Intensive Care Med (2019) 45:1503–1517
https://doi.org/10.1007/s00134-019-05801-z

STATE-OF-THE-ART REVIEW

Vasopressor therapy in critically ill patients with shock

James A. Russell*

Abstract

Background: Vasopressors are administered to critically ill patients with vasodilatory shock not responsive to volume resuscitation, and less often in cardiogenic shock, and hypovolemic shock.

Objectives: The objectives are to review safety and efficacy of vasopressors, pathophysiology, agents that decrease vasopressor dose, predictive biomarkers, β1-blockers, and directions for research.

Methods: The quality of evidence was evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: Vasopressors bind adrenergic: α1, α2, β1, β2; vasopressin: AVPR1a, AVPR1B, AVPR2; angiotensin II: AG1, AG2; and dopamine: DA1, DA2 receptors inducing vasoconstriction. Vasopressor choice and dose vary because of patients and physician practice. Adverse effects include excessive vasoconstriction, organ ischemia, hyperglycemia, hyperlactatemia, tachycardia, and tachyarrhythmias. No randomized controlled trials of vasopressors showed a significant difference in 28-day mortality rate. Norepinephrine is the first-choice vasopressor in vasodilatory shock after adequate volume resuscitation. Some strategies that decrease norepinephrine dose (vasopressin, angiotensin II) have not decreased 28-day mortality while corticosteroids have decreased 28-day mortality significantly in some (two large trials) but not all trials. In norepinephrine-refractory patients, vasopressin or epinephrine may be added. A new vasopressor, angiotensin II, may be useful in profoundly hypotensive patients. Dobutamine may be added because vasopressors may decrease ventricular contractility. Dopamine is recommended only in bradycardic patients. There are potent vasopressors with limited evidence (e.g. methylene blue, metaraminol) and novel vasopressors in development (selepressin).

Conclusions: Norepinephrine is first choice followed by vasopressin or epinephrine. Angiotensin II and dopamine have limited indications. In future, predictive biomarkers may guide vasopressor selection and novel vasopressors may emerge.

Keywords: Vasopressors, Norepinephrine, Vasopressin, Angioensin II, Septic shock, Esmolol

Introduction and rationale

The rationale for this review is that there is need for clinical guidance for use of vasopressors because there are new issues with vasopressors, a new vasopressor is available clinically and new vasopressors are in pivotal trials since recent reviews [1, 2].

Objectives

The objectives are to review general clinical comments regarding vasopressor use in shock, pathophysiology, specific vasopressor characteristics, safety, and efficacy evidence, agents that decrease vasopressor dose, predictive biomarkers, β1-blockers in septic shock, vasopressors for hypovolemic and cardiogenic shock and directions for research. Vasopressors are commonly administered for vasodilatory shock, especially septic shock, not responsive to volume resuscitation. Other causes of shock for which vasopressors are administered include vasodilatory shock post-cardiovascular surgery, post-acute myocardial infarction, post-general/abdominal surgery/anesthesia or after certain drug administration as well as

*Correspondence: Jim.Russell@hli.ubc.ca
Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, Vancouver, BC, Canada

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cardiogenic and hypovolemic shock. Most high-quality randomized controlled trials (RCTs) of vasopressors are in septic shock.

Summary of evidence

Despite international guidelines [3], the specific vasopressor chosen and vasopressor dose vary widely in clinical practice because of patient and physician practice heterogeneity [4]. For example, norepinephrine doses used in the control group of shock RCTs varied widely (mean 0.20–0.82 μg/kg min^{-1}) [5]. Furthermore, the variable use of vasopressin clinically illustrates institution and physician practice heterogeneity. An observational cohort study ($n = 584{,}421$ patients; 532 hospitals) evaluated vasopressin use in septic shock [6]. Patients in "high vasopressin use" hospitals were 2.6-fold more likely to receive vasopressin than patients in "low vasopressin use" hospitals. Interpretation is limited because of heterogeneity of patients from many community and university-affiliated small and large hospitals.

Vasopressors are indicated for patients who have not responded to "adequate" fluid resuscitation [3] but "adequate" varies widely and is difficult to measure clinically because clinicians' measurement tools of volume status are relatively inaccurate. Furthermore, the interactions of various fluid types, fluid loading volumes, and vasopressor effects introduce important potential bias in part because vasopressors (unlike fluids) exert their action on arteries and veins. There is scant evidence of alternative vasopressors as first line vasopressors because RCTs of vasopressors included patients on norepinephrine.

Vasopressors are hormones that vasoconstrict by receptor activation (norepinephrine/epinephrine: α1, β1, β2; vasopressin: AVPR1a, AVPR1b, AVPR2; angiotensin II: AGTR1, AGTR2; dopamine; DA1, DA2 (Fig. 1) perhaps limiting drug discovery opportunities. Novel vasopressors are modifications of natural hormones (e.g. selepressin, a specific AVPR1a agonist). There is complex cross-talk of these hormone systems (Fig. 2) further complicating vasopressor therapy.

All vasopressors frequently have adverse effects in practice, especially organ ischemia/infarction, metabolic changes (β1-induced hyperglycemia; β2-induced hyperlactatemia), β1-induced-tachycardia and -tachyarrhythmias). The target mean arterial pressure (MAP) during vasopressor use is 65 mmHg [3] but is debated; one RCT [8] found no difference in mortality between "usual" (65–70 mmHg) versus "high" MAP (80–85 mmHg). However, a clinically relevant result emerged that we use: in patients with chronic hypertension, the high MAP target decreased acute kidney injury.

Patients on vasopressors often—but not always—require arterial catheter for arterial pressure monitoring (and central venous pressure (CVP) monitoring (target CVP > 8–2 cm H_2O [3]). Some clinicians use a pulmonary artery catheter and monitor pulmonary capillary wedge pressure and cardiac output. However, non-invasive cardiovascular monitoring has supplanted PA catheter monitoring in many patients.

Take-home message

Vasopressors are administered to critically ill patients with vasodilatory shock not responsive to volume resuscitation, and less commonly cardiogenic shock and hypovolemic shock. Norepinephrine as first choice may be followed by vasopressin or epinephrine. Angiotensin II and dopamine have limited indications. In future, predictive biomarkers may guide vasopressor selection and novel vasopressors may emerge.

Vasopressor management was central in Early Goal-Directed Therapy, effective in an initial RCT [9] but not in subsequent RCTs [10], so EGDT is not recommended for clinical use.

The "sepsis 3.0" definition of septic shock is recommended clinically, requiring both use of vasopressor(s) and serum lactate > 2 mmol/L [11] (sepsis 2.0 required only vasopressor use). When sepsis 3.0 was applied to a prior pivotal vasopressin RCT [12], vasopressin was most effective in patients who did *not* meet the sepsis 3.0 definition (i.e. vasopressor use and lactate ≤ 2 mmol/L) [13]. The observed mortality rates are higher with sepsis 3.0 versus the sepsis 2.0 definition of septic shock [14]. Thus, the use of septic shock 3.0 will change clinical practice and RCTs of septic shock. Use of septic shock 3.0 for RCTs would tighten inclusion criteria, decrease sample size (by 50% in the retrospective analysis of the VASST RCT), and increase mortality rates [13, 14].

Finally, no RCT of vasopressors shows a significant difference in 28-day mortality rate. Some strategies that decrease norepinephrine dose (vasopressin [12, 15], angiotensin II [16]) have not decreased 28-day mortality, while another (corticosteroids) has decreased 28-day mortality significantly in some (two large trials [17, 18]) but not all trials [19, 20].

For the clinician, the vasopressor field has evolved [3]: norepinephrine remains the first line vasopressor, epinephrine or vasopressin are second line, dopamine is recommended only in highly selected bradycardic patients, a new vasopressor is available clinically (angiotensin II [16]), and a novel vasopressor, selepressin [21] is in trial.

Accordingly, we review clinically relevant pathophysiology of vasodilatory shock, pivotal vasopressor RCTs, how the clinician determines whether and what vasopressor(s) to administer, and specific vasopressor pharmacology, guidelines, effects, adverse effects, dosing, monitoring, weaning, and outcomes. We discuss

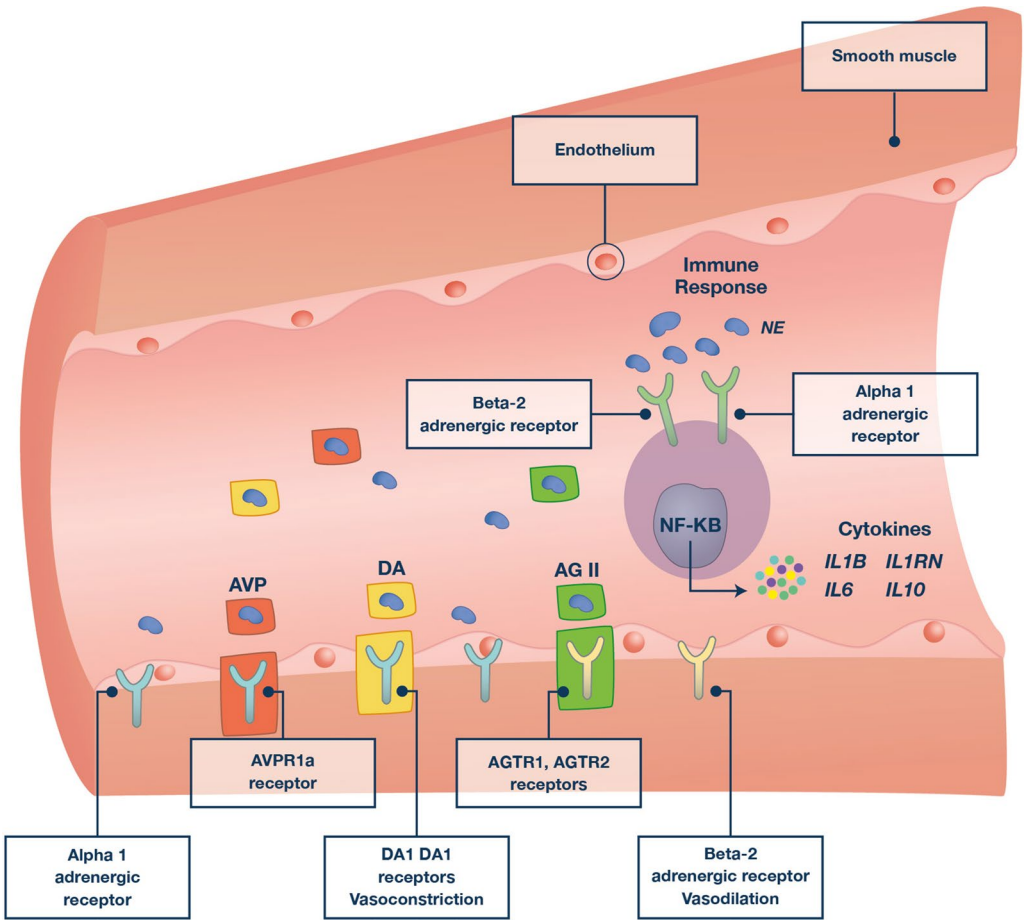

Fig. 1 Norepinephrine (NE) binds to alpha-1 adrenergic receptors of vascular smooth muscle to induce vasoconstriction, binds to beta-1 and beta-2 receptors causing vasodilation, and binds to alpha-1 and beta-2 adrenergic receptors on leukocytes to differentially modulate immune response in sepsis. Exposure to NE also down-regulates alpha-1 and beta-2 receptor density and that could alter sensitivity to NE, thereby leading to increased doses of norepinephrine 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, AGTR2), all causing vasoconstriction

inotropic agents to complement vasopressors, predictive biomarkers, and novel vasopressors. We consider the ironic role of β1-blockers in septic shock. We review vasodilatory shock post-cardiovascular surgery and post-acute myocardial infarction, cardiogenic and hypovolemic shock.

Clinically relevant pathophysiology of vasodilatory shock

Vasodilatory shock is characterized by vasodilation (identified clinically by warm skin), hypotension, tachycardia, and inadequate perfusion (impaired mentation, oliguria). When ventricular dysfunction and hypovolemia contribute, features change (cold skin, increased jugular venous pressure (JVP) and CVP if there is ventricular dysfunction and low JVP and CVP if there is hypovolemia). Vascular smooth muscle relaxation is the cardinal mechanism of vasodilatory shock [22]. While not apparent to the clinician, behind the scene there is a rapid, complex, hormonal response to hypotension: secretion of multiple hormones (norepinephrine, epinephrine, vasopressin, angiotensin II, aldosterone, adrenomedullin, and cortisol) act synergistically attempting to increase vasomotor tone, heart rate and contractility. Often vasodilation persists because of β1, β2 and other receptor down-regulation [23], inter-patient receptor genotype differences [24, 25], and genetically-variable metabolism [26]. When these regulatory multi-hormone mechanisms are overwhelmed, hypotension and shock persist.

Vasodilation in sepsis is mediated mainly by nitric oxide (NO) and prostacyclin. Inducible NO synthase (iNOS) is induced by endotoxin and cytokines; an iNOS inhibitor increased NO synthesis and blood pressure, decreased vasopressor requirements but decreased

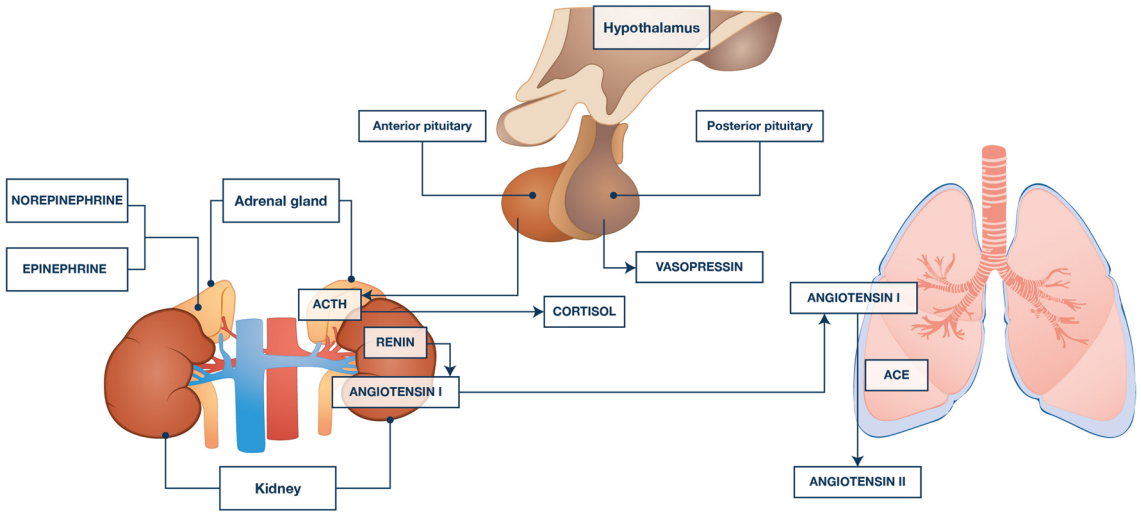

Fig. 2 The complex interplay of several key endocrine axes in septic shock includes: (1) release of norepinephrine and epinephrine from the adrenal medulla, (2) release of adrenocorticotropic hormone (ACTH) from the anterior pituitary then stimulating synthesis and release of cortisone and cortisol from the adrenal cortex, (3) release of vasopressin (AVP) from the posterior pituitary, and (4) release of renin [in response to hypotension) from the kidney. Renin is converted to angiotensin I (ANG-1) by angiotensinogen (that was released from the liver], and then angiotensin I is converted to angiotensin II (ANG-2) by angiotensin converting enzyme (ACE) in the lung. Angiotensin II increases aldosterone synthesis and release from the adrenal cortex, and aldosterone increases sodium retention in the kidney. Angiotensin II also increases release of vasopressin Adapted with permission from Russell [7]

survival in a large pivotal RCT so is not available clinically nor recommended [27, 28]. Prostacyclin is released by endothelial cells in response to endotoxin and inflammatory cytokines. A pivotal RCT of ibuprofen (prostaglandin synthesis inhibitor) had no effect on survival [29].

Adrenomedullin, a vasodilating and cardiac depressant hormone, increases in septic shock and is associated with mortality. Anti-adrenomedullin increased survival, responsiveness to norepinephrine and renal function in sepsis models and is a novel therapeutic target in septic shock [30].

Clinical and physiologic evaluation for the clinician to determine when and what vasopressor(s) to administer

Emergent assessment prioritizes airway, breathing and cardiovascular resuscitation based on clinical assessment of volume status and perfusion complemented by laboratory tests (arterial blood gases, lactate, hematology, renal and hepatic function) (Fig. 3). The quick SOFA (qSOFA: respiratory rate > or = 22/min, altered mentation, systolic blood pressure < or = 100 mmHg) is recommended screening for sepsis outside the ICU [11]. Volume resuscitation and vasopressor(s) should be started within the first hour [3] and resuscitation with crystalloid (30 ml/kg initially and more as needed) should precede vasopressors, added if perfusion remains inadequate [3].

In parallel with resuscitation, use clinical examination and laboratory evaluation to diagnose the cause of shock; fever, and leukocytosis suggest septic shock and the source of sepsis should be investigated. Sepsis mimics include pancreatitis, aspiration, Acute Respiratory Distress Syndrome (ARDS), recent surgery, post-acute myocardial infarction, trauma, and drugs (anesthetics and drug allergy/anaphylaxis).

There is no evidence that any diagnostic tool is effective to guide treatment, at least regarding mortality. Limited bedside echocardiography can be effective to guide fluid and vasopressor management. We use limited bedside echocardiography commonly because a case–control study of bedside echocardiography in ICU patients resuscitated but in shock found (1) volume status was often more than replete (2) fluid restriction was recommended (65% of patients), and (3) initiation of dobutamine was recommended (25% of patients) [31]. Mortality was lower in the echocardiography group than controls [31]. However, the mechanism by which bedside echocardiography leads to dobutamine prescription then leading to decreased mortality is uncertain.

Vasopressor class effects

See Table 1 for vasopressors, receptors, actions, dose, and biomarkers. Studies of early antibiotics [32, 33] and Early Goal-Direct Therapy [10, 33] taught clinicians to emphasize *early* recognition and treatment of septic shock within the first hour (comparable to the "golden

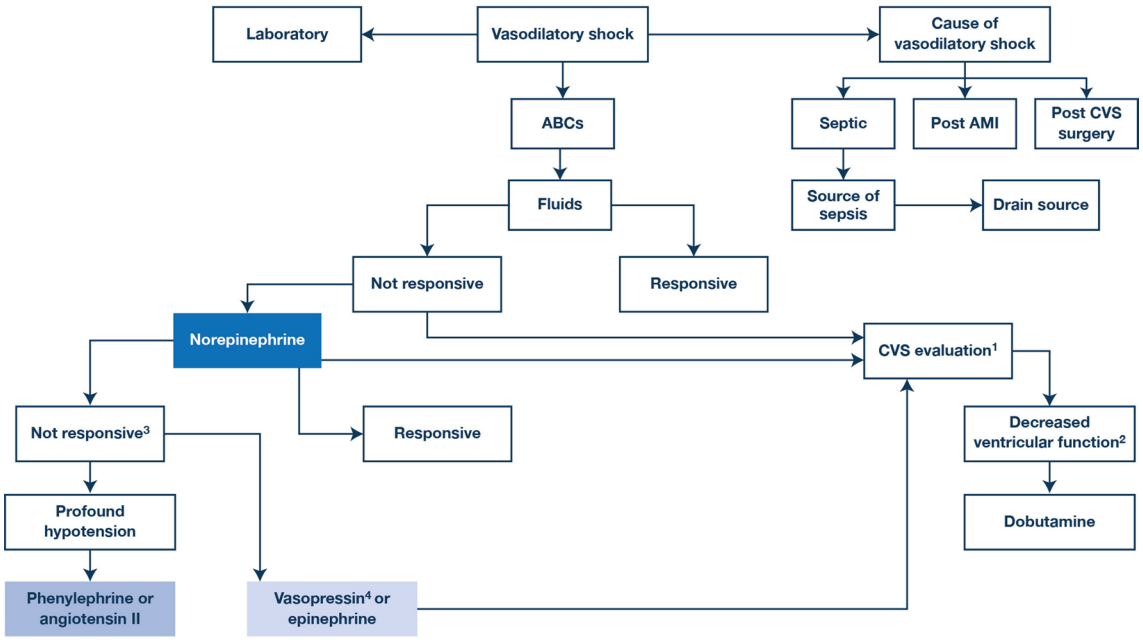

Fig. 3 Algorithm for vasopressor management. In patients with vasodilatory shock, the first priority is Airway, Breathing, and Circulation (ABCs) resuscitation, while in parallel doing laboratory evaluation (arterial blood gases, lactate, hematology, renal and hepatic function) and evaluating the cause 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 not responding to norepinephrine, vasopressin (terlipressin) or epinephrine is added. In patients who are profoundly hypotensive, phenylephrine or angiotensin II may be considered. Evaluation of the cause of shock is done in parallel with resuscitation; fever and leukocytosis suggest septic shock. Septic shock requires 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, non-invasive 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

hour" of trauma) and aligns with an artificial intelligence (AI) study. In contrast to clinical practice in a large UK cohort, the AI clinician recommended septic patients be given vasopressors more often (30% versus 17%) [34]. However, other uncontrolled observational studies found that earlier vasopressor(s) was harmful [35] suggesting equipoise regarding earlier use of vasopressors.

Pivotal vasopressor trials

Pivotal RCTs of norepinephrine vs. epinephrine [37], norepinephrine plus dobutamine vs. epinephrine [47], early vasopressin [15] vs. norepinephrine, and vasopressin vs. norepinephrine in septic shock [12] and norepinephrine vs. dopamine [48] in all types of shock established that norepinephrine is superior to dopamine and equivalent to vasopressin and epinephrine (Table 2). Some of these RCTs had only moderate sample sizes. While two RCTs had over 700 patients each (SOAP II [48] (dopamine versus norepinephrine $n=1679$; VASST [12] (vasopressin versus norepinephrine $n=778$)), ATHOS-3 [16] (angiotensin II versus placebo $n=479$), VANISH [15] (vasopressin versus norepinephrine, $n=409$, CAT [37] (epinephrine versus norepinephrine, $n=330$) and CATS [47] (epinephrine versus norepinephrine plus dobutamine $n=277$) were smaller.

There was no difference in mortality between vasopressin and norepinephrine in VASST [12] and VANISH [15], but vasopressin may have been more effective in less severe shock (baseline norepinephrine < 15 μg/min). Vasopressin was associated with similar outcomes to norepinephrine in a propensity matched cohort study [49]. A small RCT of early vasopressin and norepinephrine vs. norepinephrine alone found that the early vasopressin and norepinephrine group achieved MAP of 65 mmHg faster than the norepinephrine group [50].

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 [36]	5–100 μg/min	β2 receptor SNP [24]
Epinephrine	α1 > β1, β2 More β1 than NE	Immune activity [36]	5–60 μg/kg min [37]	β2 receptor SNP [24]
Phenylephrine	α1	Immune activity [36]	50–100 μg bolus 0.1–1.5 μg/kg min	
Dopamine	DA1, DA2	Immune activity [38, 39]	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 [40]	0.01–0.04 U/min [12, 41]	LNPEP SNP [26] Angiopoietin ½ [42] Vasopressin/copeptin
Terlipressin	AVPR1a (AVPR1b) > AVPR2	? Immune activity	1.3 μg/kg hr [43] 20–160 μg/hour [44] bolus: 1 mg	LNPEP [26] Vasopressin/copeptin
Selepressin	AVPR1a	↓ Angiopoietin-2 ↓ Vascular leak	1.25–2.5 ng/kg min in phase 2 [21] 1.25–5.0 ng/kg min in phase 3 [45]	LNPEP SNP [26] Angiopoietin 1/2 [42] 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 days [16]	AGTRAP SNP [25]
Methylene blue [46]	Inhibits GABAA receptors	↓ Vascular leak	Bolus (2 mg/kg) then infusion—stepwise increasing rates 0.25, 0.5, 1, 2 mg/kg/hr	

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

In more severe shock, clinicians often administer combinations of vasopressors but the optimal vasopressor combination remains unknown regarding mortality. In a network meta-analysis of RCTs (43 RCTs; 5767 patients) of vasopressors [51], the efficacy was greatest for norepinephrine plus dobutamine; acute myocardial infarction incidence was highest with norepinephrine plus epinephrine; arrhythmia incidence was highest with dopamine and lowest with vasopressin. This retrospective study must be interpreted cautiously and as hypothesis-generating.

Adverse effects

The commonest serious adverse effects of vasopressors are digital and organ ischemia, tachyarrhythmias, and atrial fibrillation [52] (with increased risk of stroke [53]) (Table 3). Higher cumulative vasopressor dose is associated with organ dysfunction and mortality [54], but association studies are confounded. Many vasopressors have immune effects that may be proven important in human septic shock. Norepinephrine has moderate immunosuppressive and bacterial growth-promoting effects in pre-clinical models that could increase risk of infection, but immune risk of norepinephrine infusion is uncertain [36]. Vasopressin augments the usual decrease of cytokines more than norepinephrine, especially in less severe septic shock [55].

Serious adverse events of vasopressors were similar in most RCTs but differed significantly between dopamine versus epinephrine in SOAP 2 [48] [twice as many arrhythmias with dopamine (24.1%) than norepinephrine (12.4%, $p < 0.001$), mainly atrial fibrillation (Table 4)]. There was significantly more study drug withdrawal of epinephrine than norepinephrine in CAT (12.9% versus 2.8%, $p = 0.002$) [37].

Clinical monitoring of vasopressor(s)

Vasopressors are initiated, titrated, and weaned according to MAP, measures of perfusion (mentation, urine output, lactate), and non-invasive cardiovascular assessment (e.g. non-invasive cardiac output, echocardiographic evaluation of ventricular function and volume status (i.e. inferior vena cava collapse), microcirculation). Clinical measures (e.g. capillary refill) and laboratory measures (e.g. lactate) were equivalent in association with mortality for resuscitation monitoring in a recent RCT ($n = 424$) [57].

Weaning

Vasopressor weaning is less standardized than resuscitation and there are no RCTs of weaning. Patients are judged appropriate for gradual vasopressor dose decrements when "stabile" (no universal definition), i.e. adequate volume status and perfusion. Deterioration

Table 2 Pivotal randomized controlled trials of vasopressors in septic shock

Trial (reference number)	Vasopressor intervention (*n*)	Control (*n*)	Total *n*	Intervention mortality (%)	Control mortality (%)	ARR (95% CI) *p*	Secondary outcomes *p*
SEPSIS-ACT [45]	Selepressin (562)	Placebo (266)	828	40.6%	39.4%	NA	RRT-free days, ICU-free days
VASST [12]	Norepinephrine (382)	Vasopressin (396)	778	35.4%[a]	39.3%	3.9 (− 2.9 to 10.7) 0.26	DAF vasopressors, ventilation and renal replacement therapy *p* NS
VANISH [15]	Norepinephrine (204)	Vasopressin (205)	409	30.9%[a]	27.5%	3.4 (− 5.4 to 12.3)	RRT rates, duration, organ failure-free days, ICU/hospital duration *p* NS
SOAP II [48]	Norepinephrine (821)	Dopamine (858)	1679	48.5%[b]	52.5%	1.17 (0.97 to 1.42) 0.10	DAF vasopressors, ventilation and renal replacement therapy; ICU/hospital duration
ATHOS-3 [16]	ANG II (163)	Placebo (158)	479	46%[a]	54%	HR: 0.78[c] (0.57 to 1.07) 0.12	Change in CVS and total SOFA; change in norepinephrine dose
CAT [37]	Epinephrine (139)	Norepinephrine (138)	277	23%[a]	27%	HR[c]: 0.87 (0.48 to 1.58) 0.65	Primary outcome: DAF vasopressors (time to achieve target MAP for 24 h)
CATS [47]	Epinephrine (161)	Norepinephrine plus dobutamine (169)	330	40%[a]	34%	RR[d]: 0.86 (0.65 to 1.14) 0.31	ICU, hospital and 90-day mortality; hemodynamics; SOFA; time to no vasopressors for 24 h

HR hazard ratio, *RR* relative risk, *DAF* days alive and free of interventions such as vasopressors, ventilation and renal replacement therapy (RRT), *NS* not significant

[a] 28-day mortality was a secondary outcome; renal failure-free days was the primary outcome

[b] All causes of shock; 28-day mortality

[c] Hazard ratio

[d] Relative risk

necessitates titration back to higher doses, followed when "stability" recurs by repeated weaning. Medical informatics accurately predicts successful vasopressor weaning earlier and more accurately than clinicians [58].

Outcomes in RCTs of vasopressors

Fortunately, there are several high-quality RCTs of vasopressors in septic shock. The usual primary outcome for RCTs of vasopressors in septic shock is short-term (e.g. 28-day) mortality but short-term mortality has decreased [59], so RCTs of vasopressors now focus on improving long-term outcomes and short-term organ dysfunction that aligns with long-term outcomes [60]. The pivotal RCT of selepressin in septic shock was vasopressor- and ventilation-free days [45].

Clinicians should understand pharmacology, guidelines, effects, adverse effects, and dosing of vasopressors (Table 1).

Norepinephrine

In the Surviving Sepsis Campaign (SSC) guidelines, norepinephrine is the first line vasopressor (moderate evidence) [3]. Norepinephrine's potent α1, α2, and less potent β1, β2 receptor binding increases smooth muscle intracellular calcium concentration and vasoconstriction and some positive inotropic activity (increasing ventricular contractility).

Table 3 Adverse effects of vasopressors according to specific vasopressors, mechanisms and diseases that interact with specific adverse effects with an emphasis on septic shock

Adverse effect	Mechanisms	Vasopressors causing this adverse effect	Disease interactions
Ischemia: cardiac, cerebral, splanchnic, renal, digital	α1 AVPR1a AGTR1, AGTR2	Norepinephrine, epinephrine, dopamine vasopressin, terlipressin, selepressin[a] Angiotensin II[b]	DIC
Tachycardia, tachyarrhythmias	β1 β1, DA1, DA2 β1	Epinephrine > norepinephrine > vasopressin Dopamine > norepinephrine Dobutamine[c]	CHF, IHD
Atrial fibrillation	? β1	? Epinephrine > norepinephrine	CHF, IHD
Hyperglycemia	β1	Epinephrine > norepinephrine	DM, corticosteroids
Hyperlactatemia	β1	Epinephrine > norepinephrine	
Decreased cardiac output	α1 AVPR1a	Phenylephrine > norepinephrine, epinephrine, vasopressin, terlipressin, selepressin[a]	CHF, IHD
Acute kidney injury	α1 AVPR1a	Phenylephrine > norepinephrine, epinephrine, vasopressin, terlipressin, selepressin[a]	CKD, DM, hypertension, ACE
Immune effects[d]	α1, α2, β1, β2 AVPR1a	Phenylephrine norepinephrine, epinephrine Vasopressin, terlipressin, selepressin	Corticosteroids, immunosuppressants

Vasopressin may decrease pooled adverse event rates and specific adverse events (vasodilatory shock and new onset atrial fibrillation) [56]

DIC disseminated intravascular coagulation, *CHF* congestive heart failure, *IHD* ischemic heart disease, *DM* diabetes mellitus, *CRD* chronic kidney disease, *ACE* angiotensin converting enzyme inhibitors

[a] Indicates that adverse event rates are similar in RCTs and observational studies between vasopressors mentioned

[b] Angiotensin II RCT [16) used placebo as control so it is difficult to compare adverse event rates between various comparable vasopressors

[c] Dobutamine is an inotropic agent, but it is included because it is often administered with vasopressors

[d] Immune effects are complex [36, 40] and of uncertain clinical significance to date

How early clinicians should start norepinephrine in shock is uncertain. Early low-dose norepinephrine may be more effective than later norepinephrine. In a recent proof-of-principal RCT [61] ($n=310$) of early low-dose norepinephrine versus placebo, the primary outcome (control of shock: MAP > 65 mmHg plus either urine output > 0.5 ml/kg/h or 10% lactate decline) occurred significantly more often (76.1% vs. 48.4%) and mortality was nominally lower (15.5% vs. 21.9%, $p=0.15$) in early norepinephrine group. Cardiogenic pulmonary edema and new-onset arrhythmias were halved with early norepinephrine. Early norepinephrine may be effective by decreasing organ injury, norepinephrine doses, and/or norepinephrine's immune effects [36] (Fig. 1). Further RCTs of early norepinephrine are needed. Norepinephrine's adverse events rates (10–15%) were significantly less than with dopamine [48] and similar to vasopressin [12, 15] and epinephrine [37, 47].

Epinephrine

Epinephrine is a second line agent in septic shock [3] (weak recommendation, low evidence) [3, 37, 62] in patients not responding to norepinephrine. Epinephrine has more β1 agonism than norepinephrine. Although RCTs show that epinephrine is comparable to norepinephrine [37], to norepinephrine plus dobutamine [47], and to norepinephrine and vasopressin [63], epinephrine is not first line because of increased risk of splanchnic vasoconstriction, tachyarrhythmias, and hyperlactatemia [3, 37, 47]. Epinephrine may be a first-line vasopressor in countries where norepinephrine is too costly [64], because epinephrine is less expensive and had equivalent efficacy in a meta-analysis [62].

Phenylephrine

Phenylephrine is a nearly pure α1-agonist commonly used short-term for transient profound hypotension. Phenylephrine can cause baroreceptor-mediated reflex bradycardia (because of α1-induced vasoconstriction) and splanchnic ischemia and so is not recommended for resuscitation of septic shock [3]. Phenylephrine may be less effective in practice than norepinephrine based on a natural experiment arising from a recent national US shortage of norepinephrine [65]. Phenylephrine was the most commonly used vasopressor during the norepinephrine shortage and phenylephrine use was associated with a higher mortality than norepinephrine use [65], but this was a non-randomized, non-blinded low evidence experiment.

Dopamine

Dopamine was previously a first-line vasopressor in septic shock, but dopamine's greater adverse event rates (higher heart rate and tachyarrhythmia rates) than

Table 4 Serious adverse events in pivotal randomized controlled trials of vasopressors in septic shock

Trial (reference number)	SAEs	Vasopressor intervention (*n* = %)	Control (*n*, %) *p*	Event	Vasopressor intervention (*n*, %)	Control (*n*, %) *p*	Event	Vasopressor intervention (*n*, %)	Control (*n*, %) *p*
SEPSIS-ACT [45]		Selepressin (2054/562 = 83.3%)[h]	Placebo (1086/266 = 88.3%)[h]	Ischemia	Selepressin (92/562 = 14.4%)[h]	Placebo (36/266 = 12%)[h]	Arrhythmia	Selepressin (209/562 = 27.9%)[h]	Placebo (87/266 = 25.2%)[h]
VASST [12]		Norepinephrine (40/382) = 10.5%	Vasopressin (41/396) = 10.3% $p = 1.0$	Ischemia[a]	Norepinephrine (23/382) = 6.0%	Vasopressin (26/396) = 6.6%	Arrhythmia/ arrest	Norepinephrine (14/382) = 3.7%	Vasopressin (11/396) = 2.8%
VANISH [15]		Norepinephrine (17/204) = 8.3%	Vasopressin (22/205) = 10.7%	Ischemia[b]	Norepinephrine (10/204) = 5%	Vasopressin (23/205) = 11.2%	Arrhythmia/ Arrest[c]	Norepinephrine (5/204) = 2.4%	Vasopressin (2/205) = 1%
SOAP II [48]		Norepinephrine (800/821)[g] = 97.4%	Dopamine (979/858) = 100%[h]	Ischemia	Norepinephrine (79/821) = 9.6%	Dopamine (98/858) = 11.4%	Arrhythmia/ arrest	Norepinephrine (102/821) = 12.4%	Dopamine (207/858) = 24.1% $p < 0.001$
ATHOS-3 [16]		Angiotensin II (99/163) = 60.7%	Placebo (106/158) = 67.1%	Ischemia[b]	Angiotensin II (8/163) = 4.9%	Placebo (8/158) = 5.0%	Arrhythmia/ arrest	Angiotensin II (29/163) = 17.8%	Placebo (28/158) = 17.7%
CAT [37]	SAE[d]	Epinephrine (18/139) = 12.9%	Norepinephrine (4/138) = 2.8% $p = 0.002$						
CATS [47]	SAE[e]	Epinephrine (33/161) = 20.5%	Norepinephrine plus dobutamine (41/169) = 24.3%	Ischemia[f]	Epinephrine (9/161) = 5%	Norepinephrine plus dobutamine (11/169) = 7%	Arrhythmia/ arrest	Epinephrine (31/161) = 19%	Norepinephrine plus dobutamine (30/169) = 18%

SAE serious adverse event

[a] Ischemia = acute myocardial ischemia/infarction, mesenteric ischemia, digital ischemia, cerebral ischemia/infarction

[b] Ischemia = acute myocardial ischemia/infarction, mesenteric ischemia, digital ischemia

[c] Life-threatening arrhythmia

[d] Withdrawal of study drug

[e] During catecholamine infusion

[f] Ischemia = acute myocardial ischemia/infarction, digital ischemia, cerebral ischemia/infarction

[g] SAEs include ischemia, arrhythmias, and new onset infections that were the majority of SAES (691/821 = 75.4% of norepinephrine-associated SEAs and 674/858 = 78.6% of dopamine-associated SAEs). Excluding new onset infections, SAE rates for norepinephrine and dopamine were 181/821 = 22.0% and 305/858 = 35.5%, respectively

[h] Total number of SAEs exceeded the number of patients indicating more than 1 SAE per patient

norepinephrine [48] necessitate its use only in highly selected bradycardic patients [3]. Dopamine binds α1- and β1-adrenergic and dopaminergic DA1 and DA2 receptors, the latter causing splanchnic and renal vasodilation at low doses in pre-clinical and small trials ("low-dose dopamine"). However, a pivotal high evidence RCT of critically ill patients found no benefits of low-dose dopamine versus placebo regarding renal replacement rates, renal function or mortality [48].

Vasopressin, terlipressin, and selepressin

Vasopressin is recommended [3] as a second vasopressor in septic shock. Vasopressin stimulates AVPR1a (vasoconstriction), AVPR1b (stimulation of ACTH release), and AVPR2 (anti-diuretic effects) receptors and increases NO synthesis [66], limiting vasoconstriction and preserving renal perfusion [67], but potentially contributing to cardiac depression. Plasma vasopressin levels are low early in septic shock. Vasopressin infusion decreased norepinephrine requirements, maintained blood pressure, and increased urine output in small trials [68–70].

One large RCT of vasopressin versus norepinephrine (VASST) found no difference in mortality in septic shock [71]. Individual patient level meta-analysis showed no difference in renal function (primary endpoint) or mortality of vasopressin versus norepinephrine [72]. A vasopressin/corticosteroid interaction—vasopressin's AVPR1b-induced stimulation of ACTH release—could be beneficial. However, the vasopressin/corticosteroid interaction in septic shock [73] was not confirmed beneficial in a pivotal RCT(VANISH) [15]. Vasopressin improved renal function more than norepinephrine in VASST [74] and significantly decreased use of renal replacement therapy (RRT) in VANISH [15, 72].

For the clinician, vasopressin's adverse effects are similar to norepinephrine in practice [75] as in RCTs [15, 74]. Norepinephrine should be weaned before vasopressin because weaning vasopressin first increased

hemodynamic instability in VASST [12)] and in later studies [76]. Terlipressin has more AVPR1a activity than vasopressin, and similar effects and similar mortality in recent RCTs [43, 44].

In pre-clinical studies, pure AVPR1a agonism mitigated the increased permeability of septic shock better than vasopressin and that has led to development of selepressin. Selepressin decreased lung edema and fluid balance more than vasopressin in models of peritonitis [77] and pneumonia [78]. More relevant clinically, selepressin decreased net fluid balance and some early markers of organ injury in a Phase 2 RCT in septic shock [21]. The selepressin Phase 2B/3 pivotal placebo controlled RCT in septic shock found no difference between groups in the primary endpoint, ventilator-and vasopressor-free days and there was no difference between groups in any other endpoint or adverse events so selepressin is not available for clinical use [45].

Angiotensin II

Angiotensin II, the renin-angiotensin system vasopressor, is available clinically for treatment of vasodilatory hypotension and may be useful for early resuscitation of profoundly hypotensive patients. Angiotensin II binds to angiotensin-1 and -2 receptors (AGTR1, AGTR2) inducing vasoconstriction, aldosterone synthesis, and vasopressin release. AGTR1 is down-regulated in sepsis models decreasing angiotensin II insensitivity [16, 79]. Angiotensin II more rapidly increased MAP over 3 h in the ATHOS-3 placebo-controlled RCT in refractory vasodilatory shock [80]. Larger RCTs powered for organ dysfunction and mortality are now needed. Serious adverse effects of angiotensin II (Table 4) in ATHOS 3 included ischemia (digital, gut, myocardial) and arrhythmias [16].

Metaraminol

Metaraminol, predominantly an α1 agonist that stimulates norepinephrine release, is used for complications of anaesthesia but rarely used in shock and has similar hemodynamic effects as norepinephrine but there are no RCTs of metaraminol.

Methylene blue

Methylene blue, a cyclic GMP blocker, inhibits guanylate cyclase to inhibit smooth muscle relaxation by NO and may decrease pulmonary vascular leak. Methylene blue increased MAP and decreased norepinephrine requirements in refractory hypotension post-cardiopulmonary bypass and septic shock. There are no RCTs of methylene blue, limiting recommendations for its use in septic shock [81].

Corticosteroids

Low dose corticosteroids consistently decreased norepinephrine requirements in septic shock in RCTs and are recommended in patients not responding to norepinephrine [3]. Corticosteroids reverse sepsis-associated adrenal insufficiency and mitigate the pro-inflammatory response of septic shock.

However, corticosteroids remain controversial because of conflicting results of at least four large RCTs, two finding benefit and two finding no effect on mortality. Hydrocortisone plus fludrocortisone significantly decreased mortality (35.4% versus 41.0%, $p=0.04$) in one recent RCT [17] and a previous RCT [18], but not in another recent RCT [20] (mortality: hydrocortisone 27.9% versus placebo 28.8%) or another older RCT [19]. Differences in corticosteroids used and entry criteria could partially explain this RCT equipoise.

Inotropic agents to complement vasopressors in septic shock

Sepsis-induced ventricular dysfunction is common clinically and may be exacerbated by vasopressors, so inotropic agent (dobutamine > milrinone) are commonly added to norepinephrine [47] and vasopressin [71, 82] to increase cardiac output, but with side effects (tachyarrhythmias; increased heart rate, and myocardial oxygen consumption). Milrinone is a non-adrenergic inotrope/vasodilator that is a comparable inotrope to dobutamine but has greater vasodilating action and so is less recommended than dobutamine [3] but could be effective in patients recently on β-blockers. Levosimendan, a positive non-adrenergic inotropic agent, was not effective in a RCT in septic shock [37, 47]. More patients on levosimendan had tachyarrhythmias and fewer patients on levosimendan were successfully weaned from mechanical ventilation [83]. Thus, levosimendan is not recommended in septic shock.

Biomarkers to guide vasopressor selection

Predictive biomarkers are used by clinicians to better define responders to drugs (e.g. chemotherapies for cancer) and have potential for personalized vasopressor selection. A β2 single nucleotide polymorphisms (SNP) marked increased mortality and could identify responders to norepinephrine [24]. Possible vasopressin, terlipressin, and selepressin predictive biomarkers are plasma angiopoietin-2, a mediator of increased permeability [42] (selepressin decreased plasma angiopoietin-2), leucyl/cystinyl aminopeptidase (the enzyme that catalyzes vasopressin) [26], and AVPR1a SNPs [26]. Genotypes of angiotensin-II receptor associated protein (AGTRAP) are associated with mortality of septic shock and may be biomarkers for angiotensin II [25].

The ironic role of β1-blockers in septic and vasodilatory shock

Clinicians should know that there are some patients with septic shock who may benefit ironically from β1 blockers. β1-agonists have varying chronotropic and inotropic potency; dopamine and epinephrine are greatest chronotropic agents (increase heart rate by 15% versus norepinephrine [47, 48, 84]); vasopressin reduces heart rate by 10% [12]. Levosimendan, a calcium-sensitizing agent, increases heart rate 10% more than norepinephrine [83].

Younger patients often have greater tachycardia during septic shock and greater tachycardia limits diastolic filling time and stoke volume. Esmolol infusion decreased heart rate (by 30%), fluid balance, lactate, and mortality, and improved renal function in one small ($n=154$) proof-of-principle RCT [85]. Despite a positive meta-analysis of esmolol [86], esmolol requires a pivotal RCT to better define patient selection, safety, and efficacy.

Cardiogenic shock and vasodilatory shock post-cardiovascular surgery (CVS)

Norepinephrine is recommended first in cardiogenic shock post-cardiovascular surgery, a minority of whom develop vasodilatory shock characterized by hypotension and low systemic vascular resistance [41]. Vasodilatory shock post-cardiovascular surgery, is more commn in patients on beta-blockers or angiotensin-converting enzyme inhibitors prior to surgery. If hypotension persists after adequate volume resuscitation, then norepinephrine is added, usually increasing MAP with no renal function impairment [87]. Targeting a higher MAP (70–80 mmHg versus 40–50 mmHg) during cardiopulmonary bypass by infusing higher doses of norepinephrine did not decrease the incidence of cerebral infarction in a well-conducted RCT [88].

There is a relative vasopressin deficiency post-cardiovascular surgery and benefits of vasopressin infusion. However, prior trials of vasopressin versus norepinephrine post-cardiovascular surgery were under-powered [89–94]. In a recent single center concealed norepinephrine-controlled RCT (VANCS $n=300$) in Brazil in vasodilatory shock post-cardiovascular surgery [41], vasopressin decreased the primary endpoint (mortality or severe complications), sparing norepinephrine, while shortening ICU stay, and decreasing rates of atrial fibrillation, acute kidney injury, and RRT. There was no difference in 28-day mortality.

Vasopressin was beneficial in post-cardiovascular surgery vasodilatory shock [95] but not in septic shock [15, 71] perhaps because the primary outcomes differed: "mortality and severe complications" [41] versus 28-day mortality [71]. Mortality rates were high (15.9 and 15.4% at 28-days norepinephrine vs. vasopressin) in VANCS [95] but were not reported in prior vasopressin RCTs in vasodilatory shock post-cardiovascular surgery [89, 91, 92, 94].

Cardiogenic shock and vasodilatory shock post-acute myocardial infarction (AMI)

Norepinephrine is also recommended first in cardiogenic shock post-AMI international guidelines [96, 97] because a recent RCT found that epinephrine led to more frequent refractory shock than norepinephrine in pure cardiogenic shock post-AMI [98]. Hypotension and low systemic vascular resistance characterize vasodilatory shock post-AMI. Dopamine is *not* recommended in cardiogenic shock because of its greater chronotropic effects than norepinephrine [48].

Hypovolemic and hemorrhagic shock

Vasopressors are recommended in life-threatening hemorrhagic shock if MAP and perfusion cannot be maintained by fluid resuscitation [99]. European trauma guidelines recommend permissive hypotension (MAP 50–60 mmHg) and restricted volume infusion until major hemorrhage is controlled [100] and vasopressors for life-threatening hypotension if fluids do not achieve target MAP (grade 1C) [100]. Vasopressors may limit fluid overload, cerebral edema, and ARDS in hemorrhagic shock. In a small ($n=78$) blinded RCT in trauma, vasopressin was associated with lower fluid balance and nominally lower mortality (13% versus 25%, $p=0.19$).

Questions and future directions for research

Clinically relevant questions regarding today's vasopressor use in shock include is whether use of several vasopressors that bind complementary receptors safer and more effective than a single vasopressor, how to predict responders by use of biomarkers, when and how to de-resuscitate, how to select patients for inotropic therapy, and who to select for β1-blockade. Future research should also focus on discovery and validation of biomarkers that predict response to vasopressors. The de-resuscitation phase to limit cumulative vasopressor toxicity deserves emphasis [101].

Conclusions and recommendations

Vasopressors bind to specific receptors inducing vasoconstriction but commonly have adverse effects. In practice, we recommend norepinephrine as first choice vasopressor in septic and vasodilatory shock after adequate volume resuscitation. In norepinephrine-refractory patients, vasopressin or epinephrine may be added. Angiotensin II may be useful for early resuscitation of profoundly hypotensive patients. Vasopressors may decrease ventricular contractility, so an inotropic agent (dobutamine > milrinone) may be added. Esmolol may be useful in selected

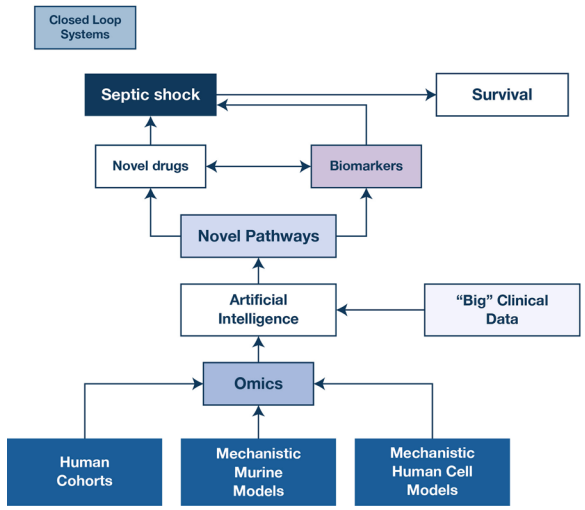

Fig. 4 A paradigm shift in research combining complementary biological and computational methods will be needed to continue to increase survival of septic and other types of shock. Human cohorts, mechanistic murine models and mechanistic human cell models will be used to measure and validate multi-omics (genomics, proteomics, metabolomics, lipidomics) that will be combined with "big" clinical data in artificial intelligence systems for discovery of novel pathways of septic and other forms of shock. These novel pathways will be scrutinized to discover novel vasopressors and predictive biomarkers for treatment of septic and other forms of shock. Closed loop systems will also be optimized to monitor tissue oxygenation during and after resuscitation. The combination of personalized medicine, artificial intelligence, "big data", closed loop systems and novel vasopressors could facilitate more effective vasopressor use increasing survival

young patients with marked tachycardia. Furthermore, personalized medicine using omics-derived predictive biomarkers, artificial intelligence derived from "big data", closed loop systems that monitor tissue oxygenation and novel vasopressors could facilitate more effective vasopressor use increasing survival (Fig. 4).

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05801-z) contains supplementary material, which is available to authorized users.

Compliance with ethical standards

Conflicts of interest

Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell was a founder, Director and shareholder in Cyon Therapeutics Inc. Dr. Russell is a shareholder in Molecular You Corp.Dr. Russell reports receiving consulting fees in the past 3 years from: (1) Asahi Kesai Pharmaceuticals of America (AKPA) (developing recombinant thrombomodulin in sepsis). (2) SIB Therapeutics LLC (developing a sepsis drug). (3) Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin). No longer actively consulting for the following: (4) La Jolla Pharmaceuticals (developing angiotensin II; Dr. Russell chaired the DSMB of a trial of angiotensin II from 2015 to 2017)—no longer actively consulting. (5) Grifols (sells albumin)—no longer actively consulting. PAR Pharma (sells prepared bags of vasopressin)—no longer actively consulting.Dr. Russell reports having received an investigator-initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that was provided to and administered by UBC.

Publisher's Note

Received: 19 July 2019 Accepted: 24 September 2019

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