Pathogenesis and Management of Septic Shock

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ABSTRACT

Despite modern advances in antibiotic therapy and cardiovascular support, septic shock remains a condition plagued by a high mortality rate, estimated at 40- 60%. The pathogenesis of septic shock involves a complex orchestration of cytokines which lead to vasodilation, increased capillary permeability, and disturbances of metabolism. The major clini-cal features include hypotension, tissue hypoperfusion, myocardial depression, and organ failures. Cur-rent therapy focuses on early broad-spectrum antibiotic treatment, correction of hypovolemia, and appro-priate use of vasopressor and/or inotropic agents. Experimental attempts to intervene in the septic cytokine cascade hold promise, but none have shown a definitive clinical benefit. This review examines the pathogenesis, clinical features, current therapeutic approaches, and future prospects for this serious prob-lem.

INTRODUCTION

Sepsis, a systemic response to infection, is marked by fever, tachycardia, tachypnea, and/or leukocytosis. Hypotension despite adequate fluid resuscitation, hypoperfusion abnormalities, and organ dysfunction may develop in the setting of sepsis, in which case the term septic shock is used (1). With a mortality rate estimated at 40-60%, septic shock is the most serious complication in a continuum of conditions associated with sepsis (2). Traditionally, the terminology used in reference to sepsis-related conditions has been an area of confusion and overlap; however, the "American College of Chest Physicians (ACCP) and the Society for Critical Care Medicine (SCCM) Consensus Conference on Standardized Definitions of Sepsis", in 1991, has helped to clarify these definitions (see Table 1) (1).

Septic shock occurs in response to the systemic spread of an infection or, less commonly, the products of an infection. While bacteria are usually the causative organisms, fungi (e.g. Candida albicans), parasites (e.g. Plasmodium), and viruses (e.g. dengue flavivirus) are all possibilities (3). The frequency of cases due to gram-negative (e.g. Escherichia coli, Klebsiella) versus gram-positive bacteria (e.g. Staphylococcus, Enterococcus) is approximately equal (4). The initial infection often occurs in the genitourinary tract, respiratory tract, gastrointestinal tract, skin, or wounds (5).

MEDIATORS IN SEPTIC SHOCK

Septic shock involves a complex series of events which are largely derived from the host's systemic response to an invading pathogen or its products. Bacteria produce extracellular products and cell wall components which can stimulate the immune system, producing the clinical features of shock. The bacterial product which has been most extensively researched is endotoxin, a lipopolysaccharide component of the outer membrane of gram-negative bacteria. Endotoxin activates the complement, coagulation, kinin, endorphin, and monokine systems (6). Gram-positive bacteria produce cell wall products which can induce inflammatory responses similar to those induced by endotoxin, but the exact antigens involved are still unknown (7).

In response to challenge by microbial antigens such as endotoxin, macrophages release a number of proinflammatory cytokines, including tumour necrosis factor (TNF)-a, interleukin (IL)-1, IL-6, IL-8, and interferon (IFN)-g (8). These cytokines promote the release of additional mediators and have multiple effects which can culminate in septic shock.

Table 1 - ACCP/SCCM Consensus Conference Definitions (1)
infection = microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
bacteremia = the presence of viable bacteria in the blood.
systemic inflammatory response syndrome (SIRS) = 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 o C or <36 o C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO 2 <32 mmHg; and (4) white blood cell count >12,000/cu mm, <4,000/cu mm, 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 o C or <36 o C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO 2 <32 mmHg; and (4) white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms. ie. sepsis is a subgroup of SIRS in which infection is the clinical insult
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.
sepsis-induced hypotension = a systolic blood pressure <90 mmHg or a reduction of 40 mmHg from baseline in the absence of other causes of hypotension.
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 abnormali-ties are measured.

Evidence suggests that TNF-a, IL-1, and IFN-g can act synergistically to induce the production of nitric oxide in smooth muscle cells of the peripheral vasculature (9-11). Nitric oxide is a potent vasodilator and its release probably represents a final common pathway in the cytokine-mediated cascade which leads to hypotension (12-14). Impaired myocardial contractility is seen in septic shock and has been attributed to a "myocardial depressant substance". Evidence suggests that this substance is endocardium and myocyte-derived nitric oxide, released in response to TNF-a and IL-1 (15-18).

While inflammatory cytokine release is central to septic shock pathogenesis, multiple other host pathways contribute. Interaction of microbial products with Hageman factor (factor XII) can activate the coagulation, fibrinolytic, and kinin systems (19). Release of bradykinin by the kinin system contributes to vasodilation. The complement system may become activated via antigen-antibody complexes, or by direct interaction of microbial products with the alternate complement pathway (20). Complement proteins result in pathogen cell membrane lysis, pathogen opsonization, mast cell degranulation, and phagocyte chemotaxis and stimulation. Activated phagocytes then release inflammatory mediators which promote vasodilation and increase capillary permeability. Neutrophils release free radicals which help to destroy pathogens, but are also toxic to the vascular endothelium and other tissues. Microvascular injury occurs, resulting in a significant loss of perfused capillaries, resulting in a decrease in the surface area available for oxygen and nutrient exchange (21).

CLINICAL FEATURES

The systemic response to sepsis is marked by tachycardia, tachypnea, and either fever or hypothermia (5). Initially, patients present with warm, dry extremities as a consequence of peripheral vasodilation. A high cardiac output is usually present, due to the combination of low systemic vascular resistance and normal or increased blood pressure (5,22). Cardiac output is maintained by an increased heart rate, despite a reduced ejection fraction due to myocardial depression.

Over the subsequent hours or days, hypovolemia occurs as a consequence of severe capillary leakage. Peripheral and hepatosplanchnic venous pooling cause a marked decrease in venous return. These factors, in conjunction with progressive cardiac depression may then lead to a decrease in cardiac output and a drop in blood pressure, which may prove unresponsive to fluid replacement, inotropes, and vasopressors (6). Refractory hypotension marks the progression from sepsis to septic shock.

Hypotension results in tissue hypoperfusion and hypoxia, with subsequent lactic acidosis. Additionally, the vasoactive mediators released in septic shock disturb normal vascular autoregulation mechanisms. This limits the ability of the microcirculation to match regional metabolic demands, thus impairing efficient oxygen utilization and exacerbating hypoperfusion and lactic acidosis (23).

Patients suffering from sepsis experience marked disturbances in metabolism, including a significant increase in energy expenditure. A neuroendocrine stress response causes the release of catecholamines, corticosteroids, and glucagon, which promotes a hypermetabolic state (24). Increased hepatic gluconeogenesis and peripheral insulin resistance often lead to hyperglycemia (25). Protein catabolism is greatly increased, with significant protein breakdown in skeletal muscle, connective tissue, and the gastrointestinal tract (26). Additionally, TNF-a and IL-1 induce fever, synthesis of acute-phase reactants, and have direct effects on metabolic pathways (5).

Increased pulmonary capillary permeability and edema often cause ventilation / perfusion (V/Q) mismatch, resulting in hypoxemia and compensatory hyperventilation. The combination of hypoxemia, low cerebral blood flow, and metabolic disturbances often causes the patient to become agitated, confused, or lethargic (6).

Multiple processes can contribute to organ failure, including hypoperfusion, hypoxemia, microvascular injury secondary to the inflammatory response, ongoing sepsis, and iatrogenic causes such as antibiotic therapy. Respiratory failure is a frequent complication of septic shock, with 30-80% of patients developing adult respiratory distress syndrome (ARDS) (27). Diaphragm and respiratory muscle impairment due to hypoperfusion, protein catabolism, and increased work of breathing can contribute to respiratory distress. Hepatic and, in later stages, renal failure may also occur. Multiple organ failure is frequently the terminal phase in septic shock, usually occurring in the second to third week of a patient's clinical course (5). In a smaller group of patients, the heart is unable to sustain cardiac output, and death results from progressive cardiac failure. (See Figure 1.)

TREATMENT

The primary goal in the treatment of septic shock is to maintain organ perfusion and tissue oxygenation, by giving fluids and vasoactive drugs, until the underlying infection and septic cascade can be brought under control.

Antibiotics

Early administration of appropriate antibiotics significantly improves survival (28,29). Therefore it is critical that patients suffering from sepsis be identified and treated as early as possible. Consequently, broad-spectrum antibiotic coverage should be started empirically on first suspicion of sepsis. Knowledge of the common local pathogens and antibiotic resistance can help to ensure that adequate coverage is achieved by this initial therapy. Once empiric therapy has been instituted, the site of infection should be aggressively searched for by culturing sputum, urine, and wound sites, and by utilizing diagnostic tests such as chest radiography. Identification of the pathogen and the site of infection will allow refinement of antibiotic therapy. In cases of abscess formation, surgical drainage is indicated.

Oxygenation

Patients in septic shock have an increased oxygen demand due to increased work of breathing and a hypermetabolic state. They often have V/Q mismatches and inefficient oxygen delivery, making lactic acidosis common. To counter these processes, oxygen should be given and increased as necessary. Some physicians promote early intubation to increase oxygen delivery and to relieve the work of breathing, with the goal of achieving better organ perfusion and thereby preventing failure (30).

Intravenous fluids
Hemodynamic supportive therapy should be given to maintain a mean arterial pressure of at least 60-70 mmHg in order to ensure organ perfusion. The first step is to give intravenous fluids, which will correct hypovolemia caused by capillary leakage. It has been suggested that colloid fluids are superior to crystalloid because the latter accumulate in the extravascular space, causing the patient to become fluid overloaded, edematous, and at increased risk of ARDS (2). Fluid resuscitation may result in hemodilution, necessitating an infusion of packed red blood cells to maintain hemoglobin concentration (5).

Vasopressor and inotropic support
If correction of hypovolemia fails to adequately improve blood pressure, vasopressor and/or inotropic therapy is indicated. The choice of agents is currently a matter of debate. Hypotension in septic shock is primarily due to vasodilation, resulting in decreased peripheral resistance. Although it has never been proven in humans, animal models suggest that myocardial depression contributes to the problem (15-18); thus, agents with combined vasopressor and inotropic actions are often used as first-line treatment. One drug commonly used for this purpose is norepinephrine (Levophed). Norepinephrine has potent a-adrenergic effects and, therefore, is an effective vasopressor. It also possesses some b-adrenergic activity (mostly b1) which may help to counter myocardial depression by increasing heart rate, contractility, and stroke volume. Other physicians prefer to use high-dose dopamine (Intropin), which has a-adrenergic, b-adrenergic, and dopaminergic effects. Alternatively, dopamine may be useful as an adjunctive therapy to norepinephrine because low-dose dopamine is reputed to promote renal vasculature vasodilation and help to maintain kidney perfusion (31). This concept of "renal-range dopamine" is, however, a matter of debate, and recent evidence suggests that it may be unfounded (32-34).

If first-line therapy proves inadequate and hypotension persists, the next step is to increase vasopressor support. If dopamine was used first, norepinephrine may be tried since it possesses greater a-adrenergic activity than does dopamine.

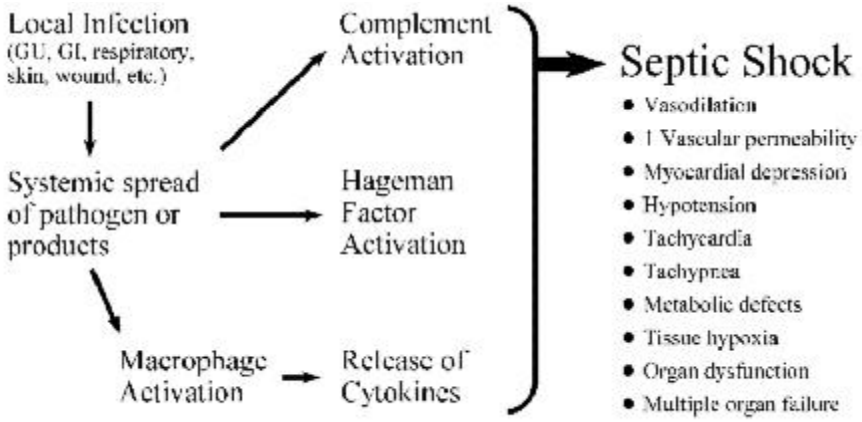

Figure 1. Pathogenesis of Septic Shock

Another choice would be phenylephrine (Neo-Synephrine), a selective a1 -agonist which increases arterial resistance and also has a modest positive inotropic effect on the heart. Unlike the catecholamine drugs, phenylephrine has little b activity, so it does not stimulate an increase in heart rate, and it may avoid an associated increase in oxygen consumption. If the patient's hypotension is still unresponsive, epinephrine (Adrenalin Chloride), a very potent vasoconstrictor and cardiac stimulant, can be tried (35). However, at this stage the patient has a very poor prognosis; although epinephrine may increase blood pressure, it is unlikely to improve survival.

Nutrition
The hypermetabolic state which occurs with sepsis must be supported with adequate nutrition to avoid malnourishment and protein wasting, since these can exacerbate respiratory distress. However, excess calories, particularly carbohydrates, can increase the production of carbon dioxide and further stress the respiratory system (6). Enteral feeding should be used, if possible, to prevent stress ulcers, reduce bacterial translocation from the gut, decrease the risk of infection by avoiding a total parenteral nutrition line, and protect from liver failure by reducing cholestasis (6).

Prevention and Early detection
Since current therapy for septic shock is limited, the most effective approach to this problem is prevention. One important but frequently neglected factor is aseptic technique (36). Hospitalized patients, especially those in intensive care units, are highly susceptible to nosocomial infection; therefore, it is critical that preventative techniques such as hand washing, regular invasive line changes, and sterile suctioning be carried out diligently (37). Susceptible patients should be monitored closely for clinical signs and symptoms of sepsis. If sepsis can be detected and treated early, the number of cases which progress to septic shock may be significantly reduced.

EXPERIMENTAL ADJUNCTIVE THERAPIES
Despite current medical management strategies, septic shock continues to have a high mortality rate. This has prompted research into a variety of methods of manipulating the host response in septic shock to improve outcome. To date, no treatment has been found to unequivocally improve survival. The following represents a summary of the literature, focusing on those treatments which have undergone randomized-controlled clinical trials.

Anti-endotoxin antibodies
Endotoxin is believed to be the major antigenic trigger in gram-negative septic shock. In theory, if endotoxin could be blocked before it initiated a host response, septic shock might be avoided or attenuated. In an attempt to achieve this, two different monoclonal antibodies against endotoxin, designated E5 and HA-1A, were developed and have been tested in large randomized-controlled trials. Two studies of the E5 antibody failed to show a survival improvement among patients with gram-negative sepsis (38-39). A randomized-controlled trial of HA-1A involving 543 patients initially appeared promising, reporting a significant decrease in 28 day all-cause mortality among the subgroup of patients with gramnegative bacteremia (40); on this basis, HA-1A was approved for clinical use in Europe. However, closer inspection revealed that early results were made available to the manufacturer/sponsor of the study, and that the analytic strategy for the study had been changed following this, thereby seriously compromising the validity of the study (41). A large (n=621) follow-up randomized-controlled trial was performed which failed to confirm any benefit of HA-1A, and, in fact, showed a higher mortality among those patients treated with the antibody (42).

Anti-cytokine therapies
A second line of attack involves blockade of the various cytokines which mediate the host response and ultimately result in septic shock. One obvious target is TNF-a, a potent mediator released by macrophages in response to endotoxin or other antigens, including those from non-gram-negative infections. As with endotoxin, several antibodies against TNF-a have been developed. The TNF-alpha MAb Sepsis Study, a randomized-controlled trial involving 971 patients, retrospectively showed a significant reduction in three-day mor-tality among the septic shock subgroup of patients treated with the TNF antibody. A trend toward reduced mortality continued until the prospectively defined endpoint of 28 days, but was not significant at that time (43). The INTERSEPT multicenter trial of a different TNF antibody failed to show any reduction in 28-day all-cause mortality among the 420 septic shock patients involved (44). Likewise, a phase II trial of a third antibody did not demonstrate any increased survival (45).

In a related strategy, recombinant soluble TNF receptors were created which theoretically bind to and neutralize circulating TNF-a. A clinical trial (n=141) of one such receptor paradoxically showed an increase in mortality associated with higher doses of the treatment (46). A 498 patient, randomized-controlled trial of a different TNF receptor complex also failed to show any decrease in 28-day all cause mortality (47).

Another important cytokine in septic shock is IL-1. Recombinant IL-1 receptor antagonists (IL-1ra) have been synthesized which competitively inhibit the effect of IL-1 at its receptor. Despite promising early trials with baboons (48), large phase III clinical trials failed to demonstrate any survival benefit with IL-1ra treatment (49-50).

Blockade of nitric oxide effects
One problem with therapies which are aimed at blocking early mediators in septic shock may be that the cascade process is too far advanced before it can be recognized clinically and treated. Identification of nitric oxide as a probable common final mediator of vasodilation holds new promise for the treatment of septic shock. Nitric oxide is produced by nitric oxide synthase (NOS), of which at least three different isoforms exist: constitutive (cNOS), inducible (iNOS), and brain (bNOS) (12). cNOS is important in the normal regulation of organ blood flow, whereas iNOS is upregulated in inflammatory processes, probably to increase blood flow to the damaged region. In sepsis, there is a generalized upregulation of iNOS, which interferes with the body's ability to regulate normal blood flow and may also lead to hypotension.

Several drugs which inhibit NOS are being investigated for their potential therapeutic value in septic shock, but few have reached clinical trials yet. One agent, N G -monomethyl-L-arginine (L-NMMA), has been shown to re-verse hypotension in endotoxin or cytokine treated animals (51-53). Small studies on humans with septic shock have shown that L-NMMA is effective at increasing systemic vascular resistance and blood pressure (54-56). However, L-NMMA is a non-specific inhibitor that blocks all forms of NOS, not only iNOS; therefore unwanted side effects are likely to occur. As an example, in a recent study using rats, inhibition of cNOS was shown to potentiate endotoxin-mediated albumin escape and losses in plasma volume, whereas inhibition of iNOS attenuated these effects (57). Furthermore, the increase in vascular tone produced by L-NMMA tends to reduce cardiac output, which may worsen tissue perfusion (54). Thus, even though L-NMMA raises blood pressure, deleterious effects on vascular autoregulation and cardiac output may prove to offset any benefits, and overall survival may not be increased. In an attempt to reduce these side effects, other drugs which are relatively selective for iNOS are now being studied (58-61); clinical trials are not yet available.

Other experimental attempts
Other therapeutic approaches have been investigated, but generally have yielded disappointing results. Naloxone, a narcotic antagonist, has been studied in an effort to block endorphins since these may contribute a vasodilatory effect (62-63). Cyclooxygenase inhibitors, such as ibuprofen, have been studied because the cyclooxygenase pathway produces prostaglandins, thromboxane, and prostacyclin which are thought to contribute to capillary leakage in septic shock. Although ibuprofen has been effective in canine models, its efficacy in humans has yet to be shown (64-66). Despite early promise of investigations using high-dose corticosteroid treatment, larger studies have shown either no improvement or detrimental effects on survival (67).

Finally, hemofiltration has been tried with the intent of eliminating sepsis mediators from the blood, but has lacked success, probably due to the current limitations in selecting between harmful and helpful molecules for removal (68-70). On the positive side, one study using multiple plasma exchanges found that 20 out of 25 patients with septic shock survived (71). This is encouraging, but unfortunately the study was not controlled so the results must be interpreted with caution.

CONCLUSION
Septic shock continues to be plagued by a high mortality rate. Early recognition and appropriate treatment are critical to improve survival. Rapid initiation of empirical broad-spectrum antibiotic treatment followed by refinement upon identification of the site and organism is essential. Of equal importance is correction of hypovolemia with intravenous fluids, and the addition of vasopressor and/or inotropic agents as necessary. Appropriate nutritional support and sufficient oxygenation with consideration of early intubation are also important. Unfortunately, despite appropriate medical treatment, a successful outcome is not guaranteed and the risks associated with septic shock remain formidable. Many innovative experimental approaches to interrupting the septic cascade have been tried, but none have shown a

definitive survival improvement in humans. While excessive cytokine activity certainly contributes to many of the pathologic features of septic shock, cytokine release does have a fundamental purpose - stimulation of immune functions to remove the infectious organisms which underlie septic shock. Thus therapies aimed at interrupting the septic cascade may inadvertently compromise the body's normal defense mechanisms. The key to success may ultimately lie in identifying and normalizing overactive pathways using multiple anticytokine therapies. Blockade of nitric oxide, the suspected final mediator in vasodilation, also holds promise as an effective therapy. Hopefully further elucidation of the complex mechanisms involved in septic shock will allow refinement of these and other experimental therapies so that recovery from this serious condition can become a common occurrence.

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