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Review

Alternatives to norepinephrine in septic shock: Which agents and when?

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ABSTRACT

Vasopressors are the cornerstone of hemodynamic management in patients with septic shock. Norepinephrine is currently recommended as the first-line vasopressor in these patients. In addition to norepinephrine, there are many other potent vasopressors with specific properties and/or advantages that act on vessels through different pathways after activation of specific receptors; these could be of interest in patients with septic shock. Dopamine is no longer recommended in patients with septic shock because its use is associated with a higher rate of cardiac arrhythmias without any benefit in terms of mortality or organ dysfunction. Epinephrine is currently considered as a second-line vasopressor therapy, because of the higher rate of associated metabolic and cardiac adverse effects compared with norepinephrine; however, it may be considered in settings where norepinephrine is unavailable or in patients with refractory septic shock and myocardial dysfunction. Owing to its potential effects on mortality and renal function and its norepinephrine-sparing effect, vasopressin is recommended as second-line vasopressor therapy instead of norepinephrine dose escalation in patients with septic shock and persistent arterial hypotension. However, two synthetic analogs of vasopressin, namely, terlipressin and selepressin, have not yet been employed in the management of patients with septic shock, as their use is associated with a higher rate of digital ischemia. Finally, angiotensin II also appears to be a promising vasopressor in patients with septic shock, especially in the most severe cases and/or in patients with acute kidney injury requiring renal replacement therapy. Nevertheless, due to limited evidence and concerns regarding safety (which remains unclear because of potential adverse effects related to its marked vasopressor activity), angiotensin II is currently not recommended in patients with septic shock. Further studies are needed to better define the role of these vasopressors in the management of these patients.

Introduction

Septic shock is one of the main causes of admission to the intensive care unit (ICU) and is associated with high mortality and morbidity.[1] It involves life-threatening organ dysfunction, which combines hypovolemia, vasodilation, cardiac dysfunction, and microcirculatory impairment. Macrocirculatory disorders result in an imbalance between oxygen supply and delivery, leading to inadequate tissue perfusion and cellular hypoxia. Microcirculatory disorders, however, result in impaired peripheral oxygen extraction and tissue oxygenation.[2]

Vasodilation and cardiac dysfunction are the main features of septic shock. Early vasopressor therapy is therefore the cornerstone of hemodynamic management in patients with septic shock, as fluid resuscitation alone cannot restore vascular tone and cardiac function.[3] The numerous available vasopressors aim to counterbalance the vasodilatory effects of a systemic inflammatory response syndrome. Among them, some are natural hormones that exert vasopressor activity through specific receptor activation (norepinephrine, epinephrine, vasopressin, and angiotensin II); however, most recent vasopressors, such as selepressin, are analogs of natural hormones.

To date, norepinephrine is recommended as first-line vasopressor therapy in patients with septic shock.[1,4] Norepinephrine is a potent α- and β1-adrenergic agonist, with little activity on β2 receptors; it, therefore, induces an increase in cytosolic calcium concentrations of smooth muscle after binding to its receptors. It exerts its vasopressor activity by causing arterial and venous vasoconstriction through its α-adrenergic effect. Thus, it enhances coronary blood flow by increasing diastolic arterial pressure. Norepinephrine also increases venous return,[5,6] by increasing the mean systemic filling pressure and thus the venous return pressure gradient.[7,8] It exerts a positive inotropic effect on both ventricles via β1

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stimulation to a lower extent than its vasopressor activity; this is evidenced by classical load-dependent systolic function parameters[5,6,9] and by relatively load-independent parameters such as the left ventricular global longitudinal strain.[10] Notably, there is limited β1-induced-tachycardia with norepinephrine due to the baroreflex secondary to increased arterial pressure. Therefore, norepinephrine increases cardiac output without increasing the heart rate or myocardial oxygen consumption. It may also improve microcirculation in patients with septic shock[11] who may have impaired microvascular blood flow.[12]

Although norepinephrine is currently recommended as the first-line vasopressor in patients with septic shock,[1] there is some evidence to suggest that the prescription of adrenergic vasopressors should be limited in these patients and that other vasopressors should be considered. First, due to the down-regulation of α1-adrenergic receptors, patients with severe septic shock often require very high doses of norepinephrine to achieve hemodynamic success.[13] However, it may induce some adverse effects such as ventricular arrhythmias, bleeding, digital ischemia, and acute mesenteric ischemia.[14] In particular, the use of high doses of norepinephrine is associated with more frequent atrial fibrillation,[14] possible induction of oxidative stress and insult to myocardial cells,[13] and possible alterations in the splanchnic circulation.[15] Second, the use of high doses of catecholamines, known as "vasopressor load," is directly related to mortality in patients with septic shock regardless of the targeted mean arterial pressure (MAP), because of catecholamine-induced cardiac toxicity.[16] Third, norepinephrine (but not vasopressin) may alter sepsis-associated immunomodulation by dysregulating the immune response through anti-inflammatory effects, thus contributing to sepsis-induced immunoparalysis with persistent adrenergic stimulation.[17–19] In conjunction, these findings have resulted in the concept of "decatecholaminization,"[20,21] which involves limiting the use of adrenergic vasopressors in patients with septic shock and favoring other non-adrenergic vasopressors. Thus, many other agents with specific properties and/or advantages that act on vessels through different pathways after activation of specific receptors could be potent vasopressors of interest in patients with septic shock. In particular, these other vasopressors may be of interest in patients with refractory shock, which has recently been defined as "*a state in which escalation of vasoactive therapy does not restore adequate tissue perfusion, that can be recognized by persistent arterial hypotension and hypoperfusion in the absence of hypovolemia, while the patient is receiving more than* 0.25 μg/kg/min of norepinephrine."[22]

This review discusses current knowledge on the different available vasopressors and their respective indications in the management of patients with septic shock. The main findings of pivotal randomized trials for vasopressors in patients with septic shock are summarized in Table 1, and a proposal for vasopressor therapy in patients with septic shock is summarized in Figure 1.

Dopamine

Dopamine is the immediate physiologic precursor of norepinephrine and epinephrine and has dose-dependent physiological effects.[23–25] At low doses (<5 μg/kg/min), dopamine induces vasodilation by activating the D1 receptors located in cerebral, coronary, renal, and mesenteric vessels, with no effect

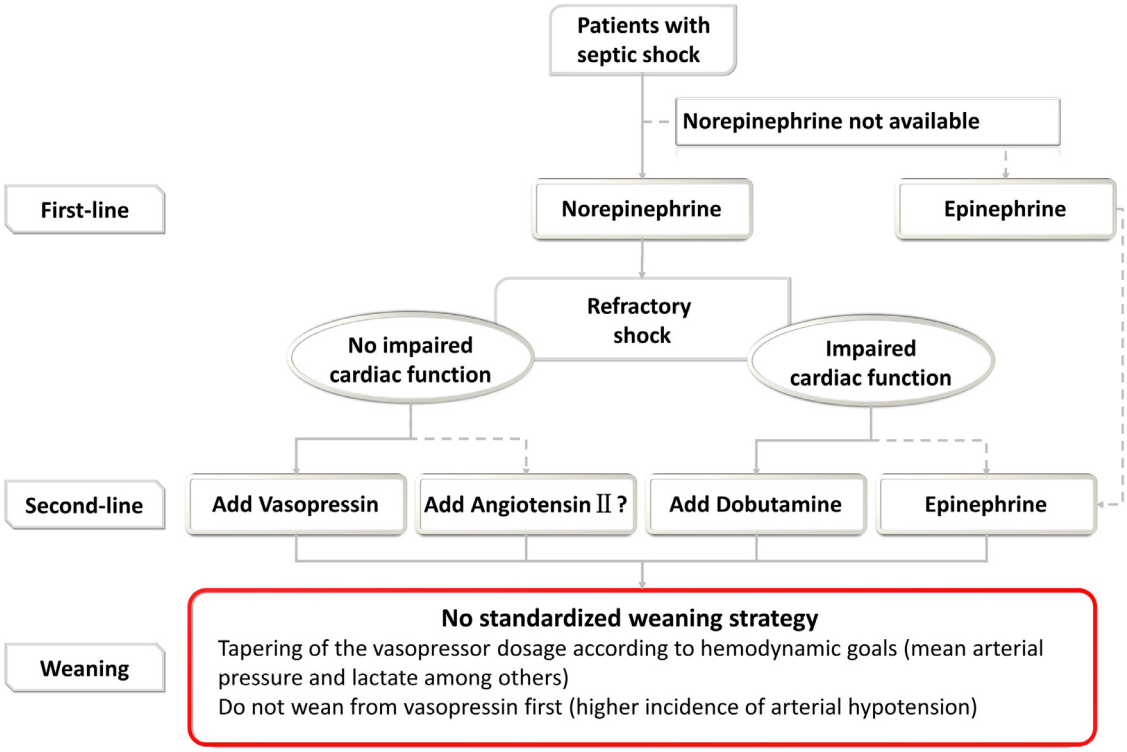

Figure 1. Proposal for use of vasopressors in patients with septic shock. MAP: Mean arterial pressure.

Table 1
Summary of pivotal multicenter and randomized trials for vasopressors in patients with septic shock.

Study	Year	*n*	Interventional group	Control group	Primary outcome	Main results	Adverse effects in interventional group
SOAP II study[26]	2010	1679	Dopamine	Norepinephrine	28-day mortality rate	No difference in 28-day mortality rate No difference in the number of days without the need for organ support	More frequent arrhythmias
CAT study[27]	2008	280	Epinephrine	Norepinephrine	Achievement of MAP goal >24 h without vasopressors	No difference in the time to achieve MAP goal No difference in 28-day and 90-day mortality rates No difference in the number of vasopressor-free days	More frequent lactic acidosis More frequent arrhythmias
CATS study[28]	2007	330	Epinephrine	Norepinephrine + Dobutamine	28-day all-cause mortality	No difference in the different mortality rates No difference in time to hemodynamic success No difference in time to vasopressor withdrawal No difference in time course of SOFA score	More frequent lactic acidosis
VASST study[68]	2008	778	Vasopressin	Norepinephrine	28-day mortality rate	No difference in 28-day and 90-day mortality rates Lower day-28 mortality rate in the less severe patients No difference in rates of organ dysfunction	Trend toward a higher rate of digital ischemia
VANISH study[72]	2016	409	Vasopressin	Norepinephrine	Kidney failure-free days during the 28-day period after randomization	No difference in kidney failure-free days Less use of renal replacement therapy No difference in the different mortality rates	Similar rate of ischemic events
Liu et al.[77]	2018	526	Terlipressin	Norepinephrine	28-day all-cause mortality	Stopped for futility No difference in 28-day mortality rate No difference in the number of vasopressor-free days No difference in time course of SOFA score during the first week	More frequent digital ischemia More frequent diarrhea
SEPSIS-ACT study[86]	2018	828	Selepressin	Placebo	ventilator- and vasopressor-free days within 30 days	Stopped for futility No difference in ventilator- and vasopressor-free days within 30 days No difference in 90-day mortality rate No difference in renal replacement therapy-free days No difference in ICU-free days Higher MAP with selepressin Lower norepinephrine requirement with selepressin	Similar rate of ischemic events
ATHOS-3 study[114]	2017	321	Angiotensin II	Placebo	Achievement of a predefined MAP target without an increase in the dose of norepinephrine	Higher proportion of patients reaching the primary outcome with angiotensin II Lower norepinephrine requirement with angiotensin II Greater improvement of SOFA score at 48 h with angiotensin II No difference in 28-day mortality rate	Similar rate of ischemic events Similar rate of arrhythmias

ICU: Intensive care unit, MAP: Mean arterial pressure, SOFA: Sequential (Sepsis-related) Organ Failure Assessment.

on arterial pressures. At intermediate doses (5–10 μg/kg/min), it exerts chronotropic and inotropic effects by activating the β1-adrenergic receptor. At high doses (10–20 μg/kg/min), it demonstrates vasopressor activity similar to that of norepinephrine by activating the α-adrenergic receptor.

There is considerable inter-individual variability in the effects of dopamine, because of an unpredictable relationship between infusion rates and plasma levels.[25] In the multicenter randomized SOAP II study, dopamine was compared with norepinephrine in 1679 patients with shock; 60% of patients in that cohort had septic shock.[26] There was no difference in 28-day or other (ICU, hospital, and 6- and 12-month) mortality rates in patients with septic shock. Patients receiving dopamine had higher urine output during the first 24 h, but also had a higher heart rate for up to 36 h after randomization; however, there was no difference in the number of days without the need for organ support.[26] Notably, dopamine use was associated with a two-fold higher incidence of cardiac arrhythmias, the most common being atrial fibrillation.[26] Owing to these reasons, dopamine is no longer recommended in patients with septic shock.[1]

Epinephrine

Epinephrine was the first adrenal medullary adrenergic hormone to be identified; it is a potent agonist of the β1, and β2 receptors. Epinephrine exerts its vasopressor activity (with marked arterial and venous vasoconstriction) through its α-adrenergic effect; its positive inotropic and chronotropic effects, which are more marked than those of norepinephrine, are mediated by β1 stimulation.[2,25]

In patients with septic shock, epinephrine has been compared with norepinephrine (CAT study),[27] norepinephrine and dobutamine (CATS study),[28] and vasopressin.[29] Although epinephrine use was never associated with reduced mortality,[27–29] shorter time to hemodynamic success, or faster weaning from vasopressors,[27,28] it was associated with more frequent lactic acidosis[27,28] and arrhythmias,[27] leading to its discontinuation in 13% of patients.[27] Epinephrine-induced lactic acidosis is a well-known metabolic effect[30,31] of the activation of β2-adrenergic receptors located on the surface of the skeletal muscle cells.[32] This β2 activity stimulates skeletal muscle Na^+/K^+-ATPase and accelerates aerobic glycolysis, thus increasing the production of pyruvate and consequently lactate in the cell.[33] In this context, it is worth noting that epinephrine-induced lactic acidosis is a physiological process that does not reflect the severity of shock.

Although epinephrine use did not increase the incidence of ischemic adverse effects or acute mesenteric ischemia,[27,28] experimental[34] and human studies[30,35–38] suggest that epinephrine may impair splanchnic circulation. Owing to the higher rate of metabolic and cardiac adverse effects compared to norepinephrine and its potential deleterious effects on the microcirculation,[2,25] epinephrine is currently considered as a second-line vasopressor in patients with septic shock. It may be considered in settings where norepinephrine is not available, in developing countries where norepinephrine is considerably expensive (epinephrine is less expensive with equivalent efficacy),[2] or in patients with refractory septic shock and myocardial dysfunction.[1]

Vasopressin and its Analogs

Vasopressin and its synthetic analogs (selepressin and terlipressin) are non-adrenergic vasopressors whose activity depends on their binding to three different receptors, all of which are sensitive to plasma osmolality, blood volume, and arterial pressure.[39,40] These include (1)V1a receptors, located on vascular smooth muscular cells, inducing vasoconstriction; (2)V1b receptors, mostly located in the anterior pituitary gland and pancreas, inducing corticotropic axis stimulation and insulin secretion; (3)V2 receptors, located on renal tubular cells, inducing aquaporin 2 recruitment and leading to water reabsorption.

While vasopressin has pleiotropic effects with similar affinity for the different receptors, its analogs demonstrate vascular selectivity.[39] Selepressin is a selective agonist of V1a receptors; it has marked vasopressor activity which can attenuate vasodilatation, vascular leakage, and tissue edema induced by sepsis. Terlipressin is mainly a V1a receptor agonist but also binds to V1b and V2 receptors.[39] Thus, selepressin and terlipressin theoretically have less V2 receptor activation-related renal and endothelial toxicity than vasopressin.[41]

Vasopressin

Vasopressin is a nine-amino-acid peptide that is produced by the hypothalamus and stored in the posterior pituitary gland. It is released in response to an increase in plasma osmolality (as detected by hypothalamic osmoreceptors) and/or a decrease in blood volume or blood pressure (as detected by baroreceptors in the carotid sinus, left atrium, and pulmonary artery). While its vasopressor activity is quite low in healthy subjects,[42,43] vasopressin demonstrates considerably more potent vasopressor activity in patients with septic shock.[44] In addition to its vasopressor activity, it also decreases pulmonary artery pressure through V1 receptor activation in low doses[45,46] and improves renal function by inducing efferent vasoconstriction; this results in a theoretical increase in glomerular renal perfusion pressure and thus higher glomerular filtration, as evidenced by increased diuresis and creatinine clearance.[39,40] Finally, vasopressin may interact with steroids. While vasopressin stimulates the corticotropic axis leading to adrenal glucocorticoid production,[47,48] steroids possibly sensitize tissues to the vasopressor activity of the former in experimental models of sepsis.[49–51] Nevertheless, the potential interaction between vasopressin and corticosteroids in patients with septic shock remains to be clarified.[52,53] Although vasopressin appears to induce less vasoconstriction in the mesenteric, coronary, and cerebral circulations than norepinephrine,[54] it induces cutaneous vasoconstriction in a dose-dependent manner.[39,40]

Vasopressin is released in the early phase of septic shock, leading to a peak in blood levels.[44,55] In later phases of sepsis, paradoxical vasopressin insufficiency can be observed in one-third of patients with septic shock,[56] suggesting that it may be an interesting vasopressor in this context. This vasopressin insufficiency may be explained by: (1) depletion of pituitary vasopressin stores,[57,58] (2) autonomic dysfunction with impairments in the baroreflex loop and osmoregulation,[58–61] and/or (3) by increased neuronal apoptosis in autonomic centers.[62,63] Several pilot clinical studies in patients with septic shock found potential beneficial hemodynamic effects of vasopressin

administration,[64–67] that were associated with norepinephrine-sparing and renal protective effects.[65] In the VASST study, the largest randomized clinical trial on vasopressin to date, vasopressin was compared with norepinephrine in 778 patients with septic shock.[68] There was no difference between the groups in terms of 28- and 90-day mortality rates and organ failure occurrence. However, the less severe cases receiving vasopressin tended to have a lower 28-day mortality rate; notably, interaction tests between severity of shock and mortality rate did not confirm this finding.[68] *Post hoc* analyses of the VASST study showed that vasopressin administration decreased the mortality rate in cases considered less severe according to Sepsis-3.[69] The findings also suggested that vasopressin administration had a protective effect on renal function in patients with septic shock who were at risk of developing acute kidney injury, with less worsening of renal function; a lower proportion of patients required renal replacement therapy.[70] Finally, the analyses also showed that vasopressin administration decreased the mortality rate in patients receiving a combination of vasopressin and hydrocortisone.[71] However, the VANISH study, a factorial, double-blind, randomized clinical trial conducted in 409 patients with septic shock (within the first 6 h of the onset of shock) showed no interaction between vasopressin and hydrocortisone; vasopressin administration neither decreased kidney failure-free days nor mortality rates.[72] A recent meta-analysis including >1400 patients with septic shock confirmed that vasopressin administration was not associated with a decrease in mortality rates, but tended to be associated with less use of renal replacement therapy.[73]

Despite the lack of superiority of vasopressin over norepinephrine in the VASST and VANISH studies, it must be noted that vasopressin administration had a norepinephrine-sparing effect by reducing norepinephrine dosage.[68,72] The rate of serious adverse effects was similar in both the vasopressin and norepinephrine groups.[68,72] Recent meta-analyses show that vasopressin use in patients with septic shock is associated with an increase in digital ischemia and diarrhea,[74] but fewer arrhythmias.[75]

Use of vasopressin at the bedside

In patients with septic shock who are receiving norepinephrine and have persistent arterial hypotension, it is currently recommended that vasopressin is used as second-line vasopressor therapy instead of increasing norepinephrine dosage.[1,4] The threshold for adding vasopressin remains unclear, but a norepinephrine dosage of 0.25–0.50 μg/kg/min may be adequate for initiating vasopressin.[1] Unlike other vasopressors, the dosage of vasopressin is not titrated based on clinical response; a fixed dosage of 0.03 units/min is recommended,[1,4] although vasopressin has been administered in doses of up to 0.06 units/min in clinical trials.[1] Given the potentially higher risk of ischemia with vasopressin, this vasopressor should not be used or be used with caution in patients with unstable coronary syndrome, known mesenteric ischemia, Raynaud phenomenon, systemic sclerosis, or other vasospastic diseases.[68,72] Regarding the weaning of vasopressin, it has been suggested that in patients with septic shock who receive concomitant norepinephrine and vasopressin, weaning from vasopressin first could be associated with a higher incidence of arterial hypotension with no effect on mortality rates or lengths of ICU stay.[76]

Terlipressin

Terlipressin, a synthetic analog of vasopressin with higher vascular selectivity, is a prodrug that is converted to vasopressin by endothelial peptidases. Thus, terlipressin has a longer half-life than vasopressin. Only a few studies have assessed its effects compared to those of norepinephrine in patients with septic shock. Terlipressin was either evaluated alone or in combination with other vasopressors, with various dosages and patient profiles.

The largest multicentric randomized controlled trial comparing terlipressin and norepinephrine as first-line vasopressor therapy in the setting of septic shock included 526 patients; it was stopped for futility.[77] There was no difference in the 28-day mortality rate, number of vasopressor-free days, or change in Sequential (Sepsis-related) Organ Failure Assessment (SOFA) scores during the first week.[77] However, a greater occurrence of serious adverse effects including digital ischemia (but not acute mesenteric ischemia) and diarrhea was reported in patients receiving terlipressin.[77] Nevertheless, recent meta-analyses have not found terlipressin use to be associated with more adverse effects.[78,79]

Selepressin

Selepressin is a more recently developed synthetic analog of vasopressin and a pure V1a agonist. In experimental models of sepsis, selepressin use reduces endothelial barrier dysfunction, vasodilatation, capillary leakage, lung edema, and pro-inflammatory cytokine release.[80–84]

Only two major studies assessed the effects of selepressin in patients with septic shock. The first, a randomized, double-blind, placebo-controlled multicenter trial including 53 patients in the early phase of septic shock, showed that compared to placebo, selepressin allowed more rapid weaning from norepinephrine while maintaining an adequate MAP, improving fluid balance, and shortening the duration of mechanical ventilation.[85] The second was the SEPSIS-ACT study, an adaptive phase 2b/3 randomized clinical trial, which was stopped for futility after including 828 patients.[86] Selepressin use was neither associated with an increase in ventilator- and vasopressor-free days within 30 days, nor with any of the key secondary endpoints (90-day mortality rate, renal replacement therapy-free days, and ICU-free days).[86] Nevertheless, patients who received selepressin had higher MAP levels, lower norepinephrine requirements, less cardiovascular dysfunction, higher urine output, and lower fluid balance without a higher rate of adverse effects.[86] To date, terlipressin and selepressin do not have a role in the management of patients with septic shock.[1]

Angiotensin II

Angiotensin II is an active octapeptide derived from the cleavage of angiotensin I by an angiotensin-converting enzyme, which is secreted in the lungs. The angiotensin-converting enzyme is derived from the cleavage of angiotensinogen in the blood circulation; the latter is synthesized in the liver by renin,

a protease synthesized in the kidney.[87] All the effects of angiotensin II are primarily mediated by its binding to its type 1 receptor (which belongs to the G protein-coupled receptor superfamily) in the blood vessels, kidneys, brain, and heart.[88] In addition to its classical cardiovascular effects (regulation of arterial pressure, regulation of aldosterone synthesis and vasopressin release, and regulation of water and salt balance), angiotensin II may also exert inflammatory, pro-proliferative and pro-fibrotic effects that are involved in oncologic and transplantation pathways.[87]

Renin-angiotensin-aldosterone system in septic shock

Activation of the renin-angiotensin-aldosterone system, which leads to the synthesis of angiotensin II and aldosterone, is one of the main physiological and adaptive mechanisms that are triggered to restore arterial pressure in patients with septic shock.[89–98] Angiotensin II exerts vasopressor activity through both venous and arterial constriction,[99] and regulates regional blood flow, especially in the kidney.[100,101] However, excessive activation of the renin-angiotensin-aldosterone system in patients with septic shock may be deleterious. Indeed, excessive angiotensin II synthesis can lead to marked vasoconstriction[97] with an increased risk of acute mesenteric ischemia and microvascular thrombosis,[90,93,98,102–104] especially in patients with impaired vascularity (smokers and elderly patients among others) and mitochondrial function.[105–108] This can lead to oxidative stress and endothelial damage.[109–111]

Experimental studies have shown that angiotensin II receptors are either down-regulated or less sensitive to angiotensin II stimulation in cases of sepsis.[95,112–115] A relative decrease in angiotensin II plasma levels has also been observed in patients with septic shock,[111] because of angiotensin-converting enzyme deficiency related to sepsis-induced endothelial damage.[116,117] Finally, patients with septic shock have recently been shown to have increased plasma levels of dipeptidyl peptidase 3 (DPP3).[118] DPP3 is a ubiquitous cytosolic enzyme with a short half-life, which is expressed in many tissues including erythrocytes, leukocytes, lung, heart, kidney, intestines, skeletal muscle, skin, brain, and the liver and spleen; it is involved in the cleavage of angiotensin II and the degradation of various other cardiovascular and endorphin mediators.[119] DDP3 therefore directly contributes to the decrease in plasma levels of angiotensin II that are observed in patients with septic shock.[119] Interestingly, in patients with septic shock, high levels of circulating DPP3 on ICU admission are associated with higher 28-day mortality and a greater need for organ support and vasopressors; conversely, a decrease in plasma levels of DPP3 during ICU stay is associated with better outcomes.[120] In this context, inhibition of circulating DPP3 by its specific antibody has been found to restore sepsis-induced cardiac dysfunction in a murine model.[121] Further studies are needed to confirm these promising experimental results in humans.

Overall, these findings suggest that decreased sensitivity to angiotensin II stimulation and a relative decrease in angiotensin II plasma levels may lead to refractory septic shock with multiple organ failure and/or death.[93,100,122]

Angiotensin II use in sepsis

Certain experimental[123–125] and human studies[122,126–129] have shown that angiotensin II administration increases arterial pressure, especially in patients with refractory septic shock who are unresponsive to high doses of norepinephrine.[122,129] They also indicated that administration of angiotensin II at doses ranging from 2 to 10 ng/kg/min even had a catecholamine-sparing effect without significant renal adverse effects, despite its marked vasopressor activity on the renal vasculature unlike norepinephrine.[113] In 2017, the multicentric randomized double-blind placebo-controlled ATHOS-3 study compared the effects of angiotensin II with those of placebo on the MAP in 321 patients; these patients had high-output catecholamine-resistant vasodilatory shock despite adequate fluid resuscitation and administration of high-dose norepinephrine for a minimum of 6 h and a maximum of 48 h.[114] Compared to placebo, angiotensin II allowed the achievement of a predefined MAP target along with a decrease in catecholamine dosage, without decreasing 7- and 28-day mortality rates.[114] *Post hoc* analyses of the ATHOS-3 study showed that patients who benefited most from angiotensin II administration had the following characteristics: (1) were the most severely affected and had relative angiotensin II deficiency,[130] (2) had markedly increased serum renin concentrations at baseline,[131] and (3) had acute kidney injury requiring renal replacement therapy.[132] In the last group of patients, angiotensin II administration was associated with better correction of arterial hypotension, more rapid recovery of kidney function, and a lower 28-day mortality rate.[132]

Despite these encouraging results, angiotensin II is currently not recommended in patients with septic shock,[1] as its safety remains unclear owing to potential adverse effects related to its marked vasopressor activity.[133,134] Nevertheless, in the ATHOS-3 study, the rate of adverse effects was similar in both angiotensin II and placebo groups; this included serious adverse effects, such as ischemic events (digital, gut, and myocardial) and cardiac arrhythmias.[114] A systematic review including 1124 studies and 31,281 patients concluded that angiotensin II-induced adverse effects were infrequent and that the most common adverse effects were transient headache, abnormal chest sensations, and orthostatic symptoms following discontinuation of the drug. Only two deaths were causally related to angiotensin II administration; none of these occurred in patients with vasodilatory shock.[135] It is essential to highlight that in this systematic review, only 13 studies included patients with vasodilatory shock; this made the external validity of these results questionable in the case of critically ill patients and, more specifically, in patients with septic shock. A recent sensitivity analysis of the ATHOS-3 study showed that angiotensin II doses could be decreased from 20 ng/kg/min to ≤5 ng/kg/min in 48% of patients within the 30-min period following treatment initiation.[111] These patients had a better MAP response, lower 28-day mortality rate, and experienced less serious adverse effects than those who received higher doses of angiotensin II.[111] This suggested that low-dose angiotensin II could be effective and safe in patients with septic shock.

Thus, angiotensin II appears to be a promising and relatively safe vasopressor in patients with septic shock, especially in the most severe cases and/or in patients with acute kidney injury requiring renal replacement therapy. Nevertheless, patients with

septic shock who are expected to benefit the most from angiotensin II administration need to be identified; the optimal dosage of angiotensin II also remains to be determined.

Methylene Blue

Methylene blue inhibits nitric oxide-induced smooth muscle relaxation by inhibiting guanylate cyclase.[2,25] To date, only two small randomized trials have assessed the effects of methylene blue in patients with septic shock.[136,137] In these two trials, methylene blue administration increased MAP compared to saline, with no effect on the mortality rate[136,137]; it also had a vasopressor-sparing effect.[136] The use of methylene blue was not associated with significant adverse effects, the most common being blue discoloration of the skin and the urine.[138] It may therefore be a potent vasopressor in patients with refractory septic shock, with an interesting catecholamine-sparing effect.[139,140] Nevertheless, its use currently remains controversial due to limited evidence.

Conclusions

Norepinephrine is currently recommended as the first-line vasopressor in patients with septic shock. Based on current evidence, epinephrine, vasopressin, and angiotensin II should only be considered as second-line vasopressor therapy in patients with refractory septic shock; further studies are needed to confirm their potential utility. The development of new-generation vasopressors that activate other receptors and intracellular pathways, and/or personalization of vasopressor therapy based on specific biomarkers, could help improve the management of patients with septic shock and avoid vasopressor-related adverse effects in the future.

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