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A Review on Pathophysiology and Treatment of Sepsis

Gajare S P[1*], Deshpande A P[1], Nilangekar A V[2], Kadarem B[3], Ingole P[4], Bhadane M A[5]

Abstracts: The pathogenesis of human sepsis involves a complex interplay between the infecting organism and the host response, with the consequent multiple organ dysfunction. Sepsis is the systemic inflammatory response to severe microbial infection which initiates important alterations in immune, metabolic, and hemodynamic function that in their most dramatic forms are recognized as sepsis and septic shock. The sepsis syndrome occurs commonly in response to lipopolysaccharide membrane (LPS) from gram-negative bacteria. LPS is a major constituent of gram-negative bacteria cell walls and is essential for membrane integrity. Injured cells releases preformed mediators and synthesize proinflammatory substances, including eicosanoids and the cytokines and tumor necrosis factor [TNF]. These mediators are responsible for the initiation of a nonspecific inflammatory response. The treatment of sepsis is multifaceted and typically requires multidisciplinary competencies. Successful treatment requires great attention to detail in the management of all aspects of the disease, including antibiotic therapy, choice of vasopressors, ventilator management, tight glucose control, and deep venous thrombosis and stress ulcer prophylaxis. Effective anti-ET (Endotoxin) or antimediator treatment such as anticytokine or other anti-proinflammatory mediator strategies need to be directed at a wide spectrum of host inflammatory mediators. Activated protein C decreases inflammation by inhibiting platelet activation, neutrophil recruitment and mast cell degeneration. Recombinant human activated protein C (drotrecogin alfa [activated]) is the first anti-inflammatory agent that has proved effective in the treatment of sepsis.

INTRODUCTION

Sepsis is a complex syndrome i.e. infection in the blood caused by an uncontrolled systemic inflammatory response, of infectious origin (bacteria/germs or a virus.), characterized by multiple manifestations and which can result in dysfunction or failure of one or more organs and even death also. Severe sepsis and septic shock are currently among the most common causes of morbidity and mortality in intensive care, and their incidences have increased during the past decade as the population has aged[1, 2, 3].

Sepsis is the systemic inflammatory response to severe microbial infection that is common in patients suffering from trauma and burn injuries. The body's immune system becomes overwhelmed by the infection which initiates important alterations in immune, metabolic, and hemodynamic function that in their most dramatic forms are recognized as sepsis and septic shock[5] and, in the case of severe sepsis this can lead to failure of one or more vital organs such as the lungs, kidney, heart and/or liver.[4] Sepsis is a complex clinical syndrome resulting from the damaging effects of a disregulated host response to infection, including uncontrolled inflammation and immune suppression.[5] SIRS (Systemic Inflammatory Response Syndrome) is the constellation of physiological signs that the host displays when reacting to an inflammatory stimulus,[6] these signs are fever, tachycardia, tachypnea and or leucocytosis.[7] The initial inflammatory stage of sepsis is characterized by the presence of proinflammatory molecules such as tumor necrosis factor-a (TNF-a), interleukin (IL)-1b and other molecules. These cytokines trigger systemic responses that include tachycardia, tachypnea, leukocytosis and fever, all fundamental features of the systemic inflammatory response.[8]

SIGN AND SYMPTOMS [9, 10]

Sign and symptoms of sepsis are highly variable, depending on patient age group and sex. Following are the variables observed in sepsis[11].

General Variables during Sepsis [12]

In sepsis fever with core temperature above 38.3˚C and sometimes hypothermia with core temperature below 36˚C may be seen. The heart rate in sepsis is always found to be above 90 bpm and positive fluid balance is observed above 20ml/kg over 24hour. The other general conditions observed are tachypnea, altered mental status and hyperglycemia.

Inflammatory Variables [13]

The septic condition shows abnormality in WBC count, that characterizes leukocytosis (WBC count>12,000/mm^3) and leucopenia (WBC count < 4,000/mm^3). The normal WBC count in sepsis is always characterized by presence of 10% immature forms. The plasma procalcitonin level is always above 25D normal value.

Hemodynamic Variables [14]

The arterial hypotension i.e. SBP is observed below 90 mm Hg and mixed venous oxygen saturation above 70%. The cardiac index is found to be above 3.5L/min/m^2.

Organ Dysfunction Variables [15]

The arterial hypoxemia is observed as Pao_2 /Fio_2 is lower than 300. The acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for ≥ 2 hr), thrombocytopenia (platelet count < 100 x 103/μL) and hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L) is observed. The creatinine increases above 0.5 mg/dl. The coagulation abnormalities and Ileus is also observed in sepsis.

[1]Yadavrao Tasgaonkar Institute of Pharmacy, Karjat, MH, India.
E-mail: sumanns912@gmail.com
*Corresponding author

[2]Sitabai Thite College of Pharmacy, Tal. Shirur, Dist - Pune, MH, India.

[3]NVT's college of Pharmacy, Ladvali Mahad. Dist Raigad, MH India.

[4]Sahayog Sevabhavi Sanstha's Indira College Of Pharmacy, Vishnupuri, Nanded, MH, India

[5]Shivajirao S. Jondhle College of Pharmacy, Asangaon, MH, India.

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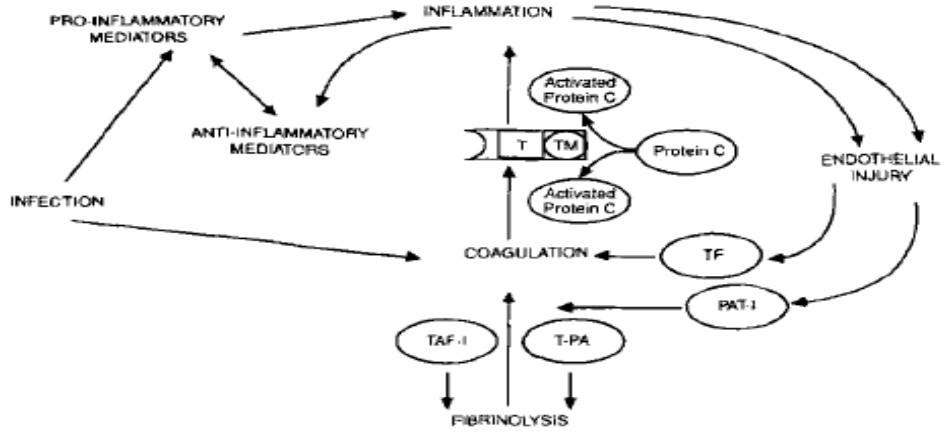

T	*Thrombin*
TM	*Thrombomodulin*
TF	*Tissue factor*
PAI-1	*Plasminogen activator inhibitor type 1*
TAF-I	*Thrombin activatable fibrinolysis inhibitor*
T-PA	*Tissue plasminogen activator*

Figure 1: Illustration of the interrelationships between endothelial injury, inflammation, coagulation and mediators in severe sepsis

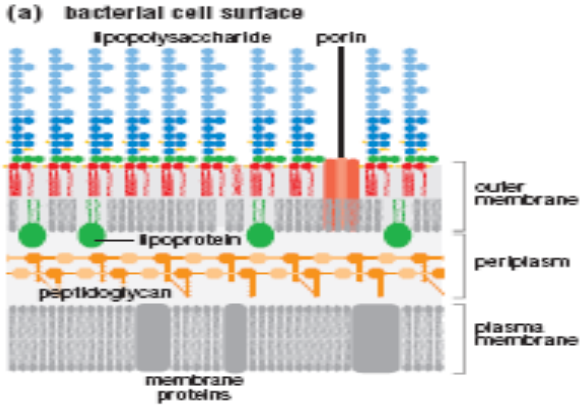

figure 2 (a): Simplified diagram of Gram-negative bacterial Cell Surface showing LPS and some other major features

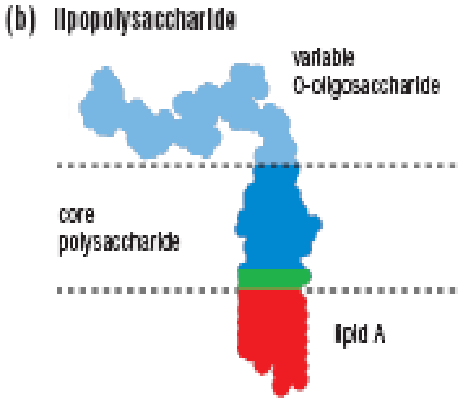

Figure 2 (b): The LPS molecule consists of an Outer O-specific oligosaccharide

Tissue perfusion Variables [16]

The hyperlactatemia (> 1 mmol/L) and decrease capillary refill or mottling is observed.

PATHOPHYSIOLOGY [17, 18]

Sepsis is the systemic inflammatory response to severe microbial infection that is common in patients suffered from trauma and burn injuries. Inflammation represents the response of tissues to either injury or the presence of microorganisms. It serves a vital role because it enhances the movement of phagocytic cells and defensive molecules (e.g., immunoglobulin, complement) from the bloodstream to the site of infection or injury. The first step in this process is the recognition of tissue injury or microbial invasion. Injured cells releases preformed mediators (e.g., histamine) and synthesize proinflammatory substances, including eicosanoids (e.g., prostaglandins, thromboxanes, leukotrienes) and the cytokines (interleukin [IL]-1 and tumor necrosis factor (TNF))[19, 20, 21]. These mediators are responsible for the initiation of a nonspecific inflammatory response. Microbial invasion may result in tissue injury, thereby initiating this process, or specific bacterial cell components may be recognized by immune cells (macrophages), which result in the production of inflammatory mediators and the initiation of an inflammatory response [22]. (Figure 1).

Although bacterial infection may be responsible for the initiation of an inflammatory response the inflammatory process it results solely from the production of endogenous mediators[23]. The bacterial cellular components that are recognized by the immune system include endotoxins (lipopolysaccharide; LPS) and exotoxins from gram-negative bacteria as well as peptidoglycans (PGs), lipoteichoic acids (LTAs), enterotoxins, and superantigenic exotoxins from gram-positive bacteria. Endotoxin makes up part of the normal cell wall of gram-negative bacteria. Sepsis can occur through infection with gram-positive bacteria and even fungi and viruses, or as a consequence of secreted toxins.

However, the sepsis syndrome occurs commonly in response to lipopolysaccharide membrane (LPS) from gram-negative bacteria. LPS is a major constituent of gram-negative bacteria cell walls and is essential for membrane integrity. The portion of LPS that causes shock is the innermost and most highly conserved phosphoglycolipid, lipid A as shown in Figure2: (b), which acts by potently inducing inflammatory responses that are life-threatening when systemic, and is known as bacterial endotoxins. Multicellular organisms from horseshoe crabs and fruit flies to humans have evolved proteins specialized for the recognition of LPS. These proteins are found both on the surface of phagocytic cells and as soluble proteins in blood.

LPS is removed by macrophages through scavenger receptors that are highly expressed in the liver and are thus positioned to remove LPS from portal blood draining the intestines, and by neutrophils through the primary granule protein, bactericidal permeability increasing protein (BPI), which is toxic to gram-negative bacteria. The homologous LPS-binding protein, LBP, transfers LPS to membrane-bound or soluble CD14, enabling interactions with Toll-like receptors (TLRs) on the phagocyte membrane and to high-density lipoprotein (HDL) particles for removal. TLRs have a lethal function in the septic shock syndrome. The physiological function of signaling through phagocyte TLRs is to induce the release of the cytokines TNF, IL-1, IL-6, IL-8 and IL-12 and trigger the inflammatory response, which is critical to containing bacterial infection in the tissues. However, if infection disseminates in the blood, the widespread activation of phagocytes in the bloodstream is catastrophic[24, 25].

Cytokine production in the bloodstream results in widespread endothelial cell activation, with expression of adhesion molecules, activation of the coagulation cascade and the production of chemokines and cytokines by the endothelial cells themselves, with consequent amplification of the inflammatory cascade[26, 27]. The adhesion and activation of circulating neutrophils at the endothelium results in both oxidative and elastase-mediated damage, resulting in the loss of vascular integrity and failure to maintain adequate blood pressure. TNF and IL-1 also depress myocardial function directly. Refractory shock, with leakage of edema fluid, and the failure of organs with large capillary beds, such as the lung and kidney, leads to death[28]. Cytokine mediators are small glycoproteins synthesized in response to a stimulus such as contact with elements of the cell wall of microbes or as a result of synthesis by activated immune cells initially cytokines are derived from macrophage activation. In sepsis, the trigger for the inflammatory cascade is a response to components of the microbial cell wall or DNA. A portion of the cell wall, lipopolysaccharide (LPS) in gram-negative, activates the cellular response in sepsis[29]. This is achieved by its binding to receptors on the surface of macrophages L gram-negative cell wall components may also form a complex with these receptors, which then results in the same effect of activating the innate immune response. Toll like receptors (TLR) on the cell wall of macrophages and natural killer cells (T-cells) are then activated and lead to gene expression and intracellular production of cytokines L. These mediators also lead directly to vasodilation and increased capillary permeability and to changes to the structure of the endothelium, enabling the adhesion of the leukocytes that are attracted to the site of infection[30].

Cytokines are the humoral components of the innate immune system and act either directly on invading pathogens, or as mediators between cells and organs. Reactive oxygen species in high concentrations have a toxic effect on bacteria by damaging their cell walls. In lower concentrations, these molecules are important for regulatory mediators interleukins (IL) and tumor necrosis factor (TNF) are other mediators that have the ability to promote inflammation from a localized to a systemic process. Some of these cytokines are stored in myeloid cells and are rapidly secreted after contact with microbes. In addition, the production of these cytokines is stimulated by complex mechanisms in a time dependent manner. During sepsis, pro-inflammatory mechanisms are heavily activated. However, anti-inflammatory mechanisms are activated at the same time. These include secretion of specific cytokines such as IL-10 and the soluble TNF receptor and a decrease in the lymphocyte cell count. The advantage of this systemic anti-inflammatory response may be the attenuation of deleterious systemic pro-inflammatory effects and the concentration and compartmentalisation of the inflammation at the site of infection. However, when anti-inflammatory mechanisms dominate, the immune system is depressed (immunoparesis), thus increasing the body's susceptibility to nosocomial infections and the reactivation of dormant pathogens such as cytomegalovirus patients with severe sepsis might therefore benefit from immune system stimulation However, more clinical studies are needed to confirm this new concept and better bedside tools are needed to confirm timing and need for such an intervention[31, 32]. The pathogenesis of sepsis begins with the proliferation of microorganisms at a nidus of infection, followed by invasion of the bloodstream, leading to bacteremia. In both instances, structural components of the microorganism, such as lipopolysaccharide, peptidoglycan and lipoteichoic acids, extracellular enzymes, and exotoxins are released, which in turn induce release of endogenous mediators of sepsis from plasma precursors of cell[33].

The resultant release/activation of mediators, such as cytokines, arachidonic acid metabolites, coagulation factors, complement, nitric oxide, endorphins, and kinins induce significant physiologic effects that, if maintained, lead to progressive failure of multiple organ systems and death[34].

Lipopolysaccharide [35]

Lipopolysaccharide (LPS), also called endotoxin (ET), is the most potent and best studied gram-negative bacteria signal molecule, and is composed of three parts, each demonstrating unique properties as mediators of direct toxicity, bacterial virulence, and immunogenicity. There are approximately 350,000 molecules of LPS on the surface of each gram-negative bacterium. O-polysaccharide chain is exposed on the outer surface of gram-negative bacteria and

is composed of repetitive sugar residues. It encapsulates the microorganism and protects it from opsonization and bacterial killing. However, when injected into animals, the 0-polysaccharide chain does not produce systemic toxicity, and after a delay, the host develops serotype-specific opsonizing antibodies.

R-Core

R-core, also known as the ketodeoxyoctonate (KDO) region or core sugar, is less exposed to the surface of the bacteria, its molecular structure is similar among diverse gram-negative bacteria, and it links the 0-polysaccharide chain to lipid A[36].

Lipid A

Lipid A is a lipophilic fatty acid and mediates the acute direct toxic effects of ET. The host response to the presence of ET is complex and varied. Any of the path physiological effects of ET are the result of activation of host cell types, including macrophages, neutrophils, and endothelial cells with the subsequent generation of proinflammatory cytokines and other inflammatory mediators. Signaling pathways by which ET stimulates various cellular responses are complex and not entirely understood, but it would appear that signal transduction occurs after the initial attachment of ET to CD14 antigen on effector cells. Recently, endogenous serum proteins that regulate the delivery of ET to the cell surface have been characterized. Two such closely related proteins-LPS binding protein (LBP), a 60-kd glycoprotein synthesized by the liver, and the neutrophil granule-derived protein bactericidal/ permeability- increasing factor (BPI) may be key determinants of the host response to ET. LBP and BP1 share up to 44% sequence homology and contain a high-affinity binding domain for the lipid a component of bacterial ET. Despite their structural similarities, LBP and BP1 differ markedly in their ability to present ET to host cells. LBP is an acute phase reactant that is present in normal plasma. LBP binds to ET and the complex then binds readily to the CD14 antigen on the cell surface, leading to activation of cells such as polymorphonuclear cells and monocytes, and induces cytokine production. By contrast, BP1 interaction with ET blocks ET delivery to the CD14 antigen. Indeed, BP1 binding to ET attenuates cytokine release by mononuclear cells and inhibits ET-mediated activation of neutrophils[36].

Biologic Actions of ET

When administered to humans, a single injection of ET causes fever, hypotension, and neutrophilia. These effects are partly caused by the induction of IL-l, TNF, IL-6, and IL-8 by ET. In healthy volunteers, an intravenous bolus of ET at a dose of 2 to 4 rig/kg produces transient circulating ET levels. Within 3 to 5 hours, tachycardia develops, cardiac index increases, and there is a decrease in systemic vascular resistance and left ventricular ejection fraction. These abnormalities revert to normal within 24 hours. Furthermore, healthy volunteers challenged with ET display elevated plasma levels of tissue plasminogen and plasminogen activator inhibitor, and there is increased intestinal permeability to lactose and mannitol. In addition, elevated plasma levels of proinflammatory cytokines such as TNF, IL-6, and IL-839 are found, as well as elevated levels of cytokine-specific inhibitors such as IL-l receptor antagonist (IL-1Ra) and soluble TNF receptors (sTNFR)[37].

TREATMENT

The pathogenesis of human sepsis involves a complex interplay between the infecting organism and the host response, with the consequent multiple organ dysfunction. An effective therapy needs to be directed at a wide spectrum of bacterial species. Likewise, an effective anti-ET or antimediator treatment such as anticytokine or other anti-proinflammatory mediator strategies need to be directed at a wide spectrum of host inflammatory mediators[38]. The methylxanthine derivative pentoxifylline, a phosphodiesterase inhibitor, specifically reduces TNF mRNA accumulation in harvested LPS-stimulated murine monocytes, thereby suppressing production of biologically active TNF. The mechanisms may be mediated via the generation of cyclic adenosine monophosphate (CAMP). Thalidomide, a synthetic derivative of glutamic acid, has recently been shown to selectively inhibit in vitro synthesis of LPS-induced TNF by monocytes by enhancing mRNA degradation[39]. Monoclonal antibodies to TNF several studies have shown that significantly they reduce mortality in animals given lethal doses of ET. Other mediators of sepsis can also be potentially targeted. These new investigational compounds include platelet-activating factor antagonists, NO synthase inhibitors, soluble complement receptors inhibitor (SCRI), leukotrienes inhibitors, and anticoagulants such as recombinant alpha-l antitrypsin Pittsburgh, antithrombin III, and protein C[40]. Following are some category of drugs used in adjunct dose in case of septic shock.

Corticosteroids [41-47]

Deficiency of adrenal steroid production in severe sepsis was originally described as acute haemorrhagic necrosis of the adrenal glands precipitating addisonian crisis and eventually leads to death, also known as Waterhouse-Friderichsen syndrome[41]. High dose corticosteroid treatment in severe sepsis was initially investigated as an anti-inflammatory treatment and found to be of no benefit. Attention has now returned to the problem of adrenal insufficiency in severe sepsis. Complete adrenal failure is rare, but relative adrenal insufficiency is much more common, although the incidence depends on the definition used. In one study, for example, which defined adrenal insufficiency as a cortisol increment of ≤ 248nmol/l (9 µg/dl) 30-60 minutes after 0.25 mg of tetracosactrin, 54% of the patients with septic shockmet the criteria. Two recent meta-analyses suggest that low dose hydrocortisone for five to 11 days in unselected patients with severe sepsis or septic shock significantly reduces both the duration of shock met and in hospital mortality, without incurring additional complications[42].

Glucocorticoids inhibit TNF synthesis at distinct points of the cytokine biosynthetic pathway. Nuclear factor kB (NF-kB), a cytoplasmic protein, is considered to be the pivot of proinflammatory gene expression, and in un-stimulated immune cells, NF-kB is bound in the cytoplasm to the inhibitory-kBo protein. When an immune stimulator such as TNF binds to its cell-surface receptor, IkBa destruction occurs, freeing NF-kB, which then moves into the nucleus and activates cytokine and other gene expression. Glucocorticoids interfere with NF-kB activity. Indeed, recent works suggest that the Glucocorticoids receptor complex migrates into the nucleus, where it increases transcription of IkB gene, leading to increased intracytoplasmic IkBa concentrations, allowing more substrate binding to NF-kl3 and preventing its intranuclear migration even under conditions of immune stimulation. In addition, Dexamethasone may inhibit TNF production, primarily post transcriptionally, by reducing translation. Despite these appealing proposed mechanisms, the results of two multicenter, prospective, randomized trials in patients with sepsis did not demonstrate improved survival rates in steroid treated groups. Similarly, somatostatin has been shown to inhibit more potently LPS-induced TNF release from human alveolar macrophages, suggesting a possible protective role in the treatment of ARDS. Somatostatin is also capable of down-regulating cell-surface TNF receptor expression in human macrophages.

The positive effect of low dose steroid replacement treatment may be even greater if it is restricted to patients selected on the basis of proved adrenal insufficiency[43]. If the need for vasopressors persists or even increases then steroids administered in physiological doses may shorten the time to resolution of shock, but without effect on mortality[44]. Because an intense inflammatory response is a component of the pathogenesis of sepsis, corticosteroids have been explored as a possible therapeutic agent. However, the use of corticosteroids in sepsis remains controversial. The SSC (Surviving Sepsis Campaign) guidelines recommend intravenous low-dose corticosteroids (hydrocortisone 200–300 mg/day) only in patients with vasopressor-dependent septic shock. Administration of higher doses of corticosteroids in septic shock has been shown to be harmful. The host response to the stress of critical illness includes increased serum cortisol levels, but an inappropriate cortisol response is not uncommon in patients with septic shock[45]. The use of adrenal function tests to detect relative adrenal insufficiency has been proposed as an approach to determining which patients might benefit from corticosteroid therapy. An absolute incremental increase of 9 µg/dL 30 or 60 minutes after administration of 250 µg of corticotropin was found to be the best cut-off value to distinguish between adequate adrenal response (responders) and relative adrenal insufficiency[46]. Corticosteroid should not be withheld while awaiting the results of the adrenal function test. Dexamethasone 4 mg for every 6 hours may be given until a low-dose corticotrophin stimulation test can be performed as this agent does not interfere with the cortisol assay but suppresses the pituitary-adrenal axis response. Corticosteroids may be continued in patients with relative adrenal insufficiency and can be discontinued in responders. In some cases it is recommended to use baseline random cortisol level of less than 25µg/dL (in a highly stressed patient) as this finding is highly suggestive of adrenal insufficiency. A recent study, however, showed that nearly 40% of critically ill patients with hypoproteinemia had below normal serum total cortisol concentrations even though their adrenal function was normal. Measuring serum free cortisol concentrations in this subset of patients can prevent the unnecessary use of glucocorticoid therapy. Corticosteroids should be continued regardless of the baseline level if the cortisol response to administration of corticotropin is blunted.

Adverse effects include neuromyopathy and hyperglycemia as well as decreased numbers of lymphocytes, immunosuppression, and loss of intestinal epithelial cells through apoptosis. Corticosteroids have also been associated with increased risk of nosocomial infection and impaired wound healing. The use of corticosteroids in the treatment of acute respiratory distress syndrome (ARDS) also remains controversial. Some earlier trials showed a mortality benefit among patients treated with methylprednisolone compared with those given placebo. A recent National Heart Lung and Blood Institute trial involving 180 patients with ARDS of at least 7 days' duration found that starting methylprednisolone therapy more than 2 weeks after the onset of ARDS was associated with an increased risk of death at 60 days and 180 days. Although methyl prednisone was associated with improvement in cardiopulmonary physiology, this study did not support the routine use of methylprednisolone for persistent ARDS. A large clinical trial called Corticosteroid Therapy of Septic Shock (CORTICUS) is currently underway to answer the remaining questions about the use of corticosteroids in septic shock. This double-blind, randomized, placebo-controlled multicenter trial is comparing hydrocortisone (50 mg IV every 6 hours for 5 days followed by tapering to 50 mg every 12 hours for 3 days and then 50 mg once daily for the last 3 days) with placebo in patients with septic shock. A total of 800 patients are being enrolled. It will compare 28-day all-cause mortality in the 2 groups in patients with less than a 9 µg/dL increase in cortisol level in response to corticotropin stimulation. The results of this trial hopefully will set the standard for the use of corticosteroids in septic shock[47].

Antibiotics

First and foremost among specific treatments are prompt appropriate empirical antibiotic treatment within four hours of admission reduce mortality, delay in hypotensive patient's increases mortality by 7.6% an hour. Gram positive organisms have replaced gram negative ones as the most common bacteria causing sepsis[48]. Retrospectively, around 20% of infections originate from each of respiratory, intra-abdominal, and urinary tract sources. Antibiotic treatment must be guided by the

patient's susceptibility group and local knowledge of bacterial resistance. Broad spectrum β lactam antibiotics would be the usual first line agent. If methicillin resistant *Staphylococcus aureus* is a risk, empirical vancomycin should be added. In the presence of risk factors for fungal infection, an antifungal agent may be prescribed initially or within 48 hours if no improvement occurs; decisions are guided by clinical judgment and the severity of the condition, ideally in consultation with infectious disease or microbiology colleagues. The importance of wide cover is illustrated by the much poorer prognosis in patients in whom the first line drugs are ineffective. If strong clues to the source of infection exist, targeted narrower spectrum treatment is probably justified. It is clear that the site of infection should be managed promptly in patients with severe infection, including emergency surgery when applicable. However, efforts should also focus on early and carefully controlled antibiotic therapy. Minimizing the delay between admissions and beginning antimicrobial treatment is key to achieving a successful outcome. The potential influence of delayed antibiotic therapy was first evaluated in patients with CAP (community-acquired pneumonia).[4] A recent retrospective analysis quantified the impact of delayed antimicrobial treatment in patients with severe sepsis. Kumar and coworkers demonstrated that every additional hour without antibiotics increased the risk for death in hypotensive septic patients by 7.6% during the first 6 hours. Early antibiotic therapy has been incorporated into the surviving sepsis campaign recommendations, and we expect compliance with this component of the guidelines to increase from its current low level. The focus of infection is sometimes difficult to ascertain, but treatment must effectively target the responsible pathogen, from among a wide range of potentially etiologic agents.[10] Initial selection of an antibiotic with good activity against the causative organism is crucial for survival. A prospective evaluation of sepsis emphasized that, other than co morbidity, the factor most strongly associated with death was ineffectiveness of antimicrobial treatment against the micro-organism identified in blood cultures. Several large reports corroborated the relation between ineffective antibiotic treatment and poor prognosis. Consequently, broad-spectrum antibiotics have been recommended, and the agent selected should provide coverage against the microorganisms that are usually involved in the suspected focus of infection. Supportive clinical evidence for use of broad-spectrum antibiotics will probably remain sparse, but effective antimicrobial management requires good microbiologic sense[49]. Adherence to such guidelines regarding use of antibiotics may positively influence prognosis, but efforts to improve detection of pathogens should continue because enhanced specificity allows one to focus treatment on the responsible micro-organism and so limit the spectrum of coverage[50].

Vasoactive Drugs

Combining norepinephrine (nor adrenaline) and dobutamine improved hemodynamic parameters of hepatosplanchnic circulation but required invasive monitoring procedures, without clinical benefit[51, 52]. Dopamine and epinephrine are vasoconstrictors that also increase cardiac output, but their metabolic effects may be harmful. They increase cardiac output since they are used in presences of fluid treatment. In addition, use of vasopressors has been associated with poorer outcomes in septic patients, but their influence on mortality was unclear. To assist physicians in their use of vasoactive drugs, professional associations have proposed guidelines that allow an opportunity to administer epinephrine or a combination of norepinephrine and dobutamine to more severely ill patients[53, 54]. A recently reported study indicated that these two strategies were equivalent in terms of both efficacy and safety. Whichever drug is selected, introduction of vasopressors should be considered after optimal fluid loading; these agents may allow therapies to be applied earlier & more aggressively in order to improve physiological parameters & ultimately outcome[55].

Activated Protein C

Activated protein C inactivates factors Va and VIIIa, preventing the generation of thrombin. This decreases inflammation by inhibiting platelet activation, neutrophil recruitment and mast cell degeneration. It has direct anti-inflammatory properties including blocking of cytokine production and blocking cell adhesion[56]. Recombinant human activated protein C (drotrecogin alfa [activated]) is the first anti-inflammatory agent that has proved effective in the treatment of sepsis. In patients, with a suspected site of infection, or more signs of systemic inflammation and at least one sepsis induced organ dysfunction, treated with activated protein C, there was a 19.4% reduction in the relative risk of death and an absolute risk reduction of 6.1%, because of its anticoagulant properties, the major risk associated with its administration is hemorrhage. 3.5% of patients treated with activated protein C had serious bleeding (intracranial hemorrhage, life threatening bleeding episode or a requirement for at least 3 units of transfused blood)[57].

Activated protein C, a component of the natural anticoagulant system, is a potent antithrombotic serine protease with substantial anti-inflammatory properties. The efficacy of drotrecogin alfa (activated) in treating severe sepsis was supported by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which was a phase3, randomized, double-blind, placebo-controlled trial. PROWESS enrolled patients with severe sepsis (systemic infection and organ failure) and randomly assigned them to receive placebo or intravenous drotrecogin alfa (activated). Treatment with drotrecogin alfa (activated) was associated with a 6.1% absolute risk reduction and a 19.4% relative risk reduction in 28-day all-cause mortality. It is important to note that in the PROWESS, ENHANCE, and ADDRESS trials, the risk of serious bleeding events was increased in patients who received drotrecogin alfa (activated). At this time, patients who fulfill the following criteria are most likely to benefit from treatment with drotrecogin alfa:

- Those who have severe sepsis with vasopressor dependence and/or require mechanical ventilation with an APACHE II score greater than 25;
- Those who have no active bleeding, have a platelet count greater than 30 × 103/μL and an international normalized ratio below 3.0, and have no identifiable risk factors for central nervous system bleeding; and
- Both the patient and medical team approve of taking an aggressive approach to care of sepsis in a patient with a reasonable baseline quality of life to return to once they survive their ICU stay.

Use of drotrecogin alfa (activated) is contraindicated in patients with known sensitivity to the drug and patients at high risk for death or significant morbidity associated with bleeding. This group would include patients with active internal bleeding, hemorrhagic stroke, intracranial or intraspinal surgery or severe head trauma, trauma with increased risk for life-threatening bleeding, presence of an epidural catheter, intracranial neoplasm or mass lesion, or evidence of cerebral herniation[58].

The use of prophylactic heparin in patients with severe sepsis undergoing treatment with drotrecogin alfa (activated) appears to be safe. Treatment with drotrecogin alpha (activated) consists of infusion of the drug at a rate of 24μg/kg/hr for total infusion duration of 96 hours. The dose is based on actual body weight. The infusion should be stopped 2 hours before patients undergo surgical procedures associated with a risk of bleeding. The infusion can be restarted immediately after minor procedures (e.g., arterial line placement, tracheotomy tube changing) if there is no sign of bleeding. However, waiting approximately 2 hours before restarting the drug after procedures with slightly increased chance of bleeding (e.g., chest tube placement, pulmonary artery catheter placement) is recommended. With major surgical procedures, a wait time of approximately 12 hours before restarting the infusion is recommended [59].

A recombinant human protein (drotrecogin alfa (activated)) was evaluated in a large prospective randomized controlled trial. It was, somewhat controversially, approved in November 2001 by the US Food and Drug Administration on the basis of a reduction in the absolute risk of death of 6.1% (P=0.005) and subgroup analysis of predefined high risk patients (APACHE II) score of ≥25). In the intervening time two further randomized controlled trials have been published, one in children and the other in adults at low risk of death. Both were stopped early on grounds of inefficacy. Overall, whether the risks of drotrecogin alfa (activated) outweigh the benefits is now far from clear, even in patients with a high risk of death [60, 61].

Fluid Treatment

Fluid resuscitation is one of the cornerstones of sepsis therapy, but the optimal choice of fluids is still a subject of debate. Two types of fluid solutions used to treat the septic patients. No studies have shown improvements or benefits in morbidity or mortality with use of colloids over crystalloids, so based on cost, crystalloids may be considered first choice, particularly as some colloid solutions may cause harm to the septic patient[62]. There are no comparative studies in sepsis resuscitation between saline or balanced crystalloid solutions such as Ringer's lactate or acetate. The initial treatment strategy is to fluid load the patient to ensure adequate filling/preload to the heart. It is important to remember that the only circulatory effect of fluid is to increase stroke volume. There is evidence that over-filling may be detrimental. The decision to stop fluid resuscitation will often be based on the observation that there is no further improvement in the markers of flow despite increases in filling pressures[63].

However, crystalloid resuscitation has been associated with lower mortality in trauma patients. A recent Saline versus Albumin Fluid Evaluation (SAFE) study was one of several studies that evaluated whether the choice of resuscitation fluid affects survival for ICU patients. This randomized, double-blind trial assigned patients to 4% albumin or normal saline for resuscitation and found similar outcomes at 28 days in the 2 groups, suggesting that the choice of fluids is probably less important than the quantity given. Cardiac output and systemic oxygen delivery increase in proportion to the degree of intravascular volume expansion achieved. Tissue perfusion is restored to the same degree when crystalloids or colloids are titrated to the same filling pressures. The availability, cost, and ease of administration of crystalloids generally make them the first-line therapy for fluid resuscitation[64, 65]. The SSC guidelines recommend administering fluid challenges of 500 to 1000mL of crystalloids every 30 minutes in patients with suspected hypovolemia; these should be repeated based on the patient's response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload). Fluid challenges are given in addition to the baseline maintenance fluid administration. Precise endpoints for fluid resuscitation have not been defined. A combination of clinical variables, including mean arterial pressure, urine flow, skin perfusion, and level of consciousness, are used to determine the adequacy of fluid resuscitation [66, 67].

Immunoglobulin

Igs are widely used both as therapeutic and diagnostic tools in many fields of medicine. On the basis of their specificity, IvIg preparations can be grouped into monoclonal – containing a single class of Ig directed against a single epitope of those present upon a target molecule (e.g. one epitope of TNF-α), or polycloclonal – containing Ig directed against multiple epitopes of the target substance. The additional immunomodulatory effects attributed to the latter class are due to naturally occurring autoantibodies and some non-immune proteins present in the preparation[35]. Several lines of evidence support the use of IvIg in sepsis, including the increased clearance of endotoxin by the RES (Reticulo endothelial system), the increased production of free radical species by macrophages and the enhancement of phagocytosis by neutrophils exposed to different Ig classes (G, M, and A) . In septic patients, spontaneously elevated levels of IgM anti-

endotoxin antibodies are associated with a better outcome, and this effect can be replicated by the administration of an IgM-enriched polyclonal IvIg preparation in patients[68]. It has also been demonstrated that IgM, and to a lesser extent IgG, can down regulate the activation of complement during inflammation. Due to their mechanisms of action, IvIgs are used in clinical practice with the dual aim of preventing the occurrence of a number of diseases by passively immunizing the subjects who are at risk, and of modulating the inflammatory reaction. Both monoclonal and polyclonal Ig preparations have been used in septic patients, with different results. Indeed, the recent history of critical care medicine has been marked by a number of RCTs (randomized, controlled clinical trials) studying the effects of monoclonal IvIg targeted against endotoxin and several different sepsis mediators[69, 70]. The production and release of sepsis mediators should be considered as a network rather than as a cascade; consequently, once the process is started, even if one of the substances responsible for the initial phase (i.e. TNF-α) is blocked, other mediators will likely maintain the septic response. Antibodies directed against some sepsis mediators are currently used to treat disorders such as Crohn's disease and rheumatoid arthritis, which, in contrast to sepsis, are characterized by a chronic and localized rather than acute and systemic inflammatory reaction. However, the blockade of inflammatory mediators is not completely risk-free; in fact, the administration of anti-TNF-α antibodies in these clinical conditions has been associated with the occurrence of pulmonary and skin infections caused by intracellular agents, and the activation or reactivation of tuberculosis[71]. Thus at the present time, although novel molecules are still being produced and tested, the clinical use of monoclonal Ig directed towards some sepsis mediators is not supported by EBM criteria, and is limited to patients enrolled in RCTs[72].

Polyclonal preparations contain variable amounts of Ig directed against a variety of gram-negative and gram-positive epitopes and bacteria-derived substances, including endotoxin. In practical terms, several preparations containing predominantly IgG with only traces of other Ig are available (Polyglobin®, Bayer, Leverkusen, Germany) whereas only one product contains elevated concentrations of IgM (in addition to IgG) and minor amounts of IgA (Pentaglobin®, Biotest, Dreieich, Germany). Aside from the concentration of Ig, the various preparations also differ with regard to the stabilizers used. Unlike monoclonal IvIg, polyclonal IvIgs are widely used in septic patients despite the lack of very large, positive RCTs. The extremely low incidence of severe side effects associated with their administration make them suitable in a wide range of clinical conditions[73, 74].

CONCLUSION

Sepsis is a clinical disorder with high mortality. The pathogenesis of human sepsis involves a Complex interplay between the infecting organism and the host response, with the consequent multiple organ dysfunction. An effective therapy needs to be directed at a wide spectrum of bacterial species. The treatment of sepsis is multifaceted and typically requires multidisciplinary competencies. Successful treatment requires great attention to detail in the management of all aspects of the disease, including antibiotic therapy, choice of vasopressors, ventilator management, tight glucose control, and deep venous thrombosis and stress ulcer prophylaxis. Appropriate use of newer therapies like drotrecogin alfa (activated) also should be considered. It is clear that the treatment of SIRS and its sequelae cannot focus solely on any single component of this process but must be directed at resolution of the initiating stimulus, modulation of the inflammatory response, and support and maintenance of organ function. From last four decades immunotherapy for sepsis with activated protein C shown better results also low dose steroid is of worth considerations. The use of low-dose corticosteroids should be restricted to patients with refractory septic shock without corticotropin test identification.

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