Vasopressor Therapy in the Intensive Care Unit

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Abstract

After fluid administration for vasodilatory shock, vasopressors are commonly infused. Causes of vasodilatory shock include septic shock, post-cardiovascular surgery, post-acute myocardial infarction, postsurgery, other causes of an intense systemic inflammatory response, and drug -associated anaphylaxis. Therapeutic vasopressors are hormones that activate receptors —adrenergic: α1, α2, β1, β2; angiotensin II: AG1, AG2; vasopressin: AVPR1a, AVPR1B, AVPR2; dopamine: DA1, DA2. Vasopressor choice and dose vary widely because of patient and physician practice heterogeneity. Vasopressor adverse effects are excessive vasoconstriction causing organ ischemia/infarction, hyperglycemia, hyperlactatemia, tachycardia, and tachyarrhythmias. To date, no randomized controlled trial (RCT) of vasopressors has shown a decreased 28-day mortality rate. There is a need for evidence regarding alternative vasopressors as first-line vasopressors. We emphasize that vasopressors should be administered simultaneously with fluid replacement to prevent and decrease duration of hypotension in shock with vasodilation. Norepinephrine is the first-choice vasopressor in septic and vasodilatory shock. Interventions that decrease norepinephrine dose (vasopressin, angiotensin II) have not decreased 28-day mortality significantly. In patients not responsive to norepinephrine, vasopressin or epinephrine may be added. Angiotensin II may be useful for rapid resuscitation of profoundly hypotensive patients. Inotropic agent(s) (e.g., dobutamine) may be needed if vasopressors decrease ventricular contractility. Dopamine has fallen to almost no-use recommendation because of adverse effects; angiotensin II is available clinically; there are potent vasopressors with scant literature (e.g., methylene blue); and the novel V1a agonist selepressin missed on its pivotal RCT primary outcome. In pediatric septic shock, vasopressors, epinephrine, and norepinephrine are recommended equally because there is no clear evidence that supports the use of one vasoactive agent. Dopamine is recommended when epinephrine or norepinephrine is not available. New strategies include perhaps patients will be *started* on several vasopressors with complementary mechanisms of action, patients may be selected for particular vasopressors according to predictive biomarkers, and novel vasopressors may emerge with fewer adverse effects.

Keywords
- septic shock
- norepinephrine
- epinephrine
- phenylephrine
- dopamine
- angiotensin II
- vasopressin
- terlipressin
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Vasopressors are the most commonly ordered drugs in vasodilatory shock, mostly septic shock, but also vasodilatory shock post-cardiovascular surgery, post-acute myocardial infarction (post-AMI), post-general/abdominal surgery, post-trauma, pancreatitis and other conditions causing a severe systemic inflammatory response, and postanesthetic and other drug administration. While evidence-based medicine emphasizes large, pivotal randomized controlled trials (RCTs), there is a place for consideration of both small and large well-controlled studies that are useful to guide clinical practice of vasopressor use. Vasopressors have been evaluated in numerous small underpowered studies but fortunately also in high quality multicenter RCTs, mainly in septic shock. These latter RCTs are the main sources of evidence for practice guidelines,[1] prior reviews,[2] and recommendations for clinical use, while the former help us understand nuances and adverse effects not seen in the constrained environment of an RCT.

Responses to Hypotension and Common Characteristics of Vasopressor Hormones

There are strategically positioned pressure and metabolic sensors that are the first responders to the existential threat of hypotension and tissue hypoxia. Pressure sensors in the carotid are stimulated by hypotension and trigger sympathetically mediated increases in heart rate to directly increase cardiac output and blood pressure. An interconnected endocrine system has widespread, redundant stores of already-synthesized synergistically acting vasopressor hormones that are rapidly secreted in response to hypotension (►**Fig. 1**). Pressure sensors in the renal vasculature increase renin secretion that increases angiotensin I synthesis and angiotensin I is secreted and converted to angiotensin II by angiotensin-converting enzyme (ACE) in the lung vasculature. The adrenal medulla is stimulated to secrete and synthesize epinephrine and norepinephrine, while the posterior pituitary is stimulated to secrete vasopressin.

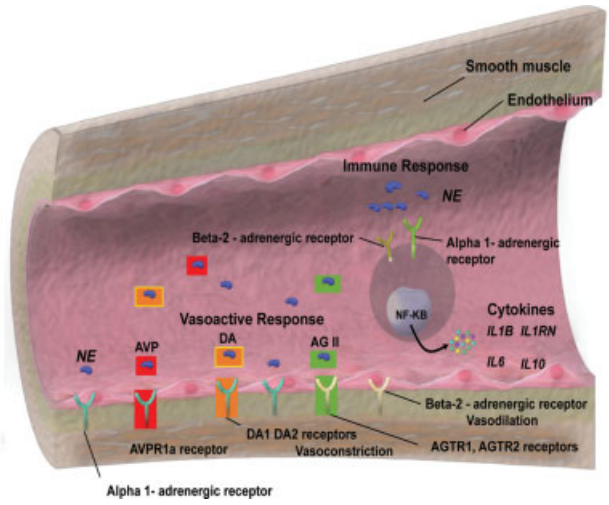

Fig. 1 Vasopressors bind to receptors on vascular smooth muscle to induce vasoconstriction. Norepinephrine (NE) binds to α-1 adrenergic receptors, β-2 receptors causing vasodilation, and α-1 and β-2 adrenergic receptors on leukocytes to modulate immune response in sepsis. NE downregulates α-1 and β-2 receptor density changing sensitivity to NE, thereby leading to increased doses of NE and greater risk of adverse vascular and immune effects. Vasopressin (AVP) binds to the AVPR1a receptor, dopamine (DA) binds to DA1 and DA2 receptors, and angiotensin II (AG) binds to angiotensin II receptors (AGTR1 and AGTR2), all causing vasoconstriction.

Virtually all therapeutic vasopressors are natural hormones (or hormone derivatives) that are critical downstream effectors of the response system to hypotension. Vasopressor hormones regulate blood pressure in health and disease by receptor binding and activation of downstream intracellular signaling systems. The hormones and their relevant receptors are norepinephrine/epinephrine: α1,β1, β2; angiotensin II: AGTR1, AGTR2; vasopressin: AVPR1a, AVPR1b, AVPR2; and dopamine: DA1, DA2 (►**Fig. 1**).

These hormone systems (►**Fig. 2**) are complex, have numerous interactions, and converge on a limited number of receptors that are widely dispersed across the arterial and venous blood vessels. Furthermore, the receptors are up- and downregulated adding to variation in response to native hormone levels and exogenous infusion. Finally, there are genetic variations of the receptors and downstream signaling systems in cells, again adding heterogeneity of patient response to these hormone vasopressors.

The Highly Variable Practice of Vasopressor Use in Shock

Vasopressor choice varies quite widely despite international guidelines (e.g., Surviving Sepsis Campaign [SSC][1]) for the above patient heterogeneity reasons and also because of behavioral variation of physician practice. The remarkably variable use of vasopressin in practice is illustrative. In a U.S. observational study of over 500,000 patients,[3,4] patients in "high vasopressin use" hospitals were about three times more likely to receive vasopressin than patients in "low vasopressin use" hospitals. Furthermore, norepinephrine doses varied widely at baseline in norepinephrine control groups of vasopressor RCTs (mean: 0.20–0.82 μg/kg/min)[5] and not entirely due to differences in severity of shock at baseline.

Vasopressors are indicated for patients with "inadequate" response to fluid resuscitation[1] but "inadequate" response to fluid resuscitation varies from patient to patient in part because methods to determine volume status are relatively inaccurate and because different physicians have different opinions about when a patient is adequately resuscitated.

Vasopressor Use and Guidelines

In the SSC guidelines, norepinephrine is the first-line vasopressor.[1] However, there is no high quality RCT evidence of alternative vasopressors as first-line vasopressors because RCTs of vasopressors include patients who are already nearly all on norepinephrine at baseline to which a second vasopressor (e.g., vasopressin, angiotensin II) is added. Recently, a Cochrane analysis concluded that there was insufficient mortality evidence to declare that any vasopressor was superior to others.[6]

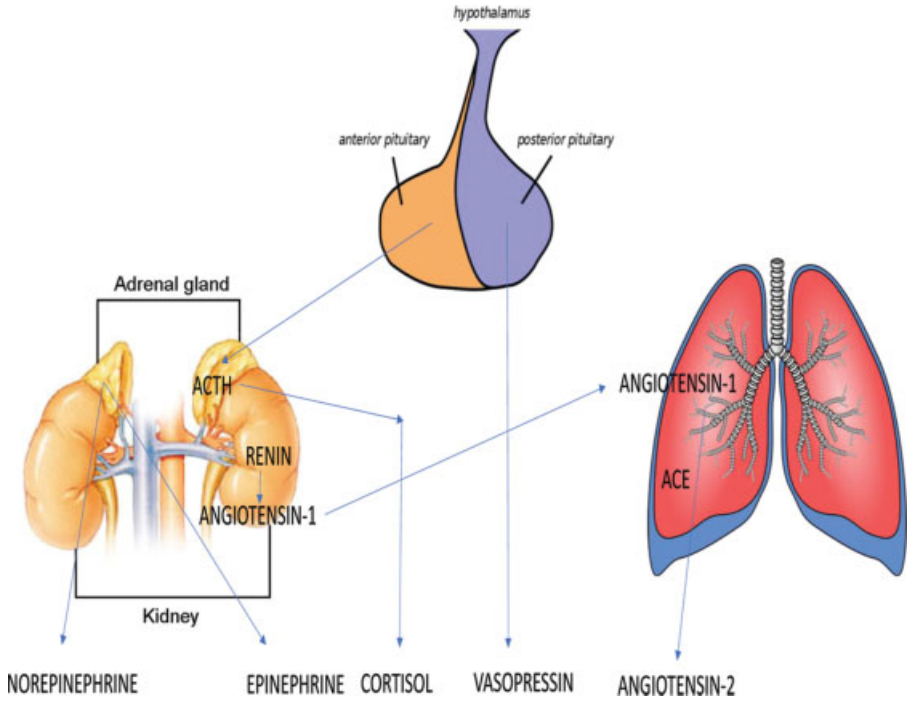

Fig. 2 The endocrine system is central to the homeostatic response to cardiovascular stress and hypotension. The complex endocrine response to septic shock includes the following: (1) release of norepinephrine and epinephrine from the adrenal medulla, (2) release of adrenocorticotropic hormone (ACTH) from the anterior pituitary then stimulating synthesis and release of cortisone and cortisol from the adrenal cortex, (3) release of vasopressin from the posterior pituitary, and (4) release of renin (in response to hypotension) from the kidney. Renin is converted to angiotensin I by angiotensinogen (released from the liver), and then angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE) in the lung. Angiotensin II increases aldosterone synthesis and release from the adrenal cortex; aldosterone increases sodium retention in the kidney. Angiotensin II also increases release of vasopressin. Norepinephrine and epinephrine bind to α-1 adrenergic receptors, vasopressin binds to AVPR1a receptors, and angiotensin binds to angiotensin receptors (AG 1 and AG 2), all on vascular smooth muscle. After ligand binding, intracellular signal transduction increases intracellular calcium, thereby causing vascular smooth muscle contraction and vasoconstriction. Corticosteroids have complex cardiovascular effects that are incompletely understood but include modulation of α-1 receptor density and other actions that quickly increase responsiveness to catecholamines, such as norepinephrine.

Giving a vasopressor for hypotension in the presence of a very high cardiac output (vasoplegia) is very different than in the presence of a normal or low cardiac output. In the former case, a pure vasopressor (vasopressin, phenylephrine, angiotensin II) may be helpful, but in the latter, it can be very harmful.

Fluid administration is important and vasopressors and inotropic agents may be required, but we emphasize that blood pressure is not the only variable to focus on. These potent interventions require titration and monitoring of markers of perfusion such as mentation, skin perfusion, urine output, and serum lactate to guide drug choice, dose, and titration.

A target mean arterial pressure (MAP) during vasopressor use of 65 mm Hg is recommended by SSC[1] and this is a general target that can be adjusted based on individual patient characteristics, i.e., one size does not fit all. Clinicians questioned whether a higher target MAP may lead to better outcomes and was the primary hypothesis of a high-quality RCT of usual versus high MAP targets.[7] Asfar and colleagues[8] found no difference in short-term mortality between "usual" MAP (65–70 mm Hg) and high MAP (80–85 mm Hg) targets. The high-target MAP group had significantly less acute kidney injury (AKI) in the subgroup of patients who had pre-existing hypertension.[8] However, a recent pooled analysis reported that lower blood pressure targets were not associated with adverse events, including chronically hypertensive patients.[9]

Septic shock is the commonest cause of vasodilatory shock and this definition was recently revised.[10] The new definition of septic shock 3.0 requires (1) infection, (2) use of vasopressor(s), *and* (3) a serum lactate >2 mmol/L.[10] The addition of the increased lactate level was based on a review of outcomes of patients in very large cohorts, and marks a higher mortality than in patients with lactate <2 mmol/L[11] and also recognizing that shock is more than simple hypotension. The new definition of septic shock 3.0 will have ramifications for practice and for clinical studies by altering the inclusion criteria of RCTs of therapies for septic shock. When this new septic shock 3.0 definition was applied to patients in a prior pivotal RCT of norepinephrine versus vasopressin (Vasopressin and Septic Shock Trial [VASST]),[12] it was predicted that patients who had lactate >2 mmol/L had higher mortality rates (~10% higher) and the response to vasopressin depended on lactate at the baseline. Vasopressin was most effective in patients who did *not* meet the new definition (i.e., patients who were on vasopressor(s) with lactate ≤ 2 mmol/L).[13] Thus, the baseline lactate level was both a prognostic (for mortality) and a predictive (for response to vasopressin) biomarker.

Vasopressor Trials: Limitations, "Misses," and Shortfalls

The septic shock vasopressor RCT field has been plagued by negative pivotal RCTs despite many positive small proof-of-principle RCTs. Indeed, to date, no RCT has found significant difference in short-term (e.g., 28-day) mortality rate between various vasopressors. VASST did show decreased mortality in prespecified, prestratified and preset *p*-values, and low severity of shock group, but this is not generally recognized. This result provides some evidence that RCTs in this area are not futile if properly powered. In addition, several strategies added a second vasopressor (e.g., vasopressin,[12,14] angiotensin II[15]) to decrease the dose and duration of norepinephrine infusion, but to date, these RCTs have not shown a significantly decreased 28-day mortality rate. One exception discussed in more detail below is that corticosteroids routinely decrease the dose requirements of norepinephrine and other catecholamine vasopressors and also decrease mortality in some,[16,17] but not all,[18,19] pivotal RCTs.

In sum, evidence-based vasopressor use has changed: although norepinephrine remains the first-line vasopressor, dopamine has a negative recommendation[1] because of its tachycardic and tachyarrhythmic adverse effects; angiotensin II[15,20,21] is now approved in the United States and by the European Union and is available clinically in the United States; and a novel vasopressin derivative (i.e., selepressin[22,23]) has completed a large Phase 2B RCT[24] with no effect on the primary outcome and so will not be available clinically.

Herein we review pathophysiology of vasodilatory shock, major vasopressor RCTs, and describe whether, when, and what vasopressor(s) to use specifically: norepinephrine, epinephrine, phenylephrine, dopamine, vasopressin, terlipressin, selepressin, and angiotensin II. We cover the pertinent pharmacology, guidelines, effects, adverse effects, dosing, and outcomes.

We briefly consider what inotropic agents to infuse to complement vasopressors because vasopressors can decrease the ventricular function and cardiac output, so an inotropic agent(s) is added to vasopressors in 15 to 30% of patients on vasopressors.[25] Several potential candidate predictive biomarkers identify patients who are good or poor responders to vasopressors. Although at first seemingly illogical, there is in fact a rationale and some evidence for an ironic role for β1-blockers in septic shock, but more RCTs are needed to extend the current incomplete evidence base in septic shock. There is also a role for vasopressors in vasodilatory shock post-cardiovascular surgery, post-general/abdominal surgery, and post-anesthetic and other drug injection. We conclude with recommendations that we will help the practicing clinician.

The Complex Pathophysiology of Vasodilatory Shock

Vasodilatory shock is characterized physiologically by excessive vasodilation (with low systemic vascular resistance), hypotension, and inadequate perfusion (hyperlactatemia, oliguria, confusion)[26] because of inappropriate vascular smooth muscle relaxation as the primary event and continued vasodilation despite hypotension, the most potent stimulus for vasoconstriction.[27,28] Septic shock is also often complicated by ventricular dysfunction and hypovolemia in septic shock.

The endocrine system has a redundant array of hormonal responses of very potent vasoconstrictor hormones that are released from stores in early vasodilatory and septic shock, leading to elevated plasma levels of norepinephrine, epinephrine, vasopressin, angiotensin II, aldosterone, adrenomedullin, and cortisol. These hormones act synergistically on their unique complementary receptors on vascular smooth muscle endeavoring to increase vasomotor tone, and occupying cardiac myocyte receptors with a usual net effect of increasing heart rate and contractility. Adrenergic receptor downregulation,[29] receptor genotype differences between patients,[30,31] decreased responsiveness in septic shock,[27] and variable hormone metabolism[32] all conspire to allow continued vasodilation and hypotension. There is also a profound deficiency of vasopressin later in septic shock.[33]

Major mediators of vasodilation in septic shock are nitric oxide, prostaglandins, and adrenomedullin. Endotoxin and cytokines induce inducible NO synthase (iNOS) to simulate NO synthesis.[34,35] Endotoxin and inflammatory cytokines stimulate prostacyclin synthesis and release by endothelial cells.[36,37] RCTs in septic shock and sepsis of an iNOS inhibitor and a prostaglandin synthesis inhibitor (ibuprofen) showed that they actually worsened[38] or had no effect respectively on mortality.[39] Adrenomedullin, a vasodilating hormone and cardiac depressant in septic shock,[40] is associated with increased mortality[40,41] and antiadrenomedullin decreases mortality,[42] increases responsiveness to norepinephrine,[43] and improves renal function in animal models of sepsis.[42,43] Antiadrenomedullin is rational for RCTs in septic shock.

Vasopressor Role and Protocols in Shock Resuscitation

Airway, breathing, and circulation resuscitation are fundamental priorities in vasodilatory shock. Intravascular volume status (jugular venous pressure) and perfusion (skin temperature, mentation, urine output) evaluation are supplemented by arterial blood gases, lactate, hematology, renal and hepatic function, and bedside echocardiography (►**Fig. 3**). Rapid, accurate screening for sepsis accelerates recognition and earlier intervention thereby improving outcomes.[44] The most recent sepsis 3.0 definition recommends screening for sepsis by using the quick Sequential Organ Failure Assessment Score (qSOFA) because it can be done quickly and does not require laboratory test results (respiratory rate $>$ 22/min, altered mentation, and systolic blood pressure $<$ 100 mm Hg) for screening for sepsis[10] based on good evidence from very large sepsis cohorts.[11] However, qSOFA criteria apply to most patients with any form of shock, so are relatively nonspecific and not useful for differentiating septic from other causes of shock.

We emphasize that vasopressors should be administered simultaneously with fluid replacement to prevent and decrease duration of hypotension in shock with vasodilation.

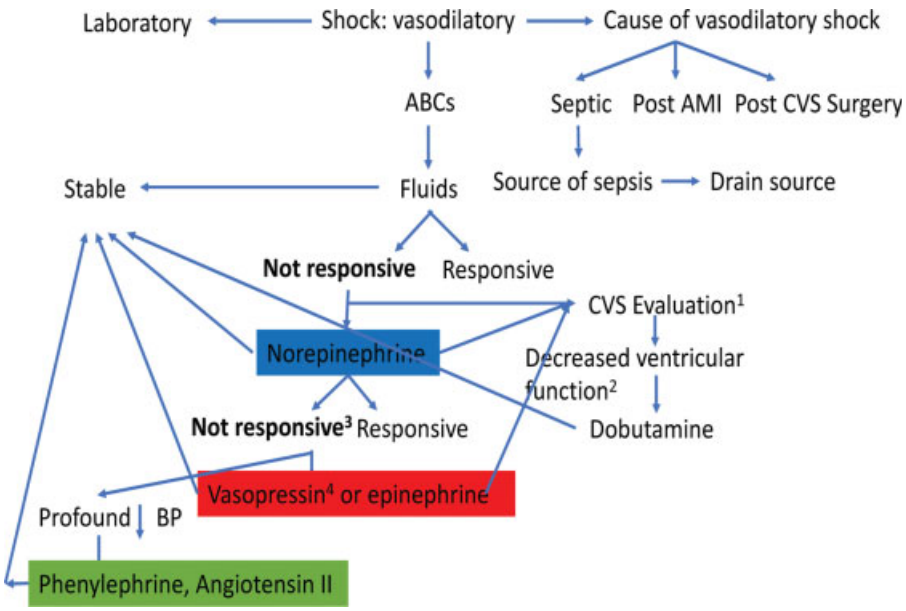

Fig. 3 Algorithm for vasopressor management in vasodilatory and septic shock. The first priority is airway, breathing, and circulation (ABC) resuscitation, while in parallel doing laboratory evaluation (arterial blood gases, lactate, hematology, renal and hepatic function) and evaluating the cause of vasodilatory shock. Initial fluids (30 mL/kg initially and more as needed) should be crystalloid. In patients not responding to adequate fluid resuscitation, norepinephrine is started. In patients unresponsive to norepinephrine, vasopressin (terlipressin) or epinephrine is added. In profoundly hypotensive patients, phenylephrine or angiotensin II may be considered. Regarding the cause of shock, fever and leukocytosis suggest septic shock and the need to search for source of sepsis and drainage of abscesses and empyema. Sepsis mimics include post-acute myocardial infarction (AMI), post-cardiovascular surgery and other causes (pancreatitis, aspiration, acute respiratory distress syndrome [ARDS], post-abdominal surgery, trauma, and drugs [anesthetics and drug allergy/anaphylaxis]). [1]In patients not responsive to norepinephrine, vasopressin, epinephrine, or angiotensin II, cardiovascular evaluation is necessary. [2]Cardiovascular evaluation should occur such as limited bedside echocardiograph, noninvasive cardiac output, central venous pressure (CVP) or pulmonary capillary wedge pressure (via pulmonary artery catheter). If there is decreased ventricular function (decreased ejection fraction), then dobutamine should be added. [3]Not responsive to norepinephrine or other vasopressors is not well defined but generally means not responsive to a high dose. [4]Vasopressin can be substituted with terlipressin but the randomized controlled trials of terlipressin are much smaller than with vasopressin. Selepressin (a highly specific AVPR1a agonist) is in development.

Volume resuscitation (30 mL/kg initially is recommended but more or less may be needed) with crystalloid should precede or coincide with norepinephrine infusion, added if perfusion remains inadequate.[1] Assessment of volume status is somewhat inaccurate; fluid overload is associated with increased mortality of septic shock[45–47]; and a restrictive fluid practice is under investigation in septic shock.[48] Consideration of the differential diagnosis of vasodilatory shock occurs while initiating resuscitation (►**Fig. 3**). Fever or hypothermia, leukocytosis or leukopenia, and an obvious source of infection (the commonest sources are pneumonia, abdominal infection/peritonitis, urinary tract infection, and skin source) suggest sepsis. The sepsis source should be investigated to ensure adequate source control of abscesses and empyema. Other prevalent conditions that can present with vasodilatory shock are acute pancreatitis, aspiration, acute respiratory distress syndrome, post-cardiovascular and other surgeries, post- AMI, trauma, and drugs (anesthetics and drug allergy/anaphylaxis).

Patients receiving vasopressors may require invasive arterial pressure monitoring by an arterial catheter (or by noninvasive automated cuff blood pressure) complemented by central venous access for vasopressor administration and central venous pressure monitoring.[1] In more severe shock, clinicians use a variety of invasive and noninvasive cardiovascular assessment and monitoring.

Early treatment of septic shock is critical as illustrated by studies of early antibiotics[44,49] and early goal-directed therapy.[44,50] These studies and a recent RCT of early use of norepinephrine[51,52] align with an artificial intelligence (AI) study in which the AI clinician recommended vasopressors be given more often (30 vs. 17%) than was used in the care of septic patients.[53] However, uncontrolled observational data found that earlier vasopressor use is harmful,[54] suggesting equipoise regarding earlier, more frequent use of vasopressors in septic shock.

See ►**Table 1** for a summary of vasopressors, their cognate receptors, actions, usual doses, and potential predictive biomarkers.

Norepinephrine is the first-line vasopressor in septic shock because it is superior to dopamine and equivalent to vasopressin and epinephrine in pivotal RCTs of norepinephrine versus epinephrine,[55] norepinephrine versus dopamine,[56] norepinephrine plus dobutamine versus epinephrine,[57] early vasopressin[14] versus norepinephrine, and vasopressin versus norepinephrine in septic shock[12] (►**Table 2**).

Adverse Effects and Risks of Vasopressors

Digital and organ ischemia/dysfunction, decreased cardiac function, tachyarrhythmias, and atrial fibrillation[8] (with increased risk of stroke in septic shock)[58] are the commonest serious

Table 1 Vasopressors, their receptor binding, possible additional beneficial actions, dose, and possible relevant biomarkers

Vasopressor	Receptor activity	Additional actions	Dose (all intravenous)	Possible predictive biomarkers
Norepinephrine	α1 > β1, β2	Immune activity[179]	5–100 μg/min	β2 receptor SNP[30]
Epinephrine	α1 > β1, β2 More β1 than NE	Immune activity[179]	5–60 μg/kg/min[55]	β2 receptor SNP[30]
Phenylephrine	α1	Immune activity[179]	50–100 μg bolus 0.1–1.5 μg/kg/min	
Dopamine	DA1, DA2	Immune activity[180,181]	1–5 μg/kg/min: "low dose." 5–15 μg/kg/min: moderate dose 20–50 μg/kg/min: high dose	
Vasopressin	AVPR1a, AVPR1b, AVPR2	Immune activity[182]	0.01–0.04 U/min[12,105]	LNPEP SNP[32] Angiopoietin 1/2[128] Vasopressin/copeptin
Terlipressin	AVPR1a (AVPR1b) > AVPR2	Immune activity	1.3 μg/kg·h[183] 20–160 μg/h,[113] bolus: 1 mg	LNPEP[32] Vasopressin/copeptin
Selepressin	AVPR1a	↓ Angiopoietin-2 ↓ Vascular leak	1.25–2.5 ng/kg/min in Phase 2[23] 1.25–5.0 ng/kg/min in Phase 3[22]	LNPEP SNP[32] Angiopoietin 1/2[128] Vasopressin/copeptin
Angiotensin-II	Angiotensin II receptors (AGTR1, AGTR2)	↑ Vasopressin ↑ Erythropoietin	5–200 ng/kg/min (first 3 h; 1.25–40 ng/kg/min up to 7 d[15]	AGTRAP SNP[31]
Methylene blue[184]	Inhibits GABAA receptors	↓ Vascular leak	Bolus (2 mg/kg) then infusion—stepwise increasing rates: 0.25, 0.5, 1, 2 mg/kg/h	

Abbreviations: AGTR1 and AGTR2, angiotensin II receptors 1 and 2; AGTRAP, angiotensin II receptor associated protein; GABAA, gamma-aminobutyric acid; LNPEP, leucyl and cystinyl aminopeptidase; SNP, single nucleotide polymorphism.

Table 2 Pivotal randomized controlled trials of vasopressors in septic shock

Vasopressor intervention	Control (reference number)	Intervention mortality (%)	Control mortality (%)	AD (95% CI) *p*-value
NE	AVP[12]	35.4%[a]	39.3%	3.9 (−2.9–10.7) 0.26
NE	AVP[14]	30.9%[a]	27.5%	3.4 (−5.4–12.3)
SE	Placebo	40.6[b] 15.0	39.4 14.5	1.1 (−6.5–8.8) 0.77
NE	DA[56]	48.5%[c]	52.5%	1.17 (0.97–1.42) 0.10
ANG II	Placebo[15]	46%[a]	54%	HR: 0.78 (0.57–1.07) 0.12
Epi	NE[55]	23%[a]	27%	HR: 0.87 (0.48–1.58) 0.65
Epi	NE + DOB[57]	40%[a]	34%	RR: 0.86 (0.65–1.14) 0.31

Abbreviations: AD, absolute difference; ANG II, angiotensin II; AVP, vasopressin; DA, dopamine; DOB, dobutamine; Epi, epinephrine; HR, hazard ratio; NE, norepinephrine; RR, relative risk; SE, selepressin.
[a]28-day mortality.
[b]90-day mortality.
[c]All causes of shock; 28-day mortality.

adverse effects of vasopressors. Higher cumulative doses of vasopressors are associated with more organ dysfunction and higher mortality,[59] but association studies may be confounded by indication and coexisting severity of illness, so it is not clear that the higher cumulative doses of vasopressors *caused* more organ dysfunction and higher mortality. Similarly, a recent study of patients on high-dose norepinephrine (>1.0 μg/kg/min) demonstrated that such high-dose norepinephrine is a strong independent predictor of mortality in a multivariate model, but it is impossible to assign causality in such an association study.[60]

Monitoring

Vasopressor use in shock requires continuous monitoring of MAP by an arterial line or by noninvasive arm cuff blood pressure, evaluation of perfusion (mentation, urine output, lactate), and noninvasive cardiovascular assessment (e.g., noninvasive cardiac output, echocardiographic evaluation of ventricular function and volume status, i.e., inferior vena cava collapse). Assessment of the microcirculation by sublingual techniques is used by some but not routinely recommended.

Goal-directed bedside echocardiography may be effective to guide fluid, vasopressor and inotropic agent choice, and infusion dose. Volume status was often more than replete in a case–control study of bedside echocardiography in resuscitated but still in shock intensive care unit (ICU) patients. Further fluid restriction was recommended in 65% of patients and initiation of dobutamine in 25% of patients[61] because of findings of decreased right or left ventricular dysfunction. Mortality was lower in the limited bedside echocardiography group than in controls.[61] To date, there is no pivotal RCT of limited bedside echocardiography-guided resuscitation versus usual care in shock.

Weaning of Vasopressors

The weaning of vasopressors has not been evaluated critically in RCTs and so the evidence of optimal best practice is missing. Generally, patients are judged appropriate for weaning (gradual, e.g., hourly, decrements of vasopressor dose) when "stable" (surprisingly there is no universal definition of hemodynamic stability) and both volume status and perfusion are adequate. Deterioration of MAP or perfusion necessitates titration of vasopressor(s) back up to higher doses, attempting to reestablish stability, and later by repeated decrements of vasopressor dose until vasopressor infusion is off. The complexity and heterogeneity of vasopressor weaning is illustrated by the insight that medical informatics accurately predicts successful vasopressor weaning both earlier and more accurately than can clinicians using standard clinical practice.[62]

We recommend that norepinephrine be weaned first followed by weaning of the second vasopressor (vasopressin or epinephrine) if the patient remains hemodynamically stable. Weaning norepinephrine first has been shown to decrease the risk of hemodynamic instability during vasopressor weaning.[63,64] Difficulties with weaning vasopressors has not been well studied but may be related to ongoing septic shock, inadequate volume resuscitation and ongoing hypovolemia, or decreased ventricular contractility due to sepsis or other causes.

Main Outcomes of Pivotal RCTs of Vasopressors

The mortality of septic shock appears to be decreasing[65] and short-term mortality has been the commonest primary outcome for pivotal RCTs of vasopressors in septic shock. Consequently, RCTs of vasopressors are evolving in two complementary directions. Some now focus on improving long-term outcomes; others aim to improve short-term organ dysfunction (e.g., days alive and free of vasopressors[22]) because short-term organ dysfunction is associated with long-term mortality.[66–69] For example, the pivotal RCT of selepressin in septic shock used vasopressor- and ventilator-free days as the primary outcome.[22,24]

For each vasopressor we now review pharmacology, guidelines, effects, adverse effects, and dosing (►**Table 1**).

Norepinephrine: The First-Choice Vasopressor

Since the initial discovery of epinephrine as the primary vasopressor hormone produced in the adrenal medulla, the pharmacology of catecholamines has been elucidated.[70] Norepinephrine is structurally similar to epinephrine except that norepinephrine lacks a methyl group on its nitrogen. Some clinicians may find it surprising that in the adrenal gland, norepinephrine is converted into epinephrine via the enzyme N-methyltransferase. This pharmacology may question the value of utilizing epinephrine in a patient with refractory shock on high doses of norepinephrine, unless it is being used for its inotropic effects. Norepinephrine has a very short half-life (<5 minutes).

Some advantages that norepinephrine has compared with other vasopressors include vasopressor potency because of α1 agonism, minimal effect on β2 adrenergic receptors (that can increase lactate levels), and the ability to increase cardiac index without increasing heart rate or myocardial oxygen consumption. Unlike epinephrine, in the United States norepinephrine is frequently programed into the intravenous pump as μg/min rather than the weight-based dosing of μg/kg/min. Commonly norepinephrine is started at 5 to 10 μg/min and titrated up to the target MAP, usually 65 mm Hg.[1] An RCT of usual versus high MAP target showed that the high MAP target (80–85 mm Hg) decreased AKI in previously hypertensive patients.[7] Similarly, two recent single-center studies suggested that higher MAP (75–85 mm Hg) was associated with less AKI and higher survival.[71,72]

One of the first studies of norepinephrine in shock in 1953 was a case cohort study ($n = 32$) with various forms of shock.[73] Twenty-six patients improved in their shock and the mortality rate (62.5%) was below the "expected" level (>80% as per the authors). Since then, most studies have compared norepinephrine to other vasopressor(s) (dopamine, epinephrine, and vasopressin). In a recent meta-analysis of 43 trials ($n = 5{,}767$ patients) that assessed 17 vasopressors and inotropic agents,[74] the combination of norepinephrine and dobutamine was associated with the lowest mortality while dopamine was associated with the highest incidence of arrhythmia. The largest RCT of norepinephrine versus dopamine was performed in approximately 1,700 patients and reported no difference in mortality between the two vasopressors, but in patients with cardiogenic shock, dopamine was associated with greater mortality.[56] Dopamine was associated with increased adverse events, particularly double the prevalence of tachyarrhythmias compared with norepinephrine. In another RCT, there was no difference in mortality or safety between a combination of norepinephrine

and dobutamine versus epinephrine.[57] Finally, an Australian RCT compared norepinephrine to epinephrine for shock and demonstrated no difference between the two vasopressors in achieving blood pressure control but significantly more patients randomized to epinephrine had the study drug stopped for adverse events.[55]

As a result of these and other well-conducted RCTs, norepinephrine is recommended as the first-line vasoactive drug for septic shock.[1] The widespread adoption of norepinephrine as a first-line vasopressor is also likely due to its ease of use, rapid onset of action, familiarity, low cost, and the lack of an alternative agent showing superiority to norepinephrine. A recent global web-based survey (839 physicians from 82 countries, 65% main specialty/activity intensive care) responded that the commonest first-line vasopressor was norepinephrine (97%), targeting predominantly a MAP >60–65 mm Hg (70%), with higher targets in patients with chronic arterial hypertension (79%).[75]

It is recommended that norepinephrine be administered via a central intravenous catheter or a large bore peripheral intravenous catheter in the antecubital vein to avoid serious complications if an extravasation occurs (https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/007513Orig1s024lbl.pdf). If extravasation does occur, infusion needs to be stopped and the affected area should be infiltrated with the α blocker phentolamine to reverse the severe vasoconstriction that can cause ischemia and necrosis. A recent study of peripherally administered norepinephrine demonstrated that extravasation occurred in only 0.035% of approximately 14,000 perioperative patients.[76] Another recent RCT of early, low dose (0.05 μg/kg/min) often started via peripheral intravenous line showed improvement of the primary endpoint, control of shock (defined by MAP > 65 mm Hg, plus urine output > 0.5 mL/kg/h or 10% decrease in serum lactate).[51]

The most common adverse effects of norepinephrine are due to activation of α1 receptors causing excessive vasoconstriction and decreased end-organ perfusion. This complication occurs more commonly when norepinephrine is infused without appropriately correcting hypovolemia. Vasoconstriction secondary to α1 stimulation can cause reflex bradycardia via the baroreceptor reflex, which is generally not compensated for by norepinephrine's weak β1 activity. The overall result is that cardiac output may decrease or not change despite β1 agonism. At the same time, the increase in systemic vascular resistance increases the work of the heart by increasing afterload, thereby increasing myocardial oxygen demand.

Norepinephrine administration may increase pulmonary vascular resistance which could have negative sequelae in patients with pulmonary hypertension. Decreased hepatic blood flow (secondary to α-mediated vasoconstriction) may alter hepatic metabolism of drugs leading to a transient increase in drug levels. Generally, the use of norepinephrine is contraindicated in patients with mesenteric or peripheral vascular thrombosis because subsequent norepinephrine-mediated vasoconstriction could increase risk of ischemia and infarction.

Epinephrine

Epinephrine has more β1 agonism than norepinephrine. Epinephrine is a second-line agent in septic shock[1,55,74] in patients not responding to norepinephrine. Epinephrine is comparable to norepinephrine,[55] to norepinephrine plus dobutamine,[57] and to norepinephrine and vasopressin[77] in efficacy in RCTs and in a meta-analysis[74]; however, epinephrine has a greater risk of mesenteric ischemia, tachyarrhythmias, and hyperlactatemia compared with norepinephrine.[1,55,57] Epinephrine is an optional first-choice vasopressor in countries where norepinephrine is more costly.[78]

Phenylephrine

At the turn of the 19th century, following the identification of the adrenal medullary hormones responsible for regulation of cardiovascular function, there was a surge of interest into modifying the core structure common to norepinephrine and epinephrine (►**Fig. 4**). In 1910 several potentially sympathomimetic chemicals were synthesized by Dale and their cardiovascular effects characterized by Barger.[79] Apart from the endogenous epinephrine and norepinephrine, phenylephrine was found to be the most potent vasopressor. Phenylephrine was later studied by Trendelenburg using reserpine, a drug which depletes presynaptic noradrenaline, and cocaine, which inhibits norepinephrine reuptake.[80,81] Using these agents Trendelenburg proved that phenylephrine is a direct-acting sympathomimetic with direct stimulation of adrenergic α1 receptors. In contrast, methamphetamine stimulates the release of endogenous norepinephrine.

In healthy subjects intravenous infusion of phenylephrine acts via the α1 adrenergic receptor, rapidly increasing diastolic and systolic blood pressure(s), decreasing renal blood flow, and yielding vagally mediated reflex bradycardia and a slight drop in cardiac output.[82,83] However, if the heart rate does not drop reflexively (using atropine or vagotomy), phenylephrine increases cardiac output, likely through increased left ventricular end diastolic volume (preload).

Phenylephrine has a much slower rate of uptake and clearance from extracellular fluid than norepinephrine, which is rapidly taken up into adrenergic nerves following intravenous injection. Additionally, unlike endogenous catecholamines, phenylephrine is not metabolized by catechol-O-methyl-transferase in liver and other tissues. In healthy individuals, this causes a vasopressor effect for 20 minutes, much longer than the 1 to 2 minutes seen with norepinephrine bolus.[84] Like epinephrine and norepinephrine, phenylephrine is metabolized by monoamine oxidase in mitochondria of nerves and liver.[84]

When compared with norepinephrine for continuous infusion in mixed shock states, phenylephrine appears less potent, requiring 220% of the dose of norepinephrine to achieve a MAP of 65 to 75 mm Hg following fluid resuscitation.[85] This likely relates to phenylephrine's lack of β adrenergic effects (positive inotropy and chronotropy) rather than tachyphylaxis. At low doses phenylephrine has only α1 adrenergic activity, while higher doses cause some β1 adrenergic activity.[82,86] At

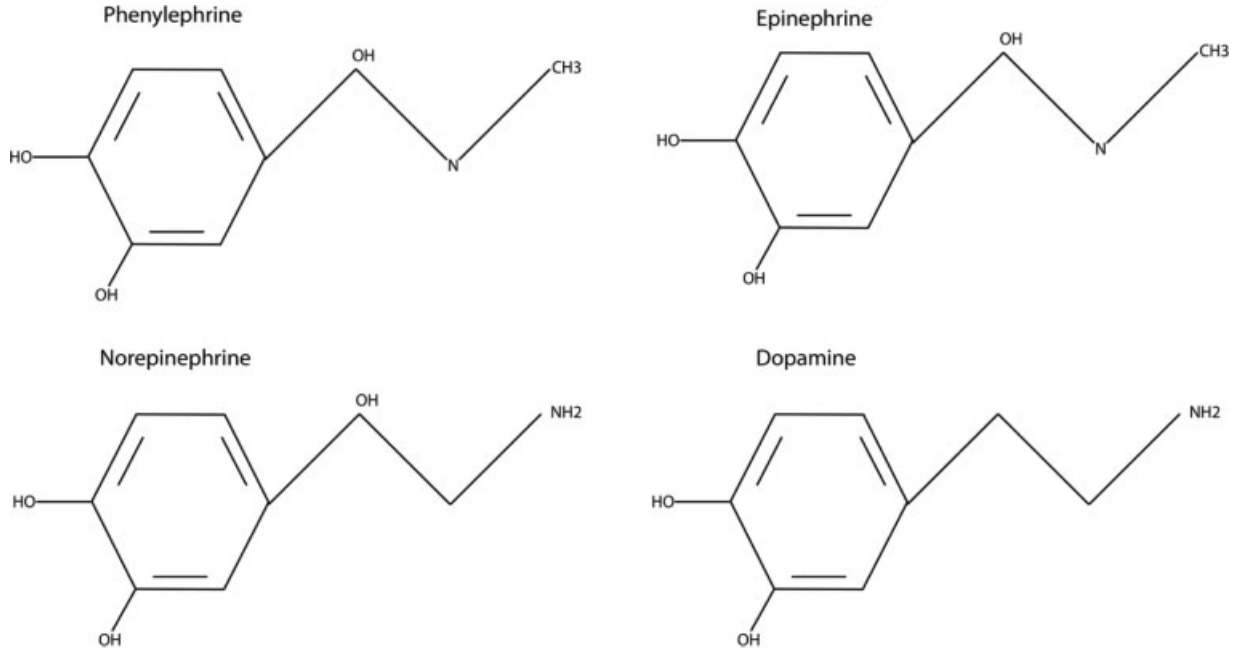

Fig. 4 Chemical structure of commonly used catecholamines. Catecholamines have a catechol group (benzene with two hydroxyl substitutions) and a side-chain amine. Phenylephrine is a synthetic derivative, while epinephrine, norepinephrine, and dopamine are endogenous catecholamines.

12 hours following infusion initiation, and at 220% of the dose of norepinephrine, phenylephrine increased the heart rate similarly to norepinephrine.

A national shortage of norepinephrine in the United States set the stage for a natural experiment comparing efficiency of norepinephrine versus phenylephrine in septic shock. Phenylephrine was the commonest replacement during the norepinephrine shortage; in a before/after observational cohort study of patients who had septic shock, phenylephrine was associated with increased mortality compared with norepinephrine.[87]

Given the favorable (prolonged) kinetic profile of phenylephrine over epinephrine and norepinephrine following a single bolus, there may be a niche for its use in early resuscitation of shock in geographic areas such as the medical ward or prehospital care where initiation of infusions is challenging and would take valuable time away from transportation. Phenylephrine's routine use as a first-line agent for continuous infusion to reverse shock states cannot be recommended because of lower potency than norepinephrine and significant tachyphylaxis requiring the introduction of an additional vasopressor.

Dopamine

Dopamine had great promise because it has potential to increase cardiac contractility and stroke volume while augmenting renal perfusion and urine output.[88–90] Although structurally very similar to the other endogenous and synthetic catecholamines (►**Fig. 4**), dopamine also stimulates dopaminergic receptors DA1, DA2, and DA4.[91]

In healthy volunteers intravenous dopamine stimulates dopaminergic receptors beginning at 1 μg/kg/min, with a plateau of stimulation at 3 μg/kg/min;[92] at less than 3 μg/kg/min there is no adrenergic receptor stimulation. When healthy volunteers are infused at or below 3 μg/kg/min, there is a large, physiologically significant 128% increase in renal sodium excretion and a 43% rise in glomerular filtration rate.[93] Dopamine also has nonreceptor-mediated renoprotective effects in profound renal ischemic insult, protection mediated by mitigation of oxidative stress induced by reactive oxygen species.[94] When low-dose (4 μg/kg/min) dopamine was added for 3 to 9 hours in neurologically deceased donors (NDDs), it significantly decreased the need for posttransplant dialysis.[95] Therefore, while the use of any catecholamine vasopressor drug is recommended to treat the NDD kidney donor,[96] the global recommendations suggest a combination of vasopressin and norepinephrine to treat shock states, while dopamine would be preferred in the absence of shock.[95]

At doses exceeding 3 μg/kg/min in healthy volunteers, dopamine has additional α and β adrenergic stimulation.[93] Consequently, in the 1980s dopamine was used as a first-line vasopressor for critically ill patients because of its distinct dose-dependent effects, low-dose (3 μg/kg/min) dopaminergic stimulation, and higher dose α and β adrenergic stimulation.

However, these uniquely titratable dopamine dose effects are reproducibly seen only in subjects with normal cardiovascular physiology. Unfortunately, in patients with shock the plasma clearance decreases by 50% compared with surgical controls, while those with shock and renal dysfunction have a 75% reduction in plasma clearance.[97] The unpredictable relationship between infusion rate and plasma levels causes variable receptor activation that can cause adverse events due to excessive α and β adrenergic stimulation.

Dopamine is not recommended for treatment of shock because of the results of a large RCT of dopamine versus norepinephrine ($n = 1{,}629$) as first-line vasopressor therapy for undifferentiated shock.[56] Dopamine-treated patients had a distinct cardiovascular profile. During the first day of therapy, those treated with dopamine had much higher heart rates (excluding arrhythmias) than norepinephrine-treated patients (102 vs. 94 beats per minute [BPM], respectively). Furthermore, dopamine was associated with significantly double the rate of tachyarrhythmias (24 vs. 12%). Urine output was higher in those treated with dopamine (by 200 mL per day during the first day of infusion).[56] While there was no statistically significant difference in 28-day mortality between dopamine and norepinephrine (52.5 vs. 48.5%), and in the prespecified cardiogenic shock subgroup ($n = 280$), there was a 5% higher 28-day mortality with dopamine versus norepinephrine.

Thus, dopamine has more risk than benefit in the treatment of shock because of its narrow therapeutic index and uncertain plasma levels as a result of decreased renal excretion leading to a higher heart rate and double the frequency of tachyarrhythmias. The use of dopamine in the critical care unit is therefore best reserved for renal protection in the NDD organ donor, although this recommendation is based on evidence from a single RCT[95] and has therefore not been widely advocated in guidelines for management of organ donors.[96]

Vasopressin Analogues

Vasopressin

Vasopressin is an endogenous hormone released from the posterior pituitary gland. In health it is mainly involved in osmoregulation because of binding to V2 receptors in the distal convoluted tubules and promoting water retention (as antidiuretic hormone). In shock states, circulating vasopressin levels rise because of rapid release of vasopressin stores from the posterior pituitary gland, and vasopressin acts as a powerful vasoconstrictor, binding to V1a receptors. Interest in administering exogenous vasopressin in septic shock began after the seminal report of a relative vasopressin deficiency in septic shock compared with other shock states.[98] Furthermore, vasopressin may maintain better perfusion of the kidney compared with norepinephrine because of the heterogeneous distribution of V1a receptors in the kidney (more V1a receptors in glomerular efferent than afferent arterioles).[99] In small clinical studies vasopressin infusion increased urine output and improved creatine clearance compared with norepinephrine.[100,101]

However, larger RCTs have not demonstrated decreased mortality compared with norepinephrine treatment of septic shock. There was no difference in overall mortality between vasopressin and norepinephrine in VASST,[12] but vasopressin may have been more effective in less severe shock (baseline norepinephrine dose < 15 µg/min). Vasopressin (<0.04 units/min) was associated with similar outcomes to norepinephrine in a propensity-matched cohort study.[102] In VANISH,[14] early vasopressin had similar mortality to norepinephrine. This lack of mortality reduction was confirmed in a recent individual patient data meta-analysis (IPDMA), including over 1,400 patients, in which the relative risk (RR) for 28-day mortality was 0.98 (95% confidence interval [CI]: 0.86–1.12).[103] Interestingly there was a signal to lower mortality at 90 days (RR: 0.91 95% CI: 0.81–1.01) with vasopressin suggesting that it is important to include long-term effects of intensive care interventions in clinical trials. In this IPDMA there was less frequent use of renal replacement therapy (RRT) with vasopressin (RR: 0.86, 95% CI: 0.74–0.99), most notably in patients without significant AKI at the time of inclusion, supporting the potential benefit of vasopressin to prevent deterioration in renal function, even if there is no benefit on mortality.

Importantly this recent IPDMA demonstrated that the number of serious adverse events was similar for both vasopressin and norepinephrine. However, vasopressin had a different side-effect profile compared to norepinephrine, notably with a lower rate of arrhythmias (absolute risk difference: −2.8%, 95% CI −0.2 to −5.3). This finding was supported in another meta-analysis including more than 3,000 patients who had any form of vasodilatory shock, not just sepsis, and also included treatment using other vasopressin analogues.[104] There was a marked reduction in the rate of atrial fibrillation with vasopressin (RR: 0.77, 95% CI: 0.67–0.88) and also a reduction in mortality in this broader population (RR: 0.89, 95% CI: 0.82–0.97). However, both meta-analyses found that treatment with vasopressin analogues also led to a higher incidence of digital ischemia, an absolute risk increase of approximately 2% in both studies.

In summary, this evidence supports the use of vasopressin as a safe adjunctive vasopressor to use in addition to norepinephrine. There is no clear evidence to support an improvement in patient survival in septic shock but there is good evidence that vasopressin can reduce rates of arrhythmias and tachycardia[25] and could reduce the requirement for RRT. Vasopressin derivatives may limit complications in distributive shock,[105] but not in distributive shock when the vasoplegia is not established. Vasopressin is not just another vasopressor to increase blood pressure. Vasopressin and its derivatives have favorable effects on hepatosplanchnic and renal perfusion,[106,107] pulmonary hypertension,[108] and mitigate edema formation and fluid loss due to increased permeability in several sepsis models[106,107,109–111] and selepressin decreases fluid balance in a proof-of-principle RCT of selepressin.[23]

However, caution must be exercised because of the increased risk of digital ischemia. Clinicians should consider this information when selecting which vasopressors to use and select the combination that best balances the benefit/risk ratio of each individual patient.

Terlipressin

Terlipressin is a synthetic analogue of vasopressin with a greater selectivity for the V1a receptor than vasopressin and is used in patients who have liver failure in an attempt to reduce hepatorenal syndrome.[112] It also has a longer half-life than vasopressin and so can be given by intermittent bolus injection rather than as a continuous infusion.

There are less clinical trial data to support the use of terlipressin in septic shock. One recent RCT was stopped for futility after the randomization and treatment of 535 patients, as it failed to show any difference in the primary outcome, 28-day mortality: 38 vs. 40% for norepinephrine- and terlipressin-treated patients respectively, $p = 0.63$.[113] However, there were markedly more serious adverse events in the terlipressin-treated patients, especially digital ischemia (0.35 vs. 12.6% for norepinephrine- and terlipressin-treated patients respectively, $p < 0.0001$). Why the rate of digital ischemia was so high in the terlipressin-treated patients is not clear but could relate to unrecognized/untreated hypovolemia or possibly the accumulation of terlipressin or its metabolites after administration of a continuous infusion, particularly at higher doses (up to 160 µg/h was allowed in this RCT).

As a meta-analysis of RCTs of terlipressin in septic shock[114] reported no mortality benefit (RR: 1.00, 95% CI: 0.83–1.20) and there is concern about its safety, terlipressin cannot be recommended ahead of vasopressin if both are available. However, vasopressin is not available in all regions and so terlipressin may be the only option, but care must be applied to first correct any hypovolemia and avoid high doses to mitigate adverse effects of terlipressin.

Selepressin

Selepressin is another synthetic vasopressin analogue and is highly selective for the V1a receptor. As well as being a potent vasoconstrictor, in both preclinical[107] and a Phase 2A proof-of-principle RCT,[23] selepressin reduced edema formation and intravenous fluid requirements. It was recently tested in a large seamless Phase 2B/3 RCT, Sepsis-adaptive clinical trial, that had four unique features for a pivotal RCT in septic shock.[24] First, there was a continuous response adaptive design,[22] meaning that assignment to a study drug group was determined in real time as new patients were included and the primary endpoint was loaded into a prespecified computer algorithm that then assigned a treatment group. Second, there was to be a seamless transition from Phase 2 to Phase 3. Third, several doses of selepressin were to be pooled for the decision to go to Phase 3. And fourth, the primary endpoint was vasopressor- and ventilator-free days. However, the RCT was stopped after Phase 2B for futility, because there was no difference in the primary outcome: the number of vasopressor- and ventilator-free days[24] (►**Table 2**). There were no differences in any of the other secondary outcomes or in any of the prespecified subgroups. As selepressin is not currently approved for clinical use, it remains to be seen if this drug can become a useful additional vasopressor agent for the treatment of septic shock.

Angiotensin II

Angiotensin II has shown promise as a potent vasopressor for patients who have marked hypotension due to vasodilatory shock based on preclinical studies and a series of RCTs from the proof of principle to pivotal Phase 3. In response to hypotension, renin is rapidly converted to angiotensin I in the kidney and then angiotensin I is secreted and converted in the lung to angiotensin II by ACE. Angiotensin II is a crucial vasopressor of the renin–angiotensin–aldosterone system (RAAS) that modulates vascular tone by binding to angiotensin 1 and 2 receptors (AGTR1 and AGTR2), G-protein-coupled receptors that increase cytosolic calcium concentrations to induce vasoconstriction (also aldosterone synthesis and vasopressin release). AGTR1 is downregulated in models of sepsis, leading to relative angiotensin II insensitivity.[15,20]

Angiotensin II was recently approved by the Food and Drug Administration[115] for treatment of vasodilatory hypotension based on the results of a clinical program including a pilot RCT[20] and culminating in the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) trial.[15] ATHOS-3 added infusion of concealed angiotensin II or placebo in refractory vasodilatory shock. Angiotensin II was initiated at 20 ng/kg/min and then increased to achieve a MAP of 75 mm Hg with up to 200 ng/kg/min and after 3 hours until 48 hours angiotensin II was adjusted to 1.25 to 40 ng/kg/min. At 48 hours angiotensin II study drug was weaned off, but if a patient became unstable, the angiotensin II could be restarted and maintained for up to 7 days. Angiotensin II more rapidly increased MAP over 3 hours, decreased norepinephrine dose, and improved the cardiovascular SOFA score compared with placebo.[15] Mortality (28-day) was 46 versus 54% ($p = 0.12$) in the angiotensin II and placebo groups, respectively.

A greater sensitivity to infused angiotensin II is associated with lower angiotensin II levels prior to treatment and lower mortality. A prespecified analysis of the ATHOS-3 RCT was that there would be a difference in mortality according to whether patients were titrated down from the initial dose of angiotensin II of 20 ng/kg/min to <6 ng/kg/min at 30 minutes versus >5 ng/kg/min at 30 minutes.[116] The hypothesis was confirmed; mortality rates were 41 versus 67% ($p = 0.0007$) in the <6 ng/kg/min of angiotensin II at 30 minutes versus >5 ng/kg/min at 30 minutes, respectively.[116] Interestingly, the mortality results were aligned with angiotensin II levels at treatment initiation that were significantly lower in the <6 ng/kg/min of angiotensin II at 30 minutes versus >5 ng/kg/min (128 pg/mL [199 pg/mL] vs. 421 pg/mL [680 pg/mL][mean, standard deviation, $p = 0.0009$; normal range in health: 5–35 pg/mL[117]]).

There were no safety issues with angiotensin II in the pivotal ATHOS-3 RCT.[15] There was no difference in the frequency of serious adverse events between angiotensin II (60.7%) and placebo (67.1%) including digital, gut, and myocardial ischemia and arrhythmias.[15] Indeed, serious adverse events that led to discontinuation of study drug occurred in 14.1% of angiotensin II-treated and 21.5% of placebo-treated patients in ATHOS-3.[15] Furthermore, cardiac disorders occurred in 16.6 versus 20.3%, respiratory disorders in 10.4 versus 15.8%, and vascular disorders in 10.4 versus 9.5%, including thromboembolic events (deep venous thrombosis 1.8 vs. 0%) (angiotensin II-treated vs. placebo-treated).[15]

Angiotensin II may be especially effective in patients who have AKI requiring RRT. A post-hoc study of the subgroup of patients in the ATHOS-3 RCT who had AKI and were on RRT at baseline found potential benefit of angiotensin II: lower mortality (47 vs. 70%, angiotensin II and placebo, respectively, $p = 0.012$) and more frequent recovery without the need for

RRT by day 7 (38 vs. 17%, angiotensin II and placebo, respectively, $p = 0.007$).[118] One interpretation is that these are patients who have more severe forms of septic shock (AKI requiring RRT), have decreased renal perfusion pressure at onset, and have shown improvement by angiotensin II, and so these patients benefit from angiotensin II. Another interpretation is that the normal ratio of angiotensin I to angiotensin II in health is 0.5, but it is 1.63 in vasodilatory shock,[15] indicating dysfunction of ACE in vasodilatory shock.[119] Infusion of angiotensin II improves the angiotensin I-to-II ratio. Genetic variations of ACE are associated with worse renal function in sepsis,[120] further emphasizing the important role of angiotensin I and II in regulatory renal function in septic AKI. Finally, an ovine model of septic AKI shows decreased renal function and urinary oxygenation and angiotensin II infusion improves renal function but does not worsen urinary oxygenation,[121] by angiotensin II preferentially constricting the efferent renal arteriole.[121,122]

Angiotensin II is especially effective in patients with a low ACE and high levels of angiotensin I (120). Renin activity seems to correlate well with ACE. Normal levels of renin activity are 0.5 to 2.0 ng/mL/h. Angiotensin II seems to be more effective in patients with a high renin activity up to three times the normal levels. Plasma renin activity could be a potential marker to select a population with a higher benefit.

Inotropic Agents to Complement Vasopressors in Septic Shock

Septic shock can decrease cardiac contractility and cardiac output and this decline may be exacerbated by vasopressors. Therefore, inotropic agent(s) such as dobutamine are commonly added to norepinephrine[57] and vasopressin[12,25] to increase cardiac output, but with side effects (tachyarrhythmias and increased heart rate and myocardial oxygen consumption). The effect of the combination of dobutamine plus norepinephrine was found to be equivalent to epinephrine alone in one large RCT.[57] Levosimendan, a positive nonadrenergic inotropic agent, was not effective in an RCT in septic shock.[55,57] More patients on levosimendan had tachyarrhythmias and fewer patients on levosimendan were successfully weaned from mechanical ventilation.[123] Thus, levosimendan is not recommended in septic shock.

Biomarkers to Guide Vasopressor Selection

Predictive biomarkers mark response to drugs and could improve the clinical efficacy and safety of vasopressors in vasodilatory shock by improving patient selection for therapy. Concentrations of proteins or drugs, RNA expression,[124,125] and rapid genotyping for single nucleotide polymorphisms (SNPs) could facilitate personalized selection of vasopressor (s). Responders to norepinephrine could be identified by a β2 SNP that marked increased mortality of septic shock.[30] Plasma angiopoietin-2[126] (selepressin-decreased plasma angiopoietin-2, a mediator of increased permeability), leucyl/cystinyl aminopeptidase (the enzyme that catalyzes vasopressin; LNPEP) SNP genotype (that altered vasopressin clearance and action),[32] and AVPR1a SNPs[32] could be possible predictive biomarkers of vasopressin, terlipressin, and selepressin. Plasma levels of RAAS[127–129] and SNPs of angiotensin-II receptor associated protein (AGTRAP) are associated with worse outcomes in septic shock and may be biomarkers for angiotensin II use.[31]

Corticosteroids and Their Interaction with Vasopressors

Corticosteroids have been used for many years in septic shock patients who are receiving vasopressors. Indeed, recommendations for corticosteroid use remain within the most recent SSC guidelines.[1] Some RCTs show modest benefit of corticosteroid use while others do not.[16,17,19,130] A pattern emerging from these RCTs is that very severely ill septic shock patients treated with very high doses of catecholamine vasopressors may benefit more,[16,17] while septic shock patients treated with modest or low doses of catecholamines do not appear to benefit.[19,130,131] Several recent reviews identify additional reasons (such as inclusion criteria,[132] prevalence of pneumonia in the RCTs,[133] corticosteroids used[132] [e.g., use of fludrocortisone or not], corticosteroid administration regimen [continuous infusion[19,133] vs. intermittent bolus],[16] differences in concomitant use of vasopressin,[133] and patient gene expression differences[124,125]) why there is controversy among RCTs of steroids in septic shock.[124,132–134]

Corticosteroids potentiate catecholamine signaling by increasing the number of β-adrenergic receptors expressed on the cell surface and also by enhancing coupling of adrenergic receptors to adenylate cyclase.[135] This likely explains the observation common to both positive and negative corticosteroid RCTs that catecholamine vasopressor use declines following administration of corticosteroids.[17,19,130] The catecholamine-sparing effect of corticosteroids in septic shock may then reduce catecholamine-induced adverse events, including tachyarrhythmias,[56] increased myocardial oxygen demand and myocardial ischemic events, increased whole-body oxygen consumption, increased glycolysis leading to elevated lactate levels,[136] alterations in immune function,[137] and other effects. RNA expression profiles effectively identified patients for steroids in septic shock in one large study.[124]

Corticosteroids may also interact with vasopressin,[138] but a recent RCT has placed doubt on the clinical relevance of such an interaction.[14] In a case–control study, septic shock patients treated with vasopressin had decreased mortality if they were also treated with corticosteroids.[139] A subsequent retrospective analysis of the VASST trial demonstrated a statistically significant interaction where catecholamine-treated septic shock patients also treated with vasopressin benefitted from additional corticosteroid administration while those patients not treated with vasopressin did not (19237882). There was a trend to increased vasopressin levels in patients treated with corticosteroids, providing insight into the mechanism of a potential interaction. However, there was no interaction of vasopressin with corticosteroid treatment on mortality in the VANISH trial.[14]

Is There a Limited Role for β1-Blockers in Septic and Vasodilatory Shock?

Vasopressors play a fundamental role in the management of hypotension in septic and vasodilatory shock. Adrenergic vasopressors such as norepinephrine, epinephrine, and dopamine have mixed α-adrenergic and β-adrenergic effects. α-Adrenergic agonists are vasoconstrictors which raise arterial resistance and therefore help raise low arterial pressures in septic and vasodilatory shock. In contrast, β-adrenergic stimulation causes smooth muscle relaxation and may reduce arterial resistance. β-adrenergic stimulation increases the rate of glycolysis which contributes to lactate production and β-adrenergic stimulation is generally calorigenic so that oxygen demand by all tissues increases.[136] In particular, β1-adrenergic agonists increase heart rate and myocardial oxygen demand, which may cause or worsen myocardial ischemia and cause or worsen cardiac arrhythmias. These concerns are borne out in several large RCTs which suggest that vasopressors with more β-adrenergic agonist effects result in increased lactate production, increased events potentially due to inadequate myocardial oxygen delivery in relation to demand, and increased incidence of cardiac arrhythmias.[12,56,103] For example, the SOAP II RCT of dopamine versus norepinephrine found that use of dopamine compared with norepinephrine infusion resulted in a doubling of supraventricular arrhythmias, particularly atrial fibrillation.[56] New-onset atrial fibrillation is important in septic shock because it can decrease cardiac output and is associated with a significantly increased risk of stroke[58] and death.[140] Although the evidence is not yet strong, there is no benefit of anticoagulation to decrease stroke risk in new-onset atrial fibrillation in sepsis, and there is a significantly increased risk of bleeding.[141]

In view of potential problems associated with β-adrenergic stimulation, the use of β-blockers in septic shock has been proposed. A small trial involving patients with exceptionally severe septic shock suggested that β-blocker use may improve survival.[142] An esmolol infusion was titrated to maintain a heart rate between 80 and 96 BPM for their ICU stay.[142] The esmolol group had a lower 28-day mortality (49.4%) compared with the surprisingly high mortality of the control group (80.5%). In a systematic review, 14 of 14 trials found that β-blockers decrease heart rates without a decrease in blood pressure in septic shock patients.[143] Whether β-blockers decrease mortality in septic shock is less certain due to the small number of trials, small number of patients, heterogeneity of the reported trials, lack of blinding, and significant asymmetry of a funnel plot suggesting potential publication bias.[143] Nevertheless, the reported trials suggest a decrease in mortality in β-blocker-treated patients but further trials are ongoing (https://doi.org/10.1186/ISRCTN12600919).

Vasodilatory Shock Post-Cardiovascular Surgery

After cardiovascular surgery a minority of patients develop vasodilatory shock characterized by hypotension and low systemic vascular resistance with or without high cardiac output. Post-cardiovascular surgery vasodilatory shock is especially common in patients on β-blockers or ACE inhibitors. Vasopressors are the main treatment after assuring adequate (but not excessive) volume status.[105] If hypotension persists after adequate volume resuscitation, norepinephrine is the vasopressor of first choice to increase blood pressure, vital organ perfusion while limiting renal dysfunction.[144]

Vasopressin has also been effective in vasodilatory shock after cardiovascular surgery. Landry's group[98,145–148] made two seminal discoveries: first, there is a relative vasopressin deficiency post-cardiovascular surgery and second, there are short-term benefits of vasopressin infusion including increasing MAP and decreasing norepinephrine dose requirements. There were several trials of vasopressin versus norepinephrine post-cardiovascular surgery but they were underpowered to evaluate patient-centered outcomes such as mortality and organ dysfunction.[98,145–149]

There was a boost to the evidence of vasopressin after cardiovascular surgery in 2019. A single center blinded RCT (VANCS; $n = 300$) in Brazil of vasopressin versus norepinephrine in vasodilatory shock post-cardiovascular surgery[105] found that vasopressin infusion significantly decreased the rates of mortality or severe complications, the primary endpoint and decreased the frequency of atrial fibrillation, decreased norepinephrine dose, shortened ICU stay, and decreased frequency of AKI and need for RRT. There was no difference in 28-day mortality—the vasopressin beneficial effect on the primary endpoint was driven by "severe complications." Sparing of norepinephrine dose[150] or nonhemodynamic effects of vasopressin could explain the benefits of vasopressin.

Vasopressin appears to be more beneficial in vasodilatory syndrome post-cardiovascular surgery than in septic shock[12,14] for several reasons. First, the primary outcome in pivotal RCTs differed in the VANCS RCT than in RCTs of vasopressin in septic shock—"mortality and severe complications"[105] in the former versus 28-day mortality[12] or AKI[14] in septic shock. Plasma vasopressin doses were similar in VASST,[12] VANISH,[14] and VANCS,[105] and yet peak vasopressin levels were much lower in VANCS[105] (20–25 pmol/L) than in VASST (80–100 pmol/L) or VANISH pilot[14,151] (300 pmol/L). This raises the hypothesis that lower vasopressin levels are optimal in vasodilatory shock. Finally, mortality rates were high (15.9 and 15.4% at 28-day norepinephrine vs. vasopressin) in VANCS.[105] Unfortunately, mortality rates were not reported in prior RCTs of vasopressin versus norepinephrine for vasodilatory shock[152] post-cardiovascular surgery.[98,147–149]

Vasodilatory Shock Post-Acute Myocardial Infarction

AMI can be complicated by vasodilatory shock and presents typical features of vasodilatory shock (hypotension, tachycardia, and low systemic vascular resistance). After assuring adequate volume status, norepinephrine or epinephrine infusion to supplement inotropic and/or device support is most often used and recommended for AMI complicated by vasodilatory shock. A recent RCT of norepinephrine versus epinephrine infusion after AMI complicated by vasodilatory shock found no differences in effects on cardiac index

(primary outcome), systemic vascular resistance, or refractory shock, but the heart rate was significantly higher with epinephrine than with norepinephrine.[153] The higher heart rate would be detrimental in AMI complicated by vasodilatory shock because of the risk of worsening myocardial ischemia and extending the infarct size, again suggesting that norepinephrine is the vasopressor of first choice in AMI complicated by vasodilatory shock.

Dopamine has more chronotropy and had a significantly higher mortality rate compared with norepinephrine and so is not recommended in cardiogenic shock.[56]

Pediatric Vasodilatory and Septic Shock

Septic shock in children may present with vasodilatation or myocardial failure in varying combinations and may change over time depending on organisms, host characteristics, and response to therapy. Thus recent adult definitions of septic shock are difficult to apply in pediatric populations.[154] In most cases it is reasonable to begin vasoactive agents after 40 to 60 mL/kg of fluid resuscitation if normal perfusion is not restored or signs of fluid overload is present.[155] As suggested by the World Health Organization, early administration of vasopressors coupled with smaller fluid boluses (10–20 mL/kg over 30–60 minutes) is reasonable in resource-poor areas without mechanical ventilatory support or RRT to treat iatrogenic fluid overload.[156] In the United States, early vasopressor use has been associated with shorter hospital and ICU length of stay.[157,158]

The choice of vasoactive agents in children is not guided by robust evidence. For instance, no studies directly compare epinephrine with norepinephrine although these are two of the most commonly used vasoactive drugs. Epinephrine has been compared with dopamine in two RCTs in children with fluid-resistant septic shock.[159,160] Across both studies, epinephrine was associated with a lower risk of mortality (RR: 0.63; 95% CI: 0.40–0.99) and more organ failure-free days among survivors by day 28. A recent RCT found that epinephrine (0.2–0.4 µg/kg/min) and dopamine (10–20 µg/kg/min) had comparable efficacy and safety in neonatal septic shock.[161] Norepinephrine has not been studied in children with septic shock, but in an RCT of norepinephrine versus saline in sedated, mechanically ventilated children, mortality was similar between groups (RR: 0.50; 95% CI: 0.10–2.43), but the norepinephrine group had higher urine output ($p = 0.016$) and blood pressure ($p = 0.04$), suggesting improved perfusion relative to saline.[162]

Epinephrine is more commonly used in children than in adults. Epinephrine or norepinephrine is the preferred first-line vasoactive drug in children; however, dopamine may be used as the first line if neither epinephrine nor norepinephrine is available. All may be administered through a peripheral vein (or intraosseous, if in place) if central venous access is not readily accessible.

Vasopressin-receptor agonists (vasopressin or terlipressin) have been studied in three RCTs in children. Vasopressin was compared with saline in one RCT of children with vasodilatory shock[163] and in one study of children with severe lung disease.[164] Terlipressin was compared with usual care in children with septic shock.[165] The mortality rate (RR: 1.14; 95% CI: 0.80–1.62) and ischemic events (RR: 1.56; 95% CI: 0.41–5.91) were higher with vasopressin/terlipressin although not statistically significant. There were fewer vasoactive-free days with vasopressin (median: 25.2 days in AVP [interquartile range, IQR: 0.0–28.3]) versus controls (median: 27.5 days [IQR: 23.1–28.9]).

There are no RCTs of inodilators (including milrinone, dobutamine, or levosimendan) in children with septic shock with persistent hypoperfusion and cardiac dysfunction. Improvement in cardiac output with the addition of inodilators was reported in two children.[166] There was improved core-to-peripheral temperature gradient, with stable blood pressure and no change in acidosis in a case series of 10 children with meningococcal septic shock treated with milrinone.[167] Despite scant evidence inodilators are frequently used in children with septic shock who have evidence of persistent hypoperfusion and cardiac dysfunction despite other vasoactive agents, especially in a pediatric ICU with advanced hemodynamic monitoring available.

Directions for Future Research

Regarding vasopressors, one could ask how much fluid defines "nonresponsive," how to identify fluid nonresponsive patients, how to predict vasopressor responders, how to de-resuscitate, which patients need inotropic therapy, are certain combinations of vasopressors better than others, and who to select for short-acting β1-blockade with esmolol.

Patients may be less reactive to one vasopressor (e.g., vasopressin[32]) but more reactive to another(s) (e.g., norepinephrine[30]) in patients who have septic shock because of differences in host genotype,[30–32] variable organ-specific receptor expression and downregulation in different tissues,[29] and native plasma norepinephrine, epinephrine, vasopressin, and angiotensin II concentrations prior to treatment (►**Fig. 1**). Discovery and validation of biomarkers that predict response to vasopressors would enable precision vasopressor therapeutics.[168,169] Perhaps patients will be *started* on several vasopressors with complementary mechanisms of action.[170] De-resuscitation to limit cumulative vasopressor toxicity deserves greater emphasis.[171] Better assessment of volume status is a priority.[61] Vitamin C has received attention[172] but a recent RCT found no benefit on cardiovascular or respiratory dysfunction in sepsis.[173] Two other RCTs of hydrocortisone, ascorbic acid, and thiamine (HAT and VITAMINS)—three readily available inexpensive agents—are underway.[174,175] The VITAMINS RCT of vitamin C, thiamine, and hydrocortisone versus hydrocortisone alone as negative for the primary outcome, time alive and free of vasopressors up to day 7.[176] Machine learning for earlier recognition[177] and better selection of vasopressors for individual patients could improve outcomes. Finally, closer collaboration of academia with industry could accelerate discovery of novel potent, safer vasopressors.[178]

Conclusion and Recommendations

Clinically available vasopressors are hormones that occupy and activate relevant receptors (adrenergic: α1, α2, β1, β2;

angiotensin II: AG1, AG2; vasopressin: AVPR1a, AVPR1B, AVPR2; dopamine: DA1, DA2) inducing vasoconstriction but commonly have adverse effects. Norepinephrine is the first-choice vasopressor in vasodilatory shock after adequate volume resuscitation. Vasopressin or epinephrine may be added to norepinephrine-refractory patients. Angiotensin II may be indicated for early resuscitation of profoundly hypotensive patients. Vasopressors may decrease ventricular contractility, so an inotropic agent (e.g., dobutamine) may be added. Future strategies could include initiation of several vasopressors with complementary mechanisms of action titrated according to response to each vasopressor. Predictive biomarkers would facilitate selection of patient-specific vasopressors. Novel vasopressors may emerge with fewer adverse effects.

Conflict of Interest
None declared.

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