

AN OVERVIEW OF SEPSIS

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SUMMARY

Sepsis is an important clinical problem particularly in intensive care units. Although sepsis can be triggered by almost all microorganisms, risk of septic shock and mortality rate are higher in Gram negative bacteremia. In this mini review, role of tumor necrosis factor and other mediators in sepsis and new therapeutic approaches such as therapy with monoclonal antibodies have been discussed.

Key words: Sepsis, Myocard Depressant Factor, Tumor Necrosis Factor, Monoclonal Antibodies

INTRODUCTION

Bacterial sepsis continues to be a frequent cause of morbidity and mortality in the world. For example the estimated incidence of Gram negative sepsis in the United States alone is 200.000 cases annually (1). Although there is no statistical data about the incidence of sepsis in our country, it is also an important clinical syndrome in certain wards.

The sepsis syndrome is a clinically defined condition that involves the physiologic alterations and clinical consequences of the presence of microorganisms or their toxins in the bloodstream or tissues. Various bacterial components are known to be potent exogenous mediators of sepsis. The lipid A moiety of lipopolysaccharide of Gram negative cell walls termed endotoxin and the peptidoglycan layer of Gram positive cell walls are capable of eliciting many of the manifestations of sepsis when injected into experimental animals (2).

Cytokins (interleukins, leukotriens, tumor necrosis fac-

tor (TNF), products of stimulated monocytes and macrophages, may produce many of the responses associated with Gram negative sepsis or endotoxemia (3). TNF (cachectin), a 17 kd polypeptide has key role in septic shock. Infusion of TNF in laboratory animals caused physiologic changes similar to those observed in animals with Gram negative sepsis (4). However, intravenous infusion of interleukin₁ in dogs caused only hypotension and none of the other sepsis associated changes (5). Mice which are unable to elaborate TNF because of a genetic defect are resistant to lethal doses of endotoxin (6). In a study, plasma concentrations of TNF, interleukin 1B and γ -interferon were measured together with physiologic and hormonal responses in 13 healthy men after intravenous administration of E. coli endotoxin and during a control period of saline administration. Although neither concentrations of circulating interleukin 1B nor γ interferon were increased in the blood, TNF became elevated after endotoxin administration (7). In a recent study, using a radiomunossay, circulating TNF concentrations of patients were measured upon hospital admission, first 12 hours, after the onset and during the first three days of shock. Circulating TNF levels determined upon admission were not specific or predictive of the outcome of septic shock but persistently high levels of TNF was well correlated with a poor diagnosis, since most of the patients with elevated TNF values died of septic shock (8). All these results indicate that TNF is a principal mediator of septic shock.

CLINICAL MANIFESTATIONS

Awareness of the signs and symptoms of the sepsis allows early recognition and appropriate management. There are no specific findings in Gram negative

bacteremia that distinguish it from Gram positive bacteremia. Table I summarizes some of the clinical manifestations of gram negative bacteremia.

TABLE I. SIGNS AND SYMPTOMS SUGGESTING GRAM NEGATIVE ROD BACTEREMIA (9)	
Primary	Secondary
Fever	Hypotension
Chills	Bleeding
Hyperventilation	Leukopenia
Hypothermia	Trombocytopenia
Skin lesions	Organ failure
Change in mental status	Lung: cyanosis, acidosis
	Kidney:olyguria, anuria, acidosis
	Liver:jaundice
	Heart:congestive heart failure

Fever and Chills are typically encountered in sepsis but hypothermia can be a manifestation and is associated with a poor diagnosis (10). Even before temperature elevation, patients often begin to hyperventilate, marked respiratory alkalosis is common. Tachypnea could be a direct effect of endotoxin or can be mediated by intravascularly activated kallikreins, bradykinin, prostaglandin or complement. In critically ill patients sudden onset of hyperventilation should be enough to lead the physician to draw blood for culture.

Sepsis also remains a common cause precipitating adult respiratory distress syndrome (ARDS). The incidence of ARDS in Gram negative bacteremia has been reported at 23 %. (11). Prognosis of sepsis related to ARDS is worse (80 % to 90 % mortality) than that of ARDS due to other causes.

Cardiovascular manifestations: They vary from tachycardia to failing myocardial function. Pathogenic mechanism underlying cardiac disfunction is very complex. Table II shows the hemodynamics of sepsis.

To characterize cardiovascular performance during endotoxemia, normal volunteers were monitored with thermodilution pulmonary artery catheters and simultaneous radionuclide cineangiography after the intravenous administration of endotoxin (purified lipopolisaccaride prepared from E. coli 0113). This process resulted in a hyperdynamic cardiovascular state characterized by an elevated cardiac index and heart rate with a decreased mean arterial pressure and systemic vascular resistance (13). This model of endotoxemia suggests that endotoxin has a major role of cardiovascular abnormalities observed in humans with septic shock.

What causes myocardial depression in septic shock? In a research, to study coronary circulation in humans, coronary sinus thermodilution catheters were placed in patients with septic shock to measure blood flow and to sample coronary sinus venous blood. There was no difference of myocardial blood flow and lactate extraction between patients with or without myocardial depression suggesting myocardial ischemia cannot be implicated as the cause of myocardial depression (14). In 1985 a myocardial depressant substance (MDS) was shown in sera of patients with septic shock. This substance depressed contraction of newborn rat myocyte in primary tissue culture. The quantity of depression invitro correlated with the amount of decrease in the left ventricular ejection fraction invivo. This depression was only seen with sera taken from patients in the acute phase of septic shock (15). (Videodensitometry was used for analyzing the movement of the cell during myocyte contraction. Microscopic latex beads can be used and movements of beads can be tracked electronically with using a videotracking system (16)). In a series of 50 patients with possible septic shock MDS was shown in the blood of at least 41 percent of patients when studied from the onset till death. This substance was detected early in the course of septic shock and MDS values were corraleted invivo with the evidence of myocardial

TABLE II. HEMODYNAMICS OF SEPSIS (12)

	Preschock	Early Shock	Late Shock
Blood pressure	→ ↓	↓ ↓	↓ ↓
Systemic vascular resistance	↓ ↓	↓ ↓	↓ ↓
Cardiac output	↑ ↑	↑ ↑	↑ ↓
Volume responsiveness	++	+	-
Acid base status	RA	RA, MA	MA

RA : respiratory alkalosis

MA : metabolic acidosis

depression quantitatively (17).

Recent experiments showed that highly purified preparations of interleukin 1-2 and endotoxin produced no depression on myocytes. However TNF produced significant depression on myocyte shortening (18). These results indicate that TNF may have a key role in producing myocardial depression in human septic shock directly.

Hematologic manifestations: Sepsis usually produces a neutrophilic leukocytosis with a left shift. Morphologic changes such as toxic granulation, Dohle bodies and vacuolisation are also observed in neutrophils. Bacteria may rarely be seen within phagocytes on peripheral blood or buffy coat smears. Another hematologic complication is DIC (disseminated intravascular coagulation) and Gram negative bacteria precipitates DIC more readily than Gram positive bacteria. TNF was shown to have an important role in DIC. At the endothelial level TNF down regulates thrombomodulin and inhibits the production of tissue plasminogen activator (tPA). On the other hand TNF upregulates the production of procoagulant factors, tissue factor and platelet activating factor. TNF also activates polymorphonuclears and increases their chemotaxis and adherence to endothelial surfaces. This endothelial damage promotes tissue factor exposure and tPA inhibitor release, with initiation of the characteristic explosive coagulation process of DIC, facilitated by the dissociation between pro and anticoagulant mechanism induced by TNF (19).

Isolated thrombocytopenia is more common than the fullblown syndrome of DIC. Its incidence has been reported to be 40% to 50% in cases of septicemia. Demonstration of increased quantities of platelet associated Ig G and circulating antiplatelet antibody has focused attention on an immune process of platelet destruction (20).

Cutaneous lesions: They are observed in *E.coli*, *Klebsiella*, *Enterobacter* and *Serratia* bacteremia. Ecthyma type lesions are suggestive of *Pseudomonas aeruginosa* infection (21). Vesicular or bullous lesions, cellulitis, diffuse erythematous reactions and petechial lesions can be observed in sepsis.

Renal manifestations: They vary from minimal proteinuria to acute renal failure that is most often attributed to acute tubular necrosis. Many patients may have transient hypotension and oliguria. Inability of compensatory mechanisms to maintain perfusion of

vital organs may lead to anuria in later stages of shock (22).

Gastrointestinal manifestations: Jaundice is an important complication of sepsis and some reports have noted an increased mortality with infections and jaundice. Reticuloendothelial system, especially liver plays an important role in bacteremia and sepsis as a major protective system. Recent studies showed that adherence of Kupffer cells to bacteria is higher than that of other phagocytic cells and this adherence may be an important factor to protect the host from the advance of bacteremia from the portal to the systemic circulation (23).

Sepsis also predisposes patients to upper gastrointestinal stress bleeding because of the erosions of mucosal layer of the stomach or duodenum (24). Decreased gastric mucosal blood flow might play an important role in this process and abnormally low gastrointestinal intramucosal pH was detected in septicemic animals, preceding microscopically detectable damage (25). Experimental evidence has implicated platelet activating factor, released by endotoxin, as a possible mediator of gut ulceration in sepsis (26).

Neurologic findings: They are usually nonfocal and accompanied by a wide range of mental status changes including mild disorientation, confusion, lethargy, agitation and obtundation. In the elderly patients changes like withdrawal or agitation can be the only manifestations of sepsis (27).

DIAGNOSIS and THERAPY

Clinical suspicion of bacteremia should be promptly confirmed by rapid identification of disease causing organism and antimicrobial susceptibility testing should be performed. Isolation of bacteria can be accomplished using new and automated methods as well as conventional blood culturing systems (28).

Analysis of risk factors and use of criteria for categorising severity of disease can be helpful in designing new treatments. Routine therapy consists of antimicrobial agents, hemodynamic monitoring, fluid replacement and metabolic support.

Antimicrobials : The clinical condition of some patients with sepsis worsens despite antibiotic therapy that is highly effective against the infecting organism *in vitro*. It has been hypothesized that endotoxins of Gram negative bacteria may be released by the action

of antibiotics resulting in clinical deterioration. In a study plasma endotoxin levels and bacteremia in patients with Gram negative sepsis were quantified before and after first dose of antibiotic administration. Plasma concentrations of bacterial cell bound endotoxin were also measured to assess the degree of bacterial cell lysis. Results of the study showed that after administering bactericidal antibiotics, plasma concentrations of free and total endotoxin were increased and this might contribute to the worsening course of disease in some patients treated with antibiotics (29).

Corticosteroids: Use of corticosteroids in the treatment of severe sepsis and septic shock has been controversial. In a randomised, double blind, placebo controlled trial, patients with septic shock did not benefit from the use of high doses of corticosteroids (30). In another study neither the very early nor the late use of high dose short term glucocorticoid therapy did alter the outcome. No improvement was found in shock prevention, shock reversal or mortality (31).

Anti-endotoxin antibodies: Since Gram negative bacterial lipopolysaccharide (LPS) is thought to be responsible for many of the direct and host mediated effect, recent studies have been centered around development and use of anti LPS antibody preparations. Six important clinical studies have been performed using core LPS polyclonal antibodies. Only two of them suggested that these antibodies could be used successfully in sepsis. In patients given J5 antiserum that was prepared by vaccinating healthy men with heat treated E.coli, deaths from Gram negative bacteremia occurred less frequently than in those given nonimmune serum (32). In a prophylactic trial in surgical patients at high risk of developing Gram negative bacterial infection repeated doses of J5 immune plasma prevented the development of septic shock (33).

Among monoclonal antibodies, E5- a murine antibody and HA1A- a human antibody have been reported to specifically bind to lipid A region of endotoxin. Clinical studies showed that E5 protected patients with sepsis like infections as long as they were not in shock, whether they were bacteremic or not. HA1A protected patients whether they were in shock or not, when they were bacteremic at the time of randomisation (34,35).

Anti TNF antibodies: Circulating levels of TNF - α correlate with high mortality of severe sepsis. Studies in animal models of septic shock TNF fragments

prevented death (36,37). In patients with suspected bacteremia CB00006 (a monoclonal antibody to TNF - α which neutralizes TNF- α cytotoxicity) was given intravenously in addition to intensive conventional therapy. Mean arterial pressure rose and sustainment of mean arterial pressure at normal levels was accomplished by CB00006 for 72 hours (38). Preclinical studies with TNF - α antibodies indicate that mortality rate may be lowered in sepsis. However, their clinical usage is restricted because of high costs.

To conclude, being an increasingly important clinical syndrome in the last 40 years, septic shock is still one of the main areas of clinical investigations. Since mortality rate remains to be 50-70 % despite conventional therapy, i.e. antibiotic administration and supportive care, new strategies have been developed. However, new approaches including monoclonal antibodies have some restrictions because timing of their administration is critical and they have very high costs. Although monoclonal antibodies being developed to prevent probable pathophysiologic and hemodynamic changes seem to be very hopeful in the treatment of sepsis, there are many unclarified points requiring more studies on this subject.

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