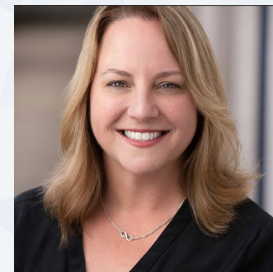


Ascorbic Acid

A Review of Pertinent Drug Information for SARS-CoV-2

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Data updated 4/17/2020

Ascorbic Acid



Recommendation?

Ascorbic Acid

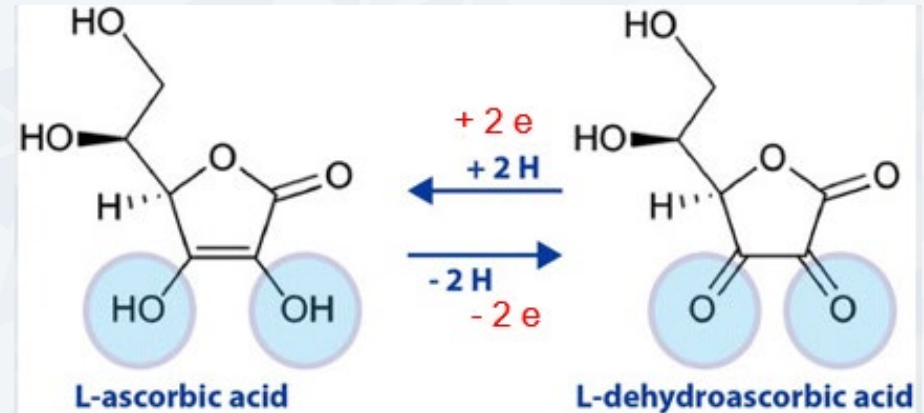
Chemistry and Metabolism

Antioxidant

- Mitigate oxidative stress
- Reduce metals such as copper and iron
 - During this process ascorbic acid is oxidized to ascorbate radical (pro-oxidant)
 - Regenerate other antioxidants (Vitamin E)

Protein synthesis

- Cofactor for enzyme processes needed to synthesize collagen, L-carnitine, catecholamines (norepinephrine & dopamine), and proteins



Chemically, ascorbic acid is an electron donor (reducing agent)

Ascorbic Acid

Deficiency



- Stores deplete in the absence of intake

- Critically ill patients and patients with sepsis have lower Vitamin C concentrations than healthy subjects

Deficient	Suboptimal	Adequate
< 11 $\mu\text{mol/L}$	11-23 $\mu\text{mol/L}$	> 23 $\mu\text{mol/L}$
< 0.2 mg/dL	0.2-0.5 mg/dL	> 0.5 mg/dL

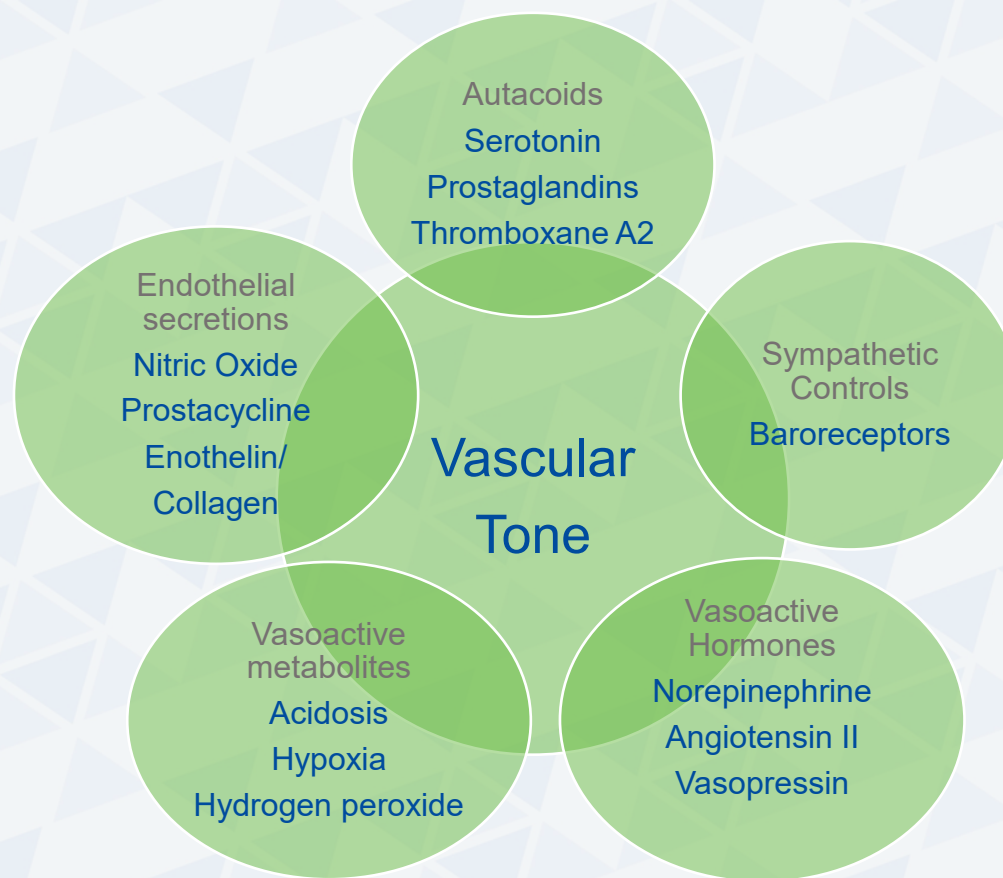
Total body stores ~ 1500 mg



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Galley HF, et al. Free Radic Biol Med 1996;20(1):139-143. [http://doi.org/10.1016/0891-5849\(95\)02022-5](http://doi.org/10.1016/0891-5849(95)02022-5)
Padayatty SJ, et al. Oral Dis. 2016 Sep;22(6):463-493. <https://doi.org/10.1111/odi.12446>
Zabet MH, et al. J Res Pharm Pract 2016;5:94-100. <https://doi.org/10.4103/2279-042X.179569>
Borelli E, et al. Crit Care Med 1996;24(3):392-397 DOI: [10.1097/00003246-199603000-00006](https://doi.org/10.1097/00003246-199603000-00006)

Ascorbic Acid & Septic Shock



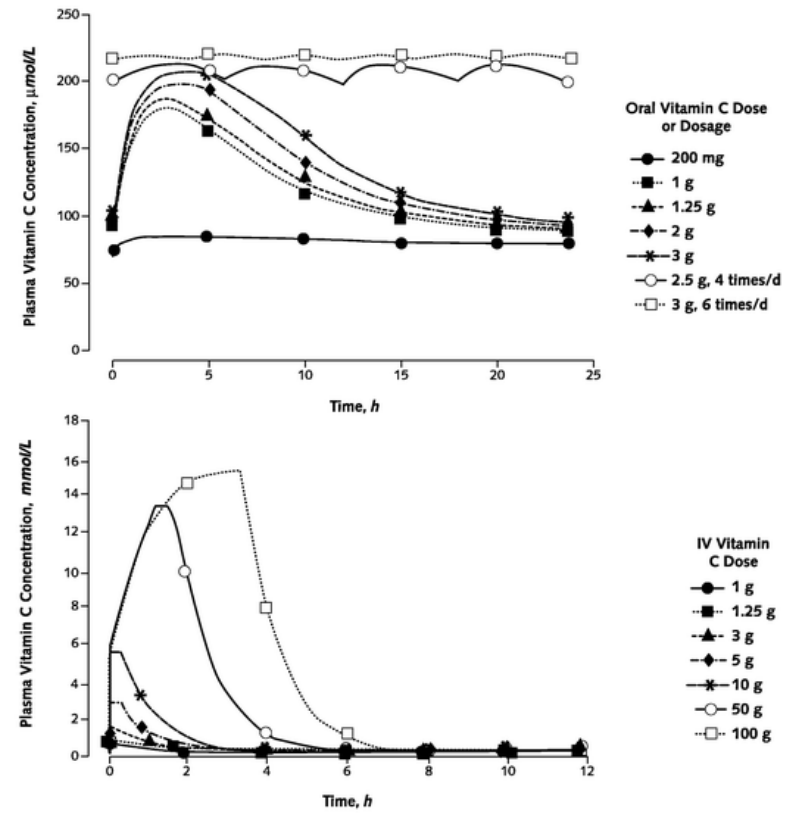
Immune Functions

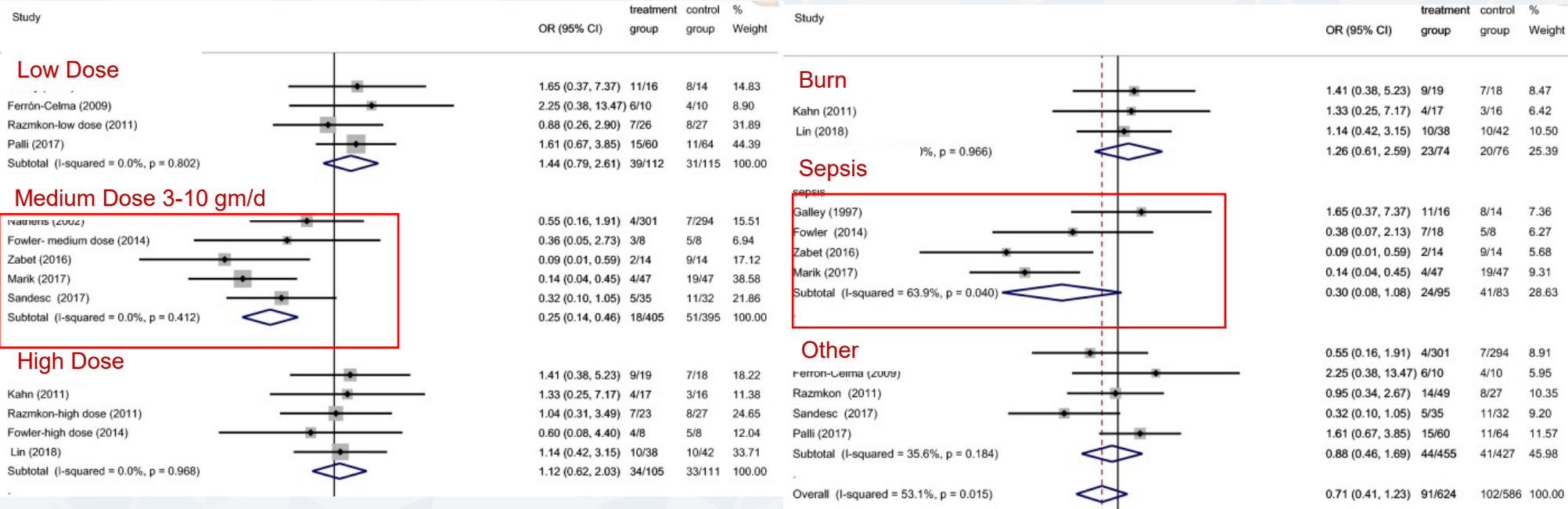
- T-cell/B-cell proliferation
- Macrophages
 - Clearance of neutrophils

↓ Proinflammatory Mediators

Dose, Frequency & Duration

- Unknown
 - 2-3 grams IV per day likely needed to normalize plasma concentrations
 - IV concentrations higher than PO
 - Rapid renal clearance
 - multiple daily doses





Author Conclusions:

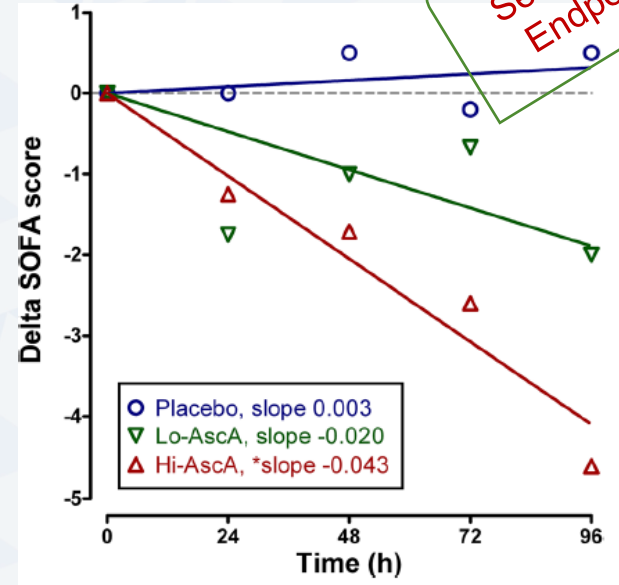
Aggressive repletion of plasma ascorbic acid levels with severe sepsis is safe.

Suggest AA reduced extent of multiple organ failure and reduces circulating injury biomarker levels.

n=26
 - Safety study
 - Baseline characteristics matched
 - Lack of standardized sepsis treatment

Table 2. Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0-4)

Low Dose
 50 mg/kg/24 h
High Dose
 200 mg/kg/24 h
 Placebo



R, DB, single-center
 N=28, surgically critically ill
 AA Dose: 25 mg/kg IV q 6 h x 72 h

Primary Endpoint:
 Vasopressor requirements (dose and duration)

Author Conclusions:

High dose AA may be considered as safe and effective adjuvant therapy



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Table 4: Primary and secondary outcomes of the study in ascorbic and placebo groups

Characteristics	Ascorbic acid group (n=14)	Control group (n=14)	P
Mean dose of norepinephrine (mcg/min) during the study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
Length of ICU stay (days)	21.45±10.23	20.57±13.04	0.85
28-day mortality	2 (14.28)	9 (64.28)	0.009

Purpose: to evaluate whether high-dose vitamin C reduces organ failure scores and biomarkers of inflammation and vascular injury among patients with Sepsis and ARDS.

Methods:

R, DB, PC
n=167

Treatment (n=84)
**AA 50 mg/kg IV q 6 h
x 96 h**
Vs. Placebo (n=83)

Primary Endpoint:

Δ SOFA score at
96 h
 Δ in CRP and
thrombomodulin
at 168 h

No
difference

Secondary Endpoints:

43/46 = no difference

↓ 28-day mortality
↓ ICU days @ 28 days
↓ Hospital days @ 60 days

Not adjusted for
multiple
comparisons

Variable	Treated (n=47)	Control (n=47)	P value
Hospital Mortality, No. (%)	4 (8.5)	19 (40.4)	< 0.001
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)	NS
Duration of vasopressors, mean \pm SD, h	18.3 \pm 9.8	54.9 \pm 28.4	< 0.001
RRT for AKI, No. (%)	3/31 (10%)	11/30 (33%)	0.02
Δ SOFA, 72h	4.8 \pm 2.4	0.9 \pm 2.7	< 0.001
PCT clearance, median % and IQR, 72h	86.4 (80.1-90.8)	33.9 (-62.4 - 64.3)	< 0.001

IV Treatment
Ascorbic Acid 1.5 gm q 6 h x 4d
Hydrocortisone 50 mg q 6 h x 7d
Thiamine 200 mg every 12 h x 4d


OR ICU discharge

Author Conclusions:
 IV Vitamin C, together with corticosteroids and thiamine, are effective in preventing organ dysfunction, [incl. AKI], and in reducing mortality of patients with severe sepsis and septic shock.

Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial

Tomoko Fujii, MD, PhD; Nora Luethi, MD; Paul J. Young, MBChB, PhD; et al.

[Abstract](#) | [Full Text](#)

 JAMA. 2020;323(5):423-431. doi:10.1001/jama.2019.22176

Multicenter, open, randomized

n= 109

Ascorbic Acid 1.5 g q 6 h

Hydrocortisone 50 mg q 6 h

Thiamine 200 mg q 12 h

vs

n=107

Hydrocortisone 50 mg q 6 h

Until shock resolution or 10 days

**Alive and vasopressor free
(hours) (n=211)**

Treatment	122.1
Control	124.6
Median difference – 0.6 hours (95% CI, -8.3 to 7.2 hours, P=0.83)	

Author Conclusions:

In patients with septic shock, vitamin C + hydrocortisone + thiamine compared with hydrocortisone alone did not significantly improve time alive and vasopressor free time up to 7 days compared with hydrocortisone alone.

Vitamin C and Viral Illness

No definitive information to suggest direct anti-viral activity of ascorbic acid in vivo

Cheng LL et al. [An in vitro study on the pharmacological ascorbate treatment of influenza virus]. Zhonghua Jie He He Hu Xi Za Zhi 2012 July;35(7):520-3

Cai Y, et al. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. Biomed Res Int 2015;2015:675149. Epub 2015 Feb 1 (accessed 4/15/2020)

Kim Y, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon- α/β at the initial stage of influenza A virus (H3N2) infection. Immune Netw 2013 Apr;13(2):70.74

Ascorbic Acid and COVID-19

BEST GUESS

- Unlikely virucidal
- Unlikely benefit in sepsis +/- ARDS

STUDY RESULTS SOON?

Safety/Tolerability

Study	Ascorbic Acid Dose
Fowler et al. J Transl Med 2014	50 mg/kg/24 h x 4 days (n=8) 200 mg/kg/24 h x 4 days (n=8)
Nathens et al. Ann Surg 2002	1000 mg q8 h while in ICU
Tanaka H, et al. Arch Surg 2000	66 mg/kg per hour
Hoffer LJ et al. Ann Oncol 2008	1.5 grams/kg three times weekly
Mastuda et al. J Burn Care Rehabil 1994	33 mg/kg per hour

Cost ?

\$300-600 per (high dose) therapy course

1.7 million Septic Americans /year

\$ 5 million?

Other:

- ↑ Oxalate Excretion
- POC Glucose test interference
- G6PD deficiency → ↑ hemolysis
- Minimal drug interactions (cyclosporine)



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Guideline Recommendations

Use of Ascorbic Acid in Selected Situations

Society	Sepsis	Sepsis + ARDS	COVID-19	COVID-19 + ARDS
Society of Critical Care Medicine and European Society of Intensive Care Medicine	No Recommendations			

* OPINION * SLIDE

A prescriber insists on trying IV ascorbic acid and wants to know what dose you recommend and why?

Dose: AA 1.5 grams q 6 hours x 4 days or until ICU discharge

Rationale:

- Total body stores are about 1500 mg
- Pharmacokinetic studies show return to at least normal levels
- Wang meta-analysis
- Marik dosing



Summary



- Consequences of ascorbic acid depletion in critical illness are uncertain
- Caution on basing therapy recommendations based on secondary outcomes or small technically flawed studies
- Data do not support the use of AA for septic shock
- No data are available for use in COVID-19
- Multiple studies underway

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