Refractory Shock

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Objectives

Pharmacist Objectives
1. Review the Surviving Sepsis Bundle 2018 update and pertinent pharmacologic aspects of the 2016 Surviving Sepsis Campaign
2. Describe mechanisms of novel pharmacologic hemodynamic support in refractory shock
3. Identify evidence based clinical roles of novel pharmacologic hemodynamic support

Technician Objectives
1. Demonstrate importance of timely application of hemodynamic supporting medications
2. Understand the use of various agents for refractory shock
Overview

- Review of Septic Shock
  - Updated definitions
  - Treatment summary
  - 2018 bundle update
- Refractory Shock
  - Definition
  - Pathophysiology
  - Treatment: angiotensin II, acidemia reversal, nitric oxide inhibitors, metabolic resuscitation

Updated Sepsis Definitions

- Sepsis: life threatening organ dysfunction caused by dysregulated host response to infection (qSOFA score ≥2)
- Septic shock: subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (persistent hypotension requiring vasopressors and lactate > 2 mmol/L)

Old Sepsis Definitions

- Sepsis: 2 or more SIRs criteria + likely source of infection
  - SIRs: WBC >12,000 or <3,000, HR>90, RR>20, temp >38 or <36
- Severe sepsis: sepsis with signs of end organ damage
  - Elevated lactate, hypotension
- Septic shock: severe sepsis refractory to fluid resuscitation
Surviving Sepsis Guidelines 2016

Initial management:

- Fluid resuscitation with crystalloid 30 ml/kg and additional PRN based on hemodynamic status
- Broad spectrum antibiotics within 1 hour
- Target mean arterial pressure (MAP) of 65
- Trend lactate, provide fluid resuscitation until normalized
- Initiate vasopressors to achieve MAP goal if unresponsive to fluid
  - Norepinephrine as first choice pressor
  - Add vasopressin or epinephrine if cannot achieve MAP goal or to reduce norepinephrine requirement
- IV hydrocortisone (200 mg/day) if fluids + vasopressors are inadequate

Surviving Sepsis Campaign Bundle

2018 Update

- Major change: three and six hour bundles combined into single “Hour 1 Bundle”
  - Begin resuscitation and management immediately
  - Reflects clinical reality of clinician at the bedside

<table>
<thead>
<tr>
<th>Bundle Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure lactate level. Re-measure if initial lactate is &gt; 2 mmol/L</td>
</tr>
<tr>
<td>Obtain blood cultures prior to administration of antibiotics</td>
</tr>
<tr>
<td>Administer broad spectrum abx</td>
</tr>
<tr>
<td>Rapidly administer 30 ml/kg crystalloid for hypotension or lactate &gt;/= 4 mmol/L</td>
</tr>
<tr>
<td>Apply vasopressors if patient is hypotensive during or after</td>
</tr>
</tbody>
</table>

*Resuscitation may take more than 1 hour
**No data specific to burn or immunocompromised populations
What is Refractory Shock?

- No universal consensus definition:
  - Failure to achieve a BP goal despite vasopressor therapy
  - Need for rescue vasopressor
  - Need for high vasopressor doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Norepinephrine Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.1 ug/kg/min</td>
<td>0.1 ug/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>15 ug/kg/min</td>
<td>0.1 ug/kg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1 ug/kg/min</td>
<td>0.1 ug/kg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1 ug/kg/min</td>
<td>0.1 ug/kg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 units/min</td>
<td>0.1 ug/kg/min</td>
</tr>
</tbody>
</table>

Refractory shock: an inadequate response to high-dose vasopressor therapy (defined as \( \geq 0.5 \) ug/kg/min norepinephrine-equivalent dose)

Pathophysiology of Refractory Shock

- Hypoxia, acidosis, hyperlactemia
  - Dysregulated nitric oxide metabolism
    - ATP-sensitive K+ channel activation
      - Membrane hyperpolarization
        - Cellular relaxation
          - Vasorelaxation
            - Impaired responsiveness to catecholamine
              - REFRACTORY VASODILATORY SHOCK
  - Reactive oxygen species overproduction
    - Endothelial dysfunction
      - Mitochondrial dysfunction
        - Vascular smooth muscle relaxation
          - Uncontrolled production of NO and PGJ2

- Hyperglycemia
- Hypocalcemia
- Corticosteroid deficiency
- Altered microcirculatory flow
  - Decreased bactericidal activity
  - Coagulation modulation
  - Dysregulated mitochondrial respiration
## Potential Treatments for Refractory Shock

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>Starting: 2-10 ng/kg/min Max: 20-40 ng/kg/min</td>
<td>Angiotensin II receptor activation</td>
<td>Hypertension, metabolic acidosis, risk of clots</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1-2 mEq/kg</td>
<td>Reversal of metabolic acidosis</td>
<td>Hypometraemia, ionized hypocalcemia, respiratory acidosis</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>5 g IV over 10 min</td>
<td>Scavenging of NO</td>
<td>Interference with hemodialysis sensors</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>Bolus: 1-2 mg/kg every 4-6 h infusion: 0.25-1 mg/kg/h</td>
<td>Inhibition of NOS</td>
<td>Serotonin Syndrome, hypoxia, pulmonary hypertension</td>
</tr>
<tr>
<td>Thiamine</td>
<td>200 mg every 12 h</td>
<td>Improved lactate clearance</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>25 mg/kg every 6 h or 1.5 g every 6 h</td>
<td>Increased catecholamine and vasopressin synthesis</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

Table adapted from Chest. 2018;154(2):416-426.

## Vasopressor/Inotrope Pharmacology Review

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>B1</th>
<th>B2</th>
<th>DA</th>
<th>V1</th>
<th>V2</th>
<th>PDE3-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>++</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
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<td></td>
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<tr>
<td>Vasopressin</td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (low) (High dose)</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td></td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Milrinone</td>
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<td></td>
<td>+++</td>
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<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>+++</td>
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</tbody>
</table>
Angiotensin II: Physiology review

- Naturally occurring hormone from renin-angiotensin pathway
- Potent vasoconstrictor
- Involved in water and sodium homeostasis

1. Renal blood flow reduced
2. Kidney converts pro-renin to renin
3. Renin converts angiotensinogen to angiotensin I
4. Angiotensin I is converted to angiotensin II via angiotensin converting enzyme (ACE)
5. Angiotensin II (potent vasoconstrictor) increases blood pressure via activation of AT1 and AT2
Angiotensin II: Physiology review

[Diagram showing the physiological effects of Angiotensin II]

History of Angiotensin II use

- Protein first isolated in 1930s
- Case reports describe the successful use of various bovine and human angiotensin II formulations as rescue therapy for patients with refractory shock
- Small pilot study published in 2014 supported its use as a vasopressor
  - 20 patients
  - Primary endpoint was effect of angiotensin II on standing norepinephrine dose required to maintain MAP of 65
  - Mean norepinephrine dose reduced from 27.6 +/- 29.3 ucg/min (in placebo) vs 7.4 +/- 12.4 ucg/min, P=0.06
  - Determined initial dose range: 2-10 ng/kg/min
Clinical Trials: ATHOS-3

- International, multi-center, randomized, double-blind, placebo-controlled trial
- Sponsored by La Jolla (manufacturer of Giapreza)
- **Primary Endpoint:** the response with respect to mean arterial pressure (MAP) at hour 3
  - Response defined as MAP of 75 mm Hg or higher or an increase in MAP from baseline of at least 10 mm Hg without an increase in the dose of background vasopressor
- **Secondary Endpoints:** changes in SOFA and cardiovascular SOFA score from baseline to 48 hours, adverse events, mortality at 7 and 28 days

ATHOS-3 Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 years or older</td>
<td>Burns &gt; 20% BSA</td>
</tr>
<tr>
<td>Vasodilatory shock despite IV volume resuscitation (minimum 25 ml/kg over past 24 hours) and high dose vasopressors</td>
<td>ACS</td>
</tr>
<tr>
<td>Shock defined as MAP between 55–70 mm Hg</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>High dose vasopressor = norepinephrine dose of 0.2 ucg/kg/min or equivalent dose</td>
<td>Liver failure</td>
</tr>
<tr>
<td></td>
<td>Mesenteric ischemia</td>
</tr>
<tr>
<td></td>
<td>Active bleeding</td>
</tr>
<tr>
<td></td>
<td>AAA</td>
</tr>
<tr>
<td></td>
<td>Neutropenic patients</td>
</tr>
<tr>
<td></td>
<td>VA-ECMO</td>
</tr>
<tr>
<td></td>
<td>Receiving high dose steroids</td>
</tr>
</tbody>
</table>
ATHOS-3 Methods

- Baseline MAP measured as mean of three readings
- Initial 3 hours: angiotensin II initiated at 20 ng/kg/min and titrated to maintain MAP of 75 mm Hg (max dose 200 ng/kg/min)
  - During this period, doses of other vasopressors were held constant
- After 3 hours, study drug or placebo or background vasopressors were adjusted to maintain MAP 65-75
- After 48 hours, study drug was titrated off per protocol

ATHOS-3 Results

- Study regimen initiated in 321 patients
  - 163 received angiotensin II
  - 158 received placebo
- No differences noted between groups in any baseline characteristics
- Patients in both groups were extremely ill (high APACHE II scores, elevated baseline vasopressor doses)
## ATHOS-3 Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
<th>Odds or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP response at hour 3 - no. (%)</td>
<td>114 (69.9)</td>
<td>37 (23.4)</td>
<td>Odds ratio, 7.95 (4.76-13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in CV SOFA score at hour 48</td>
<td>-1.75 +/- 1.77</td>
<td>-1.28 +/- 1.65</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Mean change in total SOFA score at hour 48</td>
<td>1.05 +/- 5.50</td>
<td>1.04 +/- 5.34</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Mean change in NE equivalent dose (baseline to 3 hrs) in ucg/kg/min</td>
<td>-0.03 +/- 0.10</td>
<td>0.03 +/- 0.23</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality at day 7 - no. (%)</td>
<td>47 (29)</td>
<td>55 (35)</td>
<td>Hazard ratio, 0.78 (0.53-1.16)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause mortality at day 28 - no. (%)</td>
<td>75 (46)</td>
<td>85 (54)</td>
<td>Hazard ratio, 0.78 (0.57-1.07)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

A Mean Arterial Pressure over Time

![Graph showing mean arterial pressure over time](N Engl J Med. 2017;377(5):419-430)
ATHOS-3 Results: Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event of any grade</td>
<td>142 (87.1)</td>
<td>145 (91.8)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>23 (14.1)</td>
<td>34 (21.5)</td>
</tr>
<tr>
<td>Any serious adverse event with frequency ( \geq 1% ) in either study group</td>
<td>99 (60.7)</td>
<td>106 (67.1)</td>
</tr>
</tbody>
</table>
ATHOS-3 Results: Side Effects

“Special Interest” adverse events were similar in both groups
- Rates of tachyarrhythmias, distal ischemia, ventricular tachycardia, and atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Ischemia</td>
<td>5 (3.1)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Intestinal ischemia</td>
<td>1 (0.6)</td>
<td>3 (1.9)</td>
</tr>
</tbody>
</table>

*There were no significant differences (at P <0.05) between the groups in the percentage of patients with adverse events

Study limitations (per the authors)

- Blinding may have been compromised by significant blood pressure response
- Side effects of angiotensin II may have been missed due to small study size
- Study was not powered to detect a difference in mortality
- Follow-up limited to 28 days
**Additional limitations**

- Lack of patients with low cardiac output = unknown effect in this population
- No head to head data, so no use as monotherapy
- Mortality endpoint: null hypothesis cannot be rejected
- No difference in end-organ damage
- Lack of transparency re: fluid status, no reporting of lactate

**Author’s conclusion**

- The percentage of patients who met the primary end point with respect to MAP at 3 hours was significantly greater in the angiotensin II group than in the placebo group
- Patients who received angiotensin II had lower requirements for catecholamines than patients who received placebo
- Cardiovascular SOFA scores were significantly lower in the angiotensin group than in the placebo group at 48 hours
FDA approves Giapreza for Septic Shock

- Approved December 2017 for septic or other distributive shock
- No contraindications
- **Warning and Precautions:** there was a higher incidence of venous and arterial thromboembolic events in patients who received Giapreza compared to placebo treated patients: 13% (21/163) vs 5% (8/158). The major imbalance was in venous thrombosis. Use concurrent VTE prophylaxis
- **FDA medical review:** no difference in VTE prophylaxis between groups prior to initiation of therapy
- [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209360Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209360Orig1s000MedR.pdf) (page 115-117)

Additional Information

- **Adverse Reactions (per package insert):**
  - Cardiovascular: thrombosis (13%), tachycardia (9%), deep vein thrombosis (4%), peripheral ischemia (4%)
  - Central nervous system: delirium (6%)
  - Endocrine and metabolic: acidosis (6%), hyperglycemia (4%)
  - Hematologic and oncologic: thrombocytopenia (10%)
  - Infection: fungal infection (6%)
- **Mortality benefit in patients initiated on renal replacement therapy**
  - Post-hoc analysis of the ATHOS-3 Trial
  - Patients with AKI treated with RRT at initiation of angiotensin II (n=45) or placebo (n=60)
  - Alive at day 28: 24 (53%) in angiotensin II group, 18 (30%) in placebo groups, survival through day 28 was significantly longer in angiotensin II group as compared to placebo group (unadjusted HR, 0.52; 95%CI, 0.30-0.87; p=0.012)
Sodium Bicarbonate

- Pharmacologic category
  - Alkalinizing agent
- Mechanism of action
  - Reverse acidosis through acid-base effects
- Dose
  - 1-2 mEq/kg
- Evidence
  - No studies have shown cardiovascular improvement in humans in shock states with severe lactic acidosis
- Additional considerations
  - Possible side effects include intracellular acidosis, respiratory acidosis, ionized hypocalcemia, hypernatremia

Nitric Oxide and Shock

- Constitutive nitric oxide synthase (cNOS)
  - Constantly active
- Inducible nitric oxide synthase (iNOS)
  - Induced via endotoxins, cytokines
**Hydroxocobalamin**

- **Pharmacologic category**
  - Vitamin B12 precursor

- **Mechanism of action**
  - Nitric oxide scavenger (off-label use)

- **Dose**
  - 5 grams IV over 10 minutes

- **Evidence**
  - Case reports in vasoplegic syndrome

- **Additional considerations**
  - Remains in the bloodstream and urine for days to weeks, can interfere with heme sensors on HD machines, no known serotonin considerations

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**Methylene Blue**

- **Pharmacologic category**
  - Inhibition of NOS and soluble guanylate cyclase

- **Mechanism of action**
  - Reverses vasodilation caused by excessive cyclic guanosine monophosphate

- **Dose**
  - 1-2 mg/kg (bolus, repeated boluses, low-dose infusions)

- **Evidence**
  - Only small RTCs (n=15-30)

- **Additional considerations**
  - MAOi activity, increased pulmonary pressures, methemoglobinemia, glucose-6-phosphate dehydrogenase deficiency, inaccurate pulse SpO2
**Cautionary Tale for NO pathway modulators?**

- **Tilarginine (546C88)** - Non-selective NOS inhibitor
  - **Phase II** - Randomized Placebo Controlled Trial (n=312)
    - Resolution of shock at 72 hours: 40% vs 24% (p=0.004)
    - 28 day survival: 82 (53%) vs 80 (51%) (p=NS)
  - **Phase III** - Randomized Placebo Controlled Trial (n=797)
    - Resolution of shock at 72 hours: 27% vs 16% (p=0.001)
    - All cause mortality by day 28: 59% vs 49% (p=0.003)
  - Failure of tilarginine to improve clinical outcomes casts doubt on other rescue agents affecting NO signaling for refractory shock

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**Thiamine**

- **Pharmacologic category**
  - Vitamin deficiency/repletion
- **Mechanism of action**
  - Essential metabolic cofactor
- **Dose:** 200 mg IV every 12 hours
- **Thiamine deficiency in critically ill**
  - 20-70% of septic shock patients
  - Increased metabolic demand
  - Diuretics
  - Hemodiafiltration
Thiamine Evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcome</th>
<th>Takeaways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Thiamine Concentration as predictors of Mortality (2014)</td>
<td>Prospective Observational Study (n=108) 71.3% thiamine deficient</td>
<td>No difference in mortality</td>
<td>Thiamine serum concentrations were not associated with mortality</td>
</tr>
<tr>
<td>Thiamine in septic shock with EtOH use disorder (2018)</td>
<td>Retrospective cohort study (n=53) Received Thiamine: 64%</td>
<td>Mortality: 44% vs 79% (p=0.02)</td>
<td>Thiamine may reduce mortality in septic shock pts with EtOH use disorder</td>
</tr>
<tr>
<td>Effect of Thiamine Administration on Lactate clearance and Mortality (2018)</td>
<td>Retrospective matched cohort (n=369) 1:2 match</td>
<td>Mortality: 0.666 (95% CI: 0.490-0.905)</td>
<td>Thiamine improved lactate clearance and mortality is severely ill septic shock patients</td>
</tr>
</tbody>
</table>

Thiamine Randomized Placebo Controlled Trial

- **Objective:** To determine if thiamine reduced lactate in septic shock patients
  - 88 patients in septic shock

  - **Outcomes:**
    - 24 hours lactate concentration difference: 2.5 vs 2.6 (p=0.4)
    - No difference in secondary outcomes

  - **Thiamine deficient patients**
    - 35% (15 vs 13)
    - 24 hour lactate concentrations:
      - 2.1 vs 3.1 (p=0.03)
    - Mortality: 2 vs 6 (p=0.10)
Ascorbic Acid (Vitamin C)

- Pharmacologic category
  - Vitamin deficiency/repletion
- Mechanism of action
  - Antioxidant, required for pressor synthesis, immune modulator
- Dose
  - 25 mg/kg or 1.5 g every 6 hours
- Evidence
  - Mostly animal data, several small studies
- Additional considerations
  - Converted to oxalate
  - Increased glucose readings

Vitamin C the Antioxidant

- Scavenge reactive oxygen species directly
  - Donation of an electron-generating ascorbic radical from ascorbic acid
  - Preventing damage to cellular proteins, lipids, and nucleic acids
- Reactivate other reactive oxygen species scavengers
  - Glutathione and alpha-tocopherol
- Nicotinamide adenine dinucleotide oxidase (NOX) inhibition
  - NOX activates superoxide and peroxynitrite
- Inhibits nuclear factor kappa-B
  - Preventing disruption of tight junctions leading to vascular compromise
**Vitamin C the Vasopressor Synthesiser**

- Vitamin C is a cofactor for peptidylglycine alpha-amidating monooxygenase (PAM)
  - Increased vasopressin synthesis
  - Downstream increasing corticosteroid synthesis
- Needed for catecholamine synthesis
  - Dopamine Beta-hydroxylase (forms NE)
  - Recycles cofactor tetrahydrobiopterin
- Modulates alpha and beta receptors
  - Enhancing activation by epinephrine

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**Vitamin C the Immune Modulator**

- Vitamin C and leukocytes support
  - Plays role in chemotaxis, support lymphocytic proliferation
  - Assists in oxidative neutrophil killing of bacteria
- Vitamin C deficiency
  - Delayed bactericidal activity of natural killer cell
  - Delayed suppressor T cell activity
- Inhibit tumor necrosis factor production of intercellular adhesion molecules
- At high doses may even have intrinsic bacteriostatic activity

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**References**

**Vitamin C the Evidence**

- Phase I randomized, placebo controlled trial
  - 24 medical ICU patients with severe sepsis
  - Placebo vs 50 vs 200 mg/kg/day for 96 hours
  - Reduced organ failure and reduced C-reactive protein and procalcitonin levels
- Effect on vasopressor requirements in septic shock
  - 28 adult surgical patients with septic shock
  - 25 mg/kg every 6 hours vs placebo
  - Decreased vasopressor requirements, faster weaning of pressors
  - Reduced 28-day mortality
  - No change in ICU LOS

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**The Paper Heard Around the World**

- **Design:**
  - Single center retrospective pre-post analysis
    - 1/2016 - 7/2016 (n = 47) vs 6/2015 - 12/2015 (n=47)
  - **Inclusion**
    - Severe sepsis or septic shock patients with a procalcitonin level > 2 ng/ml
  - **Treatment**
    - 1.5 g IV vitamin C every 6 hours, 200 mg IV thiamine every 12 hours, 50 mg hydrocortisone every 6 hours
- **Outcomes:**
  - Mortality 8.5% vs 40.4% (p<0.001)
  - Duration of vasopressor therapy 18.3 hours vs 54.9 hours (p<0.001)
Steroids, Vitamin C, thiamine

Synergy

- Glucocorticoids and vitamin C synergy
  - Glucocorticoids increase vitamin C cellular uptake
  - Vitamin C reverses oxidation of glucocorticoid receptors
  - Combination protects against vascular endothelium from endotoxin damage
- Thiamine’s helping hand
  - Reduces vitamin c’s oxalate production

Looking Forward

- HYVITS Trial NCT03380507 - May 2019 (n=212)
- ACTS Trial NCT03389555 - Sept 2019 (n=200)
- VICTAS Trial NCT03509350 - Oct 2021 (n=2000)
- And many, many more...
Cost Comparison (as cost per day)

- Thiamine: $16.20-$24.88
- Hydroxocobalamin (as Cyanokit): $985.58
- Ascorbic Acid: $495
- Angiotensin II: $1,800.00
- Methylene Blue: $2,007.00
- Sodium bicarbonate 8.4% (per 50 mEq ampule): $11-$24

Refractory Shock Treatment

Takeaways

- **Angiotensin II**
  - Role in therapy yet to be determined
- **Nitric oxide pathway modulators**
  - Temporarily increase SVR, questionable mortality data
- **Thiamine**
  - May be most beneficial in patients with thiamine deficiency
- **Vitamin C**
  - May be of benefit in both severe sepsis or septic shock patients
- **Vitamin C, thiamine, and hydrocortisone combination**
  - May act synergistically