11.3 Intravenous Vitamin C Supplementation

Question: Does IV Vitamin C supplementation result in improved clinical outcomes in critically ill patients?

Summary of evidence: There was one level 2 RCT of IV vitamin C supplementation that examined high dose IV vitamin C ($200\ \mathrm{mg/kg/day}$) vs low dose vitamin C (50 mg/kg/day) vs placebo (5% dextrose) (Fowler 2014) and one level 1 RCT of IV vitamin C (25 mg/kg/d every 6 hours for 72 hours) vs placebo (5% dextrose) (Zabet 2016).

Mortality: When the data from the two trials were meta analyzed, there was a trend towards a reduction in 28 day mortality in the vitamin C group (RR 0.44, 95% CI 0.13-1.47, p=0.13, heterogeneity I^2=60%; figure 1). Note that the mortality for the 2 intervention groups in the Fowler et al study have been combined for this meta-analysis.

Infections: none reported.

Length of Stay: Fowler et al found no differences in ICU LOS between the 3 groups. Zabet et al also found no difference in their study (p=0.85).

Duration of ventilation: There were no differences in ventilator free days between the 3 groups in the Fowler et al study and no difference between the 2 groups in the Zabet et al study (p=0.50).

Other: In the Fowler et al study, ascorbic acid infusion rapidly and significantly increased plasma ascorbic acid levels. No adverse safety events were observed in ascorbic acid-infused patients. Patients receiving ascorbic acid exhibited prompt reductions in SOFA scores while placebo patients exhibited no such reduction. Ascorbic acid significantly reduced the pro-inflammatory biomarkers C-reactive protein and procalcitonin. No adverse events related to vitamin C supplementation were found in the Zabet et al study. Vitamin C supplemented patients received lower doses of norepinephrine during the 72-hour trial period and a reduced total duration or norepinephrine.

Conclusions:
1. IV Vit C supplementation may be associated with lower 28 day mortality in critically ill patients.
2. IV Vit C supplementation has no effect on ICU LOS or ventilator free days in critically ill patients.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating glutamine (PN + EN) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)	Infections # (%)†
1) Fowler 2014	Septic patients N=26	C.Random: yes ITT: no Blinding: double (7)	IV low dose ascorbic acid (50 mg/kg/day) vs IV high dose ascorbic acid (200 mg/kg/day) vs placebo (5% dextrose in water).	Low dose High dose Control 28-day 3/8 (38.1) 4/8 (50.6) 5/8 (62.5) Denominator unknown p-value not specified	NR
2) Zabet 2016	Surgical ICU patients with septic shock requiring vasopressors N=28	C.Random: yes ITT: yes Blinding: double (12)	IV adcorbic acid (25 mg/kg q6h for 72h) vs IV placebo (5% dextrose)	28-day 2/14 (14) 9/14 (64) P=0.009	NR

Table 1. Randomized studies evaluating glutamine (PN + EN) in critically ill patients (continued)

Study	LOS days	Ventilator free days	Other Outcomes
1) Fowler 2014	Low dose High dose Control ICU 8.1 (1-19) 9.1 (2-25) 11 (2-25) p-value not available	Low dose High dose Control 8.4 (0-22) 4.8 (0-19) 7.6 (0-23) p-value not available	Low dose High dose Control Days on Pressors 2.1 (1-6) 3.6 (2-8) 3.9 (1-10) p-value not available
2) Zabet 2016	ICU, in days: 21.45 ± 10.23 20.57 ± 13.04 P=0.85	In hours: 36.63 ± 16.11 46.78 ± 10.11 P=0.5	Mean dose of norepi (mcg/min) during 72h study period 7.44 ± 3.65 13.79±6.48 P=0.004 Duration or norepi administration (h) 49.64±25.67 71.57±1.60 P=0.007

† refers to the # of patients with infections unless specified LOS: Length of stay ICU: intensive care unit C. Random: concealed randomization
ITT: intent to treat

Figure 1. 28-day Mortality

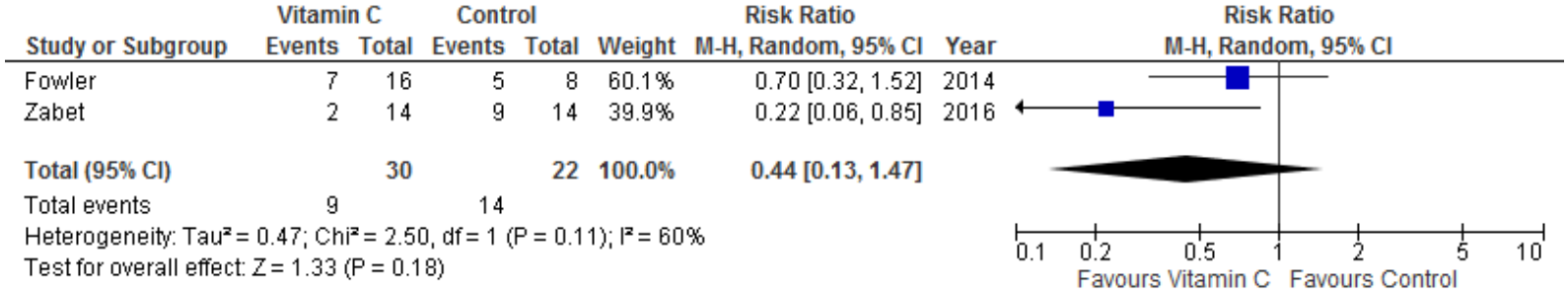

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Pseudorandomized	Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg. 2000 Mar;135(3):326-31.
2	Meta-analysis	Langlois PL, Manzanares W, Adhikari NKJ, Lamontagne F, Stoppe C, Hill A, Heyland DK. Vitamin C Supplementation in the Critically Ill: A Systematic Review and Meta-Analysis. JPEN J Parenter Enteral Nutr. 2018 Nov 19.