

Sepsis and Septic Shock: Current Treatment Strategies and New Approaches

Sepsis ve Septik Şok: Mevcut Tedavi Stratejileri ve Yeni Yaklaşımlar

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ABSTRACT

Sepsis is a complex condition characterized by the simultaneous activation of inflammation and coagulation in response to microbial insult. These events manifest as systemic inflammatory response syndrome or sepsis symptoms through the release of proinflammatory cytokines, procoagulants, and adhesion molecules from immune cells and/or damaged endothelium. Today, sepsis is a severe multisystem disease with difficult treatments for its manifestations and high mortality rates. In the last two decades in particular, many studies have been conducted on sepsis that cause shock, multiorgan dysfunction, and organ failure by especially leading to hemodynamic changes. In sepsis, increasing antibiotic resistance and medicine-resistant hemodynamic changes have resulted in further research on new treatment modalities in addition to classical treatments. In the last decade, the sepsis physiopathology has been elucidated. Various therapeutic agents have been used in addition to antibiotherapy, but no satisfactory results have been obtained. This review summarizes the sepsis pathophysiology, current treatment protocols, and new approaches.

Keywords: Critical care, sepsis, septic shock

Öz

Sepsis, mikrobiyal maruziyet sonrasında enflamasyon ve koagülasyonun birlikte aktive olmasıyla karakterize kompleks bir sendromdur. Bu olaylar, immün hücreler veya hasar görmüş endotel hücrelerinden salınan proinflatuvar sitokinler, prokoagulanlar ve adezyon molekülleri yoluyla sistemik enflamatuvar yanıt sendromu veya sepsis bulguları ile ortaya çıkar. Sepsis, günümüzde halen yüksek mortalite ile seyreden tedavisi güç bir klinik tablodur. Birçok sistemi tutan, özellikle hemodinamik değişikliklere yol açarak şok, organ fonksiyon bozukluğu ve organ yetmezliğine giden sepsis hakkında özellikle son yirmi yılda pek çok çalışma yapılmıştır. Sepsiste özellikle artan antibiyotik direnci ve septik şok fazındaki tedaviye dirençli hemodinamik değişiklikler, klasik tedavilere ek olarak yeni tedavi teknikleri geliştirme çabalarına neden olmuştur. Fizyopatolojisi daha iyi anlaşıldıkça, antibiyotik tedavisine ilave olarak birçok ajan denenmiş ama hala yeterli sonuçlar elde edilememiştir. Bu derlemede sepsis patofizyolojisi, mevcut tedavileri ve yeni yaklaşımları özetlenmiştir.

Anahtar Kelimeler: Yoğun bakım, sepsis, septik şok

Introduction

Sepsis is defined as the systemic inflammatory response to infection. Sepsis is quite important as it is seen in 10 of 1000 hospitalized patients and multiple organ dysfunction syndrome (MODS) develops in 30% of these patients; mortality is observed in 20% of patients with sepsis and 60-80% of patients with septic shock. Early diagnosis and treatment are necessary due to high mortality rates [1].

Developments in the field of molecular biology have helped understand most pathologic events that occur in sepsis. Being more aware of the sepsis pathogenesis is very important in terms of new developments in the diagnosis, follow-up, and treatment phases. The sepsis triad is systemic inflammation, coagulation, and disordered fibrinolysis. There are microbial pathogens and inflammatory responses involved in the sepsis physiopathology. In research performed, it was shown that as a result of infection in tissues and traumatic damage, the humoral system was activated in the body and several cytokines were released. The result is the systemic inflammatory response, hemostatic changes, and organ damage [2].



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In recent years, studies have been published that describe the treatment of sepsis patients. Most of these approaches aim to modulate or interrupt the sepsis physiopathology and prevent multiple organ failure. Several new approaches have been reported to reduce mortality rates in severe sepsis. These include the application of low tidal volume in acute respiratory distress syndrome (ARDS), plasma glucose control, goal-oriented treatment (central venous pressure, mean artery pressure, hourly urine output, and central venous oxygen saturation) started in the early period (in emergency service), and corticosteroid treatment at mean doses. Besides pharmacological treatment approaches, early and appropriate antibiotic treatment and cardiovascular support have great importance in sepsis treatment [3].

Incidence and Causes

While a relative decrease has been observed in the prevalence of sepsis in the population recently, the increase in the number of hospital-based sepsis patients stands out. There is a gradual increase in the frequency of hospital-based sepsis. The increase in the advanced age group in the population, extension in the life cycles of patients with chronic disease, common use of immunosuppressive drugs, and common use of invasive procedures for diagnosis or treatment purposes increase the frequency of sepsis. Hospital-based sepsis is more frequently observed in hospitals with a higher bed capacity and intensive care units and where more invasive procedures are performed [4].

It has been reported that 35 million people are hospitalized annually in the USA, and 250,000 of them develop hospital-based sepsis. The mortality rate is between 12% and 80%, and the mean mortality rate is 35% [4]. The largest study on sepsis in Turkey was conducted at Hacettepe University. Covering seven years (1983-1989), this study assessed negative bacteremia patients but did not provide information on the prevalence of sepsis [5].

Sepsis can result from bacteria, viruses, fungi, or parasites, or it can develop in noninfectious intraabdominal incidents such as severe trauma, pneumonia, pancreatitis, and other incidents such as urinary system infection.

The microorganism frequency that leads to sepsis shows chances based on sepsis develop inside or outside the hospital. The most frequently encountered active microorganisms in sepsis patients in society are *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. The microorganisms that lead to sepsis developing

Table 1. Clinical Phases of Sepsis [10]

Sepsis	<ul style="list-style-type: none"> • Infection having clinical symptoms • SIRS (having two or more of the following) <ul style="list-style-type: none"> ◦ Body temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, ◦ Tachycardia: heart rate more than $>90/\text{min}$, ◦ Tachypnea (respiratory frequency of $>20/\text{min}$) or mechanical respiratory requirement ◦ White blood cell count of $>12 \times 10^9/\text{L}$ or $<4 \times 10^9/\text{L}$
Severe sepsis	Sepsis-induced organ dysfunction or hypotension along with sepsis
Septic shock	Severe sepsis along with arterial hypotension (systolic arterial pressure of <90 mmHg or mean arterial blood pressure of <65 mmHg)
MODS	>2 organs affected
L: liters; mmHg: millimeters of mercury; $^{\circ}\text{C}$: degrees Celsius; SIRS: systemic inflammatory response syndrome	

in a hospital have showed some variations over the years [6]. In the 1950s, before antibiotics were used, gram-positive bacteria were in the forefront, and *Staphylococcus aureus* and *Streptococcus pyogenes* were frequently determined as sepsis causes [6]. However, upon the usage of antibiotics, diseases caused by gram-positive bacteria became treatable, and then, gram-negative bacteria isolates gradually became sepsis causes at an increasing rate (in more than 50% of patients) in the 1960s, 1970s, and 1980s.

In different studies, it was reported that gram-negative bacteria were isolated 20-64% of the time in sepsis patients, while gram-positive bacteria were isolated 27-74% of the time. The most frequent causes isolated in gram-negative bacterial sepsis are *E. coli*, Enterobacter, Pseudomonas, Proteus, Acinetobacter, Klebsiella, and other rare gram-negative bacteria, in order of their frequency. On the other hand, in gram-positive bacterial sepsis; coagulase negative staphylococcus, *S. aureus*, and Enterococcus were isolated as the most frequent causes. Microorganisms do not need to pass into the blood for the development of sepsis. The local or systemic extension of signal products and toxins of the pathogen might initiate sepsis [7]. Multiple bacteria can be responsible in some sepsis patients [8].

Severe rickettsial, viral, (e.g., Hantavirus pulmonary syndrome, Ebola virus disease, Lassa fever, Marburg virus disease, Crimean-Congo hemorrhagic fever), fungal, or some parasitic (e.g., malaria) infections can generate the same manifestation with sepsis [8].

Clinical Features

The occurrence of clinical findings is usually insidious. They can occur in the form of fever, mental fog, temporary hypotension, decreasing urine amount, or unexplained thrombocytopenia. If necessary actions are not taken or if sepsis is not treated, respiratory and renal failure, co-

agulation disorders, and irremediable hypotension can develop [9]. As summarized in Table 1, sepsis is divided into progressive clinical phases, and MODS is its severest clinical symptom [10].

Outcome

The mortality rate is high despite new developments in sepsis treatment. The mortality rate is reported to be between 20% and 80% [11]. Different mortality rates reported in these studies depend on the fact that the study groups were heterogeneous. The mortality rate is 45-50% in gram-negative bacterial sepsis, 20-30% in gram-positive bacterial sepsis, and 15-30% in anaerobic sepsis [5]. The mortality rate varies between 70% and 90% when shock, disseminated intravascular coagulation (DIC), ARDS, and other organ failure complications develop. Mortality rates also vary based on the causes. The highest mortality rate is reported in *Pseudomonas aeruginosa* sepsis [4].

Physiopathology

Sepsis has a complicated pathology, and it is not yet fully understood because it has a variety of clinical and physiopathological symptoms [12].

Host response

Sepsis is defined as the excessive and irregular response of the host against an existing infection [9]. After systemic inflammatory response syndrome (SIRS), i.e., an excessive proinflammatory condition, occurs at the beginning, compensatory anti-inflammatory response syndrome (CARS), i.e., an excessive anti-inflammatory condition, occurs. While SIRS results in shock-based mortality, immunosuppression in the advanced phase of CARS and sepsis lead to mortality due to secondary lethal infections. For many years, it was believed that pathogen invasion is responsible for the damage seen in sepsis. However, today, it is obvious that damage is substantially caused by an excessive uncontrolled host response [13].

It was found that the host is not passive in sepsis. The roles of indigenous inflammatory mediators in organ damage and noninfectious triggers also lead to the same inflammatory response, and the clinical response can be maintained even though the infection can be eradicated [14].

The most important factor in sepsis formation originates from the insufficiency of nonadaptive host factors. The deterioration in defense mechanisms protecting the host against infection paves the way for local or systemic infections. Host defense mechanisms include anatomic barriers, cellular immunity (phagocytic cells or lymphocytes), and specific and nonspecific humoral defenses [15].

Innate immunity

Macrophages, bacterial toxins such as lipopolysaccharides (LPSs), and proinflammatory cytokines are activated through the release of other mediators [16]. Pathogen-related molecular patterns in microorganisms, mainly antigen presenting cells, are recognized by receptors, which are called pattern recognition receptors (PRRs), found on the surface of the cells of the natural immune system [17]. As pathogen-related molecular patterns of microorganisms are recognized by PRRs in natural immune system cells, the natural immune response occurs. PRRs are proteins with different structures, and they constitute many receptor families [toll-like receptor (TLR) or collagenous lectins] [17].

In sepsis, bacterial products such as LPS from gram-negative bacteria, peptidoglycan and lipoteichoic acid from gram-positive bacteria, liparabinomannan from mycobacteria, fungal antigens, and prokaryotic DNA enter the circulation and start the immune response by means of the LPS binding protein, soluble CD14, membrane CD14, CD11/CD18 complex, and TLRs [18].

The hemodynamic, metabolic, and immune changes seen in sepsis occur through mediators and cytokines that play a role in intercellular signal transmission [19]. Cytokines show their effects not only by entering the systemic circulation but also by their direct cell-to-cell relationship and by very small concentrations [19]. With the uncontrolled activation of the natural immune response in sepsis, the recognition of macrophages and endothelial and epithelial cells of bacterial products such as LPSs or non-methylated CpG DNA fragments with their specific receptors results in the trigger of the cytokine cascade [such as the release of tumor necrosis factor- α (TNF)- α ; interleukin (IL)-1, IL-6, IL-8, IL-12, and IL-18; and interferon (IFN)- γ]. High-mobility group B1 (HMGB1) is a cytokine-like structure produced in macrophages, and it

occurs in the later phases of sepsis when compared to TNF and IL-1 [20].

Coagulation abnormalities

The function of coagulation in infection is to surround the infection and keep the inflammatory response local. However, its excessive activation leads to negative effects [13, 21].

Most of the cytokines released from the cells in sepsis stimulate thrombin formation. Firstly, the extrinsic pathway and then the intrinsic coagulation system are activated with the factor XII activation. Fibrin thrombi occur in the microvascular bed and contribute to organ failure. Consuming coagulation proteins leads to bleeding, and this is seen with both bleeding and thrombus development in the patients. On the other hand, fibrin is fragmented by the plasmin, which leads to fibrinolysis. Defined as DIC, this state is one of the most important reasons for the bad prognosis of sepsis [2].

Under normal conditions, coagulation is prevented by some natural anticoagulants, such as antithrombin (AT III), thrombomodulin, Protein C, Protein S, and tissue factor pathway inhibitor (TFPI) [22]. Beside the thrombin formation due to endothelium damage in sepsis, the thrombomodulin and endothelium protein C receptor functions are disrupted and the anticoagulant system is affected [22]. Thus, while coagulation is activated, fibrinolysis is inhibited. The reason is the increase in the two fibrinolysis inhibitors, PAI-1 (plasminogen activator inhibitor) and thrombin activated fibrinolysis inhibitor in sepsis. Protein C and AT III levels decrease due to the increase in consumption in sepsis and the reduction in the formation. Thus, the procoagulant and anticoagulant balance is disrupted, and procoagulant activity becomes prominent.

In particular, proinflammatory cytokines such as IL-1 and IL-6 strongly trigger coagulation. IL-10 inhibits the tissue factor release from monocytes and regulates coagulation. Other factors triggering coagulation in sepsis are the reduction in the anticoagulants naturally existing in the body, such as antithrombin, protein C, and tissue factor. Besides suppressing coagulation, these natural anticoagulants also attract attention with their anti-inflammatory properties. Protein C is important among the mentioned natural anticoagulants. It is activated as thrombomodulin, an endothelium membrane glycoprotein, and thrombin forms a common complex [9].

Anti-inflammatory mechanisms and immunosuppression

The excessive inflammatory response occurring in sepsis must be balanced, and is regulated by

the molecules, mediators, and cytokines showing the opposite effect. This immune suppression state is defined as CARS [12, 21, 23]. Soluble TNF receptors and IL-1 receptor antagonists can be given as examples of counter-inflammatory cytokines. IL-10 is the prototype of anti-inflammatory cytokines. In addition to these responses, an obvious increase in the metabolic activity (increase in cortisol production, increase in catecholamine release), induction of acute phase proteins, endothelium activation, increase in the adhesion molecules, prostanoids, and thrombocyte activation factor releasing also occur [9]. Lymphocyte apoptosis is an important reason for the suppression of immunity in septic patients. Interestingly, the increase in the lymphocyte apoptosis is similarly seen in non-septic patients in intensive care [11]. Septic patients are usually lymphopenic. Additionally, a reduction is seen in the B and CD4 lymphocyte subgroups in these patients. The decrease in the T-cell response and anergia seen in most of the septic patients is an excessive counter response to balance the proinflammatory response that occurs at the beginning. This can also lead to the development of organ failure, which can later occur [9]. Various researchers asserted that the prevention of immunosuppression can have a role in sepsis treatment. It was shown that preventing lymphocyte apoptosis in sepsis decreased the mortality rate after cecal ligation and penetration in experimental animals. In a small study where an interferon gamma treatment was used, a better survival was obtained in the septic patients [23].

Organ dysfunction

Usually, multiple organ failures develop in sepsis patients, and patients die. While firstly single organ failure develops in the patients, unless the sepsis origin is eliminated, multiple organ failure develops in the later phase. The death risk increases by 15-20% for each organ failure [24]. If there are four or five organ failures, the death rate goes above 90% [9].

Even though the pathogenesis of multiple organ failure is not exactly known, the main factors for its occurrence are the microvascular occlusion caused by fibrin accumulation, platelet activating factor, disruption of the microvascular homeostasis by vasoactive substances such as histamine and prostanoids, and further disruption of oxygenation with tissue exudate. Lysosomal enzymes released from neutrophils and reactive oxygen types directly damage the tissue. The inducible nitric oxide synthase enzyme excessively increases nitric oxide (NO) synthesis. The excessive increase in the NO amount leads to both vascular instability and myocardial depression. The oxy-

generation of the tissue is associated with mortality in sepsis, and survival increases as oxygenation of the tissue increases. In some patients, the mitochondria are not capable of using oxygen, and in those patients, cells are not able to use oxygen even if the oxygenation is normal [22].

The highest organ damage in sepsis is seen in the lungs, liver, kidneys, heart, and intestines. These are pathologic changes developing as a result of bacterial invasion, bacterial toxins and the direct effect of the enzymes. The effect occurs through the mediators, perfusion disorder, and DIC. Histopathological changes are characterized with the lesions including congestion, edema, fibrin thrombi, hemorrhage, and necrosis.

Treatment

The success of the treatment in sepsis depends on early diagnosis, immediately starting the appropriate antibiotic treatment and supporting treatment, and elimination of or recovery from the underlying disease. Protection is the most important way of reducing morbidity and mortality rates. Most of the attacks are nosocomial [7].

Sepsis treatment will be examined under two main headings: appropriate antimicrobial treatment and all-purpose supporting treatment. Each patient in the sepsis table should be definitely assessed in terms of resources, and if necessary, consultations should be taken in this respect [25].

Antibiotics are mostly given empirically during the time until the determination of the active microorganism. The first six hours are extremely important in terms of prognosis after the revelation of the sepsis symptoms and findings. It is known that the shock incidence is reduced by half with the appropriate antibiotic treatment no matter what the underlying disease is in sepsis developing from gram-negative bacteria.

The main target in septic shock treatment is regulating blood volume and providing sufficient tissue perfusion and tissues. To this end, the first thing to do is to regulate a sufficient liquid treatment [16]. With the liquid treatment, vasoactive drugs can be added to the treatment in the patients whose fluid deficit is met but they still have hypotension despite 15-18 mm Hg "pulmonary wedge" pressure [16]. Corticosteroids are another important agent shown to reduce death risk in sepsis treatment [26].

In a study by Rivers et al. [7], it was recommended to perform an erythrocyte transfusion and maintain the hemoglobin amount between 7 and 9 g/dL if the hemoglobin amount in the

blood is lower than 7 g/dL [27]. In patients with sepsis, heparin can be applied for deep venous thrombosis prophylaxis and stress ulcer prophylaxis [28].

In patients with sepsis, metabolic support should be provided in order to prevent malnutrition, to recover the metabolic condition, to regulate inflammation and acute phase response, and to reduce morbidity and mortality rates. To this end, it is necessary to provide nutritional support, meet energy requirements, and provide nitrogen and electrolyte balance [29]. Anabolic treatments such as glutamine and insulin are also used in patients with sepsis [30, 31].

When needed, organ-supporting treatments (respiratory failure and kidney failure treatments) should be used in sepsis treatment [24]. In particular, the load on respiratory muscles is reduced by timely intubation and mechanic ventilation, and sudden respiratory standstills are avoided [24].

Search for New Therapies

Failed approaches

It was shown that some drugs can change the metabolic response to stress. Cytokine antibodies or glucocorticoid receptor inhibitors blocked sepsis-related muscle breakdown in experimental studies (Breen, G. and A.R. Tunkel, *Adjunctive Therapies for Sepsis and Septic Shock*. Curr Infect Dis Rep, 1999. 1(3): p. 224-229.). However, there are insufficient data on clinical usage. In in-depth studies conducted on polyclonal immunoglobulin usage, there was no significant difference found in sepsis-based death and septic shock development rates. Therefore, polyclonal immunoglobulin usage is not recommended in patients with sepsis [32]. The role of the coagulation system in the sepsis pathophysiology is known, and no positive effect was seen in the survival of sepsis and septic shock patients in clinical study conducted with antithrombin III and tissue factor inhibitor [33]. Despite that, active protein C (APC) was found to be an anticoagulant reducing death rates in sepsis patients. APC is recommended in the early period in seriously ill patients as the most important side effect of APC is severe bleeding [25].

It was shown that immunity-boosting nutrition reduced infectious complications in intensive care patients. However, the up-to-date information is that it can be harmful to and should not be used in sepsis patients [30].

Glutamine had useful effects on mild sepsis patients brought about varying responses in severe

sepsis patients. Glutamine was reported to increase the mortality rate [30]. The use of glutamine in sepsis is still disputable [30].

It increases growth hormone antioxidant defense from strong anabolic agents and controls proinflammatory cytokines. However, it is reported that these positive effects do not lead to recovery from the clinical results and that they could be particularly harmful in patients with sepsis. No positive effect of endothelial nitric oxide synthase (eNOS) was observed on kidney functions [33]. Despite evidence regarding the relationship between TNF- α and kidney damage, no recovery could be observed in the survival rates in phase three studies. The inhibition of cyclooxygenase with ibuprofen in sepsis patients did not affect shock or kidney failure and did not have a positive effect on survival. Many anti-inflammatory treatments (monoclonal antibodies primarily developed against endotoxins) were used, but the effects in reducing the mortality rates could not be shown for most of these treatments.

The use of antioxidants can prevent the formation of free oxygen radicals in patients. However, even though animal experiments are not encouraging, conflicting results were obtained in some conditions such as ARDS and reperfusion damage. The general approach is replacing the missing antioxidants [34].

Experimental level studies have been conducted with natural or synthetic antioxidants, xanthine oxidase inhibitors (allopurinol), superoxide dismutase, catalase, NADPH oxidase inhibitors (such as adenosine), desferrioxamine, N-acetylcysteine, and vitamins C and E. Treatments using TNF- α , IL-1, thrombocyte activation factor, adhesion molecules, arachidonic acid metabolites, oxygen free radicals, bradykinin, NOS, etc. were attempted, but none of them were successful [35].

Beta-blockers, naloxane, nonsteroidal anti-inflammatory drugs (indomethacin or ibuprofen), antihistamines, and pentoxifylline were used in septic shock treatment but were not clinically used [16].

Concerns in therapeutic development

Most sepsis determinants are nonspecific, and they can be seen in many other circumstances. Therefore, there are delays in sepsis diagnosis, and physicians from different branches starting the treatment create differences in the treatment [23]. This leads to insufficient or incorrect treatment. Moreover, the fact that most patients have at least one comorbidity and that deaths can depend on these conditions rather than

sepsis explains the high death rate. The underlying disease and related deteriorations in the defense mechanisms of the host lead to more frequent infection by some microorganisms [6].

Failure to start a suitable antibiotic for a potential active microorganism or combined antibiotic application can do more harm than good. However, sometimes, administration for the treatment of the disease can also lead to deteriorations in the host defense mechanisms rather than the disease itself [6]. It was reported that the success rate of treatment would decrease in treatment in the case of failure to provide an all-purpose supporting treatment in the first 6 h following sepsis diagnosis [27].

New approaches

It is certain that more specific determinants are needed for sepsis treatment, and sepsis definitions should be reconsidered. Still, in recent years, there have been studies published that describe the treatment of sepsis patients. Most of these approaches aim to modulate or interrupt the sepsis physiopathology and prevent multiple organ failure. While some studies are in the early phases of the advanced phases (TNF- α antibodies, bactericidal/permeability-increasing protein, high hemofiltration, platelet-activating factor, etc.), some other approaches are in the advanced phase, and they have begun to affect results in intensive care units [19].

Several new approaches for reducing mortality rates in severe sepsis have been recently reported. These new approaches: Low tidal volume application, intense plasma glucose control in ARDS is a treatment for the target started in the earlier period (emergency service, central venous pressure, hourly urine output, and central venous oxygen saturation), and corticosteroid treatment in mean doses [3].

Corticosteroids do not increase survival when applied in high dosages in sepsis treatment, and it is known that they lead to secondary infections due to their immunosuppressive effects and adversely affect the clinical progress in sepsis [26]. However, it was shown that they reduced mortality rates when applied in low and high doses in the long term and shortened the shock period requiring use of the vasopressor [36].

LPSs, which play a role as endotoxins during sepsis, are eliminated by binding to LDLs and HDLs. It was seen that intense insulin application provided an increase in LDL and HDL levels, and it was claimed that this application could be a new method in sepsis treatment. Clinical studies continue to be conducted on other antiendotoxin

treatments for sepsis (methods such as anti-CD14 antibodies, "extracorporeal endotoxin absorption," and lipid A analogs) [37].

It was shown in vivo that being a pyruvic acid derivative, ethyl pyruvate inhibited the HMGB1 protein, and its positive effects were determined based on survival in experimental mouse models. This substance has also been attracting attention as it is effective when used in the later period as well. Hyperbaric oxygen (HBO) treatment is another method that is considered to be useful in sepsis. Phagocytic leukocytes are the first and most important defense line against microorganisms entering the body. The killing capacity of leukocytes substantially depends on the amount of oxygen given to them. HBO protects the host in aerobic septicemia and obviously increases the survival rate of the infected host by antibacterial activity. It was shown that HBO treatment affected NO production and NOS and eNOS expression. Moreover, the advantage of HBO in sepsis treatment could not be explained well [38].

Fibrates (fenofibrates) are used as triglyceride-reducing agents in clinics, and they display antioxidant and anti-inflammatory activities through peroxisome proliferator-activated receptor α activation. In experimental studies done on sepsis, it was observed that fenofibrate treatment reduced mortality rates by 12.5% and corrected the endothelium-based relaxing function [39].

Previously, levosimendan, which is a calcium-sensitizing drug with inotropic and other properties, was reported to improve outcomes in sepsis patients [40]. However, Gordon et al. [41] suggested that the addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality rates. Moreover, levosimendan was associated with a higher risk of supraventricular tachyarrhythmia.

In addition, we experimentally investigated several new therapeutic targets such as 5-HT₇ receptor agonist, salbutamol, aliskiren, amiodarone, lithium, montelukast, α -lipoic acid, and sildenafil for sepsis treatment. The beneficial effects of propofol administration on the inflammation of lungs after intravenous endotoxin administration has been shown in rats [42-50].

Conclusion

Studies show that sepsis is a highly important disease worldwide. Recent studies that focused on unclarified mechanisms underlying sepsis provided new treatment targets for clinicians.

Several treatment strategies such as balanced corticosteroid usage, antiendotoxin treatment, vasoactive agents such as levosimendan, HBO treatment, fibrates, and several antioxidant supplements are promising approaches for sepsis treatment. Because there are many experimental and clinical studies, there is a need for further research to develop new treatment methods.

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