Septic shock—an update

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Shock is a descriptive term which in the critically ill patient indicates generalized inadequacy of perfusion to several major organ systems. Shock comprises of several signs and symptoms and is therefore a syndrome. It is an acute process and patient usually dies without rapid and appropriate intervention.

Recognition of patients at risk to gram negative infections and septicemia and the pathogenesis of shock enables one to establish the diagnosis early in the course of the syndrome and institute effective therapy. The early description of septic shock resulting from gram negative bacterial infection came from the observations of Waisbren and Spink.¹ The development and use of variety of antibiotics effective in the control of gram positive infections resulted in an increasing incidence of serious gram negative infections frequently complicated by septicemia.²

Pathophysiology of Septic Shock

The initiating factor in gram negative septicemia is *endotoxin*, a lipopolysaccharide which directly and in combination

with other leukocytic components forms various vasoactive substances. Several gram positive organisms release exotoxin, which can act directly on the microvasculature; teichoic acid of their cell walls also has endotoxin like action. Septic shock can also result from certain virus, fungal, and rickettsial infections.^{3,6} Septic shock is accompanied by several pathophysiological reactions which are mediated by enzymatic systems like, the coagulation cascade, immunologic factors and the direct action of endotoxin or teichoic acid on the vascular endothelium. These reactions result in : coagulation system activation and depletion of several coagulation factors, complement activation resulting in hypocomplementemia and lysosomal enzyme leaks, kinin system activation, Schwartzman phenomena resulting in both lysosome enzyme leak and disseminated intravascular coagulation, failure of micro-circulation resulting in tissue hypoxia, diffuse loss of plasma fluid proteins and loss of intravascular volume. This failure of micro-circulation if uncorrected leads to the development of severe acidosis. Acidosis per se compromises the ability of micro-circulation to adequately respond and eventually results in tissue necrosis and death. Various therapeutic regimens are directed at interfering with the direct toxic effects of endotoxin on vascular endothelium, as well as arresting the progress of indirect pathways mediated by immunologic phenomena, com-

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FIGURE 1. PATHOPHYSIOLOGY OF SEPTIC SHOCK

lement activation, and activation of coagulation cascade. (Fig.1)

1. Direct Endotoxin Activity (Direct Pathway)

Studies performed in piglets who have no antibody (Pig placenta being impermeable to maternal antibody), have shown that they develop septic shock due to gram negative endotoxins. The direct effect, results in tissue injury, edema of vascular endothelium, and fever. Thus, both vascular damage and release of cell contents occur as a result of endotoxemia. These changes lead to increased adhesiveness of vascular endothelium with adhesions of platelets

and activation of whole coagulation cascade. The swelling and the alterations in endothelium results in leakage of plasma from intravascular spaces thus resulting in hypovolemia and shock.

2. Indirect Pathways

A. Activation of complement system: Hageman Factor (Factor XII) is directly activated by endotoxin which sets off the entire coagulation cascade through the generation of fibrin and leading to disseminated intravascular coagulation and depletion of various clotting factors.

B. Activation of complement system: Endotoxin is capable of activating complement pathways in two ways. The

first requires the interaction of endotoxin with naturally occurring antibodies to gram negative bacteria. This chain of events initiates activation of all components of complement pathways.⁸ This complement activation occur in an uncontrolled fashion throughout the vascular space and the resulting active complement components are able to exert their physiological roles i. e., platelet aggregation, increase in vascular permeability, activation of neutrophils with chemotactic migration and smooth muscle contraction. These events lead to toxic changes in the micro-circulation, tissue hypoxia, and metabolic acidosis. McCabe studied serum complement levels in bacteremia due to gram negative organisms.⁹ In the 41 patients with uncomplicated bacteremia the mean C3 levels (151 ± 51 mg/100ml) did not differ from the values in controls, however, a significant reduction in complement levels was observed in 26 patients with shock (105 ± 31) and in the 19 patients who had a fatal outcome (98 ± 38). McCabe concluded that the frequency of occurrence of shock or fatal outcome tended to parallel the degree of decrease of complement levels in serum specimens obtained shortly after the onset of bacteremia. Fenton and Strunk reported depressed levels of CH50, C3, C4, and factor B in three newborn infants with Group B streptococcal sepsis.⁶ They demonstrated that in infants infected with Group B *Streptococcus* both alternative and direct complement pathways were activated. The complement and hematologic data and the Clinical course of these infants

suggested that Group B *Streptococcus* has endotoxin-like properties which may explain the high mortality despite the prompt antibiotic therapy.⁶

C. Activation of kallikrein and kinin system: Plasma kinins are biologically active peptides and are capable of a variety of physiologic events i. e., increased vascular permeability, smooth muscle relaxation, and hypotension. Kinins are generally found in inactive precursors in certain cells and in the circulation. Kinins are activated by endotoxin through the intermediary effect of kallikrein as well as through the intermediation of natural antibody.¹⁰ Thus kinins have a crucial role in the failure of micro-circulation resulting in tissue hypoxia and intractable metabolic acidosis.

D. Antigen-Antibody Interaction : Antigen-antibody interaction between endotoxin in gram negative bacterial cell walls and natural antibodies result in activation of complement system, activation of the kinin system, and the Schwartzman reaction. Schwartzman reaction is associated with necrotizing effects on the vascular endothelium, platelet aggregation, and thrombosis which results in tissue hypoxia, metabolic acidosis and death. Schwartzman reaction also contributes to the release of lysosomal enzymes from cells. Release of lysosomal enzymes results in fluid leak, edema and tissue hypoxia.

Diagnostic Features of Septic Shock

Waisbren and Spink in 1950 provided the classic description of a patient

with septic shock.¹ They described an elderly man who seemed alert, but had no detectable blood pressure, was able to respond to the questions but was unable to perform complex intellectual functions, had high temperatures with cold extremities and high pulse pressure. During the early stages of bacteremia when the patient "looks well" but is febrile and hypotensive the diagnosis is not often suspected and the valuable time is lost. During the course of the disease the patient may present with petechial or purpuric skin rash secondary to disseminated intravascular coagulopathy or may develop erythematous gangrenous areas of skin discoloration particularly around the mouth and nose.⁴ These sharply margined circular purplish lesions are often associated with *Pseudomonas* or *Serratia* septicemia. Newborns and infants often present with hypotension and shock and early signs may not be apparent.⁶

Management of Septic Shock

A sequential approach in the management of child with septic shock is desirable (Table I). The treatment plan described here is adapted from a publication by MEDCOM and concerning gram negative sepsis.⁷

1. The first step is to quickly examine the child and establish the baseline data. Blood pressure, heart rate, and body temperature should be recorded. This examination may determine the severity of shock.

2. An airway should be provided, if patient is in need of one. Metabolic acidosis associated with micro-circulatory

Table I : Management of Septic Shock

1. Evaluation of the patient
2. Airway and respiratory support
3. Monitor C.V.P., vital signs, blood gases, electrolytes, BUN and creatinine, administration of fluids
4. Strict record of urine output (hourly)
5. Appropriate bacterial and viral cultures; administration of antibiotics
6. Glucocorticoid administration ?
7. Administration of Naloxone ?
8. Exchange transfusion

failure frequently overstimulates the respiratory center resulting in fatigue and respiratory failure.

3. Central venous pressure should be recorded, this could be difficult to achieve in a newborn or an infant. Blood gases, electrolytes, blood urea nitrogen, and serum creatinine should also be obtained. Fibrin split products, platelet count, and careful examination of peripheral smear helps in evaluation of disseminated intravascular coagulation.

The effective therapy for the expansion of vascular volume is administration of whole blood, plasma, isotonic saline solution or human serum albumin. Whole blood is preferable to packed cells because that expands plasma volume. Whole fresh blood can also provide some of the labile clotting factors.⁵

4. Strict record of fluid intake and urine output has to be maintained. Urine output should be recorded on an hourly

basis following catheterization. Catheterization should be done under aseptic conditions and connected to a closed collecting system. Administration of intravenous fluids will be guided by urine output. If there is a decrease in the urine output a diagnosis of acute tubular necrosis should be considered. A rapid acting diuretic-like furosemide (2-4 mg/kg) helps in "flushing" the renal tubules and prevents protein precipitation and augmentation of the disease process.

5. Appropriate cultures (both bacterial and viral) should be obtained. If the patient has received any prior antibiotic therapy the microbiology laboratory should be alerted. The cultures should be appropriately processed for isolation of anaerobic organisms. Depending on the patient's age and suspecting microorganisms, appropriate antibiotics should be administered. Most of the antibiotics in high doses provide significant amount of sodium or potassium ions; this load may become very crucial if patient is in renal failure and is unable to excrete these ions. Creatinine clearance should be monitored as almost all aminoglycosides which are used frequently in gram negative shock have renal toxicity. Cephalosporins and Moxalactam are not particularly toxic to kidney. If available serum levels of antibiotics should be obtained to monitor the dose and frequency of administration.

6. The use of a massive dose of glucocorticoid in endotoxemic shock remains controversial.¹¹ Some controlled clinical studies have shown favorable effects of massive doses of corticosteroids

on morbidity and mortality in septic shock while many others have not.¹²

It is speculated that the syndrome of septic shock represents the combined effects of several of the inflammatory systems already fully activated. Sheagren believes that therapy directed at inhibiting these systems at a very early stage may result in a significant decrease in mortality.¹¹ In septic shock various inflammatory processes, which are responsible for the body's defence against the microorganism, when activated results in shock producing inflammatory intravascular sequelae of bacteremia. Thus, the well-known adverse effects of glucocorticoids on tissue may be able to ameliorate the process and prevent the development of shock.¹¹ Complement pathways leading to endothelial cell damage are inhibited by high concentrations of steroids.^{13,14} Sibbald, et al recently demonstrated a decrease in capillary leakage after a large dose of glucocorticoids.¹⁵ The patients who did not respond to glucocorticoids had leaky capillaries before the dose was administered, indicating that steroids can only influence the course if given in large doses early in the stage.

Recently, Tiengo reported significant improvement after the administration of 0.01 mg/kg of naloxone in an eight year old child with meningococcal infection and septic shock.¹⁶ Recent observation of Sibbald et al, that the endorphin system is involved in early stages of septic shock suggest that glucocorticoids should be helpful if administered early.^{15,17} These speculations are based on the fact that beta-lipoprotein, the precursors of

beta endorphin originate from the same molecule as ACTH and as large amount of glucocorticoids would be expected to inhibit the release of ACTH, probably the release of endorphin could also be prevented by early administration of large doses of glucocorticoids.¹⁸ Some physicians are now routinely using large doses of glucocorticoids in patients suspected of being in the early stages of septic shock. However, that judgement is not always easy, especially in a newborn and an infant. Clearly more data is needed in this area. If steroids are used they should be used only for a brief period (36-48 hrs). Exchange transfusion should be considered in the management of disseminated intravascular coagulation secondary to septicemia.

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