Hydrocortisone, Ascorbic Acid and Thiamine for the Treatment of Severe Sepsis & Septic Shock

Paul E Marik, MD
Disclosures
VITAMINS
Vitamin C, Hydrocortisone & Thiamine in Septic Shock
Presenter - Dr Tomoko Fujii (Melbourne, Australia)
Editorialist - Prof Paul Marik (Norfolk, USA)
01. The management of sepsis: science & fiction
   Paul E. Marik

02. Role of procalcitonin use in the management of sepsis
   Claudia Gregoriano, Eva Heilmann, Alexandra Molitor, Philipp Schuetz

03. The complete blood count to diagnose septic shock
   Joshua David Farkas

04. Driving blind: instituting SEP-1 without high quality outcomes data
   Jeffrey Wang, Jeffrey R. Strich, Willard N. Applefeld, Junfeng Sun, Xizhong Cui, Charles Natanson, Peter O. Eichelberger

05. Fluid resuscitation in sepsis: The great 30 mL per kg hoax
   Paul E. Marik, Frank van Haren, Liam Byrne

06. The origins of the Lacto-Bolo reflex: the mythology of lactate in sepsis
   Rory Spiegel, David Gordon, Paul E. Marik

07. Melatonin for the treatment of sepsis: the scientific rationale
   Ruben Manuel Luciano Colunga Biancatelli, Max Berrill, Yassen H. Mohammed, Paul E. Marik

08. Timeliness of antibiotics for patients with sepsis and septic shock
   Michiel Schinkel, Rishi S. Nanman Panday, W. Joost Wiersinga, Prabath W.B. Nanayakkara

09. Early norepinephrine use in septic shock
   Olfa Hamzaoui, Rui Shi

10. Thiamine (Vitamin B1) in septic shock: a targeted therapy
    Ari Moskowitz, Michael W. Donnino

11. Vitamin C: an essential “stress hormone” during sepsis
    Paul E. Marik

12. Sepsis trends: increasing incidence and decreasing mortality, or changing denominator?
    Chanu Rhee, Michael Klompas

13. Time to stop randomized and large pragmatic trials for ICU syndromes: the case of sepsis and ARDS
    Armand R.J. Girbes, Harm-Jan de Grooth
Hydrocortisone, Vitamin C and Thiamine for the Treatment of Sepsis: A Before-After Study

Paul E. Marik, MD, FCCM, FCCP
Vikramjit Khangoora, MD
Michael Hooper, MD, Msc
John D Catravas, PhD, FAHA, FCCP
Racquel Rivera, Pharm D
CONCLUSIONS: Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including acute kidney injury, and in reducing the mortality of patients with severe sepsis and septic shock. Additional studies are required to confirm these preliminary findings.

CHEST 2017; 151(6):1229-1238
Philosophy of the Hydrocortisone, Ascorbic Acid and Thiamine (HAT) Protocol

CHEAP and readily available
SAFE – No side effects
Multiple agents with overlapping and synergistic actions
Targets the host's response to infection
Anti-inflammatory + antioxidant

NESW
The Criticisms

- Small retrospective study
- Non-concurrent controls
- Lack of blinding
- Single center
- “Results totally implausible”
- “Snake-oil Medicine”
- “No better than homeopathy”
- “Vitamin C is not safe... causes kidney injury”
- “Highly “invested” investigator who has made false and preposterous claims”
- “Local effect: Norfolk – Center of the World Scurvy outbreak”
The Scientific Evidence

- > 400 peer-reviewed experimental, pre-clinical and clinical publications evaluating vitamin C in sepsis

- Evidence summarized in numerous review papers
January 2016 – January 2020

- Treated > 1500 septic patients admitted to MICU
  - No exclusion criteria: HIV, Sickle disease, Kidney stone, ESRD, etc
- Reproducible clinical benefit
- No side effects

- Consulted on > 1000 patients' world wide
- Adopted by physicians & hospitals around the world
“After introducing HAT therapy to the equation, sepsis is no longer a concern of mine. If they are not «already dead» at arrival, the patients survive. And they survive with their health intact!
“I spent 15 years gaining expertise in deploying ICU therapeutics with the farcical goal of keeping ascorbic acid depleted patients alive and well - without giving them ascorbic acid!”
What I have Learnt

- **Timing Matters**
- **Dosing Strategy Matters**
- **Volume Matters (fluid overload)**
- Monitoring Procalcitonin matters
- “Quality” of Supportive Care Matters
What I have Learnt

- **Dose Matters**
  - Vitamin C 1.5g q 6 IV
  - Hydrocortisone 50mg q 6 IV
  - Thiamine 200mg q 12 IV (target 4 days)

- **Attenuated or limited response**
  - Q 8 or q 12 dosing
  - Continuous infusion
  - Omitting thiamine or corticosteroids
Studies Designed to FAIL?

Article
Early Vitamin C and Thiamine Administration to Patients with Septic Shock in Emergency Departments: Propensity Score-Based Analysis of a Before-and-After Cohort Study

Vitamin C administered for 1 day (3 g/12 h or 1.5 g/6 h)
What I have Learnt

- Timing matters... EARLY Rx
- “Door to needle” time < 6 hours after presentation
- Ideally at time of first dose Antibiotic
Relationship Between Delays in Administration and ICU Mortality in 90 Patients Treated with iHAT

<table>
<thead>
<tr>
<th>Delay (Hrs)</th>
<th>Observed ICU Mortality (%)</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 hrs</td>
<td>0.0</td>
<td>0/1</td>
</tr>
<tr>
<td>6-12 hrs</td>
<td>13.3</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;12-18 hrs</td>
<td>19.0</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;18-24 hrs</td>
<td>23.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

iHAT = intravenous hydrocortisone, ascorbic acid, thiamine  
Hrs = time from sepsis presentation to iHAT initiation  
O/E = observed/expected ICU mortality ratio using APACHE IV scores

Kory P et al - SCCM Abstract 2020, recently accepted by Critical Care and Shock
Killing of *S. aureus* in murine peritoneal macrophages by Ascorbic acid along with antibiotics Chloramphenicol or Ofloxacin: Correlation with inflammation

Somrita Dey, Biswadev Bishayi*

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[Diagram showing the interaction between *S. aureus* and macrophages, involving Ascorbic acid, Chloramphenicol, Ofloxacin, and various biochemical processes such as increased expression of TLR2, phagocytosis, and the involvement of antioxidants like SOD and Catalase, with arrows indicating the flow of reactions and the production of reactive oxygen species (ROS).]
What about VITAMINS
<table>
<thead>
<tr>
<th></th>
<th>Intervention (107)</th>
<th>Control (104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hours) from ICU admission to Randomization: Median (IQR)</td>
<td>13.7 (7.1-19.3)</td>
<td>11.4 (5.5-17.8)</td>
</tr>
</tbody>
</table>
Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock

Elizabeth P Hudson, Jake TB Collie, Tomoko Fujii, Nora Luethi, Andrew A Udy, Sarah Doherty, Glenn Eastwood, Fumitaka Yanase, Thummaporn Naorungroj, Laurent Bitker, Yasmine Ali Abdelhamid, Ronda F Greaves, Adam M Deane and Rinaldo Bellomo

| Time from randomisation to first dose of vitamin C (hours), median (IQR) | 14.9 (10.6–15.6) |

14.9 hours
<table>
<thead>
<tr>
<th></th>
<th>Intervention (107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation to ICU adm.</td>
<td>????????</td>
</tr>
<tr>
<td>ICU adm. to randomization</td>
<td>13.7</td>
</tr>
<tr>
<td>Randomization to first dose</td>
<td>14.9</td>
</tr>
</tbody>
</table>

**Time (hours) from presentation (door) to first dose**

Therapy initiated at a minimum of 28.6 hrs after presenting with sepsis.
Best estimate of time from presentation (door) to first dose

> 32 hours
Best estimate of time from presentation (door) to first dose

> 32 hours
# Trials of Therapies in Critical Illness Presented at Critical Care Reviews Conference 2020

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time from “Disease Onset” to Randomization - Median</th>
<th>Time From Randomization to Intervention Therapy</th>
<th>Disease Onset to Study Intervention (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>3 hours</td>
<td>&lt; 1 hour?</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>TRACT</td>
<td>&lt; 6 hours (median 3-4 hours?)</td>
<td>1.3 hours</td>
<td>4-5 hours?</td>
</tr>
<tr>
<td>COACT</td>
<td>1.5 hours</td>
<td>0.8 hours</td>
<td>2.3 hours</td>
</tr>
<tr>
<td>SPICE</td>
<td>4.6 hours</td>
<td>&lt; 1hour?</td>
<td>5-6 hours</td>
</tr>
<tr>
<td>ICU-ROX</td>
<td>2 hours</td>
<td>&lt; 1 hour?</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>VITAMINS</td>
<td>Presentation to ICU Admission</td>
<td>ICU admission to Randomization</td>
<td>Randomization to Intervention</td>
</tr>
<tr>
<td></td>
<td>4-6 hours?</td>
<td>13.7 hours</td>
<td>14.9 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;32 hours</td>
</tr>
</tbody>
</table>
What I have Learnt

- Volume Matters
  - Excess fluids “dilutes” clinical benefit
  - Hemodynamic collapse
  - Increased organ failure
  - Delayed recovery of organ failure
Association between fluid overload and SOFA score kinetics in septic shock patients: a retrospective multicenter study

Xavier Chapalain\textsuperscript{1,6,7}, Véronique Vermeersch\textsuperscript{1,6,7}, Pierre-Yves Egret\textsuperscript{e}, Gwenael Prat\textsuperscript{3}, Zarrin Alavi\textsuperscript{5}, Eric Vica\textsuperscript{2} and Olivier Huet\textsuperscript{1,6,7}
Volume overload (and associated organ dysfunction) limits the therapeutic efficacy of HAT Rx
Very BAD

Time

Fluid

Vit C
BAD

Time

Fluid

Vit C
Less BAD

Time

Fluid

Vit C
Best

Time

Fluid

Vit C
Fluids in VITAMINS
Inclusion criteria

- Need for vasopressor therapy to maintain the mean arterial pressure (MAP) $> 65$ mm Hg for $> 2$ hours

- lactate $> 2$ mmol/L, despite adequate fluid resuscitation (Lacto-bolo reflex)
VITAMINS has a fatal flaw.

Do we need more flawed RCT’s?
Conclusions:

A systematic literature search provided no conclusive evidence of any pharmacologic intervention that has consistently reduced mortality in critically ill patients. Strategies associated with improved or noninvasive mechanical ventilation were associated with reduced mortality.
We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

- Power often inadequate
- Varied Impacts on Severity
- **Poor Timing of Interventions**
- Wrong End Points Used
- Incorrect Group of Patients Identified
- Patient Heterogeneity Not Accounted For
- Clinical Applicability Limited Given High Exclusions
BMJ Open Vitamin C therapy for patients with sepsis or septic shock: a protocol for a systematic review and a network meta-analysis

Tomoko Fujii,1,2 Alessandro Belletti3,4, Anitra Carr,5 Toshi A Furukawa,2 Nora Luethi,1,6 Alessandro Putzu,7 Chiara Sartini,3 Georgia Salanti,8 Yasushi Tsujimoto,9,10 Andrew A Udy,1,11 Paul J Young,12,13 Rinaldo Bellomo1,4,14
The Cure For Sepsis!

A Real World Study

Paul Marik, MD,FCCM,FCCP
Steps to the Cure......

- Early Diagnosis
- Early administration of the correct antibiotics, in the correct dose
- Source Control
- Conservative, physiologic approach to fluid resuscitation
- Early use of Norepinephrine
- The “Metabolic Resuscitation Protocol”
  - Steroids, Vitamin C and Thiamine
- Multidisciplinary, team approach to patient care
- State-of-the-art evidence based supportive care
The changing paradigm of Sepsis: Early diagnosis, Early antibiotics, Early pressors and Early adjuvant treatment

Traditional time-course of therapies

- Antibiotics
- Fluid
- Norepinephrine
- Vasopressin
- Epinephrine
- Stress-dose steroids

Escalation-deescalation strategy

- Antibiotics
- Fluid
- Norepinephrine
- Vasopressin
- Epinephrine
- Metabolic resuscitation (Hydrocortisone/Ascorbate/Thiamine)

Marik & Farkas, Crit Care Med 2018;46:1690
“After introducing HAT therapy to the equation, sepsis is no longer a concern of mine. If they are not «already dead» at arrival, the patients survive. And they survive with their health intact!
"I spent 15 years gaining expertise in deploying ICU therapeutics with the farcical goal of keeping ascorbic acid depleted patients alive and well - without giving them ascorbic acid!?"
Thank you