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.
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
"Magic Bullets" aka Failed Novel Agents in Sepsis

- High dose steroids
- N-acetylcysteine
- Anti-thrombin III
- Statins
- Selenium
- Nitric Oxide Inhibitors
- NSAIDs
- Recombinant tissue factor plasminogen inhibitor
- Immunoglobulins
- Activated Protein C
- TNF-α
- Ketoconazole
Vitamin C Background

• Ascorbic Acid

• Discovered in 1912

• Essential vitamin in humans
  – Lack L-gulono-γ-lactone oxidase

Albert Szent-Gyorgyi  Sir Norman Haworth

Ann Nutr Metab. 2012;61(3):259-64
Vitamin C in Sepsis

Normal values: 45–90 µmol/L

- Severe Sepsis
- Septic Shocks
- Healthy Volunteers

Days: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10

µmol/L: 0, 10, 20, 30, 40, 50, 60
Animal Models

Fecal peritonitis → 2 hours → Ascorbic acid (200mg/kg) → Dehydroascorbic acid (200mg/kg)
Vitamin C Mechanisms

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

Vitamin C is required to synthesize catecholamines

L-Tyrosine $\xrightarrow{\text{Tyrosine hydroxylase}}$ Dopamine $\xrightarrow{\text{DOPA decarboxylase}}$ L-DOPA $\xrightarrow{\text{Dopamine \beta-hydroxylase}}$ Norepinephrine

Norepinephrine $\xrightarrow{\text{Phenylethanolamine N-methyltransferase}}$ Epinephrine

O$_3$ + Ascorbic acid

Zipursky JS et al. BMJ Case Rep 2014; PMID 24859547
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.
Vitamin C for Prophylaxis

Serum ascorbate levels

Multiple Organ Failure
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 (○), 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 (○), Lo-AscA (▲), Hi-AscA (△).
### Vitamin C in Septic Shock

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ascorbic Acid Group (n=14)</th>
<th>Control Group (n=14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during study period (72 h)</td>
<td>7.44±3.65</td>
<td>13.79±6.48</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during first 24 h</td>
<td>6.51±3.53</td>
<td>12.58±5.99</td>
<td>0.003</td>
</tr>
<tr>
<td>Total dose of norepinephrine during the first 24 h (mcg)</td>
<td>156.42±84.81</td>
<td>302.14±143.85</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of norepinephrine administration (h)</td>
<td>49.64±25.67</td>
<td>71.57±1.60</td>
<td>0.007</td>
</tr>
<tr>
<td>ICU Length of stay (days)</td>
<td>21.45±10.23</td>
<td>20.57±13.04</td>
<td>0.85</td>
</tr>
<tr>
<td>28 day mortality</td>
<td>2 (14.28)</td>
<td>9 (64.28)</td>
<td>0.009</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population</td>
<td>Dose</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-----------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 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    | 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                  |
|                     |        | severe sepsis                     |                                                                      |                                                                          |
| Zabet et al 2016    | RCT    | 24 SICU patients with septic      | Vitamin C 25 mg/kg q6h vs. Placebo                                   | • Less norepinephrine at 24 and 72 hours  
• Shorter duration of norepinephrine  
• Less 28 day mortality                                                  |
|                     |        | shock                             |                                                                      |                                                                          |
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

- Vitamin C 1.5 g IV q6h x 4 days
- Thiamine 200 mg IV q12h x4 days
- Hydrocortisone 50 mg IV q6h x7 days
It’s a Marikle!
Harmless?....maybe not

- Acute renal failure
  - Oxalate crystal deposition
“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
Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI)

• Recruitment was 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
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

Glucose

↓

Pyruvate
Biology 101- Krebs Cycle

Pyruvate → Lactate

Pyruvate dehydrogenase

Acetyl-CoA → Krebs Cycle

Krebs Cycle → ATP
Other Thiamine-Dependent Enzymes

- Pentose Phosphate Pathway (PPP)

Glucose 6-Phosphate (in Glycolysis) → PPP → α-ketoglutarate → Succinate

- Krebs Cycle
Are Critically Ill Patients Thiamine Deficient?
Thiamine Deficiency

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

![Graph showing % Deficient over time with 10% at 0 time and 20% at 72 hours]

*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

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

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

<table>
<thead>
<tr>
<th>Model Description</th>
<th>95% Subdistribution Hazard Ratio (SHR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine only</td>
<td>1.339 (1.044-1.717)</td>
</tr>
<tr>
<td>Thiamine, age, sex, and race</td>
<td>1.292 (1.003-1.663)</td>
</tr>
<tr>
<td>Thiamine, age, sex, race, and clinical factors</td>
<td>1.307 (1.002-1.704)</td>
</tr>
</tbody>
</table>

**Time to Lactate Clearance**

**Competing-risks regression**

Crit Care Med. 2018 [Epub ahead of print]
28-Day Mortality

<table>
<thead>
<tr>
<th>Primary Models</th>
<th>95% Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine only</td>
<td>0.806 (0.596-1.090)</td>
</tr>
<tr>
<td>Thiamine, age, sex, and race</td>
<td>0.797 (0.589-1.079)</td>
</tr>
<tr>
<td>Thiamine, age, sex, race, and clinical factors</td>
<td>0.666 (0.490-0.905)</td>
</tr>
</tbody>
</table>
What Dose Should I Give?
Well... It Depends

Oral or Per Tube

- Wernicke encephalopathy in differential?
  - No
    - Study Data
  - Yes
    - Experimental Data
    - 200-500 mg IV q8-12h

Safety of Thiamine

• Anaphylaxis likely exaggerated concern

989 patients → No anaphylaxis

>300,000 patients → No anaphylaxis

Estimated rate 1:250,000 administrations

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
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
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
Angiotensin II for Vasodilatory Shock

Joanna L. Stollings, Pharm.D., BCCCP, BCPS, FCCM, FCCP
MICU Clinical Pharmacy Specialist
Vanderbilt University Medical Center, Nashville, TN
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.
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
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

Does Your Institution Use Angiotensin II?

1. Yes
2. No
Angiotensin-Aldosterone System

Angiotensinogen → Angiotensin I → Angiotensin II

ACE

Angiotensin Receptor Type 1

Angiotensin Receptor Type 2

Angiotensin II in Septic Shock

Angiotensinogen

Angiotensin I

Angiotensin II

Angiotensin Receptor Type 1

Angiotensin Receptor Type 2

Tachyphylaxis

Downregulated Expression

Decreased Sensitivity

Decreased Activity

ACE

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

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
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)

**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

## 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

### Outcomes and Adverse Events

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

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

## Intervention

<table>
<thead>
<tr>
<th>First 3 Hours</th>
<th>3-48 Hours</th>
</tr>
</thead>
</table>
| • 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 | • 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 |

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

## Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Angiotensin II (n=163)</th>
<th>Placebo (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>21 (12.9%)</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (9.8%)</td>
<td>11 (7.0%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>14 (8.6%)</td>
<td>9 (5.7%)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10 (6.1%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Delirium</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>

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

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

Patients on ACE Inhibitors Have an Increased Response

Angiotensinogen → Angiotensin I → Angiotensin II

Angiotensin Receptor Type 1, Angiotensin Receptor Type 2

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Proposed Mechanism of Action</th>
<th>Preventative Action</th>
</tr>
</thead>
</table>
| 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                                                |

Patients on ARBs Inhibitors Have a Decreased Response

## 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 \( \geq 50 \text{ mcg/min} \), or phenylephrine at \( \geq 400 \text{ mcg/min} \) 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

1. Downtitrate the norepinephrine every 15 minutes until 30 mcg/min
2. Once norepinephrine reaches 30 mcg/min, stop vasopressin
3. Once norepinephrine reaches 10 mcg/min begin Ang 2 downtitration
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Available as</th>
<th>Drug Price per Unit (2017 USD)</th>
<th>Dosing</th>
<th>Estimated Cost PPPD (2017 USD)†</th>
<th>Estimated Cost per year‡ (2017 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>2.5 mg/mL vial</td>
<td>$1,500</td>
<td>20 ng/kg/min*</td>
<td>$1,728.00</td>
<td>$1,209,600</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>20 unit/50 mL infusion</td>
<td>$87.18</td>
<td>0.04 units/min</td>
<td>$385.52</td>
<td>n/a</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>8 mg/250 mL infusion</td>
<td>$26.90</td>
<td>50 mcg/min</td>
<td>$147.24</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*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
Angiotensin 2 Started

Norepinephrine stopped

Vasopressin stopped
ICU Course

*E. coli* bacteremia isolated, antibiotics streamlined

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

<table>
<thead>
<tr>
<th>Patient History</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yo M with septic shock, ARDS, acute renal failure, and disseminated histoplasmosis</td>
<td>Responder (deceased)</td>
</tr>
<tr>
<td>64 yo F with septic shock due to colitis with acute renal failure</td>
<td>Responder</td>
</tr>
<tr>
<td>53 yo M with SJS and septic shock due to <em>Streptococcus Viridans</em> bacteremia with acute renal failure</td>
<td>Responder</td>
</tr>
<tr>
<td>45 yo M with septic shock from gram negative bacteremia with acute on chronic renal failure</td>
<td>Non-responder (deceased)</td>
</tr>
</tbody>
</table>
Another Responder

- NE
- NE + AVP
- NE + AVP + Angiotensin 2
Future Directions

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

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
Angiotensin II for Vasodilatory Shock

Joanna L. Stollings, Pharm.D., BCCCP, BCPS, FCCM, FCCP
MICU Clinical Pharmacy Specialist
Vanderbilt University Medical Center, Nashville, TN