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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"
          1. Escherichia coli
             Klebsiella Proteus
             Enterobacter Serratia
             Acinetobacter
             Citrobacter
             Salmonella
          2. Pseudomonas aeruginosa
      - Anaerobes
        - Bacteroides *fragilis*
  - Fungi
    - Candida

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. Septic shock describes sepsis with concomitant hypotension 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 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, as well as specific virulence factors of the infecting organism.

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, and 1980'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. A 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 $Beta_1$). This novel binding permits very small amounts of these toxins to stimulate the proliferation of large population 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 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 CD_{14} (sCD_{14}) complexed to lipopolysaccharide. On the surface of the macrophage a membrane bound CD_{14} 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, TLR_4 for gram negative bacteria; TLR_2 for gram

positive bacteria) with activation of intracytoplasmic kinases and ultimately translocation of nuclear factor κB (NF-κB) 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 if 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 a contributor 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 ~4-7 L/Minute to 10-12 L/minute. 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 as measured by the thermodilution technique of the pulmonary artery catheter 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.

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-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: Clinical Presentation

Physical Exam
- Vital Signs
  - Pulse Rate – rapid, "bounding"
  - Blood Pressure – may be normal/low normal
  - Temperature - ⇑ / normal / ⇓
- Respiratory Rate – rapid
- Mental Status
  - may be confused, agitated
- Skin
  - warm, "flushed"
- Urine volumes ⇓

Laboratory Data
- ABG pH ⇑ - pCO_2 ⇓ - pO_2 – modestly ⇓
- blood lactate
- WBC ⇑ / ⇓
- Protime may be prolonged / platelets may be ⇓

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: 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 ⇓ - pCO_2 ⇓ - pO_2 ⇓
Blood lactate ⇑
WBC ⇑ / ⇓
Protime 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.

Clinical settings that suggest possible sepsis in the febrile patient include hospitalization with an intravascular catheter or a bladder catheter in place, recent trauma with skin wounds, or recent chemotherapy. The diagnosis of neonatal sepsis should be considered if there is a maternal history of premature rupture of the amniotic membranes or if the infant is lethargic or demonstrates poor feeding. The clinical signs of sepsis many of which are manifestations of the inflammatory response may be more subtle in the newborn and the less immune competent adults.

Bacterial Organisms

Sepsis and septic shock have been produced by all species of aerobic and anaerobic bacteria. Aerobic gram-negative bacilli are most commonly isolated, particularly the members of the families *Enterobacteriaceae* and the Pseudomonads. Aerobic gram-positive cocci are also important 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

Once 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 before the culture results are available. Sepsis and septic shock evolve in rapid tempo, and prompt administration of appropriate antibiotics is often life saving. Identification of a likely site (or sites) of infection as well as a knowledge of the specific epidemiology 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.

Table 3: Etiologic Agents in Bacteremia

Site of origin	*Etiologic agents*	*frequent precipitating events*
Skin	S*taph, aureus* *Staph, coagulase negative* *Corynebacterium jeikeium* *Pseudomonas Aeruginosa* *Acinetobacter*	Intravenous catheter
Respiratory tract	Out of hospital: *Strep. Pneumoniae* *Strep. Pyogenes* In hospital: *Peudomonas. aeruginosa* *Serratia* *Enterobacter* *Acinetobacter*	Aspiration
Genitourinary tract	*E. coli* *Klebsiella-Enterobacter* *Proteus sp.* *Ps. aeruginosa*	Bladder catheter, ureteral obstruction cystoscopy

Table 3: Etiologic Agents in Bacteremia (Continued)

Site of origin	*Etiologic agents*	*frequent precipitating events*
Gastrointestinal tract		
Biliary tract	*E. coli*	Cholangitis, biliary stent
	Klebsiella-Enterobacter	
Bowel abscess	*E. coli*	Perforation ,
	Klebsiella-Enterobacter	
	Serratia	
	Salmonella	
	Bacteroides	
Reproductive system	*Streptococcus*	Postpartum, instrumentation
	E. coli	
	Bacteroides	

Use of antibiotics is only part of the therapeutic approach. 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 and septic shock can be reversed.

Management of sepsis and septic shock also must include appropriate support of circulation and ventilation. Efforts to restore the circulating volume may-though certainly not always- require monitoring of central cardiac pressures. 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 the pulmonary venous bed to occlusion in a distal vein- reflecting left atrial pressure. At present, it affords the closest assessment of left ventricular pressure available at the bedside. The catheter has a thermister 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, particularly in patients with underlying cardiac, pulmonary, or renal disease.

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, airway intubation and support on a ventilator.

Volume resuscitation alone may be unsuccessful in stabilizing or restoring systemic blood pressure. Pharmacologic agents that are used for blood pressure support include dopamine in doses of < 10 ugm /kg/min and, if volume replacement is ongoing, norepinephrine. In some patients combinations of these catecholamines as well as dobutamine are used.

A keen clinical observation at the bedside has led to studies documenting both the relative depletion of vasopressin – 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 .05-.1 units/min often results in a significant decrease in norepinephrine dosing and hemodynamic stabilization.

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 lipopsaccharide (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. Corticosteroids have been submitted to a carefully designed, rigorous, prospective, randomized multi institutional trial. This trial was unable to demonstrate the usefulness of adjunctive high dose coricosteroids to (1) prevent the evolution of sepsis to septic shock, (2) reverse septic shock, or (3) improve survival. There is one caveat in regard to the use of corticosteroids. There is a 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 adrenal insufficiency with secondary worsening of the shock state. Corticosteroids for these patients are live saving.

Other pharmacologic agents that have been investigated include nonsteroidal anti-inflammatory drugs, to inhibit eicosanoids, and pentoxyphylline, 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.

Recently, 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-κB) 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%. Further trials are in progress to assess this drug. If benefit is confirmed, the mechanism may relate to both the modulation of inflammatory cytokines by Activated Protein C as well as to its antithrombotic effects.

Outcome

Sepsis is a leading cause of death in the United States. It occurs world wide and is on the rise. In the United States about 500,000 people become bacteremic and most will be clinically septic. About 30-40% of these bacteremias are caused by gram-negative bacilli. Overall, approximately 100,000 (20%) will develop septic shock. Of those with gram-negative sepsis, 50% will develop shock. The mortality of septic shock has remained approximately 50% over the last 20 years despite our improved understanding of the pathogenesis, our improved antibiotic therapy, and our improved ability to support these patients. The mortality of septic shock does not appear to be related 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 *Psuedomonas aeruginosa* sepsis due to bladder catheter infection after a prostate operation has a mortality of approximately 5%.

Ongoing investigation at the bench and at the bedside should permit improvement in the mortality of sepsis through a more precise understanding of the virulence factors of the microorganism and the response of the host.