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MERCER UNIVERSITY COLLEGE OF PHARMACY

If Patients' Lives are on the Clock, Time to Consider Adjuncts for Shock

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Disclosures

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

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Pharmacist Learning Objectives

- Review the different types of shock and their associated pathophysiology
- Identify common risk factors for developing shock
- Describe current treatment modalities and discuss alternative therapies for the management of shock

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Pharmacy Technician Learning Objectives

- Discuss the importance of true STAT medications
- Describe the disease state known as sepsis
- Identify which medications should be prioritized during compounding for patients with septic shock

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What is Shock?

Shock is defined as a state of cellular and tissue hypoxia secondary to circulatory failure causing reduced oxygen delivery and/or increased oxygen consumption or inadequate oxygen utilization.

N Engl J Med. 2013 Oct 31;369(18):1726-34.

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Types of Shock

- Distributive shock
- Hypovolemic shock
- Cardiogenic shock
- Obstructive shock

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Types of Shock

Type of Shock	Description	Examples
Distributive	• Loss of microcirculatory autoregulation • Increased metabolic demand	• Sepsis
Hypovolemic	• Reduction in intravascular volume	• Hemorrhagic shock • Fluid loss (i.e. NVD)
Cardiogenic	• Reduction in pump function	• Post-MI
Obstructive	• Impaired venous return • Decreased cardiac output	• Tension pneumothorax • Pericardial tamponade • Massive PE

NVD - nausea, vomiting, and diarrhea
MI- myocardial infarction
PE- Pulmonary embolism

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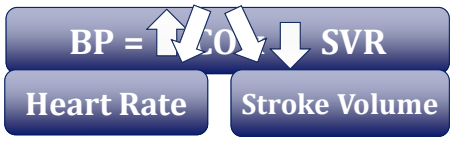
Distributive Shock: Art of Compensation

- Loss of microcirculatory regulation reduces afterload
- To compensate, heart rate and cardiac output increase



N Engl J Med 2013;369:1726-34

BP- blood pressure
CO- cardiac output
SVR- systemic vascular resistance

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Patient Case: DR

- 58 YOM who presented to the dentist with a presumed abscess and a mass that has been increasing in pain for the past month.
- Later diagnosed with head and neck cancer and had started chemotherapy shortly after.
- Code MET was called for hypotension and the patient was transferred to the medical ICU.

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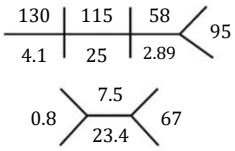
Patient Case: DR

- Vitals
  - BP: 70/40 mmHg
  - HR: 130 bpm
  - RR: 29 breaths per minute
  - Temp: 38.5°C



What else would you like to know?

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BPM- beats per min

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Septic Shock

- Most common cause of distributive shock
- Mortality ~40%
- Definitions are largely unchanged
  - Sepsis-induced hypotension persisting despite adequate fluid resuscitation
  - Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher mortality
    - Lactate > 2 mmol/L
    - Persistent hypotension requiring vasopressors to maintain MAP > 65 mmHg despite adequate volume resuscitation

Intensive Care Med. 2017 Mar;43(3):304-377
JAMA. 2016 Feb 23;315(8):801-10

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MAP- mean arterial pressure

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Septic Shock Pathophysiology

- Cytokine release
- Local mediators (nitric oxide, prostaglandins, reactive oxygen species)
- Relative vasopressin deficiency
- Adrenal insufficiency

⬆ VASODILATION
⬇ BLOOD PRESSURE

BMJ 2016;353:i1585

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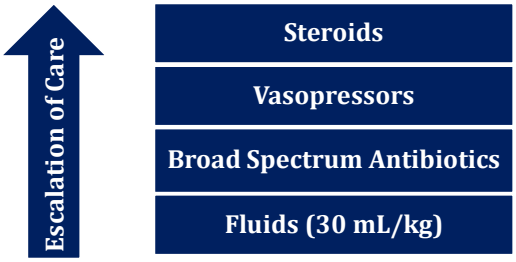
General Sepsis or Septic Shock Management



Intensive Care Med. 2017 Mar;43(3):304-377

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Patient Case: DR

- DR was diagnosed with septic shock. What is the appropriate treatment for MP?

A. Fluid resuscitation
B. Broad spectrum antibiotics
C. Use of vasopressors to maintain a MAP ≥ 65
D. All of the above
E. None of the above

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Surviving Sepsis 2021 Guideline Changes

New Recommendation	Strength
For adults with possible **septic shock** or a high likelihood for sepsis, we **recommend administering antimicrobials immediately**, ideally within **1 hr** of recognition.	***Strong***, *low quality of evidence (Septic shock).* ***Strong***, *very low quality of evidence (Sepsis without shock).* **CHANGED from previous Strong,** "…antimicrobials should be initiated as soon as possible after recognition and **within one hour for both a) septic shock and b) sepsis without shock**"
For adults with **possible sepsis without shock**, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of **antimicrobials within 3 hr** from the time when sepsis was first recognized.	***Weak***, *very low quality of evidence*

Critical Care Medicine 49(11):p e1063-e1143, November 2021

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Surviving Sepsis 2021 Guideline Changes

New Recommendation	Strength
For patients with sepsis induced hypoperfusion or septic shock we suggest **that at least 30 mL/kg** of IV **crystalloid fluid** should be given within the **first 3 hr** of resuscitation	**Weak**, *low quality of evidence* **DOWNGRADE** from ***Strong***, low quality of evidence
For adults with sepsis or septic shock, we suggest **using balanced crystalloids instead of normal saline** for resuscitation.	***Weak***, *low quality of evidence*
For adults with **septic shock and an ongoing requirement for vasopressor** therapy we suggest using **IV corticosteroids**.	***Weak***, *moderate-quality evidence* **UPGRADE from *Weak recommendation*** , *low quality of evidence*
For adults with sepsis or septic shock we **suggest against using IV vitamin C**	***Weak***, *low quality of evidence*

Critical Care Medicine 49(11):p e1063-e1143, November 2021

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Corticosteroids Controversy in Sepsis

- Suppression of the sepsis-induced inflammatory response
  - High dose steroids
  - Early studies: high dose steroids improved mortality
  - Later studies: ↑ risk and slower resolution of infections
- Reversal of shock
  - Low dose steroids
  - Relative adrenal insufficiency
    - Help with production of catecholamines
  - Reduction of cytokine production

Crit Care Med. 2017;45(9):1582-3.
Crit Care Med. 2014;42(11):2442-3.
JAMA. 2000;283(8):1038-45.

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Annane 2002

Objective

- To determine if administration of corticosteroids reduce 28-day mortality in patients with septic shock

Study Design

- Randomized, prospective, double blind, parallel group, placebo controlled trial
- Hydrocortisone 50 mg IV q6h plus fludrocortisone 50 mcg PO daily vs placebo

Population

- N=300
- Patients with septic shock separated by a ACTH-stimulation test into responders and non-responders within 8 hours of shock onset
  - Suspicion or documented infection, Temp >38.3C or <35.6C, HR >90 BPM, SBP <90 mmHg for ≥1 hour despite fluids and more than 5 mcg/kg of dopamine, NE or Epi, Lactate >2 mmol/L, and need for mechanical ventilation

JAMA. 2002 Aug 21;288(7):862-71

ACTH- adrenocorticotropic hormone
NE- norepinephrine
Epi- epinephrine

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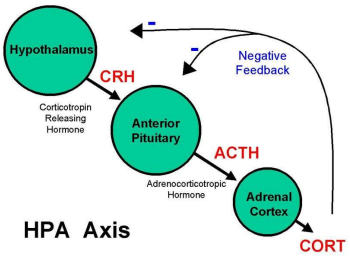
Hypothalamic–Pituitary–Adrenal axis



www.researchgate.net/figure/A-diagram-for-Hypothalamic-Pituitary-Adrenal-HPA-axis

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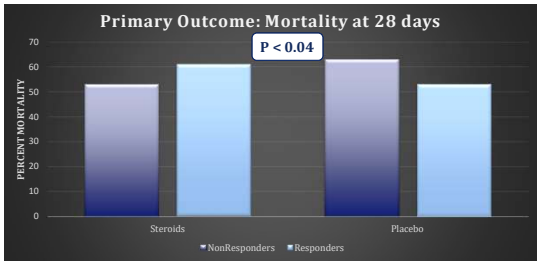
Annane 2002



JAMA. 2002 Aug 21;288(7):862-71

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Annane 2002

Nonresponder Outcomes	Steroids (n=114)	Placebo (n=115)	Odds-ratio
ICU Mortality (%)	58	70	OR 0.50; CI 0.28-0.89
Hospital Mortality (%)	61	72	OR 0.53; CI 0.29-0.96
Mortality at one year (%)	68	77	OR 0.57; CI 0.31-1.04

Responder Outcomes	Steroids (n=34)	Placebo (n=36)	Odds-ratio
ICU Mortality (%)	67	59	OR 0.99; CI 0.31-3.16
Hospital Mortality (%)	69	59	OR 1.20; CI 0.38-1.02
Mortality at one year (%)	69	71	OR 0.70; CI 0.20-2.40

Critiques:
- Patients were generally more ill limiting the generalizability
- All patients received mechanical ventilation

JAMA. 2002 Aug 21;288(7):862-71

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ICU- intensive care unit

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CORTICUS 2008

Objective

- To determine if administration of corticosteroids reduce 28-day mortality in patients with septic shock

Study Design

- Multicenter, double blind, parallel-group, randomized, placebo-controlled trial
- Hydrocortisone 50 mg IV q6h for 5 days *vs* placebo dosed at the same frequency

Population

- N=499
- Septic shock within prior 72 hours separated by a ACTH-stimulation test into responders and non-responders
  - SBP < 90 mmHg despite adequate fluid replacement
  - Or the need for vasopressors >1 hour
- Hypoperfusion or organ dysfunction attributable to sepsis

N Engl J Med. 2008 Jan 10;358(2):111-24

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IV- intravenous
SBP- systolic blood pressure

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CORTICUS 2008

Outcome	Steroids (n=251)	Placebo (n=248)	p valve
28-day mortality (%)	34	32	p=0.51
Reversal of shock (%)	76	70.4	p=0.41
Time to reversal of shock (days)	3.3	5.8	p<0.001

Adverse Event	Steroids (n=251)	Placebo (n=248)	Odds-ratio
New sepsis (%)	3	1	OR 2.97; 0.61-14.59
New shock (%)	6	2	OR 2.78; 1.02-7.58
Hyperglycemia (%)	85	72	OR 1.18; 1.07-1.31
Hypernatremia (%)	29	18	OR 1.59; 1.13-2.22

Critiques:

- Study did not meet power
- Patients were less ill than the Annane study
- Inclusion window of 72 hours may have missed the optimal window

N Engl J Med. 2008 Jan 10;358(2):111-24

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Let's Review

- Annane showed a mortality benefit for nonresponders that received hydrocortisone and fludrocortisone
- Subsequent studies have failed to duplicate the benefits seen in this trial and even suggested infection-related harm
- Hydrocortisone may lead to a more rapid reversal of shock
- ACTH-stimulation test no longer used in practice

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ADRENAL 2018

Objective

- To determine if administration of corticosteroids reduce 90-day mortality in patients with septic shock requiring ventilator and vasopressor support

Study Design

- Multicenter, double-blind, parallel-group, randomized controlled trial
- Continuous infusion of hydrocortisone 200mg IV daily for 7 days or until ICU death/discharge vs placebo

Population

- N=3,658
- Mechanically ventilated
- Strong clinical suspicion of infection with ≥2 SIRS criteria
- Continuous vasopressors/inotropes for SBP >90 mmHg or MAP > 60 mmHg for ≥4 hours

N Engl J Med. 2018 Mar 1;378(9):797-808

SIRS- Systemic inflammatory response syndrome

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ADRENAL 2018

Outcome	Steroids (n=1,832)	Placebo (n=1,826)	
Mortality at 90 days (%)	27.9	28.8	HR 0.95; 0.82-1.10
Duration of ventilation (days)	6	7	HR 1.13; 1.05-1.22
Median time to shock reversal (days)	3	4	HR 1.32; 1.23-1.41
Median time to ICU discharge (days)	10	12	HR 1.14; 1.06-1.23
28 day mortality (%)	22.3	24.3	OR 0.89; 0.76-1.03
Blood transfusions (%)	37.0	41.7	OR 0.82; 0.72-0.94

Critiques:

- Prior trials used bolus doses of steroids. Unclear if a slower infusion may delay onset.
- Adverse events were recorded on clinical judgement

N Engl J Med. 2018 Mar 1;378(9):797-808

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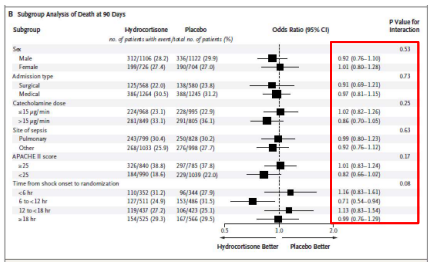
ADRENAL 2018



N Engl J Med. 2018 Mar 1;378(9):797-808

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APROCCHSS 2018

Objective

- To determine if administration of hydrocortisone plus fludrocortisone therapy would improve the clinical outcomes of patients with septic shock

Study Design

- Multicenter, double-blind, 2 by 2 factorial, randomized trial
- Hydrocortisone 50mg IV q6h and fludrocortisone 50 mcg daily for 7 days vs Placebo

Population

- N=1,241
- Admitted to the ICU <7 days with indisputable or probable septic shock <24 hours
  - Clinically or microbiologically documented infection
  - SOFA 3-4 for ≥2 organ systems for ≥6 consecutive hours
  - Receipt of vasopressor therapy (≥0.25 mcg/kg/min or ≥1mg/hr) for ≥6 hours

N Engl J Med. 2018 Mar 1;378(9):809-818.

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SOFA- sequential organ failure assessment

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APROCCHSS 2018

Outcome	Steroids (n=614)	Placebo (n=627)	
Mortality at 90 days (%)	43	49	RR 0.88; 0.78-0.99
Mortality at 28 days (%)	34	39	RR 0.87; 0.75-1.01
Mortality at ICU discharge (%)	35	41	RR 0.86; 0.75-0.99
Mortality at hospital discharge (%)	39	45	RR 0.86; 0.76-0.98
Mortality at 180 days (%)	47	53	RR 0.89; 0.79-0.99
Vasopressor-free days at 28 days (days)	17	15	p<0.001
Organ-failure-free days at 28 days (days)	14	12	p=0.003

Critiques:

- Trial conducted using the Surviving Sepsis 2008 Guidelines, which has since been updated
- Patients were generally more ill limiting the generalizability

N Engl J Med. 2018 Mar 1;378(9):809-818.

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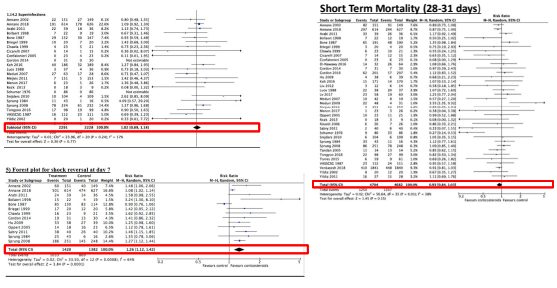
Meta Analysis



Crit Care Med. 2018 Jul 2.

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Steroid Summary

- Corticosteroids accelerate time to shock resolution and weaning of vasopressors
- To be determined:
  - Improvement in mortality
  - Optimal patient population
  - Chronic steroid use and corticosteroids in shock
- Steroid induced adverse drug events
  - Not associated with increased risk for infection
  - Probably increased risk of hyperglycemia
  - Probably increased risk of hypernatremia

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Patient Case: DR

- DR's vasopressor requirements are increasing
- Current requirements
  - Norepinephrine 0.3 mcg/kg/min
  - Vasopressin 0.03 Units/min
- The team wants to start stress dose steroids (hydrocortisone 50mg IV q6h) what is your recommendation? Are you concerned about his limited immune system?

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What if the Addition of Steroids isn't Enough?

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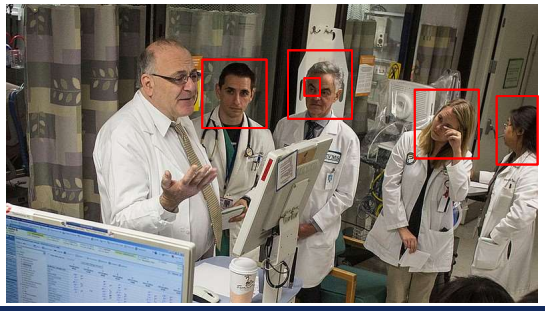
Enter Paul Marik….



www.npr.org/
www.kpbs.org

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Marik 2017

Objective

- To determine if vitamin C, thiamine, and hydrocortisone provides a mortality benefit in patients with severe sepsis or septic shock

Study Design

- **Retrospective before-after study**
- Ascorbic acid + thiamine + hydrocortisone vs. hydrocortisone alone or no therapy

Population

- N=194
- Primary diagnosis of severe sepsis or septic shock and procalcitonin ≥2

Chest. 2017 Jun;151(6):1229-1238

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Triple Therapy

Thiamine	Vitamin C
Deficiency noted in critically ill patients	Reduce oxidative stress
Prevents oxalate conversion	Increases vasopressor responsiveness
	Co-factor for NE and vasopressin synthesis

Pharmacol Ther. 2018 Apr 21
Crit Care Med. 2016Feb;44(2):360-7

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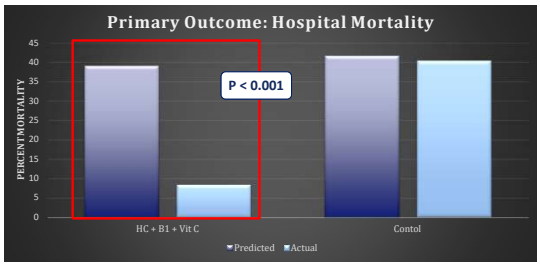
Marik 2017



Chest. 2017 Jun;151(6):1229-1238

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Baseline Characteristics

Characteristic	Treated (n=47)	Control (n=47)
Vasopressors (%)	46	46
Acute kidney injury (%)	66	64
Positive blood cultures (%)	28	28
Average WBC	20.6	17.1
Average Lactate	2.7	3.1
Average Creatinine	1.9	1.9
Day 1 SOFA	8.3	8.7
Average APACHE II	22.1	22.6

Chest. 2017 Jun;151(6):1229-1238

APACHE II- Acute physiology and chronic health evaluation

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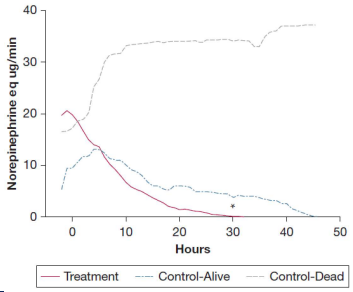
Marik 2017



Chest. 2017 Jun;151(6):1229-1238

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Next Step: VICTAS Study

Objective

- To determine if the addition of vitamin C, hydrocortisone and thiamine increased the number of days alive and free from mechanical ventilation and vasopressors in patients with sepsis-induced respiratory or cardiovascular dysfunction

Study Design

- Multicenter, randomized, double-blind, adaptive-sample-size, placebo-controlled trial
- Vitamin C 1.5gm, thiamine 100 mg, and hydrocortisone 50 mg IV q6hrs vs placebo

Population

- N = 501
- ≥18 years of age
- Acute respiratory and/or cardiovascular dysfunction caused by suspected infection
- Planned ICU admission

JAMA vol. 325,8 (2021): 742-750.

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VICTAS Results

Baseline Characteristic	VICTAS (n=252)	Placebo (n=29)
Vasopressor use	93 (36.9%)	97 (39.1%)
Ventilator	49 (19.4%)	54 (21.8%)
Ventilator + Vasopressor	110 (43.7%)	97 (39.1%)
Mean Arterial Pressure, mmHg	72 (64-82)	71 (65-79)
APACHE II Score	27 (22-33)	27 (19-33)
SOFA	9 (7-12)	9 (6-11)
Time to Treatment, hrs	15 (8-22)	14 (8-20)

Results	VICTAS (n=252)	Placebo (n=29)
Median Ventilator and vasopressor free days (IQR)	25 days (0-29)	26 days (0-28)
30 day Mortality	22%	24%

JAMA vol. 325,8 (2021): 742-750.

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Primary Outcome Measures:

1. ~~Hospital Mortality~~ *Time to vasopressor independence (hours)*
   ~~In-hospital mortality rate.~~ *Defined as the time from starting the active treatment/placebo to discontinuation of all pressors.*

   [Time Frame: Through study completion]
2. *Change in Sequential Organ Failure Assessment (SOFA) score*
   Defined as the day 4 post-randomization SOFA score minus the initial SOFA score. SOFA score ranges from 0 (no organ dysfunction) to 24 (highest possible score / organ dysfunction).

   [Time Frame: *4 days post-randomization*]

	VITAMINS (JAMA 2020)	ORANGES (CHEST 2020)	HYVCTTSSS (CHEST 2020)
Treatment	Triple therapy (109 pts) vs HC 50 mg q6hr (107 pts) for ≤ 10 days	Triple therapy (68 pts) vs placebo (69 pts) for ≤ 4 days	Triple therapy (40 pts) vs placebo (40 pts) for ≤ 4 days
Patient Population	Septic shock within 24 hours of enrollment	Sepsis or septic shock within 12 hours of admission into ICU	Sepsis or septic shock
Outcomes	No improvement in time to shock resolution	Quicker reversal of shock in favor of triple therapy	No mortality benefit
Concerns	Compared timing of vitamin C vs hydrocortisone	Primary outcome changed ~1.5 years 41% received steroids	Stopped early because of high % of ADRs Majority did steriods

JAMA vol. 323,5 (2020): 423-431
Chest vol. 158,1 (2020): 164-173
Chest vol. 158,1 (2020): 174-182

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Triple Therapy Conclusion

- Multiple trials have failed to show true benefit for patients
- One trial showed quicker time to shock reversal
  - Changed primary outcome after finalized data collection
  - Stress dose steroids have shown benefit in time to shock reversal
- The benefit Marik saw has not been replicated
- Stick to stress dose steroids only

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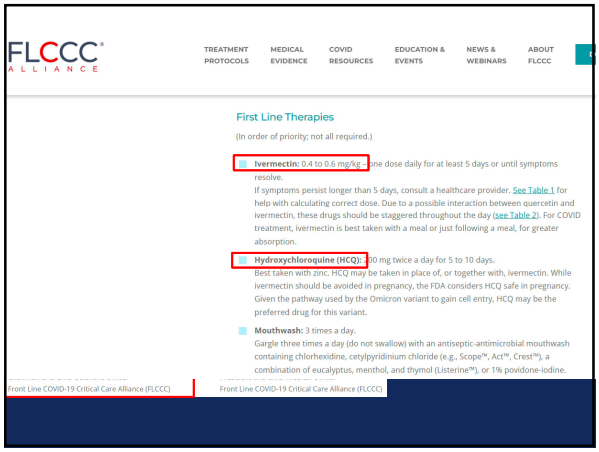

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Vitamins? Seriously?
What about the new vasopressors?

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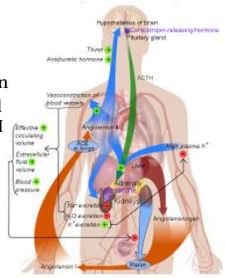
Renin Aldosterone-Angiotensin System (RAAS)

- Hormone system
  - regulates pressure and fluid balance
- Renal blood flow ↓ = prorenin→ renin
- Angiotensinogen→ angiotensin I and then ACE converts it to angiotensin II
- Angiotensin II
  - A potent vasoconstrictor
  - An aldosterone stimulator
- Aldosterone causes renal tubules to increase sodium reabsorption



J Manag Care Pharm. 2007 Oct;13(8 Suppl B):9-20. Review

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ATHOS-3

Objective

- To determine if angiotensin II improved mean arterial pressure (MAP) compared to placebo

Study Design

- Prospective, multicenter, double blind, randomized controlled trial
- Angiotensin II and placebo infusions

Population

- N=321
- Patients with catecholamine-resistant hypotension (>0.2 mcg/kg/min of NE or equivalent)
- Received at least 25mL/kg of crystalloid or colloid over the previous 24 hours
- Features of distributive shock (SvO2 >70%, CVP >8 mmHg, and CI >2.3 L/min/m2)

Crit Care Resusc 2017 Mar;19(1):43-49

SvO2- mixed venous oxygen saturation
CVP- central venous pressure
CI- cardiac index

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ATHOS-3

Outcome	Ang II (n=163)	Placebo (n=158)	
MAP response (%)	69.9	23.4	OR 7.95; 4.76-13.3
Mean change in NE-equivalent dose at 3h	-0.03	0.03	p<0.001
All cause mortality at 7 days (%)	29	35	OR 0.78; 0.53-1.16
All cause mortality at 28 days (%)	46	54	OR 0.78; 0.57-1.07

Adverse Event	Ang II (n=163)	Placebo (n=158)
ADRs leading to discontinuation (%)	14.1	21.5
Serious ADRs (%)	60.7	67.1
Deep-vein thrombosis (%)	12.9	5.1

Critiques:
- Small study size that limited power to detect difference
- Titration period may allow for inadvertent unblinding due to observable MAP changes

Crit Care Resusc 2017 Mar;19(1):43-49
Giapreza [package insert] La Jolla Pharmaceutical Company, CA; 92121

ADRs- adverse drug reactions

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Vasoplegia

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Vasoplegia

- Characterized by normal or high cardiac output with hypotension in the post-operative period
- Most commonly seen post-cardiopulmonary bypass
- Associated with mortality of up to 25%

Cardiac index ≥ 2.5L/m[illegible]/m^2
MAP ≤ 50-
SVR < 800 d[illegible]
Vasopressor require[illegible]nts

Distributive Shock

AM J Med Sci 2005;349(1):80-88

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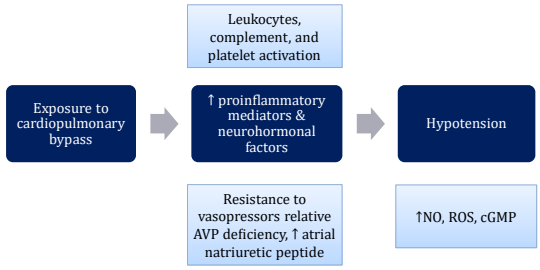
Pathophysiology



AM J Med Sci 2005;349(1):80-88

AVP- vasopressin
NO- nitric oxide
ROS- reactive oxygen species
cGMP- cyclic guanosine monophosphate

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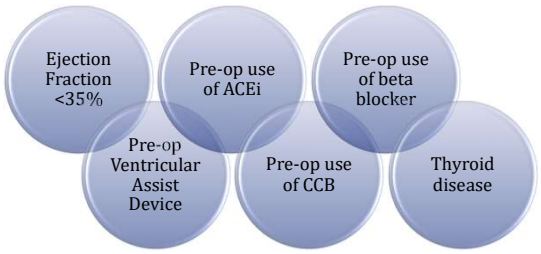
Risk factors



AM J Med Sci 2005;349(1):80-88
Ann Thorac Surg 2014;97:1785-6

EF-ejection fraction
ACEI- angiotensin converting enzyme inhibitor
CCB- calcium channel blocker

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Vasoplegia Management

- Vasopressin
- Norephinephrine/Phenylephrine
- Methylene blue
- Angiotensin II
- Hydroxocobalamin

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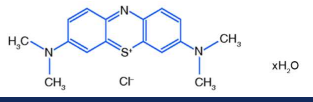
Methylene Blue

- **Salvage therapy for vasoplegia**
- Mechanism
  - Interferes with NO production by binding NO synthase
  - Inhibits guanylate cyclase resulting in ↓ cGMP
  - Leads to vasoconstriction
- Dosing: 1.5-2 mg/kg bolus



AM J Med Sci 2005;349(1):80-88
Ann Thorac Surg 2014;97:1785-6

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Methylene Blue for Septic Shock

- Majority of the data is observational
- Adverse Effects
  - Blue discoloration of skin and urine
    - Reversible
  - Alters pulse oximetry reads (falsely lowers O_2 sat)
  - At high doses, may paradoxically induce methemoglobinemia by acting as an oxidizer
  - Contraindicated in patients with G6PD
  - Monoamine oxidase-A inhibitor
    - Increased risk of serotonin syndrome

Pharmacotherapy. 2010 Jul;30(7):702-15

MAO- monoamine oxidase
G6PD- glucose-6-phosphate deficiency

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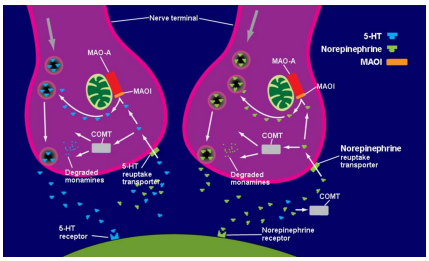
Monoamine Oxidase Inhibitors



Adapted from Medscape.org

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Early Adjunctive Methylene Blue in Patients with Septic Shock

Objective

- To determine if early adjunctive methylene blue can reduce time to vasopressor discontinuation in patients with septic shock.

Study Design

- Single-centered randomized controlled trial
- Methylene blue 100 mg over 6 hrs qday x 3 doses or placebo within 24 hours

Population

- N=91
- ≥ 18 years with septic shock as defined by Sepsis-3
  - Highly suspected or confirmed infection
  - Norephinephrine to maintain MAP ≥ 65 mmHg
  - Serum lactate > 2 mmol/L
- < 24hrs since NE initiation
- No concurrent shock state
- Death unexpected within next 48 hrs
- No history of G6PD deficiency
- No recent SSRI use

Critical care (London, England) vol. 27,1 110. 13 Mar. 2023,

SSRI- selective serotonin re-uptake inhibitor

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Baseline Characteristics

	MB (n=45)	Placebo (n=46)
Shock diagnosis to treatment, hrs, mean ± SD	8.3 ± 1.7	7.6 ± 2.3
Fluid from diagnosis to treatment, mL/kg, mean ± SD	24 ± 8.4	22 ± 9.6
Norepinephrine dose, mcg/kg/min, median (IQR)	0.45 (0.27-0.68)	0.37 (0.20-0.58)
Serum lactate, mmol/L, median (IQR)	6.3 (4.8-7.4)	5.0 (2.9-7.5)
SOFA, median (IQR)	10 (8-12)	10 (8-12)
APACHE II, mean ± SD	22.9 ± 4.4	22.4 ± 4.4

~40%Risk of Mortality

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Findings and Analysis

Methylene Blue:
- ↓ time to vasopressors discontinuation (69hrs vs 94hrs; p < 0.001)
- ↑ the number of vasopressor-free days at day 28 (p=0.008)
- ↓ ICU length of stay by 1.5 days (p=0.039)
- ↓ hospital stay by 2.7 days (p=0.027)

Analysis
- Sick patient population
- Strange dosing scheme of methylene blue
- No adverse drug reactions
- Used continuous infusion of hydrocortisone for stress dose steroids

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Hydroxocobalamin

- MOA unknown but likely related to the sequestration of NO in vascular endothelium
- Available only in Cyanokits
  - 5g IV over 15 minutes
- Concerns
  - Red color
  - Erythemia
  - Rash
  - Infusion site reactions
  - Caution use in dialysis patients

J Cardiothorac Vasc Anesth. 2017 Jun;31(3):1012-14
CClin Kidney J. 2017 Jun;10(3):357-362

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Hydroxocobalamin Case Reports

Case Report	Age (Sex)	Risk factors	Procedure	Vasoplegia resolved?	Comments
Roderique 2014	71 (M)	ACEi, BB, EF 25%	Valve repair	Yes	On citalopram
Burnes 2017	69 (M)	ACEi, BB	Aortic and Mitral valve replacement	Yes	1.5 mg/kg
Cheungpastiporn 2017	83 (M)	Not reported	Three valve replacement	No	Total of 250 mg IV

Ann Thorac Surg 2014;97:1785-6
J Cardiothorac Vasc Anesth. 2017 Jun;31(3):1012-14
CClin Kidney J. 2017 Jun;10(3):357-362

BB- beta blocker

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High-Dose IV Hydroxocobalamin in Septic Shock

Objective

- To determine if comparing IV hydroxocobalamin to placebo in patients with septic shock is feasible

Study Design

- Phase 2 single-center, double-blind, placebo-controlled, parallel-group randomized controlled trial
- A single IV hydroxocobalamin 5 gm vs equivalent volume of normal saline

Population

- N=20
- ≥ 18 years with septic shock as defined by Sepsis-3
  - Highly suspected or confirmed infection
  - Norephinephrine to maintain MAP ≥ 65 mmHg
  - Serum lactate > 2 mmol/L
- < 48hrs since MICU or SICU admission
- Primary diagnosis of septic shock
- NE equivance of >0.10 mcg/kg/min for at least 15 minutes

Chest vol. 163,2 (2023): 303-312.

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Baseline Characteristics and Outcomes

	Hydroxocobalamin (n=10)	Placebo (n=10)
SOFA, median (IQR)	14 (10.2-14)	14 (8.2-14.8)
APACHE II, median (IQR)	28 (26-35)	25 (20-37)

Total norepinephrine dose mcg/kg/min	Hydroxocobalamin (n=10)	Placebo (n=10)
At baseline, median (IQR)	0.29 (0.20-0.36)	0.34 (0.24-0.51)
1 min before infusion, median (IQR)	0.25 (0.20-0.38)	0.31 (0.20-0.54)
30 mins after infusion, median (IQR)**	0.14 (0.10-0.21)	0.30 (0.20-0.72)
3 hrs after infusion, median (IQR)	0.13 (0.10-0.21)	0.26 (0.17-0.90)

~55% Risk of Mortality

Chest vol. 163,2 (2023): 303-312.

*** significant difference seen*

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Patient Case: DR

- Despite the addition of stress dose steroids, DR's vasopressor requirements continue to increase.
- Current requirements are:
  - Norepinephrine 0.5 mcg/kg/min
  - Vasopressin 0.03 units/min
  - Stress dose steriods
- The team would like to discuss refractory options in the setting of a G6PD deficiency. What option(s) would you recommend?

G6PD- glucose-6-phosphate dehydrogenase

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Summary

- Despite multiple therapies for distributive shock, need still remains for novel therapies due to the associated mortality
- Patients should be optimized on first-line therapies prior to receiving salvage therapies
- My opinions:
  - Patients should be on NE ≥0.2 mcg/kg/min + vasopressin before receiving steroids for septic shock
  - Angiotensin II should be considered following the addition of steroids if vasopressor requires continue to increase
  - Patients on chronic steroids should be started on stress dose steroids when vasopressors are started
  - Methylene blue or hydroxocobalamin are reasonable alternatives for patients with vasopressor refractory vasoplegia/distributive shock

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If Patients' Lives are on the Clock, Time to Consider Adjuncts for Shock

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