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Septic Shock and Vasopressor Initiation: Why Earlier is Better

An overview of vasopressor management, current evidence and when to initiate vasopressor therapy for best possible patient outcome.

Vasopressor management is a cornerstone in the haemodynamic management of septic shock for reversing hypotension by increasing systemic vascular resistance and improving organ perfusion. The Surviving Sepsis Campaign (SSC) guidelines 2021 recommend an initial target mean arterial pressure (MAP) of 65 mmHg with norepinephrine (also known as noradrenaline) as first-line vasopressor agent, vasopressin (also known as argipressin, arginine vasopressin, and anti-diuretic hormone) as recommended second-line vasopressor (Evans et al. 2021). This article will try to address when to initiate vasopressor management for best possible patient outcome, based on the currently existing evidence.

Hypotension and Poor Clinical Outcomes: Benefits of Early Norepinephrine Initiation

The amount of time spent continuously below a MAP threshold of 65 mmHg is a strong predictor of mortality, with each additional 2-hour increment in the longest episode under threshold being associated with a progressive increase in mortality rate (Vincent et al. 2018). An immediate action for resolving hypotension should be taken as quickly as possible, as the early administration of a first-line vasopressor, namely norepinephrine, is associated with better patient outcomes, such as shorter periods of hypotension and higher survival rate (Bai et al. 2014; Colon et al. 2020). The SSC 1-hour bundle recommends starting norepinephrine within one hour of fluid resuscitation, if fluid administration alone is not sufficient to achieve target MAP (Levy et al. 2018). This can not only prevent prolonged periods of hypotension, but also prevent harmful fluid overload (Hamzaoui and Shi 2020).

Vasopressin As Second-Line Vasopressor: When and Why

Vasopressin is the only recommended second-line vasopressor to be added to norepinephrine if MAP is inadequate, instead of escalating norepinephrine dose or using any other agents (Evans et al. 2021); this is indicating to catecholamine refractory septic shock, where vascular responsiveness to catecholamines is impaired due to down-regulation or decoupling of α_1 adrenergic receptors (Jentzer and Hollenberg 2020). In such cases, when norepinephrine infusion is at 0.25–0.5 µg/kg/min and MAP is still inadequate, vasopressin could be added to norepinephrine in order to achieve target MAP and prevent prolonged periods of hypotension (Evans et al. 2021).

In addition to raising MAP, vasopressin also has catecholamine sparing effects, allowing for the reduction of norepinephrine dose while maintaining target MAP (Russell 2011). This early combination of moderate doses of multiple vasopressors with complementary mechanisms of action may avoid the toxicity associated with high doses of a single agent (Jentzer et al. 2018).

In a retrospective, multi-centred, observational study, higher norepinephrine-equivalent dose and higher lactate concentration at vasopressin initiation were each associated with higher in-hospital mortality in patients with septic shock (Sacha et al. 2021). The lowest mortality rates were seen when vasopressin was initiated at lower norepinephrine-equivalent doses and lower lactate concentrations. Initiating vasopressin at a norepinephrine-equivalent dose of 10 µg/min or initiating when lactate concentrations were below 2.3 mmol/L was associated with a lower likelihood of in-hospital mortality compared with delaying vasopressin initiation until a norepinephrine-equivalent dose of 25 µg/min or when lactate concentrations exceeded 3.9 mmol/L, respectively. Each 10 µg/min increase in norepinephrine-equivalent dose at the time of vasopressin initiation was associated with 20.7% higher in-hospital mortality, and each 1 mmol/L increase in lactate concentration at the time of vasopressin initiation was associated with 18.4% higher in-hospital mortality (Sacha et al. 2021). These conclusions confirm similar observations in the VASST study, where a subgroup analysis showed reduced mortality when vasopressin was administered at lower norepinephrine doses and lactate levels (Russell 2011).

Retrospective observational data have also shown an association with higher vasopressin response, when vasopressin was initiated at lower lactate and higher arterial pH levels. Vasopressin response was associated with increased in-hospital survival rates and overall better patient outcomes, such as higher MAP and lower catecholamine requirement, further supporting the early administration of vasopressin (Bauer et al. 2022; Sacha et al. 2018).

A post-hoc analysis of the VASST study has shown that the combination of vasopressin at norepinephrine 0.26±0.27µg/kg/min for patients at risk of renal failure (1.5x serum creatinine based on the RIFLE criteria) significantly decreases the need for Renal Replacement Therapy (RRT) by 55% and reduced the progression to renal failure (Gordon et al. 2010).

In a systematic review of 13 randomised controlled trials (1462 patients), the addition

of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a significant lower risk of atrial fibrillation (RR, 0.77) (McIntyre et al. 2018). This can be related to a reduction in adrenergic stimulation provided by the catecholamine sparing effect of arginine vasopressin.

Additionally, experimental studies have shown that catecholamines constrict pulmonary arteries, while vasopressin does not, which also supports the use of vasopressin in pulmonary hypertension (Currigan et al. 2014).

Why Vasopressin

Vasopressin is an endogenous peptide hormone produced in the hypothalamus which is stored and released by the posterior pituitary gland (Evans et al. 2021). Unlike catecholamines, which achieve vasoconstriction through α_1 receptor activation, vasopressin increases blood pressure by activating the V_1 receptors on vascular smooth muscles (Evans et al. 2021). This alternative mode of action allows for the increase in blood pressure in catecholamine refractory septic shock (Evans et al. 2021) and the reduction of catecholamine doses (Russell 2011).

Additionally, serum vasopressin levels in early septic shock stages have been shown to increase in most patients to reverse hypotension but decrease after 24 hours as shock continues, causing a "relative vasopressin deficiency" due to depletion of hypothalamic-pituitary stores of vasopressin (Russell 2011). This further supports the early administration of exogenous vasopressin during septic shock.

Vasopressin can be administered from doses ranging from 0.01IU/min to 0.03IU/min allowing for dose adjustment based on patient's blood pressure dynamics and needs (Summary of Product Characteristics, Empressin). With a half-life of up to 20 minutes, it offers a high degree of control as the vasopressor effect could be quickly halted once infusion is discontinued (Tanja and Jürgen 2006).

The VASST study has also shown that vasopressin is as safe as norepinephrine when administered at 0.03IU/min with similar levels of adverse events, with a trend towards digital ischaemia (0.5% norepinephrine vs 2% vasopressin, p=0.11) (Russell et al. 2008).

The SSC guidelines recommend against using terlipressin, a vasopressin analogue prodrug with a half-life of around 6 hours, due to the higher incidence of serious adverse events associated with it (Evans et al. 2021). The 6-hour half-life also makes it impractical for a rapid down-titration or quick stopping in cases of adverse events.

Conclusion

The early initiation of vasopressors in septic shock has shown to have better patient outcomes in comparison to delayed initiation. MAP response to fluids should guide the initiation of norepinephrine as first-line, while more specific parameters such as inadequate MAP, high catecholamine dose, lactate levels, arterial pH, and serum creatinine should guide the early initiation of vasopressin as second-line vasopressor. ■

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Summary of Product Characteristics, Empressin 40 I.U./2 ml concentrate for solution for infusion, AT.

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