

Sepsis and the Kidney: New Developments in Pathogenesis and Treatment

Sepsis ve Böbrek: Patogenez ve Tedavide Yeni Gelişmeler

ABSTRACT

Sepsis is a common and important cause of mortality in critically ill patients. Acute kidney injury (AKI) is one of the most important factors determining morbidity and mortality in this clinical picture. Recent studies have indicated that the pathogenetic mechanism in septic acute kidney injury (AKI) is totally different from that in non-septic AKI. Our understanding of sepsis-associated AKI pathophysiology is shifting from renal vasoconstriction, ischemia, and acute tubular necrosis to that of heterogeneous vasodilation, hyperemia, and acute tubular apoptosis.

Apoptosis is especially gradually gaining importance in the development of renal injury. In recently published studies, the frequency of renal tubular apoptosis on biopsies of septic patients has been pointed out. Apoptosis can be triggered by ischemia, exogenous toxins or endogenous mediators. In animal models, hyperglycemia, which is common in critically ill patients, has been shown to cause apoptosis in renal tubule cells.

In the light of recent findings, new treatment options have emerged. Treatment of hyperglycemia has a different significance, since besides anti-inflammatory effect it has a protective role on the kidney. Hemofiltration methods cleaning toxic mediators from the circulation should be applied in the early stages. Ghrelin that inhibits pro-inflammatory cytokines, caspase inhibitors that block the apoptotic pathway, and nitric oxide synthase inhibitors are currently under study. Regarding pathogenesis, rates of morbidity and mortality are aimed to be reduced through the new agents of therapy that are being studied.

KEY WORDS: Sepsis, Pathophysiology, Apoptosis, Renal failure

ÖZ

Sepsis yoğun bakım ünitelerindeki hastalarda mortalitenin sık ve önemli bir nedenidir. Akut böbrek hasarı (ABH) da bu tabloda morbidite ve mortaliteyi belirleyen en önemli faktörlerden biridir. Son yıllarda yapılan çalışmalar, septik akut böbrek hasarında patogenetik mekanizmanın septik olmayan akut böbrek hasarından tamamen farklı olduğunu göstermiştir. Sepsis ile ilişkili akut böbrek hasarının patofizyolojisi ile ilgili görüşler de, renal vazokonstriksiyon, iskemi ve akut tübüler nekrozdan, heterojen vazodilatasyon, hiperemi ve akut tübüler apoptoza doğru kaymaktadır.

Özellikle apoptoz, renal hasar gelişiminde giderek öne çıkmaktadır. Yakın zamanda yayımlanan çalışmalarda, sepsis hastalarından yapılan renal biyopsilerde tübüler apoptozun sıklığına dikkat çekilmiştir. Apoptoz, iskemi, eksojen toksinler veya endojen mediatörler tarafından tetiklenebilmektedir. Hayvan deneylerinde, yoğun bakım gerektiren hastalarda sık görülen hipergliseminin de böbrek tübül hücrelerinde apoptoza neden olduğu gösterilmiştir.

Bu yeni bilgiler ışığında yeni tedavi seçenekleri gündeme gelmiştir. Hiperglisemi tedavisi, antiinflatuvar etkisi yanında böbrek koruyucu rolü de olduğundan ayrı bir öneme sahiptir. Toksik mediyatorleri dolaşımdan temizleyen hemofiltrasyon yöntemleri erken dönemde uygulanmalıdır. Proinflatuvar sitokinleri inhibe eden ghrelin, apoptotik yolağı bloke eden kaspaz inhibitörleri, nitrik oksit sentaz inhibitörleri çalışma aşamasındadır. Patogeneze yönelik üzerinde çalışılan yeni tedavi ajanları ile morbidite ve mortalite oranlarının azalması hedeflenmektedir.

ANAHTAR SÖZCÜKLER: Sepsis, Patofizyoloji, Apoptoz, Böbrek yetmezliği

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Sepsis has always been one of the most important issues in medicine. Although its physiopathology has been enlightened to a great extent in the past two decades, it has still not been possible to decrease the mortality rate to a level below 40%. If a shock or multiple organ failure develops, the mortality rate increases to over 70% (1).

While the sepsis incidence is 1 per 10000 in a year, its annual rate of increase has been calculated as 9% (2). In our country, cases of gram (-) bacteremia in a period of seven years were evaluated and its incidence among clinical patients was found as 4.2% and the mortality as 45% (3). The fact that sepsis incidence has increased 140% in the last 20 years and 300-500 000 cases were reported annually prove both that the microorganisms in sepsis have been evolving and that there has not been sufficient success in the treatment.

Sepsis and septic shock are the most important causes in acute renal failure etiology and this group of patients constitutes 50% of acute kidney injury (AKI) patients in intensive care units (ICU). AKI incidence is 20% in sepsis, 23% in severe sepsis and 51% in sepsis shock. While the rate of mortality in septic patients with AKI is 74.5%, this rate has been reported as 45.2% in patients that have not developed renal failure (4). AKI that develops in the sepsis clinical picture is part of a multiorgan failure and has a remarkable effect on mortality rate. As most of the reported studies have been done on animal samples and contain contradictory results, the relationship with sepsis pathogenesis is not yet clear (5).

Sepsis, in its broadest meaning, could be defined as a systemic inflammatory response to an infection. Below are listed frequently used definitions related to sepsis:

- **Bacteremia:** Presence of living bacteria in the blood
- **Septicemia:** Bacteremia developing with a severe infection table
- **Systemic Inflammatory Response Syndrome (SIRS):** A series of systemic responses the organism developed against cases like infection, trauma, burn etc.
- **Sepsis:** SIRS which developed in the presence of a proven infection
- **Severe Sepsis:** Sepsis with evidence of hypotension and hypoperfusion
- **Septic Shock:** Clinical picture in sepsis in which hypotension continues and evidence of hypoperfusion does not improve in spite of the appropriate fluid treatment
- **Non-responsive Septic Shock:** A septic shock that lasts more than an hour and does not respond to any effective treatment

Systemic Inflammatory Response Syndrome (SIRS) is a definition used when two or more parameters in table 1 are present together.

Table I: Systemic inflammatory response syndrome (SIRS).

Response includes two or more of the following clinical conditions:
1. Temperature >38 °C or <36 °C
2. Heart rate >90 beats per min
3. Respiratory rate > 20 breaths per min or PaCO ₂ < 32 mm Hg
4. White blood cell count >12,000/ mm ³ , <4000/ mm ³ or >10% immature (band) forms.

The most important determinant in sepsis is the development of organ system dysfunctions. Of the system dysfunctions, the first to emerge is generally respiratory failure. Respiratory failure starts at an early phase and gradually increases. Increase in capillary permeability causes hypotension as a result of effective circulation volume leaking into the tissue. When peripheral vasodilatation, capillary leakages and arteriovenous shunts accompany hypotension, hypoperfusion occurs in all tissues and the clinical picture called multiorgan dysfunction syndrome develops (6).

PATHOPHYSIOLOGY

Enlightening sepsis pathogenesis is very important as regards new improvements in the phases of diagnosis, control and treatment. Researchers realized that the host doesn't remain passive against the infection and endogen inflammatory mediators with a wide spectrum are released which cause damage in the end. The triad of sepsis can be expressed as systemic inflammation, coagulation and impaired fibrinolysis (7,8).

Sepsis and severe sepsis, which occur together with organ failures, develop in the immunosuppression background. The biggest damage in the clinical table is the development of septic shock that occurs as a result of the exaggerated inflammatory response of the organism.

Leading to the development of parenchymal organ failures; disruption at the levels of immunosuppression, mitochondrial dysfunction, and microcirculation cause the high mortality rates in sepsis. Because of this, interactions between pathogenic microorganisms and natural immune system components are important in sepsis pathogenesis. Disruption of the four important balances of inflammatory - anti-inflammatory, coagulant - anticoagulant, oxidant - antioxidant, apoptotic - antiapoptotic, which have a very important role in providing homeostasis, is accepted to trigger organ failures and irreversible damage in sepsis (9).

Sepsis is a table characterized by an exaggerated inflammatory response; monocytes, macrophages, neutrophils, complement system and factor XII become active as a result of the triggering of endotoxin and other antigenic bacterial products. With the effect of both a direct antigenic triggering and other

activated cells and systems, endothelial cell stimulation occurs. Stimulated endothelial cells lead to the activation of coagulation and other fibrinolytic systems through nitric oxide (NO) release and tissue factor. Mediators and adhesion molecules increase as a result of the activated monocytes, macrophages, neutrophils and the complement system. Lysosomal enzymes and superoxide radicals are released. These lead to the development of capillary leakage, fever, metabolic and hormonal changes, vasodilation and disseminated intravascular coagulation (DIC). Thus, with sepsis syndrome, septic shock, acute respiratory distress syndrome (ARDS) and DIC tables, multiple organ dysfunction syndrome (MODS) develops, which, in the end might prove to be fatal (10, 11).

Some antigenic structures and toxins of microorganisms start the inflammation (table 2). The toxin on which the most research have been done is the gram negative bacterial endotoxin. Lipid A part of the endotoxin in the structure of lipopolysaccharide is responsible for the toxicity. Cell wall structural components of gram positive bacteria (peptidoglycan and teichoic acids), capsule antigens and exotoxins (toxic shock syndrome toxins [TSST] of *S. aureus*, pyrogenic toxins of *S. pyogenes*, the exotoxin A of *P. aeruginosa*), cell wall antigens of fungi, viral and parasitic antigens could also cause inflammation.

These antigenic structures and toxins start the stimulation by connecting to the CD14 receptor of the mononuclear phagocytic cells in the circulation. Tumor necrosis factor (TNF), interleukin 1 (IL-1), IL-6, IL-8, and the platelet activating factor (PAF) are released from the monocytes. IL-1 and IL-6 activates T cells, causing γ -interferon, IL-2, IL-4, granulocyte – monocyte colony stimulant factors (GM-CSF) to be secreted (Table 3) (6,7).

While these cytokines prove to be very useful in eliminating the local infection, they are synthesized in great quantities and enter into the circulation resulting in a widespread endothelial cell damage. Endothelial damage results in hemodynamic changes and organ dysfunctions. TNF causes neutrophils to stick to the endothelial cells by activating the adhesion molecules on the surface of the leukocytes. Proteases and toxic oxygen radicals releasing as a result of the degranulation of the activated neutrophils facilitate the damage of the endothelial cell (Figure 1). Moreover, release of arachidonic acid metabolites such as thromboxanes, prostaglandins and leukotrienes as a result of the direct effect of the endotoxin or the stimulation of cytokines leads to an increase in capillary permeability. Endothelial damage, increase of capillary permeability, accumulation of water in microcirculation and decrease of blood volume in the circulation result in a shock and organ dysfunction (12).

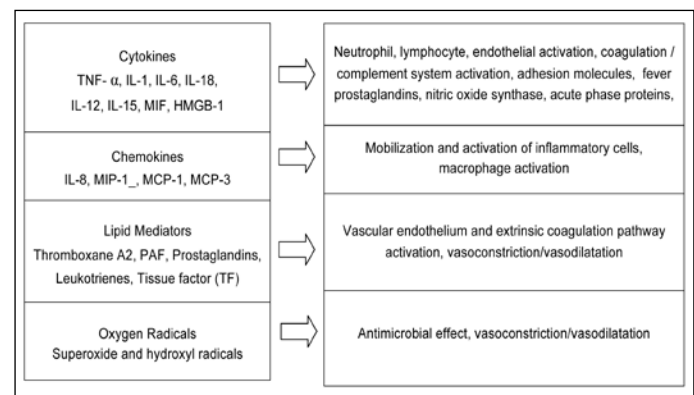


Figure 1: Mediators in the pathogenesis of sepsis (12).

Table II: Bacterial structures playing a role in septic shock pathogenesis (12).

Bacterial structure	Source	Example
Endotoxin (LPS, lipid A)	All of gram negative bacteria	<i>E. coli</i> sepsis Meningococcemia
Peptidoglycan Lipoteichoic acid	All bacteria Gram positive bacteria	
Exotoxins	<i>S. aureus</i> <i>S. pyogenes</i> <i>E. coli</i> <i>Aeromonas</i> spp.	A - hemolysin Streptolysin - O <i>E. coli</i> hemolysin Aerolysin
Superantigens	<i>S. aureus</i> <i>S. pyogenes</i>	Toxic shock syndrome toxin -1 Enterotoxin A-F Pyrogenic exotoxin A+C, SPE*
Enzymes	<i>S. pyogenes</i> <i>Clostridium perfringens</i>	IL-1b convertase Phospholipase C

*SPE: Streptococcal pyrogenic exotoxin

Table III: Inflammatory mediators in sepsis (12).

Host cell	Pro-inflammatory mediators	Regulatory mediators	Anti-inflammatory mediators
Monocyte/macrophage	TNF-a, IL-1, IL-8, IFN-g, tissue factor, prostanoids, leukotrienes, PAF, NO	IL-6 IL-12	IL-1Ra sTNFr TGF-b
Neutrophils	İntegrin expression, superoxide, TNF-a IL-1		BPI, defensins, acyloxy acyl hydrolase
Lymphocytes	IFN-g, TNF-a	IL-12	IL-4, IL-10, sIL-2r
Endothelial cell	Selectin, VCAM, ICAM, NO, tissue factor		
Thrombocytes	Serotonin, prostanoids	PDGF	
Plasma components	Coagulation cascade, complementary activation, bradykinin	CRP, LBP	

BPI, bacterial/permeability increasing protein; **CRP**, C-reactive protein; **ICAM**, intracellular adhesion molecule; **IFN-g**, interferon g; **IL-1Ra**, interleukin-1 receptor antagonist; **LBP**, lipopolysaccharide binding protein; **NO**, nitric oxide, **PAF**, platelet activating factor; **PDGF**, platelet derived growth factor; **sIL-2r**, soluble IL-2 receptor; **sTNFr**, soluble TNF receptor; **TGF-b**, transforming growth factor; **TNF**, tumor necrosis factor; **VCAM**, vascular adhesion molecule.

Endotoxin activates the complement system as well. Stimulating the released C3a and C5a basophile and mast cells, it leads to the secretion of some vasoactive mediators, principally histamine, most of which cause hypotension. C5a also activates the neutrophils and causes them to stick to the endothelial cells. Formerly known as the factor that depresses endothelium, nitric oxide (NO), which is secreted by the endothelial cell, is responsible for the widespread vasodilatation in sepsis.

One of the systems activated by the endotoxin is the coagulation system. In sepsis, most of the cytokines released from cells induce thrombin production and with the activations of, first, the extrinsic way and then factor XII, intrinsic coagulation system becomes active. Fibrin thrombus occur in microvascular bed, contributing to organ dysfunctions. Exhaustion of coagulation proteins causes bleeding, so, bleeding and thrombus development are seen together in patients. On the other hand fibrin is broken up by plasmin, thus, leading to fibrinolysis. This table, which is called the disseminate intravascular coagulation (DIC), is one of the most important causes of the poor prognosis in sepsis (6,7).

Compensatory Anti-Inflammatory Response Syndrome

Excessive inflammatory response emerging in sepsis is attempted to be balanced and regulated by molecules, mediators and cytokines displaying counter effect. Soluble TNF receptors and IL-1 receptor antagonists could be given as examples of counter-inflammatory cytokines. IL-10 is the prototype of anti-inflammatory cytokines. In addition to these responses, a

remarkable increase in metabolic activity (increase in cortisol production and catecholamine release), induction of acute phase proteins, endothelial activation, increase in adhesion molecules and release of platelet activating factor occur as well (Figure 2).

An important reason that the immunity is repressed in septic patients is the lymphocyte apoptosis. Septic patients are generally lymphopenic. In addition, a decrease in B and CD4 lymphocyte subgroups is also observed in these patients. Anergy and a decrease in T cell response seen in most of the septic patients is an excessive counter-response aimed to balance the pro-inflammatory response initially emerged. This situation

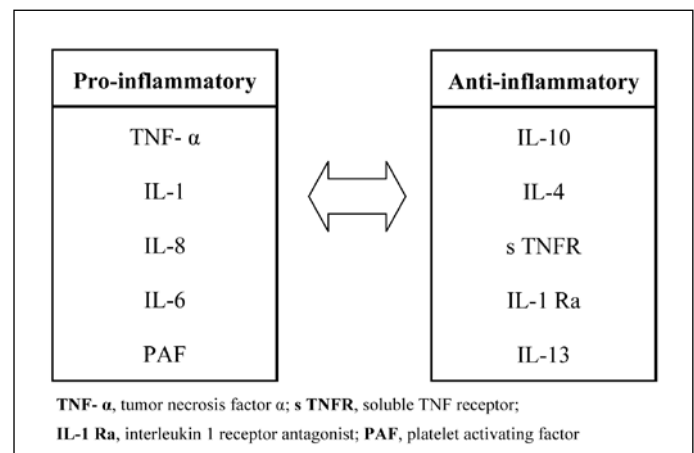


Figure 2: Cytokines in sepsis (13).

could lead to the development of an organ dysfunction that can occur afterwards. Various researchers suggested that prevention of the emerging immunosuppression might have a role in the treatment of sepsis. It has been demonstrated that prevention of lymphocyte apoptosis decreased the mortality rate in sepsis that occurs after the cecal ligation in subject animals. In another small study in which interferon gamma therapy is used, a relatively better rate of survival is obtained (6-8). If the compensatory anti-inflammatory reaction is excessive, a tendency to clinical anergy and infections occur. Upset of the balance between pro-inflammatory and anti-inflammatory mediators either leads to SIRS and uncontrolled hyperinflammation or triggers immunosuppression (14).

Septic Renal Damage

As carrying out recurring kidney biopsies is not ethical and the existing histopathological knowledge is not instructive, understanding the septic acute renal damage in humans is based on the knowledge obtained from animal studies and deductions from indirect evaluations (15).

In a systematic review on septic ABY histopathology, it has been reported that acute tubular necrosis (ATN) has been found in 22% of patients but the main common histopathological finding is the non-specific tubulointerstitial changes (16). In autopsy studies on patients with septic ABY, the ATN rate has been reported as 5%, while this rate has been found to be 0% in studies done with biopsies carried out from septic patients (16-19). Varying AKI definitions in different studies, the study subject being biopsy or autopsy material, patients in hypovolemic shock or taking high doses of furosemide being included are the main difficulties in the evaluation of the studies in this review. In consequence, the opinion that the histopathological findings in septic AKI vary within a range between completely normal findings and severe ATN, but contrary to the general thought, ATN is not, either, a frequent finding comes out on top as a general view (16).

Renal Cell Apoptosis And New Treatment Options

Apoptosis is a term in ancient Greek used for leaves that yellow and fall off the trees. Defined as a programmed cell death, apoptosis is the process of regular removal of unwanted cells through a molecular programme requiring active energy. Apoptosis is necessary for the organism to control the number of cells and the tissue volume and to protect itself from the unamenable cells threatening the homeostasis (20,21). Cells undergoing apoptosis contract rapidly, lose their intra-cellular connections and display dense chromatin intensification. As a result of apoptosis nuclear fragmentation, cytoplasmic granulation, cellular fragmentation and small apoptotic particles occur as well. These apoptotic particles are removed rapidly by the neighbouring cells and macrophages. It is difficult to determine the apoptosis in the preparations, which contain millions of cells, because the morphologic changes occurring in apoptosis take place and are completed in less than hour (22).

Many morphological changes seen in apoptotic cells are caused by the cysteine proteases active in these cells. These enzymes, which are called death enzymes, are generally similar to each other and belong to a big protein family called caspases (23). A dozen of caspases and more than 100 caspase substrates have been defined in humans, at least a third of which playing a role in the apoptosis process (24). Caspases are accepted as the central killers of the apoptosis process. Because, inhibition of caspases through mutation or using small molecules that bear inhibitor characteristics could slow down or completely stop the apoptosis process (24,25). Although it is accepted that the apoptosis process cannot be stopped once it has started, the pharmacological inhibition of caspases generally, if not always, saves the cells from apoptosis (26).

It has been shown that apoptosis occurs in renal diseases. Apoptosis can be triggered by ischemia, exogen toxins or endogen mediators. Apoptosis plays a role not only in starting the damage in the kidney but also in maintaining it as well. Mononuclear cellular infiltration, which consists basically of monocyte/macrophage and T cells, is characteristic in most of the renal diseases. Monocyte/macrophages secrete TNF- α , Fas ligand, free oxygen radicals and nitric oxide. In this way, inflammatory cells act as factors increasing the apoptosis (27).

The role of renal cellular apoptosis in septic AKI has been studied by using immune-mediated stimulants such as TNF. When high doses of TNF is added to the renal proximal cell cultures, DNA fragmentation and expressions of Fas messenger RNA and Fas related death zone protein increases (28). TNF and LPS affect the apoptotic cell death in glomerular endothelial cells, depending on time and concentration (29). This apoptotic activation is thought to occur very early in septic kidneys (15).

There is strong evidence to show that human renal tubular cells die by apoptosis as well as necrosis in experimental models of acute ischemic and toxic renal injury, such as glycerol-induced AKI (Gly-AKI), ischemia/reperfusion induced AKI (I/R-AKI) and lipopolysaccharide (LPS)-induced AKI (LPS-I-AKI). Hotchkiss and his friends demonstrated that not only necrosis but also apoptosis plays an important role in sepsis and septic shock (17). It has been claimed in a recent study that apoptosis is the most important factor in septic AKI. In this study post-mortem renal biopsies are applied to 19 patients who died of septic shock, 8 traumatic patients and 9 non-septic AKI patients. The histopathological findings observed in biopsies taken from septic AKI patients are reported to be acute tubular injury or necrosis in different degrees, leukocyte infiltration in glomeruli, interstitial capillaries and tubular lumen and apoptosis in tubular and rarely in glomerular cells. Thrombotic findings have rarely been seen. Acute tubular apoptosis hasn't been seen in non-septic AKI patients. While this study is the only controlled study evaluating biopsies taken from humans made after 1980, it has some drawbacks as well. As biopsies are taken from the traumatic patients just at the site of the accident,

it's probable that not enough time passed for the development of histopathological findings in the kidney. Another drawback of the study is that since the biopsies are taken post-mortem, the reversible changes expected to occur in recovering patients couldn't be observed (30).

The importance of treatment with caspase inhibitors in apoptotic-inflammatory AKI is increasing everyday. Indeed, caspase inhibitors ameliorate ischemia-reperfusion injury in different organs, including the kidney. Like caspase inhibition, treatment options blocking the apoptotic pathway are also promising (31). In a rat model of glycerol-induced AKI (Gly-AKI), caspases were found to participate in inflammation, apoptosis, vasoconstriction, and tubular necrosis. Early caspase inhibition attenuated these processes and significantly improved renal function (32). A recent study showed that extracorporeal therapy with polymyxin B therapy (PMX) reduced the pro-apoptotic activity of plasma of septic patients on cultured renal cells. It seems likely that plasma separation techniques can prove beneficial in renal injury through the removal of pro-apoptotic factors and cytokines (33).

Ghrelin, exerts renal protective effects by inhibiting pro-inflammatory cytokines, particularly TNF- α , in the circulation and the kidney. Ghrelin may thus hold promise for managing endotoxemia-induced AKI. Although further evidence confirming this beneficial effect is definitely needed, studies with this agent in septic AKI seem justified (34).

Vasopressor agents applied in septic AKI are also of importance. It has been shown in an animal model of septic shock, that usage of low dose arginine vasopressin causes less tubular apoptosis, systemic inflammation and renal damage when compared to noradrenalin (35).

It's been indicated in experimental studies with ischemia-reperfusion models that erythropoietin decreases apoptotic cell death and induces tubular proliferation (36). It has also been shown in a retrospective clinical study that erythropoietin decelerates the pace of developing a chronic renal dysfunction in pre-dialysis patients (37). However, high doses of erythropoietin might lead to renal vasoconstriction, hypertension and increased risk of thrombosis. Recently derived erythropoietins with no hematopoietic activity might prove to be safer in these patients.

Renal Hemodynamic Changes in Sepsis And Septic Shock

Although the renal ischemia that develops as a result of systemic hypotension in sepsis is considered to be a major factor responsible for AKI, it is not the only one. Production of inducible nitric oxide synthase (iNOS) is increased by cytokines (tumor necrosis factor α , IL-1, IL-8) released as a result of endotoxemia. As a result of this, nitric oxide that increased in circulation leads to arterial vasodilatation and decrease in systemic vascular resistance, which is the most evident hemodynamic change in sepsis. Decrease in arterial filling because of

vasodilatation activates the baroreceptors; after that, in nervous system, the renin-angiotensin-aldosterone pathway is activated through sympatic activation and arginin vasopressin release. As a result of all these, an increase is observed in the blood levels of vasopressor agents such as norepinephrine, arginin vasopressin and angiotensin and cardiac output also increases. This step is important in the protection of the unity of arterial circulation but at the same time, it causes renal vasoconstriction and lays the groundwork for AKI. The fact that renal denervation has been shown to be protective against AKI in an experimental endotoxemia model emphasizes the importance of neurohumoral pathway in pathogenesis (38,39).

It has been shown that in sepsis, much as in trauma, there is often a fluid deficit. When this deficit is met, cardiac output increases and peripheral vascular resistance decreases. As a result blood volume increases, extracellular fluid is enhanced. This phenomenon is called the hyperdynamic picture. Changes in renal blood flow in sepsis have been evaluated both in experimental studies and in studies on sepsis patients. Even though hemodynamics is normal in many experimental studies, a decrease has been observed in glomerular filtration rate (GFR) and renal blood flow. It has been reported that renal circulation isn't affected by the systemic vasodilatation in sepsis and that although cardiac output increases, renal blood flow due to selective renal vasoconstriction decreases. Yet, it has been seen in some studies that an AKI table has developed without a decrease in renal blood flow in septic table (40). Brenner and his friends placed a thermodilution renal blood flow catheter percutaneously in 8 intensive care patients with AKI and showed that septic ARF could develop although the total renal blood flow is normal (41).

It has been indicated that renal blood flow has increased and renal vascular resistance has decreased in an experimental severe sepsis and septic shock model formed by infusing *E. coli* into sheep. In this hyperdynamic sepsis model, GFR remarkably decreased, serum creatinine increased three times and the creatinine clearance decreased. In the recovery period cardiac output decreased, renal vascular resistance increased and renal blood flow decreased (42). These observations suggest that, in the first 24-48 hours of sepsis, renal vascular activity (vasodilatation) might be important in the loss of glomerule filtration pressure. Septic AKI could be considered as a hyperemic renal failure. The mechanism suggested is that afferent arteriole is dilated but on the other hand, as a result of efferent arteriole being dilated more, pressure inside the glomerule reduces in spite of the considerable increase in renal blood flow. How valid this mechanism is in the septic AKI table of humans hasn't been determined certainly (15).

It has been proved that intrinsic vasoconstrictor substances (endothelin, thromboxane A₂, leukotrienes, platelet activating factor..) are produced in kidney as a response to cytokines and to the activation of renin-angiotensin-aldosterone pathway.

Especially the endothelium released with the effect of TNF α is known to have a reducing effect on the volume of plasma through renal vasoconstriction and capillary permeability. On the other hand, it is reported that the amount of intrinsic renal vasodilators released during endotoxemia decreases as well. So, as is seen, this imbalance between the vasodilator and vasoconstrictor agents released from the kidney works in favor of intrarenal vasoconstriction. Glomerular perfusion and filtration rate and surface decrease as a result of the intrarenal constriction developing due to various mechanisms. Depending on the systemic hypotension and intrarenal vasoconstriction, prerenal AKI prevails in the table in the early phase of sepsis as a result of a decrease in renal blood flow and hypoxemia. At this phase, renal tubules haven't been affected and fractional excretion of sodium has decreased. But as the table proceeds, tubular cellular damage and acute tubular necrosis occur as a result of a long-term renal ischemia (43).

In some animal studies, some changes have been found in the intrarenal blood distribution and it has been indicated that renal blood flow is preserved and the flow has shunted from cortex to medulla. When all these are taken into consideration, we are led to think that renal ischemia is not the only factor in AKI pathogenesis, and mediators causing cellular damage (TNF α , IL-1 etc.) and other factors also have a role (43).

Kidneys are thought to be very sensitive to the damage depending on cytokines. For example, TNF α neutralization could prevent the lipopolysaccharide (LPS)-related renal failure (44). Endotoxin induces the TNF release from glomerular mesenchymal cells (45). In the sepsis model of mice, it has been indicated that a LPS-related AKI occurs as TNF connects to the TNF1 receptor in the kidney (46). Revelation of this relation between TNF and sepsis-related AKI leads us to think that toxic immunological mechanisms play a more important role in the renal damage in sepsis than the hemodynamic factors (15).

Another interesting point in septic AKI pathophysiology is the communication among the organs. In acute respiratory distress syndrome (ARDS), applying low tidal volume ventilation reduces the renal damage. Observation of apoptosis when renal cells are incubated into rabbit plasmas in which damaging ventilation methods are used lead us to think that this relationship between the organs might be with Fas-ligand mediators. In ARDS patients ventilated with high tidal volume, a significant relationship between plasma Fas-ligand levels and serum creatinine has been found as well (15,47).

Glomerular Changes

Decrease in the renal blood flow as a result of systemic hypotension reduces the glomerular perfusion pressure; and GFR decreases as well. It's indicated that GFR decrease in experimental sepsis models and septic patients is due to the decrease in the filtration fraction. Determiners of filtration fraction are the balance between glomerular afferent and efferent arteriolar

resistance and the total surface area for filtration. Contraction in afferent arteriole and/or dilation in efferent arteriole reduce the filtration fraction. Leukotrienes and vasoactive mediators such as TXA2 and AT II diminish the filtration surface area (48).

Endothelial Damage

As other vascular structures, glomerular capillaries, too, are influenced by the acute endothelial damage in sepsis. As a result of the activation of coagulation system by endotoxin, tissue factor release, thrombocyte and fibrin aggregation in the capillary and decrease in fibrinolytic activity, endothelial damage occurs. In addition, cytokines like IL-1b, TNF and PAF increase the neutrophil aggregation and toxic substance release in glomerular capillaries. In experimental endotoxemia, an increase in granulocytes in several renal structures has been observed. Proteases released from granulocytes, free oxygen radicals and vasoactive substances are among major factors in local renal damage and ischemia development (14). In sepsis related AKI, capillary microthrombus development has been found in some experimental and human studies (49).

Other Glomerular Lesions In Sepsis

The infection triggers immunological mechanisms and starts the acute glomerular inflammation. Acute proliferative glomerulonephritis in septic patients has been defined as a result of localized abscess and bacterial or rickettsial endocarditis. The infection triggers vasculitis too and also cause relapse. Vasculitis generally forms focal necrotizing glomerulonephritis in kidney. Most frequently seen vasculitis are Wegener granulomatosis and microscopic polyarteritis, but Henoch-Schonlein purpura, polyarteritis nodosa, systemic lupus erythematosus and Kawasaki disease could also be seen with severe infection. Goodpasture syndrome could rarely be triggered by sepsis (48).

Tubular Damage

In the kidney, ischemic or toxic damage primarily affects the tubules. Tubular epithelial cells provides sodium and water transport. Possessing a high metabolic activity, they are affected by the decrease in the renal blood flow to a great extent. Since tubular epithelium lose their basal membrane adhesion quality after necrosis or apoptosis, they are excreted to the tubular lumen. In the urine, these cells are seen in the shape of tubular epithelium cylinders or granular cylinders. These types of cylinders cause microobstruction in the urine flow. Waste materials, cellular debris and Tamm-Horsfall protein pile up in the damaged tubular basal membrane (50).

PROGNOSIS

Age of the patient, underlying reasons and physiological variables of many kinds affect prognosis. Underlying diseases is the most important reason affecting the mortality rate. Septic shock significantly increases mortality. Mortality rates in culture positive and culture negative sepsis are similar. Previous chronic

diseases or advanced age reduces the physiological reserve and lays the groundwork for sepsis and MODS. Mortality rate increases according to the number of organs affected in MODS (14). In a univariate analysis, mortality has been associated with age, pneumonia, peritonitis and the number of organs with dysfunctions. In a multivariate analysis, it has been found that three variables affect the result. These are; age over 60, pulmonary failure and hemodynamic failure (51). Especially, co-presence of pulmonary and renal failures is one of the most important factors threatening life.

LABORATORY FINDINGS

In the early phase, leucocytosis, shunting to left, thrombocytopenia, hyperbilirubinemia, proteinuria are seen. Toxic granulation, Dohle corpuscles, cytoplasmic vacuoles might be found in neutrophils. Leukopenia might develop as well. In later phases, thrombocytopenia becomes severe, coagulation abnormalities (DIC) are added. In course of time azotemia, hyperbilirubinemia, aminotransferase elevations and hemolysis becomes more evident. During early sepsis, hyperventilation induces respiratory alkalosis. With respiratory muscle fatigue and accumulation of lactate, metabolic acidosis (with an increased anion gap) typically supervenes. Arterial blood gas analysis reveals hypoxemia, which is initially correctable with supplemental oxygen but later refractoriness to 100% O₂ inhalation indicates right to left shunting. The chest radiograph may be normal or may show evidence of underlying pneumonia, volume overload or diffuse infiltrates of ARDS (14).

One of the most important sepsis-related laboratory parameters that should be focused on is the high lactate level. Lactate level is used as a global indicator of perfusion and the adequacy of oxygenation and microcirculatory dysfunction (52). Sepsis is a hypermetabolic syndrome and is usually with increase in glycolysis and high lactate levels. It should be kept in the mind that the increased plasma lactate level in sepsis is not a certain indicator of tissue hypoxia. In studies in which tissue PaO₂ measures are calculated, lactic acidosis presence without tissue hypoxemia has been found.

A high lactate level could be encountered due to the decrease in its hepatic clearance as well. Rather than one lactate value, the trend of lactate concentrations is more important. Especially the lactate trend is a strong determiner for the outcome in septic shock and 'lactime' (lactate clearance time) is closely related to the septic process. Blood lactate concentration has been proved to have a better prognostic importance than mixed venous saturation (SvO₂) value (53).

Role of Biological Determiners in Diagnosis

Early detection of the infection is generally difficult in critically ill patients. C-reactive protein (CRP) and white blood cell counts, which are the determiners of inflammation, aren't sufficient in determining the need for antimicrobial therapy. For

instance, if there is a case of liver failure in severe sepsis, it is difficult for such a patient to give a sufficient CRP response to the infection (54). Besides, patients might have fever, leukocytosis and increased CRP levels without the case of an infection. Procalcitonine (PCT) has been reported to give better results than the clinical findings in the determination of an infection. Importance of procalcitonine in the diagnosis of an infection, in directing the treatment and in risk determination has been mentioned (55-57). Determining the appropriate dosage in the antibiotic treatment is especially important in terms of the prevention of insufficient dosage, affectivity of the therapy, resistance development, side effects and the cost. It has been determined that, directing the antibiotic treatment with PCT in patients having a lower respiratory tract infection, cause a reduction in antibiotic usage without showing a negative effect on the result (58).

In sepsis treatment, apart from the biological determiners already in use (procalcitonine, CRP), Mid-pro-Anp (Mid-pro-atrial natriuretic peptide), LBP (Lipoprotein binding protein), sTREM-1 (Soluble triggering receptor expressed on myeloid cells-1) could be listed among the molecules on which studies are continuing and which are possible to be used in the future (59).

TREATMENT

Sepsis treatment could be examined in three basic principles:

- i) Eradication of the infection through the control of the source
- ii) Hemodynamic resuscitation of hypoperfusion
- iii) Supportive approaches aiming to prevent organ dysfunctions menacing life

The first steps of the treatment should aim to stabilize the patient and then therapeutic approaches covering a longer term should be adopted (60).

In 2003, a number of intensive care and infectious diseases specialists representing 11 international institutions came together under the name of Surviving Sepsis Campaign (SSC) and developed a guide for sepsis and septic shock care that will provide practical use for physicians (61). Today, this guide is still considered as the most useful suggestions of treatment based on proofs; and in 2008 its first revision containing the developments since 2004, the year of its first publication, was published (62).

Early Antibiotic Therapy and Control of the Source of the Infection

The first step when SIRS is detected and the existence of an infection is suspected should be to determine the source of the infection, to take cultures for this purpose and to start antimicrobial therapy as soon as possible. Appropriate and early antibiotic therapy reduces the mortality. Intravenous antibiotic therapy should start in the first hour of the diagnosis, just after taking the cultures. In a study investigating the prevalence of delay in start-

ing the effective antimicrobial therapy and its effect on mortality, it has been found that only in the 50% of the septic patients, antibiotherapy could be started in the first 6 hours although the mortality rate increases proportionally to the duration of the delay (63).

Empirical antibiotherapy should contain one or more drugs that effective against possible pathogens (bacterial or fungal). The treatment should be done with one or more antibiotics with a good penetration and according to the sensitivity model in the community and the hospital; a wide-spectrum antibiotic treatment should be continued until the microorganism and its sensitivity is determined. The treatment should be evaluated again after 48-72 hours, the duration of the antibiotherapy should be 7-10 days, and then it should be directed according to the response. If the clinical syndrome is due to a non-infectious reason, then, taking the development of resistance into consideration, antibiotherapy should be stopped.

Renal Protection

Many pharmacological drugs have been tried that are claimed to be able to protect kidneys from AKI. Renal dose dopamine (1-3 µg/kg/m) is widely used. In lower doses, too, there is the vasoconstrictor and inotropic effect and increase in renal blood flow is dependent on the blood pressure and cardiac output. It has been shown that dopamine doesn't have a positive effect on the functions of the kidney, frequency of dialysis or survival; on the contrary its potential negative effects on the immune, endocrine and respiratory systems are pointed out (It has got some side effects such as mesenteric ischemia and hypophysis suppression). Calcium antagonists are used to prevent the vasoconstriction due to calcium but it isn't found to be useful as it might worsen the hypotension. Loop diuretics and mannitol prevents the development of oliguric AKI, but it couldn't be indicated that it has ever improved the overall result (14). It is thought that mannitol shows its protective effect by preventing the cells from swelling and by increasing the tubular flow and reducing the intratubular obstruction. In the studies on humans, no positive effects of mannitol on the prevention and treatment of ischemic or toxic AKI could be shown; on the contrary, it is reported that it has a negative effect on contrast nephropathy (especially in diabetic patients). Its renal protective effect is shown to be at maximum level in compression type of injuries associated with rhabdomyolysis, when applied at rather early stages and added to organ preparation solutions during the renal transplantation (64).

Early-Goal Directed Therapy

Early-goal directed therapy has been proved to have a positive effect on survival. It has been proved that in septic patients with a systolic blood pressure of <90 mmHg, keeping CVP at 8-12 mmHg, average arterial pressure (OAP) ≥65 mmHg, urine output ≥0,5 ml/kg/hour and lactate level < 2 mmol/L decreases the mortality rate and time for stay in the intensive care unit and

ventilator. This protocol decreased the ABY rate from 55.2% to 38.9% when compared to the standard treatment. In this approach the goal of the treatment is to achieve the parameters of OAP ≥ 65 mm Hg (with fluid + vasoconstrictor), urine output ≥ 0.5 ml/kg/hour, CvO₂ (central venous O₂ saturation) ≥ 70% in the first 6 hours. If this goal isn't achieved with fluid resuscitation in the first 6 hours and the central vein saturation remains below 70% although the central vein pressure is between 8-12 mmHg; erythrocyte transfusion and/or Dobutamine (max 20 µg/kg/min) infusion is recommended until the hematocrit is ≥ 30 % (62).

Fluid Therapy

Fluid therapy should urgently be started when findings of tissue perfusion disorder are observed and it should be watched with central filling pressures. Watching the central vein pressure and pulmonary capillary wedge pressures is important in reducing the risk of pulmonary edema. The EGDT protocol emphasizes that keeping CvO₂ at or over 70% is one of the most important end points of resuscitation. For the fluid replacement in septic shock, loading fluid with regular intervals (500-1000 ml crystalloid or 300-500 ml colloid in 20-30 min) is recommended with filling pressures being watched closely.

There is still some dispute over what type of fluid should be used in sepsis for fluid resuscitation. In fact, rather than the type of the fluid its amount is of importance. In order to obtain the same response, crystalloids are applied in higher volumes. As a result, they lead to a risk of edema development by escaping to the extravascular space. Colloids, too, have unwanted side effects peculiar to themselves. In studies about colloids, albumin was particularly focused on, and when compared to crystalloids, no significant advantage could be obtained of its effects over the survival (65). Today, it is accepted that crystalloids or colloids have no superiority over one another (62).

Vasopressor or Inotropic Therapy

For cases in which sufficient blood pressure and organ perfusion couldn't be obtained through fluid resuscitation and for those having a life-threatening hypotension during fluid resuscitation, vasopressor therapy should be chosen. First agents to select to improve hypotension in septic shock are norepinephrine or dopamine. Norepinephrine is stronger and could be more effective in improving the hypotension. Dopamine might prove to be useful in patients whose systolic functions are at limits. Its potential to cause tachycardia is higher and it could prove to be arrhythmogenic. Adrenaline, phenylephrine and vasopressin shouldn't be preferred as first agents in septic shock. When the blood pressure is weakly responsive to noradrenaline and dopamine, adrenaline could be used as a first alternative in septic shock. To protect the kidneys in sepsis, low-dose dopamine should not be used. In patients with a refractor shock, vasopressin could be used alone or in addition to norepinephrine, its infusion rate being 0.01-0.04 unit/min in adults. It could reduce cardiac

output and even, when taken in high doses, it is claimed to lead to cardiac, digital and splanchnic ischemia. In the 2008 revision of Surviving Sepsis Campaign, its usage with norepinephrine is considered to be in the list of weak suggestions (62). However, popularity of vasopressin is increasing. It has been shown in an animal model of septic shock, that usage of low dose arginine vasopressin causes less tubular apoptosis, systemic inflammation and renal damage when compared to noradrenalin (35).

Steroid Therapy

Although the corticosteroids are thought to be useful in sepsis because of their anti-inflammatory effects, their usage in high doses in sepsis didn't reduce the mortality and brought about the risk of a secondary infection and some new complications. In an international, multi-center, randomized study (on 499 patients), it couldn't be proved that they have a positive effect on the mortality or on reversing the shock (66). Regardless of ACTH test results, steroids could reverse the shock only in early stages. If hypotension isn't giving an adequate response to fluid and vasopressors in septic shock, intravenous hydrocortisone could be given. Steroids shouldn't be used when there isn't a shock. When there remains no need for vasopressors, the steroid therapy should be stopped (62).

Glycemia Control

Hyperglycemia is frequent in intensive care units and in critically ill patients and has negative effects on morbidity and mortality. While hyperglycemia might be due to a previously known diabetes mellitus, the patient, being diabetic or pre-diabetic, might not have been diagnosed before. Moreover, hyperglycemia might develop only during the hospitalization due to the stress of the illness and when this stress disappears, glycemia might return to normal levels. This hyperglycemia seen in non-diabetic subjects is known as stress hyperglycemia (67). In healthy individuals the plasma glucose are kept within a narrow range by insulin and counter-regulatory hormones (glucagon, epinephrine, cortisol and growth hormone) balancing the glucose metabolism between the liver and peripheral tissues. In cases of stress, however, counter-regulatory hormones increase and this, while increasing the glucose production, decreases the usage of glucose by peripheral tissues, thus causing hyperglycemia (67,68). Apart from stress hyperglycemia, factors such as usage of steroids and vasopressor agents, immobilization and enteral and parenteral nutrition or fluid infusions containing excessive amounts of glucose also contribute to the hyperglycemia in intensive care patients. Hyperglycemia has also some negative effects such as fluid imbalance, immunosuppression, increase in inflammation, leukocyte dysfunctions, tendency to thrombosis and endothelial dysfunction (68).

It has been indicated in various studies that control of glycemia causes endothelial and mitochondrial protection and decreases the systemic inflammation (69, 70). With a tight glucose control, a remarkable decrease in mortality and morbidity

has been observed; and, in patients requiring intensive care for more than 5 days, there has been a decrease in the time they stay in the intensive care and in the development of renal failure. Also, a 46% regression in sepsis and a less critical disease polyneuropathy has been observed (70). Yet, tight glucose control bears a risk of hyperglycemia. NICE-SUGAR (Normoglycemia in Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation) study comparing the intensive insulin therapy with the traditional insulin therapy in intensive care patients, is one of the most comprehensive study on this subject (71). In this study a significant increase in mortality has been observed in the group in which intensive insulin therapy has been applied when compared to the traditional therapy group. Considering, too, the risk of hypoglycemia in general meaning, glucose level should be kept below 150 mg/dl. When a glycemic control strategy is started, a nutrition protocol in which, preferably, the enteral way is used should be adopted. The risk of hypoglycemia should be reduced by providing a continuous glucose support (72).

Apart from reducing the glycemia, insulin therapy is claimed to have some other independent effects. It is reported in some recent publications that it has a protective effect on kidneys. It is thought to prevent AKI in sepsis with its anti-inflammatory and -on tubular epithelial cells- anti-apoptotic effects (73). Although the protective role of insulin on the kidney couldn't be clearly explained, some mechanisms regarding to it have been suggested. Its effects on the lipid metabolism have been studied. In critically ill patients hypocholesterolemia (low levels of LDL and HDL) and hypertriglyceridemia are seen and intensive insulin therapy has been shown to improve this profile. Improving of the lipid profile, especially increase in LDL could be considered as a mechanism of the protective effect on kidneys. This analysis doesn't substantiate a cause-effect relationship but at least suggests that the improved lipid profile and especially the elevation of the LDL levels may represent one potential mechanism for the renoprotective effect of intensive insulin therapy, consistent with previous observations in an animal model of renal ischemia-reperfusion (74).

The damage of hyperglycemia to the endothelial cells are described in ischemia/reperfusion mediated ABH models. ICAM-1 and E selectin levels are high in ABH. In animal models, antibodies against ICAM-1, antisense oligonucleotides and E-selectin inhibition in ischemic damage, have been shown protective effects on kidneys. Therefore, it is stated that the protective effect of intensive insulin therapy on the endothelium could be observed on kidneys, too (74).

Mechanic Ventilation in Sepsis-Related Acute Pulmonary Damage

High tidal volumes leading to high plateau pressures (> 30 cm H₂O) should be avoided. According to the body weight, a tidal volume of 6ml/kg should be aimed. If necessary, hypercapnia could be permitted in order to reduce the plateau pressures

and tidal volume. At the end of the expiration, optimal positive expiration end pressure (PEEP) should be applied in order to prevent the pulmonary collapse. In patients needing high levels of FiO₂ or exposed to high plateau pressures and wouldn't be affected by position changes, the facedown position should be considered, and, unless contraindicated, the head of the bed should be raised 30° in order to prevent ventilator-related pneumonia (62).

Renal Replacement Therapy

Application of hemodialysis in the treatment of sepsis-related AKI reduced the mortality to 50% from 90%. Continuous renal replacement therapy (CRRT), besides fluid and urea clearance, removes proinflammatory cytokines from the blood. It is preferable to intermittent hemodialysis (HD) in patients whose hemodynamics isn't stable. After intermittent HD a solute increase takes place as a result of the rebound effect. CRRT is more physiological and provides a continuous clearance. In a study in which different filtration rates are compared, applying more ultrafiltration with continuous veno-venous hemofiltration (CVVH) caused an improvement in survival. In this study, it was found that septic patients benefitted from the increase in the dose of dialysis from 35 ml/h/kg to 45 ml/h/kg more than other critical patients (75).

This discovery brought forward the high volume hemofiltration in the treatment of sepsis-related AKI. Animal models have shown that high volume hemofiltration in endotoxemia improves in hemodynamics and survival. But in controlled studies it couldn't be proved that it causes significant cytokine clearance. In a controlled, randomized study, patients to whom 2L/h CVVH was applied were compared with those that didn't receive hemofiltration and levels of cytokine and anoflotoxin in the circulation weren't found to be different (76). A recent study showed that extracorporeal therapy with polymyxin B therapy (PMX) reduced the pro-apoptotic activity of plasma of septic patients on cultured renal cells. It seems likely that plasma separation techniques can prove more benefit in renal injury through the removal of pro-apoptotic factors and cytokines than traditional renal replacement therapies (33).

Nitric Oxide Synthase Inhibitors

Nitric oxide release in sepsis causes myocardial depression, non-responsiveness of vascular smooth muscles to the catecholamines and vasodilatation leading to the refractor hypotension. With free radical formation, NO in excessive amounts displays a direct cytotoxic effect.

NO synthase enzyme is seen in three forms: neuronal NO synthase (nNOS) and endothelial NO synthase (eNOS) are seen in healthy cells and are calcium (Ca)-dependent. Inducible NO synthase (iNOS) isn't Ca-dependent and induced by inflammatory cytokines. NOS inhibitors improve hypotension in septic patients, but this treatment reduces the cardiac index and oxygen

distribution (77). L-mono-methyl form of arginine (L-NMMA), is an analogue of L-arginine and inhibits all forms of NOS. It has been used in 312 patients with refractory septic shocks. Survival didn't change in the 14th and 28th days but, when compared to the traditional treatment, the shock was improved in most of the patients and there remained no need for a vasopressor support (78). Usage of NOS inhibitors in inappropriate doses could cause vasoconstriction and microcirculation disruptions in various organs. Usage of L-NMMA in patients with pulmonary hypertension might lead to a fatal right heart failure.

L-NMMA usage in healthy volunteers has decreased the renal plasma flow and the GFR. Excessive NOS inhibition is thought to be nephrotoxic and the need for selective iNOS inhibitors is emphasized. In the near future, the NOS antagonism could be a suitable option in patients with unstable hemodynamycs (14).

CONCLUSION

Sepsis-related ABH continues to be a very serious health problem today, causing significant amounts of losses due to its high incidence and mortality rate. The main reason for this is that its pathogenesis hasn't been sufficiently understood. In recent studies the view that the main pathogenetic factor in septic renal damage is not hemodynamic failures or ischemia as is thought but it is inflammation and renal cellular apoptosis that act as the main agents gained priority. As a result, searches for the therapy shifted to that direction and agents aiming to suppress apoptosis and inflammation are currently being considered. In the light of these new findings it is inevitable that the stereotyped treatment algorithms should change. Among the existing methods of treatment, usage of arginine, which is a vasopressor agent, hyperglycemia treatment, ventilation with a low tidal volume, hemofiltration methods removing inflammatory cytokines from the blood should be considered in the first place. As the mortality rate is high it would be appropriate to individualize the treatment and to plan it according to the needs of the patient.

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