MODERN VASOPRESSOR THERAPY OF SEPTIC SHOCK IN RESUSCITATION DEPARTMENT (REVIEW)

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Summary. Septic shock, as the most severe form of sepsis, is characterized by high mortality reaching 40% despite the use of the most modern standards of diagnosis and treatment. In the thanatogenesis of septic shock, vasoplegia plays a leading role, respectively, and therapy of the condition under discussion involves the use of vasoconstrictors, along with the standard prescription of infusion therapy, antibiotics and symptomatic treatment. The choice of a specific vasoactive drug is a difficult task for a practicing anesthetist, as along with undoubtedly positive properties, vasoconstrictors each have their own spectrum of undesirable side effects, which, of course, must be taken into account when determining treatment tactics.

The aim of review: A comprehensive assessment of the multifactorial effect of various vasoconstrictors on the patient to determine the criteria for choosing the optimal drug (or a combination of drugs) in septic shock. The search was carried out using PubMed and Scopus databases, the final selection of 89 articles was carried out in accordance with the following criteria: relevance to the topic of this review and the nature of the article — only randomized controlled trials, guidelines and analytical reviews were included in the final analysis. External and internal mechanisms of vascular tone regulation are considered, including factors produced by endothelium (nitric oxide, prostacyclin, endothelin); vasoactive metabolites and autocoids — signal molecules of local action (serotonin, prostaglandins, thromboxane A2). Accordingly, drugs were analyzed the mechanism of action of which is related to the effect on adrenergic (adrenaline, dopamine, norepinephrine, phenylephrine, dobutamine), vasopressin (vasopressin, terlipressin, selepressin) receptors, synthetic analogues of angiotensin (angiotensin II) and drugs the non-vasopressor effect of which is not linked with the receptor apparatus (methylene blue, levosimendan, hydrocortisone).

Conclusion. The high effectiveness of norepinephrine, its positive hemodynamic effects make the drug under discussion, in many ways, a universal remedy for the relief of septic shock. However, refractory shock may require the introduction of such high doses of norepinephrine that the occurrence of adverse reactions will become practically inevitable. The combined use of adrenergic and ligand V receptors, terlipressin, is intended to prevent these complications. However, to date, there are no clear recommendations on the use of terlipressin in septic shock, which limits its use in clinical practice.

Keywords: sepsis, septic shock; vasopressor support; vasoplegia

СОВРЕМЕННАЯ ВАЗОПРЕССОРНАЯ ТЕРАПИЯ СЕПТИЧЕСКОГО ШОКА В РЕАНИМАЦИОННОМ ОТДЕЛЕНИЕ (ОБЗОР)

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Резюме. Септический шок, как наиболее тяжелая форма течения сепсиса, характеризуется высокой летальностью, достигающей 40%, несмотря на использование самых современных стандартов диагностики и лечения. В патогенезе септического шока ведущая роль принадлежит вазоплегии, соответственно, и терапия обсуждаемого состояния предполагает использование вазоконстрикторов, наряду со стандартным назначением инфузионной терапии, антибиотиков и симптоматическим лечением. Выбор конкретного вазоактивного препарата — сложная задача для практикующего анестезиолога, т. к. наряду с, несомненно, положительными свойствами, каждый вазоконстриктор обладает своим спектром нежелательных побочных эффектов, что, конечно же, необходимо учитывать при определении тактики лечения.

Цель обзора: комплексная оценка многофакторного воздействия на пациента различных вазоконстрикторов для определения критериев выбора оптимального препарата (или комбинации препаратов) при септическом шоке. Поиск проводили по базам данных PubMed и Scopus, окончательный отбор 89 источников осуществили в соответствии со следующими критериям: отношение к теме данного обзора и характер статьи — в окончательный анализ вошли только рандомизированные контролируемые исследования, рекомендации и аналитические обзоры. Рассмотрели внешние и внутренние механизмы регуляции сосудистого тонуса, включая факторы вырабатываемые эндотелием (оксид азота, простациклин, эндотелин); вазоактивные метаболиты и аутокоиды — сигнальные молекулы локального действия (серотонин, простагландины, тромбоксан А2). Соответственно, проанализировали препараты, механизм действия которых связан с влиянием на адренергические (адреналин, дофамин, норадреналин, фенилэфрин, добутамин), вазопрессиновые (вазопрессин, терлипрессин, селепрессин) рецепторы, синтетические аналоги ангиотензина (ангиотензин II) и препараты, вазопрессорный эффект которых не связан с рецепторным аппаратом (метиленовый синий, левосимендан, гидрокортизон).

Заключение. Высокая эффективность норадреналина, его положительные гемодинамические эффекты делают этот препарат, во многом, универсальным средством для купирования септического шока. Однако рефрактерный шок обуславливает использование высоких доз норадреналина, что приводит к увеличению риска неблагоприятных реакций. Предотвратить подобные осложнения призвана сочетанная стимуляция адренергических и лиганда V — рецепторов терлипрессином. Однако, на сегодняшний день не существует четких рекомендаций по применению терлипрессина при септическом шоке, что ограничивает его использование в клинической практике.

Ключевые слова: сепсис; септический шок; вазопрессорная поддержка; вазоплегия

Introduction. Mortality from sepsis and septic shock currently reaches 40% and remains at a high level despite new methods of diagnosis and treatment [1]. The clinical picture of the early period of septic shock is largely due to vasoplegic syndrome [1], the decisive role in the treatment of which belongs to replenishment of the intravascular volume [2]. However, the violation of vascular wall permeability that occurs during sepsis leads to a decrease in the effectiveness of infusion therapy, and excessive infusion, in itself, can cause serious harm to the patient [3]. This circumstance, as well as severe vasoplegia, especially characteristic of septic shock, necessitates the use of vasopressors that are designed to maintain adequate organ perfusion in conditions of limited use of massive infusion therapy [4]. Septic shock is a variant of redistributive shock with pronounced vasoplegia, which largely determines the outcome of treatment [5]. Knowledge of the basic mechanisms of development of vasoplegia and methods of its correction using vasopressors is a necessary condition for successful therapy of the state under discussion. The purpose of the review: A comprehensive assessment of the multifactorial effect of various vasoconstrictors on the patient to determine the criteria for choosing the optimal drug (or a combination of drugs) in septic shock. Methods of search and analysis of literary sources. Search for relevant articles was done with the help of PubMed and Scopus databases using the following keywords: [Sepsis]; [Septic shock]; [Vasopressors + septic shock]; [norepinephrine` + septic shock]; [norepinephrine + complications]; [terlipressin + septic shock]; [Dopamine + septic shock]; [Methylene blue + septic shock]; [catecholamine + septic shock]; [angiotensin II]; [selepressin], [Glucocorticoid + septic shock]. The final selection of 89 articles was carried out in accordance with the following criteria: relevance to the topic of this review and the nature of the article — only randomized controlled trials, guidelines and analytical reviews were included in the final analysis. Selected publications were analyzed by the authors of this article and presented in «References». Mechanisms for the Development of Vasoplegia in Case of Septic Shock Vascular tone is determined by smooth muscle cells (VSMC) [1] located in their walls, the main regulator of their activity is a change in the intracellular concentration of calcium ions (Ca2+) [6]. External regulation is carried out due to the influence of sympathetic innervation and vasoactive hormones [6]. The internal regulators of vascular tone include [6]: 1. factors produced by endothelium (nitric oxide, prostacyclin, endothelin) [7]; 2. vasoactive metabolites (formed as a result of acidosis, hypoxia, or other damaging factors, for example, hydrogen peroxide); 3. autocoids — signal molecules of local action (serotonin, prostaglandins, thromboxane A2). Nitric oxide (NO). In case of septic shock, NO synthase is activated [7], which increases the production of NO by several times and leads to uncontrolled vasodilation, and inhibition of VSMC proliferation [8–10]. The condition is exacerbated by the fact that excessive production of NO reduces the reactivity of adrenergic receptors [11]. Prostaglandins. In case of septic shock, the formation of type 2 cyclooxygenase isoform increases and prostacyclin synthesis is enhanced [12], which contributes to uncontrolled vasodilation [13, 14]. Endothelin 1 (ET1). Hypoxia, ischemia, and stress that occur during sepsis stimulate the formation of ET1. This peptide acts as a vasoconstrictor [15, 16], but in the inflammatory process, ET1 can lead to negative effects by activating signaling pathways that enhance the synthesis of interleukin-1 [5], tumor necrosis factor α [17], and interleukin-6 [18]. Acidosis resulting from insufficiency of tissue perfusion, hypoxia and mitochondrial dysfunction leads to even greater progression of shock and the development of multiple organ failure [19].A distinct acidosis can lead to a decrease in the sensitivity of blood vessels to catecholamine

vasoconstrictors [20, 21]. Oxygen free radicals. Decoupling of the interaction of endothelial enzymes NO synthases can cause an increase of reactive oxygen species formation and enhance mitochondrial dysfunction [22]. The decomposition of superoxide anion, which is excessively formed during NO shock, leads to the hyperproduction of peroxynitrite [23]. Peroxynitrite acting as a powerful oxidizing agent provokes the development of cell dysfunction and vasoplegia [24]. Hydrogen sulfide. In sepsis, the formation of hydrogen sulfide (H2S) significantly increases; it easily diffuses into VSMC and promotes the development of vasoplegic syndrome through a number of oxygen-dependent mechanisms and the activation of ATP-sensitive potassium channels [25, 26]. But, at the same time, H2S, interacting with NO, can weaken the effect of the latter [27]. Non-endothelial mechanism. Excessive activation of potassium channels leads to hyperpolarization of the VSMC membrane, which is accompanied by the closure of voltage-gated Ca2+ channels and the development of vasodilation. In addition, K+ ions indirectly potentiate vascular dysfunction, hypoxia, a decrease in pH, and an increase in blood lactate level [28]. A decrease in the sensitivity of blood vessels to vasoconstrictors can be formed due to several mechanisms [29]. Thus, uncontrolled sustained hyperactivation of the sympathetic nervous system leads to a loss of cardiovascular variability (inadequate tachycardia with a relatively low blood pressure (BP)), excessive production of catecholamines and, as a consequence, desensitization of catecholamine receptors. This triad increases the need for exogenous catecholamines to maintain hemodynamic targets [30]. Hyposensitivity at the cellular level in case of septic shock appears due to desensitization of: adrenergic receptors, type 1 vasopressin receptors, type 1 angiotensin, which occurs already in the initial phase of shock [31]. But apparently, vasopressin receptors are less sensitive to agonistic stimulation due to low concentrations of vasopressin in the blood during shock conditions [30, 32, 33]. The intracellular mechanism of hypersensitivity is largely due to NO [34]. It activates calcium-sensitive and ATP-sensitive potassium channels, myosin light chain phosphatase and the formation of cyclic GMP, which contributes to the development of vasodilation [11]. Other mechanisms also involved in vasodilation include the prostacyclin and cyclooxygenase pathways of the second type [35].

Vasopressors Therapy in Case of Septic Shock Vasopressors therapy is used to correct hypotension with the ineffectiveness of fluid [5] maintenance — the inability to maintain MAP > 65 mm Hg after a correction of hypovolemia (starting FM at a dose of 30 ml/kg, during the first three hours [36] of septic shock with the achievement of CVP > 120 mm H2O) [2]. The earlier use of vasoconstrictors, even before the end of fluid maintenance, was justified in order to reduce the volume of fluid maintenance on the first day of septic shock [37], as well as to reduce the risk of multiple organ failure and increase survival [38]. Vasopressors can be divided into four groups: 1. Adrenergic (adrenaline, dopamine, norepinephrine, phenylephrine, dobutamine), 2. drugs acting on vasopressin receptors (vasopressin, terlipressin, selepressin), 3. drugs affecting angiotensin type 1 receptors (synthetic angiotensin II). 4. angiotonic drugs are not associated with the receptor apparatus (methylene blue, levosimendan, hydrocortisone).

Adrenergic Vasoconstrictors Adrenaline is a potent non-selective α- and β-agonist. At low doses (up to 0.1 μg / kg / min), β-effects predominate, which leads to an increase in contractility and, as a result, to an increase in heart rate. When higher doses of adrenaline are used, the α-1-mediated vasoconstrictor effect predominates [39]. Efficiency is comparable with other vasoconstrictors, the strength of inoconstriction is comparable to the combination of noradrenaline and dobutamine [39]. There were also no differences in mortality in comparison with norepinephrine (NA) [40, 41], or a combination of NA with dobutamine [42]. Despite this,

the use of adrenaline in septic shock is recommended only in the form of a secondline vasoconstrictor — for stopping hypotension when introduction of NA does not allow reaching the hemodynamic targets [2]. This is due to the fact that the drug has a number of negative effects on the circulatory system: it increases the heart rate — and, therefore, increases the myocardial oxygen demand, increases the risk of heart rhythm disturbances [40, 41], and is capable of causing hyperlactatemia [2]. Dopamine is a biochemical precursor to NA. Having a cardiotonic effect, it increases MAP due to an increase in the stroke volume and heart rate [2]; in small and medium doses it stimulates β-adrenergic receptors, in large doses- α-adrenergic receptors. The widespread use of the drug in septic shock is not recommended [2, 40, 43]. This is due to the fact that the use of dopamine often causes rhythm disturbances, as it was shown in a study of De Backer D. et al in 2010 (24.1% and 12.4%, P«0,001) [44]. In addition, a significant increase of heart rate leads to an increase in myocardial oxygen demand, making the risk of ischemia higher. In septic shock, the use of dopamine is allowed only as an alternative to NA in case of patients with a low risk of tachyarrhythmias and in the presence of absolute or relative bradycardia [2]. The use of the drug for «nephroprotection», as was recently recommended [45], is now recognized as unjustified [2], since there is no convincing evidence of its effectiveness in improving renal blood flow, increasing the rate of urine output, and reducing the need for renal replacement therapy [44,46]. Phenylephrine is an agonist of α1-adrenergic receptors. The use of phenylephrine in case of sepsis is limited to situations in which the use of NA can lead to an increased risk of life-threatening arrhythmias; with a sufficiently high cardiac output, but with persistent hypotension; or as an additional drug for refractory hypotension [47]. Its use in these cases is explained by the fact that phenylephrine, in comparison with NA, more effectively reduces the heart rate and increases systemic vascular resistance without changing other hemodynamic parameters, which was identified by Jain G. et al. in 2010 (P«001) [48]. However, it should be noted that in patients who have a cardiac pathology, the drug leads to a decrease of cardiac output [47], and vasoconstriction of the internal organs that it potentiates can aggravate their ischemia [42]. Noradrenaline (NA) is a derivative of dopamine, has a very powerful vasopressor effect and is a firstline drug for the correction of hypotension in case of septic shock [2, 5]. The administration of NA leads to mobilization of the vascular volume, the appearance of a moderate inotropic effect [49], which increases the final diastolic volume, and the cardiac index [50]. In this case, there is no increase in the heart rate, and, consequently, myocardial oxygen demand does not increase [2, 44]. In addition, the choice of NA as a firstline drug is associated with a lower risk of arrhythmias [42] and lower mortality compared to dopamine [40, 42], as confirmed by a study of Avni T. et al. (2015) which demonstrated a decrease in mortality by 11% (RR 0.89: 95% CI 0.81–0.98, high reliability) [40]. The high potency and positive hemodynamic effects make NA largely universal for stopping hypotension caused by septic shock [2]. However, when the dose is exceeded by 0.5 mg/kg/min, the effectiveness of the drug decreases and an exponential increase in the dose of NA is necessary for a further increase in MAP [51–53]. Refractory shock may require the administration of doses that exceed the recommended ones (up to 1 μg/kg/min), which increases the risk of norepinephrine-mediated unfavorable responses. Auchet T. et al. (2017) determined that the emergence of finger necrosis due to the use of NA is possible when using a dose of 1 μg/kg/min for 1 hour, and serious changes develop in 6% of patients in this case [54]. When using doses of NA more than 2 μg/kg/min, irreversible microcirculation disorders can occur, leading to ischemia of the fingers and requiring amputation. There is also evidence that high doses of NA can lead to lip ischemia

[55]. In their study, Cox J. et al. (2015) found that the use of high doses of NA is also a significant risk factor for the development of pressure bed sores by septic patients (r=0.119; P=0.04) [56]. Exceeding a dose of 0.6 μg/kg/min leads to the development of pressure sores by 50% of patients [57, 58]. A high dose of NA in excess of 1 μg/kg/min is an independent predictor of high mortality among patients with septic shock [59, 60]. During the Auchet T. et al. study (2017) it was determined that with infusion of NA at a dose of more than 1 μg/kg/min, mortality reaches 65.1% [54], and according to Jenkins C. R. (2009), at a dose of more than 2 μg/kg/min, it is 96.4% [61]. Current recommendations state that a dose exceeding 1 μg/kg/min should be avoided, and the use of NA should be discontinued as soon as possible in order to reduce the risks of developing uncontrolled vasoconstriction, intestinal, skin and finger necrosis [55]. The data make us think about using a second vasopressor to reduce the dose of NA in order to level its side effects associated with the use in high concentrations. However, no modern guidelines provide clear recommendations as to what dose of NA should be used for the second vasoconstrictor and what should be the starting dose of the second drug, depending on the initial dose of NA infusion [62]. Dobutamine is a synthetic catecholamine, which is a strong agonist of β-1 adrenergic receptors and a weak agonist of β-2 adrenergic receptors, at the same time it has a mild α-1 effect, which is manifested at doses of more than 15 μg/kg/min [47]. Current recommendations indicate the use of dobutamine among the patients with persistent hypoperfusion [63] that persists after adequate infusion therapy and the use of angiotonic drugs [2]. With the administration of the drug in a dose not exceeding 2.5 μg/kg/min, there is an increase in the stroke volume and blood pressure without changing the heart rate. A further increase in dose provides an increase in indicators only by increasing the heart rate [39]. The role of dobutamine in septic shock is ambiguous. Administration of the drug even in low doses can increase the myocardial oxygen demand and provoke rhythm disturbances [47]. Efficiency has been proven only with systolic dysfunction [64], and with diastolic dysfunction, dynamic left ventricular obstruction, indicators of heart activity, on the contrary, may worsen [39]. The alleged cause of the heterogeneous dobutamine responses is the ever-changing picture of septic shock and the ongoing pathophysiological processes during each stage. Along with this, changes occur in adrenergic receptors, leading to a decrease in their sensitivity and, as a consequence, to a change in the response to catecholamines [39].

Drugs Acting on Vasopressin Receptors. **Vasopressin (AVP)** is an endogenous peptide hormone of the infundibular body, interacting with type I vasopressin receptors in VSMC that causes a vasoconstrictor effect [65]. However, when interacting with type 2 vasopressin receptors, it can lead to fluid retention in the body, thrombosis of the microvasculature, and vasodilation [66]. The course of septic shock suggests a relative deficiency of endogenous AVP, its elimination due to exogenous intake increases vascular tone, which explains the expediency of its use in case of this disease [67]. Currently, the drug is recommended as a supplement to NA in order to reduce the dose of the latter while maintaining hemodynamic targets [2], or to increase blood pressure to the target value, provided that NA monotherapy was not effective [2]. Exceeding the recommended dose (0.03 units/min), in view of the pronounced side effects (myocardial ischemia, impaired microcirculation of internal organs and fingers), is an extreme measure and is used in the absence of the effect of using other vasoconstrictors [68]. AVP, even at a minimum dose, effectively increases blood pressure in patients with resistant hypotension in septic shock [69, 70], due to the preservation of vasoconstrictor activity in acidosis and, apparently, less sensitivity toV1 receptor stimulation. The study of Bihari S. et al. (2014)

evaluating the addition of AVP to NA as the second vasoactive drug to patients at the early stages of septic shock showed that it was possible to achieve the target MAP faster in comparison with NA monotherapy (5.7 hours and from 7.6 hours, P=0.058, respectively), and led to faster resolution of organ dysfunction [71]. These statements suggest that correction of AVP deficiency at an early stage reduces the time spent by patients in septic shock [72]. A number of studies have not revealed a decrease in mortality when using AVP compared with NA [2, 73, 74]. However, a recently conducted and fairly large randomized study by Russell J. A. et al. (2008) discovered that patients receiving the drug have a tendency to decrease mortality compared to patients receiving NA (32.2% versus 40.5%, P=0.12). However, this difference was not recognized as significant enough. Meanwhile, the use of AVP has a number of positive effects: it reduces the incidence of acute kidney injury in septic shock by 18.8% compared with NA monotherapy (P=0.03). Accordingly, there was a decrease in the need for substitutive renal therapy compared with the control group [75]. Unfortunately, the drug is not registered in Russia and therefore is not used in clinical practice. Terlipressin (TP) has similar effects to vasopressin, has a longer duration [76], and is more selective for type I vasopressin receptors [70]. This contributes to a more pronounced vasoconstriction with the least side effects [73, 77, 78]. Hemodynamic efficiency with continuous infusion of both drugs is equivalent [79].

TP, stabilizing and normalizing hemodynamics, improves tissue perfusion, promotes greater blood oxygenation, increases the rate of urine output, reduces the level of lactate in the blood, thereby reducing the frequency of complications. A small dose of the drug can be recommended as a first-line vasoconstrictor support in cases of refractory hypotension in septic shock [70]. Comparison of continuous TP infusion with NA monotherapy did not reveal a large difference in the achievement of MAP sufficient for adequate tissue perfusion [70]. Side effects associated with the introduction of these drugs according to Choudhury A. et al. (2017), were also comparable in the studied groups (70.5% versus 44.4%, P=0.06) [80]. The long half-life allows the use of TP in the form of a bolus injection, but at the same time, the risk of excessive vasoconstriction increases, which reduces the delivery of oxygen to peripheral tissues. Continuous infusion with an equivalent effect is not accompanied by a pronounced decrease in cardiac output [73], which makes this type of administration preferable. Small doses of TP (1.3 μg/kg/h) as an adjunct to NA reduce the time to reach the target hemodynamic parameters compared with NA monotherapy [73, 81]. With a high need for angiotonic support, the addition of NA infusion, continuous TP infusion at the above dose reduces the need for the main vasoconstrictor, thereby reducing the risk of developing NA-mediated complications [81]. In addition, there is evidence that the use of terlipressin improves renal hemodynamics; this may be useful for the restoration of renal function in case of its dysfunction [80]. However, a meta-analysis by Zhu Y. et al. (2019), which included 10 studies (928 patients), did not reveal the effect of TP on reducing mortality compared to catecholamines (RR=0.94; 95% CI from 0.85 to 1.05; I=0%; P=0.28). At the same time, it was shown that the target group had an ALV shorter than the control group [82]. A variety of combination options with other vasoconstrictors and TP dosing regimens make the study group not entirely correct and do not currently determine the optimal strategy for the use of this drug, as well as objectively evaluate side effects and possible complications. This limits the widespread use of terlipressin in the treatment of shock conditions [2]. Selepressin is a synthetic selective fast-release type 1 vasopressin receptor agonist. Similar to vasopressin it is an effective angiotonic drug in case of resistant septic shock [83]. However, unlike it, the side effects of AVP are deprived, so when it is applied, water retention does not

occur and the procoagulant von Willebrand factor is not released [29]. Currently, there is only one RCT devoted to the use of selepressin by patients with septic shock [83]. According to Russell J. A. et al. (2017), the use of a vasoconstrictor at a dose of 2.5 ng/kg/min effectively increased MAP, while at the same time reducing the need for NA. The effect of selepressin on the development of multi-organ failure and 7-day mortality also demonstrate a positive effect (54% versus 23%, P«0,02). When assessing a 28-day mortality, there was no difference between the groups, which is possibly a consequence of limiting the infusion of the study drug for a period of 7 days [83]. Moreover, during the study, undesirable effects associated with excessive stimulation of vasopressin receptors of the first type — cyanosis, peripheral ischemia, myocarditis — were recorded. Taking into account the uniqueness and paucity of the study, it is not possible to conduct an in-depth analysis of complications, and additional large-scale studies are required to identify the potentially positive and negative medical claims, including comparing the effects of selepressin and AVP. Despite the many potential positive effects, including the possible ability to improve the treatment of patients with septic shock, the drug is not registered in Russia and its use is not allowed.

Drugs Affecting Angiotensin Type 1 Receptors. Angiotensin II is a synthetic analogue of the endogenous angiotensin produced in the body when the reniniangiotensin of the aldosterone system is activated as a result of renal hypoperfusion [84]. The drug causes direct vasoconstriction by binding to angiotensin type I receptors in VSMC, increases the intracellular calcium concentration in VSMC, potentiates an increase in the secretion of NA, vasopressin, which leads to a vasoconstrictor effect. However, excessive production of proinflammatory cytokines can lead to deactivation of AT II, which contributes to refractory hypotension. Most of the studies have been devoted to the use of AT II in various doses as an additional vasopressor agent, as an addition to NA in refractory septic shock. The effects of monotherapy with AT have not been studied. A presumably effective initial dose of administration is 2–10 ng/kg/min [51]. The administration of AT II in refractory septic shock can effectively increase blood pressure and reduce the need for a dose of NA [51, 85]. But when using the drug, there is also a risk of a number of side effects such as the occurrence of hypertension, alkalosis, cyanosis, excessive vasoconstriction and arrhythmia, but their probability is quite comparable with the frequency of occurrence of these complications when using NA monotherapy. The study by Khanna A. et al (2017) did not reveal a decrease in 28-day mortality when using AT II as compared with NA (46% and 54%, respectively P — 0.12) [50]. As part of the study, it was not planned to compare the incidence of AKI and the need for SRT, however, it was found that the need for SRT was lower in the group of AT II compared with placebo [51]. The paucity and lack of comparative studies with other non-adrenergic vasoconstrictors in combination with unproven economic efficiency limits the use of AT II in the world practice. In Russian Federation, the drug is not registered at all.

Angiotonic Drugs That Are Not Associated With The Receptor Apparatus. Methylene blue is a water-soluble stain that inhibits the formation of NO synthases and guanylate cyclase [86], which limits the overproduction of NO thereby contributing to an increase in vascular tone in case of septic shock. The drug has a short half-life, therefore, its administration is carried out in the form of a continuous infusion. The use of methylene blue in septic shock leads to an increase in systemic vascular resistance and an increase of MAP [87]. The use of the drug as a second angiotonic agent reduces the dose of NA inputted, which reduces the risk of NA mediated harmful effects [88]. The administration of methylene blue poses a potential risk of excessive

suppression of NO synthases, which can lead to a decrease in cardiac output and increase mortality of patients with septic shock [29]. The effectiveness of methylene blue at the moment remains unknown, and the effect on mortality is poorly understood, which limits the widespread use of the drug in refractory septic shock. In addition, despite the ongoing research in the world and the potential beneficial properties of the drug, its use in Russian Federation is not allowed. Glucocorticoid therapy is a controversial method of shock treating; the effect of drugs on mortality is ambiguous. The administration of hydrocortisone is not accompanied by an increase in direct angiotonic or inotropic activity, but leads to a faster resolution of shock. Therapy increases the responsiveness of adrenergic receptors [29], suppresses the excessive pro-inflammatory reaction, reduces the production of NO thereby leading to a decrease in vasodilation, and increases the production of AT II [89]. The optimal timing of initiation of glucocorticoid therapy remains unknown, but the question of the need for this therapy is relevant for patients receiving two or more angiotonic drugs [2]. The recommended dose of hydrocortisone in case of the refractory septic shock is 100 mg every 8 hours or 50 mg every 6 hours, it is also possible to administer the drug in the form of a continuous infusion at a dose of 200 mg/day [2].

Conclusion. The high effectiveness of norepinephrine, its positive hemodynamic effects make the drug under discussion, in many ways, a universal remedy for the relief of septic shock. However, refractory shock may require the introduction of high doses of norepinephrine, which will inevitably lead to an increased risk of norepinephrine — mediated adverse reactions. The combined use of adrenergic and nonadrenergic drugs for the relief of refractory septic shock, and especially V-receptor ligands, is designed to prevent these complications. In Russia, the only drug approved for clinical use of the noncatecholamine series is the V-positive drug, terlipressin. However, to date, there are no clear recommendations on the use of terlipressin in septic shock, which limits its use in clinical practice.

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