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Old Drugs Repurposed for Sepsis: Keep Them or Throw Them Back?

Disclosures

- **Alexander H. Flannery:** La Jolla Pharmaceutical Company: Advisory Board
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Objectives

- Describe the mechanisms of action for ascorbic acid, thiamine, and angiotensin II for the treatment of sepsis and septic shock.
- List the possible pros and cons of using ascorbic acid, thiamine, and angiotensin II for a patient with septic shock.
- Given a patient in septic shock, design appropriate monitoring parameters when prescribed ascorbic acid, thiamine, and angiotensin II.

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Vitamin C

Carolyn A. Magee, Pharm.D., BCCCP
Medical-Surgical ICU Clinical Pharmacy Specialist
Medical University of South Carolina

Objectives

- Describe the mechanisms of action for **ascorbic acid**, thiamine, and angiotensin II for the treatment of sepsis and septic shock.
- List the possible pros and cons of using **ascorbic acid**, thiamine, and angiotensin II for a patient with septic shock.
- Given a patient in septic shock, design appropriate monitoring parameters when prescribed **ascorbic acid**, thiamine, and angiotensin II.

Sepsis

- Leading cause of death in hospitalized patients
- Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection
- Septic Shock: underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality
- Despite advances, mortality remains high

Crit Care Med. 2017 Sep; 45(9): 1436–1442.
JAMA. 2016;315(8):801-810

“Magic Bullets” aka Failed Novel Agents in Sepsis

High dose steroids

N-acetylcysteine

Anti-thromin III

Statins

Selenium

Nitric Oxide Inhibitors

NSAIDs

Recombinant tissue factor plasminogen inhibitor

Immunoglobulins

Activated Protein C

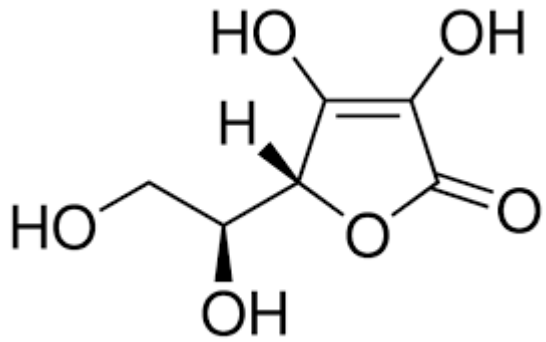
TNF-α

Ketoconazole

J Clin Invest. 2003 Aug 15; 112(4): 460–467.

Vitamin C Background

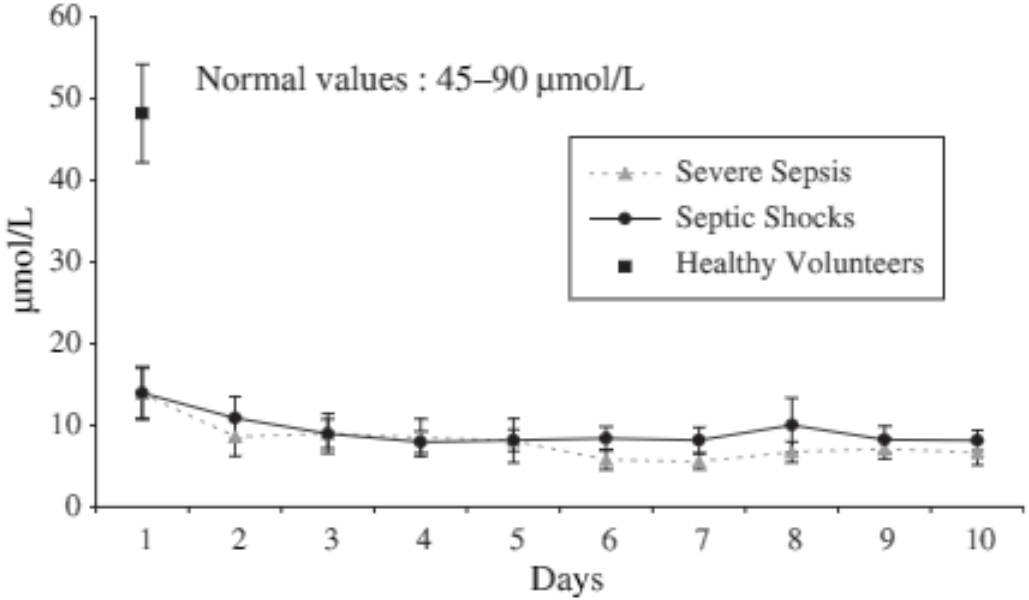
- Ascorbic Acid
- Discovered in 1912
- Essential vitamin in humans
  - Lack L-gulono-γ-lactone oxidase



Albert Szent-Gyorgyi

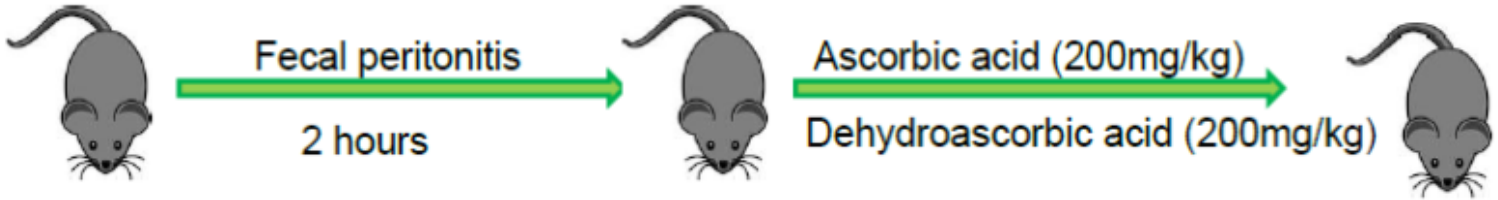
Sir Norman Haworth

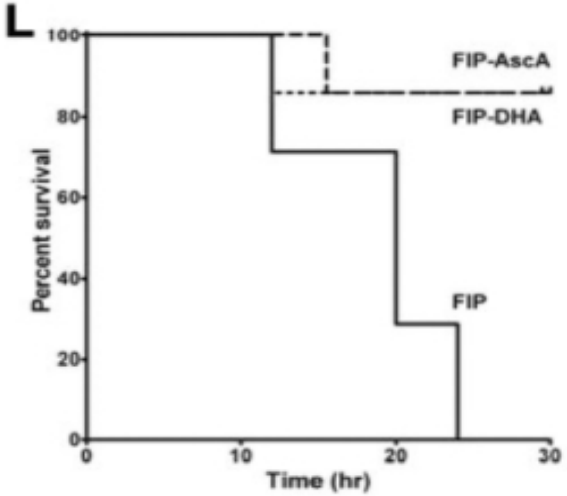
Vitamin C in Sepsis



Biofactors. 2009 Jan–Feb; 35(1): 5–13.
Fundam Clin. Pharmacol 2008;22:203–209.

Animal Models

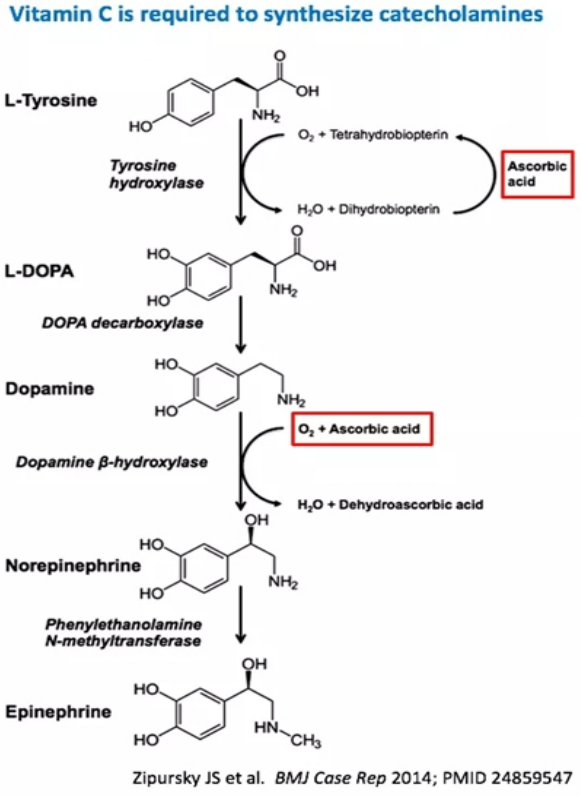




Am J Physiol Lung Cell Mol Physiol. 2012; 303:L20-L32.

Vitamin C Mechanisms

- Cofactor in enzymatic reactions
  - Conversion of dopamine to norepinephrine
  - Vasopressin production
  - Cortisol production
  - Collagen synthesis



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Proposed Vitamin C Mechanisms

- Binds and increases activation of alpha and beta receptors
- Antioxidant
- Immune function?
- Synergy with steroids?

Vitamin C in Burns

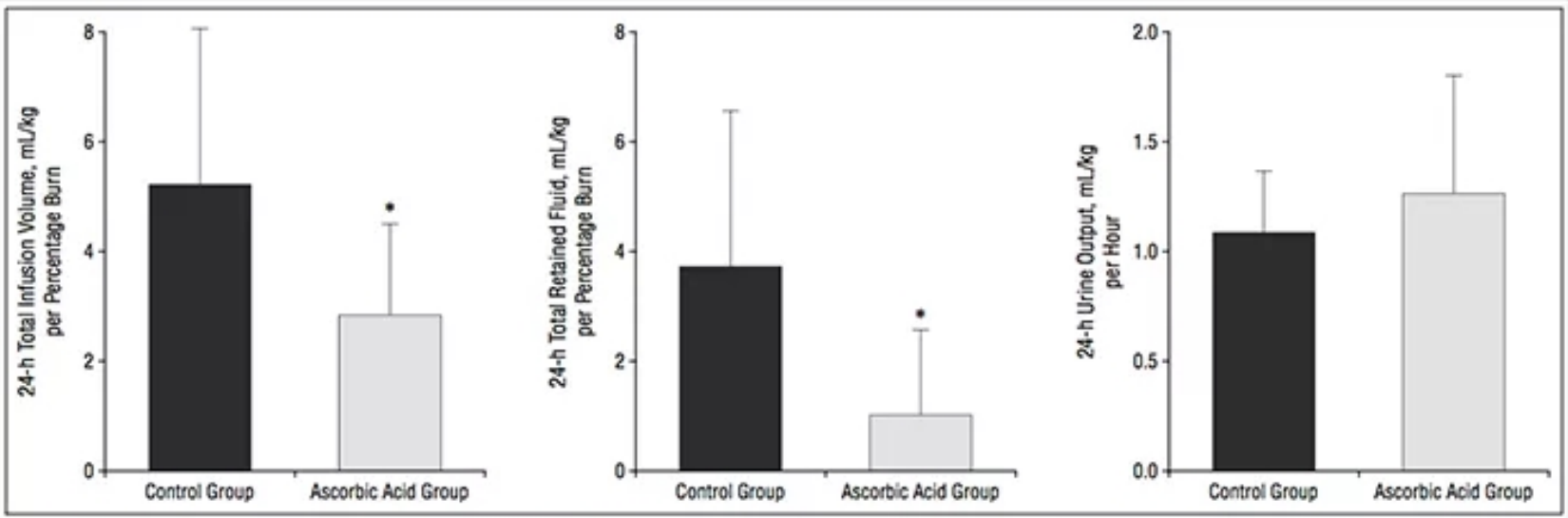
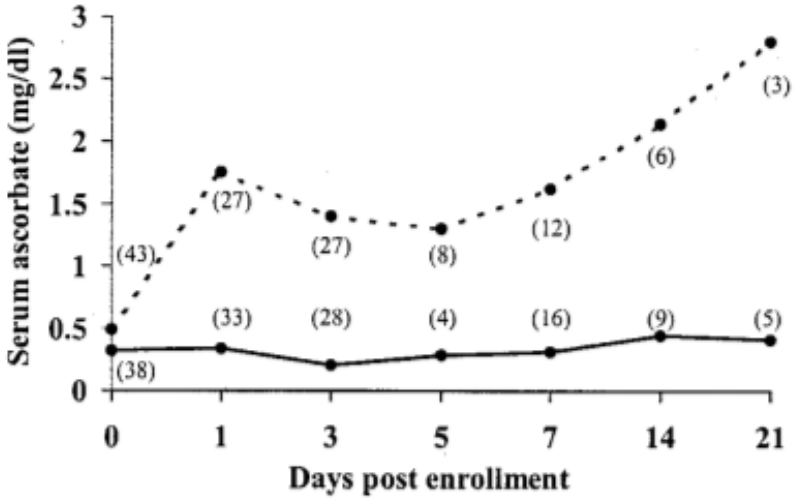


Figure 2. *The 24-hour resuscitation fluid volume requirement and urine output in both groups. Data are given as mean ± SD. Fluid volume requirement in the control group was 5.5 ± 3.1 mL/kg per percentage of total body surface area (TBSA) burn, whereas the ascorbic acid group required only 3.0 ± 1.7 mL/kg per percentage of TBSA burn, representing a 45.5% reduction. Asterisk indicates P<.05 compared with the ascorbic acid group.*

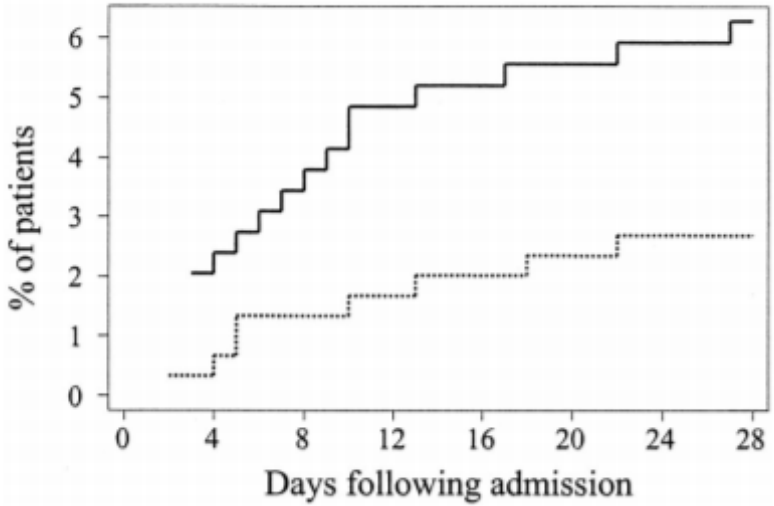
Arch Surg. 2000 Mar;135(3):326-31.

Vitamin C for Prophylaxis

Serum ascorbate levels



Multiple Organ Failure



Ann Surg. 2002 Dec;236(6):814-22.

Vitamin C in Severe Sepsis

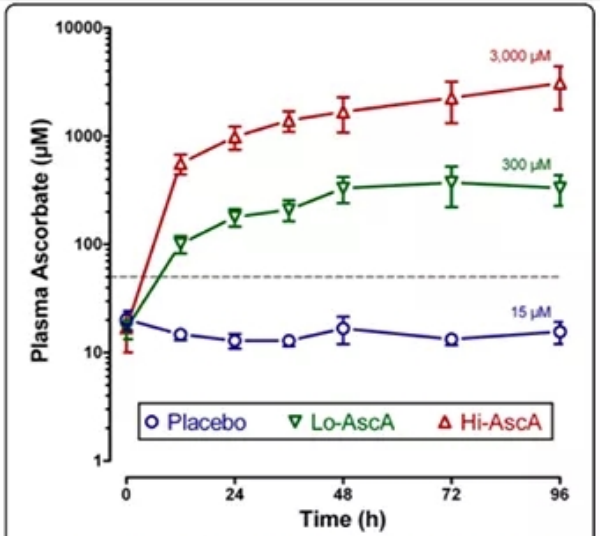


Figure 1 Plasma ascorbic acid levels following intravenous infusion of ascorbic acid. Plasma ascorbic acid levels were subnormal at entry (<50 μM, dotted line). Ascorbic acid levels rose rapidly in the two treatment groups and were significantly higher than placebo within twelve hours (Lo-AscA vs. placebo $p < 0.005$, Hi-AscA vs. placebo $p < 0.0005$) remaining consistently elevated for 96 hours. Ascorbic acid levels in the Hi-AscA group were significantly higher than the Lo-AscA group from the 12 hour point forward. These data show that an intermittent ascorbic acid infusion protocol (every 6 hours) produces sustained steady state levels in patients with severe sepsis. Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

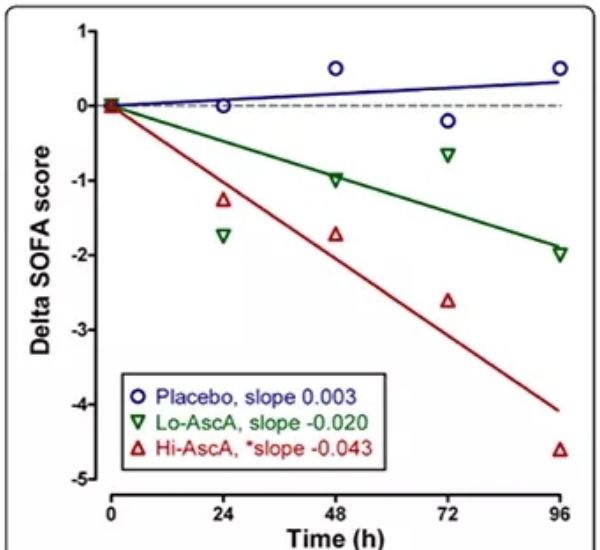


Figure 2 Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0–4). Daily mean SOFA scores decreased over time with both doses of ascorbic acid infusion ($p < 0.05$ significantly non-zero) with the higher dose significantly less than placebo (Hi-AscA vs. placebo $p < 0.01$). Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

J Transl Med. 2014;12:32.

Vitamin C in Septic Shock

Characteristics	Ascorbic Acid Group (n=14)	Control Group (n=14)	*P*-value
Mean dose of norepinephrine (mcg/min) during study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
ICU Length of stay (days)	21.45±10.23	20.57±13.04	0.85
28 day mortality	2 (14.28)	9 (64.28)	0.009

J Res Pharm Pract. 2016 Apr-Jun;5(2):94-100.

Study	Design	Population	Dose	Outcomes
Tanaka et al 2000	RCT	37 major burn injury patients	Vitamin C 66 mg/kg/hr x24 hours vs. Placebo	• Less fluid resuscitation • Higher Urine Output • Less wound edema • Fewer days on MV
Nathens et al 2002	RCT	595 SICU patients	Vitamin C 1000 mg q8h + Vitamin E PO vs. Placebo	• Less multi-organ failure
Fowler et al 2014	RCT	24 patients MICU patients with severe sepsis	Low dose (12.5 mg/kg q6h) vs. High dose (50 mg/kg q6h) vs. Placebo	• Dose dependent improvement in SOFA score over time • Dose dependent increases in plasma ascorbate levels
Zabet et al 2016	RCT	24 SICU patients with septic shock	Vitamin C 25 mg/kg q6h vs. Placebo	• Less norepinephrine at 24 and 72 hours • Shorter duration of norepinephrine • Less 28 day mortality

Arch Surg. 2000 Mar;135(3):326-31.
Ann Surg. 2002 Dec;236(6):814-22.
J Transl Med. 2014;12:32.
J Res Pharm Pract. 2016 Apr-Jun;5(2):94-100.

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

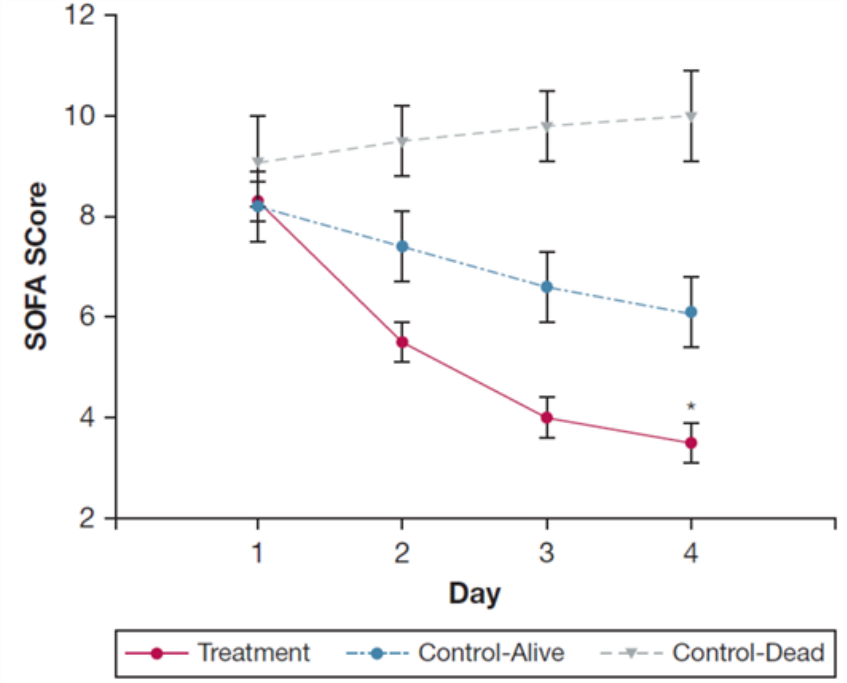
CrossMark

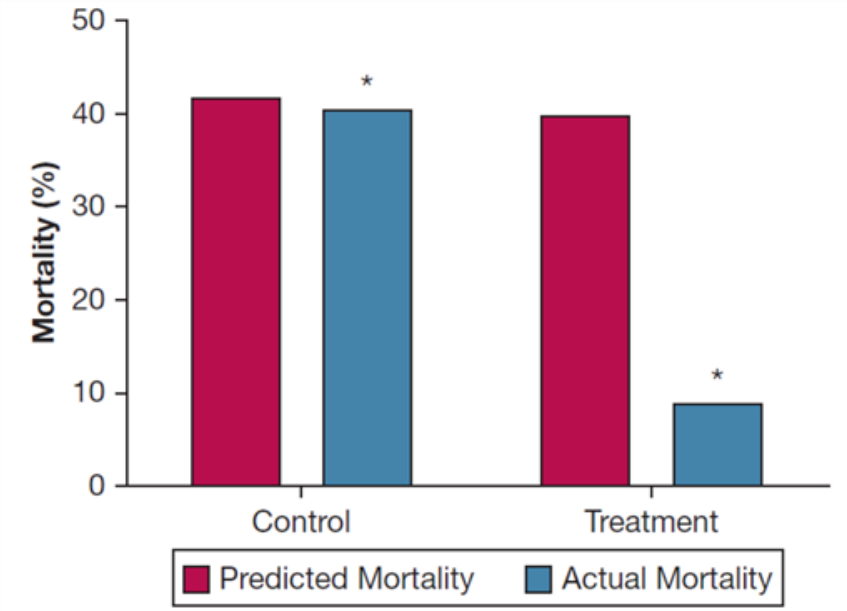
PODCAST

- Vitamin C 1.5 g IV q6h x 4 days
- Thiamine 200 mg IV q12h x4 days
- Hydrocortisone 50 mg IV q6h x7 days

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

It's a Marikle!

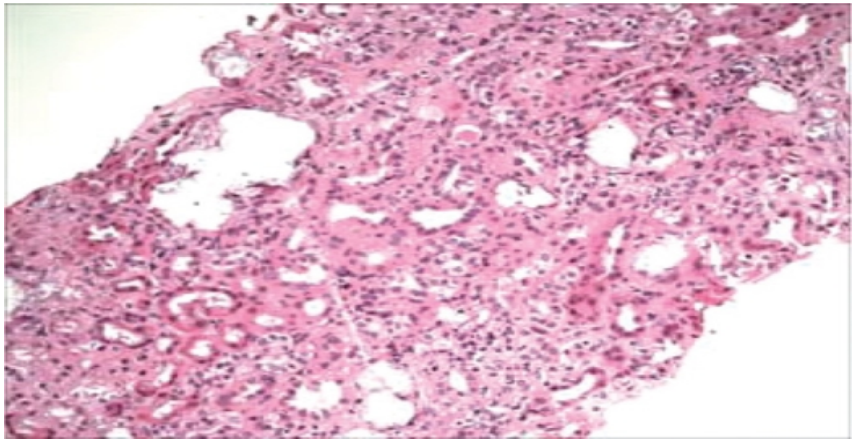


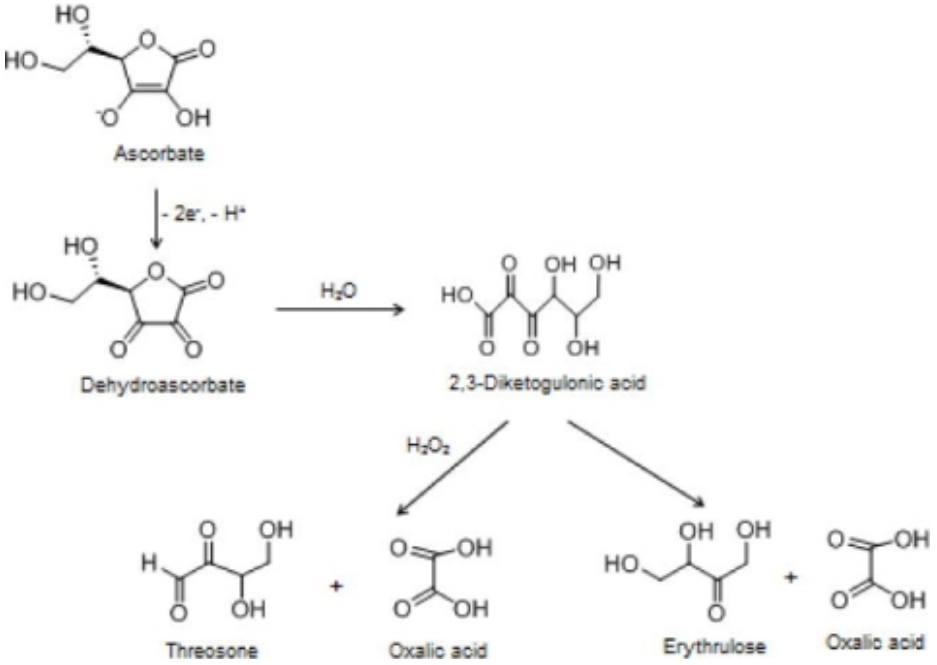


Chest. 2017 Jun;151(6):1229-1238.

Harmless?….maybe not

- Acute renal failure
  - Oxalate crystal deposition





Urolithiasis. 2016 Aug; 44(4): 289–297.
J Community Hosp Intern Med Perspect. 2012; 2(2): 10.3402

“Fictitious Hyperglycemia”

- Point of Care glucose interaction
- Glucose dehydrogenase-pyrroloquinoline quinone amperometric methods
- Discrepancies of 10 to 200 unit →iatrogenic hypoglycemia
    - At least 1 case of death

Sensors (Basel). 2010; 10(5): 4558–4576.
Chest. 2017 Aug;152(2):450-451.
J Burn Care Res, 36 (2) (2015), pp. e67-e71

Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI)

- Recruitment wass completed November 16, 2017
- Randomized, Controlled
- 170 patients with ARDS included
- Intervention
  - Ascorbic Acid 50 mg/kg q6h x 96 hours
- Primary Outcomes
  - Change in SOFA score at 96 hours compared to baseline
  - C-Reactive Protein and Thrombomodulin at study hours 0, 48, 96, 168

ARDS= Acute Respiratory Distress Syndrome
SOFA=Sequential Organ Failure Assessment

Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS)

- Estimated study completion: October 2021
- Multicenter, Prospective, Phase III, Randomized Controlled Trial
- 2,000 patients planned enrollment
- Intervention
  - Vitamin C 1.5g IV Q 6hr x 4 days
  - Thiamine 100mg IV Q6hr x 4 days
  - Hydrocortisone 60mg IV Q6hr x 4 days
- Primary Outcome
  - Vasopressor and ventilator free days at 30 days

https://clinicaltrials.gov/ct2/show/NCT03509350

KEY TAKEAWAYS

1.) *Many proposed mechanisms of vitamin C including:*
- *Repleting deficiency*
- *Decreasing vasopressor requirements*

2.) Several studies have analyzed vitamin C in the critically ill
- *Small sample sizes limit generalizability*

3.) Few adverse events have been reported however oxalate crystal deposition and fictitious hyperglycemia remain a concern

4.)EAGERLY awaiting the results of large RCTs
- *CITRIS-ALI and VICTAS*

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Thiamine

Alexander H. Flannery, Pharm.D., BCCCP, BCPS
Critical Care Pharmacist, Medical Intensive Care Unit
Program Director, PGY2 Critical Care Residency
Adjunct Assistant Professor
University of Kentucky HealthCare

Objectives

- Describe the mechanisms of action for ascorbic acid, **thiamine**, and angiotensin II for the treatment of sepsis and septic shock
- List the possible pros and cons of using ascorbic acid, **thiamine**, and angiotensin II for a patient with septic shock
- Given a patient in septic shock, design appropriate monitoring parameters when prescribed ascorbic acid, **thiamine**, and angiotensin II

Case 1

RT is a 42 y/o male with a PMH of alcoholic cirrhosis presenting with septic shock secondary to SBP. He reportedly consumes 24-30 beers per day. He presented with AMS requiring intubation.

He is on 2 vasopressors to sustain a MAP of 60 mm Hg and has a lactate of 9 mmol/L

Case 1: Would you recommend thiamine in this case?

1. Yes
2. No

Case 1: What dose of thiamine would you recommend?

1. Thiamine IV 100 mg q24h (± “banana bag”)
2. Thiamine PO/PT 100 mg q24h
3. Thiamine IV 200 mg q8h
4. Thiamine IV 500 mg q8h

Case 2

RT is a 42 y/o male with a PMH of NASH cirrhosis presenting with septic shock secondary to SBP. He presented with AMS requiring intubation. He has not drank in over 10 years.

He is on 2 vasopressors to sustain a MAP of 60 mm Hg and has a lactate of 9 mmol/L

Case 2: Would you recommend thiamine in this case?

1. Yes
2. No

Why Thiamine?

Biology 101- Aerobic Respiration

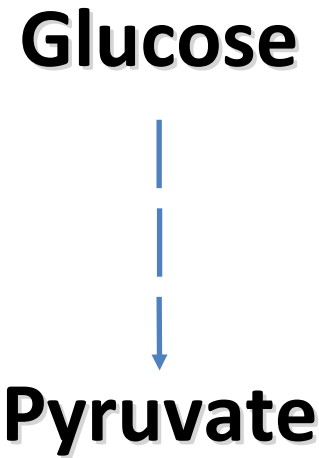
- Glycolysis
- Formation of Acetyl-CoA

- Krebs Cycle

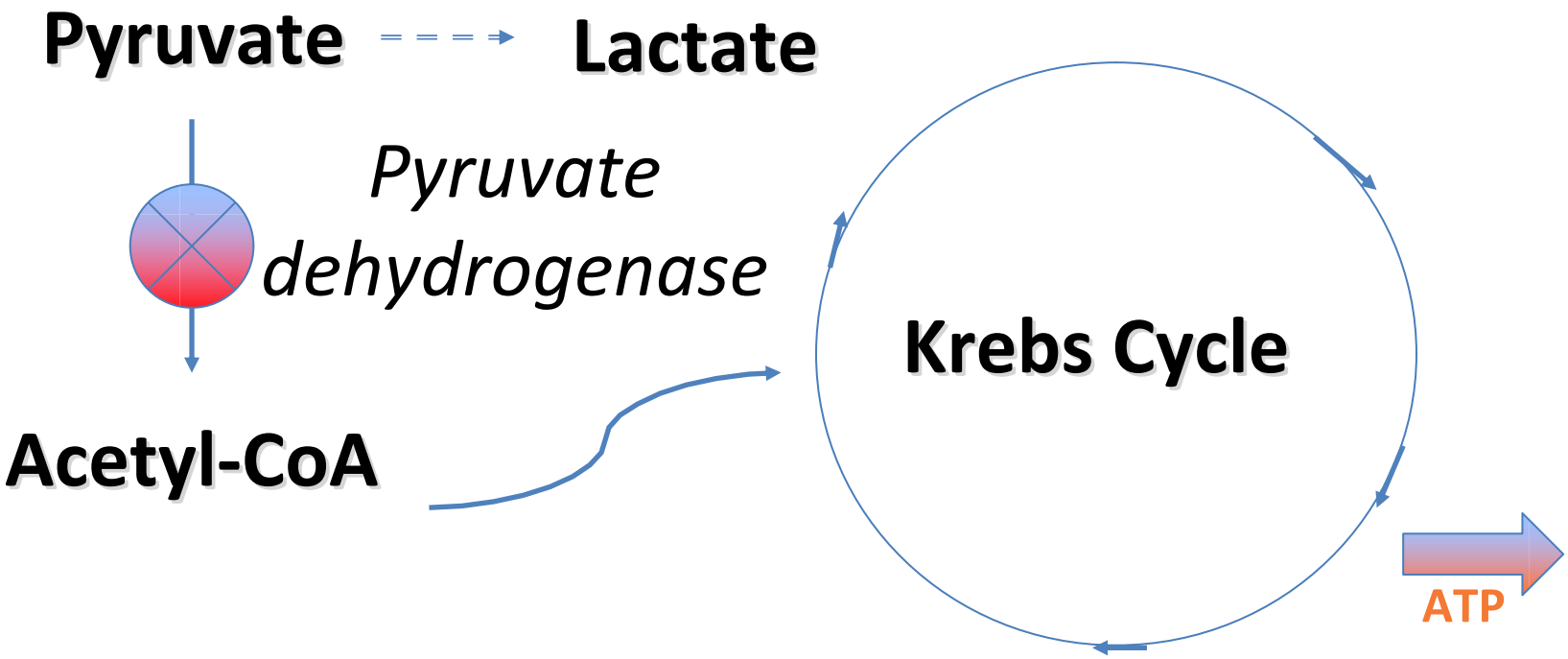
- Electron Transport Chain

ATP

Biology 101- Glycolysis



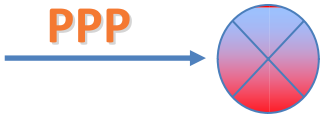
Biology 101- Krebs Cycle



Other Thiamine-Dependent Enzymes

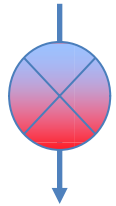
- Pentose Phosphate Pathway (PPP)

Glucose 6-Phosphate (in Glycolysis)



- Krebs Cycle

α-ketoglutarate

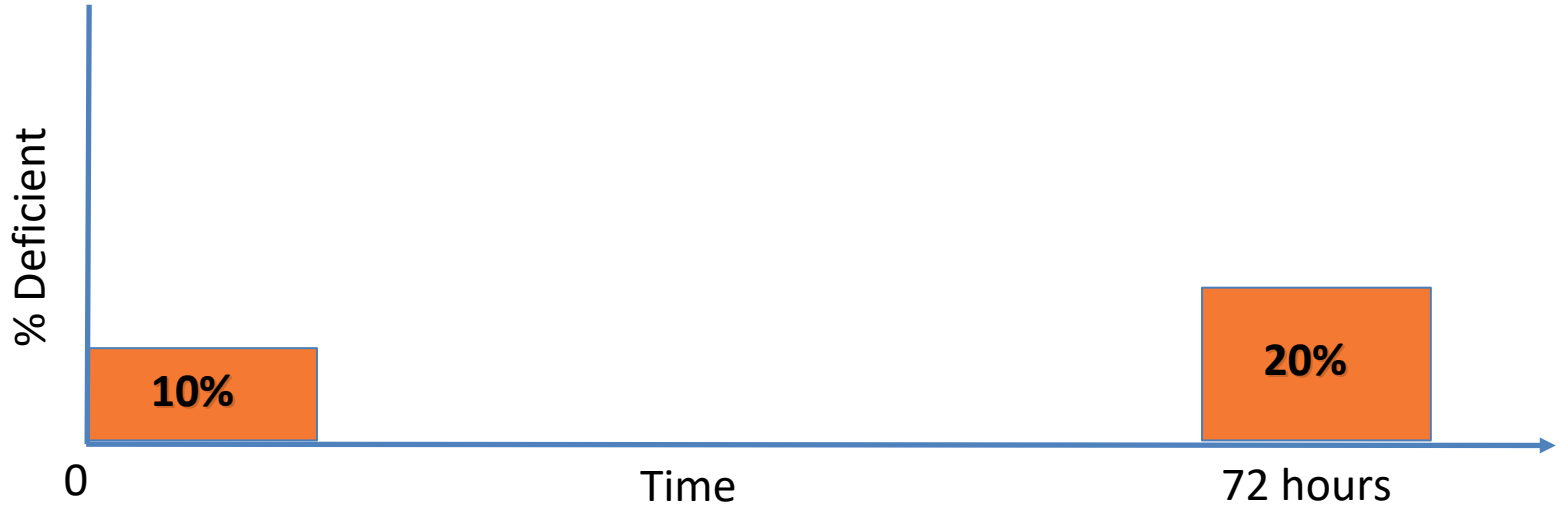


Succinate

Are Critically Ill Patients Thiamine Deficient?

Thiamine Deficiency

- ER patients with lactate >4 mmol/L or vasopressor use



J Crit Care. 2010 Dec;25(4):576-81

Risk Factors

At ICU Admission

- Malnutrition
- Gastrointestinal disorders
- Alcohol abuse
- Dialysis
- Diuretics
- Sepsis

During ICU Care

- Inadequate nutrition
- Dialysis
- Vomiting
- Metabolic stress
- Surgery

Am J Med Sci. 2018 [Epub ahead of print]

What Data Exist to Support Thiamine Administration in Sepsis?

Pilot RCT

- Two-center RCT
- Inclusion:
  - Sepsis (SIRS + infection), lactate > 3 mmol/L, + hypotension & vasopressors
- Exclusion:
  - Liver injury (including cirrhosis), thiamine indication, or competing cause for lactate elevation
- Intervention: Thiamine 200 mg BID x 7d or placebo
- Primary outcome:
  - Lactate level at 24 hours

Crit Care Med. 2016 Feb;44(2):360-7

Patient Demographics

Demographics	Thiamine (n=43)	Placebo (n=45)
Age (years)	70 ± 14	65 ± 17
Sex (% female)	40%	42%
Lactate (mmol/L)	4.1 (2.9-5.0)	4.1 (3.1-6.4)
Mechanical Ventilation (%)	74%	67%
APACHE II	25.7 ± 9.1	26.5 ± 9.2
SOFA	10.1 ± 3.7	10.2 ± 3.7

Crit Care Med. 2016 Feb;44(2):360-7

Results

- Lactate at 24 hours:
  - No difference (2.5 mmol/L vs. 2.6 mmol/L; p= 0.40)
  - Statistically significant in repeated measures model; p= 0.048
- No difference in secondary outcomes:
  - Shock reversal, time to ICU discharge, hospital LOS, inpatient mortality

Crit Care Med. 2016 Feb;44(2):360-7

Thiamine Deficient Patients

- 35% of patients thiamine deficient per laboratory testing (n=79)
- In the deficient cohort:
  - Thiamine group with lower lactate level at 24 hours:
    - 1.4 vs. 1.9 mmol/L; p=0.03
  - Kaplan Meier curves:
    - ↑ survival; p=0.047

Crit Care Med. 2016 Feb;44(2):360-7

Post Hoc Analysis

- Renal outcomes:
  - n = 70
- Baseline SCr:
  - Thiamine 1.2 mg/dl (IQR 0.8-2.5) vs. placebo 1.8 mg/dl (IQR 1.3-2.7); p=0.3
- Requirement for renal replacement therapy:
  - Thiamine 3% vs. placebo 21%; p=0.04
- Worst SCr level:
  - ↑ placebo vs. thiamine; p = 0.05

Ann Am Thorac Soc. 2017 May;14(5):737-741

Thiamine in Septic Shock With Alcohol Use Disorders

- Retrospective cohort:
  - n = 53
  - 64% received thiamine
- 100 mg IV most common dose
- Thiamine associated with reduced mortality:
  - 44% vs. 79%; p = 0.02

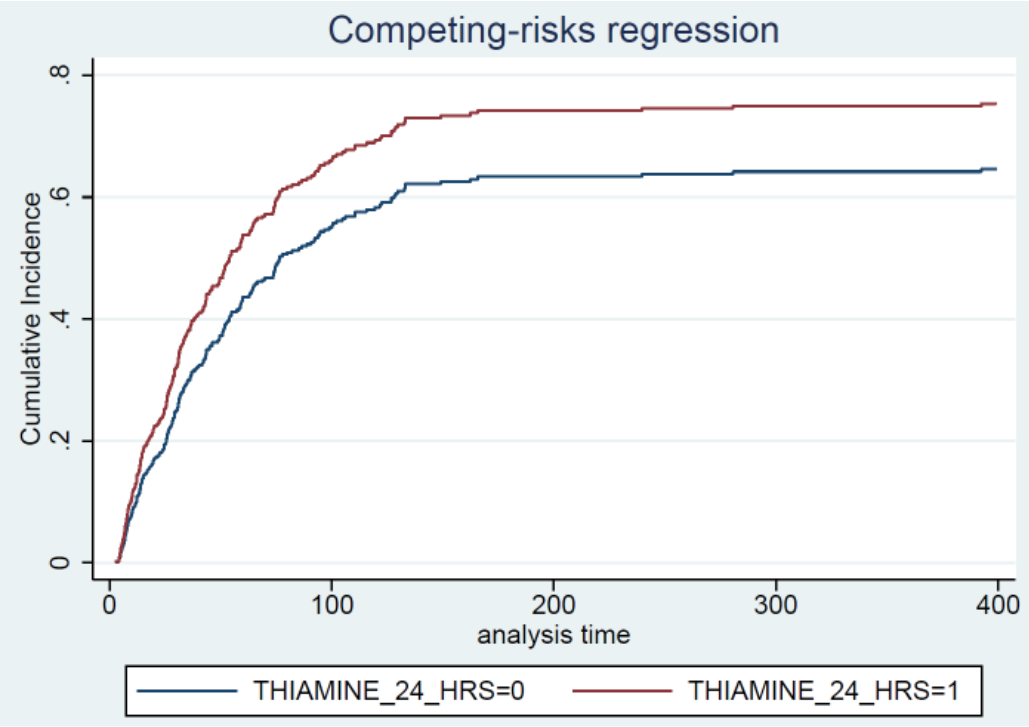
J Crit Care. 2018 Feb;43:61-64

A Larger Cohort…

- Retrospective cohort
- 123 thiamine treated patients matched with 246 controls
- Primary outcome:
  - Time to lactate clearance
- Most common dosing 500 mg IV (~67%)
- Higher cirrhotic population (65%)

Crit Care Med. 2018 [Epub ahead of print]

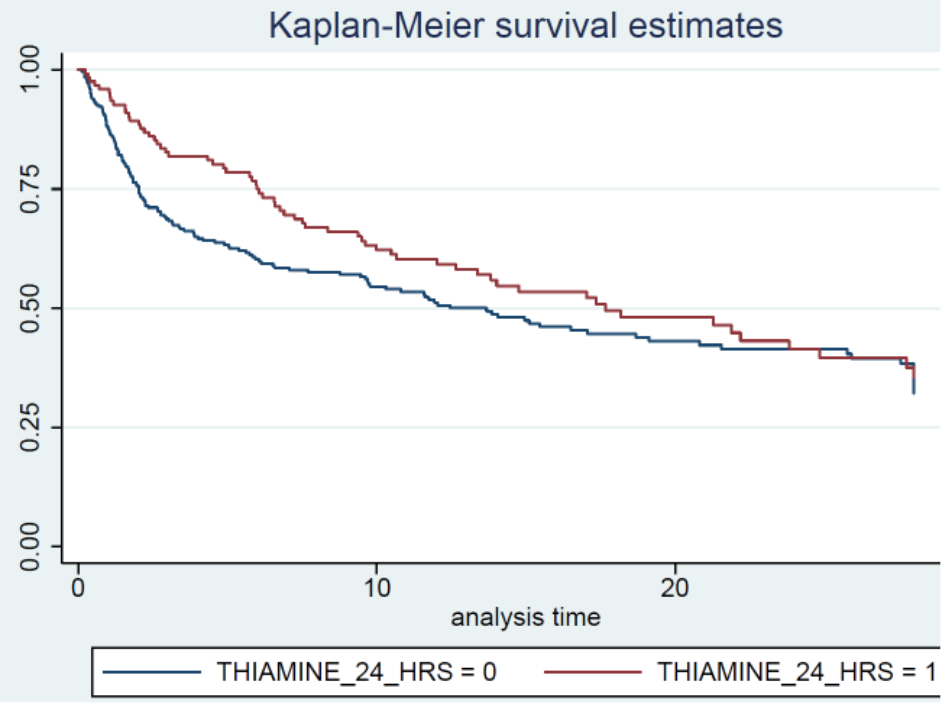
Time to Lactate Clearance



Primary Models	95% Subdistribution Hazard Ratio (SHR)
Thiamine only	1.339 (1.044-1.717)
Thiamine, age, sex, and race	1.292 (1.003-1.663)
Thiamine, age, sex, race, and clinical factors	1.307 (1.002-1.704)

Crit Care Med. 2018 [Epub ahead of print]

28-Day Mortality



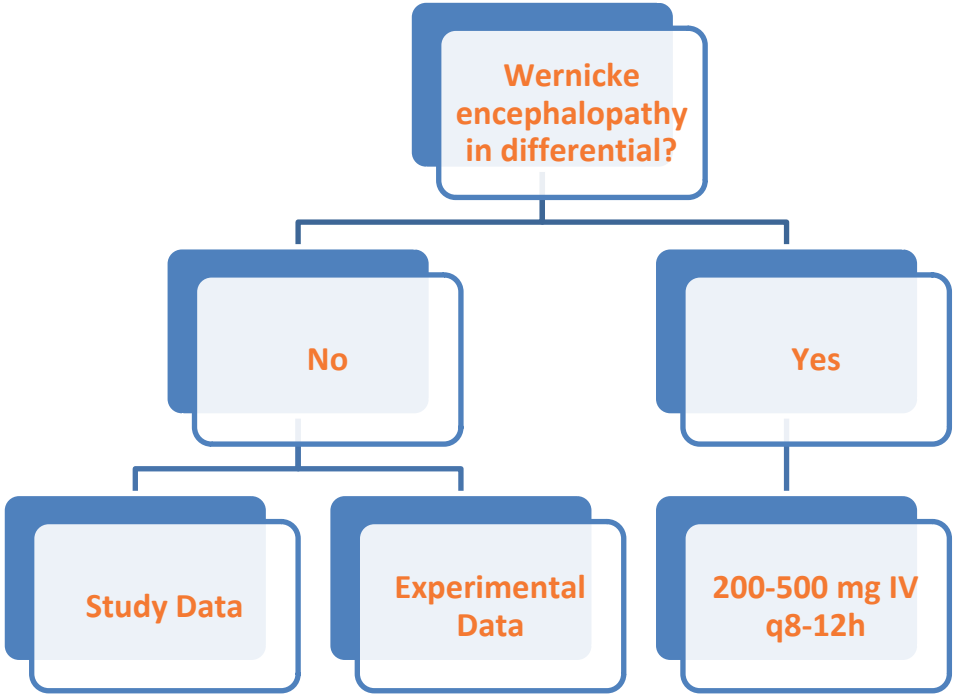
Primary Models	95% Hazard Ratio
Thiamine only	0.806 (0.596-1.090)
Thiamine, age, sex, and race	0.797 (0.589-1.079)
Thiamine, age, sex, race, and clinical factors	0.666 (0.490-0.905)

Crit Care Med. 2018 [Epub ahead of print]

What Dose Should I Give?

Well….It Depends

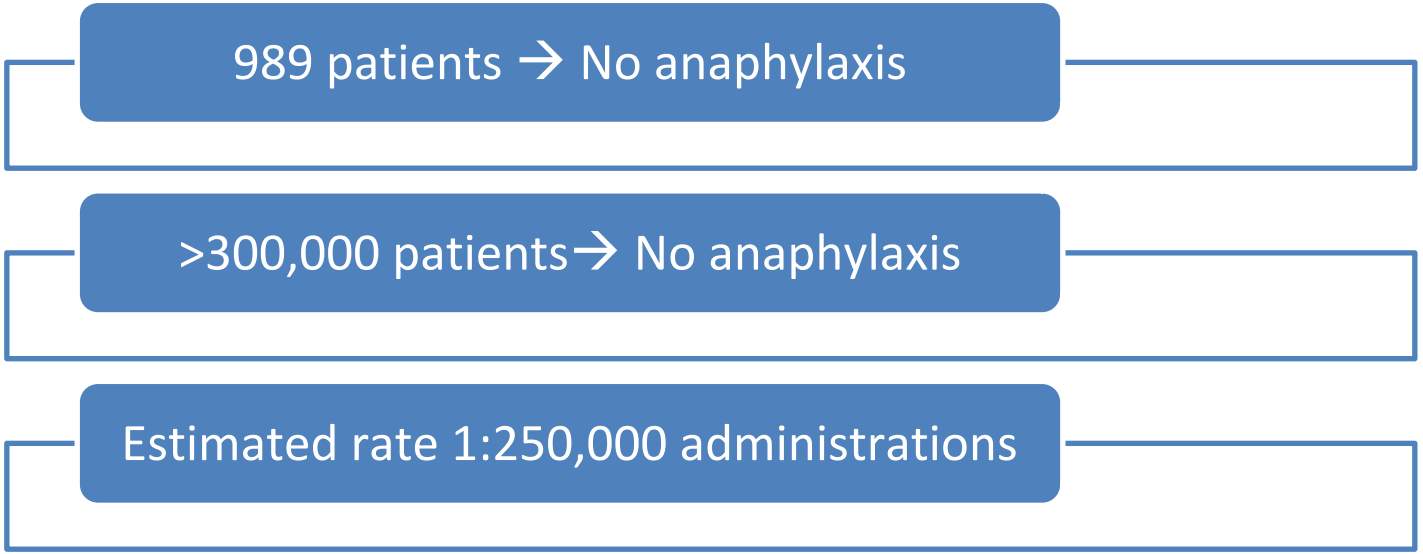
Oral or Per Tube



J Clin Pharm Ther. 2003 Feb;28(1):47-51
Crit Care Med. 2016 Aug;44(8):1545-52

Safety of Thiamine

- Anaphylaxis likely exaggerated concern



Ann Emerg Med 1989; 18:867–870
Am J Emerg Med 1992; 10:165
Alcohol Alcohol 1998; 33:317–336

Administration Method

- Prospective observational study of IV push thiamine dosing (n=989)
- Most commonly 100 mg dosing
- Adverse reactions:
  - 1.1% transient burning
  - 1 patient generalized pruritis

Ann Emerg Med 1989; 18:867–870

Practice Considerations

Arguments For

- Biologic rationale
- Commonly deficient
- Cannot rapidly test levels
- Safe
- Cheap

Arguments Against

- Weak evidence
  - 1 underpowered RCT
  - Observational data
- Unknown dose/duration
- Probably over-treating
- Adjunct treatment not primary focus in septic shock

Will We Get Answers Soon?

Sort of….

KEY TAKEAWAYS

1) *Thiamine deficiency may not be uncommon during the first 72 hours of ICU admission in septic shock*

2) *Lack of laboratory testing with rapid turnaround time limits timely identification of thiamine deficiency; focus on risk factors*

3) *Thiamine administration associated with improved surrogate and clinical outcomes in septic shock; larger trials needed*

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Thiamine

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Program Director, PGY2 Critical Care Residency
Adjunct Assistant Professor
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Angiotensin II for Vasodilatory Shock

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MICU Clinical Pharmacy Specialist
Vanderbilt University Medical Center, Nashville, TN

Objectives

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- List the possible pros and cons of using ascorbic acid, thiamine, and **angiotensin II** for a patient with septic shock.
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Patient Case

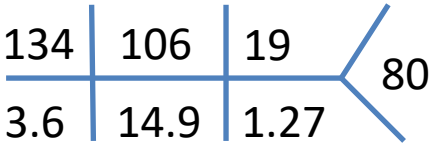
DS is a 64 yo F admitted with septic shock secondary to abdominal source (cholangitis vs colitis)

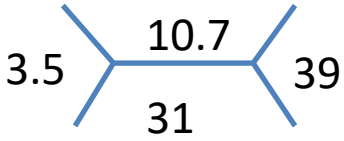
PMH: Cirrhosis, non-alcoholic

PSH: Not significant

Procedures: ERCP on 6/1

Admission Data in Emergency Department 6/3/2018 2200





Blood Pressure: 77/51

Heart Rate: 123 bpm

RR: 25

Temperature: 36.9 C

SpO2=99%

4L of Lactated Ringers given

Cefepime, Metronidazole, and Vancomycin given

Norepinephrine started

MICU Rounds 7 AM 6/4/2018

Vitals

- Blood Pressure: 77/51
- Pulse: 123
- Respiratory Rate: 25
- Temperature: 36.8 °C
- SpO_2=99%

Current Data

- Lactate 6.4->8.9->9
- Norepinephrine 80 mcg/min
- Vasopressin 0.04 units/min
- Hydrocortisone 50 mg iv q6h

Surviving Sepsis Campaign Guidelines for Vasopressors

We recommend at least a 30 ml/kg IV crystalloid be given within the first 3 hours

We recommend norepinephrine as the first choice vasopressor

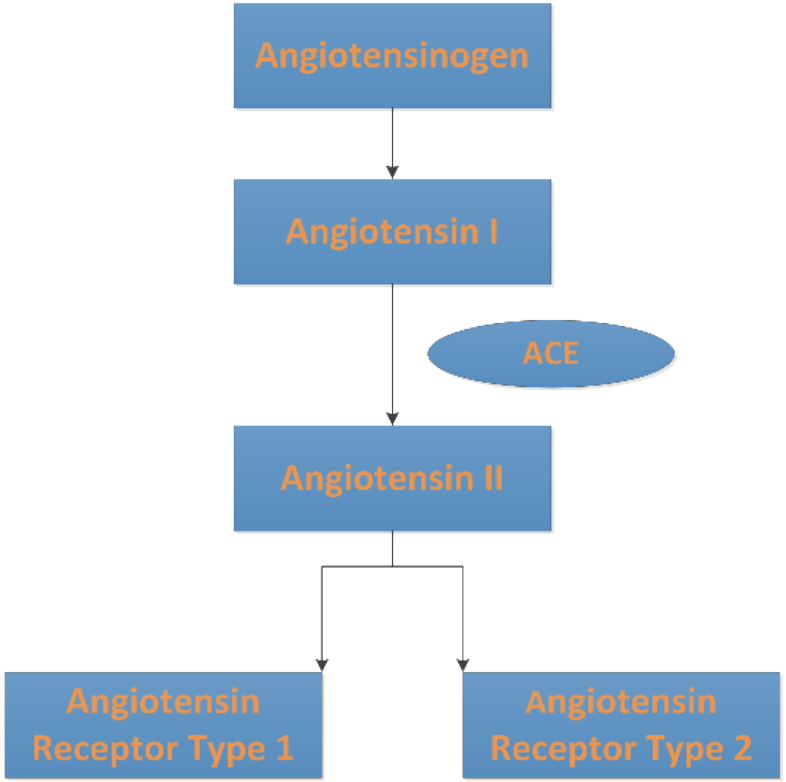
We recommend adding vasopressin or epinephrine to norepinephrine to increase the MAP

Rhodes A, et al. *Crit Care Med. 2017.*

Does Your Institution Use Angiotensin II?

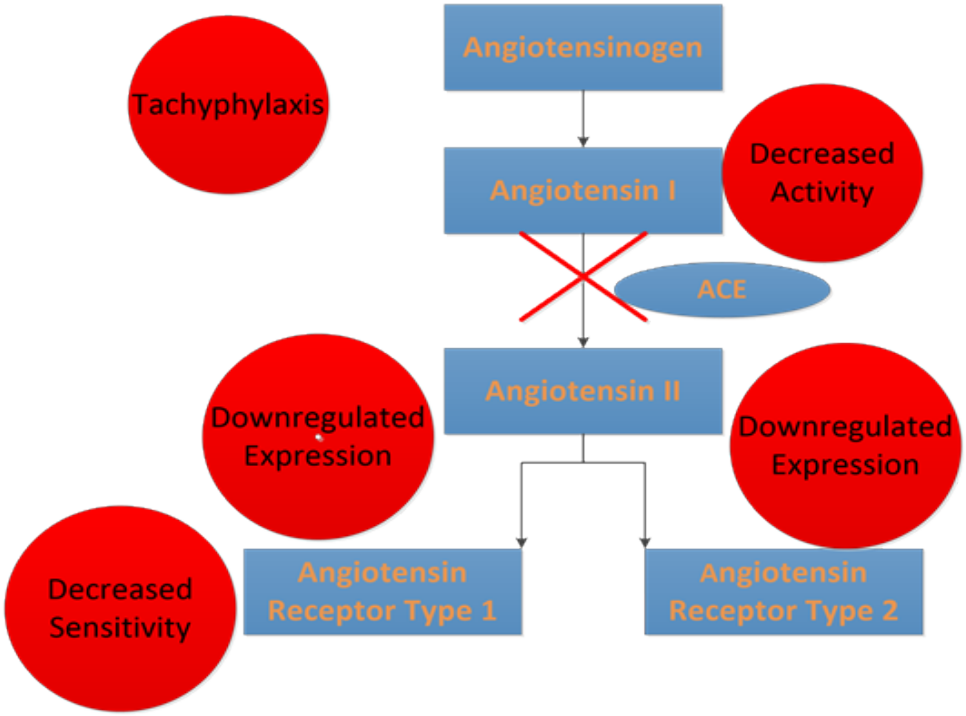
1. Yes
2. No

Angiotensin-Aldosterone System



Bissell BD, et al. *Ann Pharm*. 2018.

Angiotensin II in Septic Shock



Bissell BD, et al. *Ann Pharm*. 2018.

Angiotensin II

Indication

- Vasoconstriction to increase blood pressure in adults with septic or other distributive shock

Dosing

- Starting dose: 20 nanograms (ng)/kg/min
- Titrate every 5 to 15 minutes by increments of up to 15 ng/kg/min to goal MAP
- Do not exceed 80 ng/kg/min during the first 3 hours of treatment. Maintenance doses should not exceed 40 ng/kg/min

Giapreza [package insert]. San Diego, CA: La Jolla Pharmaceutical Company. 2017.

Angiotensin II

Discontinuation

- The rate should be down-titrated in increments of 10 ng/kg/min to a dose of 10 ng/kg/min; then from 10 to 5 ng/kg/min, and finally from 5 to 2.5 ng/kg/min before turning off

Giapreza [package insert]. San Diego, CA: La Jolla Pharmaceutical Company. 2017.

Angiotensin II Pharmacokinetics

Plasma half-life less than 1 minute

After 3 hours of treatment, the serum level of angiotensin I is reduced by 40%

Not influenced by renal or hepatic impairment, age, or gender

Metabolized by aminopeptidase A and angiotensin converting enzyme 2 to angiotensin-(2-8) [angiotensin III] and angiotensin-(1-7)

Giapreza [package insert]. San Diego, CA: La Jolla Pharmaceutical Company. 2017.

ATHOS

Study Design

- Single Center, Randomized, Placebo-Controlled Pilot Study

Population

- Adults with vasodilatory shock
- Volume Resuscitated
- Cardiovascular SOFA score 4
- Cardiac Index >2.4 L/min/BSA
- Norepinephrine plus vasopressin, epinephrine and/or phenylephrine

Intervention

- Angiotensin II
- Placebo

Chawla LS, et al. *Crit Care.* 2014.

Intervention

First 6 Hours

- Angiotensin II
  - Initiated at 20 ng/kg/min
  - Adjusted hourly by 10 ng/kg/min to maintain goal MAP of 65 mm Hg
  - Adjusted to maintain norepinephrine rate of 5 to 10 mcg/min
- Placebo

After 6 Hours

- Angiotensin II
  - Titrated off by halving the dose every 10 minutes until less than 5 ng/kg/min
- Placebo

Chawla LS, et al. *Crit Care.* 2014.

Outcomes and Adverse Events

	Angiotensin II (n=10)	Placebo (n=10)	P Value
Mean Norepinephrine Dose After 1 Hour	7.4 ± 12.4 mcg/min	27.6±29.3 mcg/min	0.06
30 Day Mortality	50%	60%	1.00

Chawla LS, et al. *Crit Care.* 2014.

ATHOS 3

Study Design

- Phase 3, International, Randomized, Double-Blind, Placebo-Controlled Trial

Population

- Adults with vasodilatory shock
- Volume resuscitation >25 ml/kg over previous 24 hours
- High-dose vasopressors (>0.2 mcg/kg/min or Norepinephrine or equivalent) for at least 6 hours but up to 48 hours

Intervention

- Angiotensin II
- Placebo

Khanna A, et al. *N Engl J Med.* 2017

Intervention

First 3 Hours

- Angiotensin II
  - Initiated at 20 ng/kg/min and adjusted during the first three hours to increase MAP to at least 75 mm Hg (maximum allowed of 200 ng/kg/min)
  - Vasopressors doses maintained
- Placebo
  - Vasopressor doses maintained

3-48 Hours

- Ang 2
  - Both Ang II and background vasopressors could be titrated to maintain a MAP of 65 to 75 mm Hg
- Placebo
  - Vasopressor doses could be titrated

Khanna A, et al. *N Engl J Med.* 2017.

Outcomes

	Angiotensin II (n=163)	Placebo (n=158)	P Value
MAP response at hour 3	114 (69.9%)	37 (23.4%)	<0.001
Mean change in norepinephrine equivalent dose from baseline to hour 3	-0.03 ± 0.10	0.03 ± 0.23	<0.001
Mean change in cardiovascular SOFA score at hour 48	-1.75 ± 1.77	-1.28 ± 1.65	0.01

Khanna A, et al. *N Engl J Med.* 2017.

Safety

	Angiotensin II (n=163)	Placebo (n=158)
Thromboembolic events	21 (12.9%)	8 (5.1%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)
Thrombocytopenia	16 (9.8%)	11 (7.0%)
Tachycardia	14 (8.6%)	9 (5.7%)
Fungal infection	10 (6.1%)	2 (1.3%)
Delirium	9 (5.5%)	1 (0.6%)
Acidosis	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)

Khanna A, et al. *N Engl J Med.* 2017.

Outcomes in Patients in ATHOS 3 that Received Renal Replacement Therapy

Study Design

- Post hoc analysis of ATHOS 3

Population

- Patients with acute kidney injury treated with renal replacement therapy

Intervention

- Angiotensin II
- Placebo

Tumlin JA, et al. *Crit Care Med.* 2018.

Outcomes

	Angiotensin II (n=45)	Placebo (n=60)	OR/HR (95% CI), p value
Alive at Day 28, % (95% CI)	53 (38-67)	30 (19-41)	HR, 0.52 (0.24-0.80), .007
Day 7 alive and renal replacement therapy free, % (95% CI)	38 (25-54)	15 (8-27)	HR, 2.90 (1.29-6.52), .007
MAP response at hour 3, n (%)	24/45 (53.3)	13/60 (21.7)	HR, 4.31 (1.77-10.5), .001

Tumlin JA, et al. *Crit Care Med.* 2018.

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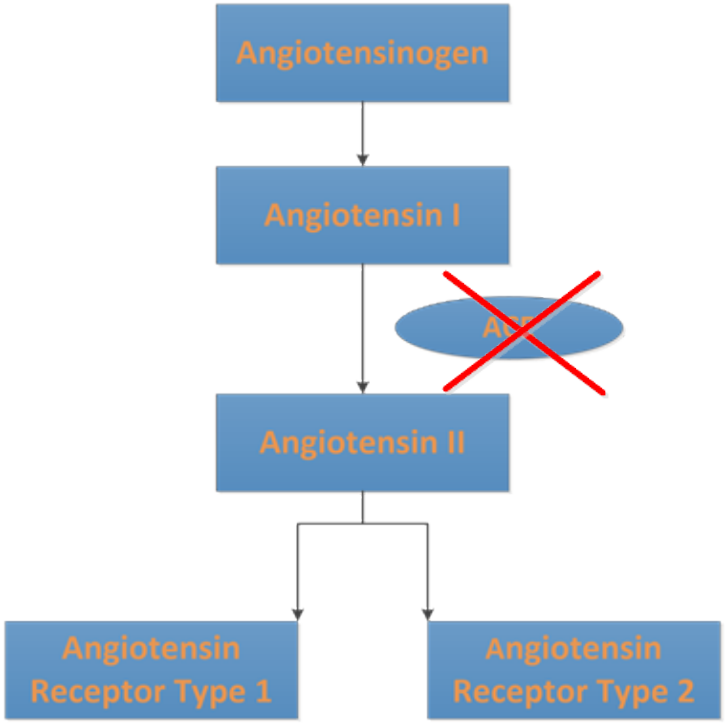
Patients on ACE Inhibitors Have an Increased Response



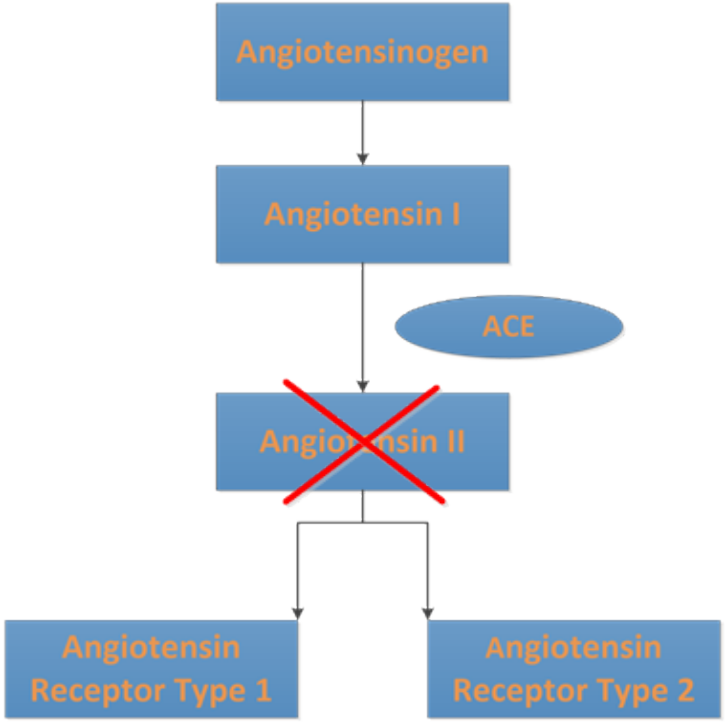
Bissell BD, et al. *Ann Pharm*. 2018.

Potential Harms Associated with Ang II

Adverse Event	Proposed Mechanism of Action	Preventative Action
Thrombosis	• AT1 stimulates the release of PAI-1 • Platelet aggregation	Chemical DVT prophylaxis?
Lactic Acidosis	• Worsens microcirculatory blood flow	Stop Angiotensin II if lactate levels continue to increase
Delirium	• May cause inadequate cerebral perfusion	ABCDEF Bundle
Heart Rate	• Increased HR due to lack of direct chronotropic effects	Avoid in those who can not tolerate increase in HR
Asthma	• Worsening of asthmatic symptoms	Avoid use
Reduced Cardiac Output	• A pure vasoconstrictor without inotropic activity	Avoid use

Bauer SR, *Pharmacotherapy*. 2018. Bissell BD, et al. *Ann Pharm*. 2018.

Patients on ARBs Inhibitors Have a Decreased Response



Bissell BD, et al. *Ann Pharm*. 2018.

Vanderbilt MICU Inclusion Criteria for Angiotensin II

Only two attending physicians can approve this

Use of angiotensin II should be restricted to use as a third-line rescue vasopressor for patients that meet all of the following criteria:

- Requiring treatment in the MICU for septic shock
- Inability to maintain MAP goals despite therapy with both high-dose norepinephrine or epinephrine at ≥50 mcg/min, or phenylephrine at ≥400 mcg/min and vasopressin
- Receiving pharmacologic venous thromboembolism prophylaxis

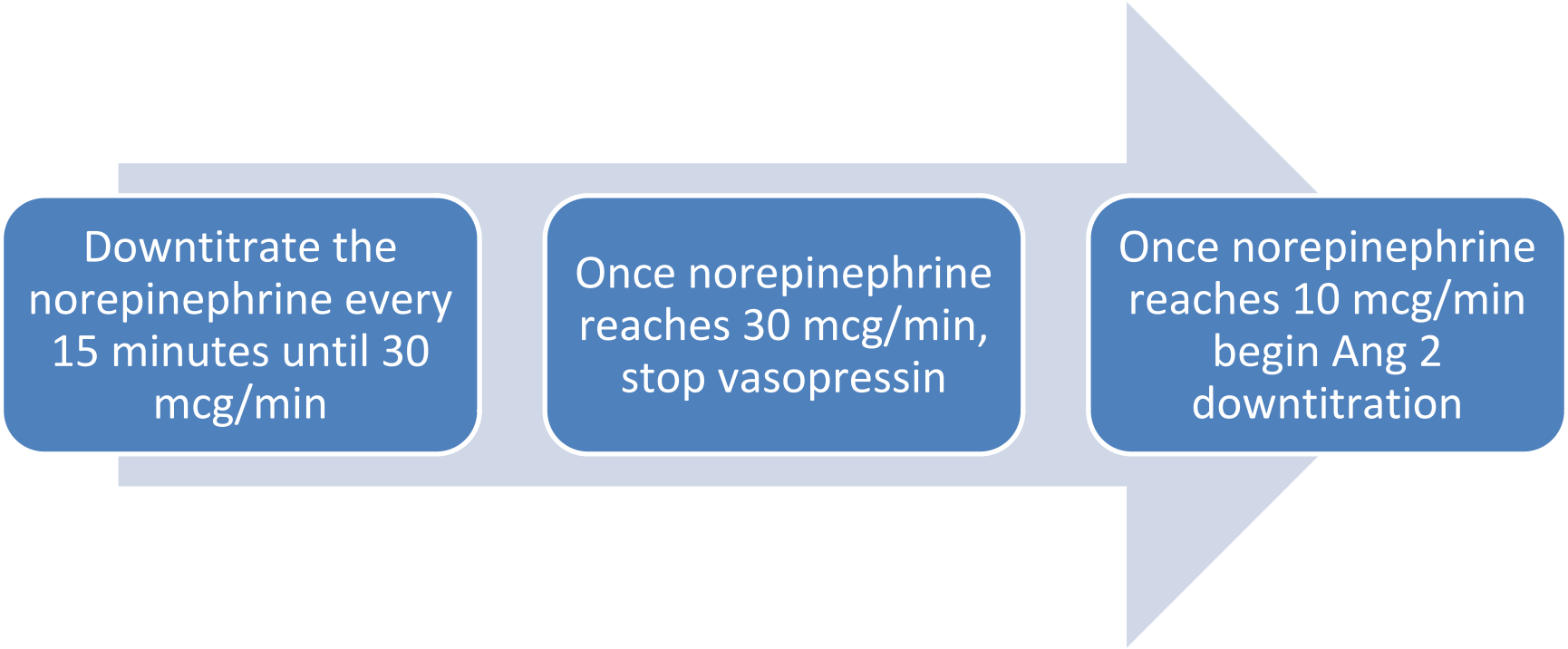
Vanderbilt MICU Titration Instructions for Angiotensin II

Start at 20 ng/kg/min. Titrate every 15 minutes by increments of 10 ng/kg/min as needed to achieve or maintain target blood pressure. Do not exceed 40 ng/kg/min.

Upon discontinuation, rate should be down-titrated in increments of 10 ng/kg/min to a dose of 10 ng/kg/min; then from 10 to 5 ng/kg/min, and finally from 5 to 2.5 ng/kg/min before turning off.

Drug therapy shall be discontinued after the first bag in patients who are considered non-responders to therapy

Vanderbilt MICU Process for De-escalation of Vasopressors When Receiving Angiotensin II



Cost

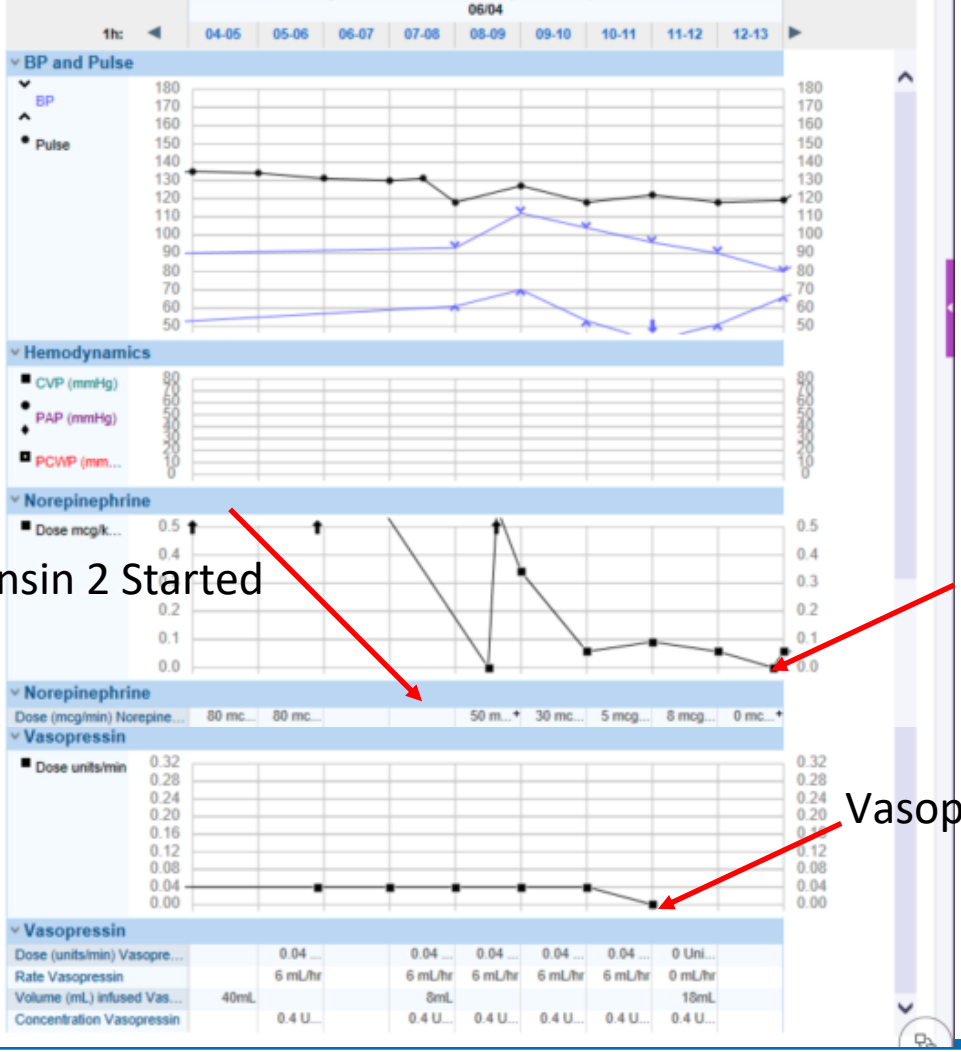
Treatment	Available as	Drug Price per Unit (2017 USD)	Dosing	Estimated Cost PPPD (2017 USD)†	Estimated Cost per year‡ (2017 USD)
Angiotensin II	2.5 mg/mL vial	$1,500	20 ng/kg/min*	$1,728.00	$1,209,600
Vasopressin	20 unit/50 mL infusion	$87.18	0.04 units/min	$385.52	n/a
Norepinephrine	8 mg/250 mL infusion	$26.90	50 mcg/min	$147.24	n/a

*Dose based on average rate of study drug required over 48 hours in the treatment arm of the ATHOS-3 study
†Calculated for body weight of a 100-kg patient
‡Based on study drug use for up to 7 days in the ATHOS-3 study
PPPD=per patient per day; USD=United States dollar

New Technology Add-on Payment Coverage

- Provides additional reimbursement to hospitals beyond the Medicare Severity Diagnosis-Related Group (MS-DRG) reimbursement
  - Equal to 50% of the amount by which the covered costs exceed the MS-DRG reimbursement
  - Or 50% of the cost of the drug
- Begins on October 1, 2018

Back to the Patient



Angiotensin 2 Started

Norepinephrine stopped

Vasopressin stopped

ICU Course

E.coli bacteremia isolated, antibiotics stremlined

Angiotension discontinued at 2200 on 6/4/2018 (14 hours)

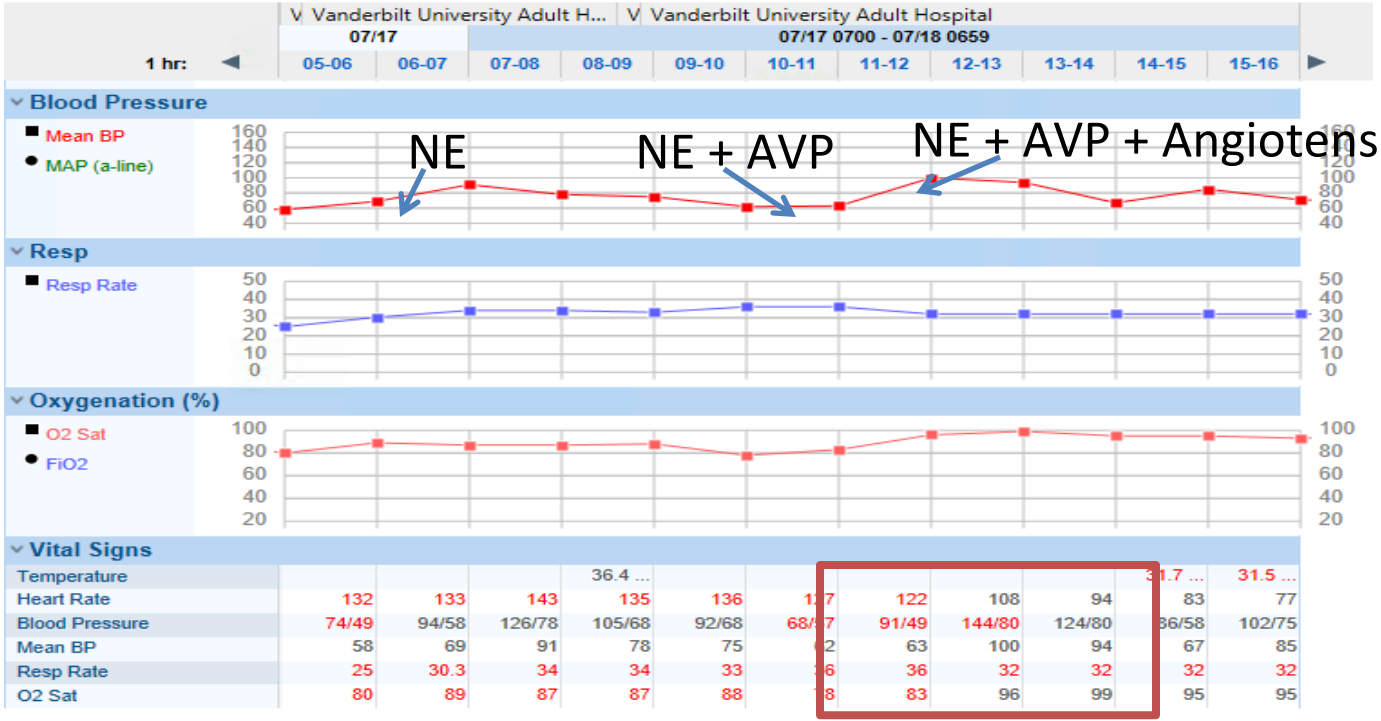
Norepinephrine discontinued at 1600 on 6/5 /2018

Patient transferred to floor on 6/7/2018

Summary of Vanderbilt Experiences

Patient History	Response
30 yo M with septic shock, ARDS, acute renal failure, and disseminated histoplasmosis	Responder (deceased)
64 yo F with septic shock due to colitis with acute renal failure	Responder
53 yo M with SJS and septic shock due to *Streptococcus Viridans* bacteremia with acute renal failure	Responder
45 yo M with septic shock from gram negative bacteremia with acute on chronic renal failure	Non-responder (deceased)

Another Responder



Future Directions

- Efficacy within special patient populations
  - Acute Respiratory Distress Syndrome
  - Cirrhosis
- Mortality Data
- Post-marketing evaluation of adverse effects
- Vasopressin vs Angiotensin II

Bissell BD, et al. *Ann Pharm*. 2018.

KEY TAKEAWAYS

1) *Angiotensin II is a novel agent for utilization in refractory septic shock*

2) *Consideration of specific characteristics is imperative in determining which patient populations to consider this agent in*

3) *Utilization of Angiotensin II may allow other agents time to work*

4) *Additional Studies need to be conducted to determine mortality and specific patient populations in which to avoid and use Angiotensin II*

ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Angiotensin II for Vasodilatory Shock

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