Nutritional support in critically ill patients with kidney disease

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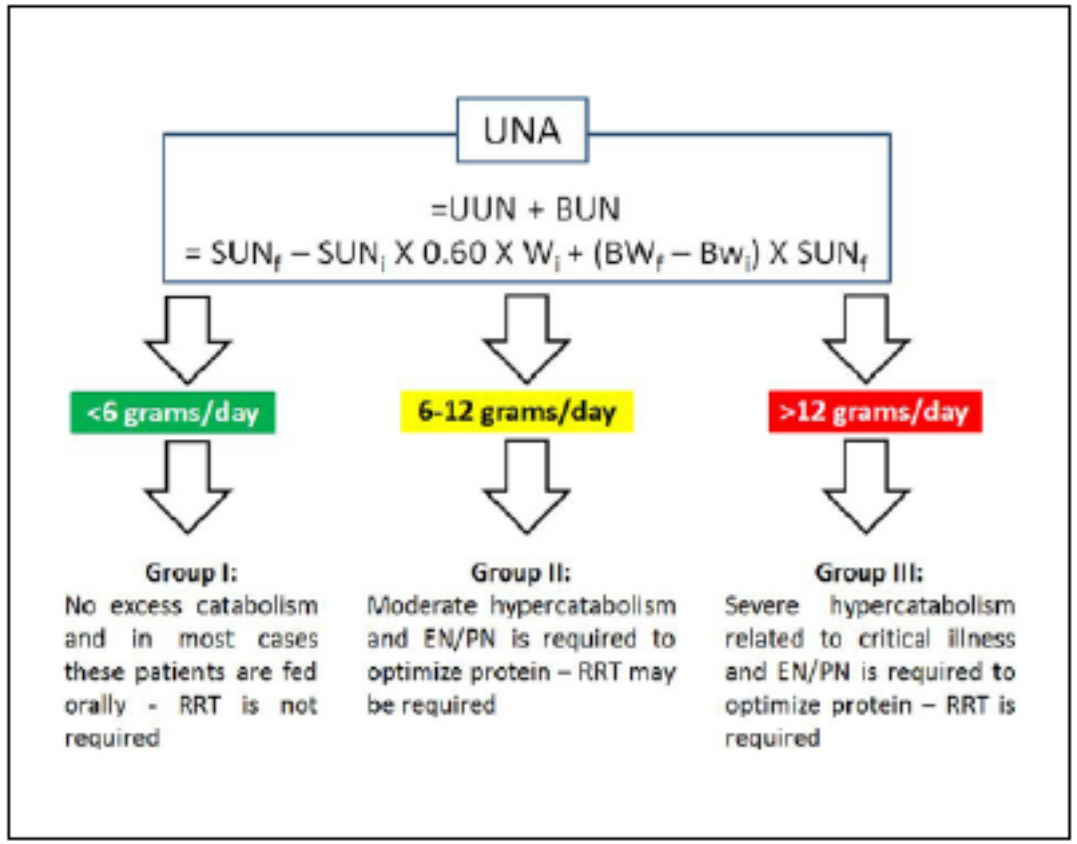

Figure 2. Urea nitrogen appearance (UNA) rate is a measure of net protein degradation in patients with renal failure. The majority of critically ill patients would fall into group III, which indicates severe hypercatabolism.[21] BUN, blood urea nitrogen; BW, body weight; EN, enteral nutrition; f, final; i, initial; PN, parenteral nutrition; RRT, renal replacement therapy; SUN, serum urea nitrogen; UUN, urinary urea nitrogen. 0.60 = estimated fraction of body weight that represents body water.

Nutritional assessment

- there is no validated screening tool to assess nutritional requirements specifically in AKI patients.
- Indirect calorimetry is not widely available, and equations estimating resting energy requirement are unreliable and have not been validated in AKI.
- Until a specific tool has been validated, it is recommended that a general nutritional assessment should include the exploration of weight loss before ICU admission, a physical examination and an assessment of body composition, muscle mass and muscle strength

- During critical illness, amino acids are released from muscle to support gluconeogenesis and the production of inflammatory mediators.

- Nutrition can only improve protein and energy balance and possibly protein synthesis but cannot suppress critical illness-induced catabolism.

- There is consensus that nutritional support should be individualised and tailored to the severity of hypercatabolism and the underlying disease, comorbidities, the need for RRT, and pre-existing nutritional status

Table 1 Nutritional recommendations in critically ill patients and patients with AKI

Nutritional parameter	Patients with AKI		General ICU patients	
	Recommendations	Level of evidence*	Recommendations	Level of evidence*
Calories	20–30 kcal/kg/day [1, 10] 25–30 kcal/kg/day [11]	5 5	Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness After day 3, caloric delivery can be increased up to 80–100% of EE [7]	2c
Protein	AKI during critical illness and not on RRT: Gradual increase to 1.3 g/kg/day [7] Up to 1.7 g/kg/day [1, 10] Critically ill patients on intermittent RRT: 1.0–1.5 g/kg/day [10] 1.5 g/kg/day [9] Critically ill patients on CRRT: Up to 1.7 g/kg/day [1, 10]	 5 5 5 5 5	Progressive increase to 1.3 g/kg/day [7]	2b
Vitamins and trace elements	Recommendation to supplement micronutrient losses during extracorporeal treatment [1]	5	Routine supplementation with glutamine or antioxidants not recommended [12] Recommendation to detect micronutrient deficiencies in patient categories at risk [7]	1b 5

AKI acute kidney injury, *CRRT* continuous renal replacement therapy, *EE* energy expenditure, *ICU* intensive care unit

Acute Kidney Injury

- There is no evidence that caloric targets should be different in AKI patients with and without RRT.
- In patients on CRRT, citrate contributes to caloric delivery and should be accounted for.
- If possible, oral diet should be the initial route of nutrition. In patients with insufficient oral intake, enteral feeding within 24–48 h is recommended.
- Limited data suggest that bolus and continuous enteral feeding can achieve similar targets. When enteral nutrition is contraindicated, parenteral nutrition is recommended within 3–7 day

- With regards to protein targets, the evidence is low.

- Observational data in the general ICU population suggest that high protein intake is associated with lower mortality; however, a slow progression to target on days 3–5 may be beneficial.

- The most recent ESPEN guidelines recommend to deliver 1.3 g/kg protein equivalents per day gradually and recommend using a standard AA
- solution for patients with AKI.

- For patients receiving CRRT, experts suggest to administer water-soluble vitamins and trace elements routinely but controversy exists about the type, dose and duration.

Micronutrient

- The majority of critically ill patients with AKI had an altered micronutrient status with a large proportion of patients having nutrient concentrations below the reference range, irrespective of CRRT.
- With the exception of glutamic acid, there were no significant differences in plasma nutrient concentrations between the CRRT and non-CRRT group during a six-day observational period. Therefore, losses from CRRT cannot be assumed to be the main reason for altered nutrient balance in severe AKI.
- All water soluble nutrients were detectable in the effluent in variable amounts.

Chronic kidney disease and COVID-19

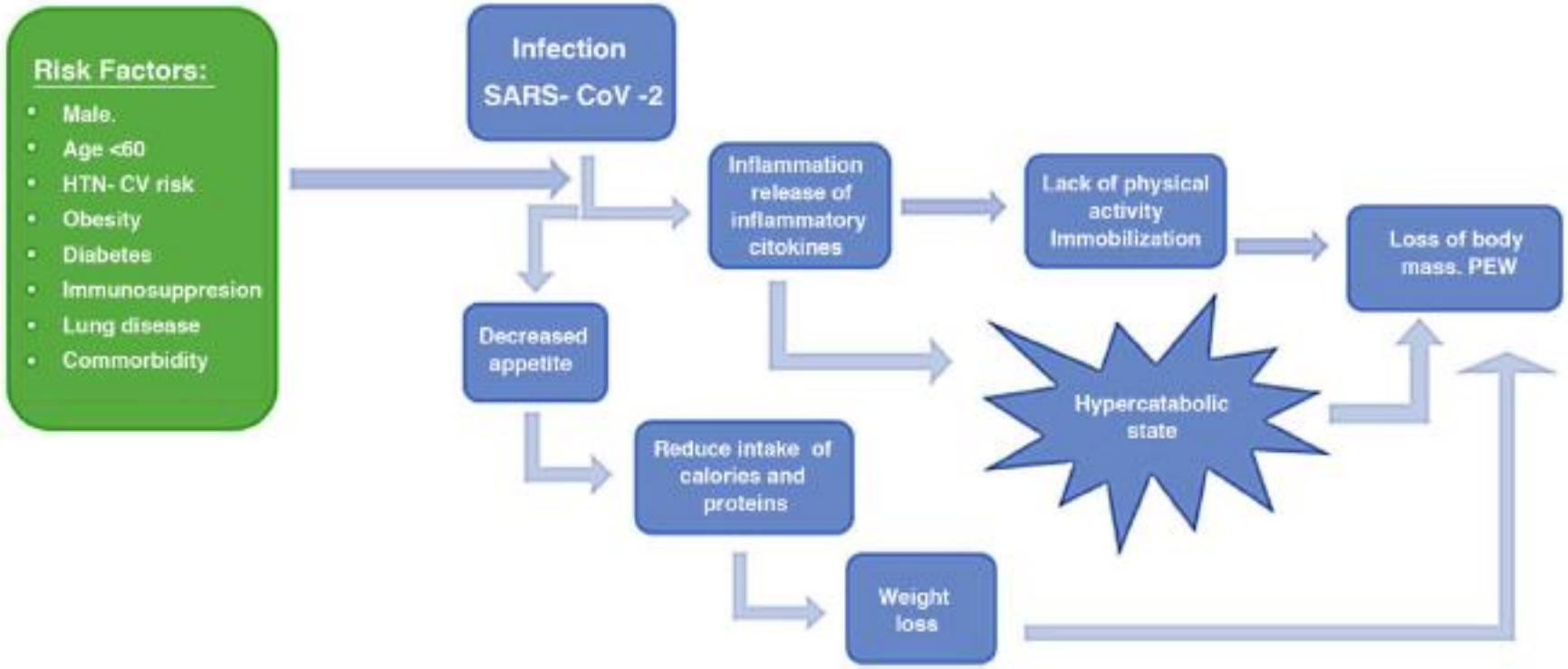

Figure 1 – Relationship of infection by SARS-CoV-2 and PEW.
CV: cardiovascular; PEW: protein energy waste; HTN: arterial hypertension.

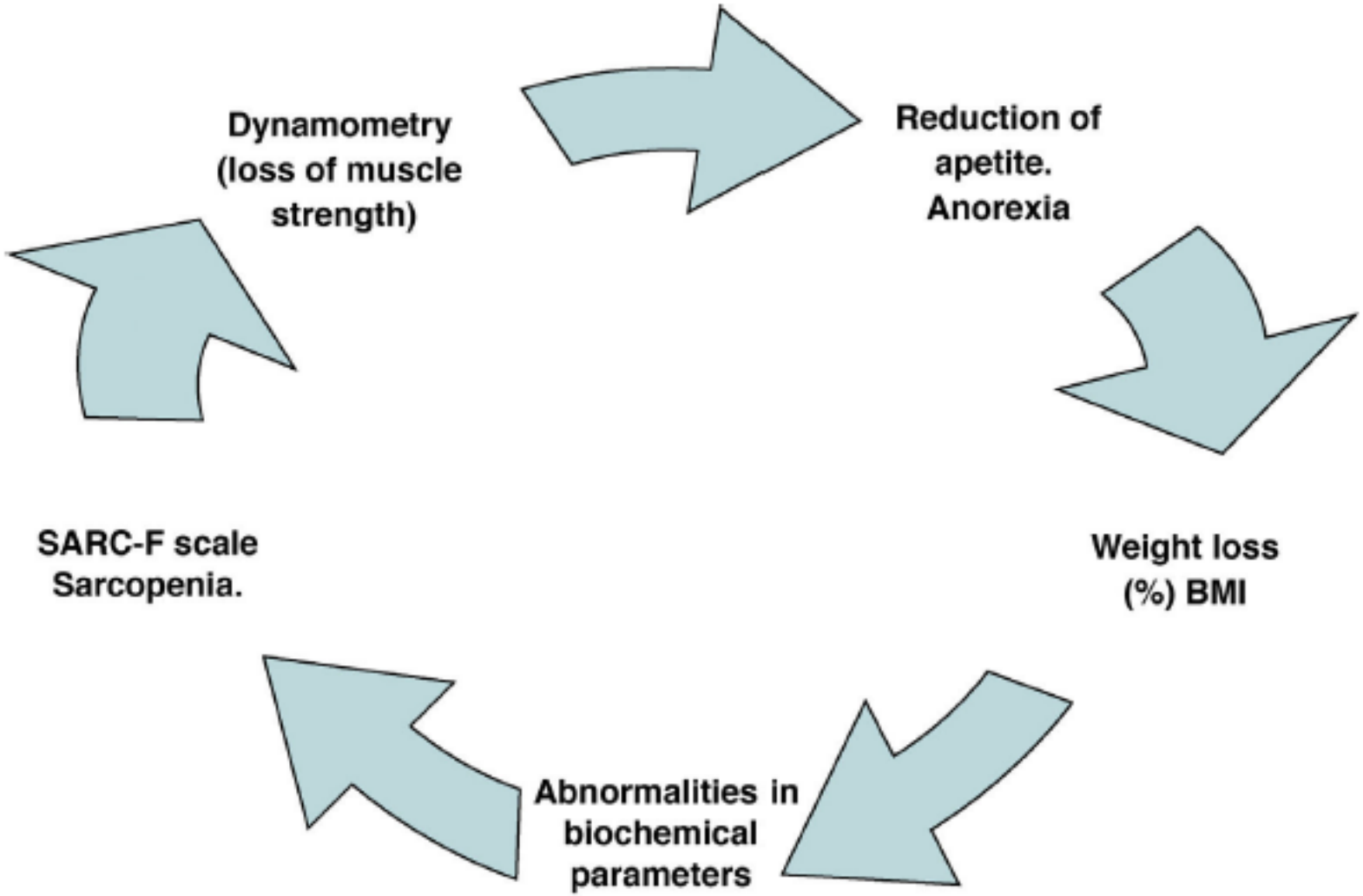

Figure 2 – Basic scheme of evaluation in patients infected by SARS-CoV-2.

Table 1 – Table of nutritional requirements according to CKD stage in patients with mild/moderate SARS-CoV-2 infection.

	Energy[a] (kcal/kg/day)	Proteins [a] (g/kg weight/day)		Potassium (g/day)	Phosphorus (g/day)
		(Mild SARS-CoV-2)	(SARS-CoV-2 moderate)		
Stages 1–2	30–35	1.0 + proteinuria [c]	Up to 1.4[e]	Individualize[d]	Individualize[d]
Stages 3–5 no in dialysis	30–35	0.8–1.0 + proteinuria [c]	0.8–1.0 + proteinuria [c,e]	If elevated: 2–4	If elevated: 0.8–1
Hemodialysis	30–35	1.2	1.2[g]	If elevated: 2–3	If elevated: 0.8–1
Peritoneal dialysis	30–35[b]	1.3	1.3–1.5	If elevated: 3–4	If elevated: 0.8–1
Transplant	30–35	1.0 + proteinuria[c]	Up to 1.4[e]	Individualize[d]	Individualize[d]

Source: Clinical Practice Guideline for Nutrition chronic Kidney Disease: 2019 Update,[13] Jin et al.[14] and National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.[16]

CKD: chronic kidney disease; TCV: total caloric value.

[a] Calculate the requirements according to actual weight, ideal weight or adjusted weight.

[b] Quantify glucose uptake.

[c] In the case of proteinuria, increase protein intake by 1 g of protein per gram of proteinuria in 24 h urine volume.

[d] Individualize according to analytical values.

[e] 1.5 g / kg / day in hypercatabolic states.

Table 2 – Nutritional requirements according to the stage of CKD in patients after SARS-CoV-2 infection.

	Energy[a] (kcal / kg / day)		Proteins[a] (g / kg weight / day)		Potassium (g/day)	Phosphorus (g/day)
	Risk or mild malnutrition	Moderate or severe malnutrition	Risk or mild malnutrition	Moderate or severe malnutrition		
Stages 1–2	30–35	30–40	1.0 + proteinuria[c]	Up to 1.4[e]	Individualize[d]	Individualize[d]
Stages 3–5 no dialysis	30–35	30–40	0.8–1.0 + proteinuria[c]	0.8–1.0 + proteinuria[c,e]	If raised: 2–4	If raised: (0.8–1)
Hemodialysis	30–35	30–40	1.2	1.2[e]	If raised: 2–4	If raised: (0.8–1)
Peritoneal dialysis	30–35[b]	30–40	1.2–1.3	1.2–1.5	If raised: up to 4	If raised: (0.8–1)
Transplant	30–35	30–40	1.0 + proteinuria [c]	Up to 1.4[e]	Individualize[d]	Individualize[d] Assess supplementation if there is hypophosphatemia

Source: Wright et al.,[12] Clinical Practice Guideline for Nutrition chronic Kidney Disease: 2019 Update,[13], Jin et al.[14] and Kidney et al.[17]

CKD: chronic kidney disease.

[a] Calculate requirements according to actual weight, ideal weight or adjusted weight.

[b] Account for glucose uptake.

[c] In the case of proteinuria, increase protein intake by 1 g of protein per gram of proteinuria in 24 h urine volume.

[d] Individualize based on analytical values.

[e] 1.5 g / kg / day in hypercatabolic states.

Table 3 – Recommendations of nutritional supplements in patients with CKD and SARS-CoV-2 infection.

Stages of CKD	Recommendations of Nutritional supplements[a]
1–2	- Hypercaloric/hyperproteic - Immunomodulatory formulas - If there is a high loss of muscle mass, consider formulas enriched in leucine or HMB
3–5 (not in dialysis)	- Specific formulas for CKD[b] - Immunomodulatory formulas - If there is high loss of muscle mass, consider formulas enriched in leucine or HMB
Patients on RRT: hemodialysis or peritoneal dialysis	
HD: combine with adequate HD schemes (*online* HDF or daily HD) PD: choose the appropriate scheme and balance with glucose absorption	- Specific formulas for CKD - Immunomodulatory formulas - If there is a high loss of muscle mass, consider formulas enriched in leucine or HMB - In peritoneal dialysis consider the use of protein modules and ctheglucose absorption
Trasplante: Ajustar to the stage of CKD and consider immunosuppressive drugs	- Hypercaloric / hyperprotein - Specific formulas for CKD[b] - Immunomodulatory formulas - If there is a significant loss of muscle mass, evaluate formulas enriched in leucine or HMB

DM: diabetes mellitus; CKD: chronic kidney disease; HMB: hydroxymethylbutyrate.
Note: Evaluate the administration of supplements of vitamins D, Zn and Se.
It is recommended to perform physical activity adapted to the characteristics of the patient as a complement to nutritional treatment.

[a] In case of DM, regardless of the stage of CKD, consider the use of specific enteral nutrition formulas for diabetics.

[b] In hypercatabolic patients, assess the use of specific formulas for CKD rich in protein in low volume, since the important goal is the treatment of acute malnutrition rather than the risk of CKD progression.

- In the case of polymorbid patients over 65 years of age it is recommended 27 kca l and 1 g of protein per kg of weight/day.

- Malnourished and polymorbid patients it is recommended 30 kcal and 1–1.5 g of protein per kg weight/day.

- In ICU patients it is recommend its initiation of it is recommended the initiation of tube feeding when they become hemodynamically stable, with compensated hypoxemia, and always with vigilance for signs of intolerance and intestinal ischemia. It is recommend 15−20 kcal and 1.3 g of protein per kg of weight per day.

- Administration in these patients should be progressive depending on GI tolerance; it may take more than 3 days to reach 80–100% of the recommended amount. Meanwhile, they will require parenteral nutrition (PN).

Key notes

- The patient with CKD and SARS-CoV-2 infection presents a high risk of malnutrition.
- In processes of infection by SARS-CoV-2 in patients with CKD it is recommended nutritional assessment by: percentage of weight loss or BMI, loss of appetite, analytical parameters and dynamometry.
- In patients with mild/moderate SARS-CoV-2 infection and CKD, it is recommended to adjust the energy and protein requirements to the stage of the disease and the presence of inflammation.
- In patients CKD post SARS-CoV-2 infection, it is recommended a complete nutritional assessment, paying special attention to the decrease in muscle mass and the appearance of sarcopenia.
- Nutritional support should begin with the adaptation of dietary recommendations, paying attention to the presence of anorexia, ageusia, anosmia, diarrhea, dysphagia, and dyspnea.

Liver failure

- Liver dysfunction is a spectrum, with decompensated cirrhosis and ALF representing more severe forms of disease requiring ICU admission.
- Decompensated cirrhosis and ALF both induce proteolysis; however, patients with decompensated cirrhosis are more likely to have PEM and a lower Fischer ratio (BCAAs/AAAs).

- With the onset of ALF, glycogen stores are depleted; insulin metabolism is reduced; and gluconeogenesis is impaired, increasing the risk for hypoglycemia.
- Ammonia clearance is impaired, leading to hyperammonemia and development of HE, cerebral edema, and intracranial hypertension.49 Furthermore, ALF can lead to multiorgan failure, including acute respiratory distress syndrome, circulatory shock, AKI (hepatorenal syndrome), and immunosuppression.
- The ALF and associated multiorgan failure increase metabolic rate and energy expenditure 20%–30% greater than healthy controls and increase proteolysis and AA loss

- liver cirrhosis is usually an irreversible late stage of progressive hepatic fibrosis. Cirrhosis is much more common than ALF and represents the eighth-leading cause of death in the United States.
- HE, spontaneous bacterial peritonitis, and hemorrhage may lead to critical illness requiring ICU admission.
- DLC is associated with preexisting proteinenergy malnutrition (PEM), whereas patients with ALF generally do not have PEM or preexisting liver disease.
- PEM occurs as a result of reduced protein intake, accelerated proteolysis, or both. PEM is present in at least 20% of compensated cirrhosis cases and at least 50% of decompensated cirrhosis cases.

Liver Failure consequences

- Poor nutrition intake
- Anorexia from symptoms such as early satiety, abdominal pain, ascites causing distention, gastroesophageal reflux, and dysgeusia
- Protein loss from large-volume paracentesis and metabolic alterations, including hormonal and nutrient utilization abnormalities, as in reduced glycogen stores creating an early fasting state that leads to concurrent breakdown of fat and AAs
- Increased beta-adrenergic activity, which leads to a hypermetabolic state creating insulin resistance, proteolysis, and AA use for gluconeogenesis
- Malabsorption of protein resulting from increased gut permeability, reduced bile salts, and bacterial overgrowth
- An overall loss of protein from reduced synthesis

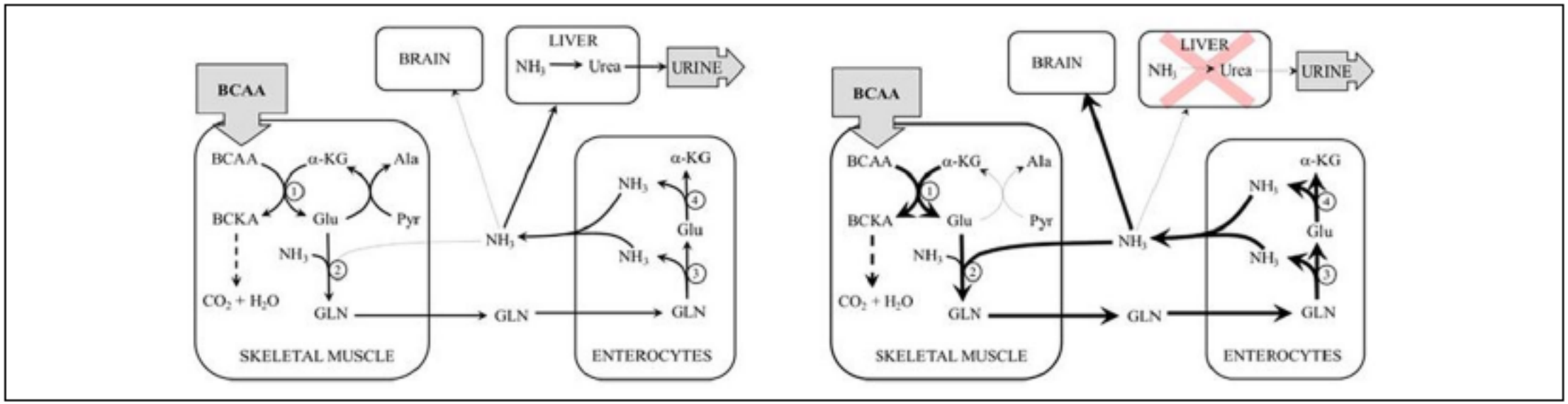

Figure 3. Effect of BCAA administration on GLN and ammonia metabolism. A, In healthy individuals, BCAAs activate GLN and alanine synthesis in skeletal muscle, which are catabolized by enterocytes to ammonia that is detoxified in the liver to urea and excreted through urine. B, In liver injury, the ammonia is not detoxified and may appear in systemic circulation, contributing to HE. Furthermore, circulating ammonia activates GLN synthesis and BCAA degradation in skeletal muscle, and alanine synthesis decreases due to use of glutamate in ammonia synthesis. BCAA, branched-chain amino acid; GLN, glutamine; HE, hepatic encephalopathy. Reaction 1 carried out by BCAA transferase; 2, GLN synthetase; 3, glutaminase; and 4, glutamate dehydrogenase. Reprinted with permission from Holecek M. Branched-chain amino acids and ammonia metabolism in liver disease: therapeutic implications. *Nutrition*. 2013;29(10):1186-1191. Copyright 2013 Elsevier.

- Protein restriction should be avoided due to (1) the heightened catabolic state leading to proteolysis in ALF and decompensated cirrhosis and (2) the PEM observed in compensated cirrhosis.

- Thus, early nutrition support may attenuate tissue protein catabolism; however, the optimal protein composition and requirements in ALF and decompensated cirrhosis are not well established. In a large Veterans Affairs Cooperative Study on hospitalized patients with alcoholic hepatitis, positive nitrogen balance was not consistently achieved until patients were consuming >85 g of protein per day (~1.2 g/kg/d).

- The 2016 ASPEN-SCCM guidelines suggest that protein requirements for patients with hepatic failure be determined in the same manner as for the general ICU patient, with the caveat that dry weight may need to be used for calculations due to ascites, circulating volume depletion, and/or hypoalbuminemia.

- BCAAs may have numerous potential benefits in liver dysfunction, including
- (1) synthesis of GLN from glutamate and ammonia in muscle, thus activating an alternative pathway for ammonia detoxification;
- (2) leucine-mediated improvement in glucose metabolism and protein synthesis by activating the mTOR pathway (mammalian target of rapamycin);
- (3) leucine-induced stimulation of hepatic growth factor;
- (4) BCAA prevention of tissue triglyceride accumulation;
- (5) improvement in neutrophil phagocytic function.

- The 2010 European Society for Clinical Nutrition and Metabolism guidelines suggest 0.8–1.2 g/kg/d (via EN or PN) in acute and subacute liver failure

- The 2016 ASPENSCCM guideline recommends against protein restriction and that protein requirements for patients with hepatic failure be determined in the same manner as for the general ICU patient.

- The 2015 Canadian critical care nutrition support guidelines suggest that there are insufficient data to make a recommendation for the use of BCAAs in critically ill patients

- Furthermore, in an era where permissive underfeeding is acceptable, reducing the total energy target inadvertently leads to a reduction in protein delivery.
- Process factors include getting enough protein in formula and delays in initiating and advancing EN.ICU-specific barriers include withholding and/or interrupting EN for surgical procedures, nursing procedures, hemodynamic instability, gastrointestinal bleeding, and gastrointestinal intolerance.
- Many reports suggest that EN is withheld for up to 8 hours prior to a scheduled test and an average of 7 h/d, thereby reducing achieved EN (and therefore protein) volume considerably

- Strategies to enhance protein delivery include providing volume based (as opposed to rate-based) EN delivery, increasing gastric residual volume threshold, optimizing enteral protein supplementation, and considering intravenous adjunct protein delivery when permissive underfeeding is employed

- Optimal protein dose and composition are not known for decompensated cirrhosis and ALF. Indeed, because proteolysis is associated with both conditions, current recommendations call for calculating protein requirements in the same manner as for the general ICU patient, with the caveat of using dry weight for cirrhotic patients.
- In decompensated cirrhosis, BCAA supplementation has not been shown to be beneficial in reducing HE recurrence, quality of life, or survival.
- Thus, a recommendation for its use cannot be made at the current time, and further studies may be warranted to determine the impact of BCAAs in critically ill patients with DLC.
- Clinical data for BCAAs in ALF are lacking. Studies evaluating the biologic plausibility for BCAA supplementation in early versus late ALF are needed.

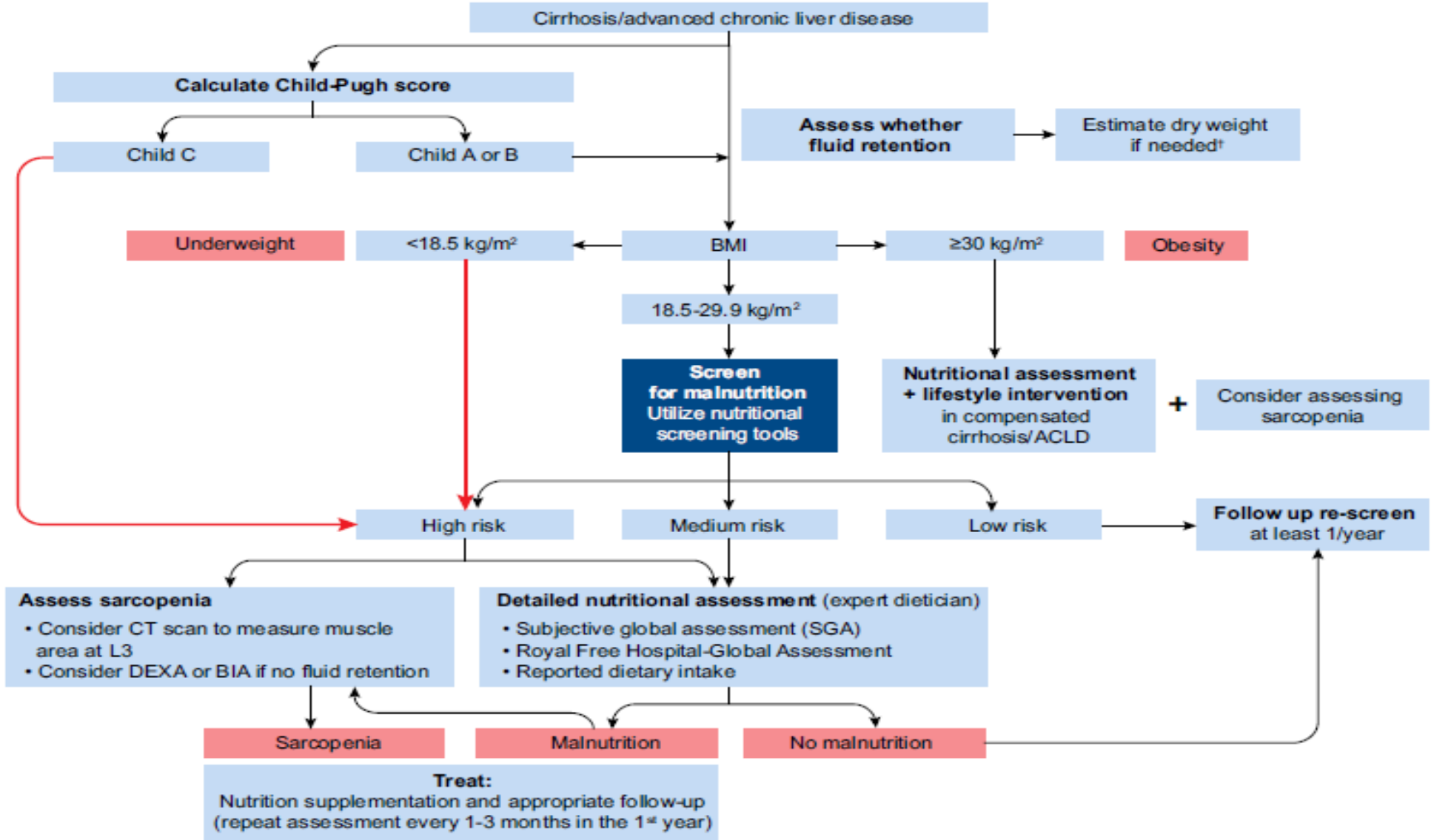

Fig. 1. Nutritional screening and assessment in patients with cirrhosis. All patients should undergo a rapid screening of malnutrition using validated, accepted tools. A liver specific screening tool which takes into consideration fluid retention may be advisable (Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT). Patients found to be at high risk of malnutrition should undergo a detailed nutritional assessment, and based on the findings they should receive either supplementation or regular follow-up. †In a case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal oedema is present. BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DEXA; dual-energy X-ray absorptiometry.

Liver transplantation

Recommendations

- After liver transplantation initiate normal food and/or enteral tube feeding preferably within 12–24 h postoperatively, or as soon as possible, to reduce infection rates. (**Grade II-2, B1**)
- When oral or enteral nutrition are not possible or are impracticable, parenteral nutrition should be used instead of no feeding in order to reduce complication rates, time on mechanical ventilation and ICU stay. (**Grade II-2, B1**)
- After the acute postoperative phase, provide an energy intake of 35 kcal/kg.BW/d and a protein intake of 1.5 g/kg.BW/d. (**Grade II-2, C1**)
- After other surgical procedures, patients with chronic liver disease can be managed according to the ERAS protocol. (**Grade III, C2**)
- Consider parenteral nutrition in patients with unprotected airways and HE when cough and swallow reflexes are compromised, or enteral nutrition is contraindicated or impractical. (**Grade II-2, C1**)
- Enteral tube feeding and/or parenteral nutrition with a reduced target energy intake (25 kcal/kg.BW/d) and an increased target protein intake (2.0 g/kg.BW/d) can be utilised in obese patients. (**Grade III, C2**)

Future Direction

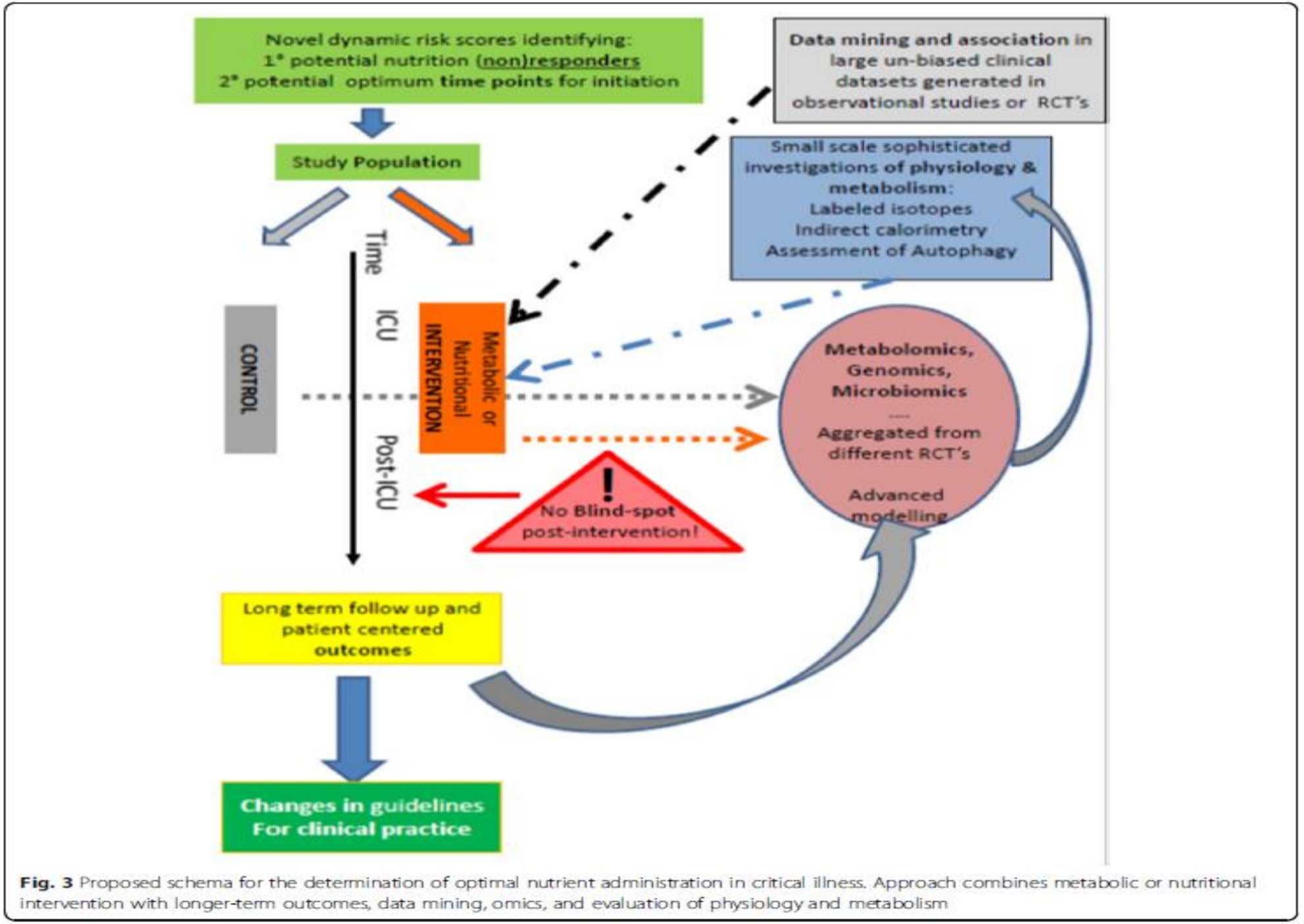

Fig. 3 Proposed schema for the determination of optimal nutrient administration in critical illness. Approach combines metabolic or nutritional intervention with longer-term outcomes, data mining, omics, and evaluation of physiology and metabolism

THE END