

Modification of Nutrition Therapy During Continuous Renal Replacement Therapy in Critically Ill Pediatric Patients: A Narrative Review and Recommendations

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Abstract

Introduction: Nutrition is an important part of treatment in critically ill children. Clinical guidelines for nutrition adaptations during continuous renal replacement therapy (CRRT) are lacking. We collected and evaluated current knowledge on this topic and provide recommendations. **Methods:** Questions were produced to guide the literature search in the PubMed database. **Results:** Evidence is scarce and extrapolation from adult data was often required. CRRT has a direct and substantial impact on metabolism. Indirect calorimetry is the preferred method to assess resting energy expenditure (REE). Moderate underestimation of REE is common but not clinically relevant. Formula-based calculation of REE is inaccurate and not validated in critically ill children on CRRT. The nutrition impact of nonintentional calories delivered as citrate, lactate, and glucose during CRRT must be considered. Quantifying nitrogen balance is not feasible during CRRT. Protein delivery should be increased by 25% to compensate for losses in the effluent. Fats are not removed by CRRT and should not be adapted during CRRT. Electrolyte disturbances are frequently present and should be treated accordingly. Vitamins B1, B6, B9, and C are lost in the effluent and should be adapted to the effluent dose. Trace elements, with the exception of selenium, are not cleared in relevant quantities. Manganese accumulation is of concern because of potential neurotoxicity. **Conclusion:** Current recommendations regarding nutrition support in pediatric CRRT must be extrapolated from adult studies. Recommendations are provided, based on the weak level of evidence. Additional research on this topic is warranted. (*Nutr Clin Pract.* 2019;34:37–47)

Keywords

indirect calorimetry; intensive care units; nutrition support; pediatrics; renal replacement therapy

Introduction

Correct prescription of nutrients alters an outcome. Solid guidelines exist on nutrition support therapy in critically ill pediatric patients. Failure to accurately estimate energy requirements has an impact on mortality, infectious complications, and length of hospital stay.¹ Several causes preclude adequate intake of nutrients. Critically ill

children are malnourished in 25% of cases and exhibit an unpredictable metabolic response to critical illness.² The nutrition intake does not always correlate with prescribed goals. Daily enteral nutrition (EN) intake only reached 38% for energy and 43% for protein compared with prescribed goals in an international cohort study.³ Treatment modalities initiated in the intensive care unit (ICU), such as anesthesia,⁴ barbiturate coma,⁵ and hypothermia,⁶

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may significantly influence metabolism and thus nutrition interventions.⁷ Continuous renal replacement therapy (CRRT) also has intrinsic and intricate effects on metabolism. CRRT has not only become standard of care for treating acute kidney failure in ICU patients but also is increasingly used to correct electrolyte disorders and to avoid fluid overload.⁸ Compared with intermittent hemodialysis (IHD) and peritoneal dialysis, it offers more stable hemodynamics with easier and more efficient removal of toxins and fluid.⁹ It works as an extracorporeal circuit in which blood is pumped through a filter. To avoid clotting, anticoagulation can be given either systemically or locally. Heparin can be given systemically or locally, and citrate can be given as a local anticoagulant. When citrate is used, this is usually given in the predilution fluid. The removed fluid is called the effluent and contains not only toxic elements but also proteins, amino acids, vitamins, and trace elements.¹⁰ Usually, this is achieved by convection (continuous venovenous hemofiltration [CVVH]) sometimes combined with diffusion (continuous venovenous hemodiafiltration [CVVHDF]), which uses an extra dialysis fluid flowing in countercurrent of the blood flow.¹¹ Figure 1 shows a schematic representation of such a setup. As nutrients are removed in the effluent, the nutrition approach during CRRT requires careful consideration and close monitoring. We reviewed the literature on nutrition of critically ill pediatric patients treated with CRRT and propose modifications of existing guidelines to optimize feeding in this particular population. Basic nutrition approaches (eg, enteral vs parenteral, somatic growth) that are not expected to be influenced by CRRT will not be the focus of this review. The recommendations are considered “on top of” current nutrition guidelines for critically ill pediatric patients.

Common abbreviations (in alphabetical order)

CO₂: carbon dioxide
 CRRT: continuous renal replacement therapy
 CVVH: continuous venovenous hemofiltration
 CVVHDF: continuous venovenous hemodiafiltration
 EN: enteral nutrition
 IC: indirect calorimetry
 ICU: intensive care unit
 IHD: intermittent hemodialysis
 NB: nitrogen balance
 O₂: oxygen
 PN: parenteral nutrition
 RDI: reference daily intakes
 REE: resting energy expenditure
 VCO₂: CO₂ flow
 VO₂: O₂ flow

Methods

In order to construct this narrative review, questions were formulated to guide the search strategy. The PubMed database was searched for relevant English-language articles using a different combination of terms, depending on which part of the review was being constructed: 1) critical illness, critically ill, ICU intensive care, critical care; 2) CRRT, continuous renal replacement therapy, continuous venovenous hemofiltration, CVVH, continuous venovenous hemodiafiltration, CVVHDF, continuous venovenous hemodialysis, CVVHD; 3) nutritional support, feeding, malnutrition, malnourished inadequate, nutritional assessment, malnutritional screening, energy needs, energy requirement, caloric requirement, energy expenditure, kcal, calorie, kcal/kg, kilocalorie, protein needs, protein requirements, amino acid, amino acid requirement, protein intake, estimated protein, estimated amino acid, fats, lipids, triglycerides, fatty acids, propofol, propofol infusion syndrome, electrolytes, potassium, hypokalemia, hyperkalemia, sodium, hyponatremia, hyponatremia, phosphorus, hypophosphatemia, hypercalcemia, hypocalcemia, magnesium, hypomagnesemia, vitamins, vitamin B12, cyanocobalamin, vitamin B1, thiamine, thiamin, vitamin B6, pyridoxine, pyridoxamine, vitamin B9, folic acid, folate, vitamin C, ascorbic acid, trace elements, zinc, copper, manganese, chromium, selenium, fluid balance, fluid overload, fluid shifts; and 4) pediatrics, pediatric, pediatric care, children, child. In vitro and in vivo studies, prospective (randomized and observational) clinical studies in pediatric and adult patients were included with enteral and/or parenteral nutrition (PN). Conference abstracts, case reports, and editorials were not withheld. Review papers were hand searched to identify potentially relevant articles. All manuscripts deemed relevant to the research question were withheld and were approved by all authors. In analogy of the use of the Grading of Recommendations Assessment, Development, and Evaluation methodology that was applied in the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines,¹ the risk vs the harm of the recommendation was weighed. If this relation favored benefit, the recommendation is strong; if the benefits do not always outweigh the harm and these need to be evaluated on a patient basis, the recommendation is deemed weak; and if trade-offs were uncertain, no recommendation is given (Table 1). A summary of the raised question with recommendations is given in Table 2.

Results

There is a dearth of information of the influence of CRRT on metabolism and nutrition requirements during this therapy in critically ill children. Data would be preferable

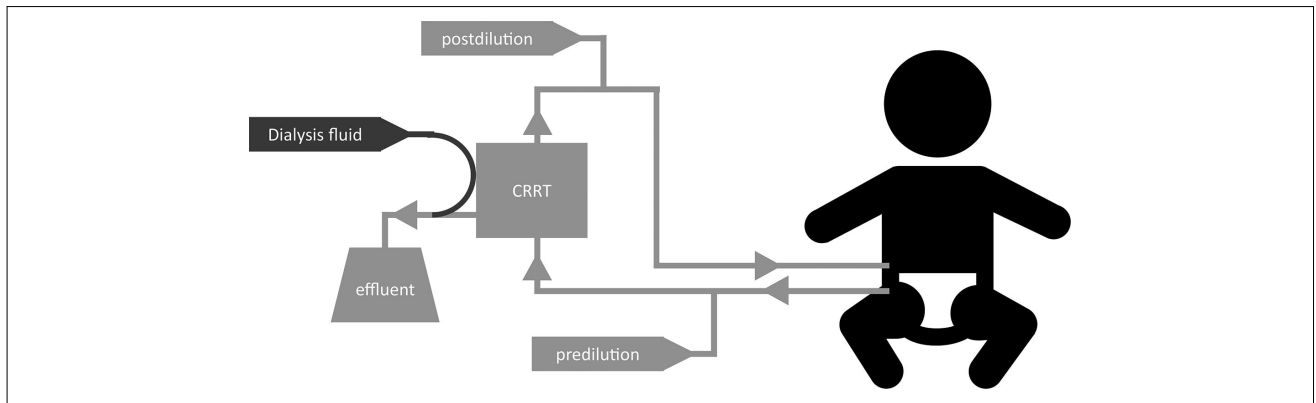


Figure 1. Schematic representation of a typical setup of continuous venovenous hemodiafiltration or continuous venovenous hemofiltration (if the darker gray color with dialysis fluid is not taken into account). CRRT, continuous renal replacement therapy.

Table 1. Language for Guidelines of Recommendations.

Quality of Evidence	Weighing Risk vs Harm	Recommendations
High to very low	Net benefit outweighs harm	Strong
High to very low	Benefit does not always outweigh harm; individual patient or patient evaluation is necessary	Weak
High to very low	Uncertain trade-off	No recommendation

based on evidence in infants during their critical illness, but this was not always possible. Although the broad-brush approach to integrate data from adult patients needs confirmation in the specific pediatric ICU CRRT population, it seemed the least inaccurate way to answer different questions that were raised. A summary of the practical approach to provide nutrition support to children requiring CRRT is provided in Table 3.

Fluid Balance

How does fluid prescription and removal need to be adapted during CRRT?

The fluid balance should incorporate EN and PN, and fluid removal by CRRT needs to be adapted (strong recommendation).

Awareness increases that fluids, and thus also nutritional liquids, should be regarded as drugs. Fluid components of nutrition should be incorporated into the 4 D theorem of fluid therapy (drug or type of fluid, dose, duration, and de-escalation).^{12,13} PN, in particular, may substantially

contribute to a positive daily fluid balance. As shown by the Fluid Expansion As Supportive Therapy trial in a sub-Saharan region, a positive cumulative fluid balance is associated with increased morbidity and mortality in children.¹⁴ Regulating net fluid removal by CRRT helps to contain this unwarranted but frequently underestimated detrimental fluid overload.

Dosing of Calories

What is the best method to estimate caloric need during CRRT? How to set the caloric target?

Indirect calorimetry (IC) should be performed and the measured resting energy expenditure (REE) used as a target without correction factors (strong recommendation).

In absence of IC, equations can be used (weak recommendation).

Knowledge of the metabolic rate of a critically ill patient is mandatory to dose calories.⁷ Formula-based calculation of REE is found to be very unreliable with variations from -802 kcal/d up to 947 kcal/d in critically ill children.¹⁵ The Schofield equation or Talbot's tables are least inaccurate for predicting REE in critically ill children when IC is not available.¹⁶ Both ASPEN¹ and the latest European Society for Clinical Nutrition and Metabolism guidelines¹⁷ recommend the Schofield equations (Table 3), but these are not validated during CRRT. Metabolic activity during CRRT could intrinsically be altered because the extracorporeal circuit induces immunologic activation and heat loss (the so-called "dialytrauma" hypothesis).¹⁸ Immunologic activation could stimulate metabolism, meaning that the patient needs more energy. The second part of this hypothesis is that the heat loss stimulates metabolism to preserve temperature.¹⁰ However, most studies in adults seem to find a diminished metabolism because of heat loss, especially in sedated

Table 2. Question Raised with Recommendations.

Question	Answer	Recommendation
How do fluid prescription and removal need to be adapted during CRRT?	The fluid balance should incorporate enteral and parenteral nutrition, and fluid removal by CRRT needs to be adapted	Strong
What is the best method to estimate caloric need during CRRT?	Indirect calorimetry should be performed, the measured REE used as a target without correction factors In absence of IC, equations can be used	Strong Weak
How does the caloric prescription need to be adapted during CRRT?	The caloric prescription should be adapted to influx and efflux of nutrients	Strong
What is the best method to evaluate protein need during CRRT?	No recommendation can be made	/
How to prescribe proteins during CRRT?	Provide 1.5 up to 2.5 g/kg/d of protein intake	Weak
How does CRRT influence fat metabolism?	There is no evidence for altered fat metabolism during CRRT	/
How does fat prescription need to be adapted during CRRT?	Olive oil-based intravenous emulsion seems to have an interesting profile in critically ill children requiring CRRT, but strong evidence is lacking	Weak
What is the best method to evaluate electrolyte status during CRRT?	Six-hour to 8-hour interval monitoring of plasma levels is warranted	Strong
How does electrolyte supplementation need to be adapted during CRRT?	Supplementation needs to be altered on an individual base, depending on plasma levels	Strong
What is the best method to evaluate vitamin needs during CRRT?	No recommendation can be made	/
How does vitamin prescription need to be adapted during CRRT?	Vitamins need to be adapted based on the removal in effluent	Weak
What is the best method to evaluate trace element balance during CRRT?	No recommendation can be made	/
How to adapt trace element supplementation during CRRT?	We recommend giving an extra weekly dose of selenium	Weak

CRRT, continuous renal replacement therapy; IC, indirect calorimetry; REE, resting energy expenditure.

patients, as compensating mechanisms, such as shivering, are disabled.^{6,19} Finally, citrate anticoagulation during CRRT directly affects metabolism by its involvement in the Krebs cycle and in regulatory mechanisms of glycolysis, proteolysis, and lipolysis. Citrate also may alter insulin resistance and satiety signals in the hypothalamus.^{20,21}

IC is the gold standard to evaluate REE.¹ IC devices derive energy expenditure by incorporating carbon dioxide (CO₂) production (VCO₂) and oxygen (O₂) consumption (VO₂) in the Weir equation. Values are obtained from breath-to-breath gas analysis and assume a stable nitrogen concentration.²² Thus, IC measures VO₂ and VCO₂ based on the assumption that gas exchange as a result of nutrient consumption and energy production is represented by the breath gas composition. IC is indicated (Appendix) in 72% of critically ill children,²³ but only 34% of patients met technical criteria for IC.²⁴ Scrutinizing the literature yielded no data on REE in CRRT-treated critically ill pediatric patients. Efforts have been made in adult patients to validate IC during CRRT by measuring REE with and without CRRT.^{25,26} This seems like oversimplification of a complex issue, as REE measurement during CRRT is underestimated

because of CO₂ removal.^{27,28} Dialysis and ultrafiltration rate, the type of filters used, and the patient's underlying condition likely contribute to variations in REE. Introducing an altered VCO₂ into the Weir equation causes incorrect calculation of REE. An in vitro model using a dialysis filter demonstrated removal at 30 mL/min at rates that could resemble adult CRRT settings.²⁸ This is approximately one-sixth of the mean VCO₂ of 180 mL/min.²⁹ When incorporated in the Weir equation (1.44 [3.94 VO₂ + 1.11 VCO₂]), this would only represent a 4% drop of the REE, as VCO₂ only accounts for less than one-fourth of the total REE.

How does the caloric prescription need to be adapted during CRRT?

The caloric prescription should be adapted to the influx and efflux of nutrients (strong recommendation).

A valid caloric prescription aims to reach clear targets. Type and dose of artificial nutrition should be determined. EN is the preferred mode of administration.¹ Other caloric sources of calories, also called nonintentional calories, should be taken into account.³⁰⁻³² Mostly these come from

Table 3. Practical Approach of Nutrition Therapy for Critically Ill Children Requiring CRRT.

Nutrition Component	EN vs PN	Recommendation During CRRT		
Calories	EN	IC, REE probably slightly underestimated		
Boys		Adapt prescription to unintended calories (see Table 4)		
Girls		If IC not available, use Schofield equation:		
		0–3 years	3–10 years	10–18 years
		$59.5 \times (\text{weight in kg}) - 30$	$22.7 \times (\text{weight in kg}) + 504$	$17.7 \times (\text{weight in kg}) + 658$
		$58.3 \times (\text{weight in kg}) - 31$	$20.3 \times (\text{weight in kg}) + 486$	$13.4 \times (\text{weight in kg}) + 692$
Proteins	EN	1.5–2.5 g/kg/d		
Fats	EN	No adaptation		
		Close monitoring		
Electrolytes	EN or PN	Monitor and supplement accordingly		
		Caveat: citrate accumulation presents as elevated total over ionized calcium ratio and high anion gap metabolic acidosis (often with lactate increase)		
Vitamins	PN	<1 year	1–3 years	>3 years
B1 (thiamin)	PN	0.3 mg/d + 0.83 $\mu\text{g/L}$ effluent	0.5 mg/d + 0.83 $\mu\text{g/L}$ effluent	1.2 mg/d + 0.83 $\mu\text{g/L}$ effluent
B6 (pyridoxin)	PN	No recommendation, although high-dose supplementation seems warranted		
B9 (folic acid)	PN	48 $\mu\text{g/d}$ + 4.4 $\mu\text{g/L}$ effluent	90 $\mu\text{g/d}$ + 4.4 $\mu\text{g/L}$ effluent	240 $\mu\text{g/d}$ + 4.4 $\mu\text{g/L}$ effluent
B12 (cobalamin)		No recommendation		
C (ascorbic acid)	PN	50 mg + 1.9 mg/L effluent	15 mg + 1.9 mg/L effluent	90 mg + 1.9 mg/L effluent
Fat-soluble vitamins	NA	No adaptation		
Trace elements		<1 year	1–3 years	>3 years
Selenium	PN	20 μg + weekly 20 μg	20 μg + weekly 20 μg	55 μg + weekly 55 μg
Zinc, copper, chromium		No adaptation		
Manganese		No adaptation		
		Caveat: intoxication		

CRRT, continuous renal replacement therapy; EN, enteral nutrition; IC, indirect calorimetry; NA, not applicable; PN, parenteral nutrition; REE, resting energy expenditure.

medication, and propofol is the most common example. Propofol 10% provides 1.1 kcal/mL. Calorie-containing substrates are also added during CRRT in the form of lactate-containing fluids, glucose-containing fluids, and citrate-containing fluids. These nonintentional calories must be considered when prescribing additional nutrients. In adult patients receiving CVVHDF, nonintentional caloric intake may be as high as 1434 kcal/d. For an adult of average 80 kg, this would be 17.9 kcal/kg/d, or 71% of caloric need. Correction formulas for adults are listed in Table 4³³ and can probably be extrapolated to children and to different forms of CRRT.

Proteins and Amino Acids

What is the best method to evaluate protein needs during CRRT?

No recommendation can be done for evaluation of protein needs.

Proteins are crucial components of nutrition. Delivering protein needs reduces inflammation and enhances recovery. Failure to achieve these targets is associated with increased mortality.² Nitrogen balance (NB), or the difference between nitrogen intake and nitrogen losses, uses urea in urine to estimate losses in urine, stool, and teguments. Protein and amino acid supplementation can be based on these results to target a positive NB. This can only be achieved if sufficient concomitant calories are given.³⁴ Different formulas to calculate NB are available, but none have been validated during CRRT, as proteins with different molecular weights are removed in various amounts.³⁵ Amino acids are the building blocks of proteins. They can be classified as the essential amino acids when they are not constructed by our metabolism and nonessential if our body can construct these based on other amino acids. However, during CRRT, both essential and nonessential amino acids are removed at different rates. This not only causes deficiencies of both “essential” and “nonessential” amino acids but also makes some amino acids classified

Table 4. Formulas to Calculate Nonintentional Caloric Intake From Glucose-Containing, Citrate-Containing, and Lactate-Containing Substitution Fluids.

	Formula Validated for CVVHDF
Citrate: 2.48 KJ/mmol = 10.38 kcal/ mmol = 2.5 kcal/g	= $Q_c \times [C]_{in} - Q_{eff} \times [C]_{eff}$
Glucose: 3.06 KJ/mmol = 12.80 kcal/ mmol = 3.8 kcal/g	= $(Q_c \times [G]_{in} + Q_d \times [G]_d + \text{post-dilution} \times [G]_d) - Q_{eff} \times [G]_{eff}$
Lactate: 1.37 KJ/mmol = 5.37 kcal/ mmol	= $(Q_d \times [L]_d + \text{post-dilution} \times [L]_d) - Q_{eff} \times [L]_{eff}$

[C]_{eff}, citrate concentration in effluent fluid; [C]_{in}, citrate concentration in citrate solution; CVVHDF, continuous venovenous hemodiafiltration; [G]_d, glucose concentration dialysate; [G]_{eff}, glucose concentration in effluent fluid; [G]_{in}, glucose concentration in citrate solution; [L]_d, lactate concentration in dialysate; [L]_{eff}, lactate concentration in effluent fluid; post-dilution, post-dilution flow; Q_c, prefilter citrate flow rate; Q_d, dialysis flow rate; Q_{eff}, effluent flow rate.

as “nonessential” and “essential,” as metabolism cannot keep up with losses.³⁶ Removal depends on the type of CRRT³⁷ and intrinsic properties and plasma concentration. Moreover, it is not established how the effluent removal rate of urea correlates with effluent removal of proteins, amino acids, and other nitrogen-containing molecules. This precludes reliable calculation based on urea removal. The Kjeldahl method can measure the removal of nitrogen-containing molecules (excluding ammoniac), but it is not used in the routine. Amino acid assays are only available for research purposes.³⁶

How does protein prescription need to be adapted during CRRT?

Dosage should be augmented and be as high as 1.5 g/kg/d up to 2.5 g/kg/d.

As NB and differentiation of protein deficiency are not feasible in daily clinical practice, pragmatic recommendations must be made. Parenteral supplements of 2.5 g protein/kg/d in adult patients receiving CRRT avoided deficiency of various amino acids.³⁶ This means an increase of 25% up to 100% of protein intake, as ASPEN guidelines in adults suggest 1.2 g protein/kg/d up to 2.0 g protein/kg/d.³⁸ Pediatric patients on CRRT kept a negative NB with a loss of 11% to 12% dietary amino acids, despite receiving PN containing 1.5 g protein/kg/d.³⁹ We recommend to increase protein intake between 25% and 100% in CRRT-treated critically ill children. ASPEN guidelines suggest 1.2 g protein/kg/d up to 2.0 g protein/kg/d. This results in a dosage of 1.5 up to 2.5 g protein/kg/day during

CRRT. The impact of the high amount of delivered proteins on morbidity and mortality in children must be carefully monitored and evaluated. EN is preferred to PN, if possible, because of its simplicity, less infectious complications, and trophic effect on the gastrointestinal tract. It should also be noticed that amino acids provided by PN are free, hydrated molecules and provide 20% less energy and protein substrate than enteral protein. However, a limiting factor in EN is the level of absorption, which could be strongly disturbed in the critically ill patient.^{40,41}

Fats

How does CRRT influence fat metabolism?

There is no evidence for altered fat metabolism during CRRT.

Fats are an indispensable part of PN in infants and children and are the primary noncarbohydrate source of energy. They are a high-density source of energy and can be used to avoid carbohydrate overload. They are the source of essential fatty acids and are crucial for the delivery of fat-soluble vitamins (vitamins A, D, E, and K). Because of their limited fat stores, children are susceptible to the development of essential fatty acid deficiencies, as early as within a few days.³

Critical illness and acute kidney failure cause impaired hepatic lipolysis with increased triglycerides and decreased low-density lipoprotein and high-density lipoprotein cholesterol.^{31,42,43} Other factors that influence the metabolic utilization of fats, and in particular lipoprotein lipase activity, are postnatal age, malnutrition, and acidosis. Fat homeostasis is not significantly altered by CRRT because of its high molecular weight and inherent lack of water solubility. Effluent samples in CRRT are fat free and contain only trace amounts of cholesterol and triglycerides. There is no arteriovenous gradient for fats across the CRRT filter, which implies the absence of membrane adsorption.^{31,42,44} Fats may accelerate the blockage of capillaries and filter clotting. This effect is more pronounced when unfractionated heparin is used as anticoagulation.³¹

Insufficient data are available to make evidence-based recommendations for fat administration during critical illness.^{1,45,46} The ASPEN and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines suggest administration of 30%–40% of calories in the form of fats^{1,43,46,47}, with a dose limitation of 3–4 g/kg/d in infants and 2–3 g/kg/d in older children.^{45,48} A general accepted approach is to start fat intake at 1 g/kg/d and slowly increase the dose over several days to 2–4 g/kg/d, with daily monitoring of triglyceride levels. After achieving the target dose without complication, monitoring can be performed less frequently.⁴⁵ Reduction

of and not stopping the dosage should be considered when triglycerides exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children. If not identified, this may rapidly evolve toward severe hypertriglyceridemia, particularly when patients are parenterally fed. Clinically, patients may develop coagulopathy, hepatomegaly, elevated liver enzymes, hyperbilirubinemia, respiratory distress, and thrombocytopenia.⁴⁵ This hypertriglyceridemia should not be confounded with the propofol infusion syndrome.⁴⁹

How does fat prescription need to be adapted during CRRT?

Olive oil-based intravenous emulsion seems to have an interesting profile in critically ill children requiring CRRT, but strong evidence is lacking (weak recommendation).

Composite lipid emulsions with or without fish oil are recommended over pure soybean fat emulsions because of their less proinflammatory effect, less immune suppression, and more antioxidant effects.⁴⁸ Olive oil-based intravenous lipid emulsions seem to have anti-inflammatory properties⁵⁰ and seem more adequate, considering the dialytrauma concept.¹⁸ More data are necessary to confirm this statement. Renal replacement-specific data are not available.

Electrolytes

What is the best method to evaluate electrolyte status during CRRT?

Six-hour to 8-hour interval monitoring of plasma levels is warranted (strong recommendation).

Serum electrolyte levels are frequently altered during critical illness, particularly if renal failure is present. Sodium, potassium, phosphorus, calcium, and magnesium are lost in the effluent.^{32,42} Electrolyte levels are strongly determined by the electrolyte composition of the balanced dialysate solution and the efficacy of solute clearance by CRRT.⁴² Electrolyte disturbances are common in critically ill children. They may not only be the reason to initiate CRRT but also occur in > 50% of cases during CRRT.⁵¹ Frequent (every 6–8 hours) assessment of serum electrolytes and acid-base status is needed to correct electrolyte losses, modify electrolyte content of CRRT or intravenous solutions, and adapt oral supplementation.^{31,51}

How does electrolyte supplementation need to be adapted during CRRT?

Supplementation needs to be altered on an individual base, depending on plasma levels (strong recommendation).

Hypokalemia and hyperkalemia increase the risk of life-threatening arrhythmias. Hyponatremia may develop when a negative sodium balance is inadequately compensated by dialysis and replacement fluids.^{51,52}

Many studies report a high incidence of hypophosphatemia.^{43,52,53} It occurs in 12%–85% of children receiving CRRT as a result of hyperexcretion in effluent and intracellular shifting.⁵² Phosphate clearance during CRRT significantly exceeds IHD clearance.³¹ The main determinants are the duration of CRRT therapy, younger age (<6 years), and the absence of phosphate in the replacement and dialysis fluids. Adding phosphate to dialysis fluids is considered to be safe and reduces the need for intravenous phosphate supplementation and the associated complications.^{42,52} Although mostly asymptomatic, hypophosphatemia can cause generalized muscle weakness, respiratory muscle paralysis, myocardial dysfunction, reduced peripheral vascular resistance, and metabolic encephalopathy.^{51,52} Hypophosphatemia should be anticipated and prevented or treated accordingly.

Hypocalcemia is reported in up to 50% of cases and occurs more frequently during citrate anticoagulation because citrate chelates calcium. Hypocalcemia and hypercalcemia may develop because of under replacement or overreplacement of calcium.^{43,51} Excessive citrate delivery or impaired hepatic function may cause insufficient hepatic metabolism and CRRT clearance. This is detected as an elevated total calcium value compared with ionized calcium (Total Ca/Ca⁺⁺ > 2.5) and a concomitant high anion gap metabolic acidosis.⁵¹ Therefore, both calcium and ionized calcium should be measured in blood samples during CRRT.

Vitamins

What is the best method to evaluate vitamin needs during CRRT?

No recommendation can be made.

Vitamins play a pivotal role in many metabolic processes and antioxidant defense mechanisms. Deficiencies may induce hematologic complications.⁵⁴ Critically ill children requiring CRRT have altered vitamin requirements. They are more frequently malnourished, and preexisting deficiencies can be present and should be revealed by a nutrition assessment.⁵⁵ A higher vitamin input is needed to face altered metabolic activity because of the underlying critical illness and dialytrauma.¹⁸ Moreover, some vitamins are lost in the effluent, but filtration fraction and removal rate of vitamins probably will differ, depending on the applied CRRT technique.

Reports on vitamin removal in critically ill children on CRRT are scarce. Most experience, once again, comes from

Table 5. Removal and RDI for Trace Elements During CRRT.

	1–3 Years				>4 Years			
	Mean removal ($\mu\text{g/d}$)	Mean suppl. ($\mu\text{g/d}$)	RDI ($\mu\text{g/d}$)	Removed/RDI(%)	Mean removal ($\mu\text{g/d}$)	Mean Suppl. ($\mu\text{g/d}$)	RDI ($\mu\text{g/d}$)	Removed/RDI(%)
Chromium	0	2.52	11	0	0.69	8.2	35	2.0
Copper	15	252	300	5	11.7	820	900	1.3
Manganese	0.275	63	1200	<0.1	0.1	372	2300	<0.1
Selenium	2.97	37.8	20	14.9	3.6	63	55	6.5
Zinc	39	2520	3000	1.3	43	4867	11,000	0.4

CRRT, continuous renal replacement therapy; RDI, reference daily intake.

adult studies. However, supplementation schemes aiming at raising plasma levels within the reference range of normality of local lab values have not been evaluated on morbidity and mortality endpoints.

How does vitamin prescription need to be adapted during CRRT?

Vitamins need to be adapted based on the removal in effluent (weak recommendation).

Thiamin (vitamin B1) levels were measured in effluent, and losses were estimated at approximately 4 mg/24 h at a set effluent flow rate of 2 L/h (1000 mL dialysate flow and 1000 mL hemofiltration rate) in adult patients under CVVHDF⁵⁶ corresponding with a removal rate of approximately 0.083 mg/L in effluent fluid. In adult patients, this would cause depletion of thiamin within 1 week of CRRT treatment.⁵⁶ Supplementation should be guided by plasma levels with daily requirements of 0.3 mg in children aged <12 months, 0.5 mg at 1–3 years, and up to 1.2 mg in patients >3 years, with the addition of 83 μg /per Liter effluent fluid.

Vitamin B6 removal rate was 3.4 ± 2.0 nmol/h for 2800 mL/h effluent rate in adult patients, corresponding with a daily loss of 80 nmol or 0.014 mg. Compared with the 1.7 mg/d reference daily intake (RDI), this is negligible, as it only represents 0.8% of RDI. However, plasma levels dropped under substitution of 2.87 mg/d up to 7 mg/d, or 165% up to 412% of RDI, reaching levels beneath the limit of normal at day 3. In critically ill adults receiving CRRT, higher supplementation more likely depends on the underlying medical condition or dialytrauma¹⁸ rather than on removal in effluent fluids. High-dose vitamin B6 supply seems warranted in critically ill children, but further studies need to assess adequate dosing schemes and their effect on outcome.

Folic acid (vitamin B9) removal was 27 nmol/h in adult patients at a 2800 mL/h effluent flow rate, hence 10 nmol/L

or 4.4 $\mu\text{g/L}$ effluent fluid, reaching 65% of RDI.⁵⁴ We recommend to supplement children under CRRT at 4.4 $\mu\text{g/L}$ effluent fluid plus RDI (48 μg under 1 year, 90 μg at 1–3 years, and 240 μg over 4 years) under guidance of plasma levels twice weekly. The frequency of sampling can be adapted to the stability of plasma levels and/or normality of levels.

Vitamin B12 does not seem to be removed in effluent.⁵⁷ No adaptation seems warranted.

Vitamin C is removed in adult patients in the effluent at a rate of 11 $\mu\text{mol/L}$ or 1.9 mg/L. This reached 528 $\mu\text{mol/d}$ or 93 mg/d,⁵⁸ which is slightly more than the 90 mg/d RDI. We recommend to add 1.9 mg/L effluent on top of RDI: 50 mg in children <1 year, 15 mg at 1–3 years, and 90 mg at >3 years.

Fat-soluble vitamins are not removed in the effluent.⁵⁹ We do not recommend adaptation of supplements related to CRRT.

Trace Elements

What is the best method to evaluate trace element balance during CRRT?

No recommendation can be made at this point.

Trace elements are involved at different levels of the immune reaction and contribute to antioxidant defense during systemic inflammation. Critical illness may change plasma levels because of cellular shifts, alterations of absorption and/or excretion, enhanced metabolism, and altered protein binding.^{18,58,60} Aiming at ranges within normal as provided by a local laboratory seems logical, but most guidelines^{1,61} do not support routine supplementation in an acute setting. No data exist on how this would alter outcome. Moreover, dialysis fluids contain trace elements in amounts that vary according to the fluid used.⁶² Bedside dosing in plasma would enhance the feasibility of trace-element monitoring and management.

How does trace element supplementation need to be adapted during CRRT?

We can recommend to give an extra weekly dose of selenium based on removal in effluent (weak recommendation).

One case series evaluated trace element removal during CRRT in 5 critically ill children. Results of removal, supplementation, and RDI are depicted in Table 5. Standard supplementation was administered for patients under 30 kg at an intravenous dose of 0.2 mL/kg/d with following concentrations per 0.2 mL: 200 µg zinc, 20 µg copper, 5 µg manganese, 0.2 µg chromium, and 3 µg selenium. Patients weighing 30 kg or more received a standard solution containing 5000 µg zinc, 1000 µg copper, 500 µg manganese, 10 µg chromium, and 60 µg selenium.

The removal of trace elements during CRRT in children was rather limited compared with RDI. On a weekly basis, only selenium removal was relevant, as up to 15% of RDI was extracted.⁶⁰ Two patients, respectively, had low plasma copper and low plasma zinc values. Four patients had excessively high manganese levels, although supplementation did not reach RDI. This raises concern because manganese accumulation may result in neurological signs, mainly mimicking Parkinsonism.^{63,64} The study provided no detailed information on the applied nutrition formula and thus on total trace element administration. Moreover, the exact time of intervention during CRRT and treatment duration is unknown.⁶⁰

Conclusion

There is a dearth of information present on nutrition therapy in critically ill children requiring CRRT. In general, nutrition recommendations in critically ill children on CRRT are not evidence based and result mainly from extrapolation of adult data. Substantial efforts should be done to produce evidence-based guidelines.

A positive cumulative fluid balance is detrimental. Fluid balance should take fluids from nutrition and removal during CRRT into account.

There is no validated method to predict REE in critically ill pediatric patients requiring CRRT. IC probably slightly underestimates REE, but it is the most accurate method. If it is not available, Schofield equations can be used. CRRT is an important source of non-intentional calories. The caloric prescription should be adapted accordingly. CRRT removes proteins and amino acids to an unknown extent, and protein supplementation should be increased. There is no evidence of altered fat metabolism during CRRT. The anti-inflammatory effect of fatty acid-derived olive oils seems favorable in this setting. Electrolytes need close monitoring and must be supplemented accordingly with special attention to avoid citrate accumulation. Thiamin

(B1), pyridoxin (B6), folic acid (B9), and ascorbic acid (C) are removed in the effluent, and supplementation should be augmented. Trace elements are not removed in the effluent fluid, with the exception of selenium, which should be supplemented on a weekly basis. Manganese accumulation can be a detrimental side effect of CRRT.

Statement of Authorship

J. Jonckheer, K. Vergaelen, H. Spapen, and E. De Waele equally contributed to the conception and design of the research; J. Jonckheer and K. Vergaelen contributed to the acquisition and analysis of the data; H. Spapen, M. L. N. G. Malbrain, and E. De Waele contributed to analysis of the data; all authors drafted the manuscript, critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Appendix

Indications for IC (ASPEN)¹

- Underweight, overweight, or obese;
- Children with >10% weight change during ICU stay;
- Failure to consistently meet prescribed energy goals;
- Failure to wean or need to escalate respiratory support;
- Neurologic trauma (traumatic, hypoxic, and/or ischemic);
- Oncologic diagnoses (including children with stem cell or bone marrow transplant);
- Children with thermal injuries or amputations;
- Children requiring mechanical ventilator support for >3 days;
- Children suspected to be severely hypermetabolic (status epilepticus, hyperthermia, systemic inflammatory response syndrome, dysautonomic storms, etc) or hypometabolic (hypothermia, hypothyroidism, pentobarbital or midazolam coma, etc).