Supplement Table 40. Characteristics of randomized controlled trials evaluating micronutrient and antioxidant supplementation in critically ill adults (KQ16)

Nutrients	Author (year)	Study population	Study design (RCT)	Study protocol		No of patients		
				Inter.	Con.	Total	Con.	Inter.
Vit C (25)	Duffy MJ (2015) [196]	Adults undergoing elective open AAA repair (perioperative ICU care)	Double blind	IV AA 2g (single dose, intra-op)	NS	31	18	13
	Zabet MH (2016) [197]	Surgical ICU patients with septic shock (MAP <65 mmHg requiring NE)	Double blind	IV AA 25 mg/kg every 6 hr for 72 hr (total 300 mg/kg over 3 days)	5% DW	28	14	14
	Emadi N (2019) [198]	Adults (50-80 years old) who had CABG surgery	Double blind	Vit C 5 g IV + 5 g in cardioplegic solution	NS	50	25	25
	Fowler AA III (2019) (199]	Adult ICU patients with sepsis and ARDS requiring MV	Double blind	IV Vit C 50 mg/kg q6h for 96 hr (4 days)	5% DW	167	83	84
	Wang D (2020) [200]	Adult patients undergoing cardiac surgery under CPB	Double blind	Vit C IV 1 g administered at three time points (total 3g/day)	NS	70	37	33
	Yanase F (2020) [201]	Adults post-cardiac surgery with vasoplegia	Double blind	High-dose IV Vit C (1.5 g q6h)	NS	50	25	25
	El-Sherazy NH (2021) [202]	Critically ill adults receiving vancomycin for ≥72 hr	Open label	Oral Vit C 2 g twice daily (total 4 g/day) plus IV Vancomycin	None	41	20	21
	Jamali Moghadam Siahkali S (2021) [203]	Adults hospitalized with severe COVID-19	Open-label	IV Vit C 1.5 g every 6 hr for 5 day (total 6 g/day)	SC	60	30	30
	Mahmoodpoor A (2021) [204]	ICU patients with severe pneumonia	Double-blind	Vit C 60 mg/kg/day IV continuous infusion for 96 hr	NS	80	40	40
	Zhang J (2021) [205]	ICU-admitted severe COVID-19 patients (18 -80)	Double-blind RCT	IV Vit C 12g q12h (total 24 g/day IV x 7 days)	water	56	29	27
	Kassem AB (2022) [206]	critically ill patients with TRALI	Double blind	AA 2.5 g IV q6h × 4 days (total 10 g/d for 96 hr)	NS	80	40	40
	El Driny WA (2022) [207]	Sepsis requiring MV, age 18–70	Double-blind RCT	Vit C 1.5g q6h IV for 4 days	LD Vit C 100 mg/day	40	20	20
	Labbani-Motlagh Z (2022) [208]	Adults with moderate-to-severe COVID-19	Double blind	IV Vit C 12 g/day × 4 days	5% DW	74	37	37
	Lamontagne F (2022) [209]	Adults (≥18) in ICU with sepsis requiring vasopressors, ICU ≤24 hr	Double blind	IV Vit C 50 mg/kg q6h × 4 days (max 16 doses)	5% DW or NS	863	434	429
	Rosengrave P (2022) [210]	Adults with septic shock on ≥0.06 µg/kg/min NE	Double blind	IV Vit C 25 mg/kg q6h for up to 96h	5% DW	40	20	20
	Wacker DA (2022) [211]	Adults with septic shock, enrolled within 24 hr of vasopressor initiation	Double-blind	IV Vit C 1000 mg bolus + 250 mg/hr continuous for 96h	NS	124	64	60
	Adhikari NKJ (2023) [212]	Adults hospitalized with confirmed or suspected COVID-19; subgroups of critically ill and non-critically ill	Harmonized RCTs	IV Vit C: 50 mg/kg every 6 hr for 96 hr (max 16 doses)	Placebo	1568	531	1037
	Anstey MH (2023) [213]	ICU patients with vasoplegic shock requiring >10 µg/min NE	Double blind	IV Vit C 1.5 g q6h for up to 5 days	NS	71	36	35
	Belousoviene E (2023) [214]	adult patients with sepsis and septic shock	Double-blind	Vit C 50 mg/kg IV q6h × 96 hr	NS	23	11	12
	Vijayaraghavan BK (2023) [215]	Adults (≥18) with sepsis requiring vasopressors in ICU	Double blind	IV Vit C (50 mg/kg q6h × 4 days)	NS	30	14	16
	Yanase F (2023) [216]	Adults with septic shock admitted to ICU within 24 hr	Double blind	AA 60g IV (30g over 1 hr + 30g over 5 hr)	5% DW	30	15	15
	Karadžić Kočica M (2024) [217]	Adult cardiac surgery patients with ECC, post-op ICU	Single blind	IV Vit C 200 mg/kg/day × 2 days	NS	150	75	75
	Li W (2024) [218]	Adult ICU patients with septic shock	Double blind	150 mg/kg/day Vit C × 4 days	Water	38	18	20
	Privšek M (2024) [219]	Adults admitted to ICU after OHCA	Double blind	Vit C 1.5 g IV every 12 hr × 8 doses (total 12 g)	NS	30	12	18
	Zhao B (2025) [220]	Adults with MSAP or SAP within 72 hr of symptom onset	Double blind	Vit C 200 mg/kg/day IV for 7 days	NS	212	103	109
Se (11)	Andrews PJ (2011) [221]	Adults ICU for ≥48 hr, with gastrointestinal failure and requiring PN	Double blind factorial	Se 500 µg/day IV (max 7d)	PN without Se	502	251	251
	Manzanares W (2011) [222]	ICU patients with SIRS and APACHE II ≥15, expected MV >48 hr	Single blind	S2 2,000 µg IV bolus + 1,600 µg/day ×10 days	NS	31	16	15
	Valenta J (2011) [223]	ICU patients with SIRS/sepsis, SOFA ≥ 5	Open label	PN Se (< 75 ug) + Se 1000 µg day 1, 500 µg/day x ≤14 days	PN Se (< 75 ug)	150	75	75
	Chelkeba L (2015)	Adult ICU patients with	Single blind	Se 2 mg bolus + 1.5 mg/day	No Se	54	25	29

	[224]	sepsis/septic shock on MV >48 hr		for 14 days				
	Bloos F (2016) [225]	Adults with severe sepsis or septic shock (within 24 hr onset)	2×2 factorial, placebo-controlled	NaSe: 1000 μg IV loading dose + 1000 μg/day continuous for up to 21 days	NS	1089	546	543
	Chelkeba L (2017) [226]	Adult ICU patients with sepsis/septic shock	Single blind	IV NaSe: 2 mg bolus + 1.5 mg/day x 14 days	SC	54	25	29
	Moghaddam OM (2017) [227]	Patients >18 yr with moderate to severe TBI (GCS ≤12), admitted within 8 hr	Double blind	Se 500 μg IV daily ×14 days	SC	113	56	57
	Schmidt T (2018) [228]	Adults undergoing elective cardiac surgery (CABG/valve/aortic)	Double-blind	NaSe: 4 mg IV bolus + 1mg /day for up to 13 days	NS	411	205	206
	Mahmoodpoor A (2019) [229]	Critically ill patients with ARDS	Double blind	IV NaSe: 4 mg loading dose, then 1 mg q12h × 3d, then 1 mg/day × 6d	NS	40	20	20
	Laaf E (2022) [230]	Adults undergoing LVAD implantation surgery with CPB	Double blind	Se 300 ug PO preop, 3000 ug IV at induction, 1000 ug daily x14 days postop	Placebo	20	10	10
	Stoppe C (2023) [231]	Adults undergoing cardiac surgery with CPB, EuroSCORE II ≥5% or planned combined procedures	Double blind	High-dose Se 2000 μg before CPB, 2000 μg after, 1000 μg daily for max 10 days	Placebo	1394	697	697
Vit D (5)	Leaf DE (2014) [232]	>18 yr, severe sepsis or septic shock, ICU	Double blind	Calcitriol 2 mcg IV (single dose)	NS	67	31	36
	Ginde AA (2019) [233]	Critically ill adult patients with confirmed Vit D deficiency (<20 ng/mL)		Vit D3 540,000 IU orally or via NG/OG tube, single dose within 12 hours of ICU admission	Placebo	1078	540	538
	Bychinin M.V (2022) [234]	ICU patients with severe or critical COVID-19, 25(OH)D <30 ng/mL	Double blind	Vit D3: 60,000 IU weekly + 5,000 IU/day, oral or via feeding tube	Sunflower oil	106	54	52
	Domazet Bugarin J (2023) [235]	Severe COVID-19	Open label	cholecalciferol 10,000 IU/day orally or via gastric tube, for up to 14 days	None	152	77	75
	Ashoor T (2024) [236]	Adult ICU patients with sepsis and vitamin D deficiency, on MV	Double blind	Enteral Vit D D 50,000 IU/day × 5 days	Enteral Vit D 5,000 IU/day × 5 days	75	38	37
Thiamine (7)	Andersen LW (2016) [237]	Adults undergoing CABG with EuroSCORE II > 1.5%	Double blind	Thiamine 200 mg IV before and after surgery	NS	64	33	31
	Donnino MW (2016) [238]	Adults with septic shock, lactate >3, vasopressor-dependent	Double blind	Thiamine 200 mg IV q12h × 7days	5% DW	88	45	43
	Harun NF (2019) [239]	Adults with septic shock and lactate ≥2 mmol/L	Double blind	IV thiamine 200 mg TID for 3 days	NS	65	33	32
	Petsakul S (2020) [240]	Adult patients with septic shock who required a vasopressor within 1–24 h	Double blind	Thiamine 200mg IV q12h × 7 days	5% DW	50	25	25
	Moslemi R (2020) [241]	Adults admitted to ICU after GI surgery	Double blind	IV Thiamine 200 mg/day × 3 days	NS	96	48	48
	Moskowitz A (2023) [242]	Adults with septic shock (vasopressor + lactate >2 + creatinine >1.0)	Quadruple blind	Thiamine 200 mg IV every 12h for 3 days (total 6 doses)	NS	88	46	42
	Donnino MW (2024) [243]	Adult OHCA patients, comatose, lactate ≥ 3 mmol/L within 4.5 hr post-ROSC	Double blind	Thiamine 500 mg IV q12h for 2 days	NS	76	36	40
NAC (5)	Najafi A (2014) [244]	Adults with sepsis and multiple trauma requiring MV	Double blind	IV NAC 3g every 6 hr for 72 hr (total 12g/day)	SC	39	18	21
	Hamamsy ME (2019) [245]	Adults (18–80 yrs) undergoing elective colon surgery requiring ICU	Double-blind	NAC IV: 100 mg/kg loading dose, then 50 mg/kg/day × 48 hr	5% DW	60	30	30
	Taher A (2021) [246]	ICU patients with mild-to-moderate COVID19-associated ARDS	Double blind	NAC 40 mg/kg/day IV for 3 days	5% DW	92	45	47
	Gamarra-Morales Y (2023) [247]	critically ill patients with COVID-19	Prospective, analytical	NAC IV (loading 150 mg/kg + maintenance)	None	140	68	72
	Rahimi A (2023) [248]	ICU-admitted adults with severe COVID-19	Single blind	IV NAC 300 mg/kg single dose	Placebo	40	20	20
Others (11)	Heyland D (2013) [249]	Critically ill adults with MOD and ≥2 organ failures within 24h of ICU admission	Double blind	IV/EN antioxidnats (with/without IV GLN 0.35 g/kg)	Placebo or IV GNL 0.35 g/kg	1218	617	601
	Hejazi N (2018) [250]	ICU patients aged 18 years or older, who were candidates for enteral feeding and expected to stay in ICU for at least seven days	double blind	ALA 900 mg/day PO, for 10 days	placebo	72	35	37
	Cherukuri L (2019) [251]	Adults with severe sepsis or septic shock	Double blind	Vit A 100,000 IU IM daily × 7 days	Placebo	64	32	32
	Hasanloei MAV	Adult patients (age: 18–65 yr)	Double blind	CoEnz Q10 400 mg/day,	Placebo	40	20	20

	(2021) [252]	with an expected need of MV for at least 48 hr and at least 7 d stay in the ICU and GCS ≥7		sublingual (100 mg q6h), 7 days				
	Yahyapoor F (2022) [253]	Critically ill adult ICU patients	Double blind	L-Carnitine 3 g/day, enteral, 3 divided doses for 7 days	Distilled water	51	27	24
	Zhong M (2022) [254]	Critically ill adults with COVID-19	Single blind	ALA (1200 mg/d IV infusion once daily for 7 days)	NS	17	8	9
	Patel JJ (2023) [255]	Adults with septic shock, on norepinephrine ≥0.10 μg/kg/min	Double-blind	5 g IV Vit B_{12} (single 15-min infusion)	NS	20	10	10
	Kim M (2023) [256]	Adults (18–80) with aneurysmal SAH admitted to ICU	Single blind	IV NAC 2,000 mg/day + Se 1,600 μg/day for 14 days	Placebo	103	50	53
	Majidi N (2024) [257]	Adult ICU patients with severe COVID-19	Double blind	Vitn B complex IV	Placebo	85	45	40
	Aghasadeghi MR (2024) [258]	Hospitalized adults with COVID-19, oxygen sat ≤94%, ICU subgroup	Open label	Oral Spirulina 15.2 g/day × 6 days	SC	99	52	47
	Makiabadi E (2024) [259]	Adult patients undergoing elective CABG with CPB	Double blind	Pre-op: Vit E 1200 IU + Zinc 120 mg (1 day before) Post-op: Vit E 200 IU/day + Zinc 30 mg/day for 3 weeks	None	78	38	40

Vit, vitamin; RCT, randomized controlled trial; Inter., intervention; Con., control; AAA, abdominal aortic aneurysm; ICU, intensive care unit; IV, intravenous; AA, ascorbic acid; NS, normal saline; MAP, mean arterial pressure; NE, norepinephrine; DW, dextrose water; CABG, coronary artery bypass graft; CABG, coronary artery bypass grafting; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; CPB, cardiopulmonary bypass; SC, standard care; EuroScore, European System for Cardiac Operative Risk Evaluation; IU, international unit; TRALI, transfusion related acute lung injury; LD, low dose; ECC, extracorporal circulation; OHCA, out of hospital cardiac arrest; MSAP, moderate severe acute pancreatitis; SAP, severe acute pancreatitis; PN, parenteral nutrition; Se, selenium; SIRS, systemic inflammatory response syndrome; APACHE, Acute Physiological and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; NaSe, sodium selenite; ARDS, acute respiratory distress syndrome; LVAD, left ventricular assist device; CPB, cardiopulmonary bypass; NG, nasogatric; OG, orogastric; GI, gastrointestinal; ROSC, recovery of spontaneous circulation; NAC, n-acetylcysteine; GLN, glutamin; ALA, α-lipoic acid; IM, intramuscular; SAH, subarachnoid hemorrhage.