardiac output) technology to initiate dobutamine (an inotrope and vasodilator) if necessary to maintain a central venous saturation of 70% and if needed, blood was transfused to a hematocrit goal of 30%. Not surprisingly, patients in the EGDT group received significantly more fluid, dobutamine and blood transfusions. The mechanisms for the better outcome were not well understood but were thought to be related to early aggressive reversal of inflammation, coagulation abnormalities, tissue hypoxia, and with early reversal of poor hemodynamics.

An understanding of the changes occurring in the lung during sepsis has increased attention to the monitoring of oxygenation, early consideration of supplemental oxygen, and in some patients, intubation and support on a ventilator. Acute lung injury and Acute Respiratory Distress Syndrome often accompanies sepsis, therefore, lung protective ventilation (the use of “small” or normal tidal volumes) is thought to be beneficial in acute lung injury. Using tidal volumes of 6 ml/kg of ideal body weight (calculated in men as $50+0.91$ [height in cm-152.4] and in women as $45.5+0.91$ [height in cm-152.4]) as compared to 12 ml/kg has been shown to decrease mortality in ARDS (Acute Respiratory Distress Syndrome) from 40% to 31% (NEJM 200;342:1301-08). The cyclic opening and overdistension of alveolar lung units may actually induce further inflammation and cause pulmonary as well as extra-pulmonary organ dysfunction. The simple choice of the tidal volume in these patients resulted in an absolute mortality reduction of 9% (a number need to treat of 11).

In regard to septic shock patients, a keen clinical observation at the bedside has led to studies documenting both the relative depletion of vasopressin and down regulation of vasopressin receptors-- one of our “stress” hormones -- and the hyper

responsiveness to low doses of vasopressin that appears to be unique to patients with septic as well as other forms of vasodilatory shock. In patients with septic shock, for example, vasopressin at doses of .03-.04 units/min often results in a significant decrease in norepinephrine dosing and hemodynamic stabilization. Vasopressin's impact on morbidity and mortality in sepsis and septic shock patients has been investigated and is the subject of ongoing studies. A recent study published by the Canadian Critical Care Trials Group, entitled VAAST (NEJM 2008;358:877-87) showed no mortality benefit with the addition of vasopressin to patients in shock and already receiving norepinephrine infusion. Patients were eligible if they were in shock and receiving at least 5 µg/min of norepinephrine or the equivalent dose of another vasopressor agent per minute for 6 hours. The primary outcome was death from any cause assessed 28 days after the start of the infusions. Secondary outcomes included 90-day mortality, days alive and free of organ dysfunction during the first 28 days. There was no significant difference in the primary outcome between the vasopressin group and the norepinephrine group (35.4% and 39.3%, respectively; P = 0.26; 95% confidence interval [CI] for absolute risk reduction in the vasopressin group, -2.9 to 10.7%). Similarly, there was no significant difference in mortality at 90 days (43.9% and 49.6%, respectively; P = 0.11; 95% CI for absolute risk reduction, -1.3 to 12.8%) or in rates of organ dysfunction. What needs to be noted is that this was not a primary vasopressor trial. Vasopressin was used adjunctively as a "norepinephrine or catecholamine sparing" agent. Furthermore, this trial also did not evaluate vasopressin's use in patients who are refractory to catecholamines -a group with a much higher mortality.

A subset of patients remains in shock despite early, appropriate antibiotic treatment, aggressive attempts at volume resuscitation and use of pressors including high doses of catecholamines, and the addition of vasopressin. These patients have been the impetus for the investigation of additional modes of treatment. Recognition of the events triggered by core lipopolysaccharide (or endotoxin) and mediated by cytokines and eicosanoids has increased interest in supplementing antibiotic use and hemodynamic support with a third approach -- the use of agents that interrupt this endogenous inflammatory cascade. These agents include antibodies (human or murine) as well as pharmacologic agents. Antibodies to the core lipopolysaccharide component of the Gram negative bacterial cell wall have been studied, but neither the human nor the murine monoclonal antibody products were demonstrated to improve overall outcome in sepsis or septic shock in clinical trials. Antibody to TNF and to IL-1 receptors have also been studied and have demonstrated no advantage.

Pharmacologic agents that inhibit the release or action of the inflammatory mediators have been studied as well. Small trials with patients in septic shock revealed possible mortality and morbidity advantage. Dr. Annane's (JAMA 2002;288:862-871) research suggested that patients that had relative adrenal insufficiency (patient's whose plasma cortisol levels did not rise appropriately (<9 mg/dL) after the administration of corticotrophin [ACTH]) and in shock would benefit from steroids. Corticosteroids were submitted to a carefully designed, rigorous, prospective, randomized multi-institutional trial named CORTICUS (N Engl J Med 2008;358:111-24). Patients who were in shock and had relative adrenal insufficiency were assigned to receive 50 mg of intravenous hydrocortisone or receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test (patients with relative adrenal insufficiency). The results revealed that At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a

response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, $P = 0.69$) or between those who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, $P = 1.00$). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock. On the basis of these findings, hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (vasopressor responsive), nor can corticotrophin testing be recommended to determine which patients should receive hydrocortisone therapy. Hydrocortisone may have a role among patients who are treated early after the onset of septic shock who remain hypotensive despite the administration of high-dose vasopressors (vasopressor unresponsive).

It must be remembered that there is another very small subset of patients who develop hemorrhagic and thrombotic injury to their adrenal glands as a result of the sepsis-associated coagulopathy (the Waterhouse-Friderichsen syndrome). In some, though not all instances, this injury to the adrenals is extensive enough to cause acute absolute adrenal insufficiency with secondary worsening of the shock state. Corticosteroids for these patients are life saving.

Other pharmacologic agents that have been investigated include nonsteroidal anti-inflammatory drugs, to inhibit eicosanoids, and pentoxifylline, which has been shown to inhibit release of TNF from macrophages. There is also interest in inhibitors of nitric oxide synthase and agents other than catecholamines for reversal of the vasodilatation of septic shock. Subsequent clinical trials of these agents have not shown any benefit.

Recently however, investigative work on the interplay between the activated coagulation and inflammatory networks has focused on Activated Protein C -- a component of the anticoagulation system and a potent antithrombotic agent. Activated Protein C has been demonstrated to have important anti-inflammatory activity as well: in rat models of ischemia induced spinal cord injury, Activated Protein C has been shown to inhibit neutrophil activation. In a monocyte cell line, Activated Protein C inhibited lipopolysaccharide induced nuclear translocation of nuclear factor kappa B (NF-KB) and Tumor Necrosis Factor alpha production. And recently, a randomized, double blind placebo controlled, multicenter trial of sepsis using recombinant human Activated Protein C was reported (Bernard et al., NEJM 2001, 344:699). The end point was death at 28 days: the mortality with placebo was 30.8%, with the study drug 24.7%, representing a relative risk reduction of 19.4%, and an absolute risk reduction of 6.1%. The mechanism may relate to both the modulation of inflammatory cytokines by Activated Protein C as well as to its antithrombotic effects. Benefit was seen mainly in patients treated within 24 hours of sepsis and in patients with APACHE II (Acute Physiology and Chronic Health Evaluation) scores of 25 or greater. Its use has not been widespread secondary to the study's numerous exclusion criteria. The subsequent trial in patients with APACHE scores less than 25 (ADDRESS trial NEJM 2005;353:1332-41) was halted after an interim analysis for lack of effectiveness. Activated protein C does not seem to be beneficial in low-risk sepsis patients.

Finally, hyperglycemia and insulin resistance is common in sepsis. Hyperglycemia has been implicated in inducing apoptosis, impairing immune function, impairing wound healing, worsening cardiac function, worsening neurologic recovery after stroke, increase the risk of infection, and has been associated with increased risk of death. Dr. Van den Berghe and her colleagues did show that in surgical intensive

care patients at her hospital, the use of intensive insulin treatment to maintain blood glucose levels between 80 to 110 mg/dl resulted in a mortality benefit (NEJM 2001;345:1359-67). Unfortunately, a similar study in medical critically ill patients did not show any mortality benefit (NEJM 2006;354:449-61) but had significant morbidity benefit. Patients in the intensive insulin protocol had statistically significantly fewer days on the ventilator, days in the ICU and days in the hospital. Unfortunately, the use of intensive insulin therapy resulted in alarmingly high rates of hypoglycemia. Furthermore, it was unclear how many patients in the study actually had sepsis. It is believed that insulin is an anti-inflammatory drug that may also protect endothelial and mitochondrial function. Glucose control remains an important goal for clinicians taking care of patients who are septic.

Outcome

Sepsis is a leading cause of death in the United States. It is the second most common cause of death in noncoronary ICU's and the tenth leading cause of overall death. Sepsis accounts for only about 2% of admissions but 59% of these patients require intensive care. Its cost alone in the United States is estimated at \$17 billion dollars. In the United States and estimated 500,000 to 750,000 people become bacteremic and most will be clinically septic. Incidence has increased from 164,000 cases in 1979 to 660,000 in the year 2000 -- an annualized increase of 8.7%. About 30-40% of these bacteremias are caused by Gram negative bacilli. As of 1987, infections due to Gram positive bacteria are the leading cause of sepsis. Fungal related sepsis has increased by 207% in the same time period (1979-2000). Surprisingly, mortality from sepsis has decreased from 27% to 17%. Unfortunately only 56% of these patients are able to go home. (NEJM 2003; 346:1546-54)

Overall, approximately 100,000 (20%) patients per year will develop septic shock. Of those with Gram negative sepsis, 50% will develop shock. Mortality associated with septic shock has remained approximately 50% for many years but with our improved understanding of the pathogenesis, our improved antibiotic therapy, and our improved ability to support these patients recent reports suggest that mortality may be decreasing. The mortality of septic shock does not appear to be related only to the particular organism but rather to the immune status of the host. In one study of patients with rapidly fatal underlying disease (defined as death anticipated within one year), for example, acute myelogenous leukemia in the adult, the mortality due to septic shock was 85%. In patients with ultimately fatal disease (defined as death anticipated in 5 years) the mortality was 45%, and in patients with nonfatal diseases, for example prostate enlargement treated with prostatectomy, the mortality was 10%. As an illustration consider a patient with leukemia who develops *Pseudomonas aeruginosa* sepsis. The mortality with our current best treatment is 50%. A patient who develops *Pseudomonas aeruginosa* sepsis due to bladder catheter infection after a prostate operation has a mortality of approximately 5%.

In the last few years there had been tremendous enthusiasm for the use of "bundles". Bundle theory is an approach to treatment that brings together multiple evidence based practices that are combined into one coordinated protocol in order to maximize effectiveness. In a recent report from Spain (Ferrer et al., JAMA 2008;299(19):2294-2303), the use of the sepsis bundle resulted in a statistically significant reduction in mortality associated with increased compliance with separate elements of the sepsis bundle. Patients in severe sepsis and septic shock constitute a medical emergency. Early and measured therapy consistently applied to all patients with sepsis is life saving.