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Drugs and procedures | Lijekovi i metode

Vasopressors and inotropes in sepsis

Vazopresori i inotropi u sepsi

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Descriptors
SEPSIS – drug therapy;
SHOCK, SEPTIC – drug therapy;
HYPOVOLEMIA – therapy;
CRYSTALLOID SOLUTIONS – therapeutic use;
HYPOTENSION – drug therapy;
VASOCONSTRICTOR AGENTS – therapeutic use;
NOREPINEPHRINE – therapeutic use;
EPINEPHRINE – therapeutic use;
CARDIOTONIC AGENTS – therapeutic use;
DOBUTAMINE – therapeutic use;
CRITICAL CARE

SUMMARY. Sepsis is defined as a dysregulated host response to infection, while septic shock is a consequence of severe sepsis, followed by hypotension that is not reversed with fluid resuscitation. These life-threatening conditions require urgent treatment and remain one of the leading causes of death worldwide. Hypovolemia and low systemic vascular resistance are significant risk factors for mortality in sepsis and septic shock. One of the goals of the global initiative to improve prognosis among patients with septic shock, the Surviving Sepsis Campaign (SSC), is the maintenance of mean arterial pressure (MAP) above 65 mmHg. Achieving this value and ensuring adequate tissue perfusion require significant amounts of resuscitation fluid. Although the debate on the preferred type of fluid continues, recent studies suggest against using hydroxyethyl starches, as their use is associated with poor prognosis, and advocate for crystalloids as the fluid of choice. Patients in whom target MAP values cannot be achieved with fluids alone are candidates for vasopressor or inotrope therapy. Norepinephrine (a potent α-adrenergic agonist with moderate β-adrenergic effects) is the first-line vasopressor therapy, with the benefit of improving blood flow to the splanchnic circulation and a lower incidence of arrhythmias. Epinephrine is recommended as second-line therapy and can be used alone or in combination with norepinephrine. Phenylephrine (a pure α-agonist) should not be used alone as it may decrease stroke volume, except as a salvage therapy combined with other vasopressors or inotropes. Vasopressin is recommended in combination with norepinephrine, but not as a monotherapy. Dopamine is not recommended for renal protection and should only be used in highly selected cases. Dobutamine remains the drug of choice for patients with myocardial dysfunction and signs of inadequate tissue perfusion, even after achieving adequate MAP.

Deskriptori
SEPSA – farmakoterapija;
SEPTIČKI ŠOK – farmakoterapija;
HIPOVOLEMIJA – liječenje;
KRISTALOIDNE OTOPINE – terapijska uporaba;
HIPOTENZIJA – farmakoterapija;
VAZOKONSTRIKTORI – terapijska uporaba;
NOREPINEFRIN – terapijska uporaba;
EPINEFRIN – terapijska uporaba;
KARDIOTONICI – terapijska uporaba;
DOBUTAMIN – terapijska uporaba;
INTENZIVNO LIJEČENJE

SAŽETAK. Sepsa se definira kao neadekvatan i poremećen odgovor organizma na infekciju, a septički šok je posljedica teške sepse praćene hipotenzijom koja ne reagira na nadoknadu tekućine. Ovo životno ugrožavajuće stanje, koje zahtijeva urgentno prepoznavanje i liječenje, i dalje predstavlja velik zdravstveni problem s visokom stopom smrtnosti. Hipovolemija i niska sistemska vaskularna rezistencija značajni su čimbenici rizika za smrtnost u sepsi i septičkom šoku. Jedan od glavnih ciljeva i preporuka jest dostizanje i održavanje srednjega arterijskog tlaka iznad 65 mmHg. Postizanje ovog cilja i zadovoljavanje adekvatne perfuzije tkiva zahtijeva nadoknadu velikih količina tekućine. Rasprava o najboljoj tekućini i dalje postoji, ali dosadašnje studije pokazale su prednosti slanih kristaloidnih otopina u odnosu na koloidne čija je primjena povezana s lošijom prognozom. Bolesnici kod kojih se prethodno spomenute vrijednosti srednjega arterijskog tlaka ne mogu postići s tekućinama kandidati su za primjenu vazopresornih i inotropnih lijekova. Prvi lijek izbora među vazopresorima jest noradrenalin (potentni α-adrenergički agonist i manje potentni β-adrenergički agonist). Njegove se prednosti očituju u tome što ima sposobnost povećanja krvnog protoka kroz sustav splanhničnе cirkulacije i manji rizik srčanih aritmija u usporedbi s drugim lijekovima. Lijek drugog izbora po preporukama jest adrenalin i treba ga koristiti kao dodatak noradrenalinu ili kao lijek prvog izbora ako adenalin pokaže neke značajnije neželjene učinke. Fenilefrin (čisti α-agonist) nije u preporukama, s obzirom na to da može smanjiti udarni i minutni volumen srca, osim kao spasonosna terapija u kombinaciji s drugim vazopresorima ili inotropima. Vazopresin se preporučuje u kombinaciji s noradrenalinom, ali ne i kao samostalni lijek. Preporuke ne podržavaju primjenu dopamina kao renoprotektivnog lijeka koji treba koristiti samo u određenim indikacijama. Dobutamin ostaje zlatni standard kod bolesnika sa srčanom disfunkcijom i znacima neadekvatne tkivne perfuzije i pored postignutih preporučenih vrijednosti srednjega arterijskog tlaka.

Sepsis is a complex disorder that occurs as a result of the host's inadequate response to infection and is associated with acute organ failure and a high mortality rate.[1] It is a critical health issue that requires urgent recognition and treatment because any delay reduces survival rates. Over the past 30 years numerous studies and research have been conducted, resulting in faster recognition of septic patients through the use of adequate scoring systems.[2,3] In 2017, the World Health Organization declared sepsis a health priority and adopted measures concerning the improvement of prevention, diagnosis, and treatment.[4]

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Definition

The definition of sepsis has undergone many revisions since it was first defined in 1992 as an inflammatory response to infection, based on two or more criteria (hypo/hyperthermia, leukocytosis/leukopenia, heart rate >90/min, respiratory rate >20/min) from the systemic inflammatory response syndrome (SIRS) with a suspected or confirmed source of infection.[5] In 2001, a criterion for evaluating organ dysfunction, the SOFA score, was introduced, indicating severe sepsis.[6] In 2016, the Third International Consensus on Sepsis and Septic Shock defined sepsis as life-threatening organ dysfunction due to an inadequate host response to infection, and septic shock as sepsis with circulatory, metabolic, and cellular abnormalities.[7] Organ dysfunction is defined as a SOFA score >2 and is accompanied by persistent hypotension (MAP <65 mmHg) and increased serum lactates >2 mmol/L after fluid resuscitation. Septic shock carries a mortality rate of approximately 40%, while sepsis alone carries a mortality rate of about 10%.[1]

Etiology

Sepsis can be caused by any microorganism (bacteria, viruses, fungi, parasites). Approximately 80% of sepsis cases occur as a result of infections in outpatient settings. The most common sites of infection are the lungs (64%), abdomen (29%), blood (15%), and kidneys/genitourinary tract (15%).[10–12] The most common causative agents among Gram-positive bacteria are *Staphylococcus aureus*, while in Gram-negative sepsis, *Pseudomonas* sp. and *Escherichia coli* are frequently involved.[10,14]

Sepsis triggers an immune response via Toll-like receptors on immune cells, leading to the release of pro-inflammatory and anti-inflammatory mediators. Cytokines such as TNF-α, IL-1, IL-6, and IL-8 promote neutrophil adhesion to endothelial cells, activation of the complement system, and the coagulation cascade, resulting in microthrombi formation.[16] Recent research indicates that sepsis is characterized by both pro-inflammatory and immunosuppressive responses occurring simultaneously, with the intensity of each depending on the host (age, genetics, comorbidities) and the pathogen (virulence, strain).[16]

Sepsis Treatment

Sepsis and septic shock must be treated as urgent conditions in critically ill patients. Early recognition and antibiotic therapy are the foundation of successful treatment.

Initial Fluid Resuscitation

Hemodynamically unstable patients (with one of the following: mean capillary pressure lower than 90 mmHg, or MAP lower than 70 mmHg) and patients with lactate levels above 2 mmol/L should be treated with rapid crystalloid resuscitation at a volume of 30 mL/kg, which should be started within the first 1–3 hours.[17,18] Balanced crystalloid solutions are preferable over normal saline, according to recommendations.[19,20] This group of patients has a lower risk of developing acute renal injury and mortality.[18]

Surgical Control of the Infection

Surgical removal of infected tissue is as important as antibiotic therapy. The method of choice may be open surgery or percutaneous drainage.

Antibiotic Therapy

Early antibiotic treatment reduces mortality in sepsis. Every hour of delay increases mortality by 7%.[20] However, one should be mindful of the side effects of premature and inappropriate use of antibiotics, as well as the increased risk of bacterial resistance. For this reason, each hospital should have its own recommendations and an antibiotic stewardship program. Empiric broad-spectrum antibiotics should be administered immediately upon diagnosis. Cultures and swabs should be sampled, and antibiotic therapy should be de-escalated based on the results. Patients with intra-abdominal infections should be considered for anaerobic coverage, and antifungal therapy should be considered for immunocompromised patients.[21]

The Surviving Sepsis Campaign (SSC) recommendations for sepsis management from 2017 are as follows:

1) Intravenous antibiotic therapy should start within the first hour of admission;
2) Broad-spectrum antibiotics, either single or in combination, should be administered;
3) The spectrum of antibiotics should be narrowed once the biogram and antibiogram are available or when the clinical picture allows;
4) The dosing strategy should be optimized based on pharmacokinetic and pharmacodynamic principles;
5) De-escalation of antibiotics should be considered on a daily basis and at the earliest stage based on the clinical picture.[22]

When is the Right Time to Start Vasopressor Therapy and How to Choose the Right One?

If a patient remains hemodynamically unstable despite fluid resuscitation, vasopressor therapy should be initiated to achieve and maintain MAP values >65 mmHg.[18] The use of vasopressors carries serious adverse effects, such as tissue ischemia, increased cardiac load, and a risk of arrhythmias. According to all recommendations, the first-line therapy is norepinephrine[22] due to its greater potency and lower risk of arrhythmias compared to dopamine.[23] The use of nor-

epinephrine and dopamine in septic patients has been compared in many randomized controlled trials and meta-analyses, several of which reported higher mortality rates associated with dopamine.[24,25] Additionally, arrhythmogenic events were more frequently reported among patients treated with dopamine.[26]

According to the literature, vasopressin reduces the doses of catecholamines, but its effect on overall survival has not been confirmed.[27] Recently, two new drugs, selepressin and angiotensin II, have been introduced.[28] Inotropic agents can be considered in patients with myocardial dysfunction and low cardiac output. However, their routine use with vasopressors is not recommended.[29]

Vasopressor Timing

The Surviving Sepsis Campaign (SSC) recommends that vasopressor therapy should be initiated within 6 hours of hypotension onset.[18] Hypotension is defined as persistent MAP values <65 mmHg after administration of 30 mL/kg of crystalloids in bolus.[18,22] Patients who receive vasopressor therapy within the first 2 hours of septic shock onset have a significantly lower 28-day mortality rate compared to those in whom vasopressors are started after 2 hours (30% vs. 43%). The same study[30] showed that mortality increased by 5.3% for each hour of delayed vasopressor therapy. Early norepinephrine infusion initiation results in fewer days of treatment and a lower total dose per patient. Additionally, target MAP values were achieved faster in the group that started norepinephrine infusion within the first 2 hours (6.1 hours vs. 4.6 hours, $p < 0.001$). There was no significant statistical difference between the groups in terms of fluid volume administered, the timing of antibiotic therapy, or corticosteroid use.[30]

Vasopressors should be administered through a central venous line, as complications like infections and phlebothrombosis are less common compared to peripheral lines.[31] Peripheral administration is considered safe if it lasts no longer than 2 hours, if a wide cannula is used, and if it is placed proximal to the cubital or popliteal fossa.[32]

Norepinephrine

Norepinephrine is recommended as the first-line therapy over other vasopressors in septic shock.[18] It is an endogenous catecholamine that primarily acts as an excitatory neurotransmitter. Its most important effect is vasoconstriction, mediated by stimulation of α and β adrenergic receptors, with a more prominent effect on α1 receptors. In sepsis, the adrenergic response to norepinephrine differs from the physiological response, resulting in increased renal vascular flow. A similar effect is observed in the splanchnic circulation, where norepinephrine normally causes decreased blood flow.[33] High doses, as well as long-term use of this catecholamine, may provoke intense vasoconstriction in renal and splanchnic circulation, leading to visceral hypoperfusion and additional organ damage.[34,35] Norepinephrine also acts as a β1 agonist, producing a positive inotropic effect. Prolonged use may have direct toxic effects on myocytes, causing reflex bradycardia, cardiac arrhythmias, and myocardial ischemia. The usual dose range is 8–10 mcg/min (0.05–0.1 mcg/kg/min), and the dose may be increased according to MAP values. However, if a patient requires therapy with doses above 0.6 mcg/kg/min, it is preferable to add a second-line vasopressor, such as dopamine or vasopressin.

Adverse effects of norepinephrine are serious and include tissue necrosis due to drug extravasation, as well as intensive vasoconstriction that may lead to organ dysfunction when therapy involves extremely high doses.

Epinephrine

Epinephrine is a potent non-selective α and β adrenergic agonist. The Surviving Sepsis Campaign (SSC) recommends epinephrine as an alternative to norepinephrine in septic shock management,[18] with usual doses ranging from 0.01 to 0.20 mcg/kg/min. Doses below 0.1 mcg/kg/min predominantly exert a β effect on cardiac contractility and heart rate.[36] Higher doses show a dominant α1 vasoconstrictor effect. A multicenter, randomized, controlled, double-blind study by Annane et al., which compared two groups of patients receiving epinephrine versus norepinephrine and dobutamine, showed no significant difference in the duration of vasopressor therapy, hospital stay, or 28-day and 90-day mortality rates.[37] However, patients treated with epinephrine exhibited lower pH in blood gas analyses during the first four days, as well as higher lactate levels on the first day of treatment. These metabolic disturbances following epinephrine infusion are well-known and are considered to be the result of strong α-1 vasoconstriction. Additionally, β-2 mediated anaerobic glycolysis may contribute to the acid-base imbalance.[38]

Vasopressin

Vasopressin is an endogenous peptide hormone that stimulates the V1 receptor in the smooth muscles of blood vessels, causing vasoconstriction.[39] In healthy subjects, vasopressin-mediated vasoconstriction is observed in the lungs and kidneys. However, very low doses of vasopressin in lung circulation stimulate nitric oxide (NO) liberation and consequent vasodilation.[40] This effect may be beneficial in acute right heart failure.[41] Vasoconstrictive effects become more pronounced in severe hypotension, when vasopressin release from the hypothalamus may increase by more than tenfold compared to basal levels.[42] Since the endogenous reserve of vasopressin depletes rapidly, the administration of exogenous vasopressin becomes

crucial to achieving and maintaining adequate MAP values.[43]

The half-life of vasopressin is 5–20 minutes, so it should be administered as a continuous infusion. Recommended doses in septic shock are 0.01–0.04 U/h.

The SSC does not recommend vasopressin as a single therapy. It is recommended to add vasopressin in patients with inadequate MAP levels, instead of escalating the dose of norepinephrine.[18] The VASST study, which included 778 septic patients, compared norepinephrine alone versus a combination of norepinephrine and vasopressin. It showed that therapy with low-dose vasopressin (0.03 U/min) reduced the need for norepinephrine during the first four days. However, there was no difference in adverse events.[44] Some evidence also suggests that adding vasopressin infusion to norepinephrine therapy (with doses below 15 mcg/min) in moderate to severe sepsis may improve survival rates.[45]

Vasopressin also affects water retention and reabsorption in the distal renal tubule through V2 receptors, and it stimulates ACTH secretion from the anterior pituitary via V3 receptors. These effects are negligible when vasopressin is administered in therapeutic doses.

Dopamine

Dopamine is an endogenous catecholamine and a precursor to norepinephrine. It is not recommended as the first-line therapy for hypotension in septic shock.[18] However, it may be administered to patients at risk of tachyarrhythmia or bradycardia.[44] Since 2013, it has also been excluded as a first-line treatment for cardiogenic shock.[46]

At lower doses, dopamine acts via presynaptic and postsynaptic DA1 and DA2 receptors which are present in the coronary, renal, cerebral, and splanchnic endothelia. In healthy individuals dopamine increases renal blood flow and promotes natriuresis in a dose-dependent manner.[47,48] For this reason, low "renal doses" of dopamine were once thought to protect and preserve kidney function in septic patients. However, none of the randomized studies have shown a benefit in terms of preventing acute renal failure.[49] It is now believed that the renal afferent arteriole is already maximally dilated in sepsis, which limits the renoprotective effect of dopamine.[50]

At doses of 2–10 mcg/kg/min dopamine primarily exerts a β-1 effect.[51] In patients receiving β-blocker therapy dopamine's effects via DA1 and DA2 receptors can still occur at these doses, potentially causing vasodilation in the renal and splanchnic vasculature, which may exacerbate existing hypotension.[52]

At doses of 10–20 mcg/kg/min the dominant effect is on α-1 receptors, resulting in an increase in systemic vascular resistance and MAP. Higher doses can lead to serious vasoconstriction, limb ischemia, and additional organ hypoperfusion. A study comparing the effects of dopamine and norepinephrine across various types of shock in critically ill patients found that dopamine use was associated with reduced survival, especially in cardiogenic shock. This may be due to dopamine-induced increases in heart rate and cardiac arrhythmias.[26]

Phenylephrine

Phenylephrine is a pure α-1 agonist with purely vasoconstrictive properties and no direct effect on the heart. This isolated increase in afterload can lead to a drastic drop in stroke volume and cardiac output. For these reasons, there is limited evidence supporting the use of phenylephrine in septic patients.[53]

In sepsis, phenylephrine is recommended under certain conditions, such as in cases of serious cardiac arrhythmias caused by norepinephrine, when cardiac output is high despite persistent hypotension, or as an adjunct to other vasopressors in cases of refractory hypotension.[18]

A study in 18 non-septic patients with cardiomyopathy showed that a dose of 50–200 mcg led to a rapid increase in MAP (within 20–40 seconds), but also a deterioration in cardiac output.[54] The negative effects on stroke volume and cardiac output are more pronounced if cardiac function is already impaired. Given that sepsis is often accompanied by impaired cardiac function and potential sepsis-induced cardiomyopathy, the use of phenylephrine is rare and should be done with extreme caution.

Recent analyses have shown that, due to a shortage of norepinephrine, phenylephrine was often used, but this was associated with increased mortality.[55]

Angiotensin II

There is still insufficient evidence regarding the benefit of this drug in refractory shock. "Decatecholaminization" is a well-known phenomenon that occurs as a result of either down-regulation of α-1 receptors or inadequate interaction between receptors and intracellular second messengers.[56] Additionally, in sepsis, the levels of endogenous vasopressin and the expression of V1 receptors decrease. This can generally be overcome by the administration of exogenous vasopressors, most commonly catecholamines.

The ATHOS study examined the effect of angiotensin II as an adjunct to norepinephrine, epinephrine, or vasopressin. The study concluded that angiotensin II is a safe drug and that its use reduces the need for norepinephrine, thus minimizing its associated side effects.[57] However, there is still considerable controversy regarding its use in septic shock. Some studies have shown that the metabolites of angiotensin II may have pro-inflammatory and pro-coagulant properties, as well as harmful microcirculatory effects.

A number of studies have examined the effects of ACE inhibitors in sepsis and concluded that while ACE inhibitors may improve microcirculation, they do not provide a survival benefit. Moreover, these studies found that ACE inhibitors could contribute to the impairment of kidney function and disrupt gas exchange in the lungs.[58] The only promising study to date is the ATHOS study, but since it is a pilot study with a small sample size, larger randomized clinical trials are needed to determine the drug's effectiveness, optimal dosage, and the appropriate timing for its use.

When to Start Using Inotropes in Sepsis?

Septic shock is a hyperdynamic state characterized by an increase in stroke volume and cardiac output with low systemic vascular resistance. Prolonged peripheral vasodilation and increased cardiac index can sometimes mask existing myocardial depression.[59] Cardiac dysfunction is very common in sepsis (60%).[60] and is thought to result from non-ischemic cardiac depression or self-protective myocardial hibernation.[61] Although coronary flow increases in sepsis, the difference in oxygenation between the coronary arteries and the coronary sinus is smaller than expected.[62] This suggests that impaired cellular metabolism and changes in microvascular autoregulation contribute to reduced cardiac contractility in sepsis.

Inotropes should be administered when signs of myocardial dysfunction, such as reduced stroke volume, low cardiac output, increased cardiac filling pressures, or persistent hypoperfusion despite fluid replacement and vasopressor support, are present. An ideal inotrope should increase cardiac contractility without significantly increasing myocardial oxygen demand.

Dobutamine

Dobutamine is a derivative of isoproterenol, with predominant β-1 and less pronounced β-2 agonistic effects.[63] It increases heart rate and stroke volume through β-1 receptor stimulation and causes vasodilation via β-2 receptor activation. It is also a mild α-1 agonist, which becomes noticeable at doses above 15 mcg/kg/min. The more common effect, however, is vasodilation caused by β-2 agonist activity at doses of 5–15 mcg/kg/min.

According to the SSC, dobutamine is the drug of choice for inotropic support in septic patients with high cardiac filling pressures and cardiac output dysfunction.[18,22] Its inotropic effect is more pronounced than its chronotropic effect. Even at lower doses, dobutamine can increase myocardial oxygen demand, potentially leading to malignant arrhythmias. A multicenter, randomized study from 2007 involving 330 septic patients showed that the combination of dobutamine and norepinephrine was associated with similar outcomes compared to epinephrine monotherapy.[37] The most common side effects in both groups were supraventricular arrhythmias (13% vs 12%) and ventricular arrhythmias (5% vs 7%).

The Surviving Sepsis Campaign and the European Society of Intensive Medicine recommend dobutamine use in septic patients with cardiac dysfunction, inadequate cardiac output, and signs of tissue hypoperfusion after optimization of preload and MAP with fluids and vasopressors.[18,22,29]

Milrinone

Milrinone is a non-adrenergic inodilator that works by inhibiting phosphodiesterase-3 (PDE3) and increasing cAMP levels. This leads to the release of calcium from the sarcoplasmic reticulum, raising intracellular calcium concentration and improving contractility. Milrinone also exerts vasodilatory effects on peripheral vessels, which may be beneficial in cardiogenic shock, especially when accompanied by right ventricular weakness, as it reduces pulmonary vascular resistance.[64]

However, the vasodilatory effect of milrinone often necessitates the addition of a vasopressor. Since it is metabolized by the kidneys, its half-life is prolonged in patients with renal impairment, requiring dose adjustments.[53]

Because milrinone does not affect catecholamines it is particularly useful in patients on chronic β-blocker therapy.[64]

Levosimendan

Levosimendan is an inotropic and vasodilatory agent. Its vasodilatory effects are observed in the pulmonary, coronary, and peripheral vasculature and are mediated via potassium channels in smooth muscle. Its inotropic effect is achieved by stabilizing intracellular calcium concentrations and prolonging its binding to troponin C.[64]

Although levosimendan is not approved in the U.S., it is approved for use throughout Europe. The Surviving Sepsis Campaign recommends against the use of levosimendan in adults with septic shock and cardiac dysfunction accompanied by persistent hypoperfusion, despite adequate volume status and arterial blood pressure.[18]

Conclusion

Sepsis and septic shock remain leading causes of long-term morbidity and mortality in the modern era. Early diagnosis and appropriate management, including the use of vasopressors, reduce complications, healthcare costs, and mortality. Norepinephrine is the first-line vasopressor according to all available recommendations, as it is associated with a lower risk of cardiac arrhythmias and mortality. Second-line agents are epinephrine, vasopressin, and, in rare and clearly defined indications, phenylephrine may be used. Vaso-

pressin has catecholamine sparing effects. According to the newest guidelines, it should be added early as a second-line vasopressor, rather than escalating doses of norepinephrine. In patients with cardiac dysfunction, inotropes can be useful.

Ongoing research based on an individualized approach will likely provide insights into earlier detection of sepsis and prevention of multiorgan failure. Additionally, further studies are needed to determine the best second-line agents and the optimal timing for their use.

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The authors declare that there are no conflicts of interest relevant to this work

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