Norepinephrine in septic shock: when and how much?

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Purpose of review
Norepinephrine is the first-line agent recommended during resuscitation of septic shock to correct hypotension because of depressed vascular tone. Important clinical issues are the best timing to start norepinephrine, the optimal blood pressure target, and the best therapeutic options to face refractory hypotension of when high doses of norepinephrine are required to reach the target.

Recent findings
Recent literature has reported benefits of early administration of norepinephrine because of the following reasons: profound and durable hypotension is an independent factor of increased mortality, early administration of norepinephrine increases cardiac output, improves microcirculation and avoid fluid overload. Recent data are in favor of targeting a mean arterial pressure of at least 65 mmHg and higher values in case of chronic hypertension. When hypotension is refractory to norepinephrine, it is recommended adding vasopressin, which is relatively deficient during sepsis and acts on other vascular receptors than α_1-adernergic receptors. However, increasing the dose of norepinephrine further cannot be discouraged.

Summary
Early administration of norepinephrine is beneficial for septic shock patients to restore organ perfusion. The mean arterial pressure target should be individualized. Adding vasopressin is recommended in case of shock refractory to norepinephrine.

Keywords
norepinephrine, septic shock, vascular tone, vasopressin

INTRODUCTION

Besides relative and absolute hypovolemia, decreased vascular tone is one of the major characteristics of septic shock causing hypotension. Nevertheless, the severity of the vascular tone depression is variable among patients and the appropriate timing of initiation of norepinephrine, which is the recommended first-choice vasopressor, is not clearly established [1▪▪]. The objective of this review is to help define the appropriate time to initiate norepinephrine in patients with septic shock and the appropriate blood pressure target to achieve.

WHEN TO START NOREPINEPHRINE?

For decades, septic shock resuscitation used substantial fluid administration before initiation of vasopressors, which were administered only when fluid therapy was unable to restore arterial pressure further. When referring to the pathophysiological mechanisms of septic shock, hypotension because of depressed vascular tone is unlikely to be corrected with fluid administration only. Data from the recent literature are in favor of early initiation of vasopressors during septic shock in order to prevent avoid deep and durable hypotension, which is a factor independently associated with increased mortality [2]. Moreover, in a recent study, early administration of norepinephrine was associated with increased survival [3]. The following arguments based on reports of clinical studies, support the idea to initiate norepinephrine early.

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KEY POINTS

- Norepinephrine should be started early during resuscitation of septic shock when depressed vascular tone is assumed to be the main cause of hypotension.
- A low diastolic arterial pressure – as a marker of depressed vascular tone – is a simple tool to identify septic patients who need norepinephrine urgently.
- The optimal mean arterial pressure target should be individualized during resuscitation of septic shock.
- Although 65 mmHg is the usually recommended mean arterial pressure target, some conditions such as history of chronic hypertension may require a MAP higher than 65 mmHg to be achieved.
- It is recommended adding vasopressin to norepinephrine in case of refractory hypotension or when high doses of norepinephrine are used, knowing that in such an uncontrolled circulatory shock, the superiority of this attitude compared to increasing the norepinephrine doses, has not yet been proven.

Norepinephrine increases cardiac output when administered in the early phase of septic shock

The majority of clinical studies performed before the first publication of the SSC guidelines in 2004 [4] reported unchanged cardiac output (*CO*) after initiating norepinephrine [5]. It is noteworthy that the average *CO* before initiation of vasopressors was high [5], because of the large amounts of fluid administered during the initial phase of resuscitation. Therefore, no supplementary effect on *CO* could have been expected after initiating norepinephrine. More recently, early administration of norepinephrine has been recommended even when hypovolemia has not yet been resolved [4], and recent clinical studies showed that norepinephrine initiation was associated with a significant increase in *CO* [5]. It is noteworthy that the *CO* values before norepinephrine initiation were quite low compared to those reported in older studies [5], probably reflecting a more restrictive fluid strategy compared to that previously used. In a series of 105 severely hypotensive patients with septic shock, we found that early administration of norepinephrine aimed at rapidly achieving a sufficient perfusion pressure was able to increase stroke volume and *CO* [6]. The decision to initiate norepinephrine was made on the basis of a low diastolic arterial pressure – considered as a marker of a low arterial tone – and not after that volume resuscitation had been fully completed. The increase in stroke volume was associated with an increased global end-diastolic volume – a marker of cardiac preload – and a reduced pulse pressure variation (PPV), which is a marker of volume responsiveness [7▪▪]. Similar results were found in a study conducted in septic patients with preload responsiveness at baseline [8]. Taken together, these results suggest that norepinephrine through its α_1-adrenergic mediated effects is able to increase cardiac preload and systemic venous return in patients with preload responsiveness, a condition which is quite common in early sepsis. It has been postulated that norepinephrine is able to redistribute venous blood from the unstressed to the stressed blood volume, as suggested by studies showing an increase in mean systemic filling pressure with norepinephrine in septic patients [9] and in cardiac surgery patients [10]. This hemodynamic effect is of particular importance in septic patients, because their unstressed blood volume is abnormally increased and can be overfilled by excessive fluid administration.

Norepinephrine can improve microcirculation when administered early

On the one hand, one could be scared to administer vasopressors at the early phase of shock resuscitation because of the potential risk of worsening microcirculation through excessive vasoconstriction of precapillary microvessels. On the other hand, severe hypotension can theoretically worsen organ hypoperfusion if the mean arterial pressure (MAP) is lower than the limit of autoregulation of organ blood flow. Data about the microcirculatory effects of early administration of norepinephrine in patients with septic shock are very scarce because studies are difficult to be performed. Our group investigated the effects of early administration of norepinephrine on microcirculation assessed using near-infrared spectroscopy at the level of thenar eminence in septic shock patients [11]. Norepinephrine was added to fluid infusion on the basis of a low diastolic pressure. The MAP significantly increased from 54 to 77 mmHg whereas tissue oxygen saturation (StO_2) increased from 75 to 78% (normal values are around 80%). Vascular occlusion tests were performed to evaluate the hyperemic response to a local hypoxic stimulus created by transient ischemia of the occluded vascular bed. Increasing MAP with norepinephrine resulted in a significant increase in the StO_2 recovery slope [11]. This result is of interest because the StO_2 recovery slope, which reflects the capacity of microvessels to be recruited in response to local hypoxia, was previously demonstrated to be a prognostic factor in septic shock patients [12]. It could be postulated that increasing the MAP in severely hypotensive patients

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improved microvascular blood flow in pressure-dependent vascular beds and hence improved muscle tissue oxygenation and microcirculatory recruitment capacities. This is in agreement with previous data showing a good correlation between sublingual microcirculatory indices and MAP in the first 6 hours of management of septic shock [13].

Early administration of norepinephrine should prevent harmful fluid overload

Positive cumulative fluid balance is an independent factor of mortality in septic shock patients: the higher the positive fluid balance, the poorer the outcome [14]. A recent analysis of a large cohort of 23 513 patients with severe sepsis and septic shock showed that administration of more than 5 l of fluid during the first day is associated with a significantly increased risk of death [15▪]. A meta-analysis of 11 studies has recently shown that in adults and children with sepsis or acute respiratory distress syndrome (ARDS) conservative or de-resuscitative fluid strategy results in an increased number of ventilator-free days and a decreased length of intensive care unit stay compared with a liberal strategy [16▪]. It could thus be tempted to restrict fluid administration even at the initial stage of resuscitation by starting vasopressors early. In this regard, in a retrospective study in septic shock patients, those in whom norepinephrine was administered within the first 2 hours of resuscitation received less fluids than those who received a delayed norepinephrine administration [3]. However, starting vasopressors early to counteract the vasomotor tone depression does not imply discontinuation of fluid infusion [17]. In this regard, a systematic and deliberate restrictive fluid strategy does not make sense because it might sometimes have long-term deleterious consequences [18] despite short-term beneficial effects [19]. Taken together all these results emphasize the need to individualize fluid management during septic shock by assessing preload responsiveness to avoid applying a too conservative strategy in preload responsive patients and to avoid applying a too liberal fluid strategy in those who are preload unresponsive [7▪▪].

To summarize, the question to start norepinephrine must be separated from that of initiating and continuing fluid administration because these two interventions refer to two different mechanisms of circulatory shock during sepsis that may vary among patients. A simple way to identify patients who need norepinephrine urgently is to consider the diastolic arterial blood pressure, which mainly depends on vascular tone, especially in tachycardic patients. Accordingly, we suggest that low diastolic arterial pressure should trigger earlier initiation of vasopressors to prevent prolonged hypotension. Another potential marker called the dynamic elastance (Ea_{dyn}) – defined as the PPV/stroke volume variation (SVV) ratio – has been proposed recently to identify preload responsive patients who will not increase their MAP in response to fluid challenge [20▪] and thus to indicate when to initiate norepinephrine. Nevertheless, this marker requires obtaining PPV and SVV from two independent signals, what is poorly realistic in clinical practice.

WHICH OPTIMAL BLOOD PRESSURE TARGET TO BE ACHIEVED WITH NOREPINEPHRINE?

The MAP is the recommended target because it reflects the perfusion pressure of most vital organs. The SSC recommends to target a MAP of at least 65 mmHg during the initial resuscitation of septic shock [1▪▪]. This makes sense because the area under a MAP of 65 mmHg was shown to be an independent predictor of mortality in septic shock patients [2]. It is generally assumed that 65 mmHg is a little higher than the lower level of the autoregulation part of the organ blood flow/organ perfusion pressure relationship and that increasing MAP above 65 mmHg cannot result in major benefits in terms of organ perfusion (Fig. 1). However, higher values of target MAP are suggested in chronic hypertension [21,22],

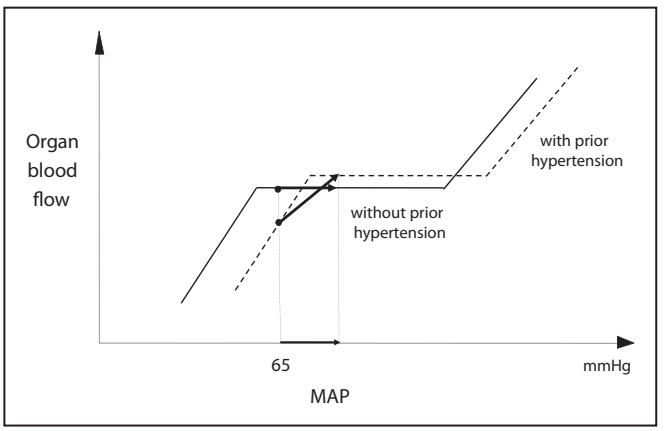

FIGURE 1. Relationship between organ blood flow and mean arterial pressure. Below a certain critical mean arterial pressure (MAP), organ blood flow depends on MAP. It is assumed that targeting a MAP above 65 mmHg would generally guarantee to reach the plateau (autoregulation) of the relationship so that increasing MAP further is not necessary since it would result in no further increase in organ blood flow. In case of history of prior hypertension, there is a rightward shift of the relationship between organ blood flow and MAP (dashed line), so that a MAP value higher than 65 mmHg would be required to reach the plateau.

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where the relationship between organ blood flow and organ perfusion pressure is assumed to be rightward shifted (Fig. 1). In such conditions, a MAP of 65 mmHg can be below the critical pressure above which no benefits are expected from a further increase in perfusion pressure. In some specific conditions, the sole MAP can be insufficient to reflect the organ perfusion pressure. This may occur when the downstream pressure of organ perfusion is assumed to be abnormally high (e.g. in case of high central venous pressure or high intra-abdominal pressure). Whether MAP values higher than 65 mmHg should be targeted to sustain the organ perfusion pressure in such conditions remains to be proven.

In all cases, achieving any specific target MAP does not guarantee successful correction of peripheral hypoperfusion because some dissociation between the macrocirculations and the microcirculations is assumed to exist in sepsis [23▪]. It is likely that better markers of peripheral perfusion and/or microcirculation than MAP will be used in the future to individually titrate vasopressors.

WHICH MAXIMAL DOSE OF NOREPINEPHRINE?

Septic shock is characterized by a decreased vascular responsiveness to adrenergic agents [24]. Consequently, high doses of norepinephrine may be required to correct hypotension in cases of severely depressed vascular tone. Hypotension is often qualified as refractory to norepinephrine when rapidly increasing doses of norepinephrine fail to achieve the MAP target, even though no maximal achieved dose of norepinephrine or no maximal rate of dosage increase has been really defined. Nevertheless, in case of a so-called refractory hypotension, the clinician has two alternative options: either adding another vasopressor to norepinephrine or increasing further the norepinephrine dose with the expectation to achieve the target. The first option is clearly recommended by the SSC [1▪▪]. One of the main arguments is that high doses of exogenous norepinephrine may have deleterious consequences such as myocardial cell injury, oxidative stress, and alteration of sepsis-associated immunomodulation [25▪]. Another argument is that other mechanisms than vascular hyporesponsiveness to α_1-adrenergic agents contribute to depress vascular tone during sepsis. Possibly because of a relative vasopressin deficiency in septic shock, adding exogenous vasopressin was demonstrated to increase MAP while reducing norepinephrine requirements in patients already receiving at least 5 μg/min of norepinephrine, although it did not reduce mortality rates as compared with norepinephrine alone in a multicenter randomized trial [26]. In spite of this latter finding, the SSC suggests adding vasopressin to norepinephrine with the intent either to reduce norepinephrine dosage – when judged to be too high – or to raise MAP in case of a so-called refractory hypotension [1▪▪]. The alternative option, which is to further increase the norepinephrine dose, is a matter of debate. In a retrospective study including 324 patients with septic shock, the average death rate was 48% but reached 90% for the quartile of patients receiving more than 1 μg/kg/min of norepinephrine [27]. Such results are in favor to consider other vasopressors when high doses of norepinephrine are used, although it cannot obviously be concluded that an alternative therapeutic option would have been more successful because patients with refractory hypotension are probably those with the most severe sepsis-induced hemodynamic and inflammatory disorders. Nevertheless, in a recent retrospective study 40% of septic shock patients, who received a dose of norepinephrine at least 1 μg/kg/min for more than 1 h, survived at day 28 after admission, suggesting that administration of high-dose norepinephrine may be useful in severely hypotensive patients [28▪]. This is line with the results of a pharmacological study in septic shock patients that found a linear relationship between epinephrine dose and response to treatment, without any saturation at high doses [29]. It was recently shown that the incidence of serious adverse events (SAEs; myocardial ischemia, mesenteric ischemia, digital ischemia, etc.) with norepinephrine infusion was around 10%, was similar to that of vasopressin infusion and was associated with increased mortality [30]. In patients who received doses of norepinephrine at least 1 μg/kg/min for more than 1 h, an incidence of serious digital or limb necrosis of 6% was recently reported [28▪]. Occurrence of SAEs with norepinephrine is difficult to predict, although a large-sized study showed that septic shock patients, who developed SAEs were older, had a higher initial lactatemia, had more organ dysfunction and received a higher norepinephrine dose at day 1 than patients who did not develop SAEs [30]. Particular genetic single-nucleotide polymorphisms seem to be associated with development of such SAEs [30]. It is likely that identification of risks of SAE development using bedside genotype markers will help in the future to make the decision of either continuing norepinephrine or adding vasopressin or another vasopressor. The SSC also weakly suggests adding epinephrine in case of refractory hypotension [1▪▪]. Compared to adding vasopressin or increasing further the dose of norepinephrine, adding

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epinephrine seems less logical since epinephrine: exerts its vasoconstricting effects through the same α_1-adrenergic receptors as norepinephrine and, may have detrimental effects such as tachyarrhythmia, through its strong β_1-adrenergic effects. Randomized clinical trials evaluating the place in septic shock of other vasopressors such as selepressin, a highly selective V1a receptor agonist, and angiotensin II are ongoing. Finally, the SSC suggests intravenous hydrocortisone (200 mg per day) if fluid therapy and norepinephrine administration fail to restore hemodynamic stability, although no precise information about the most appropriate time of hydrocortisone initiation has been provided [1▪▪].

Taken all these elements together, the option of increasing the dose of norepinephrine to correct severe hypotension at the early phase of septic shock – unless onset of SAEs – cannot be discouraged since it could prevent hypotension-induced organ dysfunction. Nevertheless, prolonged administration of high-dose norepinephrine is an indicator of uncontrolled circulatory failure. In this regard, the combination of sequential organ failure assessment score greater than 10 and high-dose norepinephrine was associated with increased mortality [28▪,31]. Unfortunately under these severe conditions, even if alternative options are suggested to decrease the norepinephrine requirements [1▪▪], there is currently no convincing data to really support the use of other vasopressors.

CONCLUSION

A low diastolic arterial pressure – as a marker of depressed vascular tone – can simply identify septic patients that need norepinephrine urgently. The optimal MAP target should be individualized since some conditions such as history of chronic hypertension may require a MAP higher than 65 mmHg to be achieved. Adding vasopressin to norepinephrine in case of refractory hypotension is a recommended option, knowing that in such an uncontrolled circulatory shock, the superiority of this option compared to increasing the norepinephrine doses has not yet been proven.

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Conflicts of interest

There are no conflicts of interest.

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