The Use of Metabolic Resuscitation in Sepsis

Jennifer M. Roth, PharmD, BCPS, BCCCP
Critical Care Clinical Specialist -
Surgical Trauma ICU
Baylor University Medical Center

Disclosures

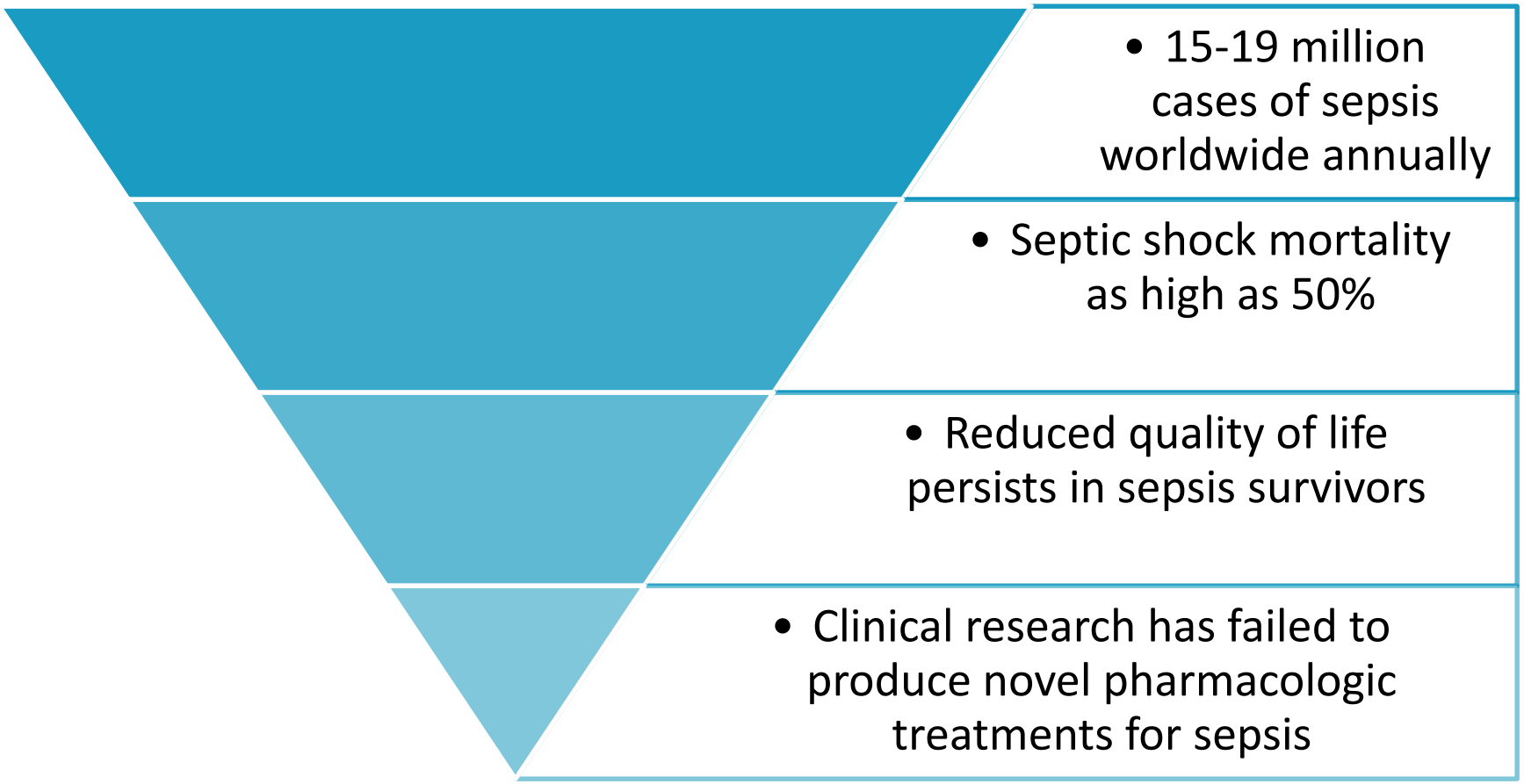
- No conflicts of interest to disclose

Objectives

Define the use of metabolic resuscitation in the critically ill

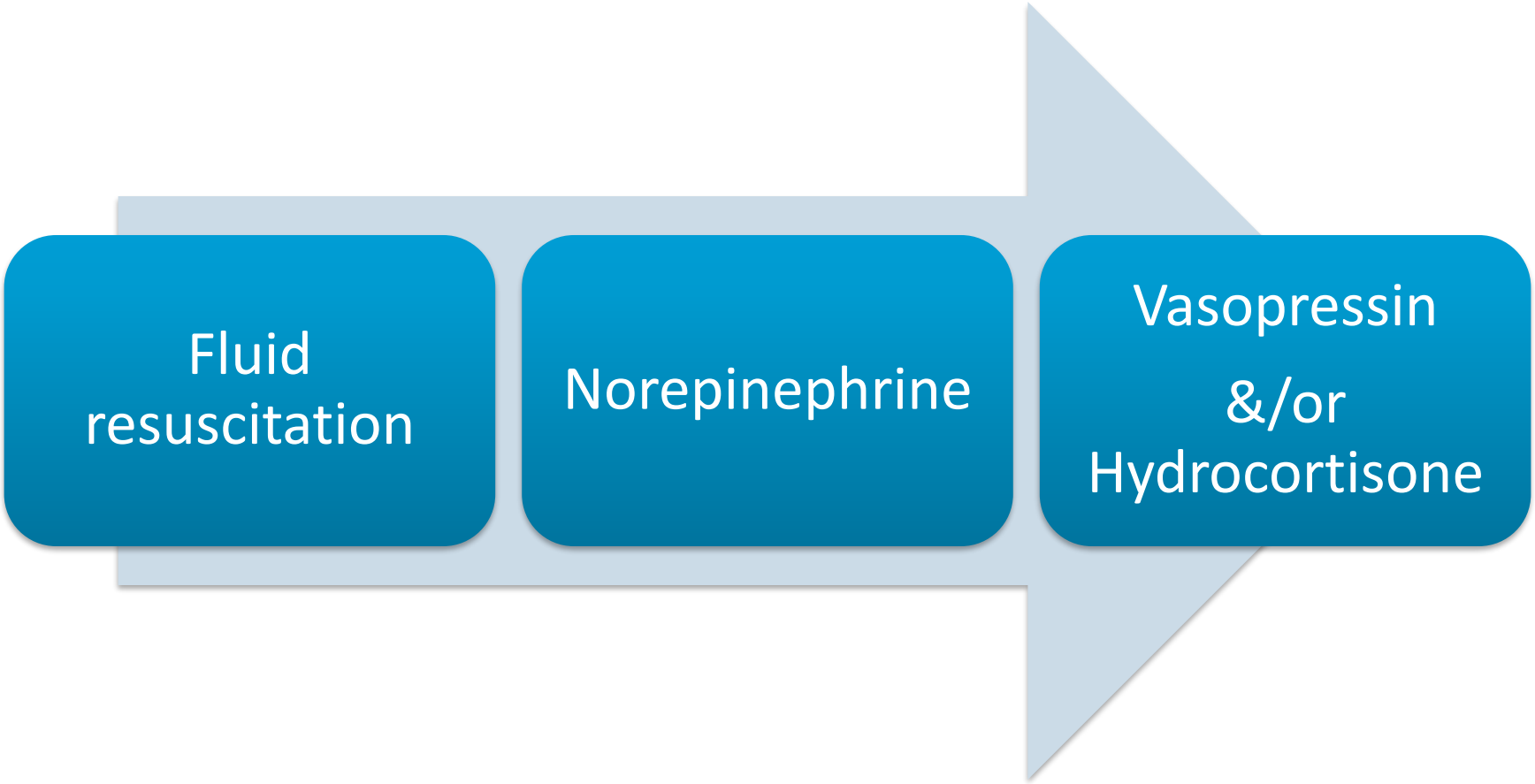
Discuss evidence evaluating resuscitation & clinical outcomes in critically ill patients

Background



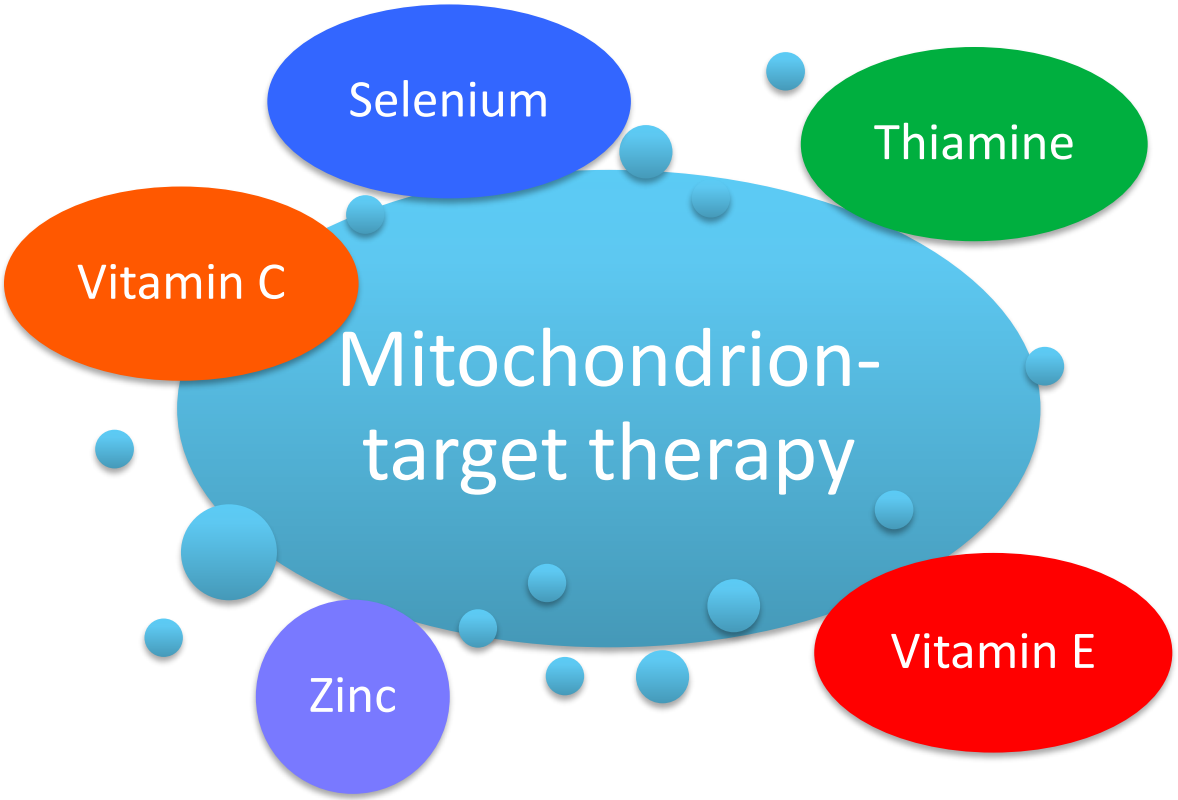
Marik PE, et al. *CHEST* 2016.

Current guideline-based resuscitation



Surviving Sepsis Campaign: International Guidelines for Sepsis and Septic Shock: 2016.

Defining Metabolic Resuscitation

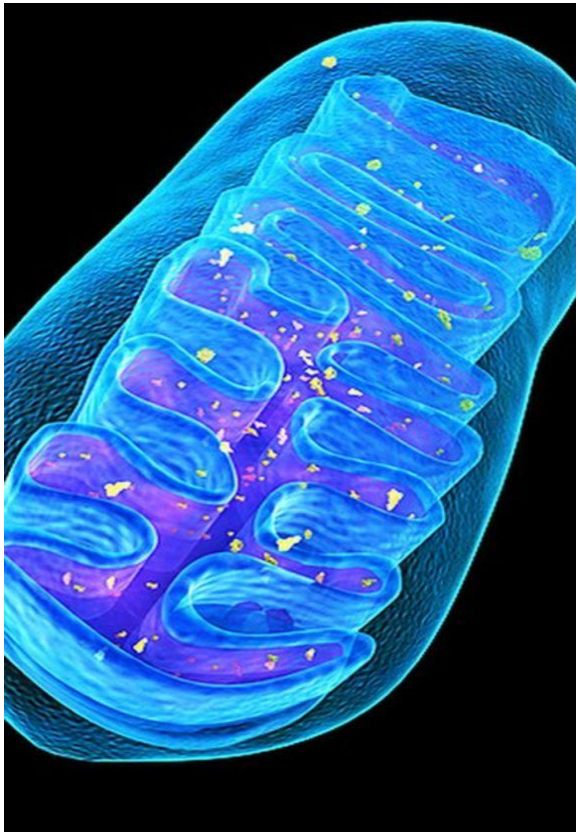


"We can deliver all the oxygen we want to the tissues, but if the mitochondria are failing, it won't work." ~ Dr. Johsua Farkas

Leite HP, et al. *J Thorac Dis* 201; https://emcrit.org/pulmcrit/metabolic-sepsis-resuscitation.

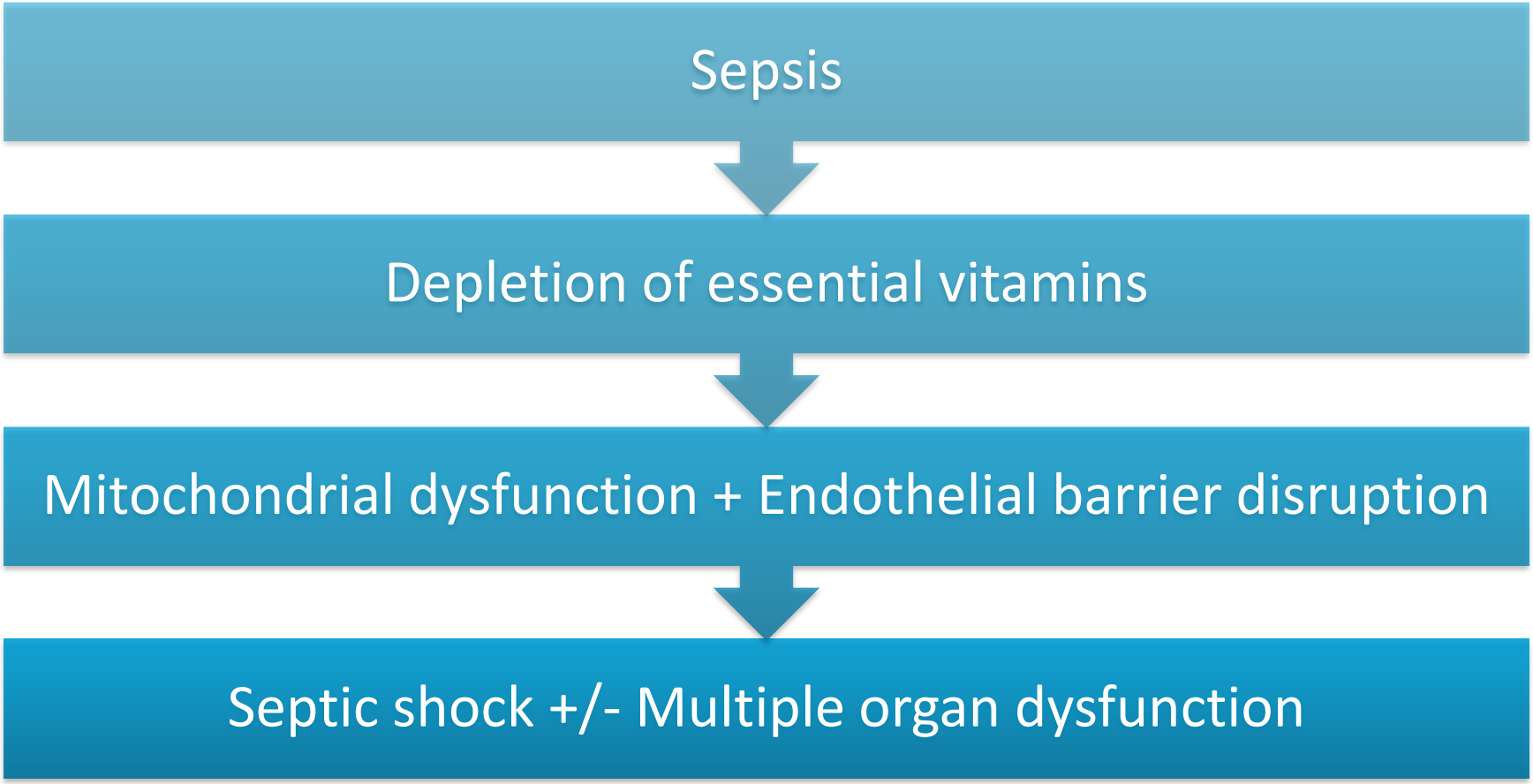
Mitochondrial Function

- **Generation of energy through Krebs cycle**
- Thermoregulation
- Calcium homeostatis
- **Production of reactive oxygen species**
- **Biosynthesis**
  - **Cortisol**
  - **Vascular endothelium growth factor**
- **Regulation of cell death**



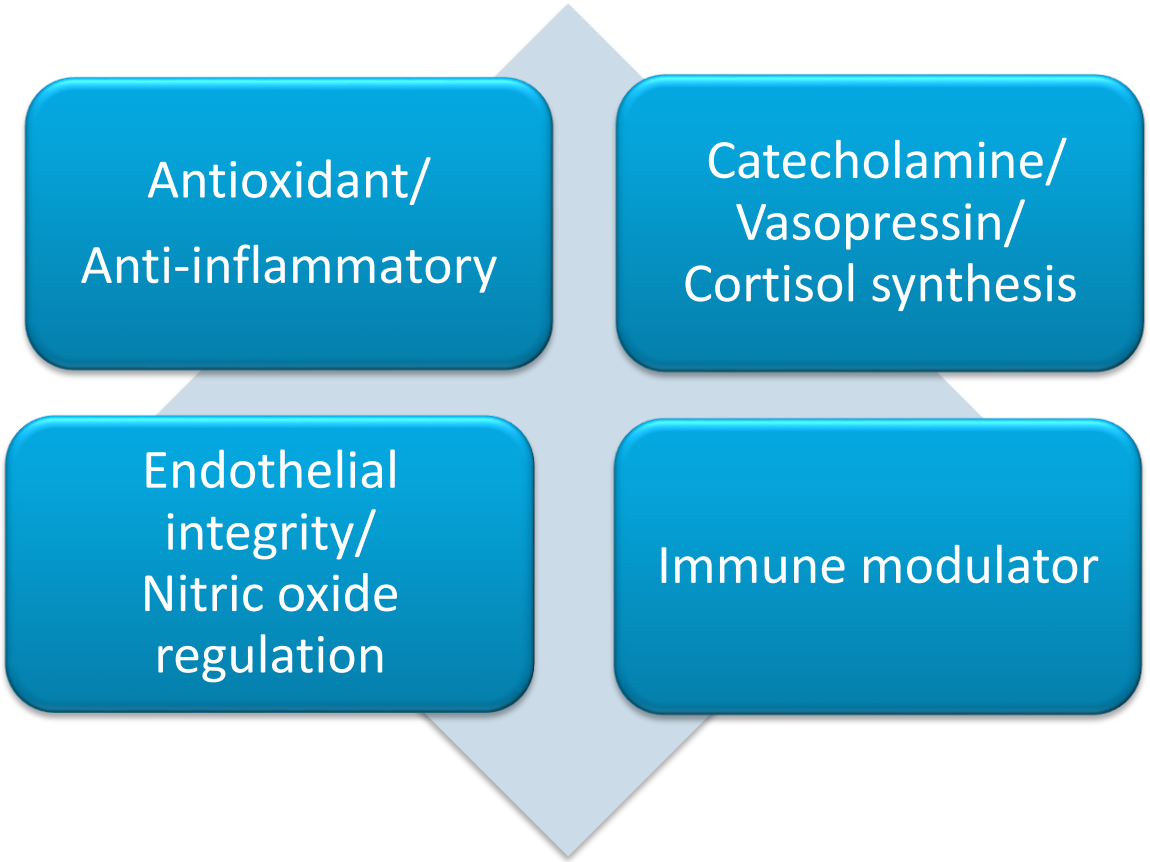
Leite HP, et al. *J Thorac Dis* 2016.

Role of Metabolic Resuscitation in Sepsis



Leite HP, et al. *J Thorac Dis* 2016.

Role of Vitamin C



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Teng J, et al. *J Crit Care* 2018 ; Zabet MH, et al. *J Res Pharm Prac* 2016.

Vitamin C Studies

Study	Population	Intervention	Outcomes	Results
Fowler, et al 2014 Randomized, double-blind, placebo-controlled	Sepsis Organ dysfunction Medical ICU- US	Low dose Vit C- 50 mg/kg/d IV x4d (n=8) vs High dose Vit C- 200 mg/kg/d IV x4d (n=8) vs placebo (n=8)	Primary: safety (tachycardia, hypotension, hypernatremia, nausea/vomiting) Secondary: SOFA, ascorbic acid levels, CRP, PCT, thrombomodulin	No adverse safety events **Ascorbic acid levels rapidly improved with Vit C** **Decline in SOFA scores, CRP & PCT with Vit C**
Zabet, et al 2016 Randomized, double-blind, placebo-controlled	Septic shock Organ dysfunction Vasopressor(s) Excluded: other antioxidants, steroids, chronic HD Surgical ICU- Iran	Vit C 25m/kg IV q6h x3d (n=14) vs placebo (n=14)	Primary: vasopressor dose & duration Secondary: ICU LOS, 28d mortality	**Vitamin C ➔ decreased norepinephrine dose & duration** No change in ICU LOS **Vitamin C ➔ decreased 28d mortality**

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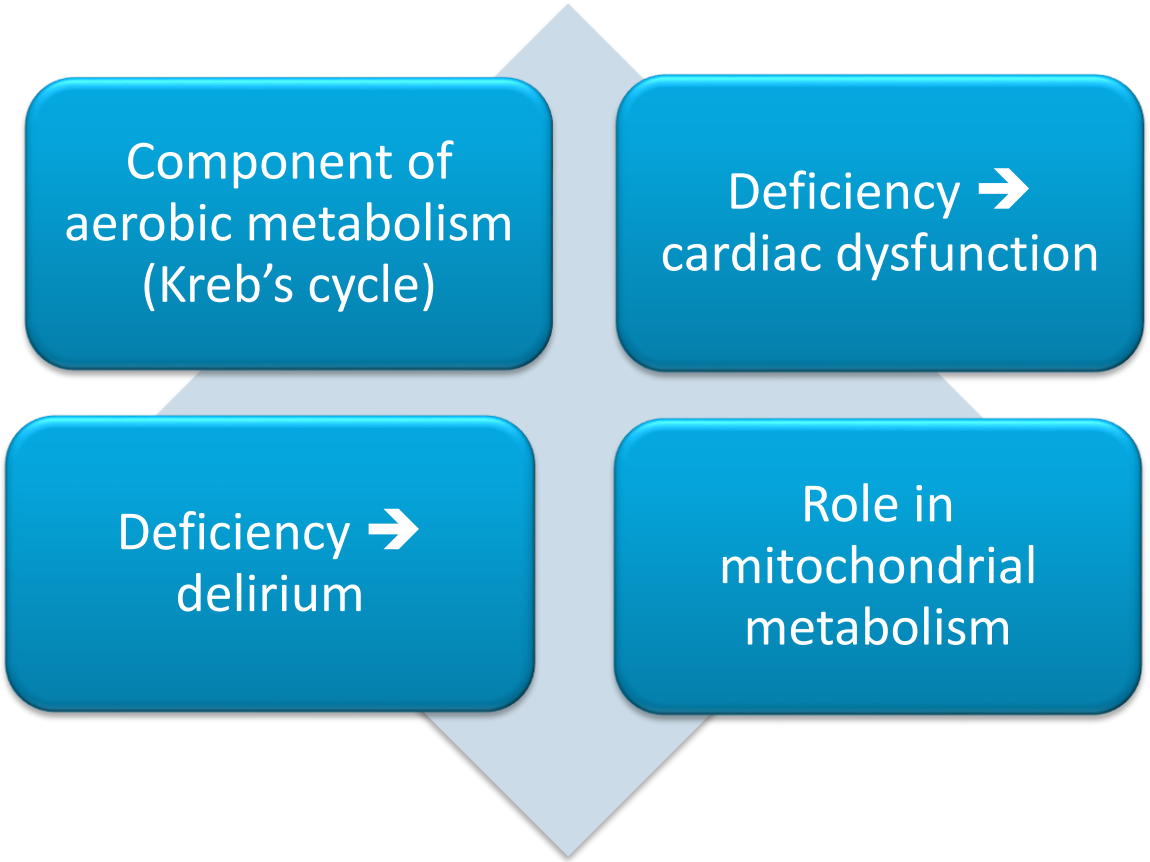
Fowler AA, et al. *J Transl Med* 2014; Zabet MH, et al. *J Res Pharm Prac* 2016.

Role of Thiamine



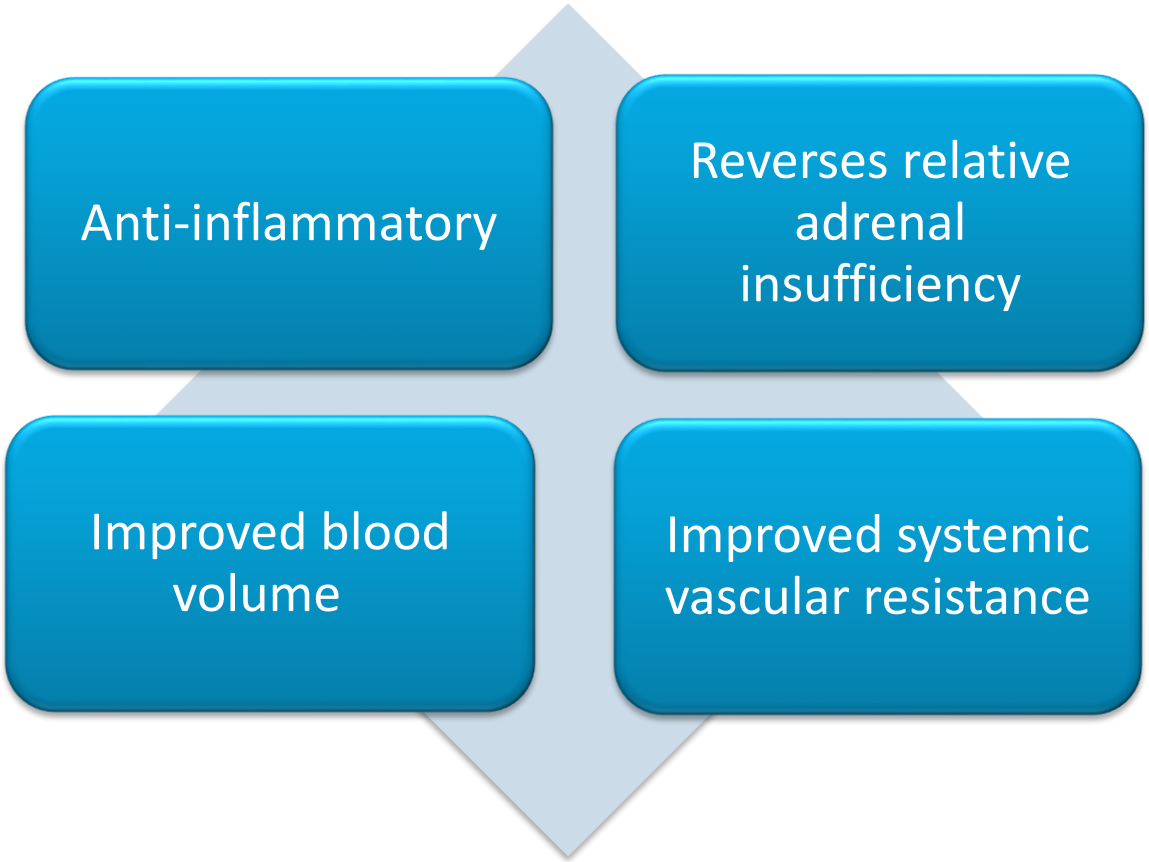
Leite HP, et al. *J Thorac Dis* 2016; Donnino MW, et al. *Crit Care Med* 2016.

Thiamine Studies

Study	Population	Intervention	Outcomes	Results
Donnino, et al 2016 Randomized, double-blind, placebo-controlled	Sepsis Lactate > 3 Vasopressor(s) Excluded: liver injury/ dysfunction, indication for thiamine, ischemia Two centers- US	Thiamine 200mg IV q12h x7d (n=43) vs placebo (n=45)	Primary: lactate at 24h Secondary: change in lactate, shock reversal, change in SOFA/APACHE II, ICU & hospital LOS, in-hospital mortality	No difference in lactate at 24h overall **Lower lactate at 24h in thiamine deficient group** No difference in shock reversal, LOS or mortality
Woolum, et al 2018 Retrospective, matched cohort	Septic shock Lactate > 2 Vasopressor(s) 65% baseline liver disease Single center- US	Thiamine IV within 24h of admission (n=123) vs matched controls (n=246) Thiamine 100mg q24h-500mg q8h, median 3d	Primary: time to lactate clearance Secondary: 28d mortality, vasopressor-free days, change in SOFA, AKI/RRT	**Thiamine associated with improved lactate clearance & 28d mortality** No difference in vasopressor-free days, SOFA, AKI/RRT

Donnino MW, et al. *Crit Care Med* 2016; Woolum JW, et al. *Crit Care Med* 2018.

Role of Hydrocortisone



Hydrocortisone

Surviving Sepsis Campaign Guidelines, 2016:

We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day. (weak recommendation, low quality of evidence).

Study	Population	Intervention	Outcomes	Results
Keh D, et al 2016 HYPRESS trial Randomized, double-blind, placebo-controlled	Severe sepsis NOT septic shock Excluded: other indication for steroids 34 centers-Germany	HC 50mg bolus, 200mg/24h continuous infusion x 5d , then tapered (n=170) vs placebo (n=170)	Primary: septic shock within 14d Secondary: time until septic shock, mortality- ICU, hospital, up to180d, secondary infections, hyperglycemia, muscle weakness	No difference in development of septic shock No difference in secondary outcomes **More episodes of hyperglycemia in HC group**

Surviving Sepsis Campaign: International Guidelines for Sepsis and Septic Shock: 2016; Keh D, et al. *JAMA* 2016

Hydrocortisone Studies

Study	Intervention	Decreased Vasopressors	Improved Mortality
Annane, et al 2002	HC 50mg q6h +fludro x7d vs placebo; n=300	✓	✓
CORTICUS 2008	HC 50mg q6h x5d (then tapered) vs placebo; n=499	✓	✗
ADRENAL 2018	HC 200mg/day (continuous) x7d vs placebo; n=3658	✓	✗
APROCCHSS 2018	HC + fludro x 7d vs placebo; n=1241	✓	✓
Systematic Review & Meta-Analysis 2018	42 RCTS ➔ 27 used HC, most < 3d; n=6922	✓	+/-

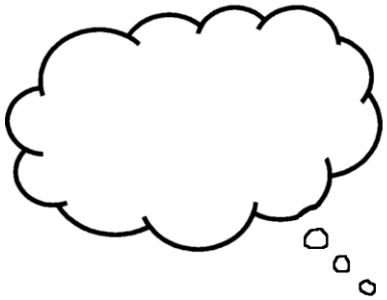
Annane D, et al. *JAMA* 2002; Sprung CL, et al. *NEJM* 2008; Ventakesh B, et al. *NEJM* 2018; Annane D, et al. *NEJM* 2018; Rochwerg B, et al. *Crit Care Med* 2018.

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

A Retrospective Before-After Study

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP



"On the basis of experimental & emerging clinical data, we decided to administer intravenous Vitamin C… as a life saving measure… All three… patients made a dramatic recovery & were discharged from the ICU within days with no residual organ dysfunction." ~Dr. Paul Marik

Marik PE, et al. *CHEST* 2016.

Role of combination

Vitamin C + Hydrocortisone work *synergistically* as antioxidants/anti-inflammatory agents

Vitamin C restores glucocorticoid function & preserves endothelial function

Thiamine decreases production of oxalate

Marik PE, et al. *CHEST* 2016.

Vitamin C
1.5gm IV q6h
x 4 days

+

Thiamine
200mg IV q12h
x 4 days

+

Hydrocortisone
50mg IV q6h
x 7 days

Study	Population	Intervention	Outcomes
Marik, et al 2016 Retrospective, before-after, propensity-matched	Severe sepsis or septic shock PCT ≥ 2 Consecutive patients during specified 7-month time periods Medical ICU Exclusion: limitations of care	Vit C + Thiamine + HC (n=47) vs control (n=47) *60% of control group received hydrocortisone	Primary: hospital survival Secondary: duration of vasopressors, RRT for AKI, ICU LOS, change in PCT & SOFA

Marik PE, et al. *CHEST* 2016.

Baseline Characteristics

Variable (%)	Treated (n=47)	Control (n=47)
Age, mean ± SD, years	58.3 ± 14.1	62.2 ± 14.3
Sex, male	27 (57)	23 (49)
Mechanical ventilation	22 (47)	26 (55)
Vasopressors	22 (46)	22 (46)
Acute kidney injury	31 (66)	30 (64)
WBC, mean ± SD, $x10^9$	20.6 ± 13.5	17.1 ± 13.4
Lactate, mean ± SD, mM	2.7 ± 1.5	3.1 ± 2.8
Procalcitonin, median & IQR, ng/mL	25.8 (5.8-93.4)	15.2 (5.9-39)
Positive blood cultures	13 (28)	13 (28)
Day 1 SOFA, mean ± SD	8.3 ± 2.8	8.7 ± 3.7
APACHE II/IV, mean ± SD	22.1 ± 6.3/79.5 ± 16.4	22.6 ± 5.7/82 ± 27.4
Predicted mortality, mean ± SD	39.7 ± 1 6.7	41.6 ± 24.2

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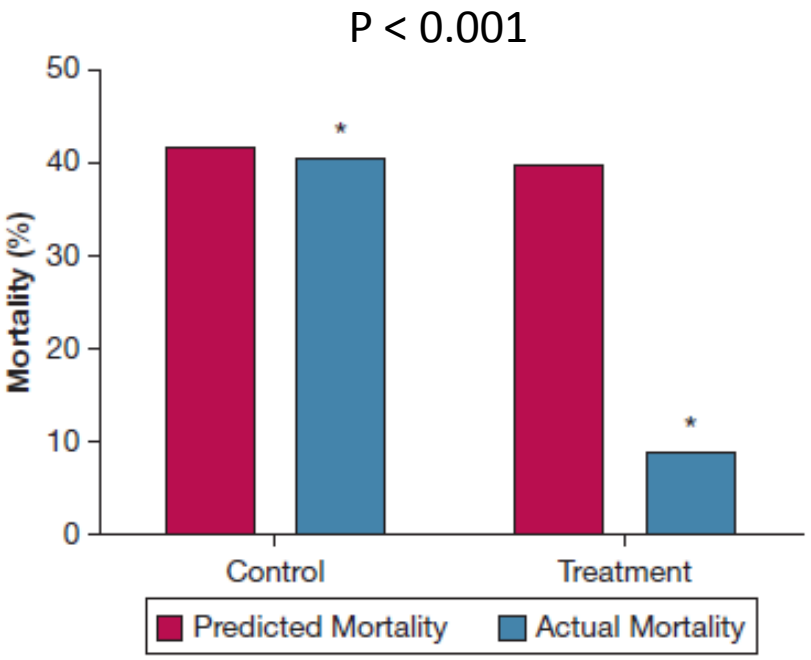
Marik PE, et al. *CHEST* 2016.

Results

Variable (%)	Treated (n=47)	Control (n=47)	P value
Hospital mortality	4 (8.5)	19 (40.4)	< 0.001
ICU LOS, median & IQR, d	4 (3-5)	4 (4-10)	
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4	< 0.001
RRT for AKI	3 of 31 (10)	11 of 30 (33)	0.02
Change in SOFA, 72h	4.8 ± 2.4	0.9 ± 2.7	< 0.001
PCT clearance, median & IQR, 72h	86.4 (80.1-90.8)	33.9 (-62.4-64.3)	< 0.001

Results: Primary Outcome



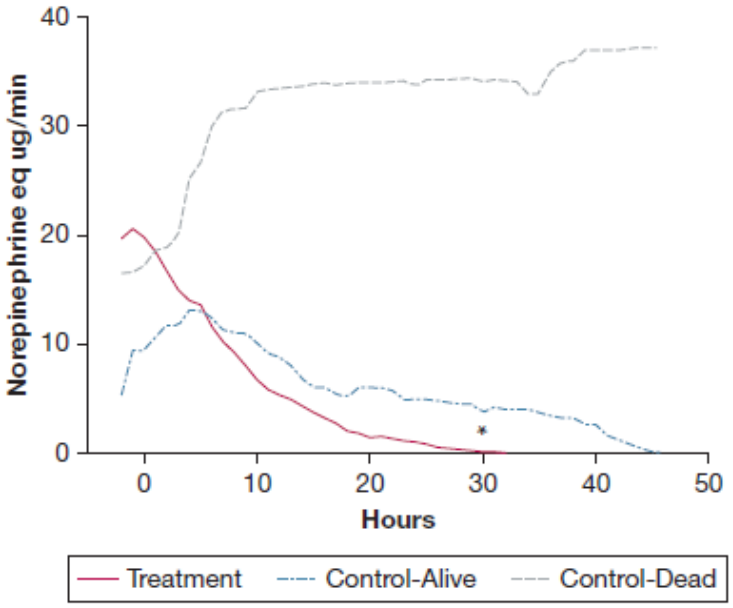
(Predicted mortality based on APACHE IV scores)

- Propensity adjusted odds of mortality with Vitamin C protocol 0.13 (95% CI, 0.04-0.48, P = 0.002)
- Independent mortality predictors
  - APACHE IV score
  - Mechanical ventilation
- "No patients in treatment group died of complications related to sepsis"

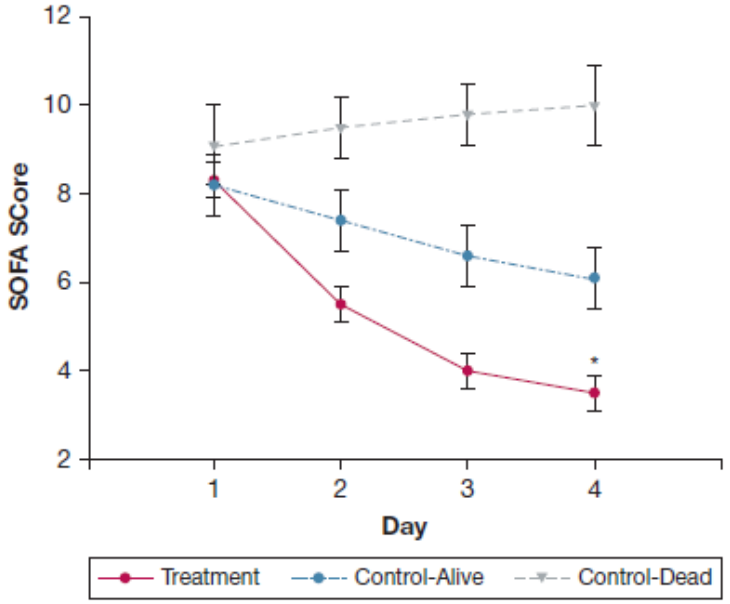
Marik PE, et al. *CHEST* 2016.

Results: Secondary Outcomes

Vasopressor Duration



Change in SOFA Score



Marik PE, et al. *CHEST* 2016.

Study Critique

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- First study to evaluate this combination of therapies
- Enrolled consecutive patients
- High predicted mortality
- Propensity score matching
- Procalcitonin utilized as screening tool
- High predicted mortality
- Baseline characteristics similar
- Sepsis “standard of care” outlined in methods

(-)

- Study design: single center, retrospective, not randomized
- Provider/selection bias
- Hawthorne effect
- Study periods not concurrent
- Procalcitonin clearance multifactorial
- Adverse events not addressed
- Death data not well described
- Hospital mortality endpoint
- Interventions studied as bundle
- 60% of controls received steroids
- Steroid use not guideline based

Practical Considerations

Fluid volume

- ≥ 300-500 mL IV fluid per day of therapy

Dispensing

- Product availability
- Compounding challenges

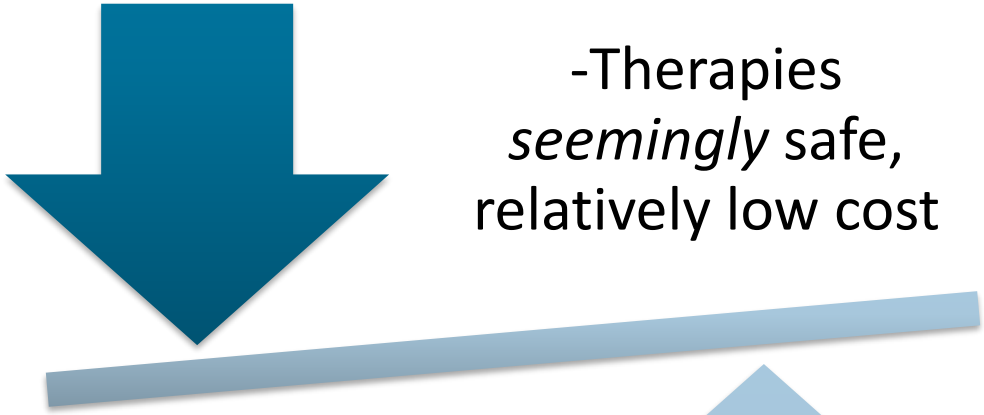
Glucose monitoring concerns

- Vitamin C may interfere with meters that utilize glucose dehydrogenase

Cost

- Relatively low, but not negligible

Discussion



-Therapies *seemingly* safe, relatively low cost

-Results show association, not causation

-Sepsis data historically hard to replicate

Conclusions

Metabolic resuscitation offers an exciting, potential new mechanism for treatment of sepsis

Quality of currently published literature is limited & should be interpreted with caution

Future studies are needed to confirm efficacy & safety of metabolic resuscitation components

Learning Assessment Question #1

- Metabolic resuscitation in sepsis focuses on which of the following:
  - A. Restoring volume loss
  - B. Repleting endogenous vasopressin
  - C. Improving mitochondrial function
  - D. Reversing the hypercoaguable state

Learning Assessment Question #2

- Which of the following regarding metabolic resuscitation in sepsis is true?
  A. Thiamine improves shock reversal
  B. Thiamine decreases production of oxylate
  C. Vitamin C is depleted in sepsis & levels increase when repleted intravenously
  D. B & C

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