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

Paul E Marik, MD

EVMS
Eastern Virginia Medical School

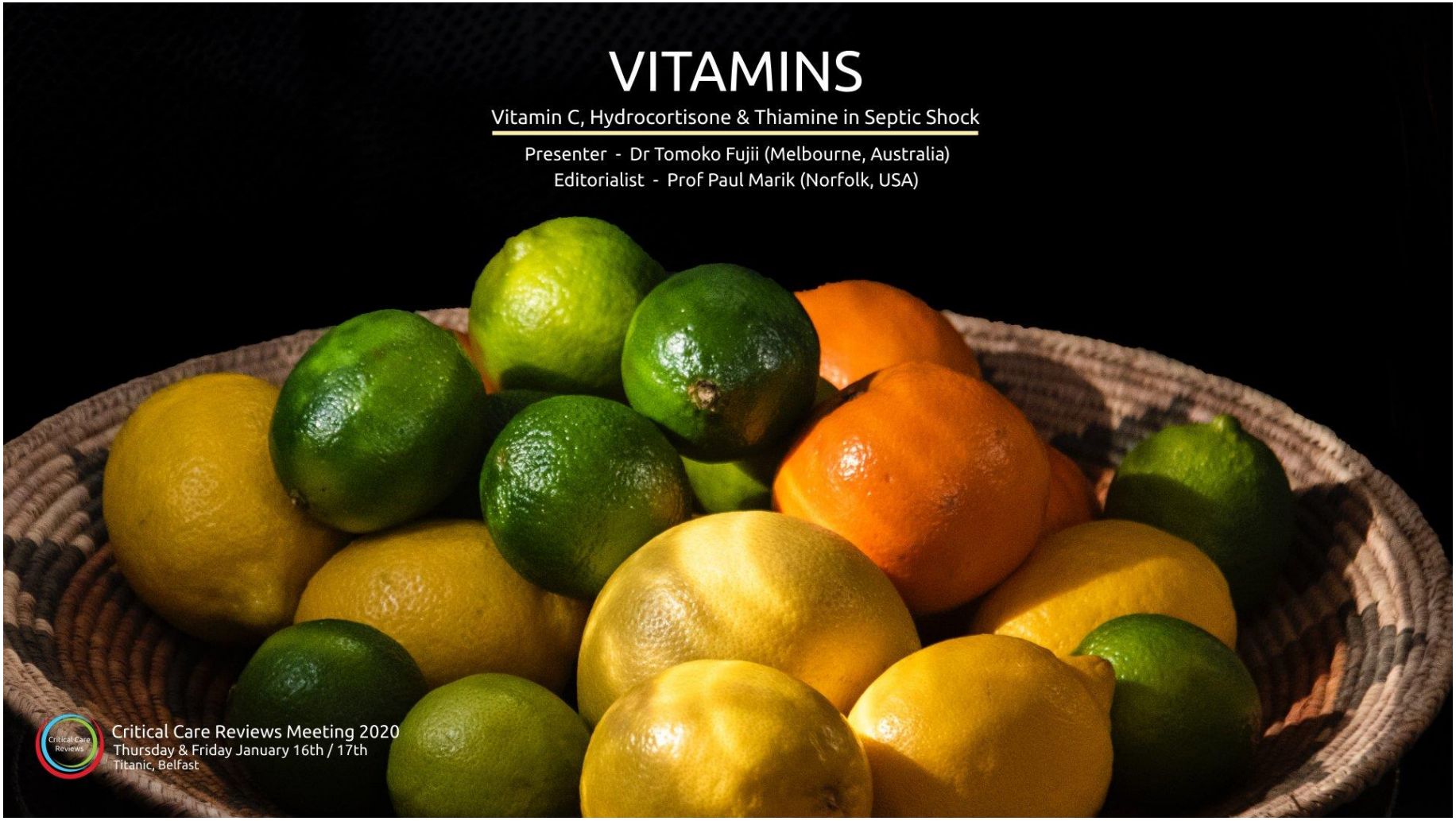
Alterative Version 7

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

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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

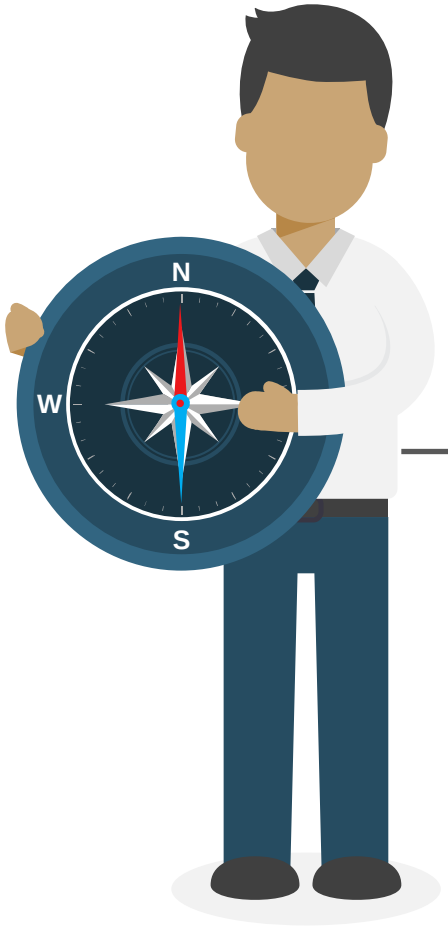
Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

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 fals 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

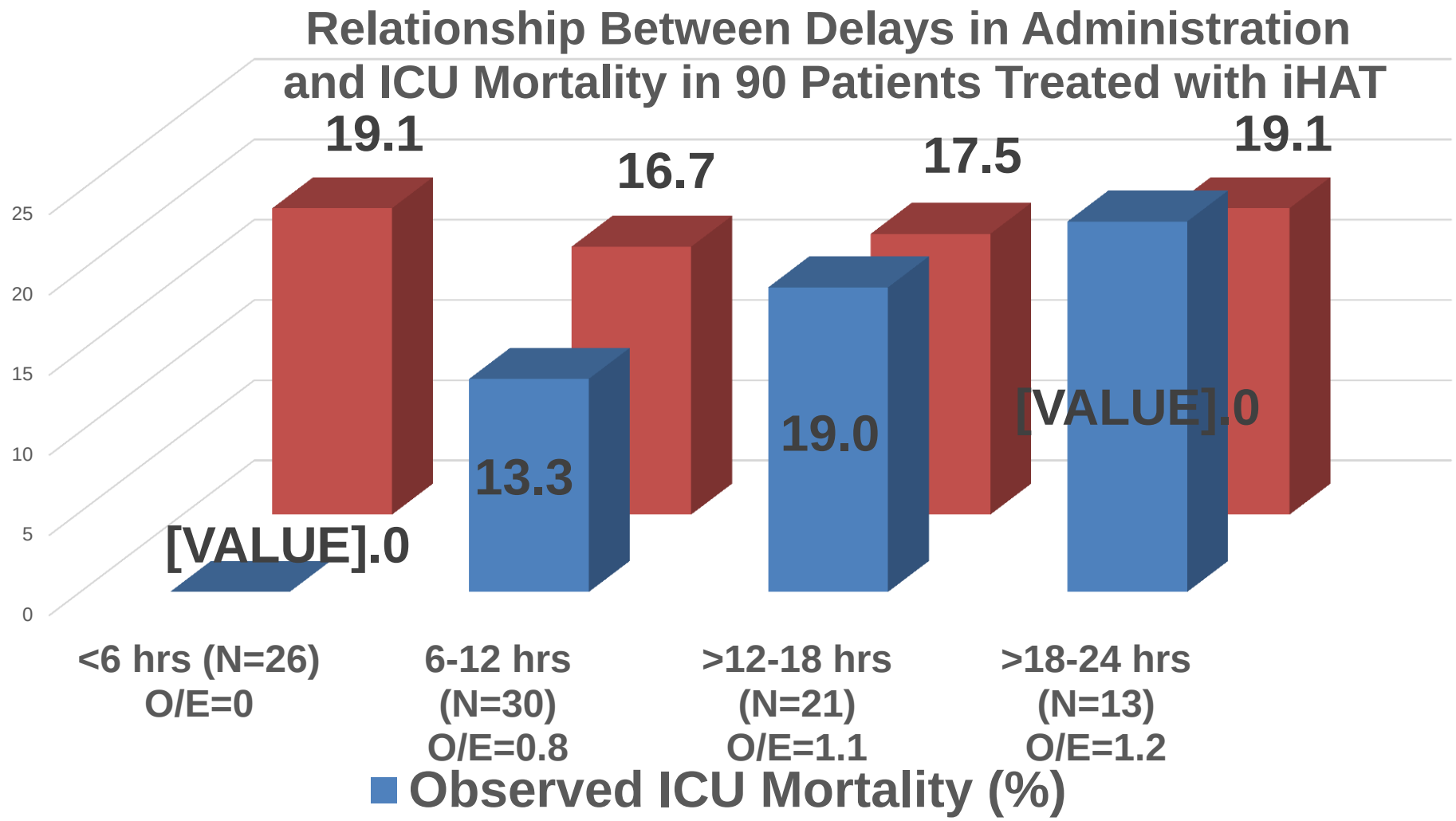
Early Vitamin C and Thiamine Administration to Patients with Septic Shock in Emergency Departments: Propensity Score-Based Analysis of a Before-and-After Cohort Study

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

J Clin Med 2019;8:102

What I have Learnt

- Timing matters… EARLY Rx
  - "Door to needle" time < 6 hours afte
    presentation
  - Ideally at time of first dose Antibiotic

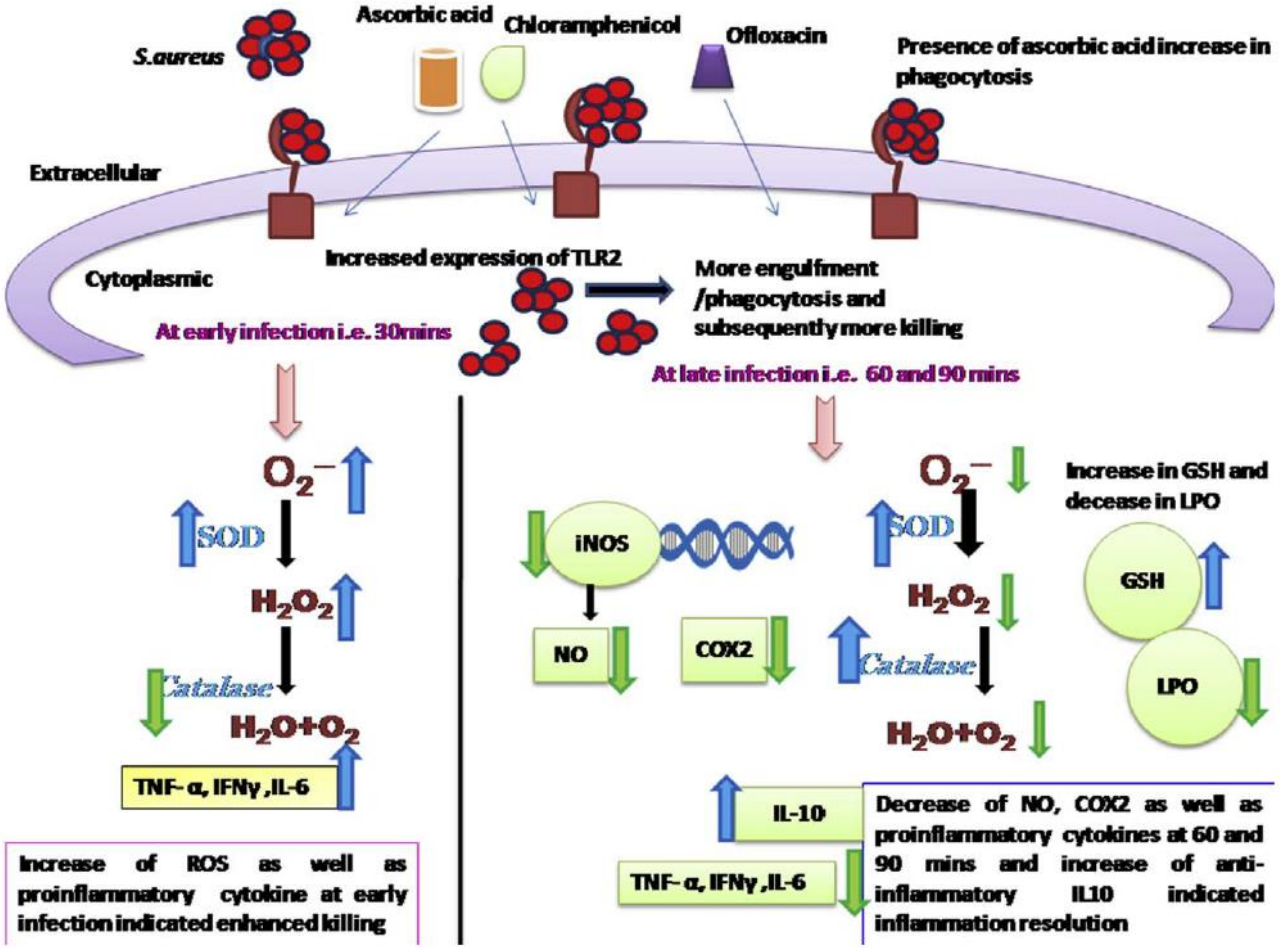


iHAT = intravenous hydrocortisone, ascorbic acid, thiamine **Hrs** = time from sepsis presentation to
O/E = observed/expected ICU mortality ratio using APACHE IV scores

Kory P et al - SCCM Abstract 2020, recently accepted by Critical Care

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

Somrita Dey, Biswadev Bishayi*



Microbial Pathogenesis 2018;115;23

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

Crit Care Resus 2019;21:2

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

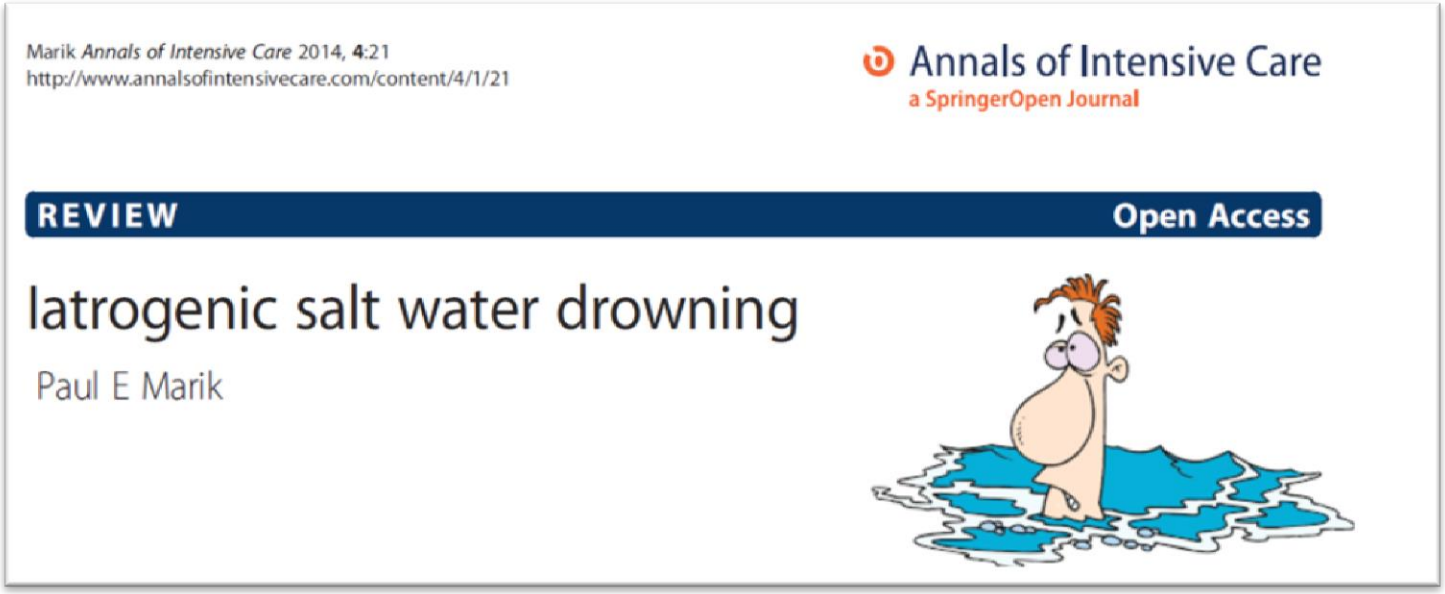
> 32 hours

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



Chapalain *et al. Journal of Intensive Care* (2019) 7:42
https://doi.org/10.1186/s40560-019-0394-0

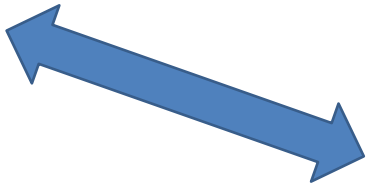
RESEARCH Open Access

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

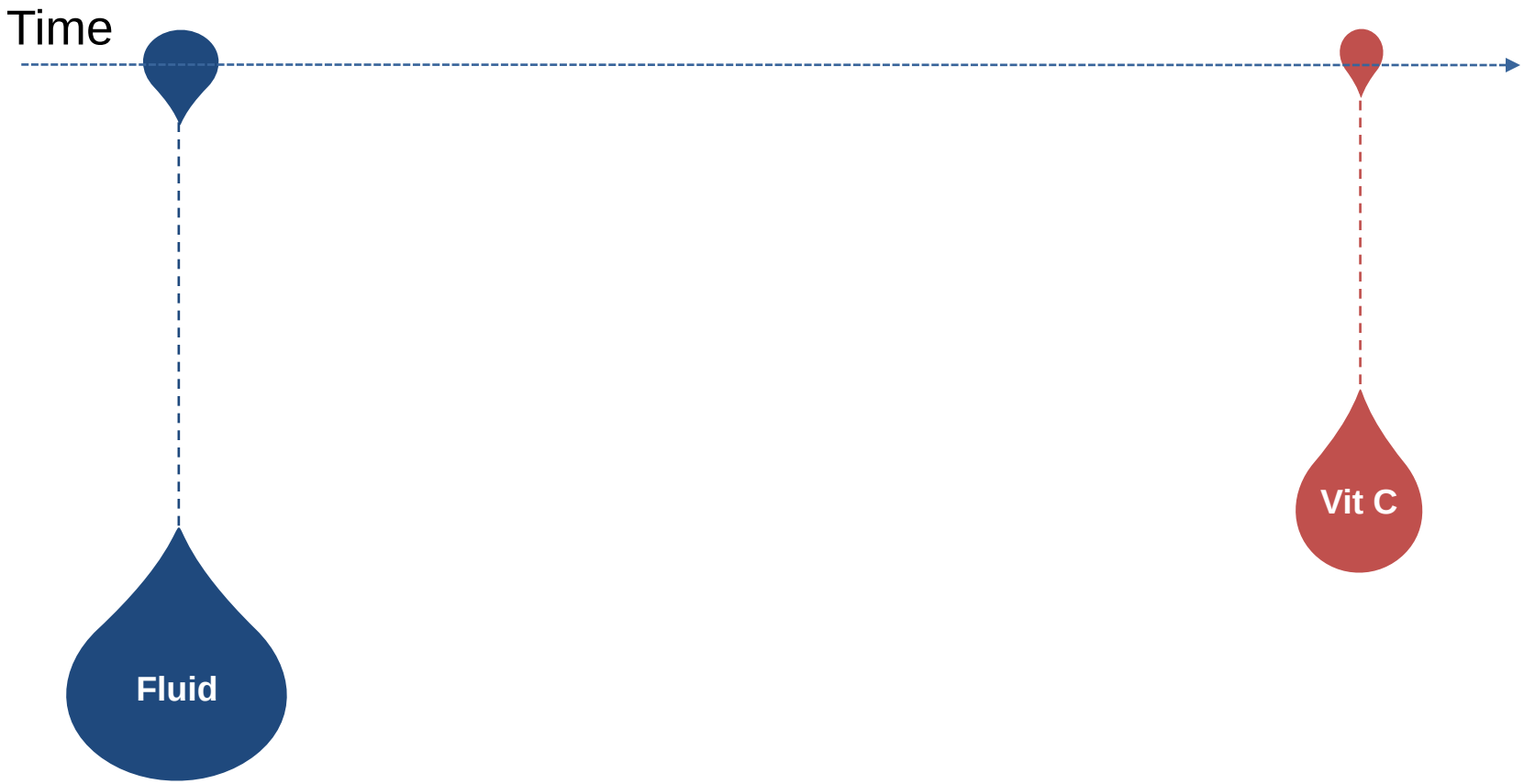
Xavier Chapalain[1,6,7*], Véronique Vermeersch[1,6,7], Pierre-Yves Egreteau[4], Gwenael Prat[3], Zarrin Alavi[5], Eric Vicaut[2] and Olivier Huet[1,6,7]

Volume overload (and associated organ dysfunction)

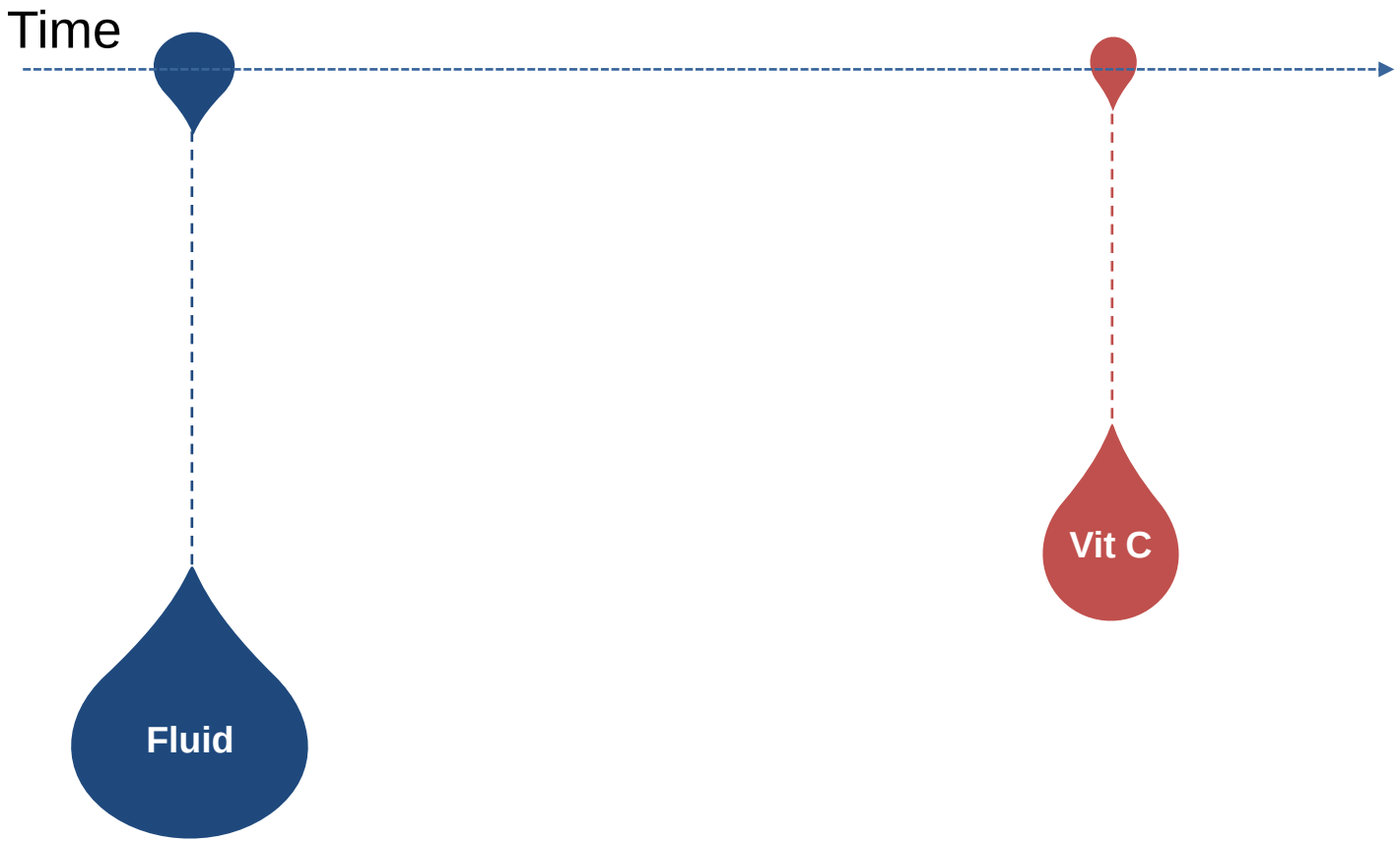
limits the therapeutic efficacy of HAT Rx



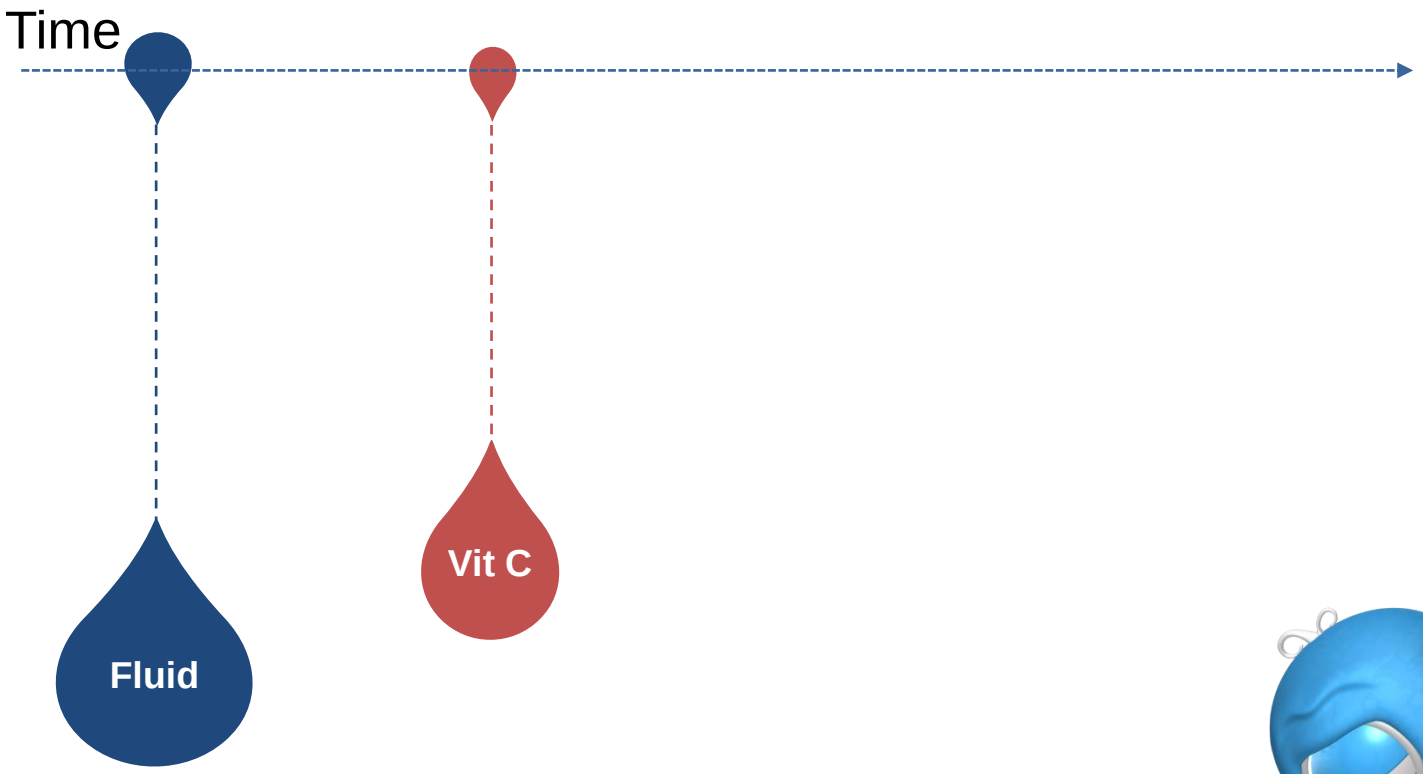
Very BAD



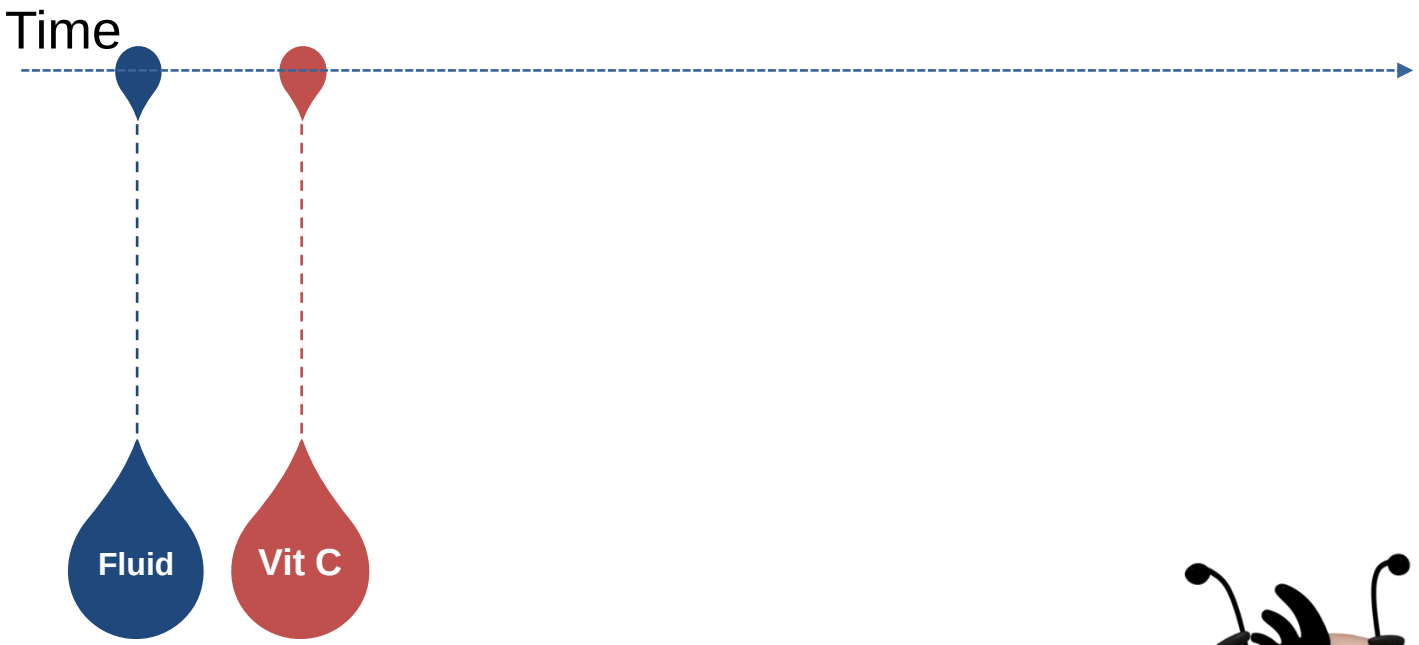
BAD



Less BAD



Best



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

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)**

Crit Care Resus 2019;21:

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[1]; Pereira, Adriano J. MD, PhD[2]; Celis, Edgar MD[1]; Vincent, Jean-Louis MD, PhD, FCCM[3] **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.

Critical Care Medicine 2010

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 ,[1,2] Alessandro Belletti ,[3,4] 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 Bellomo[1,4,14]

Critical Care Reviews – January 2017

The Cure For Sepsis!

A Real World Study

Paul Marik, MD,FCCM,FCCP

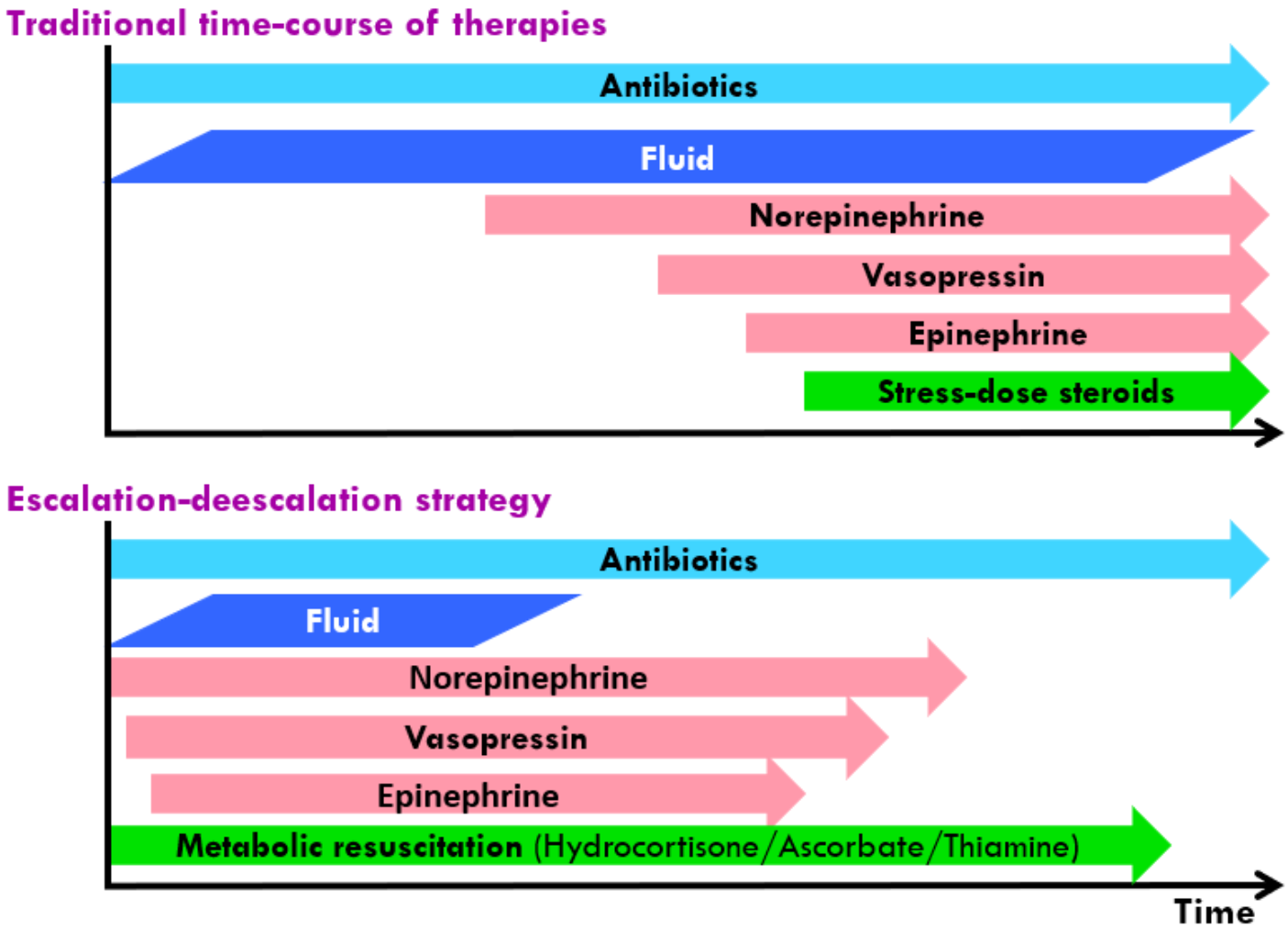
EVMS
Eastern Virginia Medical School

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



Marik & Farkas, Crit Care Med 2018;46

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Thank you