CHEST

How We Escalate Vasopressor and Corticosteroid Therapy in Patients With Septic Shock

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Septic shock is defined by the need for vasopressor agents to correct hypotension and lactic acidosis resulting from infection, with 30%-40% case fatality rates. The care of patients with worsening septic shock involves multiple treatment decisions involving vasopressor choices and adjunctive treatments. In this edition of "How I Do It", we provide a case-based discussion of common clinical decisions regarding choice of first-line vasopressor, BP targets, route of vasopressor delivery, use of secondary vasopressors, and adjunctive medications. We also consider diagnostic approaches, treatment, and monitoring strategies for the patient with worsening shock, as well as approaches to difficult weaning of vasopressors.

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Case Example, Part 1

A 65-year-old woman with atrial fibrillation sought treatment at the ED with fever and dysuria. Initial BP was 75/40 mm Hg (mean arterial pressure [MAP], 52 mm Hg), heart rate was 95 beats/min, and oxygen saturation was 92% on room air. Extremities were warm and well perfused. She received Ringer's lactate until she was no longer volume responsive by multiple measures and received antibiotics for community-acquired urosepsis. She remained hypotensive with a BP of 82/45 mm Hg (MAP, 57 mm Hg). Serum lactate was 2.5 g/L. Point-of-care echocardiography showed mildly reduced biventricular function and grade 1 diastolic dysfunction (unchanged from prior assessment). The ICU team was called for assistance, including to initiate vasopressor therapy. After discussion with the patient to determine if vasopressor therapy aligned with her goals, norepinephrine was started using a peripheral IV catheter and the patient was transferred to the ICU.

Are There Exceptions to First-Line Norepinephrine?

We rarely start an alternative vasopressor to norepinephrine as first-line therapy in septic shock. Among patients at risk for, or who have, atrial fibrillation or other supraventricular

ABBREVIATIONS: CRRT = continuous renal replacement therapy; CVC = central venous catheter; MAP = mean arterial pressure

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arrhythmias and who are expected to tolerate rapid ventricular response poorly (eg, those with poor cardiac reserve), we consider vasopressin or phenylephrine instead of norepinephrine as the initial vasopressor.

For more than a decade, guidelines have recommended norepinephrine as the first-line vasopressor in septic shock based on randomized clinical trials comparing norepinephrine (a primarily α_1 agonist with additional β_1 agonist) with other vasopressors with different mechanisms such as vasopressin, phenylephrine, dopamine, and epinephrine.[1] Although one randomized study found lower risk of arrhythmia with norepinephrine compared with dopamine,[2] other randomized studies have not shown a difference in mortality or other patient-centered outcomes when comparing norepinephrine with alternative vasopressors outside of dopamine. Guidelines thus grade for superiority of norepinephrine as high only when compared with dopamine.[1] Although generally we initiate first-line norepinephrine, we occasionally consider agents without β_1 agonist (vasopressin or phenylephrine) when adrenergic-related side effects of norepinephrine are expected to—or seem to—lead to clinical decompensation (eg, rapid ventricular rate resulting from atrial fibrillation), based on quasiexperimental observational evidence that initiation of phenylephrine leads to modestly improved heart rate control compared with norepinephrine[3] among patients with sepsis and atrial fibrillation.

After Norepinephrine Is Started, What MAP Should Be Targeted?

We target an MAP of 60 to 65 mm Hg in most patients with septic shock. The history of targeting MAP of 65 mm Hg is based on evidence that cerebral autoregulation generally begins to drop precipitously less than a MAP of 60 mm Hg. Recent trials have clarified that MAP targets of > 65 mm Hg during shock potentially are harmful, with increased risk of supraventricular tachycardia and potentially death.[4,5] The "65 Trial" randomized patients 65 years of age or older with vasodilatory shock to a MAP target of 60 to 65 mm Hg or usual care and found no difference in 90-day all-cause mortality and a possible signal for reduced mortality with the lower MAP target after adjustment for prespecified baseline variables.[6]

When Should a Central Venous Catheter Be Placed for Vasopressor Delivery?

For patients initiated on low-dose norepinephrine (eg, < 15 μg/min or < 0.3 μg/kg/min), we typically start norepinephrine infusion via peripheral IV catheters and then assess whether another catheter type may be necessary. In patients expected to require norepinephrine for > 24 to 48 h, but who otherwise are hemodynamically stable and require low doses of norepinephrine, we typically switch to infusion via a midline catheter based on local institutional expertise and experience. In patients who persistently are unstable or require higher norepinephrine doses, additional vasopressors, or additional ports for other infusions, we rapidly transition to infusion via central venous catheter (CVC).

Concern over vasopressor extravasation with subsequent tissue injury historically has limited infusion of vasopressors to CVCs. However, recent evidence suggests that delivery of vasopressors via peripheral lines has < 5% risk of extravasation when used for < 72 h,[7,8] with no reported incidents of tissue necrosis or limb ischemia in a systematic review that included seven studies with 1,382 patients.[7] Additionally, vasopressor administration via peripheral vein may decrease time to vasopressor therapy compared with infusion via CVC.[9] These data have led to a weak recommendation in the Surviving Sepsis Campaign guidelines to start vasopressors peripherally to restore MAP rather than delaying initiation until a CVC is placed.[1]

When Should We Consider Adding a Second Vasopressor?

We start a second vasopressor for patients with septic shock and increasing vasopressor requirements, generally as doses of norepinephrine approach 15 μg/min (or 0.3 μg/kg/min), a practice that generally aligns with Surviving Sepsis Campaign guidelines and current evidence from trials. When perfusion goals are not met with moderate doses of the initial vasopressor, the decision to add another vasopressor or increase the current agent must take into consideration expected benefits (improved cardiac output, BP, perfusion) and risks (increased risk of arrhythmia, digital ischemia) of each approach. Little direct evidence guides decision-making regarding addition of secondary vasopressors. In septic shock, current guidelines provide a weak recommendation to add vasopressin to norepinephrine when norepinephrine doses approach 0.25 to 0.5 μg/kg/min.[1] The weak recommendation was driven by observed catecholamine vasopressor-sparing effects obtained with addition of vasopressin, with mixed clinical outcomes across meta-analyses. For example,

a meta-analysis of 23 trials[10] showed a reduction in atrial fibrillation in arms adding vasopressin to norepinephrine, with inconsistent effects on mortality and renal replacement therapy. An individual patient-level meta-analysis of four trials[11] showed no association with mortality, but a reduction in arrhythmia, increased digital ischemia, and inconsistent effects on need for dialysis with addition of vasopressin to catecholamines.

In the absence of dose-response thresholds that show changes in BP and incidence of complications across norepinephrine doses, decisions about optimal timing of second vasopressor initiation can be informed by practical considerations and indirect evidence from trials. Practical considerations include the rate of required vasopressor escalation and availability of secondary vasopressors; escalation of primary vasopressor dose in rapidly decompensating patients should not be delayed awaiting a secondary vasopressor. However, clinicians should plan for addition of a second vasopressor early in shock for patients with increasing norepinephrine requirements. Rationale for early use of secondary vasopressors include subgroup analyses from the "Vasopressin in Septic Shock Trial" (VASST) comparing addition of vasopressin to norepinephrine with norepinephrine alone, showing lower mortality in patients receiving lower norepinephrine doses (< 15 μg/min) on enrollment who were randomized also to receive vasopressin. Similarly, the "Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock" (VANISH) trial[12] of vasopressin vs norepinephrine enrolled patients within 6 h of shock onset and showed decreased need for dialysis with addition of vasopressin.

What Should the Second Vasopressor Be?

Vasopressin is our choice of first-line second vasopressor. Decisions about choice of a second vasopressor should be guided by goals of vasopressor therapy. Generally, the goals of vasopressor therapy in distributive shock are to augment impaired vasoconstriction to meet hemodynamic goals without increasing complications, especially without evidence that perfusion goals are not met because of impaired cardiac output. Current guidelines suggest vasopressin as the preferred secondary vasopressor agent, mostly because of evidence that vasopressin reduces the need for dialysis and arrhythmias[10] and has been well studied as a secondary vasopressor that achieves hemodynamic goals. However, if arrhythmias are less likely (eg, younger patients), digital ischemia is a major concern (eg, history of Raynaud's syndrome or early signs of digital ischemia), or impaired cardiac output is thought to contribute to shock (eg, combined septic cardiomyopathy and distributive shock), then we prefer epinephrine as a second vasopressor. However, evidence supporting epinephrine as a secondary vasopressor is scant, and given that epinephrine works through most of the same adrenergic receptors as norepinephrine, hemodynamic goals may not be achieved as readily with combined norepinephrine and epinephrine as with agents that work through noncatecholamine mechanisms (eg, vasopressin or angiotensin II). Although we do not use angiotensin II routinely as a secondary vasopressor because of cost considerations and insufficient evidence of clinical outcome benefits, angiotensin II does expedite achievement of MAP goals.[13]

What Adjunctive Therapies Should Be Considered for Worsening Shock?

We add corticosteroids (hydrocortisone 50 mg IV q6h plus fludrocortisone 50 μg po daily for 7 days without tapering[14]) for patients with escalating vasopressor requirements, generally when a second vasopressor is initiated. Multiple therapies have been evaluated to improve hemodynamics for patients with shock. These include corticosteroids, methylene blue, vitamins such as ascorbic acid or thiamine, or combinations of these agents.

Corticosteroids—the most well-studied adjunct for shock—have multiple potential mechanisms of action including immunologic effects and direct effects on endothelial glucocorticoid receptors to reduce vasoplegia.[15] Evidence is strong for an effect of low- to moderate-dose (< 400 mg hydrocortisone equivalents/d) corticosteroids in increasing BP (mean increase in MAP, 5 mm Hg)[16] and shortening shock duration (mean, 1.5 fewer vasopressor days).[17] However, corticosteroids may increase adverse events such as hyperglycemia, hypernatremia, and muscle weakness. A 2019 meta-analysis of 61 sepsis trials with > 12,000 patients showed a small benefit of corticosteroids for mortality reduction (relative risk, 0.91; 95% CI, 0.84-0.99).[18] Thus, guidelines suggest use of corticosteroids for patients with septic shock and "ongoing requirement for vasopressors." Rationale for initiating corticosteroids for patients with higher vasopressor requirements (rather than lower requirements) include the concept that corticosteroids act potentially as vasopressor-sparing agents to reduce

vasopressor-associated adverse effects generally seen at higher doses, a hypothesis supported by trials and modeling studies[19] that showed benefits of corticosteroids in shock[14,20] only when enrolling patients with high baseline vasopressor requirements.

The rationale for use of fludrocortisone with hydrocortisone is threefold. First, the two largest trials demonstrating clinical benefit of steroids used hydrocortisone and fludrocortisone together,[14,20] whereas trials evaluating hydrocortisone alone did not show a mortality benefit[12,21,22]; second, a trial directly comparing fludrocortisone plus hydrocortisone with hydrocortisone alone found a 3% absolute reduction in in-hospital mortality in patients who received fludrocortisone plus hydrocortisone, but was underpowered to detect a clinically feasible effect.[23] Third, the main argument not to administer fludrocortisone is that hydrocortisone—at doses used clinically—has similar sodium-retaining activity[24] to fludrocortisone; however, mineralocorticoids have several functions in addition to sodium retention, including a neural antiapoptotic role, alveolar fluid clearance by pulmonary epithelial cells, and innate immune system activation.[25] Thus, pleiotropic effects beyond sodium retention may provide additional benefit from combining fludrocortisone with hydrocortisone.[25,26]

Although we use 7 days without taper based on the "Activated Protein C and Corticosteroids for Human Septic Shock" (APROCCHSS) trial,[14] optimal duration is uncertain and evidence is mixed regarding the risks and benefits of weaning steroids to prevent rebound hypotension.[27,28] If shock recurs after cessation without taper, we consider restarting steroids and initiate further evaluation for causes of shock.

Studies investigating methylene blue as a vasopressor adjunct are scant. Pilot trials of adjunctive methylene blue in septic shock showed improved MAP and heart rate compared with control participants, likely through inhibition of nitric oxide pathways.[29,30] Given the scant data for benefits to patient outcomes, we reserve use of methylene blue for patients with shock refractory to multiple vasopressors and corticosteroids, with the goal of temporarily increasing BP to allow initiation of other therapies (eg, infection source control measures) expected to improve longer-term outcomes.

Based on potentially promising results of a small preimplementation vs postimplementation study,[31] multiple recent trials have investigated potential benefits of high-dose ascorbic acid (with or without corticosteroids or thiamine, often called *metabolic resuscitation*). However, multiple randomized trials failed to show benefits—or showed harms—with use of ascorbic acid during shock.[32,33] We do not use ascorbic acid- or thiamine-based metabolic resuscitation for the treatment of septic shock.

Case Example, Part 2

After 24 h, the patient required norepinephrine increased to 0.5 μg/kg/min. A CVC was placed. Oxygen and vasopressor requirements improved. Antibiotics were narrowed to cover *Escherichia coli* urosepsis based on culture results.

After gradual improvement, on hospital day 5, her condition worsened. She became intermittently hypotensive despite norepinephrine 0.5 μg/kg/min, addition of vasopressin 2.4 units/h (0.04 units/min), and subsequently epinephrine 0.3 μg/kg/min. BP was 95/40 mm Hg (MAP, 57 mm Hg) and heart rate was 110 beats/min. Hydrocortisone and fludrocortisone were started. Extremities were mottled and capillary refill was 4 s. Serum lactate level was 4.5 g/L. No evidence was found of hemorrhage, abdominal compartment syndrome, or pneumothorax, and point-of-care echocardiography findings were unchanged without evidence of tamponade, new right or left ventricular dysfunction, or outflow obstruction.

What Diagnostic Evaluations Should Be Considered for Persistent or Worsening Shock?

Worsening or persistent shock despite initial source control and resuscitation should prompt consideration of additional diagnostic evaluation. Common causes and recommended evaluation of worsening shock after initial source control and stabilization during sepsis are shown in Table 1. Contributors to worsening shock often include worsening distributive shock resulting from nosocomial infections, obstructive shock resulting from pulmonary emboli or abdominal compartment syndrome, or cardiogenic shock resulting from septic cardiomyopathy or arrhythmia.

At What Vasopressor Doses Do We Stop Dose Escalation?

We do not stop escalation of norepinephrine or epinephrine dosing at any particular dose. Without evidence of an asymptote of MAP response to norepinephrine or epinephrine across higher doses, we do not have an arbitrary dose limit for further escalation of these vasopressors; however, we generally do not titrate vasopressin to $>$ 2.4 units/h (0.04 units/min) because of concerns of lower cardiac output and coronary or

TABLE 1] Clinical Considerations for Patients With Worsening Shock

Consideration	Diagnostic strategies
New or concomitant causes of shock	• Septic shock: Search for undiagnosed infection (eg, repeat culture tests, additional imaging), assess adequacy of treatment (antibiotic sensitivities, source control) • Cardiogenic shock: repeat echocardiography, central venous oxygen saturation • Hemorrhagic shock: fluid responsiveness assessment (recurrence of fluid responsiveness after resuscitation may be an early sign of occult bleeding), repeat CBC, evaluation for increased heart rate • Obstructive shock: echocardiography for tamponade, CT scan imaging to assess for pulmonary emboli, clinical assessment for abdominal compartment syndrome (eg, in patients with ascites and septic shock) • Adrenal insufficiency: review home medication list for corticosteroid use, consider potential causes of adrenal insufficiency (eg, etomidate use, pituitary disease)
Possibility of MAP underestimation by peripheral arterial line	• Begin by comparing noninvasive MAP with invasive MAP • Systolic pressure estimation by palpation • Assess other measures of perfusion (eg, changes in mental status, lactate, kidney function) • Consider placing central arterial catheter (eg, femoral or axillary)
Acidosis contributing to reduced vasopressor effect	• Assess acid and base status • Consider bicarbonate infusion or continuous renal replacement therapy
Inhibition of nitric oxide-induced vasodilation	• Consider empiric trial of methylene blue as a temporizing measure

MAP = mean arterial pressure.

splanchnic perfusion at higher doses.[34] Studies evaluating patients receiving high-dose vasopressors for septic shock (> 1 μg/kg/min norepinephrine equivalents) have found survival rates ranging from 10% to 54%.[14,35-38] In the APROCCHSS trial, the mean norepinephrine dose on enrollment was 1.08 μg/kg/min for 1,086 patients receiving norepinephrine and 2.01 μg/kg/min for 111 patients receiving epinephrine. Ninety-day survival in this trial was 53.9%.[14]

Should Central Arterial Catheters Be Placed During Refractory Shock?

Because central arterial pressure best describes perfusion pressure to vital organs, we often place central arterial catheters (femoral or axillary) in patients with seemingly refractory shock who seem to be deteriorating clinically despite increasing vasopressor doses. The Surviving Sepsis Campaign guidelines make a weak recommendation in favor of invasive monitoring of arterial pressure over noninvasive monitoring, but do not specify whether arterial pressure monitoring should be central or peripheral.[1] Hemodynamic management based on radial as opposed to central arterial pressure can lead to excess vasopressor administration.[39] One study found that systolic arterial pressure and MAP were higher when measured from femoral vs radial sites, with immediate vasopressor dose reductions facilitated in 11 of 14 patients after change to central arterial catheters.[39]

Should Acidosis Be Corrected?

For patients with severe acidemia, acute kidney injury, and refractory shock who have ventilation reserve, we administer sodium bicarbonate (HCO_3^-) targeting a pH of > 7.3[40] and initiate continuous renal replacement therapy if acidemia remains uncontrolled. Vascular reactivity and β-adrenergic receptor binding are impaired by acidosis.[41,42] Sodium HCO_3^- and renal replacement therapy can correct acidosis temporarily.[40] The "Sodium Bicarbonate to Treat Severe Acidosis in the Critically Ill" (BICAR-ICU) trial, which randomized critically ill adults with severe acidemia to sodium HCO_3^- infusion (4.2% [500 mEq/L], up to 1 L) or no sodium HCO_3^- infusion, found that among patients with acute kidney injury, those who received HCO_3^- infusion experienced lower mortality and more vasopressor-free days than those who did not.[40] We require patients to have the ability to increase minute ventilation safely to compensate for increased CO_2 production that may result after HCO_3^- administration.

Case Example, Part 3

The patient's blood culture samples returned with positive results for methicillin-resistant *Staphylococcus aureus*. Appropriate antibiotics were started and the CVC was replaced. Serum lactate and vasoplegia improve; however, she continued to receive

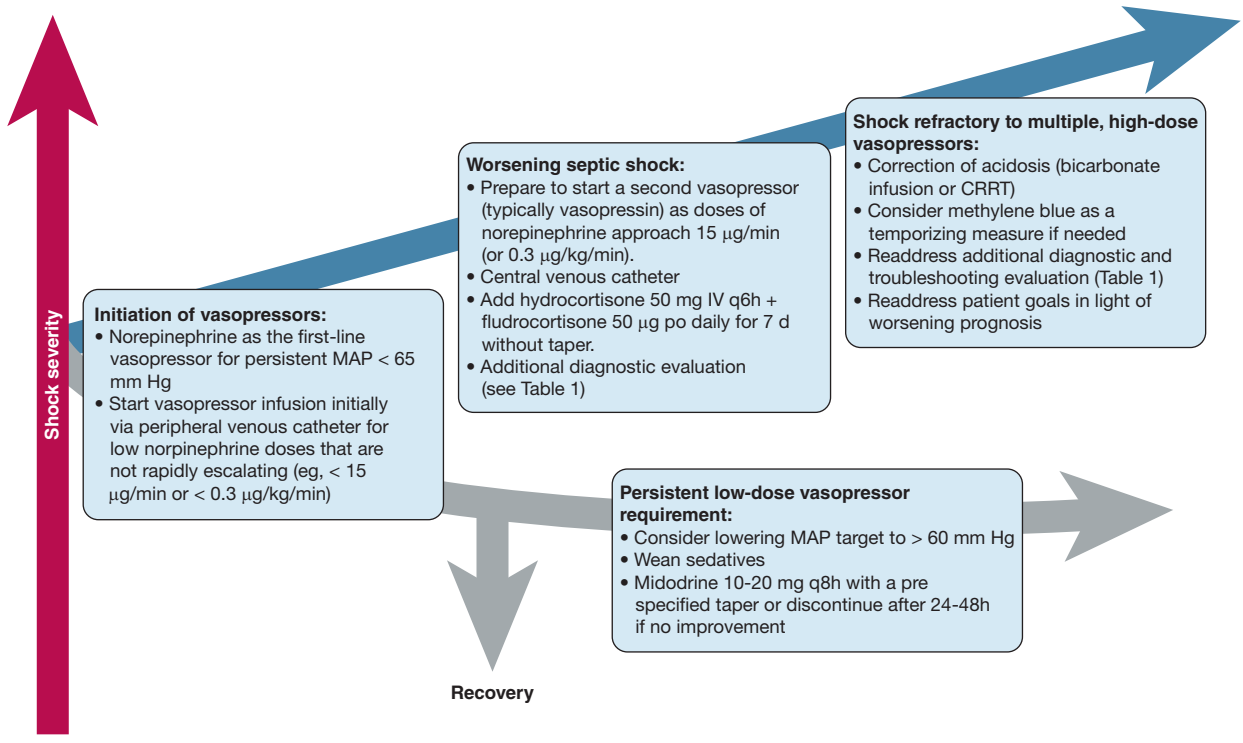

Figure 1 – *Diagram showing suggested approach to treatment of hypotension at various stages of septic shock. The y-axis represents severity of shock and the x-axis represents possible trajectories over time. CRRT = continuous renal replacement therapy; MAP = mean arterial pressure.*

norepinephrine at a dose of 0.3 μg/kg/min and vasopressin. BP was 90/50 mm Hg (MAP, 63 mm Hg) and heart rate was 95 beats/min. Point-of-care echocardiography findings were unchanged and repeat culture findings were negative.

What Should the Approach Be to Weaning Vasopressors?

We discontinue norepinephrine first, and then vasopressin last, for patients who are receiving both vasopressors but are improving clinically. Few data are available on the approach to weaning vasopressors. Several small, single-center observational studies among patients with septic shock receiving norepinephrine and vasopressin have found that discontinuing vasopressin first leads to increased incidence of hypotension,[43-46] suggesting that norepinephrine should be discontinued first.

Case Example, Part 4

Her extremities were warm and well perfused and mental status and renal function were improving, but attempts to wean low-dose vasopressin (2.4 units/h [0.04 units/min]) resulted in MAP of 60 mm Hg.

What Is the Approach to Persistent Vasoplegia and Inability to Wean IV Vasopressors?

For patients who improve clinically (reversal of organ dysfunction), but have persistent, mild vasoplegia, we reduce the MAP target to 60 mm Hg to help with vasopressor weaning. Ongoing vasopressor-dependent hypotension without evidence of end-organ hypoperfusion can limit mobilization, physiotherapy and discharge from the ICU. Lowering the MAP target to 60 mm Hg is based on the 65 trial[6] discussed in the section on MAP targets. Sometimes, sedatives also can contribute to hypotension, and we often adjust sedatives to reduce vasopressor requirements. We also consider repeating diagnostics (Table 1) to identify ongoing processes that may contribute to persistent vasopressor requirements (eg, intraabdominal abscess).

Midodrine is an oral α_1-adrenergic agonist that has received approval for use in the United States for symptomatic orthostatic hypotension. It has been used off-label to facilitate liberation from IV vasopressors; however, the recent "Midodrine as adjunctive support for treatment of refractory hypotension in the intensive care unit" (MIDAS) trial showed no benefit of midodrine in accelerating liberation from IV vasopressors.[47] Of note, this trial excluded patients with

liver failure and chronic renal failure, and a beneficial effect was found in a post hoc subgroup analysis of patients with epidural analgesia.

In patients for whom lowering MAP targets and minimizing sedation have not worked, particularly if patients have liver failure, renal failure, or a neurogenic component to hypotension, we try midodrine. One disadvantage to using midodrine is that it is often continued even after discharge from the hospital.[48] We typically prescribe midodrine 10 to 20 mg po every 8 h with a taper or stop date entered to avoid continuation after hospital discharge. If no improvement toward reaching MAP goals is achieved, we stop after 24 to 48 h.

Conclusions

The care of patients with septic shock can be complex. Our suggested approach to treating hypotension in septic shock is summarized in Figure 1. In most patients, we initiate norepinephrine first, either through a peripheral IV or midline catheter, targeting a MAP of 60 to 65 mm Hg. If norepinephrine doses approach 15 μg/min (or 0.3 μg/kg/min), we initiate vasopressin for most patients, transition to infusion via CVC, and administer hydrocortisone and fludrocortisone for 7 days. We also assess for concomitant causes of shock (Table 1). For refractory shock, we consider central arterial pressure monitoring and correction of acidosis. When mild vasoplegia persists without evidence of end-organ ischemia, we reduce the MAP target to 60 mm Hg, modify or discontinue sedatives if possible, and often try midodrine.

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