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Review

Haemodynamic management of septic shock

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Abstract

Septic shock is a significant challenge in the management of patients with burns and traumatic injuries when complicated by infection, necessitating prompt and effective haemodynamic support. This review provides a comprehensive overview of current strategies for vasopressor and fluid management in septic shock, with the aim to optimize patient outcomes. With regard to vasopressor management, we elaborate on the pharmacologic profiles and clinical applications of catecholamines, vasopressin derivatives, angiotensin II, and other vasoactive agents. Noradrenaline remains central to septic shock management. The addition of vasopressin, when sequentially added to noradrenaline, offers a non-catecholaminergic vasoactive effect with some clinical benefits and risks of adverse effects. Emerging agents such as angiotensin II and hydroxocobalamin are highlighted for their roles in catecholamine-resistant vasodilatory shock. Next, for fluid management, crystalloids are currently preferred for initial resuscitation, with balanced crystalloids showing benefits over saline. The application of albumin in septic shock warrants further research. High-quality evidence does not support large-volume fluid resuscitation, and an individualized strategy based on haemodynamic parameters, including lactate clearance and capillary refill time, is recommended. The existing knowledge suggests that early vasopressor initiation, particularly noradrenaline, may be critical in cases where fluid resuscitation takes inadequate effect. Management of refractory septic shock remains challenging, with novel agents like angiotensin II and methylene blue showing potential in recent studies. In conclusion, Further research is needed to optimize haemodynamic management of septic shock, particularly in developing novel vasopressor usage and fluid management approaches.

Keywords: Haemodynamic; Management; Shock; Sepsis

Highlights:

- Noradrenaline is effective in increasing systemic vascular resistance and cardiac preload, recommended early in septic shock treatment as per guidelines; however, careful management of catecholamine dosages and the potential side effects, such as arrhythmias and immunomodulatory effects should be noted.
- Vasopressin is known for its effectiveness in vasoconstriction and reducing catecholamine doses, thus decreasing the risk of arrhythmias, and angiotensin II may be a valuable second-line vasopressor for catecholamine-resistant hypotension.
- The critical balance of fluid resuscitation and vasopressor support to optimize tissue perfusion and prevent progression to irreversible shock is of immense importance.
- Novel strategies including methylene blue and hydroxocobalamin may have potential to improve haemodynamics when traditional vasopressors fail, whilst awaiting for ongoing research to validate their effectiveness and safety in critical care settings.

Background

In the management of critically ill patients with burns and traumatic injuries, septic shock remains a significant challenge when infection complicates the clinical course. It is characterized by life-threatening inadequate tissue perfusion, which requires timely and effective intervention, including source control of the infection [1]. Key symptoms include fever or hypothermia, tachycardia, tachypnoea, and altered mental status. The underlying pathophysiology of septic shock involves a variety of inflammatory responses, leading to vasodilatation, increased vascular permeability, and decreased systemic vascular resistance, which collectively results in severe hypotension and inadequate tissue perfusion. Pathological changes in major organs during sepsis are highly variable and can include acute kidney injury (AKI) characterized by altered renal perfusion, hepatic dysfunction with cholestasis or hepatocellular injury, and myocardial depression with impaired cardiac contractility even manifesting hyperdynamic cardiac contraction at an early stage of resuscitation. These changes are influenced by the severity of the responses, dysfunctions, and pre-existing conditions and vary across patients [2]. Treatment targets focus on early identification and management of the underlying infection, haemodynamic support, and support of organ dysfunction. Current therapeutic challenges include timely diagnosis, optimizing fluid resuscitation, managing antibiotic resistance, and providing effective supportive care for multi-organ dysfunction.

Intravenous (IV) fluid resuscitation and timely vasopressor initiation are the mainstay of the management of

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haemodynamic instability in septic shock to restore organ and tissue perfusion. As most patients with septic shock have a high cardiac output and reduced systemic vascular resistance, vasopressor therapy works to raise blood pressure and maintain adequate perfusion to vital organs. Vasopressors function through various mechanisms involving the sympathetic nervous system, the vasopressin pathways, and the renin–angiotensin system (RAS), each contributing to vascular tone regulation. The choice and timing of vasopressor administration are critical decisions that depend on the individual patient's response to initial fluid resuscitation and the specific characteristics of the shock presentation.

This review provides a comprehensive overview of the current vasopressor and fluid management strategies in septic shock.

Review

The first part covers vasopressor therapies detailing their pharmacologic profiles, clinical applications, and the implications for their use in practice. The second part elaborates on the emerging evidence concerning haemodynamic management in septic shock, focusing on fluid resuscitation targets and the timing and choice of vasopressors in optimizing patient-centred outcomes.

Vasopressors used for septic shock

Blood pressure regulation is primarily governed by three mechanisms: the sympathetic nervous system, the vasopressin pathway, and the RAS. Corresponding to each mechanism are specific agents: the sympathetic nervous system utilizes catecholamines and their derivatives; the vasopressin pathway operates with arginine vasopressin and its derivatives; and the RAS employs angiotensin II. Furthermore, several vasoactive agents with distinct mechanisms of action are used to manage septic shock. This section will provide an overview of these vasopressors and other vasoactive agents with regard to their pharmacological characteristics and clinical use. The characteristics of these vasopressors and other vasoactive agents are summarized in Table 1 [3–17].

Catecholamines and their derivatives

Catecholamines exert their pharmacological properties by binding to adrenergic receptors. Typical agents include noradrenaline, adrenaline, dopamine, phenylephrine, metaraminol, and midodrine. As an $\alpha 1$ receptor agonist, noradrenaline exerts its vasoconstrictor effects on both arterial and venous circulation. By binding to venous adrenergic receptors, noradrenaline reduces venous capacitance, decreasing unstressed volume (segment of venous blood that fills veins without contributing to venous pressure), and increases stressed volume (actively distends the veins and assists venous return to the heart) that contributes to mean systemic filling pressure [18–20]. These observations support the concept of early noradrenaline administration, prior to completion of fluid resuscitation, as is now suggested by international sepsis guidelines [1]. Noradrenaline also acts on β-adrenergic receptors, exerting inotropic effects. Adverse effects of noradrenaline include arrhythmias and ischemic events [21]. The maximal dose for noradrenaline is not established; however, harm from noradrenaline may exceed its beneficial effects when the dose reaches a high range (e.g. >1 μg/kg/min) [3, 22, 23].

When considering noradrenaline dosages, differences in noradrenaline salt formulations must be considered. This issue is of paramount importance since different noradrenaline formulations have different molecular weights, leading to inconsistent equipotency [24]. For example, the molecular weight of noradrenaline bitartrate ($C_{12}H_{19}NO_{10}$) is 337, whilst that of noradrenaline hydrochloride ($C_8H_{11}ClNO_3$) is 206 (Table 2) [24, 25]. Thus, if clinicians administer noradrenaline according to the dose of each salt, the net noradrenaline dose will vary $\sim$1.6 times or double compared to that of noradrenaline base ($C_8H_{11}NO_3$; molecular weight, 169). What further complicates the situation is the fact that the noradrenaline base itself is not commercially available because it is poorly soluble in water, ether, and alcohol but is easily soluble in acid [26].

Recently, there has been an intense discussion on how to report noradrenaline dosage. Due to variations in the presentation of noradrenaline formulations across different countries and institutions (Table 2), there is confusion regarding the current reporting of noradrenaline in the scientific literature. While the noradrenaline base is commonly used, several clinical trials used noradrenaline tartrate to express the noradrenaline dose, which is twice that of the base formulation [27]. To address this issue, the joint task force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine issued position statements, which emphasized the importance of using a uniform reporting method of noradrenaline concentrations and doses in base equivalence [25].

Adrenaline has strong $\beta 1$ adrenergic receptor activity and moderate $\alpha 1$ and $\beta 2$ adrenergic activities. The blood pressure response may vary at low doses and increase at high doses, whilst cardiac output is increased irrespective of dosage [28]. Typical adverse events include tachyarrhythmias and mesenteric ischaemia, as well as hyperlactataemia induced by increased aerobic glycolysis through $\beta 2$ activity [29]. Such lactate elevation, following the use of adrenaline, can occur even when the patient's perfusion is improving, which may lead clinicians to administer excessive fluids or additional vasopressors [30]. Therefore, it is crucial to evaluate the haemodynamic status by integrating lactate measurements with other perfusion indicators, such as capillary refill time and urine output, rather than relying on lactate levels alone. Randomized trials comparing adrenaline with noradrenaline showed no difference in the time to achieve blood pressure targets or mortality [4, 31], whilst one trial observed a significant lactate increase in the adrenaline group [31].

Dopamine exhibits vasoconstriction via $\alpha 1$ adrenergic activity, vasodilation via dopamine-1 receptor activity, and inotropic effects via $\beta 1$ adrenergic receptors. Lower doses were widely employed as 'renal-dose dopamine' to prevent AKI in the twentieth century; however, the reno-protective effect was not proven in a large multicentre randomized trial [32], and the use of low-dose dopamine in sepsis or septic shock is no longer supported. Arrhythmia due to $\beta 1$ adrenergic receptor activity is a common complication of dopamine. Indeed, when compared to noradrenaline, dopamine increases not only the risk of arrhythmias [5] but also that of death [33].

Phenylephrine is a pure $\alpha 1$ agonist, resulting in vasoconstriction and potentially peripheral ischemia. A randomized trial in 32 septic shock patients observed no difference in

Table 1. Mechanisms of action and adverse effects of vasopressors and other vasoactive agents used for septic shock

Drugs	Mechanisms of action	Dose	Adverse effects
Noradrenaline	α-1 > β-1, β-2	0.05–1 μg/kg/min [3]	Arrhythmia
Adrenaline	α-1 > β-1, β-2	0.05–0.8 μg/kg/min [4]	Arrhythmia Hyperlactatemia
Dopamine	α-1, β-1, dopamine 1 receptors	1–20 μg/kg/min [5]	Increased mortality compared to noradrenaline Arrhythmia
Phenylephrine	α-1	0.1–1.5 μg/kg/min [6]	Reduced cardiac output Reflex bradycardia Peripheral and splanchnic ischemia
Metaraminol	α-1	0.1–1.5 μg/kg/min [7]	Arrhythmia
Midodrine[a]	α-1	10–20 mg every 8 h [8, 9]	Slow onset
Vasopressin	V_{1A}, V_{1B}, V_2	0.01–0.06 U/min [6, 10]	Digital ischaemia Mesenteric ischaemia
Selepressin[b]	V_{1A}	1.25–5 ng/kg/min [11]	Ischaemic events
Terlipressin	V_{1A}, V_{1B} > V_2	20–160 μg/h [12]	Digital ischaemia
Angiotensin II	Angiotensin II receptors	1.25–40 ng/kg/min [13]	High costs
Methylene blue	Inhibit inducible nitric oxide synthase and soluble guanylate cyclase	100 mg over 6 h daily up to 3 doses [14]	Green-blue urine discoloration Methaemoglobin Serotonin syndrome
Hydroxocobalamin	Scavenge nitric oxide and hydrogen sulfide	5 g over 15 min [15]	Discoloration of urine and plasma to red
Hydrocortisone	Glucocorticoid and mineralocorticoid receptors	200 mg/day [16, 17]	Hyperglycaemia Hypernatremia Muscle weakness

Abbreviations: V_{1A}, vasopressin receptor 1A; V_{1B}, vasopressin receptor 1B; V_2, vasopressin receptor 2. [a]Selepressin was not approved after a phase IIb/III randomised controlled trial. [b]Orally administered

Table 2. Noradrenaline salt formulations

Salt formulations	Chemical formula	Molecular weight	Formulation dosage, mg	Base formulation equivalence, mg	Region or country
Noradrenaline tartrate	$C_{12}H_{17}NO_9$	337	2	1	Europe, UK, Russia, Australia
Noradrenaline bitartrate (anhydrous)	$C_{12}H_{19}NO_{10}$	319	1.89	1	North America, Russia
Noradrenaline hydrochloride	$C_8H_{12}ClNO_3$	206	1.2	1	Germany, Austria

Adapted from the references [24, 25]

various haemodynamic and perfusion parameters between phenylephrine and noradrenaline [34]. In a large cohort study during the noradrenaline shortage in the USA, there was increased use of phenylephrine as an alternative vasopressor and an increased mortality rate in septic patients [35].

Metaraminol, a sympathomimetic amine with a chemical structure close to that of noradrenaline, acts as an α1 adrenergic receptor agonist and stimulates the release of endogenous noradrenaline [36]. Adverse events include arrhythmias such as reflex bradycardia. Metaraminol is a commonly used vasopressor in Australia, often administered peripherally before transitioning to noradrenaline once a central venous catheter is established. However, noradrenaline dose equivalence for metaraminol has not yet been determined [7, 37, 38]. A small randomized trial showed comparable haemodynamic effects between metaraminol and noradrenaline [38].

In addition to IV agents, there has been growing interest in oral catecholaminergic vasopressors like midodrine, which is an oral α1 adrenergic agonist. Given that dependence on IV vasopressors can be a reason for prolonged intensive care unit (ICU) stays, two randomized trials have tested the hypothesis that midodrine could facilitate liberation from IV vasopressor infusions, thereby promoting ICU discharge [8, 9]. However, neither study found a clear benefit, and bradycardia was observed more frequently in the midodrine group [8].

Vasopressin and its derivatives

Vasopressin acts on V_1 receptors on vascular smooth muscle exerting vasoconstriction and on V_2 receptors on distal tubules, exhibiting its antidiuretic effects. An initial report found a suppressed vasopressin concentration in patients with septic shock compared to those with cardiogenic shock, leading to the hypothesis that administration of vasopressin can restore 'relative vasopressin deficiency' in septic shock and improve clinical outcomes [39]. Due to its noncatecholaminergic properties, adding vasopressin to noradrenaline reduces the risk of arrhythmia, presumably by avoiding higher catecholamine doses [40, 41]. On the other hand, adverse events associated with vasopressin include digital and mesenteric ischemia [40, 41].

Selepressin, a selective V_{1A} agonist, showed promising results regarding fluid balance and ventilator liberation in a phase IIa trial [42]. However, a phase IIb/III trial reported that the addition of selepressin to noradrenaline, compared to placebo, did not reduce vasopressor- or ventilator-free days in patients with septic shock and was terminated early for

futility [11]. As a result, selepressin failed to gain approval in Europe and the USA.

Terlipressin, a synthetic vasopressin analogue, has greater selectivity for V_1 receptors than vasopressin itself [43]. The only large randomized trial that compared terlipressin with noradrenaline in septic shock found no significant difference in 28-day mortality, but a significant increase in serious adverse events, especially digital ischemia (13% vs. 0.4%), was observed in the terlipressin group [12].

Angiotensin II

Within the context of hypotension, studies on pharmacological agents targeting RAS were rarely conducted until recently. This situation has changed with the availability of synthetic angiotensin II in 2017. Synthetic angiotensin II exerts its vasoconstrictive effects by binding to angiotensin II type I receptors on vascular smooth muscle. After a pilot trial confirming the feasibility and safety of exogenous angiotensin II administration in septic shock [44], a phase III randomized trial was performed in catecholamine-resistant vasodilatory shock [13]. Among 321 patients receiving at least 0.2 μg/kg/min of noradrenaline equivalent vasopressor therapy (with >80% of them being in septic shock), angiotensin II achieved a predefined mean arterial pressure (MAP) target more frequently than placebo without increasing the risk of serious adverse events [13]. Based on these data, angiotensin II was approved as a second-line vasopressor to treat catecholamine-refractory vasodilatory shock in the USA and in Europe. Since this trial was not designed to evaluate the efficacy of more clinically relevant outcomes like mortality, the effects of angiotensin II on such outcomes remain uncertain. Although the Federal Drug Administration issued caution on thrombotic events with the use of angiotensin II, both previous randomized trials reported no significant difference in the occurrence of venous or arterial thrombotic events compared to control patients [13, 44].

Other vasoactive agents

In addition to the three classes of vasopressors, i.e. catecholamines, vasopressin, and angiotensin II, vasoactive agents with different mechanisms of action have been evaluated in septic shock. Methylene blue is an inhibitor of inducible nitric oxide synthase and soluble guanylate cyclase, counteracting excessive nitric oxide production and restoring decreased vascular tone [45]. Common adverse events of methylene blue include a green-blue discoloration of urine and increased methaemoglobin saturation. When administered in high doses, e.g. >7 mg/kg, or via continuous infusion, impaired splanchnic perfusion or severe methemoglobinemia may be observed [46, 47]. Furthermore, in patients taking chronic selective serotonin reuptake inhibitors, a serotonin syndrome resulting in coma can occur [48].

Hydroxocobalamin has the potential to restore vascular tone and reduce capillary leak by scavenging nitric oxide and hydrogen sulfide, both of which contribute to vasodilation in septic shock [49, 50]. Hydroxocobalamin has a distinctive adverse effect, discolouration of urine and plasma to red, which can interfere with laboratory values, monitoring systems, and blood leak alarms of dialysis machines [51]. A small phase II randomized trial confirmed not only the feasibility of high-dose hydroxocobalamin (5 g) but also its catecholamine-sparing effects in patients with septic shock [15]. No serious adverse events were reported related to the use of hydroxocobalamin [15].

Considerations of vasopressor use in burns and traumatic injuries

The initial haemodynamic response to severe burn and traumatic injuries is driven by the release of inflammatory mediators, which resembles septic shock [52, 53]. The inflammatory response leads to increased capillary leakage, peripheral and splanchnic vasoconstriction, and myocardial depression, resulting in large fluid loss into the interstitial space. Fluid accumulation into the interstitial space in patients with burns is also explained as results from the imbalance between hydrostatic and oncotic pressures favouring the fluid movement into the interstitial space with increase of vascular permeability and glycocalyx degradation [54]. Commonly used burn resuscitation protocols, e.g. the Parkland formula based on total body surface area burnt, recommend the administration of large volumes of intravenous fluids to restore circulating plasma volume and prevent further organ dysfunction. However, the large positive fluid balance was reportedly associated with the risk of AKI in severe burns [55, 56] and severe sepsis [57] due to venous congestion. The risk related to a large-volume fluid resuscitation is also explained by Starling theory as a decrease in intravascular oncotic pressure due to haemodilution by crystalloids exacerbates extravascular fluid leakage. Furthermore, such hyperdynamic state observed in burns and sepsis is coupled with augmented renal clearance characterized by elevated renal solute elimination and increased glomerular filtration rate, which further complicates fluid management [53, 58]. Therefore, vasopressor agents are reasonably used even in burns and trauma injuries to restore organ perfusions in patients with burns or trauma as in sepsis.

Although historically, the use of vasopressors in burn patients was considered harmful due to concerns of reduced skin perfusion and potential worsening of burn necrosis from animal experiment [59], recent evidence from a systematic review highlights the ongoing uncertainty surrounding their benefits and risks [60]. Only two observational studies reported sufficient data on the use of vasopressors in patients with burns, both of which reported 20%–30% of patients received vasopressors, and age and TBSA were commonly associated with the need for vasopressors [60]. However, the quantity and quality of clinical data on the benefits and risks related to vasopressor use in patients with burns are still lacking.

Fluid management and vasopressor initiation in septic shock

The following sections aim to review contemporary evidence concerning the type and quantity of IV fluids and the initiation of vasopressors in septic shock. Early and aggressive fluid resuscitation is considered 'standard' in the management of septic shock [1]. Here, the rationale behind fluid administration is to restore intravascular volume, improve tissue perfusion, and prevent worsening organ dysfunction. The existing evidence for the optimal type and quantity of fluids is detailed below.

Crystalloids vs. colloids

Several large randomized controlled trials have compared crystalloids and colloids for fluid resuscitation in septic shock. Starch-based colloids have been shown to be harmful, with the

CHEST trial showing an increased need for continuous renal replacement therapy [61] and the 6S trial demonstrating an increase in mortality [62]. Overall, the SAFE study (Saline vs. Albumin Fluid Evaluation) found no significant difference in mortality between crystalloids and colloids [63]. However, in a *post hoc* subgroup analysis of the SAFE trial patients with septic shock, a mortality benefit was noted with albumin [64]. The ALBIOS trial showed an improvement in haemodynamic indices when 20% albumin was administered in addition to crystalloid resuscitation, without an improvement in mortality [65]. Based on these findings, current guidelines recommend crystalloids as the preferred choice for initial fluid resuscitation in septic shock due to their availability, cost-effectiveness, and safety profile [1]. Clinicians' preference on the use of albumin varies, and additional research on the use of albumin in septic shock is warranted [66].

Balanced crystalloids vs. saline

Balanced crystalloids are recommended by the latest edition of the Surviving Sepsis Campaign Guidelines (SSCG) [1]. Evidence suggests improved mortality and lower rates of AKI vs. saline [67–69]. In particular, a recent systematic review and meta-analysis, using a Bayesian approach, found a high likelihood that the use of balanced crystalloids also results in lower mortality in sepsis [69]. Due to their ubiquity of use, even a small difference in outcome for patients with the use of balanced crystalloid would be significant on a population scale. Balanced solutions mimic the electrolyte composition of plasma, minimizing acid–base and electrolyte changes associated with fluid resuscitation [70]. This is in contrast to saline, which has a sodium concentration of 154 mmol/L and chloride concentration of 154 mmol/L far above normal serum chloride values. The use of such a hyperchloraemic solution results in metabolic acidosis, hyperkalaemia [71, 72], and increased rates of AKI [73], likely due to reduced renal perfusion [74].

An approach that may be considered would be to base the choice of crystalloid dependent on the acid–base status of the patient. Patients with septic shock commonly present with renal impairment and resultant metabolic acidosis, and administering bicarbonate infusions to these patients may be beneficial. There is minimal current supporting evidence for this approach; however, some comes in the form of the BICAR-ICU trial published in 2018 [75]. This trial showed a significant decrease in mortality in patients with AKI who were administered bicarbonate infusions along with a decrease in need for renal replacement therapy. A large portion of the patients included had sepsis (61%) and required vasopressors for shock (80%). The upcoming SODa-BIC trial will add to the available evidence on this topic [76] (ClinicalTrials.gov; NCT05697770). A similar but converse example would be to give normal saline as a resuscitation fluid for patients with acute metabolic alkalosis and hypochloraemia that may occur as a result of large-volume vomiting that may be associated with gastrointestinal sources of septic shock. For patients without significant metabolic acidosis or alkalosis, balanced crystalloids appear to be the best choice.

Fluid quantity

There is no high-quality evidence confirming that large-volume IV fluid resuscitation is beneficial in septic shock. The recent CLOVERS trial found no difference in outcomes when comparing a liberal to restrictive fluid strategy in septic shock [77]. In the restrictive group, up to 2 L of IV fluid was given before vasopressors were commenced. This was compared to >2 L being given in the liberal arm, with further fluid boluses as required for persistent hypotension, and up to 5 L IV fluid before commencing vasopressors. The SSCG suggest an initial fluid resuscitation of 30 ml/kg of crystalloids within the first 3 h of recognition of septic shock [1]. In the most recent SSCG, the recommendation for >30 ml/kg fluid administration has been made less strongly [1].

Other evidence suggests caution regarding aggressive fluid administration, as this may lead to fluid overload, tissue oedema, and unfavourable outcomes [78, 79]. Individualized fluid resuscitation strategies based on haemodynamic parameters and markers of perfusion adequacy are increasingly advocated to avoid fluid overload whilst ensuring adequate tissue perfusion. The ARISE Fluids trial (Clinicaltrials.gov; NCT04569942) will aim to provide evidence regarding the optimal approach to haemodynamic management in early septic shock.

Fluid resuscitation endpoints

The use of dynamic parameters of fluid responsiveness theoretically may result in more targeted fluid administration and the avoidance of over-resuscitation in nonresponders; further, dynamic measures of fluid responsiveness have been associated with reduced mortality, ICU length of stay, and duration of mechanical ventilation [80]. Dynamic parameters such as passive leg raise (PLR), stroke volume variation (SVV), and pulse pressure variation (PPV) have been proposed as guides for fluid resuscitation in septic shock [1]. These parameters, derived from arterial waveform analysis, help predict fluid responsiveness and guide fluid administration to optimize cardiac preload. Other parameters such as central venous pressure (CVP) [81], pulmonary capillary wedge pressure (PCWP) [82], and the inferior vena cava (IVC) ultrasonography [83] have been shown to be unreliable predictors of fluid responsiveness.

After initial fluid resuscitation, dynamic measures of fluid responsiveness may be used to guide further administration of fluid. PLR to 45° mimics a fluid bolus to the central circulation; a >10% increase in SV predicts a fluid-responsive state [84]. The Fluid Response Evaluation in Sepsis Hypotension and Shock trial compared PLR to usual care [85]. The researchers determined a response to PLR if SV increased by >10% based on noninvasive bioreactance measures of SV and cardiac performance. Although a small trial, it showed a decrease in overall fluid administration along with decreased requirement for renal replacement therapy and mechanical ventilation [85]. In mechanically ventilated patients, changes in intrathoracic pressure can used to surmise the response to fluid administration due to varying preload conditions during the respiratory cycle. PPV and SVV in the setting of mechanical ventilation have been shown to reliably predict fluid responsiveness [86]. However, their utility may be limited in certain patient populations (such as already fluid-overloaded patients at baseline), patients who are spontaneously ventilating, poor lung compliance, tidal volumes <8 ml/kg, or in the presence of arrhythmias [87].

In critically ill patients, elevated lactate levels often indicate tissue hypoperfusion and are associated with increased mortality. As such, current guidelines recommend incorporating such measures into resuscitation algorithms [1]. Indeed, lactate clearance as a resuscitation endpoint has been a

suggested strategy to guide the titration of fluid and vasopressor therapy. A systematic review and meta-analysis demonstrated that targeting lactate clearance as part of early goal-directed therapy in septic shock was associated with reduced mortality; however, the studies included were markedly heterogeneous [88].

While elevated lactate levels often indicate tissue hypoperfusion, other factors such as liver dysfunction, medications, and certain disease states can also contribute to hyperlactataemia. Serial lactate measurements and integration with other haemodynamic parameters are therefore necessary to guide individualized resuscitation strategies. Capillary refill time has been suggested as an alternate maker of tissue perfusion. Despite the ANDROMEDA-SHOCK trial identifying no difference in mortality using lactate vs. capillary refill time as a marker for hypoperfusion [89], the SSCG suggest the use of capillary refill time as an adjunct to other measures of perfusion [1]. Finally, central venous oxygenation saturation has previously been investigated as a resuscitation endpoint, amongst a bundle of treatments aimed at increasing cardiac output and tissue oxygen delivery [90]. Subsequent large randomized controlled trials (PRoMISE, ARISE, and PRoCESS) did not demonstrate any patient-centred benefits from this approach [91].

Timing and choice of vasopressor therapy in septic shock

In cases where fluid resuscitation fails to restore adequate perfusion or is contraindicated, vasopressor therapy is commonly employed. The optimal timing of vasopressor initiation in the management of septic shock is uncertain. Early initiation of vasopressors may prevent progression to irreversible shock and improve outcomes in critically ill patients. Current guidelines recommend initiating vasopressor therapy promptly in patients with septic shock who remain hypotensive despite adequate fluid resuscitation [1]. Indeed, delayed initiation of vasopressors in order to give time to determine fluid responsiveness may exacerbate tissue hypoperfusion and increase the risk of organ dysfunction [92]. Early initiation of vasopressors has been associated with improved outcomes [93, 94], and the administration of vasopressors peripherally has been shown to be safe, with the majority of rare extravasation events being managed conservatively [95].

Noradrenaline is the vasopressor of choice in septic shock [1], supported by robust evidence from multiple randomised clinical trials (RCTs) and observational studies [93, 96]. Noradrenaline has demonstrated superiority over dopamine in terms of efficacy and safety, including lower rates of arrhythmias and mortality [33, 97]. Beyond this, current evidence does not specifically support any particular vasopressor. The CAT trial demonstrated no difference in mortality or time to achieve an MAP target between noradrenaline and adrenaline [31], whilst the VASST and VANISH trials showed no difference in mortality between noradrenaline and vasopressin [6, 10]. However, vasopressin use was associated with lower rates of renal replacement therapy, suggesting potential renal protective effects [10]. In this context, vasopressors are typically added in a sequential manner with noradrenaline commencing as the first line agent and, if an MAP is inadequate despite moderate dose noradrenaline, vasopressin can be considered.

Clinical features of cardiac impairment (poor urine output, poor capillary refill time in extremities, mottling) in addition to echocardiographic evidence, or direct measures of low cardiac output, would be an indication to add inotropes such as adrenaline or dobutamine. Low relative heart rate (either through pre-existing beta-blockade or lack of appropriate sympathetic response to sepsis) may also be a reasonable indication. Septic cardiomyopathy may be present in up to 65% of patients with septic shock [98]. There have been no large head-to-head trials comparing adrenaline, dobutamine, milrinone, or levosimendan in septic shock. Of note, the recent LEOPARDS trial demonstrated potential harm from levosimendan, when added to standard care in this setting [99]. Typically, adrenaline would often be used in such cases, if indicated, albeit this may contribute to worsening lactataemia (see Catecholamines and Their Derivatives).

Indeed, patients with septic shock are commonly tachycardic and present with arrhythmias such as atrial fibrillation. In these cases, it would be prudent to avoid excess $\beta 1$ stimulation that may exacerbate this state. A meta-analysis of patients with distributive shock demonstrated lower atrial fibrillation rates with the combination of vasopressin and noradrenaline vs noradrenaline alone [40], although the addition of vasopressin may result in higher risk of digital ischaemia [41]. The threshold for adding vasopressin remains a matter of debate. The current sepsis guidelines propose a noradrenaline dose range of 0.25–0.5 μg/kg/min [1]. A recent large-scale observational study found increased mortality for every 10 μg/kg/min increase in noradrenaline dose, suggesting potential benefits of earlier initiation [100]. Further evaluation with randomized trials is needed to optimize vasopressin use in septic shock.

Short-acting beta-blockers may prevent or treat tachycardia and arrhythmias, thereby improving relevant outcomes. However, its efficacy is not established as randomized trials yielded mixed mortality findings. A previous single-centre randomized trial using esmolol suggested potential survival benefits [101], whilst a recent multicentre randomized trial using high-dose landiolol was terminated early due to a concern for increased mortality [102].

In selected situations, vasopressors other than noradrenaline might be considered as the first-line agent. For example, given its strong $\beta 1$ adrenergic receptor activity, adrenaline might be chosen as the first-line vasopressor to restore adequate cardiac output in patients with severe bradycardia and impaired cardiac contractility. Adrenaline is also used as the first-line agent in paediatric sepsis [103] and in circumstances with limited access to noradrenaline [104]. Angiotensin II might be indicated in patients with elevated serum renin concentrations since hyperreninemia potentially reflects relative angiotensin II deficiency and is associated with poor prognosis [105, 106]. However, it should be noted that these vasopressor usages are based on their pharmacological properties or retrospective analysis and require properly designed clinical research to assess the validity of using them.

Haemodynamic goals of vasopressor therapy

Current guidelines recommend aiming for an initial MAP target of 65 mmHg [1]. a recent systematic review and meta-analysis found decreased mortality in patients who had a low blood pressure target (45–70 mmHg) versus patients who had a higher blood pressure target (65–100 mmHg) whilst also finding lower rates of atrial fibrillation and less frequent requirement for blood transfusion in the low blood pressure target group [107]. A recent RCT found that aiming for an MAP of 60–65 mmHg in older adults resulted in less vasopressor exposure, no change in 90-day mortality, and a trend towards improved survival in chronically hypertensive

patients [108]. The existing evidence is suggestive that this is an area with a need for further research, particularly with regards to how low is too low a target and whether there is benefit in individualization of blood pressure targets.

Mean perfusion pressure (MPP) is an alternate target. MPP = MAP − CVP, which is the perfusion pressure across organs. A recent prospective observational study found that an increased time spent further from a patient's baseline MPP (estimated in this trial by previous echocardiography for CVP and pre-illness blood pressures), the higher likelihood of new significant AKI or major adverse kidney events [109].

Management of refractory septic shock

Refractory shock has been defined as persistent hypotension with end-organ dysfunction requiring noradrenaline doses of at least 0.5 mcg/kg/min or equivalent [110]. At this point in resuscitation, fluid responsiveness has been exhausted and possible cardiac dysfunction has been adequately investigated. Novel or rarely used strategies are sometimes attempted, despite a >40% mortality rate in this setting [111]. Angiotensin II was recently shown to increase blood pressure significantly and conferred a mortality benefit (without statistical significance) in the ATHOS-3 trial, these patients had a median noradrenaline dose of 0.34 mcg/kg/min [13] (see Angiotensin II). Furthermore, *post hoc* analyses of the ATHOS-3 trial reported a significant mortality reduction with angiotensin II therapy in patients with high serum renin levels and those undergoing renal replacement therapy [105, 112]. Notably, the ATHOS-3 trial found similar rates of adverse events including arrhythmias and distal ischemia between angiotensin II and placebo [13].

Methylene blue is another 'last-line' vasopressor. A recent randomized controlled trial showed methylene blue, compared to placebo, extended vasopressor-free days in patients with refractory septic shock without causing serious adverse effects [14]. Furthermore, a recent meta-analysis of randomized trials suggested potential survival benefits with the use of methylene blue in septic shock [113]. Impaired oxygenation due to pulmonary vasoconstriction was reported in previous nonrandomized studies [114, 115]; however, such detrimental effects were observed only in high doses and were not confirmed in subsequent randomized trials [14, 46, 116]. Further research is needed to determine the impact of these agents on patient-centred outcomes.

Corticosteroids—another option to restore haemodynamic instability

Corticosteroids can restore haemodynamic stability through various mechanisms including sodium retention, increasing systemic vascular resistance, and enhancing catecholamine responsiveness [117]. Corticosteroids have been shown to facilitate liberation from IV vasopressors in patients with septic shock [118]. The dose and class of corticosteroids suggested in the guidelines are 200 mg/day of hydrocortisone [1]. Unlike shock resolution, uncertainty remains regarding the effects of corticosteroids on survival. Inconsistent results were reported in two large randomized trials [16, 17], which may be explained by the concurrent administration of fludrocortisone. Notably, an individual patient data meta-analysis, which included these trials, showed that hydrocortisone reduced 90-day mortality only when administered concurrently with fludrocortisone [119]. Data on fludrocortisone were obtained from two trials [17, 120] and require further validation. Corticosteroids increase the risk of hyperglycaemia, hypernatremia, and muscle weakness but have minimal effects on secondary infection or gastrointestinal bleeding [118, 119].

Conclusions

The management of septic shock remains a complex challenge, with a focus on vasopressors such as catecholamines, vasopressin derivatives, and angiotensin II. Emerging agents like methylene blue and hydroxocobalamin are also being explored. While these agents show promise, their effects, particularly on renal function (angiotensin II) and patient-centred outcomes, require further research. The effectiveness of these vasopressors is closely associated with optimal fluid management. Balanced crystalloids are recommended as the first-line fluids for sepsis, with the choice tailored to the acid–base status. The use of sodium bicarbonate for metabolic acidosis is being investigated, and the role of albumin in the management of sepsis remains an area needing further investigation. Recent clinical data may highlight the importance of early and appropriate use of vasopressors to restore haemodynamic stability and improve patient outcomes, suggesting that early intervention may be a key focus of future research. New agents may offer promising options for refractory septic shock; however, their benefits and risks need careful consideration. Future research should refine our understanding of the optimal combination of fluid and vasopressor therapy and improve methods to assess dynamic changes in haemodynamic status.

Author contributions

Yuki Kotani (Resources [equal]), Nicholas Ryan (Resources [equal]), Andrew A. Udy (Resources [equal], Supervision [equal]), and Tomoko Fujii (Conceptualisation [lead], Resources, Supervision [equal]).

Conflict of interest

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Review