Editorial Commentary

Should we start vasopressors very early in septic shock?

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Early detection and prompt reversion of sepsis-induced tissue hypoperfusion are key elements in the treatment of patients with septic shock (1,2). Fluid administration and vasopressor support are considered life-saving interventions aimed to restore macro and microcirculatory derangements induced during shock (2). Certainly, studies on implementation of therapeutic bundles in sepsis (3) and recent randomized controlled trials on early goal-directed therapy in septic shock (4-6) have highlighted the importance of initial fluid loading and reinforce its use as a standard of care. Indeed, current guidelines on sepsis management preserved the recommendation on administration of at least 30 mL/kg of IV crystalloids within the first 3 hours of identification of sepsis-induced hypoperfusion (1). Although also considered a "first-line" intervention, vasopressor support is usually used as a rescue therapy when initial fluid loading fails to correct hypotension or when arterial pressure is judged to be insufficient to ensure an adequate tissue perfusion (1). Nevertheless, while initial resuscitation is based on fluid loading, a recent update of sepsis guidelines proposed a "1-hour bundle" (7), which includes the use of vasopressors in the case of life-threatening hypotension, during or after fluid resuscitation, to maintain a mean arterial pressure (MAP) at or above 65 mmHg. Although this initiative comprises the concept of sepsis as a medical emergency, the level of evidence for this recommendation concerning both the initial volume of fluids and the blood pressure target, remain limited and highly debatable (8).

The basis for the fluid resuscitation builds on the concept that sepsis and septic shock are conditions inducing absolute or absolute or relative hypovolemia due to a combination of external fluid losses, increased capillary leakage and pathological vasodilation. However, fluid administration is not exempt from adverse effects itself, since volume expansion influences extra and intracellular electrolyte composition, acid-base equilibrium, and body volume of distribution. Moreover, when excessively administered, fluids can induce interstitial edema that may then limit oxygen diffusion to the tissues. In addition, it can also interfere with tissue perfusion by increasing downstream pressures and raising pressures surrounding capillary vessels. A number of observational studies suggest that larger volumes of resuscitation fluids and net fluid balances are associated with increased mortality in sepsis (9-21). Other studies have shown that increased downstream pressure is associated with decreased microcirculatory perfusion and increased organ dysfunction (22,23). Nevertheless, although these results question the safety of large-volume of fluids, the risk of confounding in these observations precludes a causality association since more severely ill patients are more prone to receive more intravenous fluids (24,25).

Limiting excess of fluid administration therefore seems appropriate, but it could be counterbalanced by the thought potential harm of using vasoactive drugs when hypovolemia is still ongoing. Nevertheless, the idea of testing a very early start of vasopressors in patients with suspected infection and hypotension is attractive. In line with this, a recent phase II randomized controlled trial, the CENSER study, tested the hypothesis that an early low-dose of norepinephrine in patients with sepsis and hypotension could increase control of shock defined by a composite of MAP >65 mmHg plus either urine output >0.5mL/kg/min or a lactate decline >10% from baseline, when compared with standard care (26). The authors randomized patients with suspected infection and hypotension to early low-dose of norepinephrine (n=155) or placebo (n=155) plus standard care, which included open-label vasopressors. The experimental group received norepinephrine up to 0.05 μgr/kg.min^{-1} plus open-label vasopressors and fluid resuscitation, while control group received standard care. Finally, the "early low-dose norepinephrine" group achieved the primary goal in 76.1% *vs.* 48.4% (P<0.001) in the control group. However, there were no significant differences in 28-day mortality. Although very interesting, these results might be highly debatable as the protocol requested the administration of a fixed dose of norepinephrine, which is not the usual way to use vasopressors. Nevertheless, the more rapid control of shock is in line with recent experimental evidence (27).

An early start of vasopressor therapy may have several potential beneficial effects. First, rapid introduction of vasopressor support might shorten the duration of hypotension, which could influence clinical outcomes since duration and severity of hypotension have been associated with increased risk of death in septic patients (28-30). Second, in addition to the net vasopressor effect, norepinephrine may increase cardiac output by increasing preload (31), by improving myocardial contractility (32) and through improvement of ventriculo-arterial coupling (33). Third, an increase in diastolic pressure could improve coronary artery perfusion and myocardial dysfunction in septic patients with hypotension (34). Fourth, norepinephrine might increase microcirculatory perfusion in septic shock (35-37), especially when initial microcirculatory blood flow is abnormal (38). Also, microvascular reactivity during ischemia-reperfusion might be significantly improved by restoring arterial pressure with norepinephrine in severe hypotensive septic patients (37). Fifth, the use of norepinephrine has been associated with improved mean arterial pressure, sustained aortic and mesenteric blood flow and better tissue oxygenation when compared with fluid resuscitation alone (39). Moreover, when introduced early, norepinephrine might improve the regional distribution of blood flow to the mesenteric area (39). Sixth, recent experimental data suggest that initial fluid resuscitation might be related with a paradoxical increase in vasopressor requirements and no improvement of any microcirculatory or organ specific marker of perfusion (27). Although the initial fluid resuscitation resulted in a higher cardiac output during the infusion period, they also showed higher lactate values and more severe endothelial damage at the end of the experiment (27). Seventh, it is unlikely that severe hypotension resulting from serious vasodilation could be reversed by simple fluid administration. Instead, unnecessary fluids and harmful fluid accumulation can occur (21). Eighth, most patients with septic shock do not reveal a gross decrease in stressed volume at the beginning of the process, unless of course, there is an evident loss of fluid. Although stressed volume would remain nearly unaltered in some cases, vasodilation would reduce mean systemic filling pressure thus limiting venous return and ultimately reducing cardiac output. Norepinephrine might increase mean systemic filling pressure by changes in venous capacitance thus mobilizing non-stressed to stressed circulatory blood volume (31). Ninth, some observational evidence indicates that delayed start of vasopressors could be related with adverse clinical outcomes (40). However, the recent CENSER trial demonstrated no differences in 28-day mortality when early but non-titrated doses of norepinephrine were administered to patients with suspected infection and hypotension, although a more rapid "control of shock" was apparent (26).

Optimal timing for starting vasopressors (VP) in sepsis has not been adequately tested since guidelines recommend fluids to be administered first. Some physiological reasons supported by observational and experimental studies suggest that an early start of vasopressors could be advantageous. Nevertheless, benefice or harm of the early introduction of vasopressors, even preceding initial fluid loading, remains unanswered. Prospective studies evaluating the impact of very early start of vasopressor support on the development of multiorgan dysfunction and the total volume of resuscitation fluids required during the early phases of septic shock are thus required.

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Footnote

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