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 mg/kg/day) vs low dose vitamin C (50 mg/kg/day) vs placebo (5% dextrose) (Fowler 2014) ; one level 1 RCT of IV vitamin C (25 mg/kg/d every 6 hours for 72 hours) vs placebo (5% dextrose) (Zabet 2016), and one phase 2 RCT of intravenous vitamin C (50 mg/kg actual body weight every 6 hours for 96 hours) vs. dextrose 5%inwater alone (Fowler 2019).

Mortality: When the data from the three RCT were meta analyzed, there was a trend towards a reduction in 28 day mortality in the vitamin C group (RR 0.41, 95% CI 0.23-0.72, p=0.25, heterogeneity I^2=29%; figure 1). Note that the mortality for the 2 intervention groups in the Fowler et al 2014 study have been combined for this meta-analysis.

Infections: none reported**.**

Length of Stay: Fowler et al 2014 found no differences in ICU LOS between the 3 groups. Zabet et al also found no difference in their study (p=0.85). Fowler et al 2019 reported that compared to placebo, patients in the intervention arm had greater ICU 28-free days (10.7 vs 7.7; 0.03) and greater HOSP free days (22.6 vs. 15.5; p=0.04)

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). Fowler et al 2019 reported that when compared to control arm, subjects in the intervention arm had greater mechanical ventilator free days (13.1 vs. 10.6; p=0.15)

Other: In the Fowler et al 2014 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. In the Fowler 2019 study there were no unexpected study-related adverse events reported. Vitamin C serum levels were higher in subjects on the intervention arm. There were no significant differences in biomarkers of inflammation (C-reactive protein), cardiovascular injury biomarkers (thrombomodulin levels), and mSOFA score between study groups.

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.
3. IV Vit. C supplementation has no effect on markers of inflammation, organ dysfunction score, and vascular injury in critically ill patients with sepsis and ARDS

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 vitamin C 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
3) Fowler 2019	ICU patients with sepsis and ARDS N=167	C. Random (1:1); NO ITT. YES Blinding: double (12)	**intravenous vitamin C** (50 mg/kg actual body weight, every 6 hours for 96 hours) vs. dextrose 5% in water alone (50 mg/kg actual body weight, every 6 hours for 96 hours)	**at day 28 25/84 (29%) vs. 38/82 (46%); p=0.03**	NR

Table 1. Randomized studies evaluating vitamin C 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
3) Fowler 2019	**Intervention vs. Control** **ICU 28 free days:** 10.7 vs 7.7 days: p=0.03 **HOSP Free days:** 22.6 vs. 15.5 days: p=0.04	**Intervention vs. Control** 13.1 vs. 10.6 days: p= 0.15	**mSOFA** score from baseline to 96 hours decreased from 9.8 to 6.8 in the vitamin C group (3 points) from 10.3 to 6.8 in the placebo group (3.5 points) difference, –0.10; 95% CI, −1.23 to 1.03; P = 0.86; **C-reactive protein** 54.1 µg/mL 46.1 µg/mL difference , 7.94; 95% CI, −8.23 to 24.1; P = 0.33; T**hrombomodulin** levels at 168 hours 14.5 ng/mL 13.8 ng/mL difference, 0.69; 95% CI, −2.8 to 4.2; P = 0.70

† 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

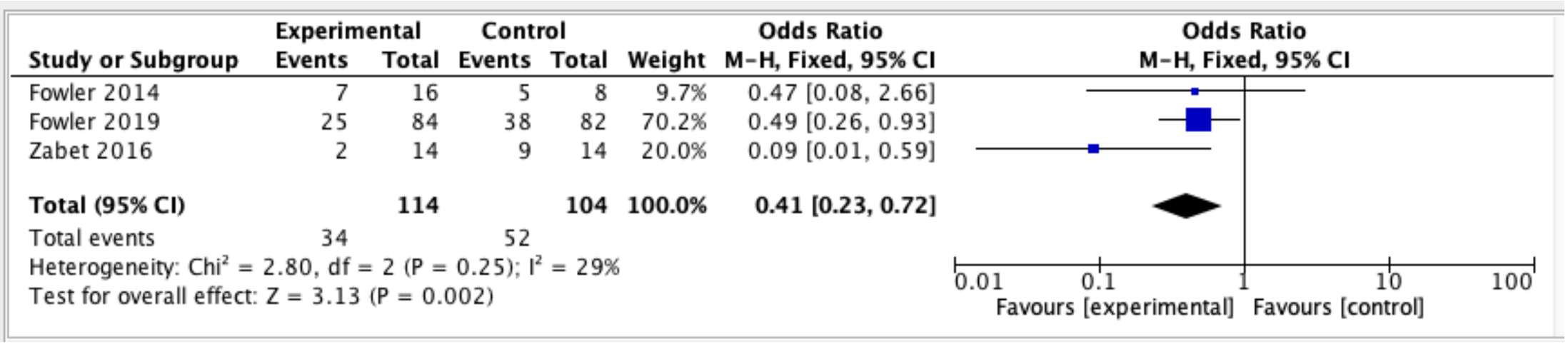

Table 2. Excluded Articles

# Reason excluded Citation	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: Meta-analysis A Systematic Review and Meta-Analysis. JPEN J Parenter Enteral Nutr. 2018 Nov 19.