

# ICU

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IV fluid boluses and persistent positive fluid balance for more than two days, contributing to global increased permeability syndrome (GIPS) and multi-organ oedema, association with higher incidence of acute kidney injury (AKI), increased days under mechanical ventilation (MV) and more days of hospital stay which can lead to multi-tissue oedema, thereby directly impacting ICU length of stay and mortality (Acheampong and Vincent 2015; Koonrangsombon et al. 2015; Sakr et al. 2017; Shen et al. 2018; Tigabu et al. 2018; Zhang et al. 2021; Pérez-Nieto et al. 2021).

Experts recommend that the dose of fluids needed for initial and subsequent resuscitation in patients with septic shock should always be individualised according to the clinical characteristics of the patient and based on dynamic assessments of fluid responsiveness. An example of this is that a young patient without comorbidities is more likely to tolerate the administration of a large volume of fluid compared to a frail elderly patient with chronic cardiac or renal disease (Vincent et al. 2021). One of the many limitations of maintaining a fixed dose of fluids for patients with sepsis and septic shock is that the response to fluids decreases significantly over time elapsed from initiation of resuscitation (liquid responders: at 0 hours, only 57%; 2 hours, only 22%; 4 hours, only 11%; 6 hours, only 10%; and 8 hours, only 3%) (Hernández et al. 2019).

Physicians should avoid using static

measures to assess volume status (e.g. central venous pressure) and volume response in these patients. To identify those patients who will or will not respond to fluid administration, it is advisable to use dynamic measures to estimate the effect of the additional volume on cardiac filling pressures and stroke volume (SV). Practical options are to administer a bolus of crystalloid fluids (usually no more than 500 ml, e.g., 3–4 ml/kg) or to passively raise the legs (which would produce a return of 200–300 ml of venous blood from the lower limbs), and then directly measure the change in systolic volume (e.g., with thermodilution, echocardiography, or pulse wave analysis). A 10–15% increase in SV is associated with an adequate fluid response. These changes can also be assessed by heart-lung interaction in patients on MV based on changes in intrathoracic pressure during the inspiratory and expiratory cycle, using pulse pressure variation (PPV), systolic volume, velocity-time integral (VTI) with Doppler ultrasound at LV outflow tract or arterial vessel level (e.g., carotid artery), and variation in the diameter of the inferior vena cava (ICV) or internal jugular vein (IJV) (Dugar et al. 2020). The greater the variability of any of these parameters (PPV, SV, VLT, etc), usually above 10–15%, the greater the response to IV fluids (in the absence of right ventricular dysfunction, common arrhythmias, significant tachycardia, and spontaneous and forceful ventilations). A recent randomised clinical trial in patients

with sepsis, hypotension, and shock found that physiologically reported fluid and vasopressor resuscitation using passive leg raise induced systolic volume change to guide treatment was safe and effective in reducing net fluid balance, with reduced risk of renal and lung injury (Douglas et al. 2020).

Regarding the type of solutions to be administered, there is no benefit when comparing 0.9% saline versus balanced solutions (Finfer et al. 2022), the latter of which are more expensive. IV albumin may be useful when a significant dose of crystalloid solutions has already been administered or for patients with significant hypoalbuminaemia (Joannidis et al. 2022).

## Vasopressors

### Catecholamines

Since vasodilatation is the main cause of shock—not hypovolaemia—the administration of vasoconstrictive agents should be considered. The decision to initiate vasopressor therapy to achieve mean arterial pressure (MAP) goals must be balanced against potential adverse effects, including tachyarrhythmias and cardiac, intestinal, or peripheral ischaemia. Norepinephrine has been considered the first-choice vasopressor for more than a decade due to its effect on vascular alpha receptors to generate vasoconstriction and cardiac beta receptors which cause a modest inotropic effect. Patients with MAP <66 mmHg and those who require >2,000 ml of IV fluids are at a higher mortality risk (Sivayoham et al. 2020). Early initiation of norepinephrine has been shown to be safe and could limit the amount of fluid required during resuscitation, thereby improving patient outcomes (i.e., faster resolution of shock, reduced mortality) (Permpikul et al. 2019; Ospina et al. 2020). Epinephrine is considered a second-choice vasopressor agent that should be used in the absence of response to norepinephrine (with or without added vasopressin or in the absence of vasopressin availability) with caution due to its association with tachyarrhythmias, hyperlactataemia and ischaemia. Dopamine is currently not recommended as the vasopressor of choice in septic shock for

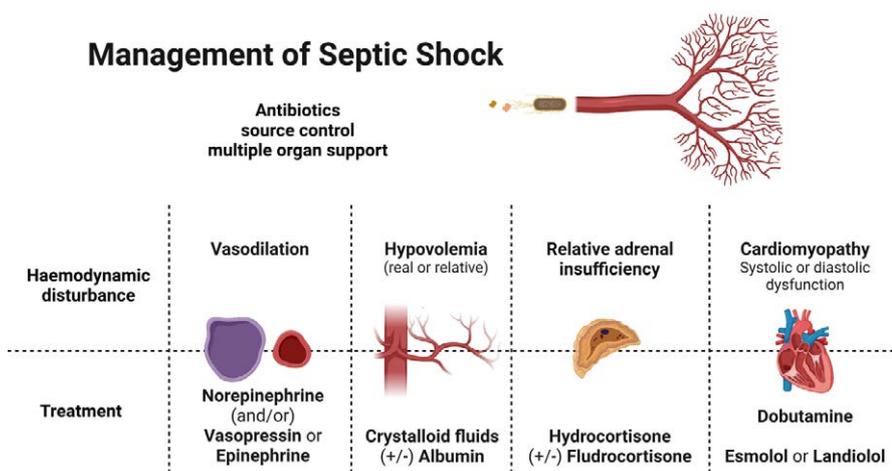


Figure 1. Haemodynamic management of septic shock

its higher incidence of tachyarrhythmias compared with norepinephrine.

### Vasopressin and analogues

Vasopressin is commonly considered a second-line agent, commonly used in vasoplegia. The VANISH clinical trial directly compared the use of vasopressin versus norepinephrine in patients with septic shock (in addition to hydrocortisone) and failed to demonstrate significant differences in a 28-day mortality; however, the use of vasopressin significantly reduced the risk of renal replacement therapy (Gordon et al. 2016). In terms of combination therapy, the VASST randomised clinical trial compared norepinephrine versus norepinephrine plus vasopressin (at low doses), finding no significant differences in mortality, neither at 28 days nor 90 days. However, in a subgroup analysis, patients with milder shock who received norepinephrine at doses  $<15 \mu\text{g}/\text{min}$  had increased survival with the addition of vasopressin (Russel et al. 2008). For adults in septic shock who are on norepinephrine administration while maintaining inadequate mean arterial pressure levels, the Surviving Sepsis Campaign 2021 suggests adding vasopressin rather than progressively increasing the dose of norepinephrine (when the dose of norepinephrine is in the range of  $0.25\text{--}0.5 \text{ mcg}/\text{kg}/\text{min}$ , as a weak recommendation with moderate quality of evidence). Terlipressin and selepressin are synthetic vasopressin analogues used in the management of patients with septic shock. Terlipressin was associated with reduced mortality in septic shock patients less than 60 years old and may also improve renal function but cause more peripheral ischaemia (Huang et al. 2020).

There are other vasopressor agents for the management of septic shock including IV methylene blue and angiotensin II. Despite their vasoconstrictor effect and increase in blood pressure, their availability is limited, and clinical trials have not shown a greater benefit in survival or days of shock when compared with norepinephrine. More studies are needed to assess their clinical utility (Scheeren et al. 2019).

The combination of persistent diastolic

hypotension and its correlation with heart rate (HR) may reflect severe vasodilatory conditions. The diastolic shock index (heart rate/diastolic blood pressure) calculated before and during vasopressor use is an early identifier of patients at high risk of mortality when its value is above 2 (Ospina et al. 2020).

### Corticosteroids

“Critical illness related corticosteroid insufficiency” has been defined as a condition in which the patient may not be able to produce the required amount of cortisol for survival. Patients in septic shock with a prolonged stay in the ICU have a particular risk of developing septic shock (Annane et al. 2017). It has recently been shown that the amount of cortisol produced by patients during critical illness is not much higher than that produced by healthy patients. The increased availability of systemic cortisol during critical illness is mostly driven by decreased binding proteins, reduced binding affinity of these proteins and suppression of cortisol degradation (Téblick et al. 2019). Randomised clinical studies have compared the use of corticosteroids versus placebo in patients with septic shock without direct survival benefits (Sprung et al. 2008; Venkatesh et al. 2018); however, these studies had an impact on vasopressor-free days and lower undesirable effects. Only one multicentre randomised clinical trial found a reduction in 90-day mortality with the administration of hydrocortisone combined with fludrocortisone for 7 days (no stepdown) (Annane et al. 2018).

Considering resource requirements, cost of intervention, and feasibility, the Surviving Sepsis Campaign 2021 gives a weak recommendation in favour of the use of low-dose corticosteroids in adults with septic shock who continuously require norepinephrine or epinephrine at doses  $\geq 0.25 \text{ mcg}/\text{kg}/\text{min}$  for at least 4 hours after initiation (Evans et al. 2021).

### Inotropic Drugs

Sepsis induced myocardial dysfunction is recognised as an important contributor to the haemodynamic instability of persistent septic shock. It can manifest in multiple

forms and affect both ventricles through primary myocardial cell injury (Beesley et al. 2018). It is characterised for being acute and reversible within the first 7–10 days and for presenting global biventricular dysfunction (systolic and/or diastolic) with contractility impairment and may present left ventricular dilatation. Septic cardiomyopathy is associated with decreased fluid and catecholamine response, contributing even more to haemodynamic deterioration (L’Heureux et al. 2020). After adequate fluid therapy and use of vasopressors, inotropic agents may be required if sepsis or septic shock leads to decreased cardiac output with persistent hypoperfusion.

There is no inotropic drug of choice, but epinephrine and dobutamine are the most employed drugs despite their lack of clinical benefit in multiple indirect comparison studies. It should be noted that both should be stopped in the absence of improvement of hypoperfusion or in presence of adverse events (Belletti et al. 2017; Wilkman et al. 2013). Despite scarce strong evidence in favour of their use to improve clinical outcomes in patients with septic shock, experts recommend their use when there is low cardiac output with clinical signs of hypoperfusion. Dobutamine is recommended as the inotrope of choice (Scheeren et al. 2021). According to the Surviving Sepsis Campaign 2021 update, in adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and blood pressure, they suggest adding dobutamine to norepinephrine or using epinephrine alone (weak recommendation with low quality of evidence). They do not suggest using levosimendan due to the absence of benefit in clinical studies, in addition to its undesirable safety profile (e.g., increased risk of supraventricular arrhythmias), cost, and limited availability (Evans et al. 2021).

### Negative Chronotropic Drugs

In the clinical stage of sepsis, the adrenergic system functions as an initial adaptive response to maintain homeostasis. However, excessive increases in catecholamines can cause adverse effects such as persistent tachycardia, which can lead to altered

cardiovascular haemodynamic with worsening prognosis. There are multiple factors for tachycardia in sepsis (e.g., inflammatory state, fever, pain, etc.), but persistent tachycardia is likely to manifest as a non-compensatory arrhythmia due to sympathetic overstimulation (Hasegawa et al. 2021). A randomised clinical trial in patients with septic shock compared the use of esmolol (short-acting selective beta-1 blocker) against a control group,

finding that esmolol was associated with reductions in heart rate to achieve primary endpoints without an increase in adverse events and lower mortality (Morelli et al. 2013). Several clinical studies have now been published with similar pharmacological interventions. A systematic review with meta-analysis of six randomised clinical studies (including 572 patients) on the effect of ultra-short-acting beta-blockers in patients with sepsis and persistent tachycar-

dia despite initial resuscitation showed that the use of esmolol or landiolol in patients with sepsis and septic shock was significantly associated with lower mortality at 28 days, with no significant heterogeneity between the studies analysed (Hasegawa et al. 2021). Ivabradine has also been studied in patients with septic shock and persistent tachycardia, being safe but with questionable efficacy (Datta et al. 2021).

Drug	Dose	Mechanism of Action	Adverse Effects	Comment
<b>VASOPRESSORS</b>				
Norepinephrine	0.025–3.3 µg/kg/min	α1 receptor agonist β1,β2 receptor agonist (mild effect)	Intestinal and renal hypoperfusion (uncommon) Bradycardia (uncommon) Tachyarrhythmia	First-choice vasopressor. Associated with lower mortality. Early treatment recommended.
Vasopressin	0.01–0.04 units/min	V1a, V2, and V1 <sub>b</sub> receptor agonist.	Intestinal, hepatic, and splenic hypoperfusion (uncommon) Thrombocytopenia (uncommon) Hyponatraemia (uncommon)	Second-choice vasopressor. Treatment for vasoplegia. Infusion is usually stopped after retiring norepinephrine.
Epinephrine	0.01–2 µg/kg/min	α1, β1, and β2 receptors non-selective agonist	Tachyarrhythmia, hyperglycaemia, splanchnic ischaemia, and hyperlactataemia.	Second-choice vasopressor. Higher incidence of tachyarrhythmia compared with dopamine and norepinephrine.
Dopamine	2–20 µg/kg/min	Dose-dependent agonist of α1, β1, and β2 D <sub>1</sub> , and D <sub>2</sub> receptors	Tachyarrhythmia, peripheral ischaemia, splanchnic hypoperfusion, delayed gastric emptying.	Consider in patients with shock and bradycardia. Higher incidence of tachyarrhythmia than norepinephrine. Does not diminish the incidence of acute kidney injury.
Terlipressin	1.3–5.2 µg/min	Synthetic arginine-vasopressin analogue with higher selectivity for receptors V1 <sub>a</sub> and V1 <sub>b</sub> > V2.	Peripheral vasoconstriction. Mesenteric ischaemia. Bradyarrhythmia.	Higher incidence of adverse effects than vasopressin. Longer half-life.
Selepressin	1.7–5 ng/kg/min	Selective V1 <sub>a</sub> receptor agonist	Arrhythmia, myocardial ischaemia, mesenteric ischaemia.	Not superior to norepinephrine and vasopressin. Low availability worldwide.
Angiotensin II	1.25–40 ng/kg/min	ATR <sub>1</sub> and ATR <sub>2</sub> receptor agonist in smooth muscle cells.	Thromboembolism, thrombocytopenia, delirium, hyperglycaemia, tachycardia.	Not superior to norepinephrine. Low availability worldwide.
Methylene Blue	2 mg/kg bolus 0.25–2 mg/kg/h infusion	Nitric oxide synthesis inhibitor.	Blue-green pigmentation of skin, mucosa, and secretions. Arrhythmia (uncommon).	Contraindicated in chronic kidney disease without renal replacement therapy.

INOTROPES				
Dobutamine	2–20 µg/kg/min	β-adrenergic receptor agonist	Tachyarrhythmia, vasodilation.	First-choice inotropic drug in sepsis-associated cardiomyopathy with hypotension.
Levosimendan	0.05–0.2 µg/kg/min in continuous IV infusion	Enhances sensitivity to calcium of proteins in contractile cells through binding of troponin C.	Headache, nausea, extrasystole, hypotension.	Not superior to dobutamine. Contraindicated in kidney disease with creatinine clearance <30 ml/min.
NEGATIVE CHRONOTROPICS				
Ivabradine	5–7.5 mg orally every 12 hours	Selective inhibitor of the If current in nodal heart cells.	Phosphenes, bradycardia, atrial fibrillation.	Useful for diastolic dysfunction.
Esmolol	0.05–0.2 mg/kg/min	Selective antagonist of short-acting β1 receptor	Hypotension	Easy to titrate.
Landirolol	1–20 µg/kg	Super-selective β1-adrenergic receptor antagonist of ultra-short action.	Hypotension	Lower impact on blood pressure lowering. Faster onset than esmolol. Shorter half-life.
CORTICOSTEROIDS				
Hydrocortisone	50 mg every 6 hours or 200 mg/day continuous IV infusion	Increased vascular reactivity.	Hyperglycaemia	Corticosteroid of choice. Widely available.
Fludrocortisone	50–100 µg orally every 24 hours	Increased vascular reactivity.	Oedema, hypernatraemia, hypokalaemia.	Can be used alongside hydrocortisone. Low availability worldwide.

Figure 1. Cardiovascular pharmaceuticals used for the treatment of septic shock

### Discontinuation of Therapy

Intravenous fluids should be suspended as soon as possible. Fluid intake in the form of nutrition, drug vials, transfusions and so on should be considered. Positive fluid balance should be avoided for longer than two days. Regarding vasopressor withdrawal, the DOVSS study (prospective, randomised) evaluated the incidence of hypotension according to the order of vasopressor withdrawal in septic shock, demonstrating that gradual reduction of norepinephrine instead of vasopressin was statistically significantly associated with a higher incidence of hypotension

(Jeon et al. 2018). A recent systematic review with meta-analysis that evaluated the effects of the order of norepinephrine and vasopressin interruption in the recovery phase of septic shock showed that norepinephrine interruption, before vasopressin, resulted in less hypotension, with no difference in mortality or length of hospital stay (Hammond et al. 2019). As for inotropic drugs used for myocardial dysfunction caused by sepsis, it is known that this complication is usually reversible within days and should be suspended upon evidence of improvement in LV systolic function, for which echocardiography can be very useful.

### Goals of Macrohaemodynamic Resuscitation in Septic Shock

Recommendations indicate to maintain a mean arterial pressure target >65mmHg, compared to higher targets (as a strong recommendation with moderate quality of evidence (Evans et al. 2021); however, patients with systemic hypertension or chronic kidney disease may require a target >80 mmHg MAP for better results.

The ANDROMEDA-SHOCK study evaluated the use of capillary refill time (CRT) compared to serum lactate levels as a resuscitation strategy in patients with septic shock, finding that 28-day mortal-

ity was not statistically different between the two groups (Hernández et al. 2019). Nevertheless, a post-hoc analysis using Bayesian mixed logistic regression showed that peripheral perfusion-guided resuscitation can reduce mortality and lead to rapid resolution of organ dysfunction compared to lactate-guided resuscitation, the latter being associated with over-resuscitation with fluids, vasopressors, and inotropes (Zampieri et al. 2020).

Serum lactate has been strongly associated with mortality in critically ill patients, however, its usefulness in monitoring patients with sepsis is controversial. Although the Surviving Sepsis Campaign 2021 suggest guiding resuscitation to lower lactate levels in septic shock (Gómez and Kellum 2015), other causes associated with lactate elevation should be ruled out or assessed (e.g., acute liver failure, intestinal ischaemia, diabetic ketoacidosis, adrenergic effect, etc.). It has also been shown that hyperlactataemia is often caused by impaired tissue oxygen utilisation (bioenergetics failure) in sepsis, rather than oxygen transport impairment as the single main cause. Thus, the current

resuscitation strategy could be modified according to the origin of lactate excess (Marik 2019). Central venous oxygen saturation (ScvO<sub>2</sub>) has prognostic value in critically ill patients. Levels <70% are associated with increased mortality; however, despite the recommendation to maintain a

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SvcO<sub>2</sub> greater than this level (Rivers, 2008) through IV fluids, vasopressors, inotropes, transfusion of red blood cell concentrates and increased inspired oxygen fraction (FiO<sub>2</sub>) have no impact on mortality.

Other invasive and minimally invasive monitoring strategies to improve

the prognosis of patients in septic shock have been proposed (intrapulmonary and transpulmonary thermodilution, pulse wave analysis, etc.), but the perfect monitoring strategy that represents an improvement in outcomes, with the least possible invasiveness and at the lowest cost has not yet been developed. The best monitoring is done by the clinician who is aware of the haemodynamic changes in the patient and who takes appropriate actions based on the best available evidence.

### Conclusion

Haemodynamic management of patients in septic shock is a challenge for the clinician. Detection of haemodynamic changes and appropriate therapeutic action with fluids, vasopressors, inotropes, corticosteroids and/or beta-blockers, combined with infection control can improve the prognosis of these patients.

### Conflict of Interest

None. ■

## References

- Acheampong A, Vincent JL (2015) A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care*. 19:251.
- Annane D, Pastores S et al. (2017) Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society

of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med*. 43:1751–1763.

Annane D et al. (2018) Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med*. 378:809–818.

Bakker J, Kattan E, Annane D et al. (2022) Current practice and evolving concepts in septic shock resuscitation. *Intensive*

*Care Med*. 48:148–163.

Datta PK, Rewari V, Ramchandran R et al. (2021) Effectiveness of enteral ivabradine for heart rate control in septic shock: A randomised controlled trial. *Anaesth Intensive Care*. 49(5):366–378.

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