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The Role of Thiamine, Vitamin C and Hydrocortisone in the Management of Septic Shock

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Disclosure

The author of this presentation has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation

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Objectives

1) Describe the multifaceted pathophysiology of sepsis and septic shock
2) List the proposed mechanisms of action of thiamine and ascorbic acid in septic shock
3) Evaluate the pertinent literature regarding thiamine, ascorbic acid and corticosteroids for the treatment of septic shock

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Background

- At least 1.7 million American adults develop sepsis annually
- Nearly 270,000 deaths as a result of sepsis each year
- Sepsis remains to be the most common cause of death in non-cardiac ICUs
- Antibiotics and appropriate fluid resuscitation remain to be the foundation of treatment for sepsis
- Recent studies suggest that the combination of thiamine, vitamin C and corticosteroids may improve outcomes in patients with sepsis or septic shock

Rhee C, et al. JAMA 2017;318(13):1241-9.
Rhodes A, et al. Crit care Med 2017;45(3):486-552.

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Definitions

	2001	2016
Sepsis	A clinical syndrome defined by the presence of both infection and a systemic inflammatory response to the infection.	Life-threatening organ dysfunction caused by a dysregulated host response to infection.
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension.	Term no longer exists.
Septic Shock	Sepsis with hypotension despite resuscitation with perfusion abnormalities.	Sepsis with underlying circulatory and cellular/metabolic abnormalities that can result in substantially greater mortality.

JAMA 2016;315(8):801-810.

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SOFA Score

Sequential [Sepsis-Related] Organ Failure Assessment Score

System	0	1	2	3	4
Respiration					
PaO2/FiO2, mmHg	≥400	<400	<300	<200	<100
Coagulation					
Platelets, x10³/µL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
CNS					
Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine Output, mL/d				<500	<200

JAMA. 2016;315(8):801-810.

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Pathophysiology

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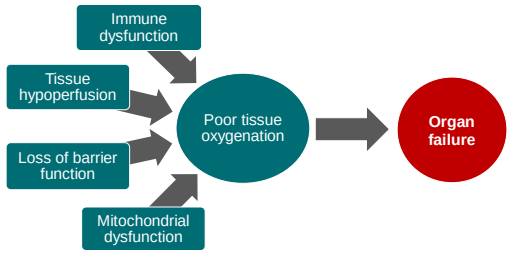
Pathophysiology



N Engl J Med 2013;369:840-51.

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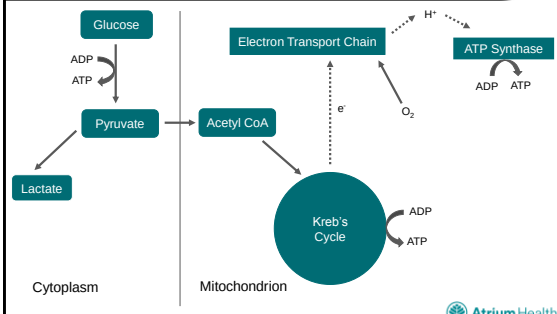
Mitochondrial Dysfunction



Ruggieri A, et al. Crit Care Clin 2010;26(3):567-575.

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Mitochondrial Dysfunction

1) Impaired perfusion leading to insufficient oxygen to drive oxidative phosphorylation
2) Generation of excess amounts of reactive oxygen species
   - Direct inhibition of mitochondrial respiration
   - Direct damage to mitochondrial proteins and membranes
3) Downregulation of gene transcription for mitochondrial proteins

Singer M. Virulence 2014;5(1):66-72.

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Metabolic Consequences

Decline in ATP levels

Decrease in cell functionality

Altered physiological functioning of organs

Singer M. Virulence 2014;5(1):66-72.

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Organ Dysfunction

- Multiple Organ Dysfunction Syndrome (MODS)
  - Shock
  - Respiratory failure
  - Thrombocytopenia/DIC
  - Altered mental status
  - Renal failure
  - Hepatic failure
  - Adrenal dysfunction
  - Ileus
  - Endocrine dysfunction

McConnell K, et al. Presse Med 2016;45(4):93-98.

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Audience Question

Do you currently use combination therapy with hydrocortisone, thiamine and ascorbic acid in septic shock patients?

A. Yes
B. No

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Hydrocortisone

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Hydrocortisone

Proinflammatory mediators = Inhibition of inflammation

Annane. Ann Intensive care 2011;1:7.

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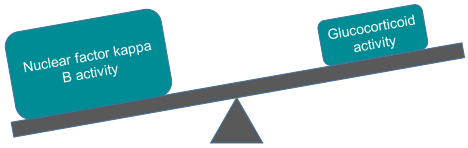
Hydrocortisone



Adrenal insufficiency → uncontrolled inflammation → organ dysfunction

Annane. Ann Intensive care 2011;1:7.

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Previous Studies

	Annane, 2002	CORTICUS, 2008
Design:	Multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	Multicenter, randomized, double-blind, placebo-controlled trial
Intervention:	Hydrocortisone (50 mg IV bolus Q6H) and fludrocortisone (50 mcg PO once daily) x 7 days or matching placebos	Hydrocortisone 50 mg IV Q6H x 5 days followed by 6 day taper or matching placebo
Outcomes:	28-day survival in non-responders to corticotropin testing	Rate of death at 28 days in non-responders to corticotropin testing
Patients:	• N = 300 • 229 non-responders to corticotropin test • Higher baseline SAPS II scores • Enrolled within 8 hours of meeting inclusion criteria	• N = 499 • 233 non-responders to corticotropin test • Lower baseline SAPS II scores • Enrolled within 72 hours of meeting inclusion criteria
Results:	Lower mortality in treatment group (63% in placebo group vs 53% in the corticosteroids group; P=0.2)	No difference in mortality (39.2% in hydrocortisone group vs 26.1% in placebo group; P=0.69)

Annane D, et al. JAMA 2002;288:862-871.
Sprung C, et al. N Engl J Med 2008;358:111-24.

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Surviving Sepsis Recommendations

H. CORTICOSTEROIDS

1. 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).

Rhodes A, et al. Crit Care Med 2017;45(3):486-552.

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ADRENAL, 2018

Objective:	To test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock
Design:	International, double-blind, parallel-group, randomized controlled trial
Patients:	• At least 18 years of age • Undergoing mechanical ventilation • Fulfilled 2 or more SIRS criteria • Had been treated with vasopressors or inotropic agents for ≥ 4 hours
Intervention:	• Hydrocortisone 200 mg IV infused over 24 hours x 7 days • Matching placebo
Results:	• N = 3658 • At 90 days, 511 patients (27.9%) in the hydrocortisone group died vs 526 patients (28.8%) in the placebo group (P=0.50)
Author's Conclusion:	Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality

Venkatesh, et al. N Engl J Med 2018;378:797-808.

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APROCCHSS, 2018

Objective:	To test the hypothesis that hydrocortisone plus fludrocortisone therapy or drotrecogin alfa would improve the clinical outcomes of patients with septic shock
Design:	Multicenter, double-blind, 2-by-2 factorial, randomized controlled trial
Patients:	• Indisputable or probable septic shock for less than 24 hours • Clinically or microbiologically documented infection • SOFA score of 3 or 4 for ≥ 2 organs and ≥ 6 hours • Receipt of vasopressor therapy for ≥ 6 hours
Intervention:	• Hydrocortisone 50 mg IV Q6H plus fludrocortisone 50 mcg PO daily x 7 days • Matching placebo
Results:	• N = 1241 • 90-day mortality was 43% in the treatment group and 49.1% in the placebo group (P = 0.03)
Author's Conclusion:	In patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo

Annane, et al. N Engl J Med 2018; 378:809-18.

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Trial Summary

Trial	Hydrocortisone Dosing	Norepinephrine Requirement	Mortality Benefit	Shortened Duration of Vasopressors
Annane[1]	200 mg IV daily (plus fludrocortisone 50 mcg daily)	~ 1 mcg/kg/min	Yes	Yes
CORTICUS[1]	200 mg IV daily	~ 0.5 mcg/kg/min	No	Yes
ADRENAL[2]	200 mg IV daily	~ 0.5 mcg/kg/min	No	Yes
APROCCHSS[1]	200 mg IV daily (plus fludrocortisone 50 mcg daily)	~ 1 mcg/kg/min	Yes	Yes

1) 50 mg IV Q6H
2) 200 mg IV over 24 hours

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Rochwerg, 2018

Objective:	To assess the efficacy and safety of corticosteroids in critically ill patients with sepsis
Design:	Systematic review and meta-analysis
Population:	• 42 randomized controlled trials • N = 10,194 • 24 studies examined patients with septic shock
Intervention:	• 27 studies utilized hydrocortisone • 37 studies utilized <400 mg/day or equivalent

Rochwerg, et al. Crit Care Med 2018;46(9):1411-1420.

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Rochwerg, 2018

	Outcome:	No corticosteroid:	Corticosteroids:
Results:	Long-term mortality (60d-1yr)	371/1000	349/1000
	Short-term mortality (28-31d)	255/1000	236/1000
	ICU LOS	13.13 days	12.4 days
	Organ dysfunction (7d)*	7.61 points	6.22 points
	Neuromuscular weakness	250/1000	303/1000
Author's Conclusions	In critically ill patients with sepsis, corticosteroids possibly result in a small reduction in mortality while also possibly increasing the risk of neuromuscular weakness		

*Measured by SOFA scores
LOS: length of stay

Rochwerg, et al. Crit Care Med 2018;46(9):1411-1420.

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BMJ Recommendation

Our panel make a weak recommendation to give corticosteroids to people with all types and severity of sepsis, based on new evidence. Because we are not certain that they are beneficial, it is also reasonable not to prescribe them. Patients' values and preferences may guide this decision-making process.

Lamontagne F. et al. BMJ 2018;362:k3284.

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Place in Therapy

- May consider empiric use of hydrocortisone in septic shock patients
- Dose as 200 mg IV daily in divided doses

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Thiamine

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Audience Question

JR is a 64 yo female (80 kg) with PMH of HTN, type II DM, CAD and COPD admitted to the ICU for septic shock 2/2 untreated pneumonia. In the ED, the patient was started on an antibiotic regimen of vancomycin and piperacillin-tazobactam and has received adequate fluid resuscitation. Her current BP is 81/52, HR 114, RR 23 and Tmax of 101.3F. She is being started on norepinephrine and hydrocortisone. In addition to vasopressors and steroids, would you give JR intravenous thiamine?

A. Yes
B. No

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Audience Question

AD is a 52 yo male (49 kg) with a PMH of depression, alcoholic cirrhosis and polysubstance abuse admitted to the ICU for sepsis. Despite adequate fluid resuscitation, AD has a BP of 82/60 and lactate of 4.3 mmol/L with worsening respiratory status requiring mechanical ventilation. In addition to initiating vasopressors, would you give AD intravenous thiamine?

A. Yes
B. No

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Thiamine

- Commonly known as Vitamin B_1
- Water-soluble vitamin involved in utilization of carbohydrates
- Available in oral and injectable formulations
- Indications for beriberi, Wernicke's encephalopathy and thiamine deficiency

Lonsdale D. Evid based Complement Alternat Med 2006;3(1):49-59

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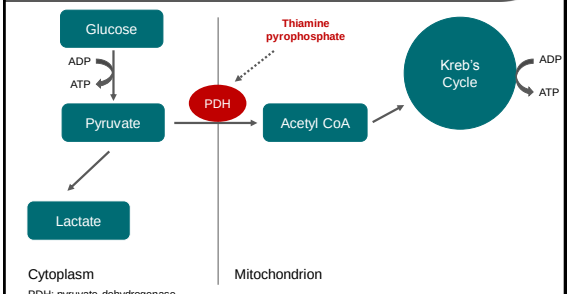
Thiamine



PDH: pyruvate dehydrogenase

Moskowitz A, et al. Critical Care 2018;22:283.

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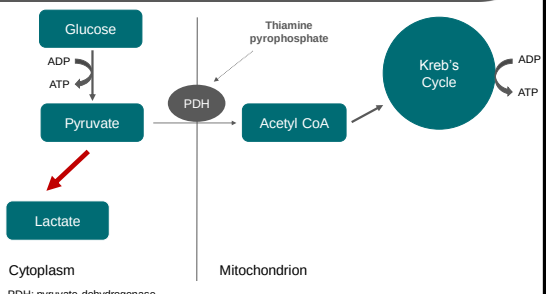
Thiamine Deficiency



PDH: pyruvate dehydrogenase

Moskowitz A, et al. Critical Care 2018;22:283.

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Donnino, 2016

Objective:	To determine if intravenous thiamine would reduce lactate in patients with septic shock
Design:	Randomized, double-blind, placebo-controlled trial
Patients:	• At least 18 years of age • Presence of ≥2 SIRS criteria • Documented or suspected infection • Lactate >3 mmol/L • Hypotension (SBP <90 mmHg after ≥2 L fluid bolus) • Vasopressor dependence
Intervention:	• Thiamine 200 mg IV twice daily x 7 days • Matching placebo
Results:	• N = 88 • No difference in lactate levels at 24 hours between thiamine and placebo groups (median 2.5 mmol/L vs 2.6 mmol/L; p = 0.40) • 35% of the 88 patients had baseline thiamine deficiency • In the above subgroup, lactate levels of median 2.1 mmol/L in the thiamine group vs 3.1 mmol/L in the placebo group; p = 0.03)
Author's Conclusion:	Administration of thiamine did not improve lactate levels in the overall group of patients with septic shock however, in those with baseline thiamine deficiency, patients in the thiamine group had significantly lower lactate levels at 24 hours

Donnino M, et al. Crit Care Med 2016;44(2):360-367.

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Holmberg, 2018

Objective:	To explore the association between receipt of thiamine and mortality in patients with **alcohol use disorder**
Design:	Retrospective, single-centered, cohort study
Patients:	• Septic shock between 2008 and 2014 • Diagnosis of alcohol use disorder • Orders for microbial cultures and use of antibiotics • Vasopressor dependency • Lactate levels ≥ 4 mmol/L
Dosing:	• Most commonly given as 100 mg • Intravenous in 68% of initial doses and 33% of total doses
Results:	• N = 53 • 34 (64%) of patients received thiamine • Mortality was lower in patients receiving thiamine compared to those not receiving thiamine (44% vs 79%; P=0.02)
Author's Conclusion:	Thiamine administration in patients with alcohol use disorder was associated with decreased mortality

Holmberg, et al. J Crit Care 2018;43:61-64.

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Woolum, 2018

Objective:	To test the hypothesis that patients with septic shock exposed to thiamine would demonstrate improved lactate clearance and more favorable outcomes
Design:	Retrospective, single-center, matched cohort study
Patients:	• At least 18 years of age • Coded for diagnosis of septic shock at admission • Admitted to medical or surgical ICU services
Dosing:	• Most commonly given as 500 mg IV Q8H • Median duration of 3 days
Results:	• N = 369 • Matched in 1:2 (thiamine:control) • Thiamine associated with improved likelihood of lactate clearance (hazard ratio 1.307; 95% CI, 1.002-1.704) • Thiamine associated with reduction in 28-day mortality (hazard ratio 0.666; 95% CI, 0.490-0.905)
Author's Conclusion:	Thiamine administration within 24 hours of admission patients presenting with septic shock was associated with improved lactate clearance and a reduction in 28 day mortality

Woolum J, et al. Crit Care Med 2018;46:1747-1752).

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Thiamine Deficiency

Wide range of prevalence in septic shock patients

Study	Prevalence of TD
Cruickshank, 1988	20%
Donnino, 2010	20%
Lima, 2011	28.2%
Costa, 2014	71.3%
Donnino, 2016	35%

Manzanares, et al. Curr Opin Clin Nutr Metab Care 2011;14(6):610-7.

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Thiamine Deficiency

- Burns
- Alcoholism
- Chronic malnutrition
- Long-term parenteral feedings
- Bariatric surgery
- Congestive heart failure

Manzanares, et al. Curr Opin Clin Nutr Metab Care 2011;14(6):610-7.

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Place in Therapy

- Empiric use not supported by randomized, controlled trials
- Use should be patient specific and based on presence of risk factors for thiamine deficiency
- If utilized, will likely need high-dose intravenous therapy
- Regimens of at least 200 mg IV twice daily used in studies

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Ascorbic Acid

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Ascorbic Acid

- Water-soluble vitamin
- Indication for the prevention and treatment of vitamin C deficiency including scurvy
- Available in oral and injectable formulations
- Up to 1.5 grams IV every 6 hours utilized in sepsis studies

Chambial S, et al. Indian J Clin Biochem 2013;28(4):314-328.

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Ascorbic Acid

Proposed mechanisms:

- Scavenges free radicals
- Suppression of NADPH oxidase pathway
- Recycling of other anti-oxidants
- Regeneration of endogenous catecholamines

Moskowitz A, et al. Critical Care 2018;22:283.

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Clinical Effects

- Reduced endothelial permeability
- Attenuated cellular apoptosis
- Regulation of macrophage function
- Reduction of inflammatory mediators
- Maintenance of vascular responsiveness

Moskowitz A, et al. Critical Care 2018;22:283.

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Fowler, 2014

Objective:	To determine the safety of intravenously infused ascorbic acid in patients with severe sepsis
Design:	Randomized, double-blind, placebo-controlled, phase 1 trial
Patients:	• Presence of a systemic inflammatory response • Suspected or proven infection • Presence of sepsis induced organ dysfunction
Intervention:	• Low dose ascorbic acid (50 mg/kg/day) • High dose ascorbic acid (200 mg/kg/day) • Placebo (5% dextrose/water)
Results:	• N = 24 • Ascorbic acid infusion rapidly increased plasma ascorbic acid levels • No adverse safety events were observed • Patients receiving ascorbic acid exhibited reductions in SOFA scores
Author's Conclusion:	IV ascorbic acid was safe and well tolerate and may positively impact the extend of multiple organ failure

Fowler, et al. J Transl Med 2014; 12:32.

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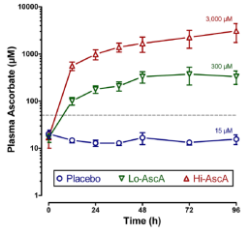
Fowler, 2014

Plasma ascorbic acid levels following intravenous infusion of ascorbic acid



Fowler, et al. J Transl Med 2014; 12:32.

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Audience Question

What are some potential risks for using high dose IV ascorbic acid?

A. Interference with blood glucose labs
B. Accumulation leading to hepatic toxicity
C. Increased oxalate formation and excretion
D. A and C
E. All of the above

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Audience Question

What are some potential risks for using high dose IV ascorbic acid?

A. Interference with blood glucose labs
B. Accumulation leading to hepatic toxicity
C. Increased oxalate formation and excretion
D. A and C
E. All of the above

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Zabet, 2016

Objective:	To evaluate the effect of high-dose ascorbic acid on vasopressor drug requirement in surgical critically ill patients with septic shock
Design:	Double-blinded, randomized clinical trial
Patients:	• Adults between 18 and 65 years of age • Diagnosis of septic shock
Intervention:	• Ascorbic acid 25 mg/kg IV Q6H x 72 hours • Matching placebo
Results:	• N = 28 • Mean dose of norepinephrine was 7.44 mcg/min in treatment group vs 13.79 mcg/min in placebo group (p = 0.004) • Mean duration of norepinephrine administration was 50 hours in treatment group vs 72 hours in placebo group (p = 0.007)
Author's Conclusion:	High-dose ascorbic acid may be considered as an effective and safe adjuvant therapy in surgical critically ill patients with septic shock

Zabet M, et al. J Res Pharm Pract 2016;5(2):94-100.

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Putzu, 2019

Objective:	To assess the effect of vitamin C administration on major clinical outcome in ICU or cardiac surgery patients
Design:	A systematic review and meta-analysis
Population:	• 44 randomized controlled trials • 16 studies in the ICU setting • N = 6,455 • 2,857 patients from ICU setting
Intervention:	ICU setting • 5 studies using vitamin C only • 5 studies utilizing oral vitamin C • 10 studies utilizing IV vitamin C • 4 studies using high dose vitamin C (>5 grams/day)
Results:	ICU population • No difference in mortality at longest follow-up (p = 0.31) • No significant reduction in ICU length of stay • No significant difference in AKI (p = 0.78)
Author's Conclusions	In a mixed population of ICU patients, vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay.

Putzu, et al. Crit Care Med. 2019 Feb 26.

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Use in Therapy

- Lack of robust evidence to support empiric use in septic shock population
- Low cost profile but potential for increased oxalate excretion with high dose therapy
- Documented interactions with blood glucose readings

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Combination Therapy

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Ascorbic Acid and Corticosteroids

Glucocorticoid binding to glucocorticoid receptors negatively affected by oxidizing molecules

↳ Restoration of glucocorticoid receptor function by ascorbic acid

Cellular uptake of ascorbic acid mediated by SVCT2 which is downregulated during inflammatory states

↳ Increased expression of SVCT2 transporter by glucocorticoids

SVCT2: Sodium Dependent Vitamin C Transporter

Moskowitz A, et al. Critical Care 2018;22:283.

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Marik, 2017

Objective:	To compare the outcome and clinical course of septic patients treated with intravenous vitamin C, hydrocortisone and thiamine with a control group
Design:	Retrospective, before-after clinical study
Patients:	• At least 18 years of age • Primary diagnosis of severe sepsis or septic shock • Procalcitonin level of ≥2 ng/mL
Outcomes:	Primary: • Hospital survival Secondary: • Duration of vasopressor therapy • Requirement for renal replacement therapy • ICU length of stay • Change in serum procalcitonin level over first 72 hours • Change in SOFA score over first 72 hours

Marik P, et al. CHEST 2017;151(6):1229-1238.

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Marik, 2017

Intervention:	Treatment • Between January 2016 and July 2016 • Medications started within 24 hours of ICU admission • Vitamin C 1.5 g IV q6h x 4 days or until ICU discharge • Hydrocortisone 50 mg IV q6h x 7 days or until ICU discharge • Thiamine 200 mg IV q12h x 4 days or until ICU discharge Control • Between June 2015 and December 2015 • Hydrocortisone 50 mg IV q6h at the discretion of attending physician

Marik P, et al. CHEST 2017;151(6):1229-1238.

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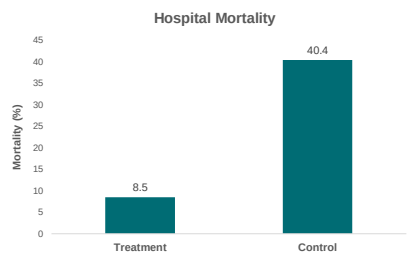
Marik, 2017

Results:

N = 94



Marik P, et al. CHEST 2017;151(6):1229-1238.

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Marik, 2017

Results:	Secondary • Mean 18.3 hours duration of vasopressor use in treatment vs 54.9 in control • 10% required RRT in treatment group vs 33% in control • No significant different in ICU length of stay • Median PCT clearance of 86.4% in treatment group vs 33.9% in control • Change in SOFA score of 4.8 points in treatment group vs 0.9 points in control
Author's Conclusion:	The 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.

Marik P, et al. CHEST 2017;151(6):1229-1238.

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Marik, 2017

Limitations:	• Not a randomized controlled trial • Small sample size • Single center • Treatment and control periods not concurrent • 59.6% of patients in control group received hydrocortisone • No report of adequate antibiotic coverage or fluid resuscitation • Multiple interventions • Use of procalcitonin levels to drive diagnosis of sepsis • Details of cause of death not reported for control group • Death rate in control group much higher than in previous sepsis and septic shock studies

Marik P, et al. CHEST 2017;151(6):1229-1238.

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Need for Further Research

- Randomized, controlled trials
- Large sample sizes
- Multiple centers
- Diagnosis of septic shock
- Clear standard of care in control groups
- Primary outcome of mortality

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Future Studies

Trial Name	Location	Population	Primary Outcome
Ascorbic acid, Corticosteroids and Thiamine in Sepsis (ACTS) Trial	USA	Septic shock	Change in SOFA score
Vitamin C, Thiamine and Steroids in Sepsis (VICTAS)	USA	Sepsis with acute cardiovascular or respiratory compromise	Vasopressor- and ventilator-free days
Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis and Septic Shock (HYVCTTSSS)	China	Sepsis or septic shock (Sepsis-3 Criteria)	Hospital mortality
The Effect of Vitamin C, Thiamine and Hydrocortisone on Clinical Course and Outcome in Patients with Severe Sepsis and Septic Shock	Slovenia	Severe sepsis or septic shock	Hospital mortality
Metabolic Resuscitation using Ascorbic Acid, Thiamine, and Glucocorticoids in Sepsis (ORANGES)	USA	Sepsis or septic shock	Hospital mortality
The Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock Trial (VITAMINS)	Australia and New Zealand	Septic shock	Vasopressor-free days
Evaluation of Hydrocortisone, Vitamin C and Thiamine for the Treatment of Septic Shock (HYVITS)	Qatar	Septic shock	Hospital mortality
Steroids, Thiamine, and Vitamin C in Septic Shock (STACSS)	India	Septic shock	Shock reversal
Thiamine, Vitamin C and Hydrocortisone in the Treatment of Septic Shock	USA	Septic shock	Mortality

Moskowitz A, et al. Critical Care 2018;22:283.

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Final Recommendations

Hydrocortisone	• Consider initiation in septic shock patients • 200 mg IV daily
Thiamine	• Not for empiric use • Initiate if patient has risk factors for thiamine deficiency
Ascorbic Acid	• Not for empiric use • Additional data needed to support provided benefit

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Summary

- The pathogenesis of sepsis and septic shock is complex involving multiple mechanisms aside from an inflammatory response
- Literature has shown that hydrocortisone may provide benefit in reversal of shock
- Thiamine and ascorbic acid provide a potentially novel and biologically plausible mechanism in the treatment of septic shock
- Robust evidence is lacking to support the use of thiamine and ascorbic acid for the treatment of septic shock however, there are several large studies on the horizon to evaluate the use of this combination regimen

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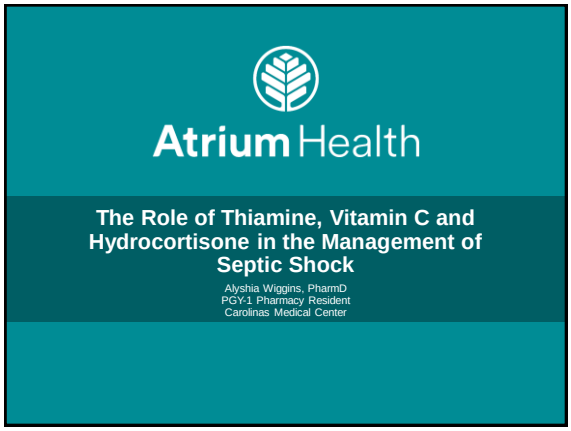
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The Role of Thiamine, Vitamin C and Hydrocortisone in the Management of Septic Shock
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