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RESEARCH **REVIEW ARTICLE**

# Use of Inotropes and Vasopressors in Septic Shock: When, Why, and How?

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## ABSTRACT

Septic shock, a severe and sometimes fatal condition caused by systemic infection, demands immediate and focused therapies to restore hemodynamic stability and prevent organ failure. The use of vasopressors and inotropes has become the foundation in the treatment of septic shock, with the goal of reversing the vasodilatory condition and increasing cardiac contractility.

Vasopressors are an effective class of medications that cause vasoconstriction and, hence, increase mean arterial pressure (MAP). Norepinephrine is recommended as the first-line agent to use in septic shock. However, many medications have both vasopressor and inotropic actions, distinguishing them from inotropes, which increase heart contractility.

Inotropes work by increasing cardiac contractility and thereby increasing cardiac output. Dobutamine is still the mainstay of treatment based on the latest Society of Critical Care Medicine (SCCM) guidelines.

This review provides a comprehensive overview of the rationale, indications,doses, and major side effects surrounding the administration of these pharmacological agents in septic shock. Our team explored various databases regarding this subject, and most included articles were retrieved through PubMed. We thoroughly examined these articles and synthesized the information within our review.

We recommend that more clinical trials are needed to compare the effectiveness of dobutamine compared to other inotropes in the setting of septic shock, as the latest guidelines are based on a shortage of randomized control trials. Furthermore, emphasis on the importance of continuous hemodynamic monitoring during vasopressor therapy should be performed, which highlights the necessity for personalized changes to reach and maintain target blood pressure targets.

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# INTRODUCTION

Shock is a critical medical condition characterized by an imbalance between tissue perfusion and cellular oxygen utilization, ultimately leading to organ dysfunction, and is life-threatening with high mortality rates (Patel et al., 2022). he causes of shock are classified into four main categories: hypovolemic shock, cardiogenic shock, distributive shock, and obstructive shock; this classification is essential since the pathophysiology behind each type of shock and their management vary depending on the type (Standl et al., 2018).

Hypovolemic shock occurs when there is a reduction in the intravascular blood volume, ultimately resulting in a decrease in the cardiac preload, and can be triggered by hemorrhagic factors, such as traumatic injuries and gastrointestinal bleeding, as well as non-hemorrhagic factors such as loss of body fluids through diarrhea and vomiting (Marik & Weinmann, 2019). Cardiogenic shock, often arising as a result of myocardial infarction with the resultant loss of ventricular function, can induce tissue hypoperfusion as the case in hypovolemic shock; however, cardiogenic shock occurs mainly in states of cardiac dysfunction (Harjola et al., 2015).

Distributive shock is a condition that encompasses septic shock, anaphylactic shock, and neurogenic shock and arises due to vascular system dysregulation, involving the loss of vascular tone leading to a pathological redistribution of intravascular volume within the vascular system, or it can result from abnormal vascular permeability, which causes a volume shift from the vascular system to the interstitial space (Standl et al., 2018). Obstructive shock appears to be related to mechanical obstruction of the great vessels or heart, which can result in impaired cardiac function and reduced cardiac output. While it may present along with symptoms similar to those of cardiogenic shock, it is essential to distinguish between the two conditions as they require different therapeutic interventions (Pich & Heller, 2015).

Cardiogenic shock due to myocardial infarction is associated with increased production of proinflammatory cytokines, such as plasma IL-1β, IL 6, IL 8, tumor necrosis factor-alpha (TNF-α), and soluble adhesion molecule (sICAM 1, sE-selectin) (Pudil et al., 2001). Likewise, hemorrhagic shock is associated with increased transcription of inflammatory genes and production of NF-κB-dependent cytokines (Lu et al., 2016). Notably, TNF-α is a major inflammatory mediator expressed during various inflammatory conditions and triggers the expression of a wide range of inflammatory cytokines, including interleukins and interferons (Zhang, 2008).

These proinflammatory cytokines can negatively impact cardiovascular function as constantly elevated levels of TNF-α attenuate β1-adrenergic responsiveness, induce dilated cardiomyopathy (Kuhota et al., 1997), impede endothelium-dependent NO-mediated coronary dilation (Zhang et al., 2006), and activate Caspase-3 protein which in turn can induce myocardial dysfunction and promote expression of apoptotic proteins (Carlson et al., 2005). Likewise, IL-1β can cause a temporary decrease in contractile function, which is related to a reduced sensitivity to β-receptors stimulation. (Van Tassell et al., 2013); furthermore, its level increases in tissue hypoperfusion states (Kacimi et al., 1997). While the exact causality relationship requires further investigation, it is noteworthy that IL-6 is commonly found in individuals experiencing cardiogenic shock; moreover, elevated levels of this cytokine have been associated with a higher risk of developing multi-organ failure (Geppert et al., 2002).

Generally, elevated inflammatory markers levels are observed in all types of shock, either early or later in the course of the circulatory failure; however, these mediators are generally higher in septic patients and are associated with increased mortality (Cecconi et al., 2014; De Werra et al., 1997; Geppert et al., 2002). A significant correlation exists between the severity of global tissue hypoxia and the levels of inflammatory markers, as patients with severe global tissue hypoxemia had higher concentrations of all inflammatory markers compared to those with moderate or resolved global tissue hypoxia; meanwhile, proper hemodynamic optimization strategies resulted in a significant drop of these markers (Rivers et al., 2007).

The management of shock is routinely guided by the target blood pressure regardless of the treatment strategy. For instance, current guidelines suggest an initial targeting of mean arterial blood pressure (MAP) of > 65 mm Hg for septic shock patients (Rhodes et al., 2017). However, several experts recommend adopting a personalized approach to accommodate potential adverse events in shock resuscitation, which considers the patient's pre-existing blood pressure status and whether they have a history of normal, high, or low blood pressure (Cecconi et al., 2014). This is because patients with a history of hypertension who undergo treatment with a standard MAP target of 60-70 mm Hg may experience a greater need for renal replacement therapy than those treated with a higher MAP target of 80-85 mm Hg (Asfar et al., 2014). In the management

of cardiogenic shock, aiming for a MAP range of 80-100 mm Hg within the first 36 hours of admission to the intensive care unit is significantly linked with decreased myocardial damage (Ameloot et al., 2020).

Shock can have a devastating impact on patients, with mortality rates varying depending on the type and cause of shock; in fact, septic shock has a 90-day mortality rate of almost 40% (Bauer et al., 2020), cardiogenic shock can range from 50-75%; however, hypovolemic and obstructive shock have lower mortality rates and greatly respond to timely treatment (Shock - StatPearls - NCBI Bookshelf, 2020).

This review article aims to comprehensively summarize the evidence regarding the use of inotropic therapy in different types of shock, including the associated safety, efficacy, and potential side effects.Furthermore, this article explores the optimal dosages and titrations along with the factors that influence decision-making in clinical practice, ultimately providing healthcare professionals with a valuable resource for evidence-based treatment strategies.

## VASOPRESSORS USED IN SEPTIC SHOCK

**NOREPINEPHRINE (NE) -** is a catecholamine that functions as a neurotransmitter of most postganglionic sympathetic fibers, a vasoconstrictor, an alpha-adrenergic agonist, and a sympathomimetic agent. NE largely elevates systolic, diastolic, and pulse pressure and has a negligible overall effect on cardiac output (Overagaard et al., 2008). This agent is recommended as the first-line agent to use in septic shock (Rhodes et al., 2017). The standard dose range for NE is 0.01 to 3 g/kg/min (Overagaard et al., 2008). The main clinical adverse effects of this agent include peripheral ischemia, inadvertent immunomodulation, and cardiac arrhythmia (Shi et al., 2020).

**EPINEPHRINE -** Epinephrine has a high affinity for the beta 1, beta 2, and alpha 1 receptors found in cardiac and vascular smooth muscle (Overagaard et al.2008).Since epinephrine has a potent beta-1 adrenergic impact, it is sometimes used when there is cardiac dysfunction (Belletti et al., 2020). The standard range of dose used is 0.01 to 0.10 μg · kg−1 · min−1 in infusion and 1 mg IV every 3 to 5 min as bolus doses (max 0.2 mg/kg) (Overagaard et al., 2008). However, epinephrine can cause significant side effects such as tachycardia, tachyarrhythmias, and increased blood lactate levels (Belletti et al., 2020).

**DOPAMINE -** Dopamine is an endogenous central neurotransmitter that acts immediately as a progenitor to norepinephrine in the catecholamine synthetic pathway (Overagaard et al., 2008). It increases contractility, heart rate, venous and arterial tone, and renal and mesenteric vasodilation (Shi et al., 2020). The standard dose range is 2.0 to 20 μg · kg−1 · min−1 (max 50 μg · kg−1 · min−1) (Overagaard et al., 2008). There are significant side effects for dopamine , such as severe hypertension (especially in patients taking nonselective β-blockers), ventricular arrhythmias, cardiac ischemia, and tissue ischemia/gangrene (at high doses or due to tissue extravasation) (Overagaard et al., 2008).

**ANGIOTENSIN II -** AT-II is a non-adrenergic vasoconstrictor that is the product of the renin-angiotensin-aldosterone system. A recent RCT (ATHOS-3 trial) showed that AT-II (compared with placebo) effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of common vasopressors (Khanna et al., 2017). Angiotensin II acts by increasing venous and arterial tone, ACTH, ADH, and aldosterone reabsorption (Shi et al., 2020). Nevertheless, angiotensin II can cause significant side effects such as tachycardia, peripheral ischemia, and thromboembolic events (Shi et al., 2020).

**VASOPRESSIN -** Vasopressin is a hormone that causes vasoconstriction and water retention by acting on V1 and V2 receptors. Vasopressin levels are low in septic shock, and its administration may help to restore vascular tone and blood pressure. After norepinephrine, vasopressin is commonly utilized as a second-line vasopressor (Yao et al., 2020) In septic shock, the dosage range for vasopressin is 0.01 to 0.04 units/min, and it can be titrated according to the MAP goal, which is often 65 mmHg or higher depending on individual factors (Nagendran et al., 2019). Vasopressin differs from norepinephrine in that it can produce hyponatremia, cardiac arrhythmias, digital ischemia, and mesenteric ischemia. As a result, in septic shock patients, vasopressin should be given with care and under continuous monitoring.(Jentzer et al., 2015).

**TERLIPRESSIN -** Terlipressin is a vasopressin analog with antidiuretic and vasoconstrictive effects. It constricts blood arteries by binding to V1 receptors and increases water reabsorption by binding to V2 receptors. Terlipressin, like vasopressin, may help restore blood pressure and minimize reliance on catecholamines (Huang et al., 2020). Terlipressin is often used as a second-line vasopressor following norepinephrine, which is considered the preferable drug by trained pro-

fessionals. In septic shock, the normal dose of terlipressin is 0.01 to 0.06 mg/kg/h, which can be modified based on the goal mean arterial pressure (MAP) (Zhu et al., 2019). Terlipressin has the same side effects as vasopressin since it acts on the same receptors (Jentzer et al., 2015).

**SELEPRESSIN -** is a new vasopressin analog that primarily activates V1 receptors to cause vasoconstriction and blood pressure elevation. Selepressin may be an alternative to catecholamines in septic shock, which have limited effectiveness and deleterious consequences (Russell et al., 2017). Selepressin is now being studied in a phase III randomized controlled trial (RCT), comparing it against the usual vasopressor for septic shock, norepinephrine. In septic shock, the dosing range for selepressin is 0.05 to 0.15 g/kg/min, and it may be modified based on the desired mean arterial pressure (MAP) (Laterre et al., 2019).Selepressin, like vasopressin and terlipressin,may cause hyponatremia, cardiac arrhythmias, digital ischemia, and mesenteric ischemia. (Lewis et al., 2018)

**INOTROPES -** are drugs that affect the contractility of the heart. There are both positive and negative inotropes. The inotropes used in shock are positive , which we will address here.

**DOBUTAMINE-** Dobutamine activates the beta-one receptors in the heart, increasing cardiac output. As for the effect on vasculature , the systemic vascular resistance decreases because of both a baroreceptor-mediated response and a minor effect on beta-two receptors. There is also some vasoconstriction due to a minor alpha-one effect. The net effect , however, is unchanged blood pressure.

Dobutamine's Major hemodynamic effect depends on the dose: at low doses, dobutamine increases cardiac output and lowers afterload; at intermediate doses, it causes vasoconstriction; and at high doses, it worsens tachycardia in patients without additional CO increase (Hamdallah Ashkar,2023).

**MILRINONE -** Milrinone is a phosphodiesterase 3 (PDE3) inhibitor. In the heart, this inhibition increases calcium availability in myocyte sarcomere, causing its inotropic effect and some chronotropic effects. This also leads to increased calcium uptake by the sarcoplasmic reticulum, which improves myocardial relaxation (lusitropy). Milrinone also has a vasodilatory effect on vessels, but its use in shock is due to its effect on the heart. Milrinone doses >0.5 µg/kg/minute can lead to hypotension (Jack K. Ayres,2022)

**LEVOSIMENDAN -** Levosimendan increases cardiac contractility by increasing the sensitivity of troponin C to intracellular calcium in the cardiomyocyte. It is not used in septic shock, and it is also not approved by the United States FDA for any use. (Aditi Shankar,2022)

**INOTROPES IN SEPTIC SHOCK** - According to SCCM (Society of Critical Care Medicine) guidelines, dobutamine should be administered or added to vasopressors if there is a heart failure component or signs of low blood volume despite achieving the appropriate intravascular volume or MAP. However, more research and data are required as this guideline is based on a scarcity of RCTs. No studies compare Dobutamine and Milrinone in septic shock. However, Dobutamine is typically administered more in cases of kidney injury or hypotension, which are the main components of septic shock (Sacha Pollard,2015).

## CONCLUSION

Shock remains a persistent challenge within the realm of critical care medicine. The utilization of vasopressors and inotropes constitutes the foundation of shock management, with the goal of reinstating tissue perfusion and averting multi-organ failure.

In cases of septic shock, norepinephrine is widely acknowledged as the primary choice among other vasopressors. In contrast, epinephrine, dopamine, and angiotensin II are considered alternative options, each distinguished by its characteristics. These options allow for customized utilization based on the patient's individual requirements. Moreover, the emergence of vasopressor analogs like terlipressin and selepressin might offer an alternative to catecholamines or act as a second-line treatment after norepinephrine, especially in refractory cases. Nevertheless, careful monitoring of vasopressor analogs is essential due to their potential adverse effects.

Addressing cardiac dysfunction in shock commonly involves employing inotropic agents, notably dobutamine, milrinone, and levosimendan. Despite variations in their mechanisms of action, these agents ultimately enhance myocardial contractility, thereby improving forward stroke volume and augmenting tissue perfusion. Although guidelines advocate for the use of dobutamine in cases of reduced blood volume and instances with heart failure components, further research is imperative, as these recommendations were formulated based on limited randomized controlled trials (RCTs).

It is pivotal to recognize that shock is not a uniform condition; rather, it necessitates tailored management that considers the underlying causes

and patient characteristics. Navigating the management of septic shock mandates healthcare professionals to integrate evidence-based medicine. The dynamic nature and the emergence of novel insights regarding shock management modalities permit the continual expansion of therapeutic alternatives and heighten the expectations of efficacious shock treatment.

This review aims to empower healthcare providers with a comprehensive grasp of current therapeutic approaches, enabling them to make well-informed decisions that pave the way for optimal patient care when confronted with this critical medical condition.

**RECOMMENDATIONS -** We suggest the following recommendations for the use of inotropes and vasopressors in septic shock based on current research and clinical practice:

1.Norepinephrine should be used as the first-line vasopressor in septic shock since it improves hemodynamic stability and survival outcomes when compared to other agents.

2.Depending on the patient's hemodynamic condition, comorbidities, and reaction to norepinephrine, epinephrine, dopamine, and angiotensin II might be used as alternative or complementary vasopressors. These medications, however, have possible side effects, including an increased risk of arrhythmias, tachycardia, and ischemia, and should be taken with caution and strict monitoring.

3.Vasopressin analogs like terlipressin and selepressin may have certain advantages over catecholamines, such as lowering norepinephrine needs, maintaining renal function, and decreasing inflammation. Their effectiveness and safety, however, are still being investigated, and they are not generally accessible or licensed for septic shock. As a result, until additional data is available, they should be reserved for refractory patients or clinical studies.

4.Dobutamine is the inotrope of choice in individuals with septic shock who have cardiac dysfunction and poor cardiac output. It has the potential to increase myocardial contractility and tissue perfusion, but it can also produce hypotension and arrhythmias. As a result, it should be administered in conjunction with a vasopressor and titrated based on hemodynamic characteristics.

5.Milrinone and levosimendan are inotropes with distinct modes of action than dobutamine. They may be superior to dobutamine in terms of lowering afterload, enhancing diastolic function, and exhibiting anti-inflammatory actions. Their involvement in septic shock, however, is unknown, and they may also produce hypotension and arrhythmias. As a result, they should be used cautiously and only in certain instances or clinical trials.

6.Inotropes and vasopressors should be chosen and dosed individually based on the patient's clinical state, hemodynamic objectives, and response to therapy. A full assessment of the patient's perfusion state, including clinical symptoms, laboratory testing, and sophisticated monitoring techniques, should guide the administration of these medications.

7.The use of inotropes and vasopressors should be part of a multimodal strategy for septic shock management that includes early infection detection and treatment, effective antibiotic medication, fluid resuscitation, and supportive care.

Despite progress in understanding and management of septic shock, there are still many knowledge gaps and obstacles that need to be addressed.Future studies are recommended to explore the following areas:

1.The optimal timing and dose of vasopressors and inotropes in septic shock, as well as the potential benefits and harms of combining different agents or switching from one agent to another.

2.The role of biomarkers in guiding vasopressor and inotrope selection and titration, as well as predicting the response and prognosis of septic shock patients.

3.The discovery and testing of new vasopressors and inotropes with more specific and beneficial effects on microcirculation, inflammation, and organ function in septic shock.

4.Identification of septic shock subgroups that may benefit from customized or precision medicine treatments based on genetic, epigenetic, or phenotypic markers.

5.Implementing and disseminating evidence-based recommendations and practices for the use of vasopressors and inotropes in septic shock, as well as evaluating their influence on clinical outcomes and resource consumption.

**Table 1.** Lung Ultrasound dynamic reaeration score as suggested by Bouhemad et al. (7)

| Vasopressor Agents | Mechanism Of Action | Standard Dose Range | Major Side Effects |
|---|---|---|---|
| Norepinephrine | ↑venous and arterial tone preload, and contractility | 0.01 to 3 g/kg/min | Peripheral ischemia, inadvertent immunomodulation and cardiac arrhythmia |
| Epinephrine | ↑contractility, preload , venous and arterial tone and heart rate | Infusion: 0.01 to 0.10 μg · kg−1 · min−1 Bolus: 1 mg IV every 3 to 5 min (max 0.2 mg/kg) IM: (1:1000): 0.1 to 0.5 mg (max 1 mg) | Tachycardia, tachyarrhythmia and increased blood lactate levels |
| Dopamine | ↑contractility, heart rate, venous and arterial tone and renal and mesenteric vasodilation | 2.0 to 20 μg · kg−1 · min−1 (max 50 μg · kg−1 · min−1) | Tachycardia, tachyarrhythmia |
| Vasopressin | Restore vascular tone and blood pressure | 0.01 to 0.04 units/min | Hyponatremia, cardiac arrhythmias, digital ischemia, and mesenteric ischemia |
| Terlipressin | Constricts blood arteries by binding to V1 receptors and increases water reabsorption by binding to V2 receptors | 0.01 to 0.06 mg/kg/h | Same as Vasopressin |
| Selepressin | Activates V1 receptors to cause vasoconstriction and blood pressure elevation | 0.05 to 0.15 g/kg/min | Same as Vasopressin |

## AUTHORS' CONTRIBUTION

B Qura'an: Writing, drafting and editing the manuscript and leading the team. H Bani Omar:Writing, drafting and editing the manuscript.O Al-Qaqa:Writing, drafting and editing the manuscript.M Abu-Jeyyab: Writing, drafting and editing the manuscript. M Gazi Hattab:Editing the manuscript. M Ruzieh:Team supervisor and critical review of the article.

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## DISCLOSURE

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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