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Management of Refractory Vasodilatory Shock

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Refractory shock is a lethal manifestation of cardiovascular failure defined by an inadequate hemodynamic response to high doses of vasopressor medications. Approximately 7% of critically ill patients will develop refractory shock, with short-term mortality exceeding 50%. Refractory vasodilatory shock develops from uncontrolled vasodilation and vascular hyporesponsiveness to endogenous vasoconstrictors, causing failure of physiologic vasoregulatory mechanisms. Standard approaches to the initial management of shock include fluid resuscitation and initiation of norepinephrine. When these measures are inadequate to restore BP, vasopressin or epinephrine can be added. Few randomized studies exist to guide clinical management and hemodynamic stabilization in patients who do not respond to this standard approach. Adjunctive therapies, such as hydrocortisone, thiamine, and ascorbic acid, may increase BP in severe shock and should be considered when combination vasopressor therapy is needed. Novel vasopressor agents, such as synthetic human angiotensin II, can increase BP and reduce the need for high doses of catecholamine vasopressors in severe or refractory vasodilatory shock. Few effective rescue therapies exist for established refractory shock, which emphasizes the importance of aggressive intervention before refractory shock develops, including the earlier initiation of rational combination vasopressor therapy. The present review discusses the diagnosis and management of refractory shock to offer guidance for management of this important clinical problem and to provide a framework for future research.

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Circulatory shock is the most serious manifestation of cardiovascular failure encountered in critically ill patients and is characterized by hypotension and tissue hypoperfusion that can lead to inadequate cellular oxygen utilization and organ failure.[1] Management of shock involves correcting the triggering cause and restoring adequate organ perfusion by using fluid resuscitation and vasoactive medications, as necessary.[1] Circulatory shock develops in approximately 33% of critically ill patients worldwide.[2,3] Vasodilatory or distributive shock is the most common form of shock and will typically

ABBREVIATIONS: iNOS = inducible nitric oxide synthase; MAP = mean arterial pressure; NO = nitric oxide; NOS = nitric oxide synthase; RCT = randomized controlled trial

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require the use of vasopressor agents to restore adequate vascular tone.[1,4] Despite recent advances in therapy, the mortality of patients with shock remains as high as 30% to 50%, mainly due to multiorgan failure.[4-10]

The vasopressor dose required to maintain adequate mean arterial pressure (MAP) is one of the strongest predictors of short-term mortality in critically ill patients.[11-14] High doses of catecholamine vasopressors can produce a variety of adverse effects, contributing to morbidity and mortality.[15,16] The increased mortality in patients with higher vasopressor requirements reflects both a greater severity of underlying illness and potentially harmful effects of vasopressor drugs.[12,16,17] Adverse events are common during catecholamine therapy for shock, leading some authors to propose that high catecholamine doses are directly toxic to various tissues and organs. This theory may be supported by evidence suggesting a possible beneficial effect of β-blockade in patients with sepsis.[18] In addition, the use of higher vasopressor doses to achieve a higher MAP goal in patients with sepsis was associated with increased rates of cardiovascular adverse effects, although not with increased mortality.[19]

Refractory Shock Definition

There is no universal consensus definition of refractory shock. Proposed definitions include failure to achieve a BP goal despite vasopressor therapy, need for rescue vasopressor therapy, or need for high vasopressor doses.[20-23] Conventional methods of comparing total vasopressor dose among patients include conversion to norepinephrine equivalents (Table 1) or use of one of several previously published scores.[4-6,8,10,12,13,23-27] The recent Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) clinical trial used a norepinephrine-equivalent dose > 0.2 μg/kg/min to define refractory shock and reported worse outcomes in patients requiring ≥ 0.5 μg/kg/min of norepinephrine equivalents at baseline.[24,26] Norepinephrine-equivalent doses of 0.5 μg/kg/min or 1 μg/kg/min have been proposed as thresholds to define high-dose vasopressor therapy and refractory shock.[20-23] On the basis of these observations, a reasonable definition of refractory shock would be an inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 μg/kg/min norepinephrine-equivalent dose).[20] Observational studies suggest that, using this definition, 6% to 7% of critically ill patients may develop refractory shock.[21,28] Mortality rates in patients with refractory shock greatly depend on the definition used (e-Tables 1 and 2), with hospital mortality rates generally exceeding 50%.[21-24,28-31] There is no consistent relationship between norepinephrine-equivalent dose and short-term mortality in patients with refractory shock, implying that outcomes are poor once a refractory shock state develops independent of vasopressor dose.

TABLE 1] Converting Vasopressor Doses to Norepinephrine Equivalents[4-6,8,10,12,23,24,26,27]

Drug	Dose	Norepinephrine Equivalent
Epinephrine	0.1 μg/kg/min	0.1 μg/kg/min
Dopamine	15 μg/kg/min	0.1 μg/kg/min
Norepinephrine	0.1 μg/kg/min	0.1 μg/kg/min
Phenylephrine	1 μg /kg/min	0.1 μg/kg/min
Vasopressin	0.04 U/min	0.1 μg/kg/min

Pathophysiology of Refractory Shock

A central pathophysiologic feature of refractory shock is the impairment of vascular response to catecholamine stimulation (Fig 1).[20] Reduced catecholamine responsiveness and uncontrolled pathologic vasodilation (vasoplegia) can occur because of changes in receptor signaling, metabolic derangements, and depletion of endogenous vasoactive hormones. Inappropriate vasodilation typically occurs from the effects of inducible nitric oxide synthase (iNOS), which produces excessive amounts of vasodilatory nitric oxide (NO). NO increases vascular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate to trigger vasodilation.[32,33] Activation of adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells prevents calcium entry required for vasoconstriction, representing a final common pathway linking metabolic derangements (tissue hypoxia and acidosis) and inflammation (including NO production) with vasoplegia.[20,32] Absolute or relative deficiencies of endogenous vasoactive hormones, such as cortisol, vasopressin, and angiotensin II, can develop in shock states, further decreasing vasopressor responsiveness.[34-36] Not all vascular beds are dilated in shock, and microcirculatory defects that create low- or no-flow zones are surrounded by areas of profound vasodilation and rapid flow, leading to inadequate tissue oxygen delivery.[37] The combination of pathologic vasodilation with vasoconstriction from vasopressor drugs produces heterogeneous effects on different

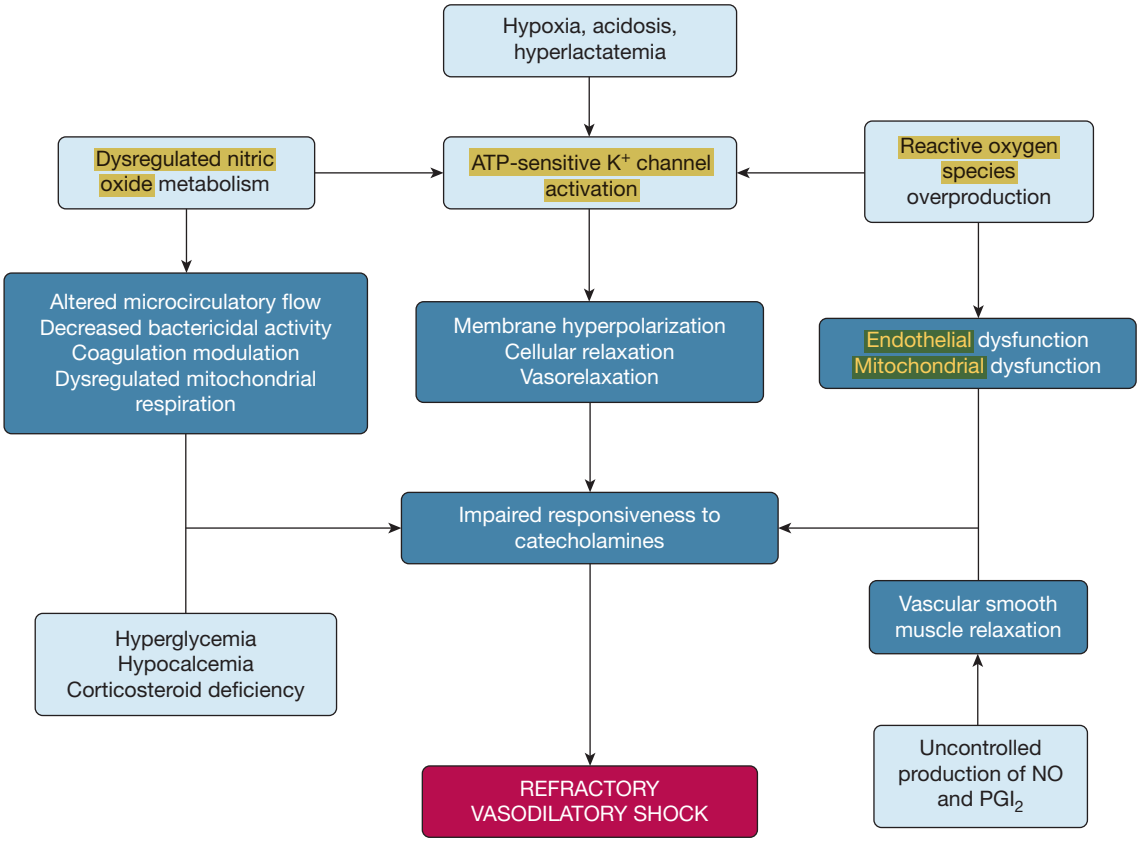

Figure 1 – *Pathophysiologic mechanisms contributing to refractory vasodilatory shock. Light blue represents initial physiologic insults, dark blue represents shared pathophysiologic mechanisms, and red represents the end result. ATP = adenosine 5′-triphosphate; NO = nitric oxide; PGI_2 = prostacyclin.*

vascular beds, leading to maldistribution of blood flow despite acceptable systemic hemodynamic parameters.[38,39]

Evaluation of Refractory Shock

The first step in the evaluation of refractory shock is to exclude factitious BP measurements and identify the primary cause and reversible secondary contributors, such as hypovolemia, uncontrolled vasodilation, pump failure, or obstructive shock (Fig 2). Bedside diagnostic testing for patients with refractory shock may include a combination of hemodynamic, laboratory, and imaging parameters. Empiric broad-spectrum antibiotics are often considered until sepsis can be excluded.[40] An objective assessment of cardiac output is critical to help guide clinical management, including surrogate measures such as Doppler-derived estimates, minimally invasive pulse-contour analysis, and central venous oxygen saturation.[41] Low cardiac output or central or mixed venous oxygen saturation requires further testing to differentiate into hypovolemic, cardiogenic, or obstructive shock. Elevated central or mixed venous oxygen saturation levels and high cardiac output typically indicate vasodilatory shock. Despite lack of evidence supporting a survival benefit in critically ill patients, a pulmonary artery catheter can be considered when the hemodynamic state remains uncertain despite other testing.[41,42]

Patients with inadequate cardiac output should be assessed for fluid responsiveness, and objective measures of fluid responsiveness should be used to guide resuscitation. Measures of fluid responsiveness frequently require patients to undergo mechanical ventilation at 8 to 10 mL/kg ideal body weight and be in sinus rhythm, which might not always be possible. A controlled fluid challenge can be considered in the absence of fluid overload, particularly when measures of fluid responsiveness are indeterminate.[40,43] After addressing contributing causes and fluid responsiveness, initiation and optimization of vasopressor therapy should be considered (Fig 3).[12,20]

Vasopressor Therapy in Refractory Shock

When adequate MAP > 65 mm Hg cannot be established with other measures, vasopressor therapy

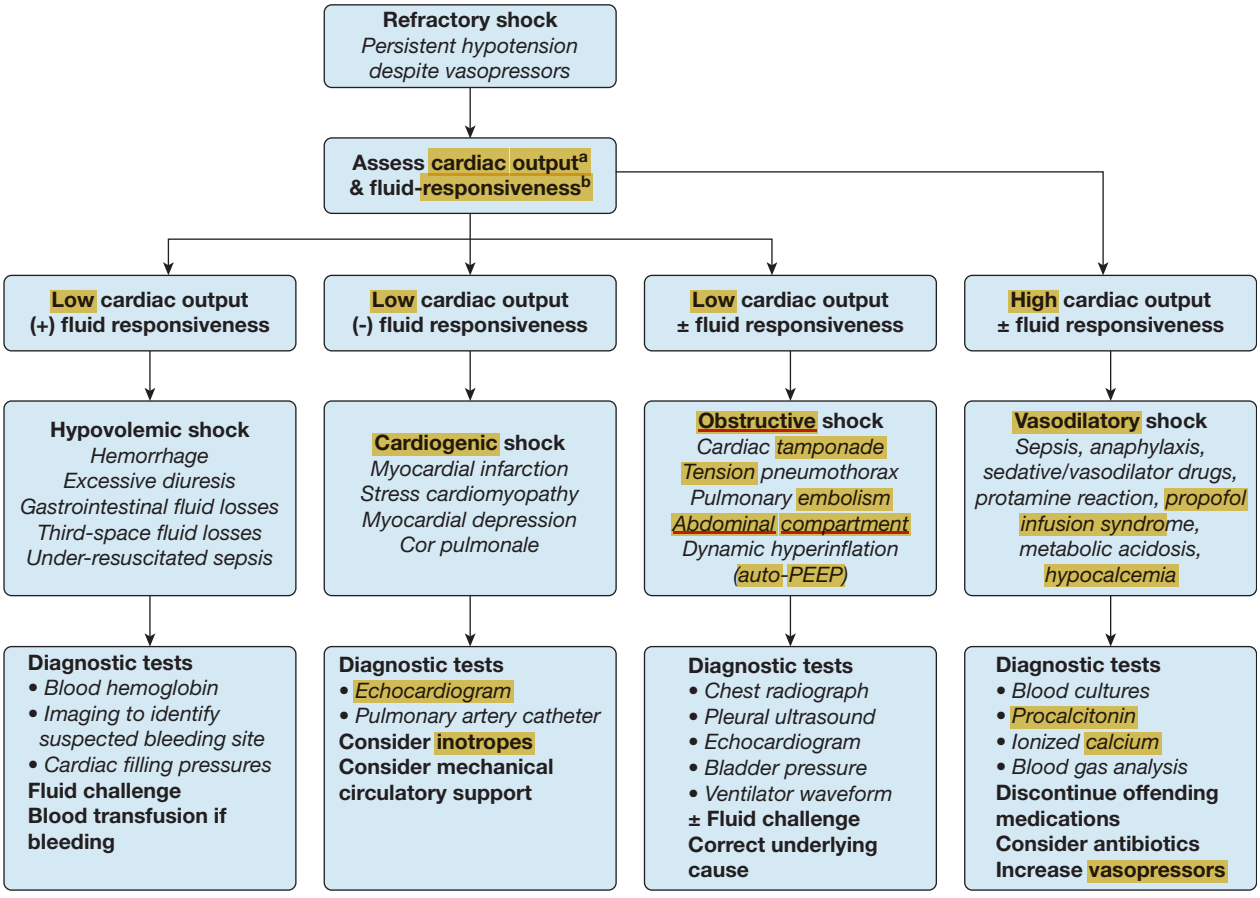

Figure 2 – *Suggested diagnostic approach for identifying reversible contributors to refractory shock, based on assessment of cardiac output and fluid responsiveness.* [a]*Measurement of central or mixed venous oxygen saturation can be used as a surrogate for cardiac output in many patients.* [b]*Measures of fluid responsiveness can include respiratory pulse-pressure or stroke volume variation and passive straight-leg raise. PEEP = positive end-expiratory pressure.*

should be initiated. Because untreated or persistent hypotension is an important driver of organ dysfunction, restoring and maintaining an adequate MAP is a central goal of therapy in refractory shock. A MAP goal > 65 mm Hg seems adequate for most patients, although patients with preexisting hypertension may have a lower risk of kidney injury if a higher MAP goal is used.[19,44] Despite multiple, large randomized controlled trials (RCTs), no vasopressor has been conclusively shown to be superior as first-line therapy for vasodilatory shock, and no other vasopressor has been found to be superior to norepinephrine for prevention of death.[4-6,8] Norepinephrine has been compared with either dopamine or epinephrine in large RCTs, showing similar or improved clinical outcomes and fewer arrhythmias.[4,6,8,45] Small RCTs have compared norepinephrine and phenylephrine but were underpowered for mortality.[12] Vasopressin has been studied in large RCTs as either an alternative or adjunct to norepinephrine, without evidence of a mortality benefit.[4,10,46,47] The consensus view is that norepinephrine should be the recommended first-line vasopressor for most critically ill patients in whom vascular tone needs to be increased.[1,12,40] The maximum effective dose of norepinephrine remains uncertain, but vasopressor responsiveness seems to decline at norepinephrine doses > 0.5 μg/kg/min.[12,20,24] All vasopressor agents display a log-linear dose response curve with decreasing incremental effectiveness at higher doses and likely a greater potential for toxicity.[12] Increasing the norepinephrine dose to very high levels (ie, > 4 μg/kg/min) can increase vascular tone and MAP in selected patients, although the potential toxicity of this approach remains a concern.[48]

The use of moderate doses of multiple vasopressors with complementary mechanisms of action may avoid the toxicity associated with high doses of a single agent, and we advocate for earlier use of rational combination vasopressor therapy for severe shock.[35] On the basis of

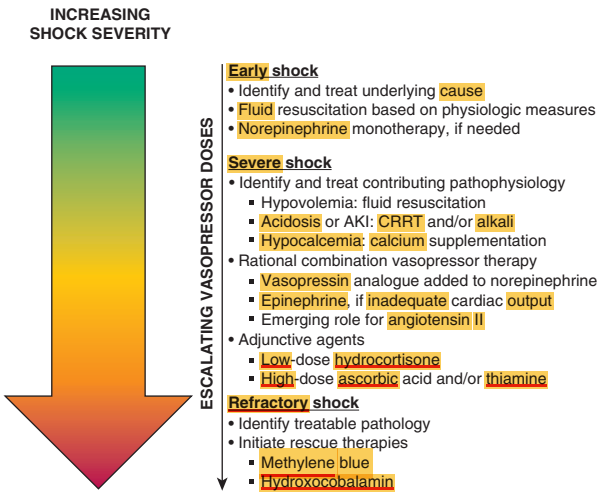

Figure 3 – *Suggested treatment algorithm for management of vasodilatory shock.*[20,24] *AKI = acute kidney injury; CRRT = continuous renal replacement therapy.*

supporting meta-analyses of RCTs, the Surviving Sepsis Campaign guidelines recommend the addition of vasopressin (moderate-quality evidence) or epinephrine (low-quality evidence) for patients with inadequate response to catecholamine therapy; no studies directly compare these drugs as second-line vasopressors.[40] Epinephrine produces substantial β-adrenergic stimulation that can obviate the need for additional inotropic drugs when cardiac output is inadequate.[6] Dopamine and phenylephrine are weak vasopressors and are typically not effective in severe or refractory shock; dopamine is associated with an increased rate of cardiac arrhythmias and may worsen outcomes in cardiogenic shock.[12,40,45]

Clinical end points for hemodynamic support may include adequate urine output, lactate clearance, or central/mixed venous oxygen saturation.[40] There is no added advantage to targeting a supranormal cardiac output in patients with vasodilation. Excessive β-adrenergic stimulation by high-dose catecholamines may produce myocardial toxicity and other adverse effects, although data supporting the superiority of catecholamine-sparing vasopressors are limited.[15,49] Epinephrine is known to exacerbate hyperglycemia and lactic acidosis, and predisposes to arrhythmias.[6,8] Early initiation of combination vasopressor therapy before the onset of refractory shock is expected to yield better outcomes,[5] as was shown with vasopressin (Fig 3).

Vasopressin has been studied as a therapeutic agent for the management of refractory vasodilatory shock.[36] Hypothalamic-pituitary stores of vasopressin can become depleted during shock, leading to relative or absolute vasopressin deficiency and pathologic vasodilation that can be reversed by vasopressin supplementation at physiologic doses (0.03-0.04 U/min).[36] Vasopressin effectively increases vascular tone and does not exacerbate tachycardia or arrhythmias but can reduce cardiac output.[12,50] Vasopressin may have a role in maintaining vascular tone during acidemic conditions that reduce vascular responsiveness to catecholamines.[36] Vasopressin has been shown in multiple studies to increase MAP and decrease catecholamine requirements, but it has not shown definitive benefits on mortality and adverse events.[22,29-31,36] The large, multicenter Vasopressin and Septic Shock Trial (VASST) examined the use of low-dose (0.03 U/min) vasopressin or norepinephrine added to baseline catecholamine therapy in patients with septic shock and found no difference in mortality.[5] Decreased mortality was observed with vasopressin in patients with less severe shock (baseline norepinephrine requirements < 15 μg/min), but patients with higher norepinephrine requirements and those requiring multiple vasopressors reported no mortality benefit from the addition of vasopressin.[5,51] Patients receiving both vasopressin and corticosteroid therapy seemed to have the lowest mortality rates in VASST, suggesting the possibility of synergy between these agents.[51] Recent meta-analyses have yielded conflicting results regarding whether vasopressin or other noncatecholamine vasopressors may reduce mortality in vasodilatory shock.[46,47,49] The totality of the evidence suggests that vasopressin is a safe and effective adjunctive vasopressor in patients with shock who are receiving catecholamines. The recent Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock (VANISH) study, which compared norepinephrine with vasopressin (titrated up to 0.06 U/min) in early septic shock, did not report any significant differences in mortality or adverse events, implying that higher vasopressin doses can be used safely in selected patients.[10] Studies comparing low-dose (0.03 U/min or 2.0 U/h) with high-dose (0.06 U/min or 4.0 U/h) vasopressin for refractory shock reported greater hemodynamic effects with the higher dose.[29-31] Use of vasopressin doses > 0.04 U/min can result in an increase in levels of hepatic transaminases and bilirubin.[22] However, these studies were underpowered to show significant differences in mortality or adverse effects and should therefore be interpreted with caution.

Rescue Therapies for Refractory Shock

Table 2 summarizes the various rescue treatment options for refractory shock. Despite favorable hemodynamic effects, none of these therapies has been conclusively shown to reduce mortality of patients after the onset of refractory shock, nor has any agent proven superior in a large RCT. Outcomes of patients with established refractory shock are poor despite the use of these rescue therapies, arguing in favor of earlier initiation of better-studied and safe therapies, such as combination vasopressor therapy and glucocorticoid supplementation.

Glucocorticoid Therapy

Glucocorticoid therapy for the treatment of shock remains controversial, with conflicting evidence regarding a mortality benefit but clear evidence supporting improved shock reversal. Glucocorticoid receptors augment vascular α-adrenergic responsiveness and reduce inflammation-mediated vasodilation. Patients with shock may develop relative or functional adrenal insufficiency, which could contribute to refractory vasodilation.[34] Clinical trials of corticosteroid supplementation in critically ill patients have shown that low doses of hydrocortisone (200-300 mg/d) can reduce vasopressor requirements and duration of vasopressor support, independent of standard measures of adrenal gland function.[7,9,34] Despite clear evidence supporting the ability of glucocorticoid therapy to increase MAP, the effects of low-dose hydrocortisone supplementation on mortality remain uncertain. Low-dose hydrocortisone may reduce mortality of patients with sepsis and vasopressor-dependent shock and multiorgan failure.[7] Less severely ill patients do not seem to have a mortality benefit from glucocorticoid therapy; therefore, glucocorticoid therapy may not have a role for patients with adequate MAP after fluid resuscitation and moderate doses of vasopressors.[9] The optimal timing of hydrocortisone initiation remains uncertain, but hydrocortisone therapy should be considered for patients requiring multiple vasopressors (Fig 3).[40] A synergistic benefit has been reported from the combination of hydrocortisone and vasopressin.[51,52] The recommended dosage of hydrocortisone for refractory shock is 100 mg every 8 h or 50 mg every 6 h, without the need for fludrocortisone.[34,40]

TABLE 2] Potential Rescue Therapies for Refractory Shock

Therapy	Dose	Mechanism of Action	Adverse Effects
Hydrocortisone	Bolus: 50 mg every 6 h or 100 mg every 8 h Infusion: 10 mg/h	Increased vascular catecholamine response	Secondary infection Hyperglycemia Hypernatremia
Calcium chloride	Bolus: 1-2 g Infusion: 20-50 mg/kg/h	Increased vascular calcium signaling	Hypercalcemia Inhibition of β-adrenergic effects
Sodium bicarbonate	1-2 mEq/kg	Reversal of metabolic acidosis	Hypernatremia Ionized hypocalcemia Respiratory acidosis
THAM	9 mL/kg (324 mg/kg or 2.7 mEq/kg) up to 500 mg/kg/dose over 60 min	Reversal of metabolic acidosis	Hyperkalemia Fluid overload
Methylene blue	Bolus: 1-2 mg/kg every 4-6 h Infusion: 0.25-1 mg/kg/h	Inhibition of NOS	Serotonin syndrome Hypoxia Pulmonary hypertension
Hydroxocobalamin	5 g	Scavenging of NO	Interference with hemodialysis sensors
Ascorbic acid	25 mg/kg every 6 h or 1.5 g every 6 h	Increased catecholamine and vasopressin synthesis	Minimal
Thiamine	200 mg every 12 h	Improved lactate clearance	Minimal
Terlipressin (not available in the United States)	Bolus: 1 mg every 6 h Infusion: 1.3 μg/kg/h	Activation of vasopressin-V_{1a} receptors	Reduced cardiac output Increased pulmonary vascular resistance
Angiotensin II	Starting: 2-10 ng/kg/min Maximum: 20-40 ng/kg/min	Angiotensin II receptor activation	Hypertension Metabolic alkalosis

NO = nitric oxide; NOS = nitric oxide synthase; THAM = tris-hydroxymethyl-aminomethane (tromethamine).

Correction of Acidemia

Although metabolic abnormalities are often associated with refractory shock and vasopressor hyporesponsiveness, correction of metabolic abnormalities has never been shown to improve clinical outcomes in patients with shock.[53,54] Metabolic (lactic) acidosis is a major contributor to vascular hyporesponsiveness to catecholamine vasopressors.[32,55] Tissue hypoperfusion and mitochondrial dysfunction from shock contribute to lactic acidosis, and systemic acidemia leads to worsening tissue perfusion, triggering a vicious cycle of organ dysfunction.[55] Vasopressor responsiveness declines markedly when arterial pH is < 7.15 due to impaired catecholamine signaling.[54] Sodium bicarbonate can be used to reverse acidosis, although increases in MAP after administration of hypertonic sodium bicarbonate may be due to volume expansion and not related to acid-base effects.[56] Administration of sodium bicarbonate can produce harmful effects such as intracellular acidosis, respiratory acidosis, ionized hypocalcemia, hypernatremia, myocardial depression, and increased serum lactate levels.[54,55] Tris-hydroxymethyl-aminomethane (tromethamine) is a synthetic nonbicarbonate buffer that can be used as an alternative to sodium bicarbonate, although information regarding its efficacy and safety is scarce.[55] Use of alkali therapy requires administration of a substantial volume of IV fluid and is at best a temporizing measure.

Renal Replacement Therapy

Acute kidney injury associated with severe shock may limit clearance of acidemia. Continuous renal replacement therapy can correct metabolic derangements and improve vasopressor responsiveness in selected patients with acute kidney injury.[57] A shorter duration between vasopressor initiation and initiation of continuous renal replacement therapy may be associated with improved outcomes in patients with septic shock who have severe acute kidney injury.[58] Observational studies of high-volume hemofiltration to clear metabolic toxins and inflammatory mediators in patients with septic shock and acute kidney injury have shown favorable effects on hemodynamic variables but not on mortality.[59,60] Vasopressor requirements are reduced and microcirculatory parameters improved with hemofiltration in some patients, an effect more pronounced with higher volume hemofiltration.

Calcium

Contraction of cardiac and vascular smooth muscle is mediated by intracellular calcium signaling, making calcium essential for cardiovascular function. Hypocalcemia is commonly observed in critically ill patients, with causes that include chelation of calcium by citrate in transfused blood products, saponification of the necrotic tissues, acquired parathyroid gland insufficiency, renal 1α-hydroxylase insufficiency, vitamin D deficiency, and acquired calcitriol resistance.[61] Severe hypocalcemia can depress cardiovascular function and produce hypotension.[53,62] Bolus administration of calcium chloride increases MAP by increasing vascular tone without augmenting cardiac output but may potentially blunt cardiac β-adrenergic responses.[63] No evidence suggests that calcium administration improves patient-centered outcomes, and cellular calcium overload is potentially harmful in sepsis and shock.[53,64,65] Studies have suggested that patients taking calcium channel blockers who develop sepsis may have a lower risk of adverse outcomes, arguing against use of high-dose calcium in these patients.[64,65]

NO Inhibitors

Unregulated NO overproduction by iNOS is an important contributor to vasodilatory shock, and excessive NO may have harmful secondary effects on mitochondrial and organ function.[32] There has been substantial interest in drugs that inhibit iNOS to improve hemodynamic parameters and reverse vasodilatory shock. L-N^G-monomethyl-arginine (tilarginine) is a nonselective nitric oxide synthase (NOS) inhibitor that has been studied in patients with shock.[66-68] In patients with sepsis, NOS inhibitors were shown to increase vascular tone and MAP, leading to vasopressor withdrawal or dose reduction, but were associated with increased mortality. The failure of iNOS inhibitors to improve clinical outcomes despite a favorable hemodynamic effect casts doubt on the mortality effects of other rescue agents affecting NO signaling for refractory shock. Increased mortality with NOS inhibitors may be explained in part by the various beneficial physiologic effects of NO signaling that are lost with nonselective inhibition of NOS, including maintenance of microvascular and endothelial function and immunomodulatory effects.[32] NOS inhibitors represent an important example of a therapy that is associated with higher mortality despite increasing MAP. Hence, clinical outcome studies are needed before these drugs should be applied routinely in refractory septic shock.

Methylene blue, a water-soluble dye that inhibits NOS and soluble guanylate cyclase, has been evaluated for

refractory vasodilatory shock, particularly after cardiac surgery.[33] Methylene blue seems to reverse vasodilation caused by excessive NO signaling and may be effective for increasing vascular tone in septic shock or for preventing vasoplegia after cardiac surgery.[69,70] Methylene blue may inhibit monoamine oxidase, potentially causing serotonin syndrome via drug-drug interactions,[71] and its effect is short, requiring repeated dosing or continuous infusion.[33,70] However, methylene blue can increase pulmonary vascular resistance and worsen oxygenation in some patients.[33]

Hydroxocobalamin (Cyanokit; Meridian Medical Technologies), a vitamin B_{12} precursor used clinically to reverse cyanide toxicity, acts as an NO scavenger that can reverse NO-mediated vasodilation. Clinical experience with this agent for off-label use in refractory shock is limited, but it has been shown to effectively reverse refractory vasodilation in selected patients.[72] Hydroxocobalamin remains in the bloodstream and urine for days or weeks following administration and can interfere with proper functioning of heme sensors on hemodialysis machines; it should therefore be used with caution in patients with acute kidney injury.[73]

Vitamin Deficiency and Repletion

Endogenous norepinephrine and vasopressin synthesis are governed by enzymes requiring ascorbic acid (vitamin C) as a necessary cofactor.[74,75] Absolute or relative vitamin C deficiency in critically ill patients may contribute to shock by reducing the availability of these endogenous vasopressors. Administration of high-dose, IV ascorbic acid (25 mg/kg or 1.5 g every 6 h) may improve inflammation, hemodynamic variables, and organ function in critically ill patients, even without documented vitamin C deficiency. Thiamine (vitamin B_1) is an essential cofactor in oxidative energy metabolism, specifically lactate metabolism, and thiamine deficiency can cause cardiovascular compromise and exacerbate lactic acidosis.[76] In a pilot study of patients with septic shock, administration of IV thiamine, 200 mg twice daily, failed to improve lactic acid clearance or shock reversal; however, in the predefined subgroup of patients with thiamine deficiency, there was a suggestion of improved lactate clearance and lower mortality with thiamine supplementation. In an observational study of patients with septic shock, a protocol combining hydrocortisone, high-dose vitamin C, and thiamine was associated with improved shock reversal and decreased severity of organ failure.[75]

Future Therapies for Refractory Shock

Terlipressin is a long-acting vasopressin analogue with partial selectivity for the vasopressin-V_{1a} receptor. Terlipressin can increase MAP and reduce vasopressor requirements in vasodilatory shock; however, it is not currently available in the United States.[77-79] Terlipressin, administered as a bolus, seems to produce a marked reduction in cardiac output that requires substantial doses of inotropic support to counteract.[77] Continuous infusion of terlipressin seems to have similar effectiveness without the same pronounced reduction in cardiac output.[78]

Selepressin is a synthetic selective vasopressin-V_{1a} receptor agonist that may be effective in refractory shock.[80] As with vasopressin, selepressin restores and maintains vascular tone, but it is not associated with the nonvascular adverse effects of vasopressin, such as fluid overload from water retention and thrombosis from von Willebrand factor release. In a randomized, phase 2 pilot study of 53 patients with septic shock, selepressin 2.5 ng/kg/min increased MAP and lowered norepinephrine requirements more effectively than placebo or a lower dose of selepressin and may have had a favorable effect on clinical outcomes. Despite these promising early data, a randomized phase 3 trial of selepressin for septic shock, the Selepressin Evaluation Programme for Sepsis-Induced Shock–Adaptive Clinical Trial (SEPSIS-ACT),[81] was terminated due to futility.

Angiotensin II has been recognized for many years as a potential therapy for refractory shock.[82] Endogenous angiotensin II works with catecholamines and vasopressin to maintain blood pressure, especially in the face of a hypotensive insult. Patients with sepsis may develop a functional angiotensin-converting enzyme or angiotensin II deficiency, leading to refractory shock. IV synthetic human angiotensin II has been evaluated in patients with refractory shock. The Angiotensin II in High-Output Shock (ATHOS) pilot study showed favorable hemodynamic effects of angiotensin II infusion in patients with vasodilatory shock who required high doses of norepinephrine and vasopressin; angiotensin II infusion allowed other vasopressors to be discontinued in many patients.[35] The recently published phase 3 ATHOS-3 trial compared angiotensin II infusion (La Jolla Pharmaceutical Company) with placebo in 321 patients with refractory vasodilatory shock predominantly caused by sepsis, with a median norepinephrine-equivalent dose of 0.34 μg/kg/min.[24] Angiotensin II infusion significantly increased MAP in

70% of patients by 3 h, although patients with a baseline norepinephrine-equivalent dose ≥ 0.5 μg/kg/min were less likely to respond to angiotensin II. Adverse events and short-term mortality were not significantly different for patients receiving angiotensin II. As with vasopressin in VASST, patients with less severe shock in ATHOS-3 who received angiotensin II seemed to have more favorable outcomes.

Conclusions

Refractory shock, defined herein as persistent hypotension despite high-dose vasopressor therapy, is a lethal manifestation of profound cardiovascular failure with multiple potential causes and complex underlying pathophysiology. The standard management strategy includes identification and correction of the underlying cause, administration of fluids based on measurable clinical metrics, and vasopressor support using norepinephrine, which is the current standard of care as a first-line vasopressor. When this approach is inadequate to restore adequate MAP to support organ perfusion, the current standard of care dictates that vasopressin or epinephrine should be added. There is a physiologic rationale for combining lower doses of multiple agents as part of multimodal therapy targeting multiple receptor systems in patients requiring high vasopressor doses (especially > 0.5 μg/kg/min norepinephrine-equivalents), although evidence supporting a mortality benefit is limited. Multimodal therapy may include IV catecholamines, vasopressin analogues, or angiotensin II, as in physiologic BP regulation. In addition, adjunctive agents, such as low-dose hydrocortisone, high-dose thiamine, and ascorbic acid, can be added. Aggressive intervention shortly after the development of severe shock might prevent progression to refractory shock, which has no definitive therapy that has clearly been shown to reduce mortality. The safety and efficacy of rescue therapies such as calcium infusion, alkali therapy (if indicated), and NO antagonists remain uncertain, but these can be used in selected cases. We advocate for earlier use of catecholamine-sparing adjunctive agents in severe shock, with the goal of preventing progression to refractory shock.

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