I Have
No Disclosures
Bacterial Sepsis

• Approximately 1 million people in the U.S. develop sepsis each year
• 35% to 40% of septic patients develop Acute lung injury
• 25% to 35% of septic lung-injured patients die
832 Passengers

416 Passengers

1 Fully Loaded Boeing 747

Muhammad Ali
Sepsis - Pneumonia
June 3, 2016
Vitamin C in Disease

Normal Plasma Vitamin C Level

Plasma ascorbate (µM)

Healthy
Gastritis
Diabetes
Pancreatitis
Pneumonia
Osteoporosis
Arthritis
Cancer

Trauma
Sepsis
Surgical Sepsis

Detailed Study of Lung Tissue

20 Hours

Surgical Sepsis

Detailed Study of Lung Tissue

20 Hours

Vitamin C
Septic Murine Lung  Vitamin C Treated Septic Lung
Vitamin C Attenuates Histological Evidence Of Lung Injury
Plasma Ascorbate Levels In Human Sepsis

- Subnormal levels a constant feature in septic patients
- Ascorbate levels correlate inversely with the incidence of multiple organ failure
  (low levels higher numbers of organs failed)
- Ascorbate levels correlate directly with survival
  (low levels low survival)

Phase I Safety Trial

- Severe Sepsis
- Septic Patients: Geographic MRICU patients
- Randomized, double blind, placebo-controlled
- **AE**: Systemic hypotension, tachycardia, nausea
- 1) **Placebo**, 2) **50 mg/kg/24 hr**, 3) **200 mg/kg/24 hr**
- IV VitC ¼ dose infused 6 hours D5%W
- Blood Draw (0, 12, 24, 36, 48, 72, 96 hours)

Oral Dosing

Plasma Vitamin C Concentration μmol/L

Δ: Intravenous Dosing
O: Oral Dosing

Time, min

Vitamin C Dose, g

Assessing Organ Injury

SOFA SCORE

Shock
Extent of Pharmacologic Support

Brain

Respiratory Failure

Liver

Bone Marrow Dysfunction

Renal Failure

Brain

Shock

Liver

Bone Marrow Dysfunction

Renal Failure
### Sequential Organ Failure Assessment Score (SOFA)

<table>
<thead>
<tr>
<th>Lung (PaO2/FiO2 mm/Hg)</th>
<th>Brain (Coma)</th>
<th>Cardiovascular (Shock)</th>
<th>Liver (Bilirubin)</th>
<th>Bone Marrow (Platelet)</th>
<th>Renal Failure (Creatinine)</th>
</tr>
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<tr>
<td>&lt; 400</td>
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<td>13-14</td>
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<td>1.2-1.9</td>
<td>&lt;150</td>
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<tr>
<td>&lt; 300</td>
<td>2</td>
<td>10-12</td>
<td>2 Dopamine ≤ 5 µg/kg</td>
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**Organ Failure Scores**

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**SOFA Score = Sum of Organ Failure Scores**
Phase I Safety Trial

- 31 patients screened – 24 enrolled and randomized
- **Placebo**: (4M, 4F, age 54-68 yrs)
- **Lo-VitC**: (5M, 3F, age 30-70 yrs)
- **Hi-VitC**: (4M, 4F, age 44-92 yrs)
- SOFA - **Placebo**: 13.1, SOFA - **Lo-Vit C**: 11.6
  SOFA **Hi-Vit C** - 12.2

Ascorbate Consumed In Sepsis

- By reduction of plasma free iron
- By the scavenging of aqueous free radicals
- By destruction of dehydroascorbic acid
- Destruction permits uncontrolled oxidant activity

SOFA Scores

Intravenous Vitamin C

- Safe
- Mortality reduced
- Multiple organ failure significantly reduced
- Blood markers inflammation and vascular injury significantly attenuated

Plasma Vitamin C Augmentation

Human Studies

- Lowered Incidence of ARDS and MOF in surgically critically ill
- Lowered capillary leak in patients with 50% full thickness burns
- Vit C + selenium + n-acetyl cysteine + Vit E lowered ARDS mortality by 50%

(Published in abstract only)

Acute Respiratory Distress Syndrome: E. Coli Sepsis

**Baseline**

**Day 2**

**Day 3 AM**

**Day 3 PM**

**Day 3**

**Intubation/Mechanical Ventilation**

**Day 21**
Neutrophil Activation – NET Formation

- Bacteria
- Cytokine
- Endotoxins
- Fungi
- Oxidants
- Proteases

NETOSIS
ARDS Bronchoalveolar Lavage Cytology
Vitamin C Infusion
UM1 Program
(Novel Therapies of Lung Diseases)

• Phase II multi-center trial – proof of concept
• Randomized, double blinded, placebo-controlled
• Employ “physiological” and “chemical measures” of efficacy rather than mortality
• Data collected on well-characterized subjects
• Common drug with low toxicity
• Immuno-modulating therapy for ALI
Vitamin C Infusion for TReatment In Sepsis-Induced Acute Lung Injury

CITRIS-ALI

Assess Efficacy
96-hour Vitamin C Infusion (200 mg/kg/24 Hours)
Septic Acute Lung Injury
CITRIS-ALI

- Multi-Center Trial
  - VCU
  - The Cleveland Clinic
  - The Medical College of Wisconsin
  - The University of Kentucky
  - Emory University (First Trial Year)

- Proposed 170 patients with sepsis-induced ARDS
- Trial completed (November 2017)
Hypotheses

• Attenuate septic lung injury
  \((\text{oxygenation index and } \dot{V}_E \text{ 40})\)
• Attenuate sepsis-induced organ failure
  \((\text{SOFA Score})\)
• Attenuate injury biomarkers
  - Inflammation
  - Alveolar Epithelial Injury
  - Fibrinolysis
  - Vascular Injury
  - Barrier Function
“Phases” of ARDS

Day → 0 2 7 14 21…..

Exudative | Proliferative | Fibrotic
Clinical Recognition of Organ Injury

Sepsis Onset (Risk Period) Days

Days

-3 -2 -1 0 2 7 10

Immune Cell Activation

Microvascular Thrombosis

Bacteremia, Endotoxemia Cytokine Surge
Prevention of ARDS

Timing of Intervention

Exudative
Proliferative
Fibrotic

Day → 0 2 7 14 21.....

Post Vitamin C Intervention

Prevention of ARDS

Onset of ARDS Risk Period

Timing of Intervention
Biomarkers
By “Compartment”
**Systemic Inflammation**

C-Reactive Protein
Procalcitonin
Receptor for Advanced Glycation End Products (RAGE)
C-Reactive Protein
Procalcitonin

Receptor for Advanced Glycation End products
RAGE

Fibrinolysis

Tissue Factor Pathway Inhibitor
ONSET LUNG INJURY

Active Treatment

200 mg/kg/day
50 mg/kg/Every 6 hours
4 days
Assessment Schedule

- SOFA Score
- Plasma Ascorbate
- Biomarkers
Physiological Assessment

Oxygenation Index

\[ OI = \frac{\text{Mean Airway Pressure} \times F_iO_2}{P_{aO_2}} \]

\[ \dot{V}_E - 40 = \frac{\dot{V}_E}{\text{Weight (KG)}} \times \frac{\text{PaCO}_2}{40} \]
“Responder Phenotype”

- ↓ C-Reactive Protein and Procalcitonin
- ↓ RAGE
- ↑ Tissue Factor Pathway Inhibitor
- ↓ Serum-free Thrombomodulin
- ↓ Angiopoietin-2
Epidemiological Assessment
(Secondary Outcomes)

- Ventilator Free Days
- ICU Free Days
- All Cause Mortality
- Hospital Free Days
Vit C Infusion Started
