The Squeeze Squad:
Multimodal Hypotension Management in Refractory Septic Shock

Sarah Blackwell, PharmD, BCPS, BCCCP
Clinical Pharmacy Specialist, Medical Critical Care
Princeton Baptist Medical Center
Birmingham, AL

Financial Disclosure

Dr. Sarah Blackwell has no relevant financial relationships with ineligible companies to disclose.

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Learning Objectives

1. Recognize possible adverse effects of vasopressors.
2. Identify appropriate candidates to receive adjunctive agents for refractory septic shock.
3. Recall the efficacy and safety of adjunctive agents used for refractory septic shock.
4. Recognize a patient-specific multimodal hypotension treatment regimen.

Abbreviations

- APACHE: Acute Physiology and Chronic Health Evaluation
- ATP: adenosine triphosphate
- AT2: angiotensin II
- CI: confidence interval
- G6PD: glucose-6-phosphate dehydrogenase
- ICU: intensive care unit
- IQR: interquartile range
- IV: intravenous
- LOS: length of stay
- MA-SOFA: Mortality-adjusted Sequential Organ Failure Assessment
- MAP: mean arterial pressure
- NE: norepinephrine
- NEE: norepinephrine equivalents
- NO: nitric oxide
- PGI_2: prostacyclin
- RRT: renal replacement therapy
- SD: standard deviation
- SOFA: Sequential Organ Failure Assessment
- SSC: Surviving Sepsis Campaign
- XBJ: xuebijing

Septic Shock

- Sepsis with profound circulatory and metabolic abnormalities that significantly increase mortality
- Clinical identification: hypotension requiring vasopressor therapy to maintain mean arterial pressure (MAP) ≥65 mmHg and lactate >2 mmol/L after fluid resuscitation
- Prompt identification coupled with aggressive antimicrobial treatment and resuscitation are vital to reverse the process

Sources: Crit Care Med. 2021;49(11):1-81.
JAMA. 2016; 315(8):801-810.

Intravenous (IV) Fluids

- Surviving Sepsis Campaign (SSC) recommendations
  - Suggest ≥30 mL/kg crystalloid fluid in the first 3 hours (*weak recommendation, low-quality evidence*)
  - Suggest dynamic measures to guide fluid resuscitation (*weak recommendation, very low-quality evidence*)
  - No guidance on restrictive versus liberal fluid strategy with ongoing hypoperfusion and volume depletion

- Risks
  - ≥30 mL/kg dose based on observational evidence
  - Lack of fluid responsiveness or transient hemodynamic effect
  - Worse outcomes in the setting of volume overload

Sources: Crit Care Med. 2021;49(11):1-81.
Military Med Res. 2021;8(1):40.
Am J Emerg Med. 2016;34(11):2122-2126.
Ann Am Thorac Soc. 2015;12(12):1837-44.

Vasoactive Medications: SSC Recommendations

- Recommend norepinephrine first-line (*strong recommendation, very low- to high-quality evidence*)
- Suggest vasopressin as first adjunct (*weak recommendation, low-quality evidence*)
  - Consider addition when norepinephrine 0.25-0.5 mcg/kg/min
- Suggest epinephrine as second adjunct (*weak recommendation, low-quality evidence*)
- Suggest dobutamine + norepinephrine or epinephrine alone for cardiac dysfunction despite adequate volume status and MAP (*weak recommendation, low-quality evidence*)

Source: Crit Care Med. 2021;49(11):1-81.

Vasopressor Strategies

- Norepinephrine first-line
  - Potent vasoconstrictor
  - Lower myocardial oxygen consumption than dopamine or epinephrine
  - Risk of ischemia, acute liver injury with high-dose vasopressin
  - Very-low quality angiotensin II data
  - Decreased cardiac output and increased mortality with phenylephrine
- Scant evidence for the optimal high-dose vasopressor strategy
- Risks
  - Ischemia – cardiac, digital, mesenteric
  - Tachyarrhythmias

Sources: Crit Care Med. 2021;49(11):1-81.
JAMA. 2017;317(14):1433-42.
N Engl J Med. 2010;362(9): 779-89.
Crit Care Med. 2003;31(5):1394–98.

High-Dose Vasopressors and Mortality

- Increasing vasopressor exposure is associated with mortality
  - Consistent if increasing doses required to maintain MAP 65-75 mmHg or if targeting MAP >75 mmHg
  - Unclear whether correlation or causation

- Multicenter observational cohort of 1610 patients with septic shock
  - At vasopressin initiation, survivors had decreased lactate, norepinephrine equivalent (NEE) dose, time to vasopressin initiation
  - Mortality increased 20.7% for every 10 mcg/min NEE dose increase under 60 mcg/min

Sources: Intensive Care Med. 2016;42(4):542-50.
N Engl J Med. 2014;370(17):1583-93.
Crit Care Med. 2020;48(10):1445-53.
Crit Care Med. 2022;50(4):614-23.

Hydrocortisone IV

- SSC recommendations
  - Suggest IV corticosteroids in the setting of ongoing vasopressor requirement (*weak recommendation, moderate-quality evidence*)
  - Typical dose 200 mg per day (50 mg Q6H or continuous infusion)
  - Advocated when norepinephrine or epinephrine ≥0.25 mcg/kg/min persistently

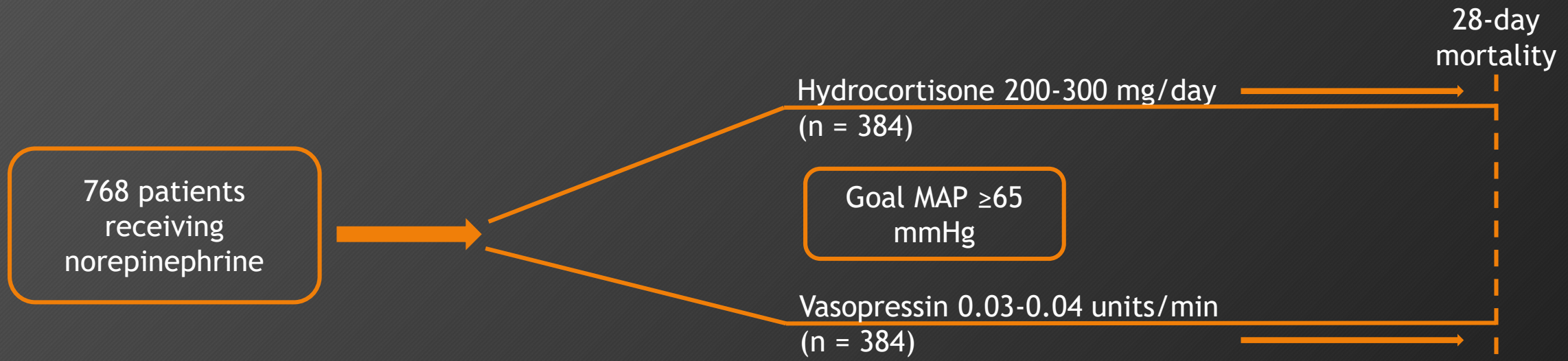
- Risks
  - Muscle weakness
  - Hyperglycemia
  - Hypernatremia

Sources: Crit Care Med. 2021;49(11):1-81.
Crit Care Med. 2018;46(9):1411-20.
JAMA. 2016;316(5):509-18.
Intensive Care Med. 2018;44(7):1003-16.
N Engl J Med. 2018;378(9):797-808.

Hydrocortisone vs. Vasopressin as First Adjunct

Inclusion: septic shock, receipt ≥30 mL/kg IV fluid bolus + antibiotics, lactate >2 mmol/L, receipt of norepinephrine followed by either vasopressin or hydrocortisone

Exclusion: other vasopressors, mechanical circulatory support, recent glucocorticoid use, vasopressin + hydrocortisone within 6 hours



Source: Pharmacotherapy. 2023;00:1-8.

Hydrocortisone vs. Vasopressin as First Adjunct

Baseline characteristic	Hydrocortisone (n = 384)	Vasopressin (n = 384)	P value
Age, years	69 (60-77)	69 (61-78)	0.81
Body mass index, kg/m^2	26.1 (22.3-31.2)	27.3 (22.7-32.9)	0.04
SOFA score	10 (8-12)	11 (9-13)	0.41
Lactate, mmol/L	3.1 (2.2-5.1)	5 (2.8-8.6)	<0.01
Mechanical ventilation	215 (56)	280 (72.9)	<0.01
NE dose, mcg/kg/min	0.2 (0.1-0.3)	0.4 (.2-0.6)	<0.01
NE initiation to study drug, hr	8.5 (4.1-17.6)	6.8 (3.3-14.4)	0.012

Data expressed as n (%) or median (interquartile range [IQR])
LOS: length of stay, NE: norepinephrine, SOFA: Sequential Organ Failure Assessment

Source: Pharmacotherapy. 2023;00:1-8.

Hydrocortisone vs. Vasopressin as First Adjunct

Outcome	Hydrocortisone (n = 384)	Vasopressin (n = 384)	P value
28-day mortality	162 (42.2)	281 (73.2)	<0.01
Hemodynamic response	353 (91.9)	262 (68.2)	<0.01
Shock resolution	264 (68.8)	121 (31.5)	<0.01
Shock recurrence at 72 hours*	23 (8.7)	25 (20.7)	<0.01
ICU LOS†	5.5 (3.5-10.5)	9.5 (5.5-17)	<0.01
Hospital LOS†	12.5 (8.5-21.5)	19.5 (12.5-30)	<0.01

Data expressed as n (%) or median (IQR)
*following shock resolution, †survivors
ICU: intensive care unit

No difference in adverse effects: hypernatremia, hyponatremia, hyperglycemia, GI bleeding, superinfection

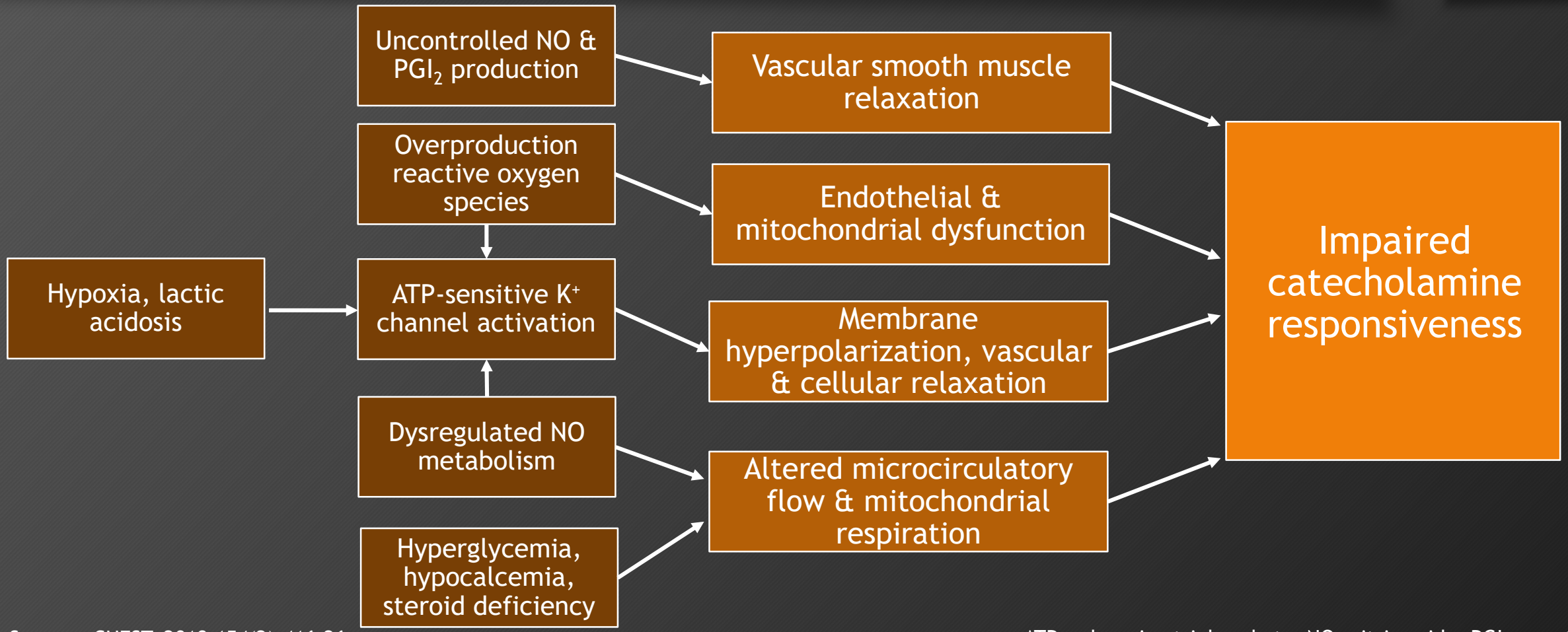
Source: Pharmacotherapy. 2023;00:1-8.

Need for Alternative Multimodal Agents

- Septic shock involves a complex constellation of cellular disturbances and inflammation
- Refractory shock often due to vasoplegia
  - Normal or high output (cardiac index ≥2.2 L/min/m^2)
  - Low systemic vascular resistance (<800 dynes*sec/cm^5) despite high-dose vasopressors (≥0.5 mcg/kg/min norepinephrine)
- Limitations exist with standard therapy

Sources: Crit Care. 2018;22:52.
CHEST. 2018;154(2):416-26.

Vasoplegic Shock Pathophysiology



Source: CHEST. 2018;154(2):416-26.

ATP: adenosine triphosphate, NO: nitric oxide, PGI_2: prostacyclin

Assessment Question #1

Which of the following are possible adverse effects of high-dose norepinephrine?

A. Bradycardia, decreased cardiac output
B. Elevated lactate, increased oxygen consumption
C. Atrial fibrillation, cardiac ischemia
D. Mesenteric ischemia, acute liver injury

Assessment Question #1

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B. Elevated lactate, increased oxygen consumption
C. Atrial fibrillation, cardiac ischemia
D. Mesenteric ischemia, acute liver injury

Angiotensin II (AT2)

AT2

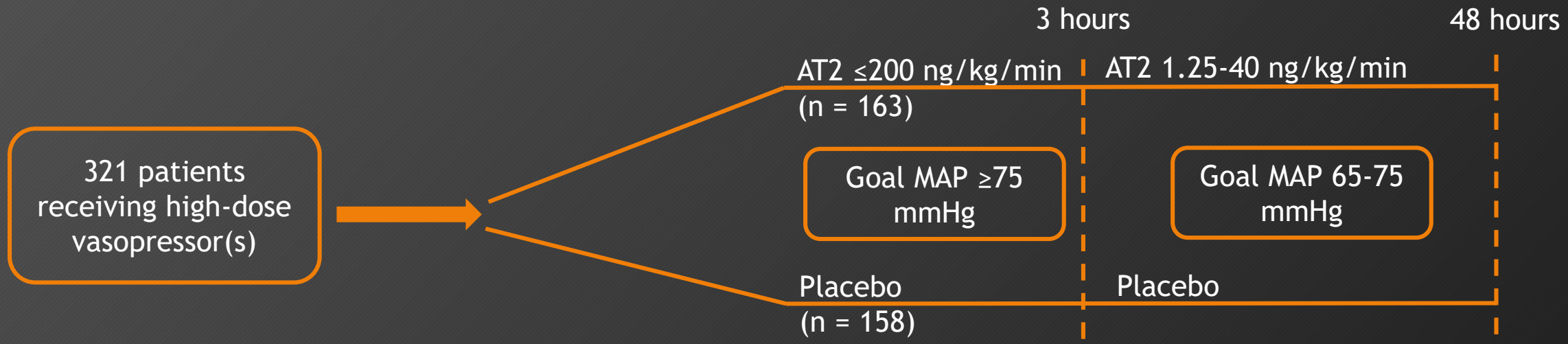
- Endogenous AT2 levels depleted in septic shock
- Restoration improves vascular tone via direct vasoconstriction and augmentation of sympathetic activity
- Dosing: 10-80 ng/kg/min, maximum dose of 40 ng/kg/min after 3 hours
- Significant cost: >$500 (0.5 mg/1 mL)

Sources: CHEST. 2018;154(2):416-26.
Lexi-Drugs.

ATHOS-3

Inclusion: vasodilatory shock, receipt ≥25 mL/kg IV fluids over 24 hours, receipt of >0.2 mcg/kg/min NEE for 6-48 hours

Notable exclusions: large burns, acute coronary syndrome, bronchospasm, liver failure, mesenteric ischemia, active bleeding, venoarterial extracorporeal membrane oxygenation



Source: N Engl J Med. 2017;377(5):419-30.

ATHOS-3

Outcome	Placebo (n = 158)	AT2 (n = 163)	P value
MAP response at 3 hr	37 (23.4)	114 (69.9)	<0.001
NEE dose change 0-3 hr	0.03 ± 0.23	-0.03 ± 0.1	<0.001
Cardiovascular SOFA score change at 48 hr	-1.28 ± 1.65	-1.75 ± 1.77	0.01
Total SOFA score change at 48 hr	1.04 ± 5.34	1.05 ± 5.5	0.49
7-day mortality	55 (35)	47 (29)	0.22
28-day mortality	85 (54)	75 (46)	0.12

Data expressed as n (%) or mean ± standard deviation (SD)

No difference in adverse effects of interest: tacharrhythmias, ventricular arrhythmias, distal ischemia

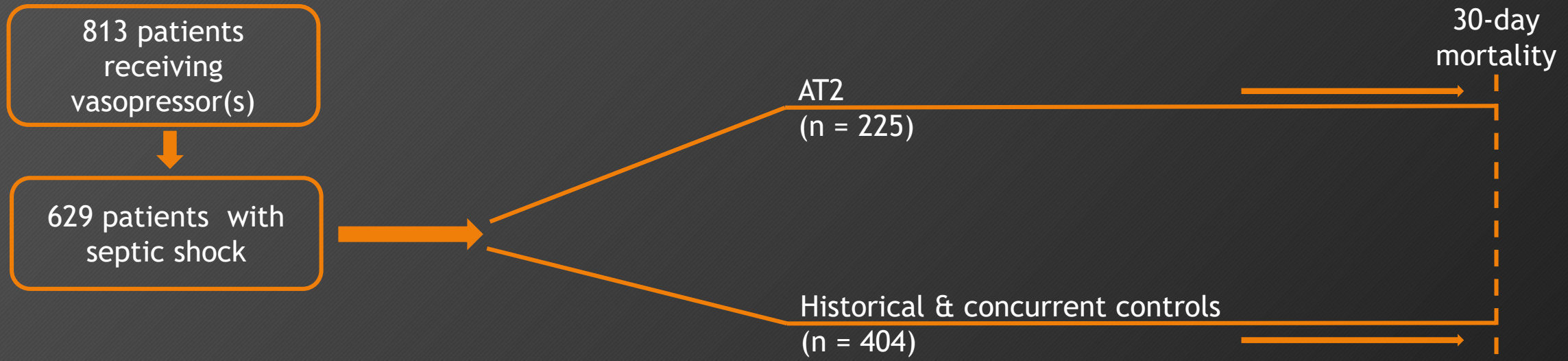
Source: N Engl J Med. 2017;377(5):419-30.

AT2 for Refractory Shock

Inclusion: receipt of adrenergic vasopressor(s), vasopressin, or AT2

Exclusion: AT2 initiation in the operating room

Matching: AT2 matched to historical and concurrent control based on NEE dose of other vasopressor(s) at AT2 initiation



Source: Crit Care Med. 2023;51(00):1-11.

AT2 for Refractory Septic Shock

Unadjusted Outcome	Control (n = 404)	AT2 (n = 225)	P value
30-day mortality	252 (62)	142 (63)	0.864
90-day mortality	281 (70)	155 (69)	0.857
New RRT*	89 (28)	57 (41)	0.004
New mechanical ventilation*	83 (72)	13 (72)	0.226
MA-SOFA, day 1	10 ± 4	13 ± 4	<0.001
MA-SOFA, day 5	8 ± 5	10 ± 4	<0.001

Data expressed as n (%) or mean ± SD
*Excluding patients receiving therapy pre-enrollment
MA-SOFA: mortality-adjusted Sequential Organ Failure Assessment, RRT: renal replacement therapy

No significant differences after adjustment; disparities driven by pre-enrollment organ dysfunction

Source: Crit Care Med. 2023;51(00):1-11.

Adjunctive Agent Effects

Agent	NEE dose	Mortality	Multiorgan failure	LOS	Quality of evidence
AT2	↓/↔	↔	↔	--	Low/moderate

Methylene Blue

Methylene Blue

- Inhibition of NO synthase and soluble guanylate cyclase reverses vasodilation
- Risks
  - Monoamine oxidase inhibition Methemoglobinemia
  - Hemolysis with glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Increased pulmonary vascular resistance
- Preliminary data from small prospective studies suggest increased MAP but no difference in clinical outcomes

Sources: CHEST. 2018;154(2):416-26.
Crit Care Med. 2001;29(10):1860-7.
Anesth Intensive Care. 2002;30(6):755-62.
Nitric Oxide. 2010;22(4):275-80.

Methylene Blue Dosing Strategies

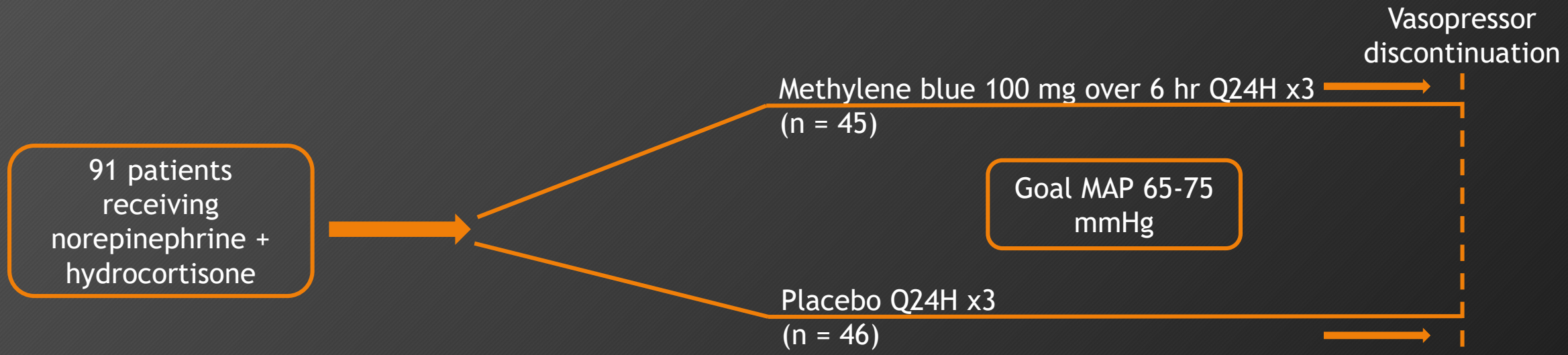
- Retrospective cohort of patients receiving norepinephrine ≥0.1 mcg/kg/min
- Dosing strategies
  - 2 mg/kg bolus + 0.25 mg/kg/hr infusion (n = 111)
  - 2 mg/kg bolus only (n = 59)
  - 0.25 mg/kg/hr infusion only (n = 39)
- All strategies effective in promoting hemodynamic stabilization
  - Increased MAP response with bolus + infusion and bolus only
  - Decreased mortality with bolus + infusion
- Improved pharmacodynamics with bolus + infusion may sustain NO pathway inhibition

Source: Front Med (Lausanne). 2022;9:1014276.

Early Methylene Blue in Septic Shock

Inclusion: septic shock, adequate volume resuscitation, antibiotics within 3 hr, hydrocortisone 200 mg/day infusion

Notable exclusions: >24 hr since norepinephrine initiation, concurrent obstructive or hypovolemic shock, moribund status, family history of G6PD deficiency, serotonin re-uptake inhibitor use within 4 weeks



Source: Crit Care. 2023;27:110.

Early Methylene Blue in Septic Shock

Baseline characteristic	Placebo (n = 46)	Methylene blue (n = 45)
Age, years	47 (31-60)	46 (38-54)
SOFA score	10 (8-12)	10 (8-12)
APACHE II score	22.4 ± 4.4	22.9 ± 4.4
Time to intervention, hours	7.6 ± 2.3	8.3 ± 1.7
Fluid load, mL/kg	22 ± 9.6	24 ± 8.4
NE dose, mcg/kg/min	0.37 (0.2-0.58)	0.45 (0.27-0.68)
Vasopressin use	34 (74)	36 (80)
Methylene blue dose, mg/kg	--	1.2 (1.1-1.4)

Data expressed as n (%), mean ± SD, or median (IQR)
APACHE: Acute Physiology and Chronic Health Evaluation

Source: Crit Care. 2023;27:110.

Early Methylene Blue in Septic Shock

Outcome	Placebo (n = 46)	Methylene blue (n = 45)	P-value
Time to vasopressor discontinuation, hr	94 (74-141)	69 (59-83)	<0.001
Vasopressor reinitiation within 48 hr	13 (28)	5 (11)	0.06
28-day vasopressor-free days	19.5 (0-23.7)	23.9 (0-24.8)	0.008
28-day mortality	21 (46)	15 (33)	0.23
ICU LOS, days	7.9 (5-10)	6.6 (4.8-7.6)	0.039
Hospital LOS, days	10.5 (6.1-14)	9 (6.3-9.3)	0.027
Maximum methemoglobin saturation, %	0.5 (0.4-0.7)	2.9 (2.2-3.3)	<0.001

Data expressed as n (%) or median (IQR)

No difference in adverse effects: left ventricular ejection fraction, oxygenation, acute kidney injury, acute liver injury

Source: Crit Care. 2023;27:110.

Adjunctive Agent Effects

Agent	NEE dose	Mortality	Multiorgan failure	LOS	Quality of evidence
AT2	↓/↔	↔	↔	--	Low/moderate
Methylene blue	↓	↔	↔	↓	Low

Assessment Question #2

JH is a 30 yo white man with no past medical history presenting with septic shock secondary to community-acquired pneumonia. He has received a 30 mL/kg IV bolus of lactated Ringer's solution and prompt broad spectrum antibiotic therapy. Norepinephrine is started as his mean arterial pressure remains below goal. The intensivist advanced practice provider asks you about starting methylene blue concomitantly with norepinephrine. What is the most appropriate evidence-based response?

A. Start methylene blue 8-24 hours from norepinephrine initiation
B. Hold methylene blue until the patient is receiving high-dose norepinephrine, vasopressin, and epinephrine
C. Hold methylene blue; no evidence supports its use in septic shock
D. Start methylene blue concomitantly with hydroxocobalamin

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Hydroxocobalamin

Hydroxocobalamin

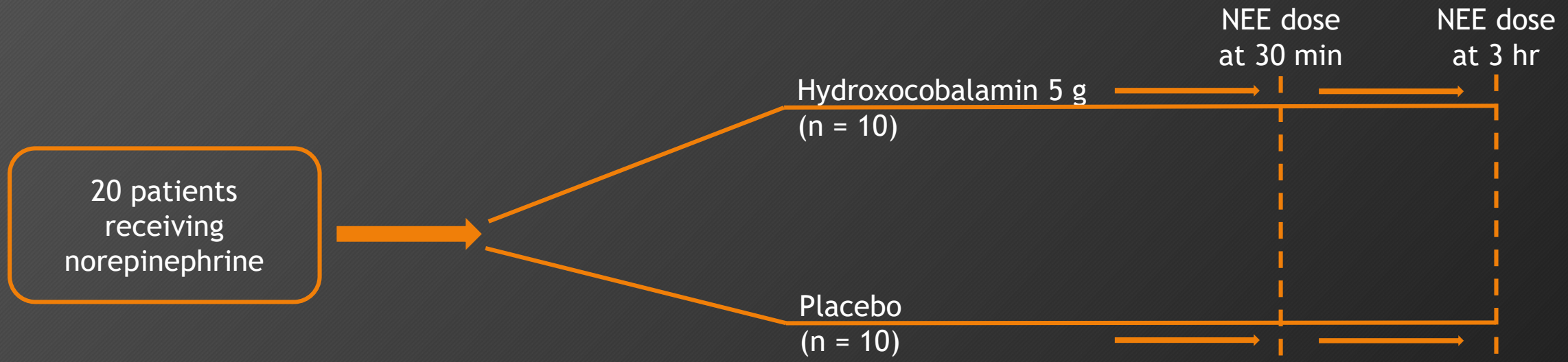
- NO scavenger and NO synthase inhibitor
- 5-10 g over 15 minutes
- Significant expense: $1000 per 5 g
- Risks
  - Colorimetric laboratory value interference
  - “Extreme” hypertension
- Majority of reported use limited to case reports/series outside of septic shock

Sources: CHEST. 2018;154(2):416-26.
J Cardiothorac Vasc Anesth. 2019;33:894-901.
Lexi-Drugs.

Hydroxocobalamin in Septic Shock

Inclusion: septic shock, receipt ≥30 mL/kg IV fluid bolus receipt of norepinephrine ≥0.1 mcg/kg/min

Notable exclusions: ICU admission >24 hr, moribund status, history of urinary calcium oxalate crystals, active bleeding or hemolysis



Source: CHEST. 2023;163(2):303-12.

Hydroxocobalamin in Septic Shock

Outcome	Placebo (n = 10)	Hydroxocobalamin (n = 10)	P value
NEE dose, mcg/kg/min			
Baseline	0.31 (0.2-0.54)	0.25 (0.2-0.36)	0.7
30 min	0.3 (0.2-0.72)	0.14 (0.1-0.21)	0.01
3 hr	0.26 (0.17-0.9)	0.13 (0.1-0.21)	0.06
Hospital mortality	4 (40)	4 (40)	1
28-day vasopressor-free days	22 (0-26)	18 (0-26)	0.81
28-day ICU-free days	6 (0-17)	10 (0-21)	0.63

Data expressed as n (%) or median (IQR)

No difference in adverse effects: calcium oxalate nephropathy, laboratory interference

Source: CHEST. 2023;163(2):303-12.

Adjunctive Agent Effects

Agent	NEE dose	Mortality	Multiorgan failure	LOS	Quality of evidence
AT2	↓/↔	↔	↔	--	Low/moderate
Methylene blue	↓	↔	↔	↓	Low
Hydroxocobalamin	↓	↔	↔	↔	Very low

Assessment Question #3

Which of the following patients with septic shock is the best candidate for use of hydroxocobalamin?

A. A 62 yo white woman with depression and chronic pain treated with citalopram and transdermal fentanyl who is maintaining a mean arterial pressure of 75 mmHg with norepinephrine 0.05 mcg/kg/min
B. A 50 yo black woman with no past medical history who is maintaining a mean arterial pressure of 70 mmHg after a 2000 mL IV bolus of lactated Ringer's solution
C. A 78 yo man of Asian descent with a family history of G6PD deficiency who has received escalating doses of norepinephrine over the past 6 hours despite the addition of hydrocortisone and vasopressin
D. A 43 yo black man with HTN on amlodipine whose mean arterial pressure is less than 65 mmHg despite a 1000 mL IV bolus of 0.9% sodium chloride and norepinephrine 0.1 mcg/kg/min

Assessment Question #3

Which of the following patients with septic shock is the best candidate for use of hydroxocobalamin?

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B. A 50 yo black woman with no past medical history who is maintaining a mean arterial pressure of 70 mmHg after a 2000 mL IV bolus of lactated Ringer's solution
C. A 78 yo man of Asian descent with a family history of G6PD deficiency who has received escalating doses of norepinephrine over the past 6 hours despite the addition of hydrocortisone and vasopressin
D. A 43 yo black man with HTN on amlodipine whose mean arterial pressure is less than 65 mmHg despite a 1000 mL IV bolus of 0.9% sodium chloride and norepinephrine 0.1 mcg/kg/min

Vitamin C & Thiamine

Vitamin C & Thiamine

- Vitamin C: cofactor for catecholamine and vasopressin synthesis
  - 1.5 g Q6H
- Thiamine: cofactor in oxidative energy metabolism, prevents accumulation of potentially nephrotoxic vitamin C metabolite
  - 200 mg BID
- Retrospective before/after study of the “metabolic resuscitation cocktail” of vitamin C, thiamine, and hydrocortisone in 94 patients published in 2017 sparked a flurry of interest

Sources: CHEST. 2018;154(2):416-26.
CHEST. 2017;151(6):1229-38.

Vitamin C, Thiamine, & Hydrocortisone Metaanalysis

Outcome	N (8 trials)	Weighted mean difference or risk ratio	95% CI	I^2
Change in SOFA score at 72 hr	1253	-0.82	-1.15 to -1.48	0%
Vasopressor duration, hr	540	-15	-25 to -4	60%
AKI or need for RRT at 72 hr	1219	1.02	0.8 to 1.3	0%
28-day mortality	1333	1.02	0.86 to 1.2	0%

Conflicting results from other trials assessing vitamin C and thiamine individually

Sources: Crit Care Med. 2021;49(12):2112-20.
N Engl J Med. 2022;386(25):2387-98.
Crit Care Med. 2016;44(2):360—67.
Crit Care Med. 2018;46(11):177-52.

Adjunctive Agent Effects

Agent	NEE dose	Mortality	Multiorgan failure	LOS	Quality of evidence
AT2	↓/↔	↔	↔	--	Low/moderate
Methylene blue	↓	↔	↔	↓	Low
Hydroxocobalamin	↓	↔	↔	↔	Very low
Vitamin C +/- thiamine	--	↔	↓/↔	--	Moderate

Xuebijing (XBJ)

XBJ background

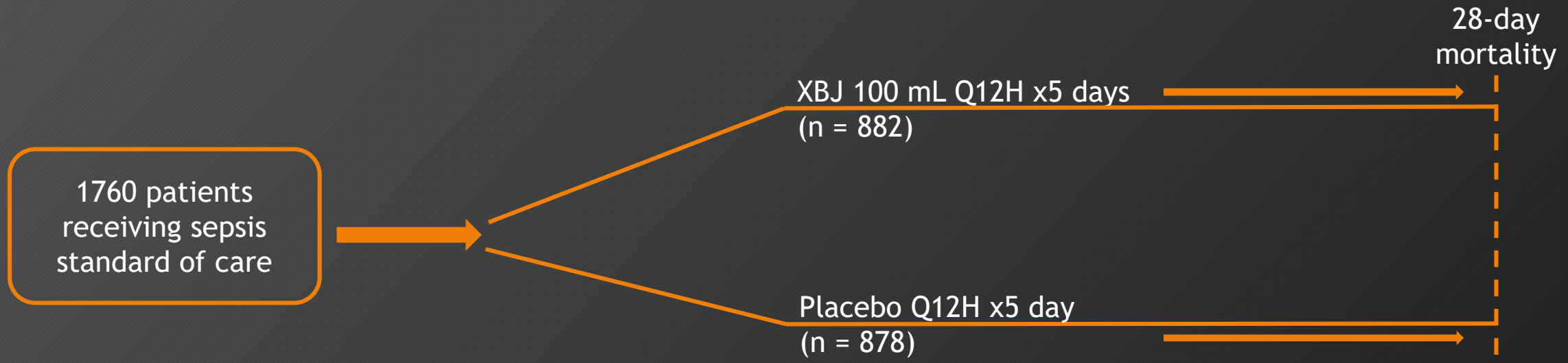
- Herbal-based IV preparation used in China
- Inhibits inflammatory release of inflammatory mediators & antagonizes endotoxin

Source: JAMA Intern Med. 2023;183(7):647-55.

EXIT-SEP

Inclusion: sepsis, age 18-75 years, SOFA score 2-13

Notable exclusions: >48 hr since sepsis diagnosis, severe primary disease, severe liver or kidney dysfunction, immunosupression



Source: JAMA Intern Med. 2023;183(7):647-55.

EXIT-SEP

Baseline characteristic	Placebo (n = 906*)	XBJ (n = 911*)
Age, years	56.8 ± 13.6	56.3 ± 13.4
Septic shock	415 (47.3)	415 (47.6)
SOFA score	7.1 ± 3	7.1 ± 3
APACHE II score	12.7 ± 6.1	12.5 ± 6.2
Mechanical ventilation	492 (54.8)	483 (53.4)
RRT	93 (10.6)	79 (9.1)
Vasopressor(s) within 48 hr	411 (45.4)	439 (48.2)
Glucocorticoid(s) within 48 hr	129 (14.2)	121 (13.3)

Data expressed as n (%) or mean ± SD
*Includes patients who did not receive assigned treatment

Source: JAMA Intern Med. 2023;183(7):647-55.

EXIT-SEP

Outcome	Placebo (n = 906)	XBJ (n = 911)	P-value
28-day mortality	230 (26.1)	165 (18.8)	<0.001
ICU LOS	10.6 (10.1 to 11)	9.8 (9.3 to 10.3)	0.03
Hospital LOS	15.4 (14.8 to 16)	15.9 (15.3 to 16.5)	0.23
Change in SOFA score			
3 days	-0.9 (-1.1 to -0.7)	-1 (-1.2 to -0.8)	0.55
6 days	-1.7 (-1.9 to -1.5)	-2.4 (-2.6 to -2.1)	<0.001
Change in APACHE II score			
3 days	-2 (-2.3 to -1.7)	-2.1 (-2.4 to -1.8)	0.75
6 days	-2.3 (-2.6 to -1.9)	-2.8 (-3.2 to -2.4)	0.046
Alanine aminotransferase elevation	42 (4.8)	51 (5.8)	--

Data expressed as n (%) or mean (95% CI)

Source: JAMA Intern Med. 2023;183(7):647-55.

Adjunctive Agent Effects

Agent	NEE dose	Mortality	Multiorgan failure	LOS	Quality of evidence
AT2	↓/↔	↔	↔	--	Low/moderate
Methylene blue	↓	↔	↔	↓	Low
Hydroxocobalamin	↓	↔	↔	↔	Very low
Vitamin C +/- thiamine	--	↔	↓/↔	--	Moderate
XBJ	--	↓	↓	↓	Low

Summary

Assessment Question #4

MP is a 67 yo black woman with rheumatoid arthritis on methothrexate and chronic prednisone presenting with septic shock secondary to pyelonephritis. She remains hypotensive despite norepinephrine 0.5 mcg/kg/min, vasopressin 0.03 units/min, and continuous infusion hydrocortisone. Which agent has the most robust data as adjunctive therapy?

A. Vitamin C and thiamine
B. Angiotensin II
C. Hydroxocobalamin
D. Methylene blue

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Refractory Septic Shock Therapy

Agent	Mechanism of Action	Dose	Considerations
Fluid resuscitation	Restore intravascular volume	≥30 mL/kg IV	Baseline therapy
Norepinephrine	Vasoconstriction & chronotropy	0.05-0.5 mcg/kg/min IV	Baseline therapy
Vasopressin	Vasoconstriction	0.04-0.04 units/min IV	Baseline therapy
Hydrocortisone	↑ catecholamine response	200 mg/day IV	Baseline therapy
Other catecholamines	Vasoconstriction &/or chronotropy	0.05-0.5 mcg/kg/min NEE IV	First adjunct, reasonable to limit total NEE dose
AT2	Vasoconstriction	10-80 ng/kg/min IV	Reasonable option, may be limited by cost
Methylene blue	↓ vasodilation	100 mg IV over 6 hr Q24H x3	Reasonable option
Hydroxocobalamin	↓ vasodilation	5 g IV x1	Methylene blue alternative
Vitamin C +/- thiamine	↑ catecholamine & vasopressin synthesis	1.5 g IV Q6H +/- 200 m IV Q12H	Limit use

Withdrawal of Treatment

- Limited guidance once shock resolves
- Methylene blue: complete 3-day course
- Hydrocortisone
  - Discontinue once vasopressors discontinued
  - Discontinue at 5-7 days
  - Taper once vasopressors at a persistently low dose
- Vasopressors
  - Withdraw in reverse order of addition
  - Decrease doses of each agent
  - Withdraw AT2 first followed by catecholamines
  - Discontinue vasopressin last

Unknowns

- Ideal NEE dose cutoff for addition of adjunctive therapies to catecholamines
- Ideal order of adjunctive therapy addition or combination of therapies
- High-quality data on clinical outcomes
- Withdrawal of multimodal therapy once shock resolves

Conclusions

- Refractory septic shock is a complex syndrome requiring a multimodal approach to limit adverse effects of individual agents
- Limited high-quality data exists to guide choice of adjunctive agents
- AT2 and methylene blue currently have the most evidence beyond SSC guideline-recommended therapy

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Thank you!

Sarah Blackwell, PharmD, BCPS, BCCCP
Clinical Pharmacy Specialist, Medical Critical Care
Sarah.Blackwell@bhsala.com