I'm Shocked: Adjunctive Vasoactive Therapies in Septic Shock

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1

Disclosures

- SB: serves on the speaker's bureau for LaJolla Pharmaceutical Company. All relevant conflicts have been resolved.

2

Objectives

1. Illustrate a classic presentation of septic shock.
2. Interpret hemodynamic variable alterations and compensatory mechanisms associated with septic shock.
3. Explain adjunctive therapies and considerations for use.

3

AUDIENCE ENGAGEMENT ACTIVITY #1

Framing of Outcomes in Septic Shock

4

Conceptualizing Septic Shock

- Sepsis = *sēpein*
- Shock = state in which there is failure of the circulatory system to maintain adequate cellular perfusion and/or oxygen delivery
- Three vital components
  - Arterial hypotension (absolute or relative)
  - Clinical signs of hypoperfusion
  - Abnormal cellular oxygen metabolism (hyperlactatemia)

N Eng J Med. 2013; 369:1726-1734.

5

Epidemiology of Septic Shock

- > 750,000 cases of severe sepsis/septic shock annually
- Sepsis accounts for 6-30% ICU admissions
  - Severe sepsis/septic shock ~10%
  - Type of ICU dependent
- Morality is associated with progression within disease continuum
  - 600 deaths per day from severe sepsis/septic shock
- Mortality is time dependent
  - Significantly increases if undetected for > 6 hours

N Eng J Med. 2003; 348:1546
Crit Care Med. 2004; 32:2207

6

History of Septic Shock has evolved to implicate the host response

"...hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat." Dr. William Osler

"They will invade and replicate if given the chance... but it is our response to their presence that makes the disease." -Germs Dr. Lewis Thomas

1513 1900 1972 1991 2002

"Patients appear to die from the body's response rather than from the infection itself."

Surviving Sepsis Campaign

ACCP/SCCM named condition	Defining criteria
SIRS	Core body temperature >38°C or <36°C HR >90 bpm Respirations ≥20/min (or $PaCO_2$ <32 mmHg) WBC ≥12,000/µl or ≤4000/µl or >10% immature forms
Sepsis	As least two SIRS criteria caused by known or suspected infection
Severe sepsis	Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis
Septic shock	Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation

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Expert Rev Anti Infect Ther. 2012;10(6).

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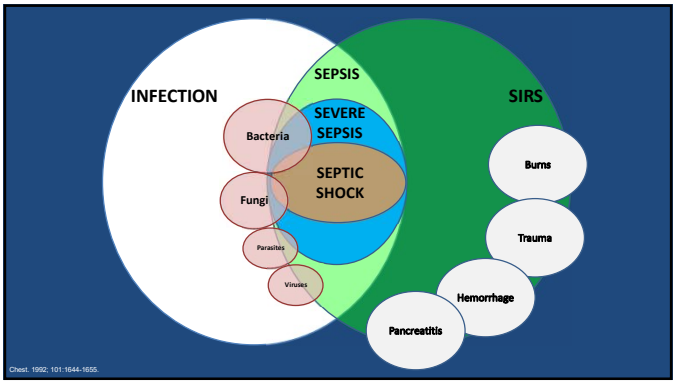

Chest. 1992; 101:1644-1655.

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Sepsis-3: Sepsis

INFECTION

CHANGE IN:

Sequential
Organ
Failure
Assessment

≥2

JAMA. 2016; 315(8): 801-810.

9

Pathophysiology

- Involves multiple interactions
  - Infecting microorganism
  - Host immune response
  - Inflammatory cascade
  - Procoagulant cascade
  - Anti-fibrinolysis cascade

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N Eng J Med 2003;348:1546

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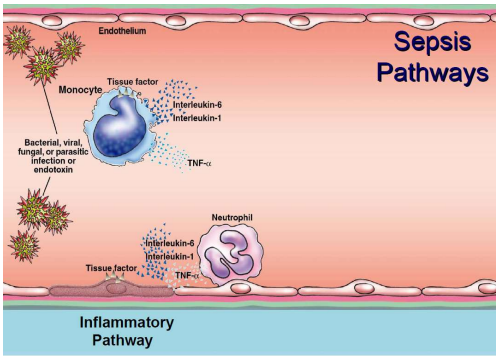

Ann Pharmacother. 1995; 29: 892-905. N Engl J Med. 2008; 358: 1037-1052. N Engl J Med 2006; 355:1699-1713

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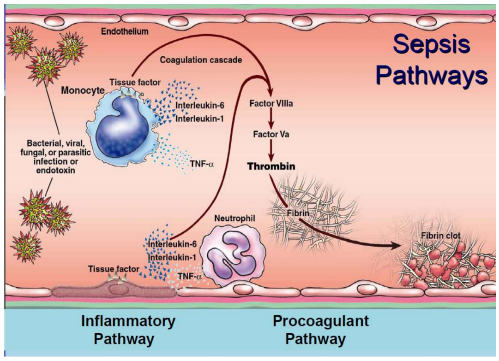

Ann Pharmacother. 1995; 29: 892-905. N Engl J Med. 2008; 358: 1037-1052. N Engl J Med 2006; 355:1699-1713

12

Test Your Knowledge 1

The pathophysiology of septic shock requires the interaction of the infecting microorganism and the:

A. Host immune response
B. Environmental adaptive response
C. Host fibrinolytic cascade
D. Host anti-inflammatory cascade

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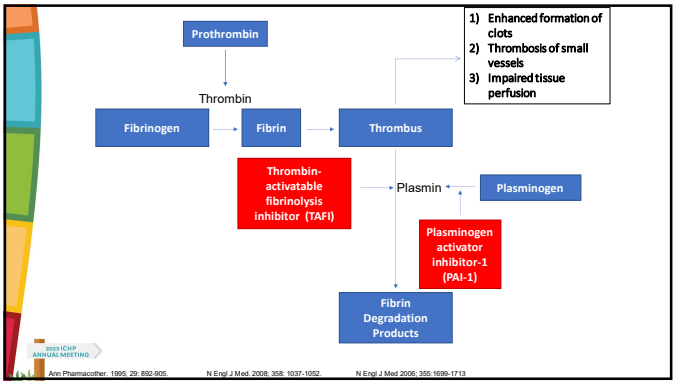


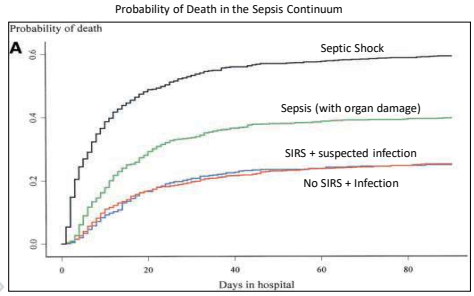
14

ORGAN	SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE				
	0	1	2	3	4
CV	MAP ≥ 70 mmHg	MAP < 70 mmHg	DA < 5 or DB	DA 5.1-15 or EPI/NE ≤ 0.1	DA > 15 or EPI/NE > 0.1
RESP (PaO_2:FiO_2)	≥400 mmHg	< 400 mmHg	< 300 mmHg	< 200 mmHg w/ support	< 100 mmHg w/ support
RENAL -SCr -UOP	< 1.2 mg/dL	1.2-1.9 mg/dL	2-3.4 mg/dL	3.5-4.9 mg/dL < 500 mL/24hr	> 5 mg/dL < 200 mL/24hr
HEPATIC	< 1.2 mg/dL	1.2-1.9 mg/dL	2-5.9 mg/dL	6-11.9 mg/dL	> 12 mg/dL
COAG (Plt x 10^3)	≥ 150 /mcL	< 150 / mcL	< 100 /mcL	< 50 / mcL	< 20 /mcL
CNS (GCS)	15	13-14	10-12	6-9	< 6

JAMA. 2016; 315(8): 801-810.

15

Disease Continuum vs. Mortality



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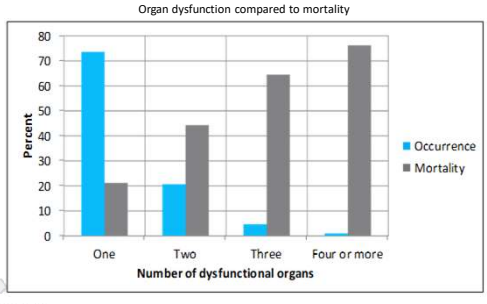
Organ Dysfunction vs. Mortality



17

Test Your Knowledge 2
Case A

HPI: Patient is a 72 y/o M who is POD4 from a planned admission for extensive abdominal surgery (abdominal exenteration with ileal conduit) and POD1 pelvic reconstruction. The nurse is calling the team to report fever and that his urine output has dropped to 0.3 mL/kg/hr.

PMH:
- Colon cancer s/p resection, chemotherapy, and radiation (2010)
- HTN
- HLD
- Stroke (2000, 2011)
- L hemiparesis
- Hypothyroidism
- IDDM

Allergies: NKDA
Anthropometrics: Weight 95kg

Vital Signs:
Temperature: 39.2°C (max 39.5°C)
HR: 135 beats/min
RR: 38 breaths/min
BP: 87/51 mmHg

Labs:

139 | 109 | 40 / 120
3.7 | 23 | 1.69 (baseline 0.4)

20 \ 8.2 / 90
/ 23.9\

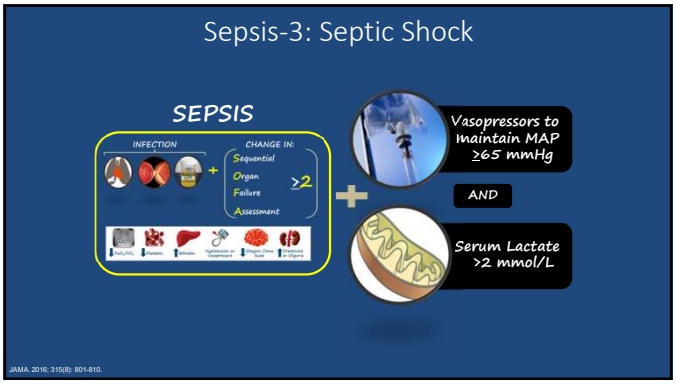
18

Test Your Knowledge 2

- What part of this patient case raises the suspicion of sepsis?

19

Sepsis-3: Septic Shock



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Shock States

Cardiogenic:
Acute myocardial infarction
End-stage cardiomyopathy
Advanced valvular heart disease
Myocarditis
Acute arrhythmias

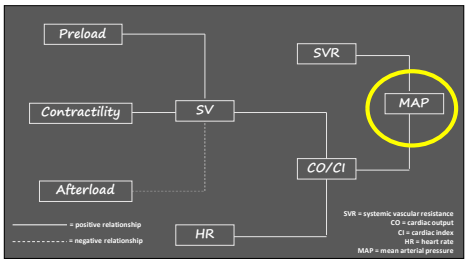
Hypovolemic:
Internal or external blood loss

Obstructive:
Pulmonary embolism
Cardiac tamponade
Tension pneumothorax

Distributive:
Anaphylaxis
Neurogenic
SEPTIC SHOCK

21

Global Hemodynamic Interactions



N Eng J Med 1974; 290: 1124.-1129.

22

Hemodynamic Compensation

Preload (CVP, PAOP)*	CO	SVR	HR
↓	EARLY ↑ LATE ↓	↓	↑

*Relative hypovolemia due to increase in the "tank" size (massive vasodilation)

23

Test Your Knowledge 3

The underlying hemodynamic dysfunction in septic shock primarily involves:

A. Cardiac output
B. Contractility
C. Systemic vascular resistance
D. Heart rate

24

Test Your Knowledge 4
Case B

HPI:
Patient is a 72 y/o M who is POD4 from a planned admission for extensive abdominal surgery (abdominal exenteration with ileal conduit) and POD1 pelvic reconstruction. The nurse is calling the team to report fever and that his urine output has dropped to 0.3 mL/kg/hr.

Diagnostics:
TTE demonstrating LVEF 75%

Arterial Line:
MAP 63 mmHg
HR: 135 beats/min

Cuff blood pressure:
BP: 87/51 mmHg

Pulse oximeter:
SpO2 = 96%

25

Test Your Knowledge 4

Which of the following hemodynamic variables are most likely a compensatory response for this septic shock patient?

a. **MAP = 63 mmHg**
b. **BP = 87/51 mmHg**
c. **LVEF = 75%**
d. **Oxygen saturation = 96%**

26

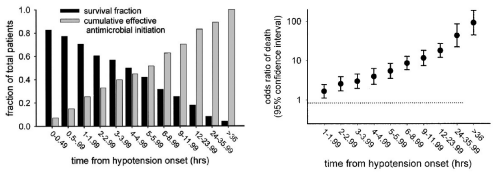
Treatment of Septic Shock

Antimicrobial Therapy | EARLY GOAL DIRECTED THERAPY | Adjunctive Therapy

27

Antibiotic therapy

- Goal:
  - Administration of **effective** antibiotics within the **first hour** of recognition



Critical Care Med 2006; 34(6) 1589-1596

28

Antibiotic therapy

- Additional considerations:
  - Activity against likely pathogens
  - Penetrate adequately to presumed tissues
- *Source control*
  - Rapidly identify sources
  - Intervene to control source as soon as feasible (ideally within 12 hours)
    - Exception – peripancreatic necrosis
  - Consider hemodynamic instability
    - Least physiologic insult (eg. percutaneous interventions vs. surgical)
  - Removal of infected devices as able

Critical Care Med 2006; 34(6) 1589-1596

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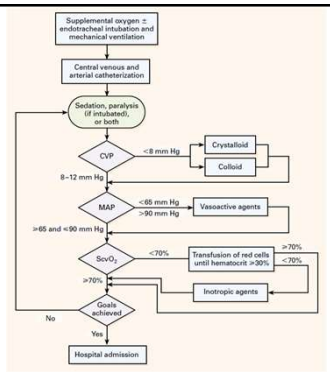

N Eng J Med. 2001; 345: 1368.

30

Fluid Resuscitation

- Crystalloids first line
  - 30 mL/kg as **initial** intravenous bolus over minutes
  - Within the **first 3 hours** of diagnosis
  - Balanced crystalloids instead of normal saline for resuscitation (weak recommendation)
- Followed with "hemodynamic" techniques
  - Non-invasive
  - Invasive

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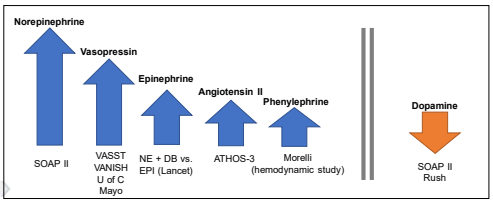
Crit Care Med 2013; 41(2): 580-637.
Intensive Care Med 2021; 47: 1181–1247
EARLY GOAL DIRECTED THERAPY

31

Vasopressors

- Fluid refractory
- Goal:
  - MAP ≥ 65 mmHg
  - **Should be individualized: "normal" BP and comorbidities**



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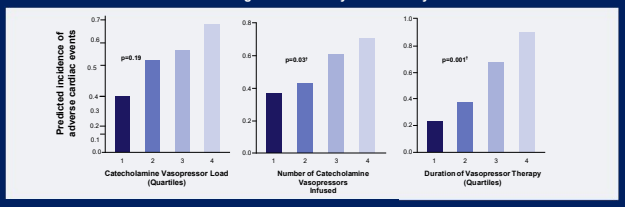
Crit Care Med 2013; 41(2): 580-637
EARLY GOAL DIRECTED THERAPY

32

Catecholamine Vasopressor Therapy & AE's

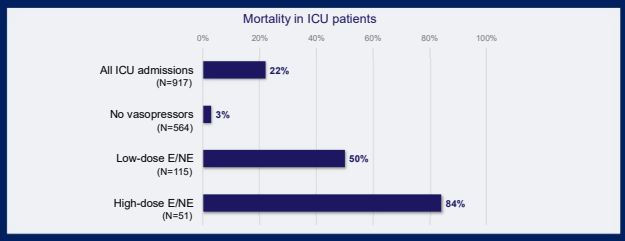
- In a prospective observational study of 112 SICU patients, catecholamine vasopressor therapy* was associated with greater adverse event rates
- 48.2% experienced cardiac AEs during catecholamine vasopressor therapy
  - Number of agents infused and duration of therapy independently associated with cardiac AEs‡
  - Cardiac AEs associated with greater morbidity and mortality



*Epinephrine, NE, dopamine, and phenylephrine. †Independent association with the occurrence of cardiac AEs
‡ New-onset tachyarrhythmia [49.1%], prolonged elevated heart rate [23.7%], myocardial cell damage [17.5%]
SICU=surgical intensive care unit; AE=adverse event; NE=norepinephrine.
Intensive Care Med. 2012;38:950-958.

33

Catecholamine Vasopressor Therapy & Mortality



In patients treated with high-dose catecholamines at any time during their ICU stay, the odds ratio of mortality was 5.1 (CI, 2.02–12.9; p=0.001)

E/NE=epinephrine/norepinephrine; CI=confidence interval.
J Crit Care. 2014;29:157-160.

34

Adjunctive Therapy

- Steroids
- "Fruit Cocktail"
- Blood product administration (goal Hgb > 7 g/dL)
- Mechanical ventilation in ARDS
- Sedation, analgesia, and paralysis
- Glucose control (<180mg/dL)
- Renal replacement therapy
- DVT prophylaxis and SUP
- Nutrition
- Goals of care

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Crit Care Med 2013; 41(2): 580-637

35

AUDIENCE ENGAGEMENT ACTIVITY #2

RE-framing of Outcomes in Septic Shock

36

Inadequate or Ineffective Natural Vasoconstrictive Response

- Peripheral levels of catecholamines are dramatically increased but **decreased responsiveness to natural vasoconstrictors**
- Evidence of activation of the renin–angiotensin system - **? inconsistent interpatient response**.
- **Deficiency in vasopressin** - Vasopressin is a nonapeptide potent vasopressor hormone released by the posterior pituitary gland in response to hypotension

37

37

Induced Vasodilatory Response

- Nitric oxide (NO)
- Prostacyclin synthesis
- Adrenomedullin
- Activation of the transient receptor potential vanilloid type 4 (TRPV4)

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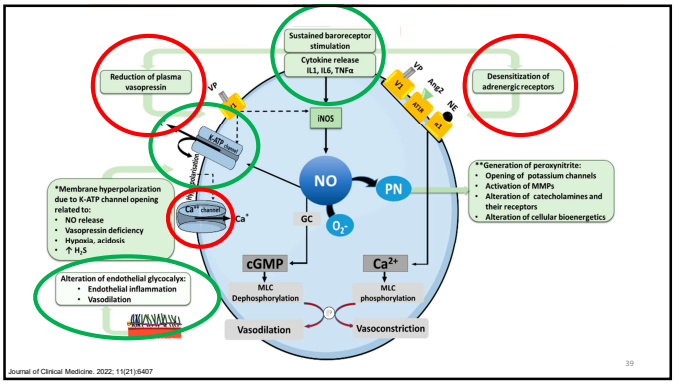

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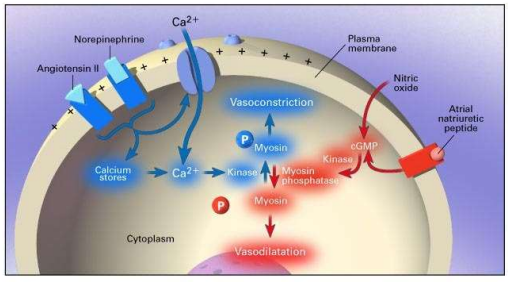

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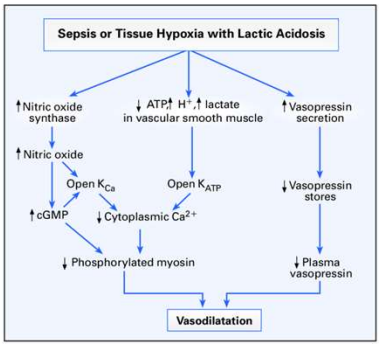

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Proposed Adjunctive Therapies

- Ascorbic Acid (Vitamin C)
- Hydroxocobalamin (Cyanokit)
- Methylene Blue (ProvayBlue)
- **Goals of these therapies?**

42

42

Ascorbic Acid (Vitamin C)

Proposed benefit

- Cofactor in the biosynthesis of cortisol, norepinephrine (restoring receptor sensitivity)
- Critically ill patients are at risk of low plasma ascorbic acid due to decreased intake, absorption, and acutely increased metabolism
- Clinical studies have investigated its use in septic shock among various ICU populations

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43

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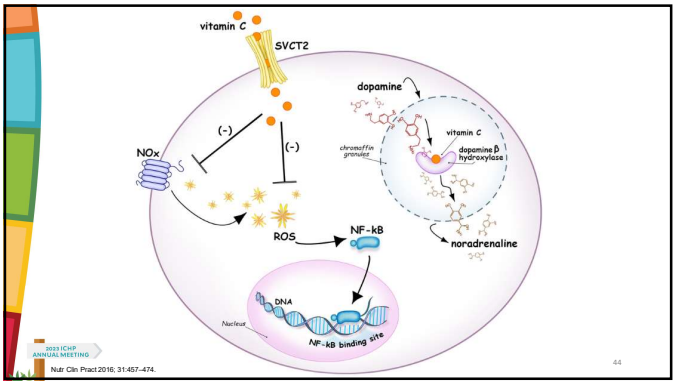

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Nutr Clin Pract 2016; 31:457–474.

44

44

ANIMAL MODEL OF SEPSIS	EARLY EXCITEMENT – MARIK HAT STUDY
Exogenous vitamin C increases perfused capillary density and arteriolar vasoconstrictor responsiveness	Before–after study assessing the combination of IV vitamin C (1.5 g every 6 h), hydrocortisone (50mg every 6 h), and thiamine (200mg every 12 h) in 94 patients with severe sepsis or septic shock Hospital mortality -4 (8.5%) vs. 19 (40.4%) – p < 0.001 -Duration of pressors -18.3 ± 9.8 vs. 54.9 ± 28.4 – p < 0.001 -RRT for AKI3 -3/31 (10%) vs. 11/30 (33%) – p = 0.02

Free Radic Biol Med 2004, 37(8):1282–1289

Chest. 2017; 151(6):1229–1238

45

45

ATESS STUDY	VITAMINS STUDY
Prospective RCT to evaluate effect of Vitamin C (50mg/kg q12hr) and Thiamine (200mg q12hr) on organ function in first 72 hours (SOFA score) and outcomes of shock reversal and mortality 111 of 116 randomized patients were included in the analysis Delta SOFA score -3 (1 to 5) vs. 3 (0–4) - p = 0.96 7-day, 28-day, and 90-day mortality, -9.4% vs. 10.3%, p = 0.87 -20.8% vs. 15.5%, p = 0.47 -32.1% vs. 27.6%, p = 0.61 No differences in RRT for AKI, mechanical ventilation free days, shock reversal, vasopressor free days (p > 0.05)	Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock 216 patients – IV vitamin C (1.5 g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (200mg every 12 hours) vs. IV hydrocortisone (50mg every 6 hours) alone until shock resolution or up to 10 days. Alive and vasopressor free at 7 days - 122.1 hours (76.3-145.4) vs.124.6 hours (82.1-147) (95%CI, –8.3 to 7.2 hours; p = 0.83). Change in SOFA score at 3 days – 2 (–4 to 0) vs. –1 (–3 to 0), p = 0.02 No difference in mortality, mechanical ventilation free days, RRT for AKI free days, ICU LOS, mortality (p > 0.05)

Intensive Care Med. 2020 Nov;46(11):2015-2025

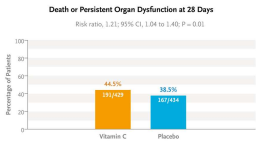
JAMA. 2020;323(5):423-431.

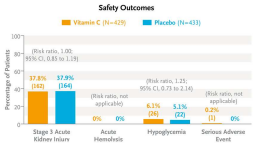
46

46

LOVIT Trial: Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

- RCT infection + vasopressor within 24 hours of diagnosis
- Infusion of either ascorbic acid (50 mg/kg) or matched placebo administered every 6 hours for up to 96 hours





N Engl J Med 2022; 386:2387-2398

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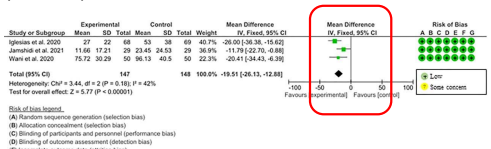
Meta analysis

- Nine RCTs were identified and included in the outcome evaluation.
- HAT therapy did not improve the 28-day and ICU mortality, new-onset AKI, ICU-LOS, or SOFA scores.



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In Vivo. 2023 May-Jun;37(3):1236-1245.

48

48

Ascorbic Acid Takeaways

- No improvement in mortality
- Inconsistent results surrounding organ function
- Potential impact on vasopressor duration

49

Hydroxocobalamin (Vitamin B12)

- Directly inhibits NO and iNOS, which prevents myosin dephosphorization minimizing the vasodilatory effects of these pathways
- Binds to hydrogen sulfide (H_2S), an endogenous vasodilator, by modifying potassium channels and amplifying its elimination

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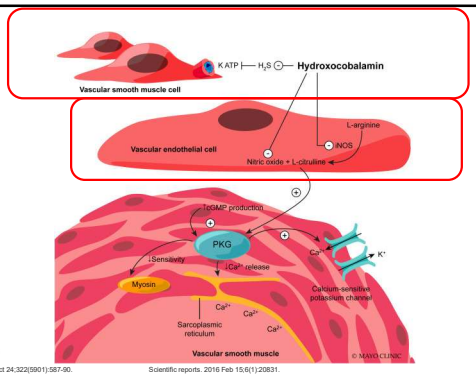

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Hydroxocobalamin in refractory septic shock: a retrospective case series.

- Case report and case series of 26 patients in refractory septic shock
- At least one dose of 5 g IV over 15 minutes
- Primary outcomes were the change from baseline in MAP and NE at 1, 6, and 24 hours after hydroxocobalamin administration.

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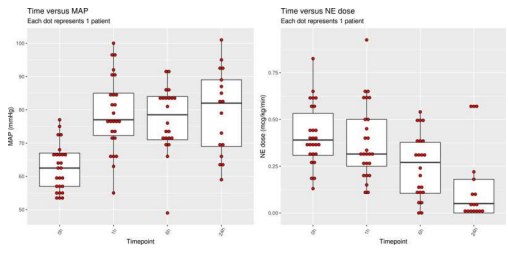
Hydroxocobalamin in refractory septic shock: a retrospective case series.



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The Intravenous Hydroxocobalamin in Septic Shock Trial

- Phase 2 single-center, double-blind, allocation-concealed, placebo-controlled, parallel-group pilot randomized controlled trial comparing high-dose IV hydroxocobalamin with placebo in critically ill adults with septic shock
- The primary outcome was study feasibility (enrollment rate, clinical and laboratory compliance rate, and contamination rate).
- Secondary outcomes included between-group differences in plasma H_2S concentrations and vasopressor dose before and after infusion.

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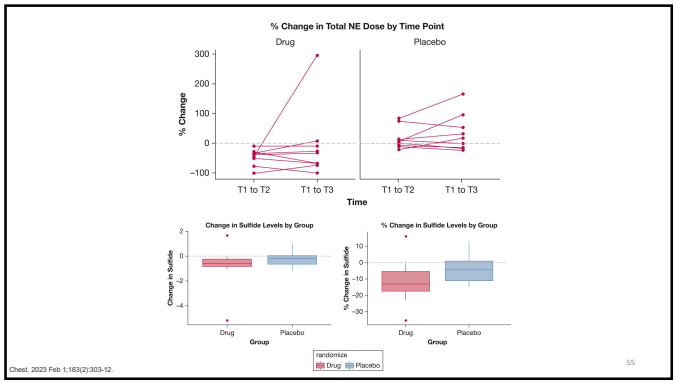

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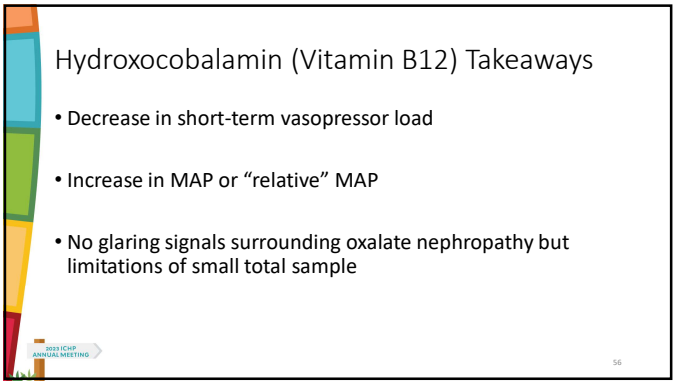

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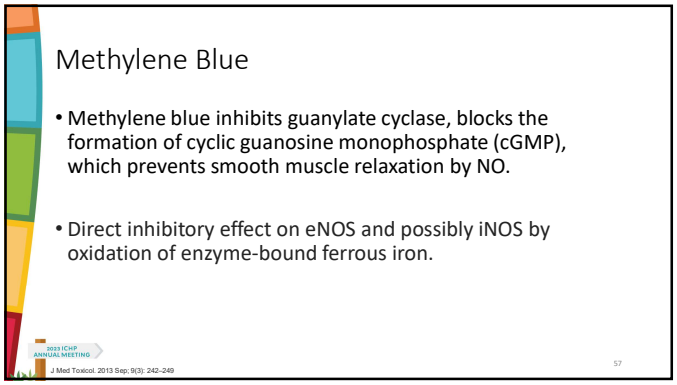

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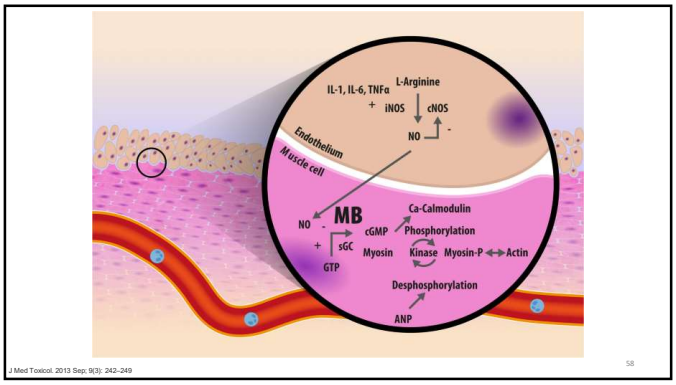

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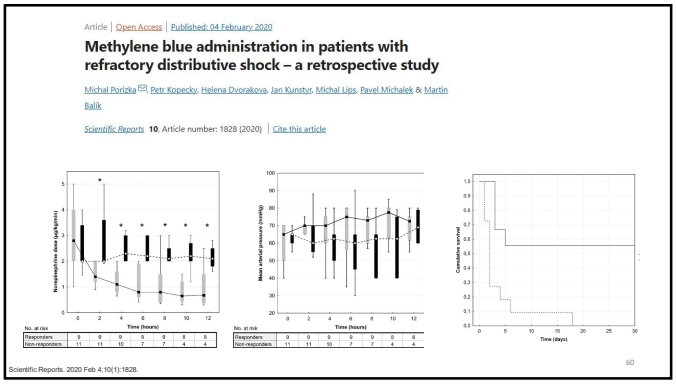

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Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial

- 100 mg of methylene blue over six hours, once a day for a total of three doses/days
- Primary outcome: Time to vasopressor discontinuation
- Secondary outcome: Vasopressor free days at 28 days

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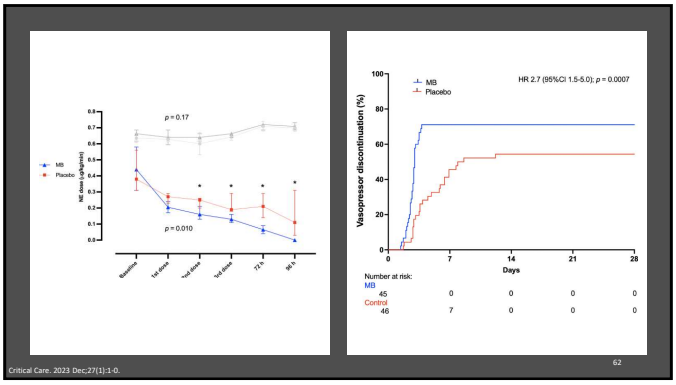
Critical Care. 2023 Dec;27(1):1-0.

61

61



Critical Care. 2023 Dec;27(1):1-0.

62

62

Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial

- Methemoglobin saturation between the two groups.... This did not cause any clinical effects.

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63

63

Methylene Blue Takeaways

- Decrease in short-term vasopressor load and earlier discontinuation
- Possible decrease in vasopressor free days which could impact ICU length of stay and hospital length of day

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64

64

Test Your Knowledge 5

Studies surrounding early high dose ascorbic acid as part of HAT therapy in septic shock have consistently shown:

A. Mortality benefit
B. Vasopressor benefit
C. Significant toxicities
D. Organ function improvement

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65

Test Your Knowledge 6

Studies surrounding hydroxocobalamin in refractory septic shock have primarily demonstrated:

A. Increased rates of oxalate nephropathy
B. Improved mortality
C. Decrease in vasopressor load
D. Decrease in mean arterial pressure

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66

66

Test Your Knowledge 7

Studies surrounding methylene blue in both early and refractory septic shock have demonstrated:

A. Improved survival
B. Unacceptable rates of serotonin syndrome
C. Organ function improvement
D. Decreased vasopressor duration

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67

67

Summary

- Ascorbic acid, hydroxocobalamin, and methylene blue all appear to have a positive impact on vasopressors
- Unclear clinical impact of these findings
- Strong consideration in refractory septic shock
- MORE RESEARCH NEEDED

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68

68

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69

69