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CLINICAL OBSERVATIONS

Severe vitamin C deficiency associated with continuous renal replacement therapy: A case report

Ryan Burslem RD[1] | **Susan Roberts DCN, RDN**[1] | **Kapil Rajwani MD**[2] | **Jane Ziegler DCN, RDN**[1]

[1]Department of Clinical and Preventive Nutrition Sciences, Rutgers University, Newark, New Jersey, USA

[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Weill Cornell Medical College, New York, New York, USA

Correspondence
Ryan Burslem, RD, Department of Clinical and Preventive Nutrition Sciences, Rutgers University, 65 Bergen St, Suite 157, Newark, NJ 07107-1709, USA.
Email: rburslem@shp.rutgers.edu

Abstract

Hypovitaminosis C is prevalent in critically ill patients. Continuous renal replacement therapy (CRRT) clears vitamin C, increasing the risk for vitamin C deficiency. However, recommendations for vitamin C supplementation in critically ill patients receiving CRRT vary widely, from 250 mg/day to 12 g/day. This case report describes a patient who developed a severe vitamin C deficiency after prolonged CRRT despite receiving ascorbic acid (450 mg/day) supplementation in her parenteral nutrition. This report summarizes recent research investigating vitamin C status in critically ill patients receiving CRRT, discusses the patient case, and provides recommendations for clinical practice. In critically ill patients receiving CRRT, the authors of this manuscript suggest providing at least 1000 mg/day of ascorbic acid to prevent vitamin C deficiency. Baseline vitamin C levels should be checked in patients who are malnourished and/or have other risk factors for vitamin C deficiency, and vitamin C levels should be monitored thereafter every 1–2 weeks.

KEYWORDS

continuous renal replacement therapy, critical care, intensive care unit, vitamin C

BACKGROUND

Vitamin C is an essential micronutrient with physiologic roles including protection against reactive oxygen species and involvement in gene transcription, gene translation, and the synthesis of catecholamines, collagen, and carnitine.[1] The recommended daily intake of vitamin C is 90 mg/day for men and 75 mg/day for women.[2] In healthy adults, vitamin C deficiency can develop within a month with vitamin C intake of <10 mg/day.[2] Signs of hypovitaminosis C, defined as a plasma vitamin C level between 11 and 23 μmol/L (Table 1), include fatigue, malaise, and gum inflammation.[2] Ongoing inadequate vitamin C intake leads to vitamin C deficiency, also known as scurvy, defined as a plasma vitamin C level of <11 μmol/L.[1] A major implication of scurvy is impaired collagen synthesis, resulting in poor wound healing and bleeding (eg, bleeding gums, petechiae, ecchymoses).[1,2] Additional signs include hyperkeratosis, corkscrew hairs, joint pain, and depression.[2] Scurvy is fatal if left untreated.[1] Treatment for scurvy is individualized with ascorbic acid dosage recommendations ranging from 100–300 mg/day orally to

TABLE 1 Reference ranges for plasma vitamin C levels.[3,4]

Range, μmol/L	Interpretation
<11	Deficient
11–23	Hypovitaminosis C
>23	Sufficient

300–1000 mg/day intravenously.[5] Most signs of scurvy resolve within days to a few weeks after initiation of vitamin C supplementation.[6]

Vitamin C metabolism is altered in critical illness; as such, vitamin C requirements established for healthy individuals do not apply to critically ill patients. A study of 44 critically ill patients meeting the recommended daily intakes of vitamin C for healthy individuals found that 68% of patients had hypovitaminosis C, with 32% classified as having a vitamin C deficiency (Table 1).[7] A pharmacokinetic trial of vitamin C dosing in critical illness randomized patients to receive intravenous (IV) ascorbic acid as 2 g/day continuously, 2 g/day as two 1-g boluses, 10 g/day continuously, or 10 g/day as two 5-g boluses.[8] Whereas the 10-g/day infusions led to supratherapeutic levels, the 2-g/day infusions normalized plasma vitamin C concentrations.[8] As such, critically ill patients have higher vitamin C requirements compared with healthy individuals, although the exact requirements depend on disease- and treatment-related factors.

A subset of critically ill patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) has received increased attention regarding micronutrient deficiencies. AKI is a common complication of critical illness associated with a hypermetabolic, proinflammatory state that may require treatment with renal replacement therapy (RRT).[9] CRRT offers more gradual fluid removal than other RRT modalities and is often employed for patients who have hypotension and/or hemodynamic instability.[10] CRRT effectively clears solutes, placing patients receiving CRRT at risk for nutrient deficiencies.[11]

Significant clearance of vitamin C has previously been detected in CRRT effluent,[12] which may be influenced by several factors. First, there are three primary CRRT modalities: continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). These modalities refer to the use of convection and/or diffusion to clear solutes from the blood.[13] Convection utilizes a hydrostatic pressure gradient in which solutes are "dragged" with the flow of water across a semipermeable hemofilter membrane.[13] Diffusion occurs through the passage of solutes across a dialysis membrane via a concentration gradient.[13] Both processes yield an effluent with the cleared solutes.[13] CVVH uses convection, CVVHD uses diffusion, and CVVHDF uses both convection and diffusion.[13] The use of convection vs diffusion influences which solutes are cleared from the blood. Diffusion clears low-molecular-weight solutes but does not effectively remove medium-molecular-weight solutes.[13] Convection clears low- and medium-molecular-weight solutes, but the clearance is also dependent on the porosity size of the hemofilter.[13] A study investigating the impact of convection vs diffusion on vitamin C clearance found that diffusion accounted for two-thirds of vitamin C losses, whereas convection accounted for one-third of losses.[14] As such, CVVHD and CVVHDF may clear vitamin C at higher rates relative to CVVH.

A second factor affecting solute clearance is the solute's sieving coefficient (SC), defined as the effluent-to-serum solute concentration ratio, ranging from 0 to 1.[15] Factors influencing a solute's SC include the physical properties of the solute (eg, size, electric charge), degree of protein binding, and RRT-related factors such as filter porosity size and filter adsorption.[15] (Of note, SC refers to hemofiltration used in CVVH and CVVHDF, whereas saturation coefficient, which has slightly different factors affecting solute removal, refers to hemodialysis.) Reported SCs for vitamin C have ranged from 0.83 to 1.0,[15,16] suggesting vitamin C is readily cleared by CRRT. Finally, the effluent flow rate and duration of therapy also affect solute clearance.[9,13,15]

Whereas vitamin C clearance by CRRT is known, vitamin C supplementation recommendations vary widely, from 250 mg/day[9] to 12 g/day.[17] Some recommendations suggest avoiding supplementing >250 mg/day to reduce the risk of nephrotoxic oxalate deposition in the kidneys,[9] whereas others contend that higher doses of supplementation are required to overcome the net negative balances induced by CRRT.[17] The European Society for Clinical Nutrition and Metabolism (ESPEN) clinical practice guidelines comment that patients receiving CRRT may develop severe micronutrient deficiencies and that vitamin C status should be monitored and supplemented based on serum levels and effluent losses, although they do not comment on specific dosage recommendations.[11,18]

A patient developed a severe vitamin C deficiency after receiving prolonged CRRT despite receiving ascorbic acid supplementation of 450 mg/day in her parenteral nutrition (PN). This report discusses the patient case, summarizes recent literature describing vitamin C status in critically ill patients receiving CRRT, and provides recommendations for clinical practice.

CASE STUDY

The patient was a 62-year-old woman with a medical history including end-stage renal disease requiring intermittent hemodialysis and Crohn's disease with multiple bowel resections, most recently complicated by an enterocutaneous fistula after jejunal exclusion and venting percutaneous gastrostomy, receiving home PN. She presented to the hospital with complaints of dyspnea, fatigue, and myalgias and was found to have coronavirus disease 2019. She had a prolonged hospitalization with numerous complications, including central line–associated bloodstream infection, atrial fibrillation with rapid ventricular response warranting transfer to the intensive care unit, a large pericardial effusion complicated by tamponade after intubation and emergent pericardiocentesis, ventilator-associated pneumonia after tracheostomy placement, and AKI requiring CRRT using CVVHD, which was started 39 days into her admission. CRRT was administered using a high-permeability, glycerin-free, polyethersulfone membrane (NxStage acute care cartridge; NxStage Medical Inc). At the time of CRRT initiation, her PN was supplemented with 250 mg/day ascorbic acid in addition to 200 mg/day ascorbic acid from PN multivitamin for a total of 450 mg/day. Owing to a total bilirubin level >2 mg/dl, copper and manganese were withheld from her PN by removing the trace element injection and supplementing back 60 mcg selenium, 10 mcg chromium, and 5 mg zinc as per institutional guidelines. She continued to receive CRRT for most of the following 138 days. The CRRT dose varied over the course of her hospitalization but was typically prescribed between 18 and 30 ml/kg/h.

One-hundred thirty-six days into her admission, she had worsening skin breakdown and minor bleeding from an abdominal wound and around her tracheostomy site. She had been receiving prophylactically dosed heparin for deep vein thrombosis (5000 units subcutaneously every 8 h); this treatment was paused, but the bleeding continued. Her international normalized ratio was normal, and there was no significant thrombocytopenia. Given her risk for micronutrient deficiencies, nutrient level measurements (including vitamin C) were ordered to assess for deficiencies. For simplicity, this text will refer to the day of measurement as day 1. At the patient's institution, plasma vitamin C measurements take up to 6 days to process. Over the course of several days while these blood samples were being processed, the bleeding from her abdominal wound increased and did not respond to medical and nursing interventions. On day 5, the plasma vitamin C level measurement indicated vitamin C deficiency (6 μmol/L; reference range, 23–114 μmol/L). The C-reactive protein (CRP) level was not measured. On this day, her ascorbic acid dose was increased as follows: 700 mg/day in her PN (including 200 mg/day from PN multivitamin) plus 500 mg given twice daily enterally for a total of 1700 mg/day. The following day, this was converted entirely to 1700 mg/day in her PN (200 mg/day from PN multivitamin plus an additional 1500-mg supplementation). On day 6, the bleeding from her abdominal wound and around her tracheostomy site had improved, and by day 7, the bleeding had fully resolved. The improvement was attributed to treatment of a severe vitamin C deficiency.

On day 16, a repeated measurement of vitamin C showed supratherapeutic levels (150 μmol/L). Given these results and that the patient was being transitioned from CRRT to intermittent hemodialysis in which vitamin C clearance would be lower, the ascorbic acid supplementation in her PN was held, and she received only 200 mg/day ascorbic acid via her PN multivitamin.

On day 26, the patient was transitioned back to CRRT, and as such, ascorbic acid was increased in her PN for a total of 700 mg/day to target a dose between one that yielded deficient and one that yielded supratherapeutic levels. On day 29, a repeat vitamin C measurement resulted in 26 μmol/L. The patient continued to receive 700 mg/day ascorbic acid via PN, with plans to serially monitor vitamin C levels every 1–2 weeks. On day 31, a repeat vitamin C test was ordered, which later showed levels below the reference range (15 μmol/L). At this point, the patient's family elected to transition the patient to comfort care, and the patient died shortly thereafter.

In addition to vitamin C, several other micronutrient levels were measured (Table 2). The most notable results were a copper deficiency found on day 7 (<10 μmol/dl; reference range, 80–155 μmol/dl) and a vitamin B_6 deficiency found on day 15 (15.2 nmol/L; reference range, 20–125 nmol/L). The vitamin B_6 deficiency was treated with 25 mg/day pyridoxine supplemented in her PN for 1 week, which resulted in improvement to normal levels (34.2 nmol/L on day 27). Her copper deficiency was initially treated with 1 mg/day copper chloride supplemented in her PN for 5 days, a dose reduced by 50% of the institution's standard repletion guidelines because of a total bilirubin level of >2 mg/dl. A repeat level on day 17 showed copper levels remained undetectable. She was thereafter supplemented with 2 mg/day copper chloride in her PN for an additional 5 days. A repeat copper measurement on day 30 showed improvement, but levels were still deficient (41.7 μmol/dl). By this time, the patient's family had elected to transition the patient to comfort care, as noted.

TABLE 2 Timeline of blood micronutrient levels for patient case.

	Reference range	Day 1[a]	Day 7	Day 12	Day 15	Day 16	Day 17	Day 23	Day 27	Day 30	Day 31
Vitamin C, μmol/L	23–114	6[c] (resulted on day 5)		150 (resulted on day 16)		223 (resulted on day 21)		26 (resulted on day 29)			15[c] (resulted on day 36)
Vitamin B_{12}, pg/ml	211–911										1237
Vitamin B_6, nmol/L	20–125				15.2[c]				34.2		
Thiamin, nmol/L	70–180				196						
Folate, ng/ml	≥5.39										9.04
Copper, μg/dl	80–155		<10[c]				<10[c]			41.7[c]	
Selenium, μg/L	23–190[b]		84.9								65.5[b]
Zinc, μg/dl	60–120	123.8									109.8

[a]Day 1 refers to the first day that a micronutrient level was checked.
[b]The reported reference range for selenium at the patient's institution is 23–190 μg/L. Of note, other agencies have reported 70 μg/L to be the lower limit of selenium's reference range for adults.[19] In this case, the selenium level noted on day 31 would have been below the reference range.
[c]Serum level below the reference range.

LITERATURE REVIEW

Publications from 2013 to 2023 discussing vitamin C status in critically ill patients receiving CRRT are summarized in this section and Table 3. Of note, all studies defined vitamin C deficiency as a plasma level below the reference range and did not specifically distinguish between hypovitaminosis C and vitamin C deficiency.

Kamel et al[25] retrospectively assessed the prevalence of micronutrient deficiencies in 75 critically ill patients receiving CRRT. Micronutrient levels were only included when measured during CRRT treatment.[25] Most patients received PN (89%) as well as CVVH ($n = 39$) or CVVHD ($n = 21$).[25] Within the cohort, 15 patients had vitamin C levels recorded, of whom 12 patients (80%) had a vitamin C deficiency.[25] No patients had received vitamin C supplementation for 7 days before blood draw aside from patients receiving vitamin C from PN multivitamin.[25] The authors concluded vitamin C deficiency is common in critically ill patients receiving CRRT and patients may require aggressive supplementation to prevent deficiencies.[25] A limitation of this study is possible selection bias, as micronutrient levels were measured according to clinician judgment.

Ostermann et al[26] serially measured nutrient levels in 55 critically ill patients with stage 2 or 3 AKI to determine the prevalence of nutrient deficiencies and to calculate nutrient losses induced by CRRT.[26] Blood and effluent nutrient levels were measured for 6 days; blood levels were compared between those receiving and not receiving CRRT (given as CVVH or CVVHD).[26] All patients received full enteral nutrition with or without oral diet; patients receiving PN or IV micronutrients were excluded.[26] Plasma vitamin C levels were lower in the CRRT group compared with the non-CRRT group after 24 h (9.2 vs 16.8 μmol/L; $P = 0.09$) and after 6 days (14.8 vs 17.6 μmol/L; $P = 0.33$).[26] There were no differences in CRP levels between groups.[26] The differences in plasma vitamin C levels were not statistically significant, but this was a pilot study and the results were underpowered.[26] Vitamin C deficiency was common in both groups; comparing patients in the CRRT group with those in the non-CRRT group, 60% vs 78% had vitamin C deficiency on day 0, 83% vs 82% had vitamin C deficiency on day 1, and 88% vs 78% had vitamin C deficiency on day 6.[26] Median vitamin C loss in CRRT effluent over the first 24 h was 395 μmol (interquartile range [IQR], 870 μmol/L), ranging from 0.01 to 4172 μmol/day.[26] When including a third "mixed" group (patients in the CRRT group for whom CRRT was paused during the study period, and patients in the non-CRRT group who received CRRT during the study period), the CRRT group had lower vitamin C levels at day 6 (10.1 μmol/L)

TABLE 3 Recent studies that reported on vitamin C status in critically ill patients receiving CRRT

Study information	Study purpose	Population	Intervention	Outcomes	Conclusions	Limitations of findings
Kamel et al,[20] 2018 Retrospective cohort study United States Funding source: None	To determine the prevalence of micronutrient deficiencies in critically ill patients receiving CRRT.	Patients admitted to ICU at tertiary academic medical center who were referred to nutrition support team and had at least one micronutrient level measured while receiving CRRT ($n = 75$, after 6 dropouts due to lack of micronutrient levels). No specific exclusion criteria. Most patients received CVVH ($n = 39$) or CVVHD ($n = 21$). 89% of patients received PN during hospital course.	Retrospectively reviewed patients who had thiamin, pyridoxine, vitamin C, folate, zinc, and/or copper levels measured while receiving CRRT. No specific protocol for micronutrient monitoring during study period.	15 patients had vitamin C levels measured. 12 patients (80%) had vitamin C deficiency. No patients with vitamin C deficiency had received ascorbic acid supplementation in PN within 7 days before blood draw.	Critically ill patients receiving CRRT had a high prevalence of vitamin C deficiency and may require aggressive supplementation to prevent deficiency.	- Possible selection bias. - Baseline vitamin C levels before CRRT not recorded. - Vitamin C levels measured at varying time points during CRRT treatment. - Vitamin C level in effluent not measured.
Ostermann et al,[21] 2020 Prospective cohort study United Kingdom Funding source: None	To serially measure serum nutrient levels in critically ill patients with stage 2 or 3 AKI who were receiving CRRT compared with those not receiving CRRT, to determine the prevalence of nutrient deficiencies, and to calculate nutrient losses induced by CRRT.	Adult ICU patients ($n = 55$, after 8 dropouts) with stage 2 or 3 AKI in two tertiary care hospitals receiving full EN ± oral diet. CRRT given as CVVH or CVVHD. Relevant exclusion criteria: Baseline dialysis dependence; receiving IV micronutrients; and receiving PN. CRRT ($n = 33$), mean ± SD: - APACHE II: 20.4 ± 5.3 - SOFA: 8.3 ± 2.6 Non-CRRT ($n = 24$), mean ± SD: - APACHE II: 18.3 ± 5.1 - SOFA: 7.6 ± 2.1 No difference in APACHE II, SOFA, or CRP levels between groups.	Blood and CRRT effluent samples of selenium, zinc, copper, iron, vitamin B_{12}, vitamin C, vitamin D, folate, carnitine, thiamin, vitamin B_6, and amino acids collected at baseline, 22–26 h, 46–50 h, 94–98 h, and 142–146 h after enrollment. Blood nutrient levels were compared against reference ranges over the study period. Blood nutrient levels compared between CRRT and non-CRRT groups at 24 h and 6 days after enrollment. Daily nutrient effluent losses calculated by multiplying nutrient concentration in effluent by daily CRRT dose.	Median plasma vitamin C levels in CRRT vs non-CRRT groups: - After 24 h: 9.2 vs 16.8 μmol/L ($P = 0.09$) - After 6 days: 14.8 vs 17.6 μmol/L ($P = 0.33$) - After 6 days, including third "mixed" group: 10.1 vs 19.0 vs 19.3 μmol/L ($P = 0.7$) Median (IQR) vitamin C loss during first 24 h: 395 (870) μmol (range, 0.01–4172 μmol)Patients with vitamin C deficiency, CRRT vs non-CRRT: - Day 0: 60% vs 78% - Day 1: 83% vs 82% - Day 4: 92% vs 85% - Day 6: 88% vs 78%	In critically ill patients with stage 2 or 3 AKI, most had vitamin C deficiency. CRRT cleared vitamin C, and plasma vitamin C levels were lower in the CRRT group compared with the non-CRRT group, although these differences were not significant.	- Study was underpowered to detect differences between groups. - Some patients in CRRT group had CRRT postponed during study period (and vice versa), confounding the results. - Vitamin C levels before CRRT initiation not explicitly reported. - Patient numbers in groups not reported consistently.

(Continues)

TABLE 3 (Continued)

Study information	Study purpose	Population	Intervention	Outcomes	Conclusions	Limitations of findings
Schneider et al,[22] 2021 Prospective cohort study France Funding source: National grant from French Ministry of Health in the National Hospital Programme for Clinical Research	Observational study within an RCT to measure nutrient levels in patients with sepsis receiving CRRT and to assess their relationship with CRRT dose.	Adult patients with septic shock and stage 2 or 3 AKI ($n = 57$) in a tertiary ICU receiving CVVH at a dose of 35 ml/kg/h or 70 ml/kg/h. Most receiving surgical treatment for abdominal sepsis. Relevant exclusion criteria: End-stage renal disease. Patients missing >33% of values and only having baseline measurements excluded, resulting in final $n = 30$.	Patients randomized to CRRT dose of 35 ml/kg/h or dose 70 ml/kg/h for 96 h reduced to 35 ml/kg/h thereafter. CRRT could be discontinued per clinician judgment. Patients received nothing by mouth for 48 h; then, PN was initiated with standard vitamins/trace elements (provided 125 mg/day ascorbic acid). Alanine, glutamine, valine, vitamin A, and vitamin C levels measured at days 0, 4 (end of intervention period), and 8. Nutrient levels over the course of study period compared between groups.	Mean serum vitamin C level, day 0: 11 μmol/L (reference range: 25–100 μmol/L). Below reference range in 100% of patients. Mean serum levels on day 4 significantly lower than day 0 ($P < 0.01$). No significant difference between CRRT groups, including when adjusting for CRP levels. No significant difference in levels comparing day 0 with day 8.	In adult patients with septic shock and stage 2 AKI, CRRT led to a significant decline in vitamin C levels. There was no difference in vitamin C levels based on CRRT dose. Supplementation is recommended.	- Serum vitamin C levels not explicitly reported aside from mean total sample at day 0. - No discussion regarding lack of difference in vitamin C levels between days 0 and 8. - Vitamin C levels in effluent not measured. - 47% of patients were missing data.
Gundogan et al,[23] 2022 Prospective cohort study Turkey Funding source: Grant from Erciyes Üniversitesi	To prospectively measure micronutrient levels in critically ill patients receiving CRRT.	Adult ICU patients with AKI requiring CRRT for >24 h ($n = 50$). All patients received CVVHDF. Relevant exclusion criteria: History of CKD requiring hemodialysis or kidney transplant and history of gastric bypass. APACHE II, median (IQR): 24.0 (6.0–33.0) SOFA, median (IQR): 8.0 (6.0–10.0)Moderate inflammation (CRP, 11–80 mg/L): $n = 18$;	Vitamin B_6, folate, vitamin C, ceruloplasmin, chromium, copper, selenium, and zinc levels measured at 10–15 min before CRRT initiation, 24 h and 72 h after CRRT initiation, and 24 h and 48 h after CRRT discontinuation (final $n = 9$). Only patients given PN received micronutrient supplementation	Vitamin C levels, median (IQR), mg/L (reference range: 4–15 mg/L) with P values compared with baseline: - Baseline: 2.42 (1.39–4.42) - 24 h during CRRT: 1.69 (0.64–3.93; $P = 0.030$) - 72 h during CRRT: 0.71 (0.40–1.56; $P = 0.001$) - 24 h after CRRT: 1.07 (0.67–2.41; P value not significant) - 48 h after CRRT: 0.83 (0.57–1.50; $P = 0.021$)	In adult ICU patients receiving CRRT, vitamin C levels were low at baseline, but CRRT led to significant reductions in vitamin C levels, which remained low after CRRT discontinuation. Recommend ensuring adequate vitamin C	- Vitamin C levels in effluent not measured. - High attrition rate.

TABLE 3 (Continued)

Study information	Study purpose	Population	Intervention	Outcomes	Conclusions	Limitations of findings
		Severe inflammation (CRP, >80 mg/L): $n = 32$ Patients receiving nutrition at CRRT initiation: - None: 35 (70%) - Oral diet: 3 (6%) - EN: 8 (16%) - PN: 4 (8%)	(125 mg/day ascorbic acid).	- $P < 0.001$ for differences between all time points. Median (IQR) vitamin C levels (mg/L) in severe vs moderate inflammation: 1.89 (0.33–11.64) vs 2.87 (1.25–17.77), $P = 0.077$	provision early in patient course and monitoring vitamin C levels.	
Fah et al,[24] 2022 Retrospective cohort study United States Funding source: Grants from the National Institutes of Health, Canadian Institutes of Health Research, Baxter, and Fresenius	Single-center retrospective cohort study to assess the prevalence of micronutrient deficiencies in critically ill patients at risk for malnutrition and to compare prevalence between those receiving and not receiving CRRT.	Adult patients ($n = 106$) admitted to ICU who had at least one micronutrient level measured and were at risk for malnutrition, defined as having one of the following risk factors: CRRT; protein-calorie malnutrition diagnosis per AND/ASPEN criteria; GI malabsorption; GI surgery; history of alcohol use disorder. Patients with a history of metabolic disorders associated with micronutrient deficiencies were excluded.	Retrospective review of patients who had at least one of the following measured: carnitine, copper, zinc, selenium, thiamin, vitamin B_6, folate, and vitamin C. For patients in CRRT group, levels were only included if level was measured while patient was receiving CRRT or after CRRT was discontinued (latter constituting 7% of patients). No specific protocol for micronutrient monitoring during study period.	35 patients had vitamin C levels measured; 29 patients in CRRT group, 6 patients in non-CRRT group. 44.8% of patients in CRRT group had vitamin C deficiency, greater than in non-CRRT group (16.7%; difference, $P = 0.41$). No patients had received vitamin C supplementation. Mean ± SD vitamin C level: 0.06 ± 0.05 mg/dl (reference range: 0.2–2.0 mg/dl)	In adult patients who were admitted to an ICU and at risk for malnutrition, vitamin C deficiency was more prevalent in patients receiving CRRT than those not receiving CRRT. CRRT initiation increases the risk for vitamin C deficiency.	- Possible selection bias. - Baseline vitamin C levels before CRRT not recorded. - Vitamin C levels measured at varying time points during or after CRRT treatment. - Underpowered to detect differences between groups. - CRRT modality not disclosed.

Abbreviations: AND/ASPEN, Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition; AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; EN, enteral nutrition; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; PN, parenteral nutrition; RCT, randomized controlled trial; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

relative to the non-CRRT group (19.0 μmol/L) and mixed group (19.3 μmol/L), although the difference remained insignificant ($P = 0.7$).[26] The authors concluded that vitamin C levels were low in critically ill patients with stage 2 or 3 AKI regardless of treatment with CRRT and that although vitamin C was removed by CRRT, there was no difference in vitamin C levels between the CRRT and non-CRRT groups.[26] Aside from the underpowered results, a limitation of this research is that many patients switched groups during the study period (patients in the CRRT group had CRRT postponed during the study period, and vice versa).

As part of a larger randomized controlled trial, Schneider et al[27] prospectively measured nutrient levels in 30 patients with sepsis receiving CRRT and assessed the relationship between nutrient levels and CRRT dose. Patients were randomized to a CVVH dose of either 35 or 70 ml/kg/h for 4 days, after which the dose was adjusted to 35 ml/kg/h for both groups.[27] CRRT could be discontinued at any point per clinician judgment.[28] Median CRRT duration was 7 days in the 70-ml/kg/h group and 6 days in the 35-ml/kg/h group.[28] Nutrient levels were measured at days 0, 4, and 8 and compared between groups.[27] All patients received nothing by mouth initially for 48 h, after which PN was initiated, providing 125 mg/day ascorbic acid.[27] Vitamin C levels were below the reference range in all patients throughout the study period.[27] The mean plasma level on day 0 was 11 μmol/L and decreased significantly by day 4 ($P < 0.01$).[27] There was no significant difference in vitamin C levels between groups, including when adjusting for CRP levels.[27] The authors concluded that CRRT leads to vitamin C losses and recommended supplementation to prevent deficiencies.[27] Of note, there was no difference in vitamin C levels between days 0 and 8, which was not discussed by the authors[27]; this could possibly be related to CRRT being paused for some patients.

Gundogan et al[20] prospectively measured micronutrient levels in 50 critically ill patients receiving CVVHDF. Micronutrient levels were measured 10–15 min before CRRT initiation, 24 h and 72 h after CRRT initiation, and 24 h and 48 h after CRRT discontinuation.[20] Only patients receiving PN ($n = 4$) received ascorbic acid supplementation of 125 mg/day as part of the PN multivitamin.[20] Median (IQR) vitamin C levels (μmol/L) were as follows, respectively: 13.8 (7.9–25.1); 9.6 (3.6–22.3); 4.0 (2.3–8.9); 6.1 (3.8–13.7); and 4.7 (3.2–8.5).[20] The differences between all time points were significant ($P < 0.001$), with specific significant differences between baseline levels and 24 h after CRRT initiation, 72 h after CRRT initiation, and 48 h after CRRT discontinuation.[20] In a subgroup analysis of patients that was based on CRP level, patients with severe inflammation (CRP, >80 mg/L) had lower vitamin C levels than patients with moderate inflammation (CRP, 11–80 mg/dl), although this difference was not significant (10.7 vs 16.3 μmol/L, respectively; $P = 0.077$). The authors concluded that vitamin C levels in critically ill patients receiving CRRT were low at baseline but that CRRT led to significant reductions in vitamin C levels, which remained low after CRRT discontinuation.[20]

Finally, Fah et al[3] retrospectively assessed the prevalence of micronutrient deficiencies in 106 critically ill patients at risk for malnutrition, in both those receiving and those not receiving CRRT. The CRRT modality was not reported.[3] For patients receiving CRRT, micronutrient levels were only included if the level was measured while the patient was receiving CRRT or after CRRT was discontinued (the latter constituting 7% of patients).[3] Thirty-five patients had vitamin C levels measured: 29 patients in the CRRT group and 6 patients in the non-CRRT group.[3] Vitamin C deficiency was more prevalent in the CRRT group (44.8% of patients) than in the non-CRRT group (16.7% of patients).[3] The difference was not statistically significant ($P = 0.41$), although the study was underpowered.[3] No patients received vitamin C supplementation.[3] The mean (standard deviation [SD]) plasma vitamin C level in CRRT patients was 3.4 ± 2.8 μmol/L (reference range, 28–85 μmol/L).[3] The authors concluded that vitamin C deficiency was more prevalent in patients receiving CRRT than in those not receiving CRRT and that CRRT increases the risk for vitamin C deficiency.[3] Similar to the study by Kamel et al,[25] a limitation includes possible selection bias, as micronutrient levels were measured per clinician judgment.

Of note, all studies defined vitamin C deficiency as a plasma level below the reference range but did not differentiate between hypovitaminosis C and vitamin C deficiency, which are typically defined as plasma levels <23 μmol/L and <11 μmol/L, respectively (Table 1).[7,21,22] Additionally, studies typically provided incomplete details regarding the handling and analysis of the blood samples. Improper handling or analysis of vitamin C samples may lead to inaccurate results; Collie et al[21] provide recommendations for proper procedures.

In summary, vitamin C levels are low at baseline in critically ill patients with AKI. CRRT removes vitamin C, which could lead to significant reductions in plasma vitamin C levels and increase the risk for vitamin C deficiency.

DISCUSSION AND APPLICATIONS TO PRACTICE

In the case described in this article, a critically ill patient on prolonged CRRT developed a severe vitamin C deficiency despite receiving ascorbic acid supplementation

of 450 mg/day in her PN. It is unclear to what extent the deficiency was due to her chronic critical illness or to her CRRT treatment, although the research summarized in the previous section suggests CRRT was a contributing factor. The deficiency was effectively treated with a dose of 1700 mg/day ascorbic acid, with resolution of bleeding within 2 days. Over the course of 11 days, the 1700-mg/day dosing led to supratherapeutic vitamin C levels, and as such, vitamin C supplementation was reduced. Upon restarting CRRT, the patient was given ascorbic acid supplementation of 700 mg/day; however, this may have been insufficient, as her vitamin C levels dropped back below the reference range.

A pharmacokinetic trial of vitamin C supplementation in critically ill patients (not specifically those receiving CRRT) found that 2 g/day IV ascorbic acid maintained plasma vitamin C levels within reference range (which the authors defined as between 21 and 100 μmol/L).[8] In a follow-up letter from their group, the authors calculated a daily vitamin C loss of 830 mg/day in a patient receiving CVVH.[16] By contrast, a follow-up letter from Ostermann et al found a mean ± SD daily loss of 100.5 ± 15.3 mg/day, or 59.0 ± 9.2 mg/day when standardized to an effluent flow rate of 25 ml/kg/h.[15] The variability in reported vitamin C losses is likely due, in part, to CRRT-related factors discussed earlier that affect vitamin C clearance.

One factor making the assessment of vitamin C status during critical illness challenging is that plasma vitamin C levels are affected by the systemic inflammatory response seen in critical illness. A recent systematic review of patients with acute or chronic tissue injury found vitamin C levels declined significantly in association with increasing CRP levels.[29] Plasma vitamin C levels declined by 50%–60% in the setting of severe inflammation (CRP > 80 mg/L); by contrast, vitamin C levels in patients with minor inflammation (CRP < 10 mg/L) were within reference range in eight of eight studies reviewed.[29] In one study of patients undergoing elective hip arthroplasty, vitamin C levels dropped by 74% postoperatively coinciding with a rise in CRP levels, suggesting that the decline in vitamin C levels is related to an increased rate of vitamin C depletion and redistribution to other body compartments rather than an acute decline in vitamin C intake.[23] The decline in vitamin C levels may partly be an adaptive response, and as such, the benefits of vitamin C supplementation are unclear.[24] This may explain, in part, why recent trials of vitamin C supplementation in critically ill patients have yielded mixed outcomes.[4] Nonetheless, plasma vitamin C levels remain the most common method of assessing vitamin C status.[29] Of note, total vitamin C levels (ascorbic acid plus dehydroascorbic acid levels) have been recommended as a more accurate measure of vitamin C status than ascorbic acid levels alone,[21] although dehydroascorbic acid levels were not available for measuring at the patient's institution.

On the basis of this case and the research published thus far, the authors of this manuscript suggest providing at least 1000 mg/day ascorbic acid to patients receiving CRRT to prevent deficiency. Baseline total vitamin C levels should be checked in patients who are malnourished and/or have other risk factors for vitamin C deficiency, and vitamin C levels should be monitored thereafter at least every 1–2 weeks. Clinicians should measure CRP levels to assist with interpretation of the plasma level. CRP levels <10 mg/dl have been associated with normal vitamin C levels[29]; as such, plasma vitamin C levels during mild inflammation may be valid indicators of vitamin C status, whereas levels in patients with moderate or severe inflammation should be interpreted more cautiously. Next, clinicians should avoid excessive doses of vitamin C, which have pro-oxidant properties and may be harmful.[1] High doses of vitamin C increase the risk of calcium oxalate stones[30] and thus should be administered cautiously in patients with a history of nephrolithiasis. High doses of IV vitamin C can also yield falsely elevated glucose readings via point-of-care testing.[31] Finally, clinicians should consider the route of vitamin C administration. Depending on the dosage, IV repletion may be needed, as enteral absorption of vitamin C is saturable.[32] At low doses, the bioavailability of oral vitamin C is 100%; this declines at doses of >500 mg.[32]

Further research is needed to better measure vitamin C clearance by CRRT and assess how CRRT-related factors (including modality and dosage) affect vitamin C clearance. Results of these studies could guide more specific recommendations for vitamin C supplementation. Studies should also compare measurement of plasma vitamin C levels with CRP levels and report procedures used for sample handling and analysis to assure accurate results. Finally, research could investigate the impact of vitamin C supplementation on clinical outcomes.

Although vitamin C has been the focus of this manuscript because of the increased attention vitamin C has received in critically ill patients and the clear implications of the patient's case, it is important to note that CRRT has been associated with other micronutrient deficiencies (see the summarized articles and clinical practice guidelines for further details[3,11,18,20,25–27]). In the case described in this article, the patient also had copper and vitamin B6 deficiencies. The copper deficiency likely developed from complete withholding of copper for

several months. Institutional guidelines have since been updated to recommend routine monitoring of serum copper levels in patients for whom copper is withheld from PN. Although the copper deficiency based on serum laboratory work was quite significant, there were no clinical signs that could clearly be attributed to the copper deficiency, nor did these potential signs (including a macrocytic anemia) show improvement with copper repletion.

CONCLUSION

Plasma vitamin C levels are low in critically ill patients owing to increased rates of depletion and redistribution secondary to the systemic inflammatory response. CRRT clears vitamin C from the blood which increases the risk for vitamin C deficiency. In the case of a critically ill patient receiving prolonged CRRT, supplementation with 450 mg/day IV ascorbic acid was inadequate to prevent a severe vitamin C deficiency. Critically ill patients receiving CRRT require vitamin C supplementation. Monitoring of vitamin C status should be a practice standard.

AUTHOR CONTRIBUTIONS

Ryan Burslem contributed to the conception and design of the manuscript; Susan Roberts, Kapil Rajwani, and Jane Ziegler contributed to the design of the manuscript; Ryan Burslem contributed to the acquisition, analysis, and interpretation of the data; and Ryan Burslem drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be fully accountable for ensuring the integrity and accuracy of the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Ryan Burslem http://orcid.org/0000-0003-4319-8275

REFERENCES

1. Doseděl M, Jirkovský E, Macáková K, et al. Vitamin C-sources, physiological role, kinetics, deficiency, use, toxicity, and determination. *Nutrients*. 2021;13(2):615. doi:10.3390/nu13020615
2. National Institutes of Health. *Vitamin C: fact sheet for health professionals*. Accessed November 16, 2022. https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/#h7
3. Fah M, Van Althuis LE, Ohnuma T, et al. Micronutrient deficiencies in critically ill patients receiving continuous renal replacement therapy. *Clin Nutr ESPEN*. 2022;50:247-254. doi:10.1016/j.clnesp.2022.05.008
4. Dresen E, Lee ZY, Hill A, Notz Q, Patel JJ, Stoppe C. History of scurvy and use of vitamin C in critical illness: a narrative review. *Nutr Clin Pract*. 2023;38(1):46-54. doi:10.1002/ncp.10914
5. Ascorbic acid. Lexi-Drugs. Lexicomp; 2022. Accessed November 20, 2022. http://online.lexi.com/
6. Hirschmann JV, Raugi GJ. Adult scurvy. *J Am Acad Dermatol*. 1999;41(6):895-910. doi:10.1016/s0190-9622(99)70244-6
7. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care*. 2017;21(1):300. doi:10.1186/s13054-017-1891-y
8. de Grooth HJ, Manubulu-Choo WP, Zandvliet AS, et al. Vitamin C pharmacokinetics in critically ill patients. *Chest*. 2018;153(6):1368-1377. doi:10.1016/j.chest.2018.02.025
9. Wiesen P, Van Overmeire L, Delanaye P, Dubois B, Preiser JC. Nutrition disorders during acute renal failure and renal replacement therapy. *JPEN J Parenter Enteral Nutr*. 2011;35(2):217-222. doi:10.1177/0148607110377205
10. Oh WC, Gardner DS, Devonald MAJ. Micronutrient and amino acid losses in acute renal replacement therapy. *Curr Opin Clin Nutr Metab Care*. 2015;18(6):593-598. doi:10.1097/mco.0000000000000220
11. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48-79. doi:10.1016/j.clnu.2018.08.037
12. Story DA, Ronco C, Bellomo R. Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. *Crit Care Med*. 1999;27(1):220-223. doi:10.1097/00003246-199901000-00057
13. Tandukar S, Palevsky PM. Continuous renal replacement therapy. *Chest*. 2019;155(3):626-638. doi:10.1016/j.chest.2018.09.004
14. Morena M, Cristol JP, Bosc JY, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. *Nephrol Dial Transplant*. 2002;17(3):422-427. doi:10.1093/ndt/17.3.422
15. Lumlertgul N, Bear DE, Ostermann M. Clearance of micronutrients during continuous renal replacement therapy. *Crit Care*. 2020;24(1):616. doi:10.1186/s13054-020-03347-x
16. Spoelstra-de Man AME, de Grooth HJ, Elbers PWG, Oudemans-van Straaten HM. Response to "Adjuvant vitamin C in cardiac arrest patients undergoing renal replacement therapy: an appeal for a higher high-dose". *Crit Care*. 2018;22(1):350. doi:10.1186/s13054-018-2200-0
17. Honore PM, De Bels D, Preseau T, Redant S, Attou R, Spapen HD. Adjuvant vitamin C in cardiac arrest patients undergoing renal replacement therapy: an appeal for a higher high-dose. *Crit Care*. 2018;22(1):207. doi:10.1186/s13054-018-2115-9
18. Fiaccadori E, Sabatino A, Barazzoni R, et al. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. *Clin Nutr*. 2021;40(4):1644-1668. doi:10.1016/j.clnu.2021.01.028
19. Centers for Disease Control and Prevention. *Trace elements: selenium*. Accessed April 2, 2023. https://www.cdc.gov/nutritionreport/pdf/nr_ch4b.pdf
20. Gundogan K, Yucesoy FS, Ozer NT, et al. Serum micronutrient levels in critically ill patients receiving continuous renal replacement therapy: a prospective, observational study. *JPEN J Parenter Enteral Nutr*. 2022;46(5):1141-1148. doi:10.1002/jpen.2378

21. Collie JTB, Greaves RF, Jones OAH, Eastwood G, Bellomo R. Vitamin C measurement in critical illness: challenges, methodologies and quality improvements. *Clin Chem Lab Med*. 2020;58(4):460-470. doi:10.1515/cclm-2019-0912
22. Sauberlich HE. Vitamin C status: methods and findings. *Ann NY Acad Sci*. 1975;258:438-450. doi:10.1111/j.1749-6632.1975.tb29302.x
23. Conway FJS, Talwar D, McMillan DC. The relationship between acute changes in the systemic inflammatory response and plasma ascorbic acid, alpha-tocopherol and lipid peroxidation after elective hip arthroplasty. *Clin Nutr*. 2015;34(4):642-646. doi:10.1016/j.clnu.2014.07.004
24. Thurnham DI, Northrop-Clewes CA. Inflammation and biomarkers of micronutrient status. *Curr Opin Clin Nutr Metab Care*. 2016;19(6):458-463. doi:10.1097/mco.0000000000000323
25. Kamel AY, Dave NJ, Zhao VM, Griffith DP, Connor Jr. MJ, Ziegler TR. Micronutrient alterations during continuous renal replacement therapy in critically ill adults: a retrospective study. *Nutr Clin Pract*. 2017;33(3):439-446. doi:10.1177/0884533617716618
26. Ostermann M, Summers J, Lei K, et al. Micronutrients in critically ill patients with severe acute kidney injury—a prospective study. *Sci Rep*. 2020;10(1):1505. doi:10.1038/s41598-020-58115-2
27. Schneider AG, Picard W, Honoré PM, et al. Amino acids and vitamins status during continuous renal replacement therapy: an ancillary prospective observational study of a randomised control trial. *Anaesthesia Crit Care Pain Med*. 2021;40(2):100813. doi:10.1016/j.accpm.2021.100813
28. Joannes-Boyau O, Honoré PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39(9):1535-1546. doi:10.1007/s00134-013-2967-z
29. McMillan DC, Maguire D, Talwar D. Relationship between nutritional status and the systemic inflammatory response: micronutrients. *Proc Nutr Soc*. 2019;78(1):56-67. doi:10.1017/s0029665118002501
30. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol*. 2004;15(12):3225-3232. doi:10.1097/01.Asn.0000146012.44570.20
31. Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. *J Burn Care Res*. 2015;36(1):50-56. doi:10.1097/bcr.0000000000000142
32. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Nat Acad Sci*. 1996;93(8):3704-3709. doi:10.1073/pnas.93.8.3704

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