ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research

Available Online at www.jbpr.in

CODEN: - JBPRAU (Source: - American Chemical Society)

Index Copernicus Value: 72.80

PubMed (National Library of Medicine): ID: (101671502)

Volume 7, Issue 1: January-February: 2018, 88-95

Research Article

Recent advances in the treatment of Sepsis and septic shock; potential therapy based on biochemical evidence

Manoj G Tyagi

Department of Biotechnology, VIT, Vellore, Tamilnadu

Received 22Jan. 2018; Accepted 13Feb. 2018

ABSTRACT

The clinical syndrome sepsis and septic shock comprise of disorders which are increasingly common, potentially lethal, yet not clearly understood clinical syndromes. The rise in the incidence is well documented and thought to be ascribed to the ageing of the population, the prevalence of immune compromised patients and implantable medical devices and the progressive increase in antimicrobial resistance amongst common bacterial pathogens. Septic shock is a manifestation of sepsis and recent evidence suggests that the endothelial surface does not have a passive role in systemic inflammatory states such as septic shock. In fact, endothelial cells are in dynamic equilibrium with a myriad of inflammatory mediators and elements of the innate immune and coagulation systems to orchestrate the host responses in sepsis. There is considerable progress in the understanding of the biochemical and metabolic disturbances occuring during this patho-physiological state and henceforth reduction in mortality rates. This article illustrates the recent advances in the management and treatment of this serious anomaly.

Keywords: Septic shock, chloride, pulmonary renal, erythropoietin, metabolic, oxygen

INTRODUCTION:

The clinical syndrome sepsis has been defined as a life-threatening organ dysfunction caused by aimproperhost response to infection [1]. This dysregulation is particularly observed in the cells, organelles and overall system involved in the delivery and consumption of oxygen, or more specifically, the erythrocytes [2-3], mitochondria [4-5] and microcirculation [6-7]. Sepsis remains a highly lethal entity resulting in more than 200000 USA deaths per year and an in-hospital mortality still unabating despite recent advances in critical care. During the last several decades, the mortality rates have decreased, but the incidence of sepsis is rising. Sepsis has profound effects on all aspects of oxygen physiology, from its transport in red blood cells (RBCs) and its distribution via the microcirculation to its ultimate utilization in the mitochondria to produce energy in the form of ATP [8-10]. In addition, of seemingly critical importance to the septic patient is the conversion of oxygen into oxygen free radicals, reactive oxygen species and oxidizing species, as shown by Mariket al. [11]. Developing new therapeutic agents to manage patients with sepsis has proven difficult with a large number of clinical trials [12]. Despite the failures to demonstrate survival benefits for a number of promising novel therapeutic agents for the treatment of sepsis in Phase III clinical trials, the news regarding clinical outcomes in patients with sepsis is not all that bad [13-15]. The mortality rate is certainly reducing in many clinical studies worldwide, which is primarily a reflection of improved supportive care and early diagnosis and treatment protocols [16-18]. Additionally, substantial progress has been made in understanding the basic pathophysiology of sepsis from the molecular level to the level of organ communication and systems integration [19-20]. This review outlines the recent understanding of this disorder and septic shock along with the treatment of this serious clinical syndrome.

Clinical features of sepsis and septic shock:

The occurrence of clinical findings relating to septic shock is usually insidious. They can develop in the form of fever, mental fog, transient hypotension, decreasing urine amount, or unexplained thrombocytopenia. If necessary

*Corresponding author: Manoj G Tyagi |E-mail: tyagi239@yahoo.co.in

actions are not taken orif sepsis is not treated, respiratory and renal failure, coagulation disorders, and irremediable hypotension can occur which could be life threatening [21].As summarized in Table 1, sepsis is divided into progressive clinical phases and multi-organ disorder syndrome (MODS) is its severest clinical symptom [22].The mortality rate is still high despite new developments in sepsis treatment. The mortality rate is reported to be between 20% and 70 % [23]. Different mortality rates reported in these studies depend on the fact that the study groups were heterogeneous. The mortality rate is 40-50% in gram-negative bacterial sepsis, 20-30% in gram-positive bacterial sepsis, and 15-30% in anaerobic sepsis. The mortality rate varies between 70% and 90% when shock, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS) and other organ failure complications develop (Refer Fig.1) [24]. Mortality rates amongst patients also vary based on the aetiological factors. The highest mortality rate is reported in Pseudomonas aeruginosa sepsis [25].Sepsis has a complicated pathology, and it is not yet fully understood because it has a variety of clinical and physiopathological symptoms [26].

The importance of Embden Meyerhof pathway and the role of 2,3DPG in Red Blood Cells:

An important component essential to red blood cells (RBC) function is a side-branch of glycolysis (Rapoport-Lubering shuttle) that produces 2,3-disphosphoglycerate, also referred to as 2,3-DPG is an allosteric regulator of haemoglobin that binds to the central cavity of the hemoglobin molecule and decreases the affinity of haemoglobin for oxygen by a factor of 26. It is present at high concentrations under normal physiology and is synthesized by the RBC under hypoxic conditions. An experimental pilot study using endotoxemic mice suggested that, in the early hypoglycaemic phase of endotoxemia, the RBC increased its 2,3-DPG level, suggesting the RBC was attempting to release more oxygen in hypoxic regions. However, in critically ill and septic patients, acidemia, hypophosphatemia and transfusion of 2,3-DPG depleted blood are all factors that can shift the ODC to the left, decrease the P50, increase Hb affinity for oxygen and decrease oxygen release. Hypophosphatemia has been found to associate with lower RBC levels of 2,3-DPG as per previous studies [27]. Extracellular phosphate and RBC intracellular phosphate concentrations are linked through at least three phosphate transporters in RBC membranes: band 3, Na/phos co-transporter, and sodium-independent transport. Activation of phosphate influx by these transport mechanisms depends on extracellular phosphate. Another potential cause of RBC 2,3-DPG depletion during extracorporeal blood purification treatments is erythrocyte trauma secondary to the mechanical stress during the procedure itself, as found during the first hour of hemodialysis by Nielsen et al [28] by the changes in 2,3-DPG, a reduction in intracellular phosphate also increases erythrocyte chloride concentration, which by itself blunts the allosteric effects of both 2,3-DPG and pH. One of the key component of Embden Meyerhof glycolytic pathway is methylglyoxal which is a reactive carbonyl species (RCS) and is produced from dihydroxyacetone phosphate (DHAP). Thus attempts should be made to down regulate methoxyglyoxal and upregulate glyoxalase 1(GLO-1) by manipulating or targeting DHAP. DHAP could be a target for future drugs to treat sepsis and also metabolic/endocrine disorders [29].

Lactate generation and metabolic acidosis in shock syndrome: Lactate generation along with release of H+ ions via carbonic anhydrase enzyme pathway is key to metabolic acidosis. Current clinical practice considers a pH ≤7.35 and lactatemia>2.0 mmol.l−1 with a PaCO2 ≤ 42 mmHg as defining lactic acidosis. The patho-physiology of shock-associated lactic acidosis is considered as a direct marker of oxygen debt or hypoperfusion in tissues (type A lactic acidosis) [30]. Lactate is produced from pyruvate and through the glycolysis cascade. Thus when pyruvate production exceeds beyond mitochondrial capacity, lactate generation increases. At the cellular level, in response to adrenergic stress in shock patients, accelerated glycolysis enhances lactate production. In shock patients, acute liver or renal dysfunctions are most often associated with decreased lactate clearance and a pronounced increase in blood lactate level compared with patients without liver or renal dysfunction [31]. The consequences of lactic acidosis on the apoptosis pathway have been widely investigated in myocardial ischemia models but poorly studied in sepsis-induced cardiovascular dysfunction. Among the numerous studied

mechanisms, BNIP3, a member of the Bcl-2 pro-apoptotic protein family, mainly contributes to cardiomyocyte cell death. As in myocardial cells, intracellular metabolic acidosis, including lactic acidosis, also alters the calcium transient and reduces the number of adreno-receptors on the cell surface (NOAM) [32]. More specifically, lactic acidosis induces vascular smooth muscle relaxation via the opening of ATP-sensitive potassium channels. As in myocardial cells, intracellular metabolic acidosis, including lactic acidosis, also alters the calcium transient and reduces the number of adrenoreceptors on the cell surface. More specifically, lactic acidosis induces vascular smooth muscle relaxation via the opening of ATP-sensitive potassium channels. In experimental studies, the buffering capacity oftris-hydroxymethylamino-methane (THAM) is compare-able to that of bicarbonate but without the generation of carbon dioxide. In a blood-perfused isolated heart model with a pH lowered to 7.0, THAM also partially corrects pH and improves myocardial contractility and relaxation. Interestingly, a mixture of sodium bicarbonate with THAM has been shown to enable a complete recovery of pH, improve myocardial function and prevent intracellular paradoxical acidosis. Carbicarb was also developed in order to reduce carbon dioxide generation. This molecule, in theory, would limit the drop in intracellular pH compared with that induced by a bicarbonate load. Experimental studies in dogs comparing carbicarb versus bicarbonate therapy showed the superiority of carbicarb in improving intracellular pH and cardiac output [33-34].Targeting the pH regulatory protein NHE could represent an innovative approach to lactic acidosis management. NHE activation results in intracellular sodium and calcium overloads, which exert deleterious effects on cardiovascular function. A recent experimental study, with a relevant LAM, demonstrated that sabiporide improved myocardial function, reduced systemic inflammation and prevented multiple organ failure. As renal physiology is also affected by metabolic acidosis the plasma chloride concentrations seems to be relevant in terms of renal physiology [35]. Hyperchloremia is frequently seen in patients with acute renal failure and is generally considered to be, at least in part, caused by kidney dysfunction. However, some ancient studies in animals have pointed out that the chloride concentration may modulate renal vascular tone. Hyperchloremia may actually increase the renal vascular responsiveness to vasoconstrictor agents such as angiotensin II and arginine vasopressin, with the opposite occurring in the presence of low chloride levels. Chloremia's influence on renal blood flow and glomerular filtration rate is mediated by prostaglandins and thromboxane A2 [36]. The vasoconstrictor effect of hyperchloremia is independent of the renal nerve innervation, related to tubular chloride reabsorption and is specific to renal vessels.

Importance of vasopressors in septic shock:

Three vasopressor agents need to be mentioned here which are important in treating septic shock i.e vasopressin, norepinephrine and angiotensin II congener. The La Jolla pharmaceutical company makers of LJPC-501 an angiotensin II congener [37] have made some trials with their under development drug and have found that this vasopressor requires lower dose than norepinephrine and epinephrine. Approximately 70% patients receiving this drug had a MAP of 75mm of Hg and showing a reduction in mortality. According to AshishKhanna, MD this drug is a new agent to manage cases of septic shock and vasodilatory shock. While, vasopressin the antidiuretic hormone is also an important hormone to alleviate the symptoms of sepsis. Vasopressin has been shown to improve renal function and glomerular filteration rate reduce the need for conventional vasopressors like the norepinephrine. Terlipressin, a comparatively cheaper and longer acting synthetic analogue of vasopressin in small doses (0.25-05 mg), repeated at 20 minute interval should be used observation of cardiac output [38]. On the other hand there is evidence that nitric oxide (NO) production is increased in human sepsis and preliminary studies in patients with septic shock suggested that NOS inhibitors for e.g L-NMMA were safe and could restore vasomotor tone and maintain blood pressure. Further studies are required to explore the possibility of using a novel NOS inhibitor [39].

The significance of the pulmonary renal cascade:

The pulmonary renal cascade is dependent on the three critical components i.e Urokinase, erythropoietin (EPO) and heparin binding growth

factors. PAI-1, a 48-kDa serine proteinase inhibitor of urokinase type plasminogen activator (SERPIN), produced by various cells such as vascular endothelial cells, platelets, smooth muscle cells, fibroblasts, adipose tissue, and monocytes /macrophages [40], is the main physiological plasminogen activator inhibitor. In pathogenesis of sepsis, PAI-1 plays a role in several biological processes dependent on the inhibition of plasminogen activators and plasmin activity. As a consequence, overproduction of PAI-1 may contribute to organ dysfunction in patients suffering from severe infection and DIC. Microorganisms including bacteria, fungi, and parasites have been proven to interact in a specific manner with the components of fibrinolysis regulators, i.e., pathogenic microorganisms are capable to destabilize the function of proteases, activators, or inhibitors of fibrinolysis to disseminate in the host and evade from the immune response but uPAactvators or urokinase can be helpful in such conditions [41]. EPO treatment exerts complex actions for promoting the maintenance of homeostasis of the organism and for ameliorating the tissue-induced injury under diverse kinds of stress. It is well recognized that EPO rescues cells from apoptosis, reduces inflammatory responses, restores vascular autoregulation, and promotes healing. EPO exerts is biological functions through its receptor (EPO-R), which is extensively distributed in numerous tissues and organs, included vascular endothelial cells, kidney cells, bronchiolar epithelial cells, and type II alveolar epithelial cells [42]. The present results clearly show that the beneficial effects of EPO are mediated, in part, by the recovery of EPO-R, as evidenced by the higher levels of protein expression in kidneys and lungs of mice undergoing CLP-induced sepsis. Exogenous EPO administration is related to the EPO/EPO-R and the VEGF/ VEGF-R2 systems in the amelioration of kidney and lung acute injury during polymicrobial sepsis [43]. Thus EPO, urokinase and heparin binding factors all endogenously available contribute to the ability of the patient suffering with sepsis and external interventions have been found to be helpful as mentioned above [44].

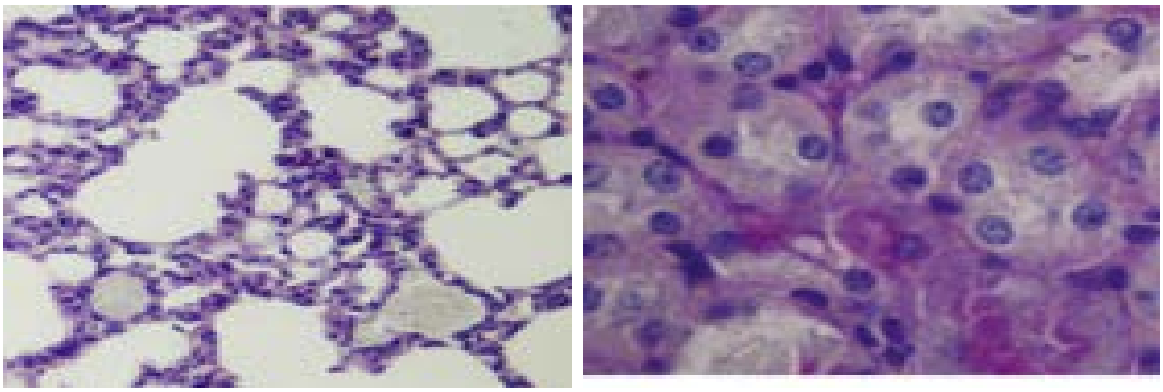

Figure 1: Lung (1) and renal (2) morphology during sepsis in albino rats

Table 1. Clinical Phases of Sepsis (52)

1.Sepsis • Infection having clinical symptoms 2.SIRS (having two or more of the following) 3.Body temperature of >38°C or <36°C, 4.Tachycardia: heart rate more than >90/min, 5.Tachypnea (respiratory frequency of >20/min) or mechanical respiratory requirement 6.White blood cell count of >12×109/L or <4×109/L 7.Severe sepsis Sepsis-induced organ dysfunction or hypotension along with sepsis 8.Septic shock Severe sepsis along with arterial hypotension (systolic arterial pressure of <90 mmHg or mean arterial blood pressure of <65 mmHg) 9.MODS >2 organs affected
L: liters; mmHg: millimeters of mercury; °C: degrees Celsius; SIRS: systemic inflammatory response syndrome

Future directions and newer drugs for treating sepsis and sepsis induced shock:

Many recent metabolomics experiments in animals have shown that metabolomics profiles change dramatically and that metabolite profiles also change accordingly. Some lipid metabolites could hold the key to understanding the severity of the sepsis condition and also indicate the survival chances of patients in these clinical conditions.A targeted metabolomics study revealed that lipid compounds e.g., acylcarnitines and glycero-phosphatidylcholine may be helpful in differentiating infections and could be potential biomarkers of sepsis [45]. Another area under investigation is the understanding of molecular and cellular basis of platelet-neutrophil interaction in sepsis, a growing body of studies focuses on the interference with platelet-neutrophil interaction in sepsis. Ogura H et al. reported P-selectin dependent platelet-neutrophil interaction is implicated in the outcome of severely septic patients and P-selectin blockade markedly inhibited this interaction[46] Exposed to cecal ligation and puncture (CLP), CD40L gene-deficient mice show a significantly inhibited platelet-neutrophil interaction and alleviated pulmonary damage. Experimental inhibition of PSGL-1 significantly abolished CLP-induced platelet neutrophil aggregation which has no effect on neutrophil expression of Mac-1 owing to crucial role on platelet neutrophil interaction, TREM1-silenced mice are highly resistant to a lethal endotoxin challenge and partial silencing of TREM1 in the bacterial peritonitis model produces a significant survival benefit. Development of novel neutral endopeptidase activators or ACE enzyme stimulators could also be novel drugs to treat septic shock [47-48]. But the ultimate drug in combating could be the one which induces sufficient increase in vasoconstriction/ blood pressure and combats the metabolic acidosis along with agents which can improve the immunity of the fighting patient against sepsis.

New antimicrobials for treating Sepsis;

Antibiotic development is always a tedious and tough task as microbes have a tendency to develop resistance to antimicrobials and bactericidal mechanisms are multifaceted. For treating polymicrobial sepsis some new agents are at the verge of launch into the market and for patient usage. Few new antibiotics have been developed over the past 10 years but there are some promising agents in the pipeline[49]. Solithromycin, is a new macrolide (fluorketolide), effectively kills macrolide-susceptible pathogens, like Streptococcus pneumoniae, Haemophilus influenzae, and atypical pathogens, and is also effective against macrolide-resistant bacteria. Solithromycin resistance has not yet been identified. In a phase II study in 132 patients with moderate to severe CAP, clinical and microbiological success rates were similar in patients treated with solithromycin (800 mg on day 1, 400 mg from day 2) or levofloxacin (750 mg daily). Omadacycline (an aminomethylcycline) and eravacycline (a fluorocycline) are developed from the tetracyclines and have now entered phase II clinical trials. Omadacycline is available for intravenous and oral therapy. It is effective against a large number of sensitive but also resistant Gram-positive pathogens (including vancomycin-resistant enterococci and MRSA) and against some Gram-positive pathogens, such as H. influenzae, Klebsiella, and Escherichia coli. Tedizolid is a new oxazolidinone that is more bactericidal than the currently used linezolid [50]. Although differences in clinical response rates have not been very significant, the rate of adverse events seems to be somewhat lower with tedizolid [51]. Human monoclonal antibodies are also being developed that specifically bind and neutralize the alpha-toxin of S. aureus, for adjunctive therapy in sepsis. In a mouse sepsis model, treated animals had a significant reduction in mortality.

Conclusion:

Sepsis is still considered a serious clinical syndrome. Sepsis, frequently occurs after hemorrhage, trauma, burn, or abdominal surgery, and subsequent infections and remains a major challenge both for clinicians and researchers. Despite many years of intensive research and numerous clinical studies, its pathophysiology is still incompletely understood, and some specific treatments have not been successful in clinical trials. Complex metabolic acidosis is common in critically ill septic patients. Furthermore, its severity is associated with poor clinical outcomes and organ dysfunction. Tham, carbicarb or chloride poor balanced solutions do provide the answer to

metabolic acidosis. Erythropoietin and a potentially potent vasopressor could also be extremely useful along with the highly specific antimicrobial agents. We expect that this novel strategy will continue to be clinically assessed and potentially exploited for the more effective future treatment of sepsis and its clinical manifestation i.e septic shock.

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