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Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review

Hang-Xiang Zhou, Chun-Fu Yang, He-Yan Wang, Yin Teng, Hang-Yong He

Abstract

Septic shock treatment remains a major challenge for the ICU, despite the recent prominent advances in both management and outcomes. Vasopressors serve as a cornerstone of septic shock therapy, is yet still controversial over the timing of administration. Specifically, it remains unclear whether vasopressors should be used early in the course of treatment. Herein, we provide a systematic review of the literature on the timing of vasopressor administration. Researches were systematically identified through PubMed, Embase and Cochrane searching according to PRISMA guidelines. Fourteen studies met the eligibility criteria and were therefore included in the review. The pathophysiological basis for early vasopressors use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or Angiotensin-II. We found that mortality was reported 28.1%-47.7% in the early vasopressors group, and 33.6%-54.5% in the control group. We also investigated the issue of vasopressor responsiveness. Furthermore, we acknowledged the subsequent challenge of administering high-dose norepinephrine via the peripheral vein with early vasopressor use. Based on the literature review, we
propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

INTRODUCTION
Sepsis and septic shock were still considered a major challenge in healthcare, associated with significant morbidity and mortality\cite{1-3}, where septic shock is the most severe form, also considered one of the most prominent challenges in critical care medicine, characterized by persistent hypotension and the presence of tissue hypoperfusion, with a mortality of 28.6\%\cite{4-6}.

The primary therapies to resuscitate septic shock are to hold the systemic blood pressure and promote the regional and microcirculatory perfusion. According to the Surviving Sepsis Campaign (SSC) guidelines, it is recommended to increase blood pressure with intravenous fluids and vasopressors treatment, and fluid resuscitation without vasopressors is not recommended until a lack of hypotension correction is confirmed. However, recent studies have proposed that early initiation of vasopressors such as norepinephrine with fluid loading may allow for an early resolve of the hypotension by reaching the target arterial pressure\cite{7}. Therefore, the timing of vasopressors therapy is speculated to be crucial to optimize the outcomes of septic shock patients\cite{8}. Furthermore, adding other vasopressors such as vasopressin and Angiotensin-II to norepinephrine may decrease the norepinephrine dosage by raising arterial pressure\cite{9-12}. Recent studies have also been focused on whether an early initiation of vasopressin or Angiotensin-II to norepinephrine as a combined therapy could lead to a better outcome in septic shock patients compared to norepinephrine monotherapy\cite{13,14}. 
Herein, we conducted a systematic review on the available evidence regarding the physiological and clinical effects of early initiation of single or combined vasopressors during septic shock treatment for adult subjects, aiming to provide evidence on optimal timing and protocol for vasopressors administration during septic shock resuscitation.

THE RATIONALE FOR EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK

An early administration of vasopressors may exert several potential beneficial effects in septic shock. According to clinical and experimental studies, several possible mechanisms may support the idea to initiate vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow increase and fluid overload prevention.

*Early vasopressors can improve perfusion in septic shock*

The early initiation of vasopressors could reduce the time of insufficient perfusion caused by hypotension. Previous studies have suggested a relation of risks for mortality and acute kidney injury with a long duration and a high severity of hypotension in septic patients\(^ {15-17}\). As a result, the earlier administration of vasopressor, the quicker relief of the hypotension, and the shorter duration of organ hypoperfusion, thus achieving a better outcome\(^ {16}\).

Early initiation of vasopressor therapy raises the mean arterial pressure to a contributing level to facilitate tissue perfusion and prevent the onset or progression of organ dysfunction\(^ {18}\). It is widely recognized that organs require a critical mean arterial pressure to allow an adequate perfusion. When the mean arterial pressure is maintained below to organ’s critical perfusion pressure, organ injury may occur\(^ {19}\),
Early initiation of vasopressors may promote the microcirculatory perfusion in septic shock[20,23]. Traditionally, the administration of vasopressors at the early phase of septic shock is concerned to potentially lead to the worsened microcirculation through excessive vasoconstriction of precapillary microvessels[24]. However, if the mean arterial pressure is below the threshold of autoregulation of organ blood flow, severe hypotension can theoretically worsen organ hypoperfusion. When norepinephrine is added to fluid infusion on the basis of a low diastolic pressure, the increased mean arterial pressure with norepinephrine will significantly elevate the tissue oxygen saturation (StO$_2$) recovery slope[22]. The StO$_2$ recovery slope reflects the capacity that microvessels are recruited in response to local hypoxia, as well as serving as a prognostic factor in septic shock patients. Furthermore, restoring arterial pressure with norepinephrine could significantly improve the microvascular reactivity during ischemia-reperfusion in severely hypotensive septic patients[22,25].

Early initiation of vasopressors modifies the coronary artery perfusion in septic patients by maintaining a proper diastolic arterial pressure[26]. Diastolic arterial pressure refers to the upstream pressure for the perfusion of the left ventricle. Indeed, the left ventricle is perfused only during the diastole, unlike the right ventricle during the whole cardiac cycle. Therefore, the low diastolic arterial pressure as frequently the case in early septic shock due to arterial tone depression will induce an increased risk of myocardial ischemia[26]. Early regain of a target diastolic blood pressure could be recommended for patients with unstable coronary artery disease or chronic pulmonary hypertension at risk of low coronary perfusion pressure[27].

*Early vasopressors can increase blood flow in septic shock*
Vasopressors can allow a higher blood flow by enlarging the stroke volume and cardiac output in the early stage of septic shock\textsuperscript{[28]}. In a study covering 105 patients with severely hypotensive septic shock, early administration of norepinephrine achieved an increase in stroke volume and cardiac output, which were revealed by an elevation of cardiac preload and systemic venous return in patients with preload responsiveness, through norepinephrine’s \( \alpha \)-adrenergic-mediated effects\textsuperscript{[23,29]}.

Early initiation of vasopressors increases organ blood flow and improves blood flow distribution. The improvement in mean arterial pressure by norepinephrine was associated with maintenance of aortic and mesenteric blood flow, achieving a better tissue oxygenation compared with fluid alone\textsuperscript{[30]}. Furthermore, norepinephrine may optimize the distribution of blood flow to the mesenteric region with an earlier administration\textsuperscript{[31]}.

\textit{Early vasopressors can prevent fluid overload during resuscitation in septic shock}

Early initiation of vasopressors was related to the decreased infused fluid volume. Two recent studies have demonstrated it in association with less fluid treatment volumes and the improved outcomes\textsuperscript{[32,33]}, and multiple studies have shown that large amounts of resuscitation fluids and positive cumulative fluid balance have correlation to the increased mortality in sepsis\textsuperscript{[32,34-38]}, and the increased incidence of pulmonary edema\textsuperscript{[39]}. Early administration of vasopressors induces an endogenous fluid recruitment by promoting venous return\textsuperscript{[40]}. Vasodilation would result in a reduced mean systemic filling pressure thus limiting venous return during septic shock. While vasopressors raise the blood pressure through the increase of systemic vascular resistance. The vasoconstrictive effect on venous system also contributes to increasing the venous return through mobilizing
non-stress volume to stress volume\cite{41,42}. Administration of vasopressors can therefore simulate a fluid bolus through endogenous fluid recruitment\cite{29}.

Early administration of vasopressors can diminish the capillary permeability by inhibiting inflammation. In one experiment, norepinephrine prominently reduces the endothelial permeability resulting from agonists of multiple Toll-like receptors in vitro, suggesting that both $\beta_1$- and $\beta_2$- adrenergic receptor could mediate the stabilizing effects of norepinephrine on the endothelial barrier\cite{43}.

THE EVIDENCES THAT SUPPORT EARLY INITIATION OF VASOPRESSORS: SYSTEMIC REVIEW OF CLINICAL STUDIES

*Literature search*

In accordance with the 2020 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org/PRISMAStatement), a systematic review was conducted. (Page et al, 2021). Pubmed, Medline, Embase, and Cochrane database from 2012 to September 28, 2022 were searched using the following search terms: ("early"[All Fields] OR "Time Factors"[MeSH Terms] OR ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]) OR ("delay" or "delayed"[All Fields])) AND ("vasopressor"[All Fields] OR ("noradrenaline"[All Fields] OR "norepinephrin"[All Fields] OR "norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields] OR "noradrenaline"[All Fields] OR "noradrenaline"[All Fields] OR "norepinephrine"[All Fields] OR ("vasopressin"[All Fields] OR "Vasoconstrictor Agents"[MeSH Terms]) AND "shock, septic"[MeSH Terms]). The search was slightly adjusted to different databases. In addition, we also reviewed the references listed in the identified articles, which were manually searched for the related articles to identify all relevant and eligible articles and to minimize publication bias.
Two researchers independently screened and evaluated the eligibility of all studies, and a third reviewer intervened if a disagreement emerged. Studies meeting the (1) Original research reports of septic shock patients; and (2) patients were treated with vasopressors early, were enrolled. The exclusion criteria were: (1) languages other than English; (2) study protocols, review articles, abstracts, editorials; (3) research on children or animals; and (4) case reports. The flow chart of the search strategies is depicted in Figure 1.

The primary outcome assessed was mortality, while the other endpoints included shock control rate, time to achieve target mean arterial pressure (MAP), incidence of organ failure and lactate clearance rate.

**Study characteristics**

The characteristics of the included trials are summarised in Tables 1 and 2. A total of 14 studies were included in this systematic review, including 3 randomized controlled trials (RCTs) and 11 observational studies, covering 11327 patients. The 14 studies were conducted in 8 countries, that were, United States (n = 5), Canada (n = 1), China (n = 1), Thailand (n = 1), Egypt (n = 1), Colombia (n = 1), Korean (n = 1), France (n = 1), and 2 were international studies.

**Definition of early initiation of vasopressors in septic shock:** There conclude two definitions for “early initiation of vasopressors in septic shock” employed in previous studies.

First, in most studies, “early initiation” was defined as the initiation of a vasopressor such as norepinephrine during the early stage of hypotension or shock onset as a mono-vasopressor therapy, and as the same time (< 1 h) or even before the administration of loading fluid in 3 studies; Initiation of vasopressors after a short time (within 2, 3, and 6 h) of hypotension or shock onset was employed in other 3 studies; And 3 studies defined the early start
of vasopressors at an average of 30 minutes or 90 minutes after emergency room arrival or even prehospital. The studies above were summarized in Table 1.

Second, in other recent studies, the “early initiation” stood for an early addition of a second vasopressor such as vasopressin or Angiotensin-II to the first-line used norepinephrine as a multi-vasopressor therapy in severe septic shock patients, as summarized in Table 2.

Major outcomes and findings of studies for early administration of single vasopressor in septic shock.

Mortality was 28.1%-47.7% in the early group, and was 33.6%-54.5% in the control group. In 5 studies, norepinephrine was employed as a first line vasopressor early in septic shock. The 28/30 d mortality and hospital survival were reported as the primary outcome in 6 and 2 studies, respectively. And the lower mortality was reported in early vasopressor group by 7 studies. Other findings for early vasopressor initiation associated with lower occurrence of organ failures were reported in 2 studies; shorter time to MAP achievement in 3 studies; better lactate clearance in 4 studies; lower volume of fluid use in 2 studies; and less norepinephrine use (shorter duration or less dose) in 2 studies (Table 1).

Major outcomes and findings of studies for early administration of a second vasopressor as a combination therapy in septic shock.

A total of 5 studies involved the vasopressin or Angiotensin-II as an early second vasopressors for catecholamine-resistant septic shock. In 3 studies, vasopressin was added in 4 to 6 h after the addition of norepinephrine or one kind of catecholamine. In other 2 studies, angiotensin-II was added when the dose of norepinephrine reached over 0.2 μg/kg/min. A lower mortality was reported in the Angiotensin-II group in 1 study. Other 3 studies reported an
early administration of the second vasopressor for septic shock could contribute to achieving the target mean arterial pressure (Table 2).

**THE MARKERS PREDICTING OR SUGGESTING VASOPRESSOR’S RESPONSIVENESS**

A key point is which markers or indexes could provide a clue for selecting the most appropriate population from septic shock patients who could mostly benefit from an early initiation of vasopressors. Several potential markers predicting vasopressor requirements were proposed in previous studies, such as diastolic arterial blood pressure\(^{26,44}\) and dynamic elastance to identify early initiation of norepinephrine in the first line mono-vasopressor therapy. Moreover, kinetics of norepinephrine dose increment, serum lactate level and rennin level were employed to identify the timing for early administration of vasopressin or Angiotensin-II based on a norepinephrine multi-vasopressor therapy.

**Norepinephrine responsiveness predictors**

**Diastolic arterial pressure:** Physiologically, a low diastolic arterial pressure can essentially result from the depression of arterial tone, bradycardia, or arterial stiffness. In case of tachycardia, a value of diastolic arterial pressure < 40 mmHg strongly suggested a markedly depressed arterial tone and the requirement to prompt initiation of a vasopressor\(^{24}\). Therefore, a low diastolic arterial pressure could serve as a simple indicator to identify patients requiring norepinephrine urgently at the early stage of septic shock\(^{26}\).

**Dynamic arterial elastance:** Dynamic arterial elastance (\(E_{\text{a,dy}}\)) is defined as the pulse pressure variation/stroke volume variation ratio. Arterial pressure in a hypotensive patient will be increased, if \(E_{\text{a,dy}}\) is high and the cardiac...
output is increased. In contrary, the low $E_{a,\text{dy}}$ will not elicit a proportionally increased arterial pressure despite the increased cardiac output in response to volume challenge. In such hypotensive cases, the addition of vasopressors should be considered to correct hypotension. $E_{a,\text{dy}}$ has been demonstrated to be superior to diastolic arterial pressure as a marker of early initiation of vasopressors in septic shock patients\textsuperscript{[45]}. 

**Vasopressin responsiveness predictors**

Norepinephrine-equivalent dose. Norepinephrine-equivalent dose may serve as an easily accessible marker to utilize with a consideration of an early vasopressin initiation before doses higher than 10-15 \( \mu g/min \) (0.1-0.2 \( \mu g/kg/min \) in a patient weighing 80 kg)\textsuperscript{[44]}.

Norepinephrine dose escalating kinetics. Clinically, two dose-requirement profiles, "refractory" and "controlled", can be observed at the patient's bedside. A "refractory" profile meets the requirements of an exposure to an exponential increase in norepinephrine dose, and a "controlled" profile with a gradual increase in norepinephrine dose to a plateau does not reach toxic levels of norepinephrine. In the refractory profile, the earlier vasopressin is started, the greater the chance of avoiding norepinephrine surge and exposure to harmful norepinephrine doses. In the "controlled" profile, it may not be necessary to add vasopressin at the norepinephrine threshold of 0.5 \( \mu g/kg/min \)\textsuperscript{[46]}.

**Angiotensin-II responsiveness predictors**

It appears that a subgroup of patients with impaired endogenous renin-angiotensin system\textsuperscript{[47]} function exhibit a pronounced response to Angiotensin-II and may derive benefits from earlier administration. Therefore, due to the robust relationship between hyper-reninemia and favourable Angiotensin-II
response, renin is rapidly emerging as a promising prognosticator for the early initiation of Angiotensin-II in septic shock\[14,48]. Bellomo et al\[49\] investigated the role of Angiotensin-II in patients with catecholamine-resistant vasodilatory shock and revealed the high renin levels in majority of these patients (76%). Using a cut-off of 173 pg/mL, Angiotensin-II administration was found to improve the mortality in the subset of patients with high renin levels, suggesting that measurement of renin levels may contribute to identifying patients who might benefit from Angiotensin-II therapy. It is worthy to note that 173 pg/mL as the median renin level of the participants in the study and cannot be directly applied in clinical practice, further prospective trials are required to confirm these findings.

POSSIBLE ADVERSE EFFECTS OF EARLY INITIATION OF VASOPRESSORS

Feasibility and safety of peripheral infusion of high concentration of norepinephrine

The application of high concentrations of norepinephrine via the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock who meet the indications. Considering the strong vasoconstriction due to norepinephrine, the most appropriate approach is to administer the drug in the intensive care unit (ICU) after placing a central venous catheter. However, if the timing of norepinephrine administration is advanced to admission to the ICU, in the emergency department, or even prehospital\[50\], central venous catheter placement may not be generally feasible.

A previous study\[51\] has systematically reviewed the literature on the peripheral infusion of norepinephrine and noted that the available data failed to reveal a correlation between the occurrence of adverse events and the
application of peripheral vein access. The administration of norepinephrine through the peripheral vein requires concerns of concentration, dosage, duration, and infusion site. In a study by Nguyen et al[52], the concentration of norepinephrine administered via the peripheral vein was 64 μg/mL, and the median dosage as 10 μg/min, which is ranked as the higher concentration and dosage employed in the current data, the anterior elbow/external jugular vein was considered the site of infusion, with the median duration of infusion of 62 min, and the incidence of adverse events of 4.5%.

Myocardial ischemia in septic shock with early initiation of vasopressors

Septic shock is complicated by myocardial ischemia, which exacerbates diastolic shock symptoms such as tachycardia and hypotension. Norepinephrine can be administered after adequate fluid resuscitation. An RCT[53] comparing the efficacy of norepinephrine and epinephrine in patients with diastolic shock complicated by acute myocardial infarction revealed no significant difference in cardiac index. It does, however, show a notable disparity in heart rate; epinephrine results in a faster heart rate, which is particularly unfavorable for patients with myocardial ischemia. Additionally, dobutamine also elevates heart rate and directly contributes to increased morbidity and mortality[54], and should be avoided in these patients. An RCT[55] also compared early use of vasopressin vs norepinephrine, revealing a higher incidence of life-threatening arrhythmia in the NE group (0.98% vs 2.5%), and a higher incidence of acute coronary syndrome in the VP group (3.4% vs 1.0%). These findings suggest that patients with coronary artery disease may benefit from avoiding vasopressin, while those with tachyarrhythmias may consider early co-administration of this drug. In contrast, Reardon's study[56] found a trend toward improvement in cardiac biomarkers in the early VP group; however, no specific etiology was
identified and the research was limited to a single center retrospective analysis.

**A POSSIBLE PROTOCOL FOR CONSIDERING THE EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK**

A possible protocol for early administration of vasopressors in septic shock patients is depicted in Figure 2, based on the literature reviewed above.

As the time point of vasopressors initiation is the primary focus of our protocol, the source control of sepsis, use of albumin and early steroid use are not included in the figure. However, there are four prominent randomized controlled trials investigating the administration of corticosteroids in patients with septic shock, yet their findings yield contradictory results. The enrollment time across the four studies were from 8 h\(^{[57]}\) to 24 h\(^{[58,59]}\) and 72 h\(^{[60]}\). Two trials demonstrated that early adding corticosteroids to vasopressors significantly reduce all-cause mortality among patients with septic shock. Additionally, it is noteworthy that the majority of these trials initiated hydrocortisone administration concurrently with norepinephrine at a dosage range of 0.5-1 μg/kg/min. The Surviving Sepsis Campaign guidelines recommend administering intravenous corticosteroids to septic shock patients who require ongoing vasopressor therapy, commencing as early as 4 hours after the initiation of vasopressors and at a minimum norepinephrine dosage of 0.25 μg/kg/min.

Moreover, source control should be required as an emergent intervention as soon as a specific anatomical diagnosis of infection is identified. And early albumin infusion also should be considered when patients receive large volumes of crystalloids.

**CONCLUSION**
In septic shock, an early start of vasopressors may exert several potential beneficial effects. Several mechanisms possibly support the idea to initiate vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow enlargement and fluid overload prevention. Clinical evidences have suggested possible benefits of early initiation of mono-vasopressor or combined several kinds of vasopressors in the resuscitation of septic shock. Several potential markers predicting vasopressor requirements were mentioned, where diastolic arterial blood pressure and dynamic elastance are taken to identify early initiation of norepinephrine in the first line mono-vasopressor therapy, and kinetics of norepinephrine dose increment, serum lactate level and rennin level were applied to identifying the timing for early start of vasopressin or Angiotensin-II based on a norepinephrine multi-vasopressor therapy. And using high concentrations of norepinephrine via the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock.
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