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ABOUT COVER

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MINIREVIEWS

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

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Abstract

Septic shock treatment remains a major challenge for intensive care units, despite the recent prominent advances in both management and outcomes. Vasopressors serve as a cornerstone of septic shock therapy, but there is still controversy over the timing of administration. Specifically, it remains unclear whether vasopressors should be used early in the course of treatment. Here, we provide a systematic review of the literature on the timing of vasopressor administration. Research was systematically identified through PubMed, Embase and Cochrane searching according to PRISMA guidelines. Fourteen studies met the eligibility criteria and were included in the review. The pathophysiological basis for early vasopressor use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or angiotensinII. We

found that mortality was 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 administration of high-dose norepinephrine *via* peripheral veins with early vasopressor use. Based on the literature review, we propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

Key Words: Septic shock; Resuscitation; Vasopressor; Norepinephrine; Vasopressin; Timing

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Core tip: It remains unclear whether vasopressors should be used early in the course of treatment of septic shock. Here, we provide a systematic review of the literature on the timing of vasopressor administration. 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 angiotensinII. We also investigated the issue of vasopressor responsiveness and the subsequent challenge of administrating 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.

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INTRODUCTION

Sepsis and septic shock are still considered a major challenge in healthcare, associated with significant morbidity and mortality[1-3]. Septic shock is the most severe form, and 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%[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, 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 early resolve of hypotension by reaching the target arterial pressure[7]. Therefore, the timing of vasopressor therapy is speculated to be crucial to optimize the outcomes of septic shock patients[8]. Furthermore, adding other vasopressors such as vasopressin and angiotensinII to norepinephrine may decrease the norepinephrine dosage by raising arterial pressure[9-12]. Recent studies have also been focused on whether an early initiation of vasopressin or angiotensinII to norepinephrine as a combined therapy could lead to a better outcome in septic shock patients compared to norepinephrine monotherapy[13,14].

Here, we conducted a systematic review of the available evidence regarding the physiological and clinical effects of early initiation of single or combined vasopressors during septic shock treatment in adults, aiming to provide evidence on optimal timing and protocol for vasopressors administration during septic shock resuscitation.

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 (MAP) 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 MAP to allow an adequate perfusion. When the MAP 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 MAP 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 MAP with norepinephrine significantly increases 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, induces 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[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 the α 1-adrenergic-mediated effects of norepinephrine[23,29].

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

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[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[32,34-38], and the increased incidence of pulmonary edema[39].

Early administration of vasopressors induces endogenous fluid recruitment by promoting venous return[40]. Vasodilation results in reduced mean systemic filling pressure, thus limiting venous return during septic shock. Vasopressors raise blood pressure through increased systemic vascular resistance. The vasoconstrictive effect also contributes to increasing the venous return through mobilizing non-stress volume to stress volume[41,42]. Administration of vasopressors can therefore simulate a fluid bolus through endogenous fluid recruitment[29].

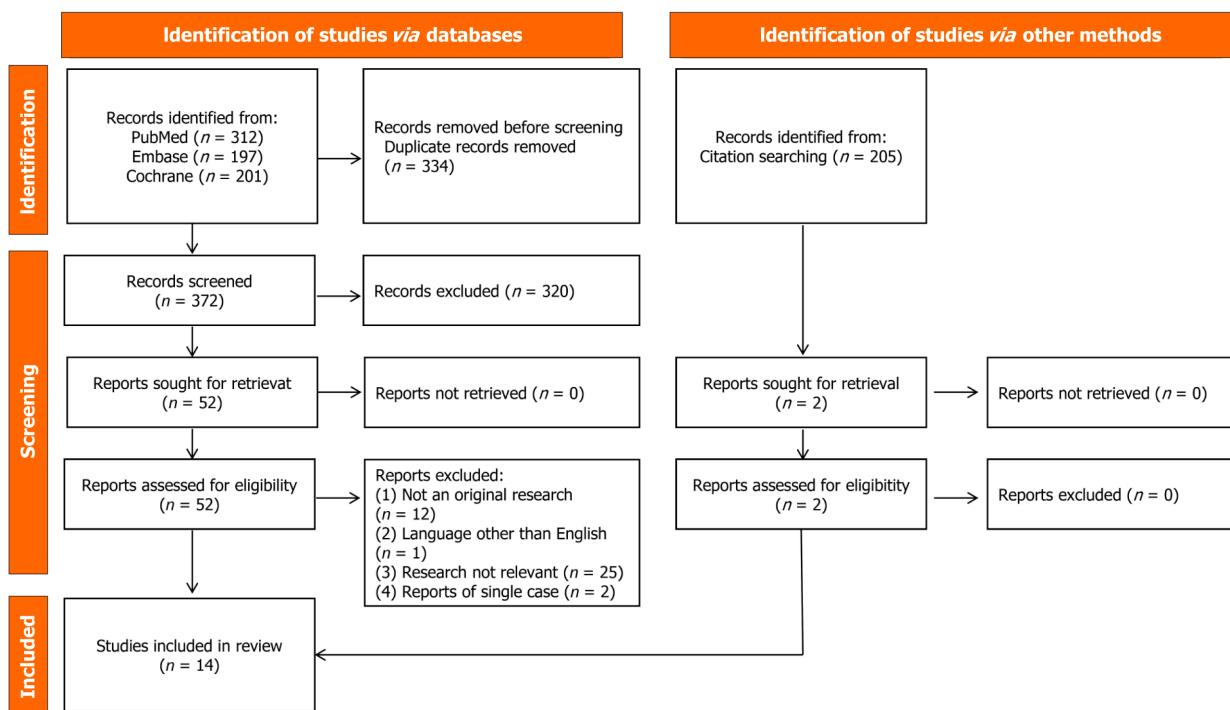
Early administration of vasopressors can diminish the capillary permeability by inhibiting inflammation. In one experiment, norepinephrine prominently reduced the endothelial permeability resulting from agonists of multiple Toll-like receptors *in vitro*, suggesting that both β 1- and β 2-adrenergic receptors mediate the stabilizing effects of norepinephrine on the endothelial barrier[43].

EVIDENCE THAT SUPPORTS 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](http://www.prisma-statement.org/)), a systematic review was conducted. 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*"[All Fields]) AND ("vasopressor*"[All Fields] OR ("noradrenalines"[All Fields] OR "norepinephrin"[All Fields] OR "norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields] OR "noradrenalin"[All Fields] OR "noradrenaline"[All Fields] OR "norepinephrines"[All Fields]) OR "vasopressin*"[All Fields] OR "Vasoconstrictor Agents"[MeSH Terms]) AND "shock, septic"[MeSH Terms]). The search was slightly adjusted to different databases. 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. Original research reports of septic shock patients, and studies in which patients were treated with vasopressors early were enrolled. The exclusion criteria were: (1) Languages other than English; (2) study protocols, review articles, abstracts, and editorials; (3) research on children or animals; and (4) case reports. The flow chart of the search strategies is depicted in Figure 1.



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Figure 1 The PRISMA flow diagram of literature search, screen, and selection criteria.

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

Study characteristics

The characteristics of the included trials are summarized in Tables 1 and 2. A total of 14 studies were included in this systematic review, including three randomized controlled trials (RCTs) and 11 observational studies, covering 11327 patients. The 14 studies were conducted in the USA ($n = 5$), Canada ($n = 1$), China ($n = 1$), Thailand ($n = 1$), Egypt ($n = 1$), Colombia ($n = 1$), Korea ($n = 1$), France ($n = 1$), and two were international studies.

Definition of early initiation of vasopressors in septic shock: There were two definitions for early initiation of vasopressors in septic shock used 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 at the same time (< 1 h) or even before administration of loading fluid in three studies. Initiation of vasopressors after a short time (within 2, 3 or 6 h) of hypotension or shock onset was used in other studies. Three studies defined the early start of vasopressors at an average of 30 or 90 min after emergency room arrival or even before hospital. The studies above were summarized in Table 1.

Second, in other recent studies, early initiation stood for early addition of a second vasopressor such as vasopressin or angiotensinII to the first-line norepinephrine as multi-vasopressor therapy in severe septic shock (Table 2).

Major outcomes and findings of studies for early administration of single vasopressors in septic shock: Mortality was 28.1%–47.7% in the early group and 33.6%–54.5% in the control group. In five studies, norepinephrine was used as a first-line vasopressor early in septic shock. The 28–30-day mortality and hospital survival were reported as the primary outcome in six and two studies, respectively. Lower mortality was reported in the early vasopressor group in seven studies. Other findings for early vasopressor initiation associated with lower occurrence of organ failure were reported in two studies; shorter time to MAP achievement in three studies; better lactate clearance in four studies; lower volume of fluid use in two studies; and less norepinephrine use (shorter duration or lower dose) in two 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 five studies involved vasopressin or angiotensinII as an early second vasopressor for catecholamine-resistant septic shock. In three studies, vasopressin was added at 4–6 h after addition of norepinephrine or one type of catecholamine. In two other studies, angiotensinII was added when the dose of norepinephrine reached >0.2 µg/kg/min. A lower mortality was reported in the angiotensinII group in one study. Three studies reported that early administration of the second vasopressor for septic shock contributed to achieving the target MAP (Table 2).

Table 1 Basic characteristics of studies on early initiation of vasopressors included in the systematic review

No.	Ref.	Study design and period	No. of patients/early/late group	Agents	Time 0	Definition for early initiation	Primary outcome reported	Primary outcome	Other points	Comments
1	Beck et al [31], 2014, Canada	Multicenter, retrospective cohort study 1996-2008	6514/-/-	NE, Dopamine, Phenylephrine, VP, Epinephrine			Survival to hospital discharge	A weak correlation between vasopressor delay and hospital mortality (adjusted OR 1.02/h, $P < 0.001$)	The significance was found between the delay to vasopressor initiation (> 14 h post hypotension) and the occurrence of organ failure	1 Markedly delayed initiation of vasopressor (> 14 h after hypotension) in septic shock patients is associated with a small increase in mortality risk. 2 Delays in vasopressor initiation is only weakly associated with mortality, while delays in antimicrobial is more higher
2	Bai et al [61], 2014, China	Two centers, retrospective cohort study, Jan. 2011-Dec. 2012	213/86/127	NE	Septic shock onset	NE administered within 2 h after onset of septic shock	28 d mortality	The early group was lower than the late group, 29.1% vs 43.3%, $P < 0.001$	1 Duration of NE was significantly shorter in the early-NE group (2.6 ± 0.6 d vs 2.9 ± 1.0 d, $P = 0.001$). 2 Serum lactate levels at 2, 4, 6 and 8 h after septic shock onset were significantly lower in the early-NE group ($P < 0.05$)	1 Early administration (within 2 h after the septic shock onset) of NE in septic shock patients is associated with an increased survival rate. 2 Early NE initiation can increase MAP, shorten the duration of hypotension and, improve vital organ perfusion and decrease serum lactate levels
3	Permpikul et al [39], 2019, Thailand	Single center, RCT, Oct. 2013-Mar. 2017	310/155/155	NE	ED arrival	Median time from emergency room arrival to NE administration was 93 min	Shock control rate	Early NE administration resulted in significant higher shock control rate than standard treatment, 76.1% vs 48.8%, $P < 0.001$	1 Achievement of target MAP (> 65 mmHg), urine output (> 0.5 mL/kg) and lactate clearance ($> 10\%$) were all significantly higher in the early-NE group (all $P < 0.05$). 2 There was no difference between groups for the rates of mechanical ventilator support or RRT. 3 patients in the early-NE group had a lower rate of cardiogenic pulmonary edema (14.4% vs 27.7%, $P = 0.004$) and new-onset arrhythmia (11% vs 20%, $P = 0.03$)	This study confirms that the early use of NE, can enable septic shock patients to benefit in short-term endpoints, such as shock control rate, urine output and lactate clearance, represented both macro- and micro-circulation restoration
4	Colon et al [62], 2019, United States	Single center, retrospective cohort study Jan. 2017-Jul. 2017	119/76/43	Vasopressors	Initial hypotension	Received vasopressor within 6 h from initial hypotension	30 d mortality	Vasopressor initiation after 6 h from shock onset is associated with a significant increase in 30 d mortality, 25% vs 51.1%, $P < 0.01$	1 Logistic regression analysis: administration of vasopressors after 6 h from hypotension were independently associated with increased 30 d mortality. 2 The time to target MAP was shorter in the early vasopressor group (1.5 h vs 3 h, $P < 0.01$)	1 Demonstrates that there is a mortality benefit with early use of vasopressor. 2 Early administration of vasopressor in septic shock patients (< 6 h from initial hypotension) is associated with decreased mortality, that is likely secondary to faster achievement of MAP goals
5	Elbouhy et al	Single center,	101/57/44	NE	ED admission	NE infusion started	In-hospital	Early NE in septic	1 MAP of 65 mmHg was achieved after 2 h	1 They found that early use of

	al[63], 2019, Egypt	RCT Jan. 2017-Dec. 2018								
6	Ospina-Tascón et al [64], 2020, Colombia	Single center, prospective cohort study, Jan.2015-Feb.2017	186/93/93	NE, VP	First resuscitative fluid load	Vasopressor support initiated within the next hour or even before the first fluid load with resuscitative intention (FRLload)	Association between early vasopressor and 28 d mortality	Early vasopressor was associated with a significant reduction in the risk of death compared to delayed vasopressor (HR 0.31, 95%CI 0.17-0.57, $P < 0.001$) at day 28	1 Patients in the early vasopressor group received less resuscitation fluids in the first 8 h of resuscitation ($P < 0.001$). 2 There were no significant differences regarding the maximal dose of NE, steroids and VP use, or requirement of RRT. 3 No cases of severe digital or severe vasopressor-induced splanchnic ischemia were documented	1 Early vasopressor support is associated with less use of resuscitation fluids, less fluid accumulation, and shortening of hypotension time. 2 Early vasopressor was not associated with increased kidney injury or ischemia-related adverse effects, and it might decrease mortality in patients with septic shock
7	Yeo et al [65], 2021, Korean	Multicenter, prospective observational study Sep. 2019-Feb. 2020	298/149/149	NE, VP, epinephrine, dopamine	First resuscitative fluid load	Vasopressor was initiated within 1 h of the first resuscitative fluid load	28 d mortality	Vasopressor initiation within 1 h was associated with higher 28 d mortality, 47.7% vs 33.6%, $P = 0.013$	1 Volume of fluid given within the initial 6 h was significantly lower in the early group ($P = 0.046$). 2 The total SOFA score on day 3 in ICU was significantly lower in the late group than that in the early group ($P = 0.045$). Lactate levels were significantly lower on day 3 in the late group than that in the early group ($P = 0.014$)	1 Use of a vasopressor within 1 h of the first fluid loading was related to higher mortality in patients with septic shock. 2 Less fluid was administered to the early group, but inadequate fluid resuscitation exhibited worse organ function and lactate clearance 3 d after septic shock onset
8	Jouffroy et al[50], 2022, France	Multicenter, retrospective study, Apr. 2016-Dec. 2020	478/143/335	NE	Prehospital	Patients with prehospital NE administration (early NE)	30 d mortality	Prehospital NE infusion (early NE) is associated with a decrease in 30 d mortality	N/A	A strength of this study is that NE administration is started within 1 h after septic shock onset and before the completion of the fluid resuscitation
9	Xu et al[7], 2022, United States	Single center, retrospective observational cohort study 2008-2019	2862/1431/1431	NE	Septic shock onset	Receiving NE within the first 3 h	28 d mortality	Early group had lower 28 d mortality, 30.0% vs 37.8%, $P < 0.001$	Patients in the early-NE initiation group had a significantly shorter duration of ICU and hospital stay, shorter duration of supportive NE and invasive mechanical ventilation, lower incidence of acute kidney injury, and lower proportion of organ failure progression than patients in the delayed NE initiation group	NE initiation within the first 3 h, regardless of preload dependency, was associated with longer survival time and shorter duration of supportive NE and invasive mechanical ventilation and may delay or partially reverse rapid onset organ failure

Sum	USA 2, other countries 1	2 RCTs	11081/2190/2377	NE 5	Shock onset 3, ED arrival 2, First fluid 2, Prehospital 1	Within 2, 3 and 6 h after shock, Within 0, 0.5, 1 h of fluid start, Prehospital	28 d mortality 4 and 30 d mortality 2 hospital survival 2	Mortality was lower in early group in 7 studies; mortality in early group was 28.1%-47.7%, in control group was 33.6%-54.5%
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ED: Emergency department; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; VP: Vasopressin; N/A: Not applicable.

MARKERS PREDICTING OR SUGGESTING VASOPRESSOR 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 first-line mono-vasopressor therapy. The kinetics of norepinephrine dose increment, and serum lactate and rennin levels were used to identify the timing for early administration of vasopressin or angiotensinII based on a norepinephrine multi-vasopressor therapy.

Norepinephrine responsiveness predictors

Diastolic arterial pressure: Physiologically, a low diastolic arterial pressure can result from depression of arterial tone, bradycardia, or arterial stiffness. In case of tachycardia, diastolic arterial pressure < 40 mmHg strongly suggests 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 ($E_{a,dyn}$) is defined as the pulse pressure variation/stroke volume variation ratio. Arterial pressure in a hypotensive patient is increased, if $E_{a,dyn}$ is high and the cardiac output is increased. In contrast, low $E_{a,dyn}$ does 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. $E_{a,dyn}$ has been demonstrated to be superior to diastolic arterial pressure as a marker of early initiation of vasopressors in septic shock patients[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 μ g/min (0.1-0.2 μ g/kg/min in a patient weighing 80 kg)[14].

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 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

Table 2 Basic characteristics of studies on early combination with another vasopressor included in the systematic review

No.	Ref.	Study design and period	No. of patients	Agents	Time 0	Definition for early combination	Primary outcome reported	Primary outcome	Other points	Comments
1	Reardon et al [56], 2014, United States	Single center, retrospective study Jan. 2010-Dec. 2011	71, 35 (early)/36 (late)	VP	Catecholamine initiation	VP was initiated within 6 h of catecholamine therapy	Impact of VP on catecholamine dose and duration	No difference in dose and duration of catecholamine or VP therapy between the 2 groups	1 There was a significant difference in incidence of new-onset arrhythmias between the early VP and late groups ($P < 0.001$). 2 There was a trend toward worsening troponin T and CK-MB in the late VP group	1 Early VP therapy was associated with no difference in total catecholamine requirements but decreased incidence of new-onset arrhythmias. 2 There was also a trend toward improvement in cardiac biomarkers in the early VP group
2	Hammond et al [11], 2018, United States	Single center, prospective trial Nov. 2015-Jun. 2016	82, 41 (VP)/41 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP faster than those receiving initial NE alone ($P = 0.058$)	-	Early concomitant VP and NE achieved and maintained a target MAP faster than initial NE alone, particularly in those in whom absolute or relative VP deficiency is suspected or confirmed
3	Hammond et al [13], 2019, United States	Single center, retrospective cohort study, May 2014-Oct. 2015	93, 48 (VP)/48 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP sooner than later or no initiation ($P = 0.023$)	1 Changes in SOFA at 76 h since septic shock onset, the early VP saw a significant decrease of 4 compared to a decrease of 1 for NE alone ($P = 0.012$). 2 Early VP were discharged from the hospital 10 d sooner than those in the NE alone (14.3 vs 25.2 d, $P = 0.014$). 3 Incidence and duration of RRT were comparable between groups (17% vs 25% and 6.7 vs 11.2 d, respectively)	Early VP in combination with NE achieved a target MAP faster than the NE alone and may be more likely to resolve organ dysfunction at 72 h, although the in-hospital and 28-d mortalities were similar between groups, patients who survived benefited from earlier achievement and maintenance of goal MAP
4	Khanna et al [66], 2017, International	Multicenter, RCT May. 2015-Jan 2017	321/163/158	ATII	NE initiation	> 0.2 µg/kg/min of NE	Response to MAP at 3 h	More patients in the ATII response to MAP at 3 h (69.9% vs 23.4%, $P < 0.001$)	1 At 48 h, mean doses of background vasopressors were consistently less in the AT II group. 2 At 48 h, the mean improvement in the cardiovascular SOFA score was greater in the ATII group (-1.75 vs -1.28, $P = 0.01$). 3 No difference between the two groups for serious adverse reactions. 4 No difference between the two groups for 28 d mortality	1 Demonstrates the safety and efficacy of widespread clinical use of ATII. 2 ATII reduces the need for catecholamines in patients with catecholamine-resistant vasodilatory shock (CRVS), while reducing the cardiovascular injury it causes
5	Bellomo et al [49], 2020, International	Multicenter, Retrospective study	255/127 (low)/119 (high)	ATII	NE initiation	> 0.2 µg/kg/min of NE	Renin kinetic changes and their prognostic value in CRVS	In patients with higher renin concentrations, ATII significantly reduced 28-d mortality compared with placebo ($P = 0.012$)	1 Baseline serum renin concentration was above the upper limits of normal in 194 of 255 (76%) patients with a median renin concentration of 172.7 pg/mL. 2 At 3 h after initiation of ATII therapy, there was a 54.3% reduction in renin compared with a 14.1% reduction with placebo ($P < 0.0001$)	Serum renin concentrations are significantly higher in CRVS and may identify patients in whom early combination with ATII has a beneficial effect on clinical outcome
Sum	United States 3, International 2	RCT 1, Retrospective study 3	822, 414/402	VP 3, ATII 2	Vasopressors initiation 5	Within 4, 6 h of catecholamine, > 0.2 µg/kg/min of NE	Time to target MAP 2	1 VP, Achieved target MAP faster 2, No difference 1. 2 ATII response to MAP 1		

reduced mortality 1

ATII: Angiotensin-II; CRVS: Catecholamine-resistant vasodilatory shock; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; VP: Vasopressin.

necessary to add vasopressin at the norepinephrine threshold of 0.5 µg/kg/min[46].

Angiotensin-II responsiveness predictors

It appears that a subgroup of patients with an impaired endogenous renin-angiotensin system[47] exhibit a pronounced response to angiotensinII and may derive benefits from earlier administration. Therefore, due to the robust relationship between hyper-reninemia and favorable angiotensinII response, renin is rapidly emerging as a promising prognosticator for the early initiation of angiotensinII in septic shock[14,48]. Bellomo *et al*[49] investigated the role of angiotensinII in patients with catecholamine-resistant vasodilatory shock and revealed the high renin levels in most of these patients (76%). Using a cutoff of 173 pg/mL, angiotensinII administration improved 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 angiotensinII therapy. Median renin level of 173 pg/mL in the study cannot be directly applied in clinical practice; therefore, further prospective trials are required to confirm these findings.

POSSIBLE ADVERSE EFFECTS OF EARLY INITIATION OF VASOPRESSORS

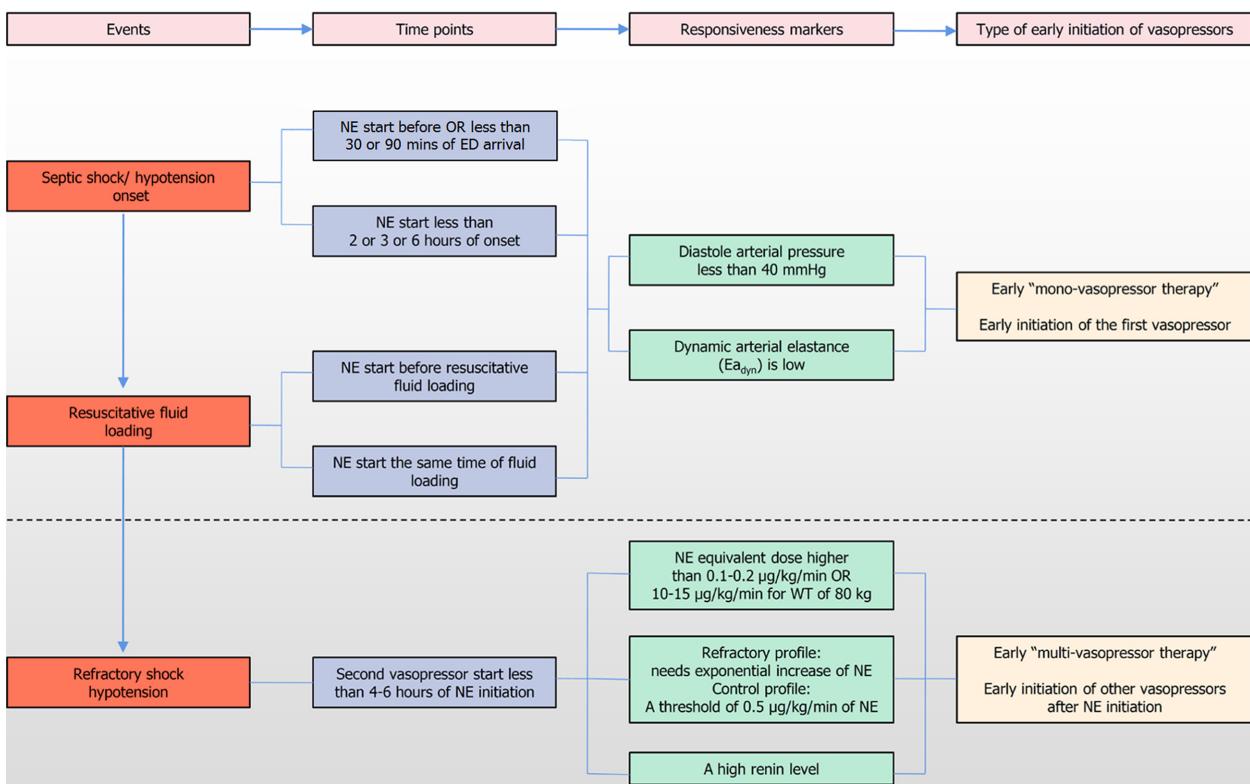
Feasibility and safety of peripheral infusion of high concentration of norepinephrine

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 intensive care units (ICUs) after placing a central venous catheter. However, if the timing of norepinephrine administration is advanced to admission to ICUs, emergency departments, 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 knowledge of concentration, dose, 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 dose as 10 µg/min, which was considered to be a high dose; the anterior elbow/external jugular vein was considered the site of infusion, with a median duration of infusion of 62 min; and the incidence of adverse events was 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



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Figure 2 A possible protocol for early administration of vasopressors in septic shock patients. During septic shock resuscitation, although not mentioned in the protocol, volume status and responsiveness should be assessed repeatedly and titrated crystalloids. NE: Norepinephrine.

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 *versus* norepinephrine, revealing a higher incidence of life-threatening arrhythmia in the norepinephrine group (0.98% *vs* 2.5%), and a higher incidence of acute coronary syndrome in the vasopressin group (3.4% *vs* 1.0%). These findings suggest that patients with coronary artery disease may benefit from avoiding vasopressin, while those with tachyarrhythmia may consider early co-administration of this drug. In contrast, Reardon *et al*[56] found a trend toward improvement in cardiac biomarkers in the early vasopressin group; however, no specific etiology was identified and the research was limited to a single-center retrospective analysis.

POSSIBLE PROTOCOL FOR CONSIDERING 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.

The timing of vasopressor initiation was the primary focus of our protocol, control of the source of infection in sepsis, use of albumin, and early steroid use are not included in the figure. However, four prominent RCTs investigated the administration of corticosteroids in patients with septic shock, but they yielded contradictory results. The enrollment time across the four studies was from 8 h[57] to 24 h[58,59] and 72 h[60]. Two trials demonstrated that early addition of corticosteroids to vasopressors significantly reduced 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 dose 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 h after the initiation of vasopressors and at a minimum norepinephrine dose of 0.25 µg/kg/min.

Control of the source of infection should be required as an emergency intervention as soon as a specific anatomical diagnosis of infection is identified. Early albumin infusion also should be considered when patients receive large volumes of crystalloids.

CONCLUSION

In septic shock, early initiation of vasopressors may exert several potential beneficial effects. Several mechanisms support

initiation of vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow enlargement and fluid overload prevention. Clinical evidence has suggested possible benefits of early initiation of single or combined vasopressors in the resuscitation of septic shock. Several potential markers predicting vasopressor requirements were mentioned. Diastolic arterial blood pressure and dynamic elastance indicated early initiation of norepinephrine in first-line mono-vasopressor therapy. Kinetics of norepinephrine dose increment, serum lactate and rennin levels were applied to identify the timing of early initiation of vasopressin or angiotensin II based on norepinephrine multi-vasopressor therapy. Administration of high concentrations of norepinephrine via the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock.

FOOTNOTES

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