

# 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)



Critical Care Reviews Meeting 2020  
Thursday & Friday January 16th / 17th  
Titanic, Belfast

## Focused Issue on Sepsis: Science and Fiction

- 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 Q. Eichacker
- 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. Nannan 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



# Critical Care Reviews – January 2017



**CHEST** The Cardiopulmonary  
and Critical Care Journal  
*The Official Journal of the American  
College of Chest Physicians*

## 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

**EVMS**  
Eastern Virginia Medical School

 **SENTARA**

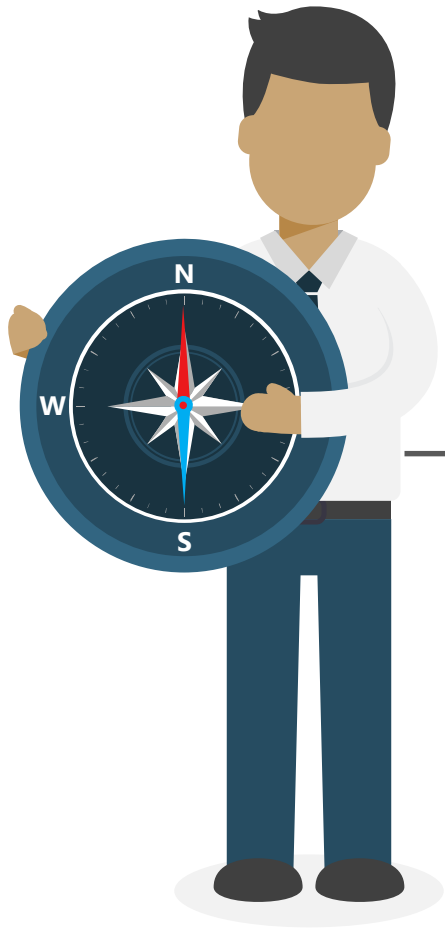
# Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

**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



Targets the hosts response to infection  
Anti-inflammatory + antioxidant



Multiple agents with overlapping  
and synergistic actions



**SAFE** – No side effects



**CHEAP** and readily available

# 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



# Dr EV. Volda, Norway



"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!

# Dr PK. Madison, Wisconsin



"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

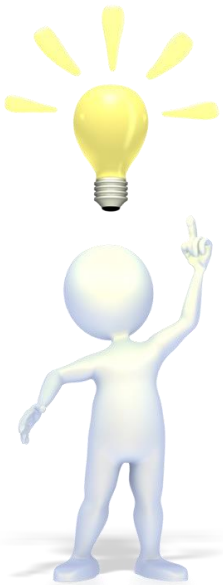
- **Timing Matters**
- **Dosing Strategy Matters**
- **Volume Matters (fluid overload)**
- Monitoring Procalcitonin matters
- “Quality” of Supportive Care Matters





# 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?



Journal of  
*Clinical Medicine*

*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**

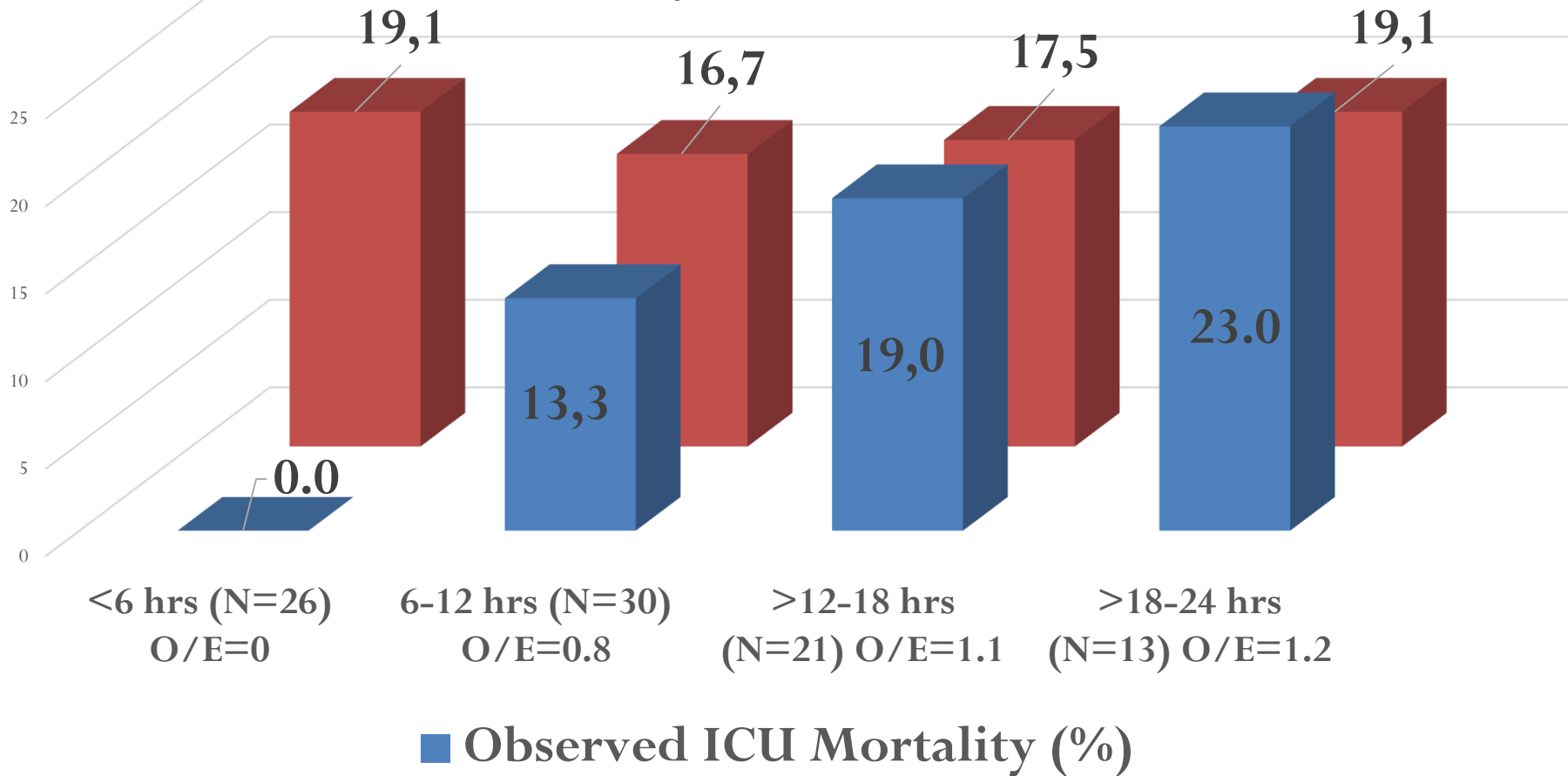
Vitamin C administered for 1 day (3 g/12 h or 1.5 g/6 h)

# What I have Learnt

- Timing matters... EARLY Rx
  - “Door to needle” time  $< 6$  hours after presentation
  - Ideally at time of first dose Antibiotic



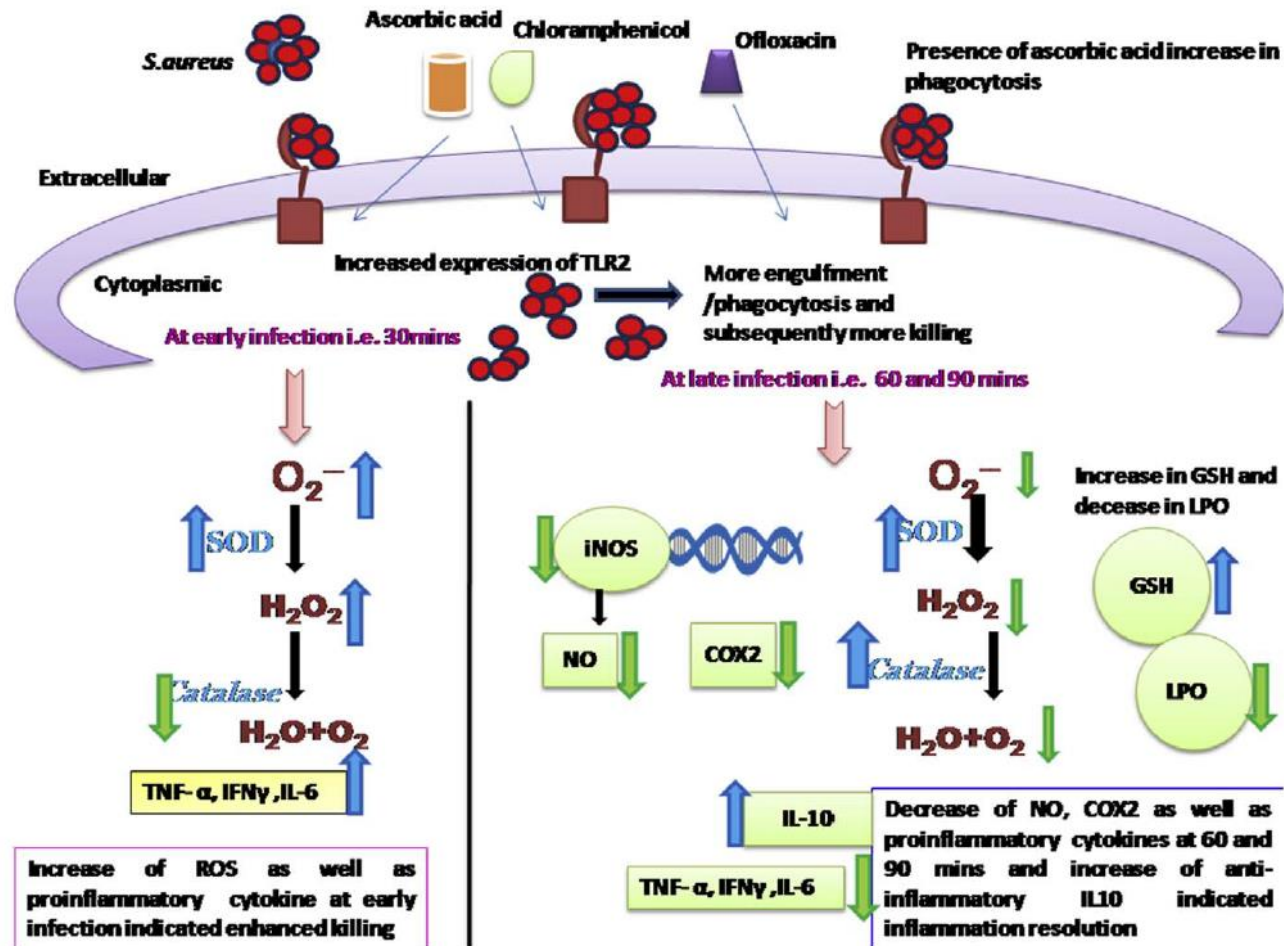
# Relationship Between Delays in Administration and ICU Mortality in 90 Patients Treated with iHAT



**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

# Killing of *S. aureus* in murine peritoneal macrophages by Ascorbic acid along with antibiotics Chloramphenicol or Ofloxacin: Correlation with inflammation

Somrita Dey, Biswadev Bishayi\*





# What about VITAMINS



# Time (hours) from ICU admission to Randomization: Median (IQR)

Intervention (107)	Control (104)
13.7 (7.1-19.3)	11.4 (5.5-17.8)

# 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



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

	Intervention (107)
Presentation to ICU adm.	???????
ICU adm. to randomization	13.7
Randomization to first dose	14.9

Therapy initiated at a minimum of 28.6 hrs  
after presenting with sepsis

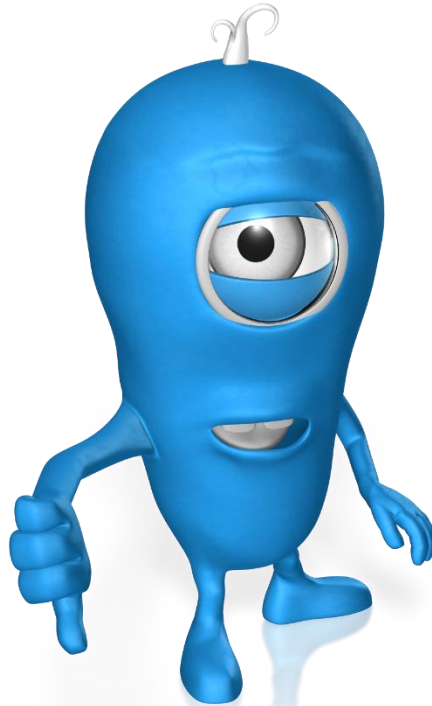
Best estimate of time from presentation  
(door) to first dose

> 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

TRIAL	Time from “Disease Onset” to Randomization - Median		Time From Randomization to Intervention Therapy	Disease Onset to Study Intervention (median)
65	3 hours		< 1 hour?	3-4 hours
TRACT	< 6 hours (median 3-4 hours?)		1.3 hours	4-5 hours?
COACT	1.5 hours		0.8 hours	2.3 hours
SPICE	4.6 hours		< 1hour?	5-6 hours
ICU-ROX	2 hours		< 1hour?	2-3 hours
VITAMINS	Presentation to ICU Admission	ICU admission to Randomization	Randomization to Intervention	
	4-6 hours?	13.7 hours	14.9 hours	>32 hours

# What I have Learnt

- Volume Matters
  - Excess fluids “dilutes” clinical benefit
  - Hemodynamic collapse
  - Increased organ failure
  - Delayed recovery of organ failure

Marik *Annals of Intensive Care* 2014, 4:21  
<http://www.annalsofintensivecare.com/content/4/1/21>

 **Annals of Intensive Care**  
a SpringerOpen Journal

**REVIEW**

**Open Access**

## Iatrogenic salt water drowning

Paul E Marik




RESEARCH

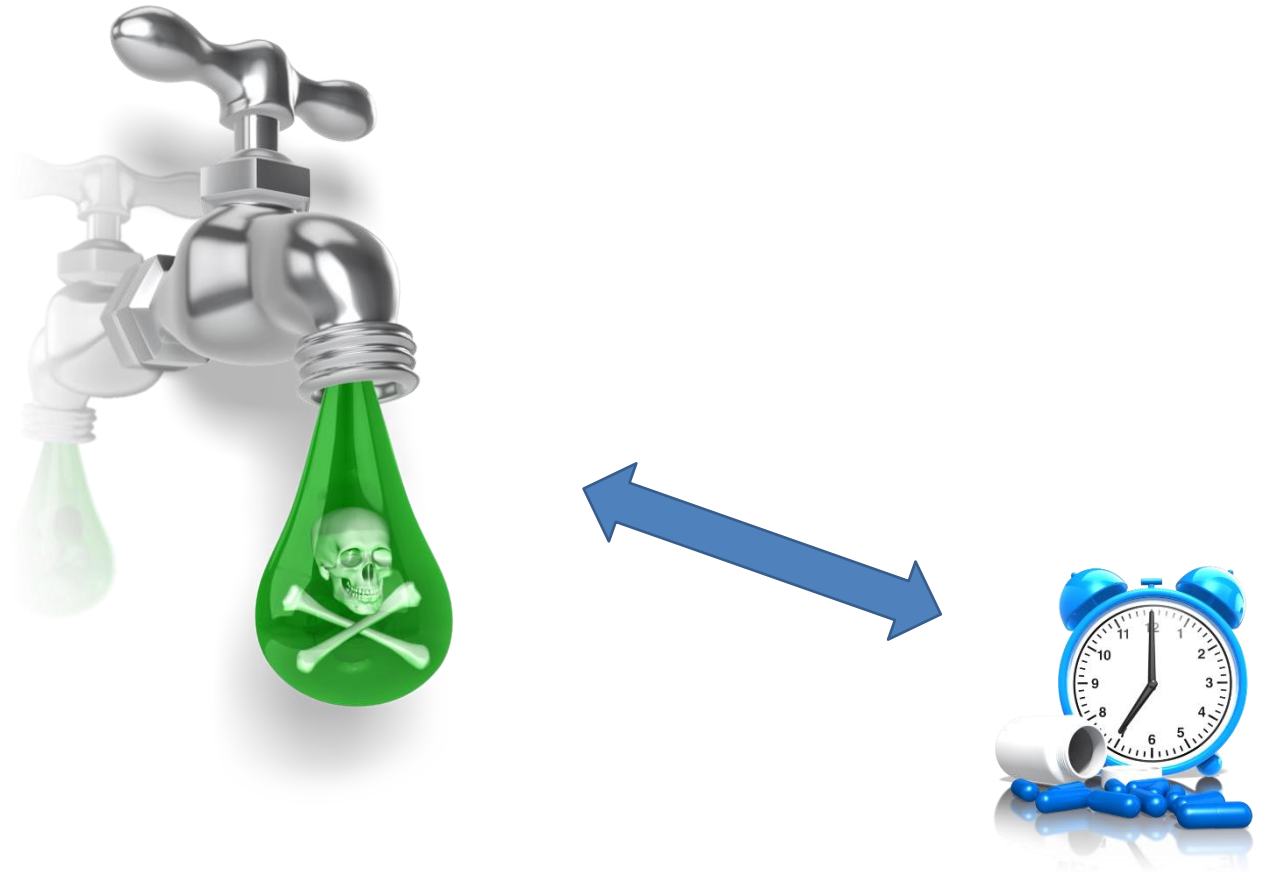
Open Access

# Association between fluid overload and SOFA score kinetics in septic shock patients: a retrospective multicenter study



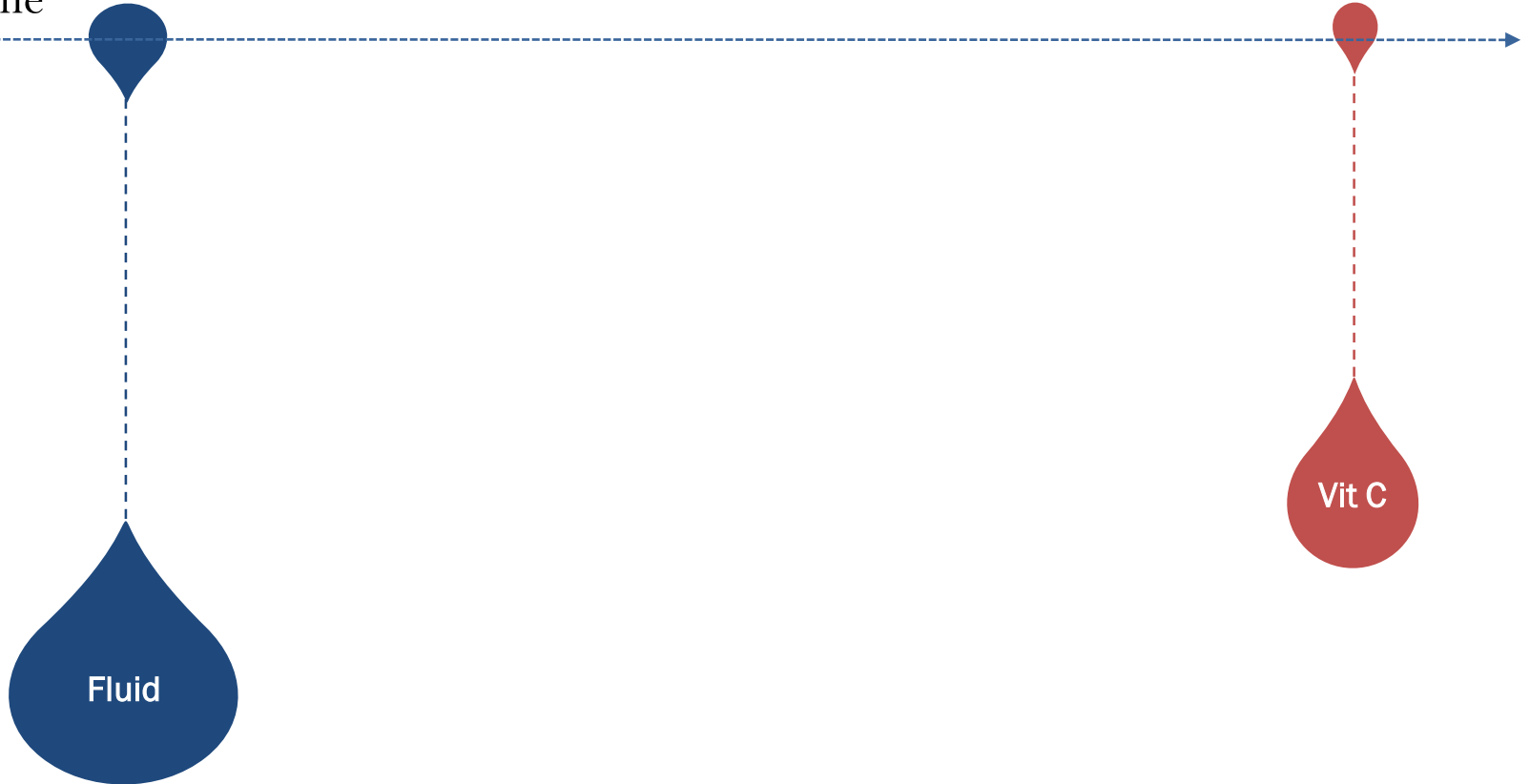
Xavier Chapalain<sup>1,6,7\*</sup> , Véronique Vermeersch<sup>1,6,7</sup>, Pierre-Yves Egreteau<sup>4</sup>, Gwenael Prat<sup>3</sup>, Zarrin Alavi<sup>5</sup>, Eric Vicaut<sup>2</sup> and Olivier Huet<sup>1,6,7</sup>

Volume overload (and associated organ dysfunction)  
limits the therapeutic efficacy of HAT Rx



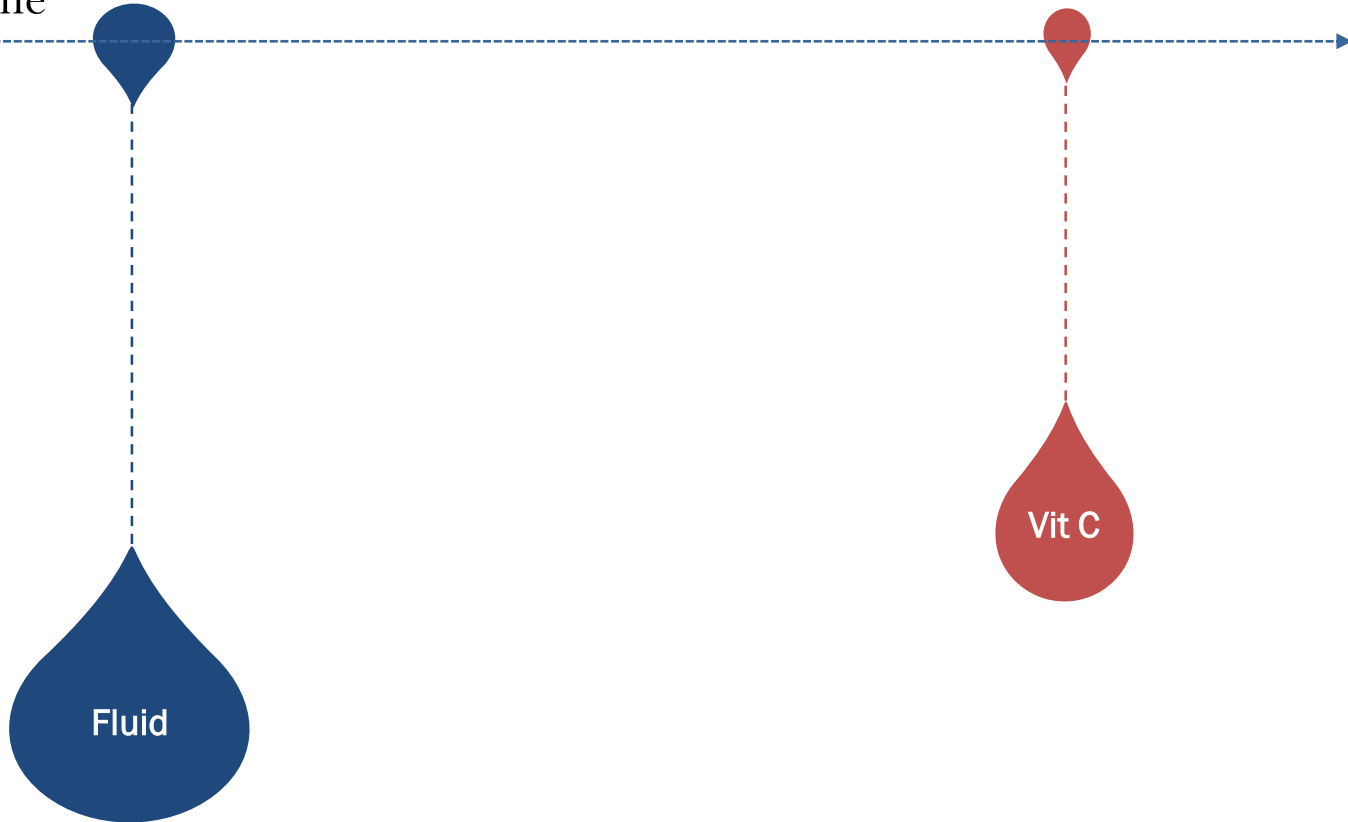
**Very BAD**

Time



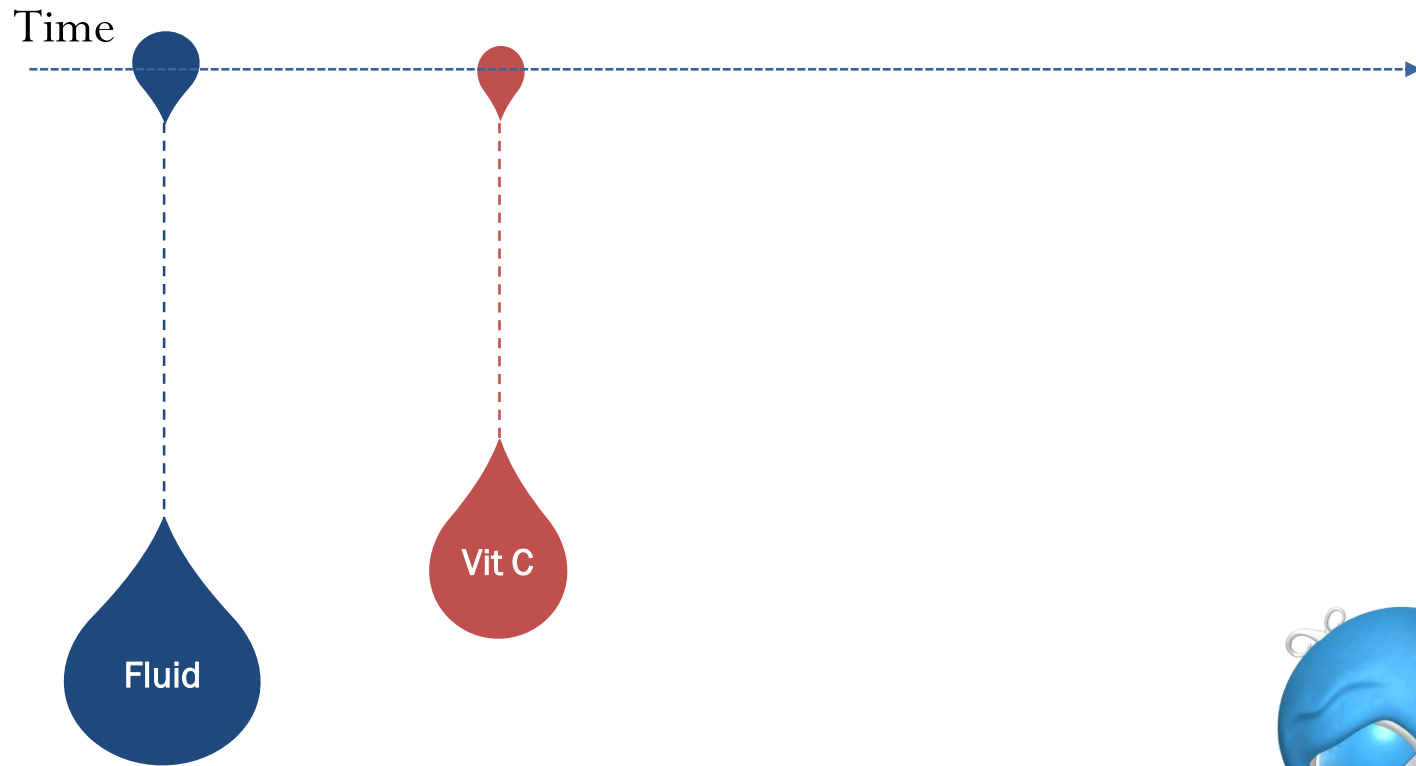
**BAD**

Time



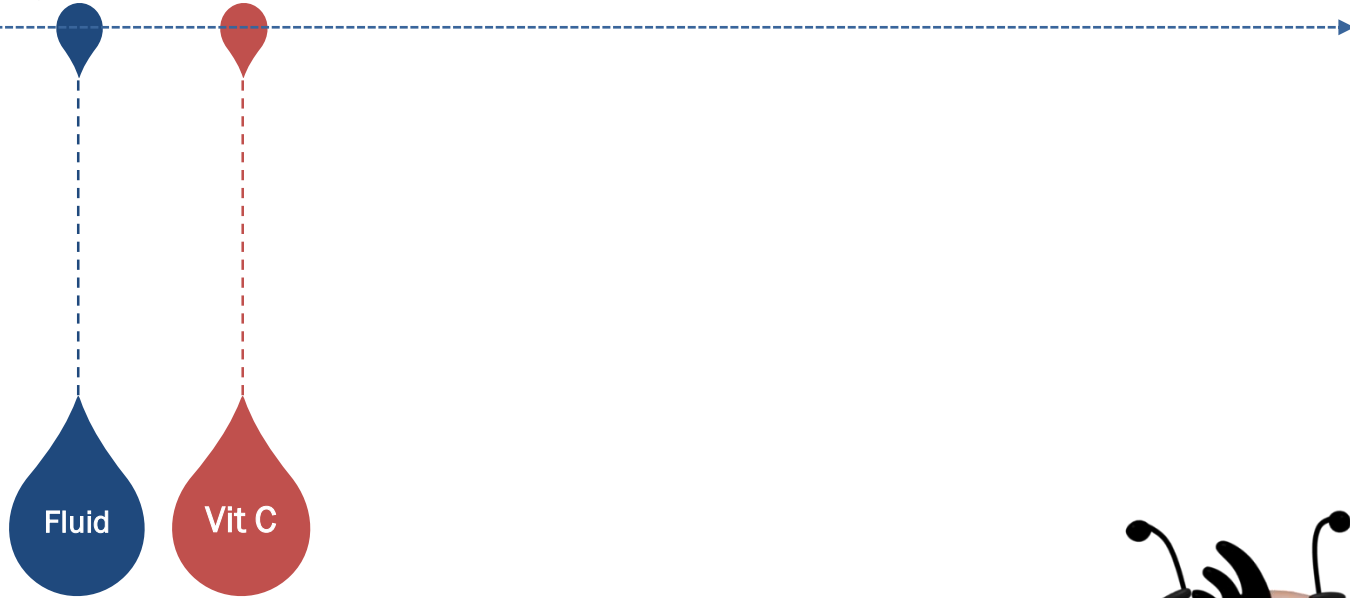


# Less BAD



# Best

Time



# Fluids in VITAMINS



# Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan

Tomoko Fujii, Andrew A Udy, Adam M Deane, Nora Luethi, Michael Bailey, Glenn M Eastwood, Daniel Frei, Craig French, Neil Orford, Yahya Shehabi, Paul J Young and Rinaldo Bellomo,  
on behalf of the VITAMINS trial investigators

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## 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)**

# Assessment

**VITAMINS has a fatal flaw.**

**Do we need more flawed RCT's?**

# Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? A Systematic Review

Santacruz, Carlos A. MD<sup>1</sup>; Pereira, Adriano J. MD, PhD<sup>2</sup>; Celis, Edgar MD<sup>1</sup>; Vincent, Jean-Louis MD, PhD, FCCM<sup>3</sup> [Author Information](#) 

Critical Care Medicine: [December 2019](#) - Volume 47 - Issue 12 - p 1680-1691  
doi: 10.1097/CCM.0000000000004000

## 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





# No. Please No

Open access

Protocol

## 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 ,<sup>1,2</sup> Alessandro Belletti ,<sup>3,4</sup> Anitra Carr,<sup>5</sup> Toshi A Furukawa,<sup>2</sup> Nora Luethi,<sup>1,6</sup> Alessandro Putzu,<sup>7</sup> Chiara Sartini,<sup>3</sup> Georgia Salanti,<sup>8</sup> Yasushi Tsujimoto,<sup>9,10</sup> Andrew A Udy,<sup>1,11</sup> Paul J Young,<sup>12,13</sup> Rinaldo Bellomo<sup>1,4,14</sup>



# Critical Care Reviews – January 2017



## The Cure For Sepsis! *A Real World Study*

Paul Marik, MD, FCCM, FCCP

**EVMS**  
Eastern Virginia Medical School

*Teaching. Discovering. Caring™*

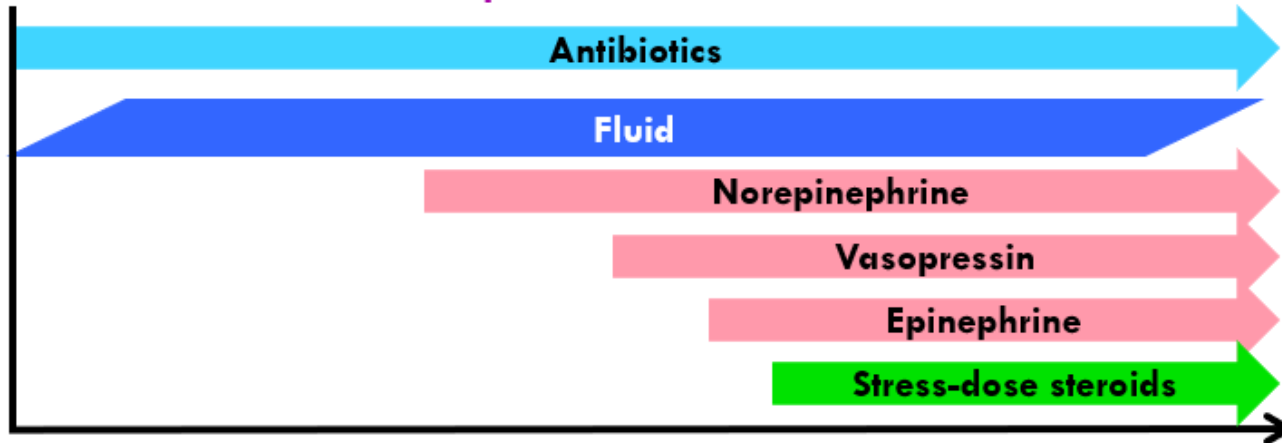
# Steps to the Cure.....



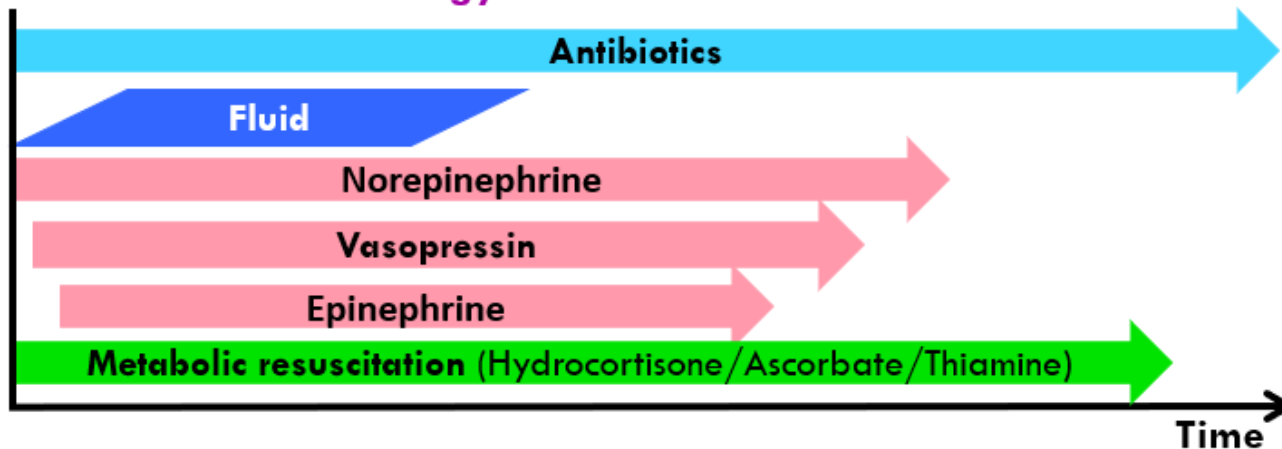
- Early Diagnosis
- Early administration of the correct antibiotics, in the correct dose
- Source Control
- Conservative, physiologic approach to fluid resuscitation
- Early use of Norepinephrine
- The “Metabolic Resuscitation Protocol”
  - Steroids, Vitamin C and Thiamine
- Multidisciplinary, team approach 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



## Escalation-deescalation strategy



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