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Managing the Crashing Patient: Refractory Shock

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Disclosure

No one involved in the development of the educational content has a relevant financial relationship to disclose

Objectives

- Assess critical hemodynamic parameters and clinical indicators to recognize refractory shock in crashing patients
- Apply evidence-based pharmacologic strategies, including the selection of vasoactive agents, to manage refractory shock effectively

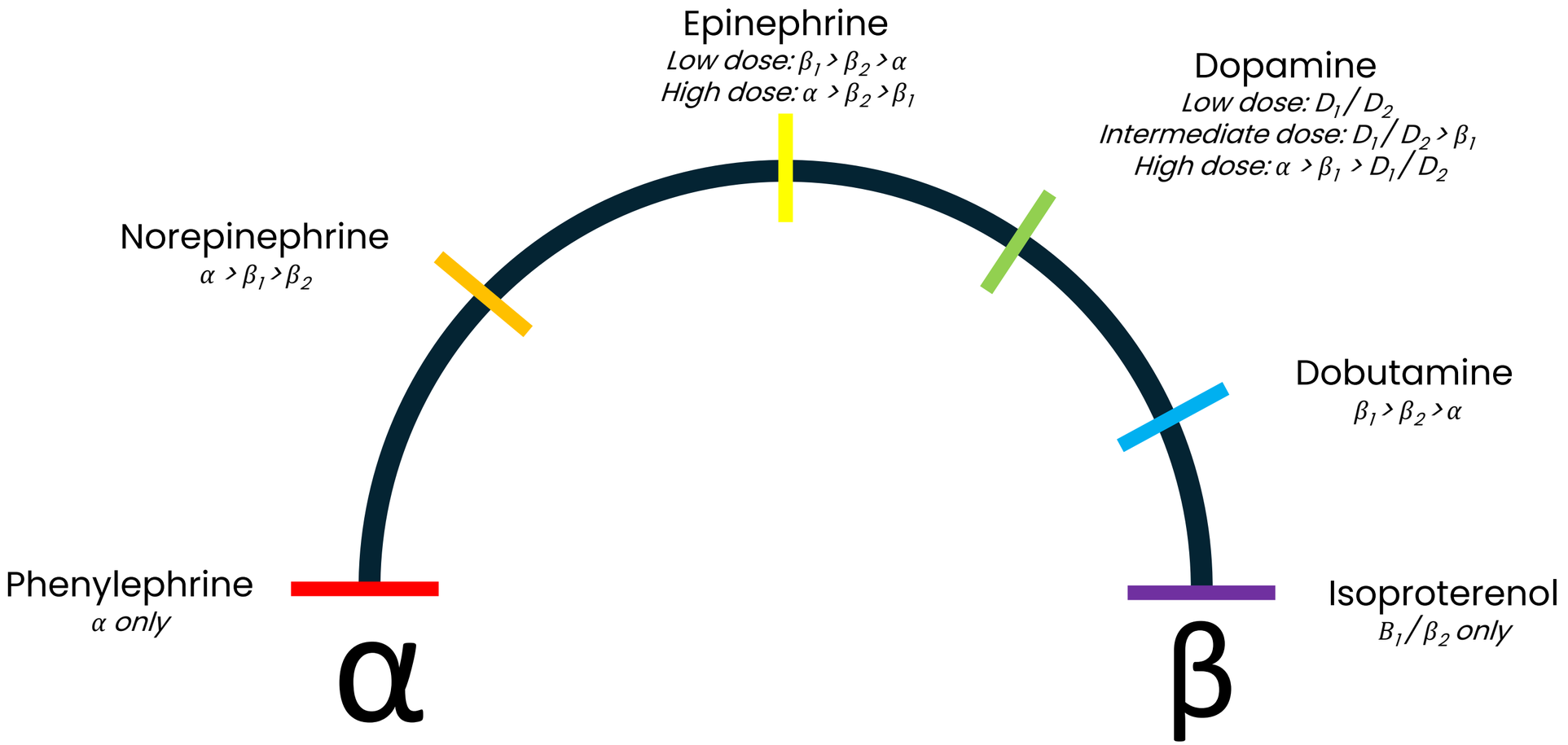
What is shock?

Vasodilatory Shock

- Most common form of shock seen in critical care patients
- Can be caused by:
  - Sepsis
  - Vasoplegia after cardiopulmonary bypass
  - Anaphylaxis
  - Acute pancreatitis
  - Spinal cord injury
  - General anesthesia
- Decreased systemic vascular resistance (SVR) and hypotension
- Inadequate tissue extraction of oxygen → hypotension, peripheral vasodilation, lack of vasopressor response → tissue ischemia, organ failure, death
- Treat with fluids and vasopressors

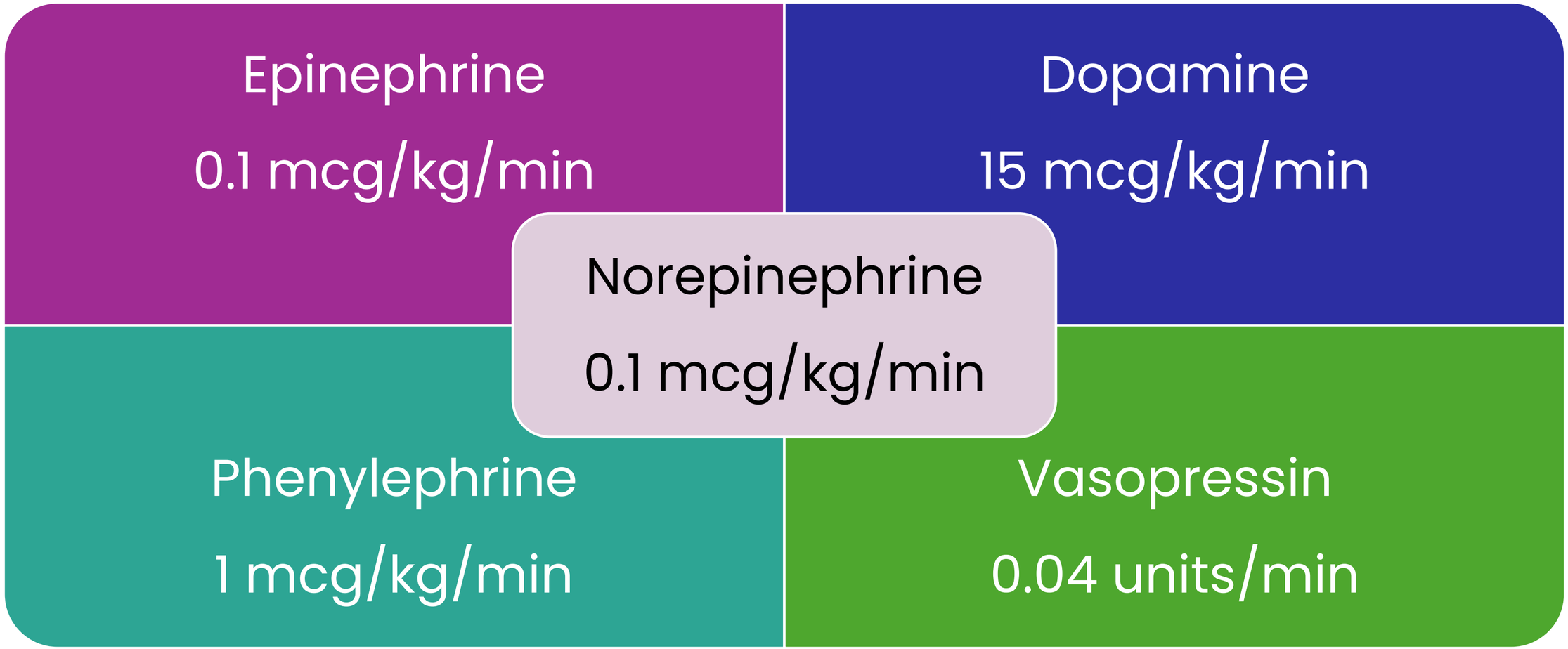
J Cardiothorac Vasc Anesth. 2023;37(9):1757-1772
Crit Care. 2022 Mar 22;26(1):76

Vasopressors



Intensive Care Med. 2019 Nov;45(11):1503-1517
ATS Sch. 2023 Feb 13;4(2):216-229

Vasopressor Equivalents



Chest. 2018 Aug;154(2):416-426

What if vasopressors fail?

Refractory Shock

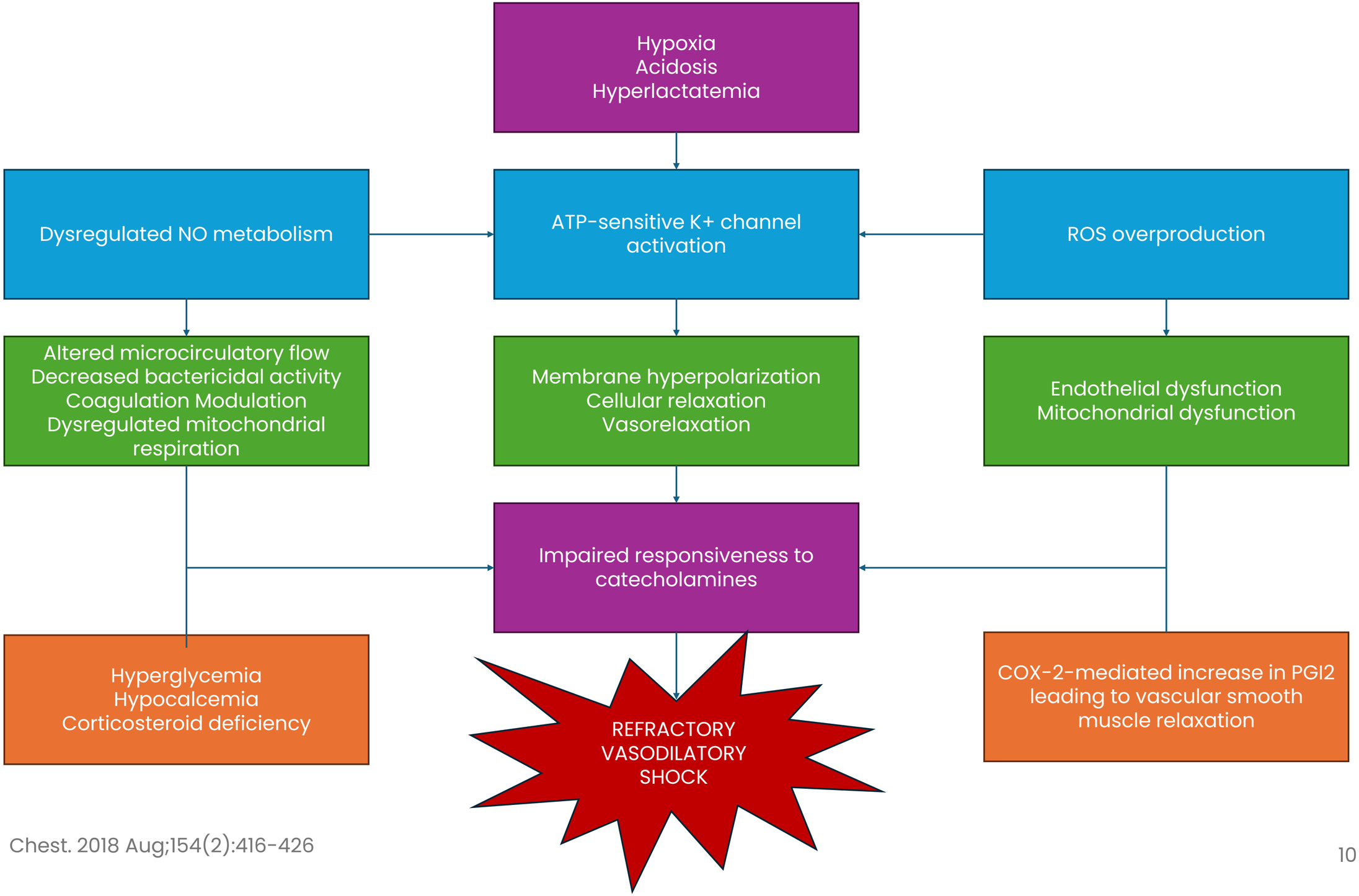
Failure to achieve a blood pressure goal despite vasopressor therapy

Need for rescue vasopressor therapy

Need for higher vasopressor doses

Norepinephrine-equivalent doses >0.2 mcg/kg/min (ATHOS-3)

Chest. 2018 Aug;154(2):416-426
J Cardiothorac Vasc Anesth. 2023;37(9):1757-1772



Chest. 2018 Aug;154(2):416-426

Treatment

- High-dose norepinephrine mortality 60-90%
- Vasopressor-sparing strategies to decrease adverse effects of high-dose catecholamines
  - Ischemic digits
  - Splanchnic hypoxia
  - Arrhythmia
- Rescue therapies
  - Lack of clinical evidence

J Cardiothorac Vasc Anesth. 2023;37(9):1757-1772
Crit Care. 2022 Mar 22;26(1):76

Rescue Therapies

- Hydrocortisone
- Calcium Chloride
- Sodium Bicarbonate
- THAM
- Ascorbic Acid
- Thiamine
- Methylene Blue
- Hydroxocobalamin
- Vasopressin Analogues
- Angiotensin II

Chest. 2018 Aug;154(2):416-426

Medication	Mechanism	Dose	Adverse Effects
Hydrocortisone	Increases vascular catecholamine response	50 mg IV every 6 hours	Hyperglycemia Secondary infection
Calcium Chloride	Increases vascular tone	1-2 g IV over 1 hour, followed by continuous infusion 20-50 mg/kg/h based on ionized calcium levels	Hypercalcemia Beta-adrenergic effect inhibition
Sodium Bicarbonate	Metabolic acidosis reversal	1-2 mEq/kg IV bolus	Metabolic abnormalities, myocardial depression
THAM	Metabolic acidosis reversal	324 mg/kg over 60 minutes	Hyperkalemia Fluid overload
Ascorbic Acid	Repleting required cofactors, catecholamine and vasopressin synthesis	25 mg/kg IV every 6 hours OR 1.5 g IV every 6 hours	Minimal
Thiamine	Treat thiamine deficiency, improve lactate clearance	200 mg IV twice daily	Minimal

Chest. 2018 Aug;154(2):416-426
Anesth Analg. 2023 Nov 1;137(5):1007-1018
Crit Care Med. 2016;44:360-367
Calcium Chloride. Lexi-drugs .UpToDate Lexidrug

Methylene Blue

- Conventionally used for methemoglobinemia treatment
- Catecholamine-sparing effects
  - Selectively blocks soluble guanylyl cyclase (sGC) and inhibits nitrous oxide (NO) synthase
  - Oxidizes NO to inactive nitrate and reducing vasodilation
  - Suppresses superoxide production, decreasing liver and kidney damage
  - Inhibits sGC → reduces NO-sGC binding and cGMP production

Methylene Blue

- SHOCKEM-Blue
  - Methylene blue vs usual care
  - Patients on norepinephrine and vasopressin
  - Time to vasopressor discontinuation - 69 vs 94 hours ($p < 0.001$)
  - Decreased ICU length of stay – 6.6 vs 7.9 days ($p = 0.0339$)
  - Decreased hospital length of stay – 9 vs 10.5 days ($p = 0.027$)
  - No mortality benefit at 28 days – 33% vs 46% ($p = 0.23$)

Crit Care. 2023;27(1):110

Methylene Blue

Dose	Administration	Pharmacokinetics	Adverse Effects
2 mg/kg IV once daily for up to 3 doses OR **2 mg/kg IV bolus**, followed by **0.25-2 mg/kg/h** continuous infusion for up to 48 hours	Can give bolus over 15 minutes–6 hours Central line recommended Solubility reduced by chloride – can only be diluted in D5W	Onset: 30-60 minutes Half-life: 5-6.5 hours	• Chromaturia • Skin discoloration • Serotonin syndrome • Paradoxical induction of methemoglobinemia

Pediatr Emer Care. 2021;37(9):474-479
Methylene Blue. Lexi-drugs. UpToDate Lexidrug

Hydroxocobalamin

- Conventionally used to treat cyanide poisoning
- Impacts vasodilation pathways that traditional vasopressors cannot
  - Scavenges NO
  - Inhibits NO synthase and hydrogen sulfide

J Cardiothorac Vasc Anesth. 2023;37(9):1757-1772

Hydroxocobalamin

- Ritter et. al 2022
  - Single-center observational study of 35 patients who received a single dose of hydroxocobalamin for the treatment of refractory shock
  - Not associated with a significant improvement in hemodynamics at 24 hours
  - No significant change in MAP, SBP, DBP, or NED
  - 74.3% received stress-dose steroids and 48.6% of patients received methylene blue before hydroxocobalamin administration
  - Larger studies are needed to determine its role in refractory shock

J Crit Care. 2022 Feb;67:66-71

Hydroxocobalamin

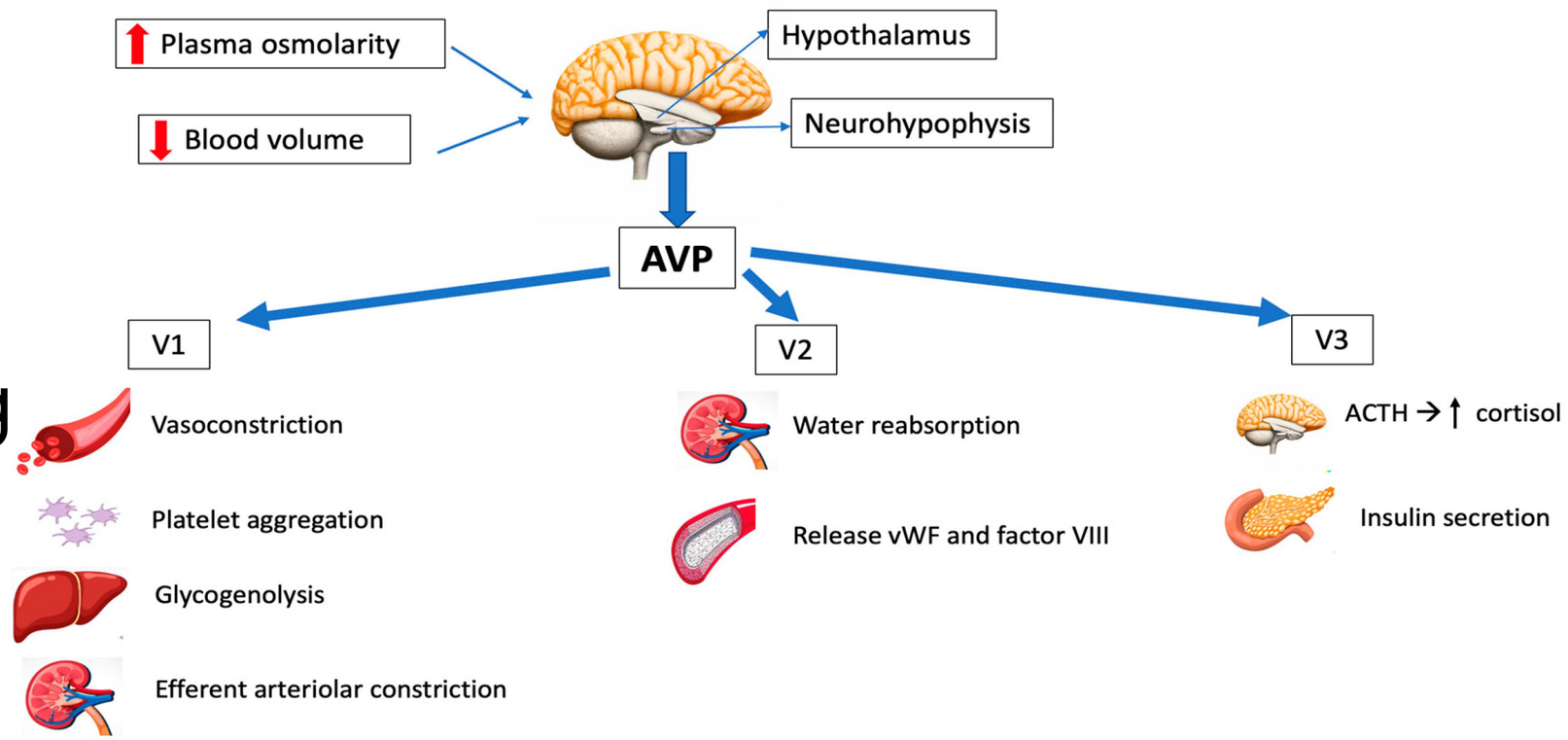
Dose	Administration	Pharmacokinetics	Adverse Effects

5 g IV once	Give over 15 minutes	Half-life: 26-31 hours	• Allergic reactions
			  • Angioedema
			  • Anaphylaxis
			• Red discoloration of skin, mucus membranes, and urine
			• Transient increase in blood pressure

Goldfrank's Toxicologic Emergencies 11e: c2019
Hydroxocobalamin. Lexi-drugs. UpToDate Lexidrug
J Crit Care. 2022 Feb;67:66-71

Terlipressin

- Used for vasodilatory shock in other countries
- Synthetic vasopressin analog
- Stimulates V_{1a}, V_{1b}, and V_2 receptors
- Greater affinity for the V_1 receptor



https://encyclopedia.pub/entry/51203

J Intensive Care Med. 2020 Apr;35(4):327-337

Terlipressin

- Sahoo et. al 2022
  - Prospective, randomized controlled trial of 50 adult patients with septic shock who received a combination of terlipressin + norepinephrine vs norepinephrine alone
  - Terlipressin dose 0.02 mcg/kg/min infusion (fixed dose)
  - Norepinephrine dose lower at 12 hours in terlipressin group – 0.141 vs 0.374 mcg/kg/min ($p < 0.001$)
  - No difference in MAP at 12 hours – 69.44 vs 69.12 ($p = 0.655$)
  - Low-dose terlipressin may have a role in ensuring organ perfusion, preventing renal injury, and improving SOFA score when used in adjunct to norepinephrine

Indian J Crit Care Med. 2022 Jun;26(6):669-675

Terlipressin

Dose	Administration	Pharmacokinetics	Adverse Effects

1 mg IV bolus every 6 hours
 	
OR
 	
0.02 mcg/kg/min continuous infusion
	Give over 2 minutes via peripheral or central line	Onset: 5 minutes
		
		Half-life:
		• Terlipressin
		  • 50-55 minutes
		• Lysine-vasopressin
		  • 3 hours
		
		Duration: ≥6 hours
			• Reduced cardiac output
			• Increased pulmonary vascular resistance
			• Ischemic events
			• Digital ischemia
			• Hyponatremia

J Intensive Care Med. 2020 Apr;35(4):327-337
Terlipressin. Lexi-drugs. UpToDate Lexidrug

Selepressin

- Selective vasopressin V_{1a} receptor agonist
- SEPSIS-ACT trial
  - Blinded, randomized trial of 828 patients with septic shock (requiring >5 mcg/min of norepinephrine) who received either selepressin or placebo
  - Starting infusion rates of 1.7 or 2.5 or 35 ng/kg/min
  - Ventilator and vasopressor free days – 15 vs 14.5 ($p = 0.30$)
  - 90-day mortality -40.6% vs 39.4% ($p = 0.77$)
  - Selepressin did not result in improvement in vasopressor and ventilator free days within 30 days
  - Terminated early due to futility

JAMA. 2019 Oct 15;322(15):1476-1485

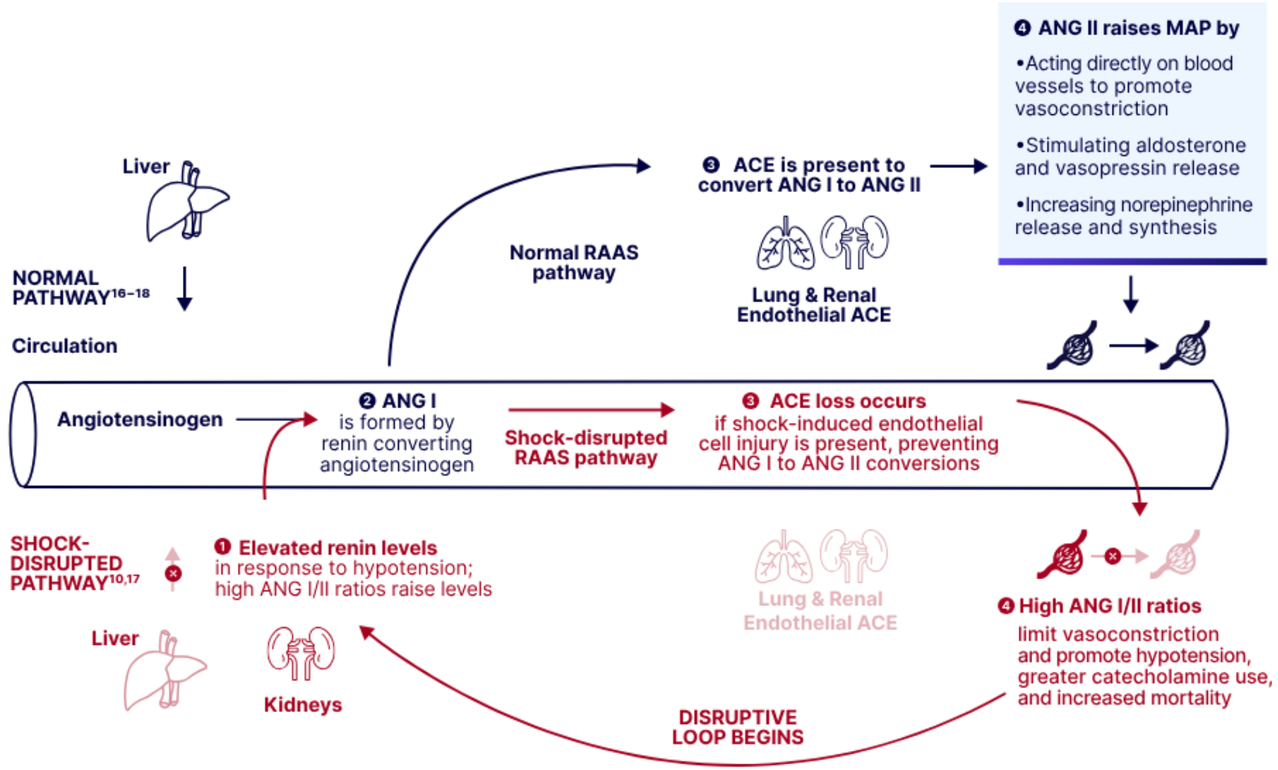
Selepressin

Dose	Administration	Pharmacokinetics	Adverse Effects
2.5 ng/kg/min IV continuous infusion	Central line	Half-life: 1.5-2.5 hours	• Peripheral ischemia • Cyanosis • Myocardial ischemia

J Intensive Care Med. 2020 Apr;35(4):327-337
JAMA. 2019 Oct 15;322(15):1476-1485

Angiotensin II (AT_2)

- Acts via the Renin-Angiotensin-Aldosterone System (RAAS)to increase blood pressure through direct vasoconstriction



ACE=angiotensin-converting enzyme; ANG=angiotensin.

https://www.giapreza.com/static/LethalLoop-a253e238cb64cdda246cb0fef30bc001.svg

Crit Care Med. 2023;51(12):1674-1684
J Intensive Care Med. 2020 Apr;35(4):327-337
Crit Care Resusc. 2017 Mar;19(1):43-49

Angiotensin II (AT_2)

- ATHOS-3 trial
  - Randomized controlled trial of 321 patients who either received AT_2 or placebo while on high-dose vasopressors to achieve a MAP of 75mmHg
  - Starting dose of 20 ng/kg/min
  - Utilized a 3-hour period where only AT_2 could be titrated to a max dose of 200 ng/kg/min
  - AT_2 increased blood pressure in patients with vasodilatory shock that did not respond to conventional vasopressors at 3 hours– 69.9% vs 23.4% ($p < 0.001$)
  - Subgroup analysis suggested mortality benefit in those receiving renal replacement therapy, APACHE II >30, and elevated renin levels at baseline

Crit Care Med. 2023;51(12):1674-1684
J Intensive Care Med. 2020 Apr;35(4):327-337
Crit Care Resusc. 2017 Mar;19(1):43-49

Angiotensin II

Dose	Administration	Pharmacokinetics	Adverse Effects
10-20 ng/kg/min IV continuous infusion • Titrate by 10-15 ng/kg/min every 5 minutes based on goal MAP • Max initial dose: 80 ng/kg/min in the first 3 hours • Max maintenance dose: 40 ng/kg/min	Central line recommended Vesicant-like properties	Time to peak: 5 minutes Half-life: <1 minute	• Hypertension • Metabolic acidosis • Thrombosis • Delirium

J Intensive Care Med. 2020 Apr;35(4):327-337
Angiotensin II. Lexi-drugs. UpToDate Lexidrug

Dosing Summary

Rescue Therapy	Dosing Strategies
Hydrocortisone	50 mg IV q6h
Calcium Chloride	1-2 mg IV
Sodium Bicarbonate	1-2 mEq/kg IV
Ascorbic Acid	25 mg/kg IV every 6 hours OR 1.5 g IV every 6 hours
Thiamine	200 mg IV twice daily for 4-7 days
Methylene Blue	2 mg/kg IV once daily for up to 3 doses OR 2 mg/kg IV bolus, followed by 0.25-2 mg/kg/h continuous infusion for up to 48 hours
Hydroxocobalamin	5 g IV once
Terlipressin	1 mg IV bolus every 6 hours OR 0.02 mcg/kg/min continuous infusion
Selepressin	2.5 ng/kg/min IV continuous infusion
Angiotensin II	10-20 ng/kg/min IV continuous infusion

Assessment Question 1

Which of these patients would possibly benefit from the addition of refractory shock rescue therapies

A. 66-year-old patient post cardiothoracic surgery on norepinephrine 0.1 mcg/kg/min with improving hemodynamics

B. 35-year-old patient diagnosed with sepsis on norepinephrine 0.7 mcg/kg/min, vasopressin 0.03 units/min, and phenylephrine 300 mcg/min with MAPs of 50-55

C. 22-year-old patient whose MAP is now 70 mmHg after receiving 2 liters of lactated ringers

D. 72-year-old patient being weaned off phenylephrine 1 mcg/kg/min

MAP: Mean Arterial Pressure

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MAP: Mean Arterial Pressure

Assessment Question 2

Your patient is maxed on multiple vasopressors while treating septic shock. Which rescue therapy could you recommend to the physician to aid in treating the patient's refractory vasodilatory shock?

A. Thiamine 100mg PO once daily for 14 days
B. Methylprednisolone 60mg IV every 6 hours
C. Methylene blue 2 mg/kg IV once daily for 3 doses
D. Hydroxocobalamin 10 g IV bolus

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