



## ESPEN Guideline

# ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease



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## S U M M A R Y

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Hospitalized patients  
Intensive care unit  
Malnutrition  
Muscle wasting  
Parenteral nutrition

Acute kidney disease (AKD) - which includes acute kidney injury (AKI) - and chronic kidney disease (CKD) are highly prevalent among hospitalized patients, including those in nephrology and medicine wards, surgical wards, and intensive care units (ICU), and they have important metabolic and nutritional consequences.

Moreover, in case kidney replacement therapy (KRT) is started, whatever is the modality used, the possible impact on nutritional profiles, substrate balance, and nutritional treatment processes cannot be neglected.

The present guideline is aimed at providing evidence-based recommendations for clinical nutrition in hospitalized patients with AKD and CKD. Due to the significant heterogeneity of this patient population as well as the paucity of high-quality evidence data, the present guideline is to be intended as a basic framework of both evidence and - in most cases - expert opinions, aggregated in a structured consensus process, in order to update the two previous ESPEN Guidelines on Enteral (2006) and Parenteral (2009) Nutrition in Adult Renal Failure. Nutritional care for patients with stable CKD (i.e., controlled protein content diets/low protein diets with or without amino acid/ketoanalogue integration in outpatients up to CKD stages four and five), nutrition in kidney transplantation, and pediatric kidney disease will not be addressed in the present guideline.

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## 1. Introduction

The present guideline represents an updating and expansion of the existing ESPEN Guidelines on Enteral Nutrition in Adult Renal

Failure 2006 [1] and Parenteral Nutrition in Adult Renal Failure 2009 [2] and has been jointly prepared by a multidisciplinary group of experts from different specialties (Nephrology, Intensive Care Medicine, Internal Medicine) based on the new methodology defined by the Standard Operating Procedures for the ESPEN Guidelines and Consensus Papers [3].

The aim of the project has been the development of guidelines for hospitalized patients with acute kidney injury/acute kidney disease (AKI/AKD) and/or chronic kidney disease (CKD) with or without kidney failure (KF). This guideline is not intended to be

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**List of abbreviations**

APD	automated peritoneal dialysis	KF	kidney failure
AKD	acute kidney disease	KRT	Kidney replacement therapy
AKI	acute kidney injury	MNA-SF	mini-nutrition assessment -short form
BIA	bioelectric impedance analysis	MRC	Medical Research Council
BMI	body mass index	MUST	malnutrition universal screening tool
CAPD	continuous ambulatory peritoneal dialysis	NRS	nutritional risk screening
CKD	chronic kidney disease	ONS	oral nutritional supplements
CKRT	continuous kidney replacement therapy	PIKRT	prolonged intermittent kidney replacement therapy
CT	computed tomography	PD	peritoneal dialysis
CVVH	continuous veno-venous hemo-dia-filtration	PN	parenteral nutrition
DEXA	dual energy X-ray absorptiometry	PUFA	polyunsaturated fatty acids
EN	enteral nutrition	RCT	randomized controlled trial
GH	growth hormone	REE	resting energy expenditure
ICU	intensive care unit	renal iNUT	renal inpatient nutritional screening tool
IDPN	Intradialytic parenteral nutrition	sCr	serum creatinine
IGF	insulin-like growth factor	SGA	Subjective global assessment
		SLED	sustained low-efficiency dialysis

applied in the outpatient setting of stable patients with CKD stages 1–5 or on chronic dialysis. Abnormal kidney function, usually indicated in the literature with the broad terms AKI/AKD or CKD, is highly prevalent among hospitalized patients in different clinical settings, including nephrology and internal medicine wards, surgery wards, and intensive care units (ICU). As far as nutrition is concerned, the approach to these patients when hospitalized is highly complex since they represent a very heterogeneous group of subjects, with variable and widely differing metabolic characteristics and nutritional needs.

In all of these clinical settings AKI/AKD and CKD (especially in its most advanced stages, from 3 to 5), as well as their specific treatments, may have important adverse effects on both substrate metabolism and nutritional status. Moreover, in case kidney replacement therapy (KRT) is started, and whatever is the modality used (conventional intermittent hemodialysis; prolonged intermittent kidney replacement therapies PIKRT), or continuous kidney replacement therapies (CKRT), its impact on nutritional profile, substrate balance, and nutritional treatment processes cannot be neglected.

The present guideline is aimed at providing evidence-based recommendations for clinical nutrition in hospitalized patients with AKI/AKD or CKD. Due to the paucity of high-quality evidence data, the present guideline is to be intended as a basic framework of both evidence and - in most cases - expert opinions, aggregated in a structured consensus process. Nutritional care for outpatients with metabolically stable CKD (i.e., patients on controlled protein content diets with or without amino acid/ketoanalogue integration), as well as nutrition in kidney transplant or pediatric KD will not be addressed here. As will be discussed more in-depth in the following section, the 2012 nomenclature of the “Kidney Disease Improving Global Outcomes” (KDIGO) for AKI and AKD [4], and the 2012 KDIGO nomenclature for CKD [5], as recently updated in a 2019 KDIGO consensus conference [6] will be applied in the text.

## 2. Methods

### 2.1. General aspects and guideline development process

The present guideline started as a basic framework of evidence and expert opinions subsequently structured into a consensus process following the standard operating procedure for the development of ESPEN Guidelines [3]. On this basis, the concept of

“Medical nutrition aimed at prevention and treatment of malnutrition in the context of diseases” was focused on, with a comprehensive approach not separating enteral nutrition (EN) and parenteral nutrition (PN) as in the past ESPEN guidelines for adult renal failure, and including screening, assessment, nutritional counseling, oral nutritional supplements (ONS), as well as EN and PN [7]. Thus, the present guideline is an update and revision of the two existing ESPEN guidelines, respectively on Enteral Nutrition in Adult Renal Failure 2006 [1] and on Parenteral Nutrition in Adult Renal Failure 2009 [2]. The two previous guidelines were joined and integrated by a multidisciplinary working group of seven specialists (Nephrology, Intensive Care, Internal Medicine) from three European countries (Italy, Sweden, Belgium), based on the new methodology defined by the standard operating procedures for the ESPEN Guidelines and consensus papers [3]. The working group members declared their conflicts of interest according to the rules of the International Committee of Medical Journal Editors. No individual employed by the industry was allowed to participate in the guideline development process. No industry sponsoring was obtained, and the costs for the development process of the guideline were entirely covered by ESPEN. The new ESPEN guideline standard operating procedures [3] is based on the methodology followed by the Association of Scientific Medical Societies of Germany, the Scottish Intercollegiate Guidelines Network (SIGN), and the Centre for Evidence-based Medicine at the University of Oxford. Accordingly, a sequential approach is requested, that includes the structuring of clinical questions according to the PICO system (Patient, Intervention, Control, Outcome) when possible, systematic literature search, with the evaluation of recent other relevant guidelines/consensus, and the identification of specific keywords. Non-PICO clinical questions were also structured, concerning basic and general concepts related to acute and chronic kidney diseases, definitions regarding renal function impairment syndromes, classifications of AKI/AKD, and CKD, KRT modalities, and indications. Each question led to one or more recommendation/statement and related commentaries. Different topics concerning nutrition in hospitalized patients with AKI/AKD or CKD were covered, such as the metabolic background of reduced renal function, the metabolic effects of AKI/AKD, AKI on CKD with or without KRT, CKD, and CKD on KRT, screening of patients at risk, nutritional status assessment, indications and timing of nutritional support, route of feeding, macro- and micronutrient requirements, disease-specific nutrient use, integration of nutritional therapy with KRT, as well as

monitoring of nutritional status and nutritional therapy. Existing evidence was graded, as well as recommendations and statements were developed and agreed in a multistage consensus process. Levels of evidence for literature selection were provided according to the SIGN evidence classification (NICE 2012), which ranks the evidence from 1++ for high quality studies (meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias) up to low level of evidence graded as 4 in the case of expert opinion (Table 1) [3].

## 2.2. Search strategy

We searched the PubMed and Cochrane Library databases for studies and systematic reviews published until January 1st, 2020, using selected keywords (Table 2). Only articles on studies in human adult patients published in English or with an English abstract were considered. RCTs, meta-analyses, and systematic reviews were also hand-searched for studies not included in the initial database search.

## 2.3. Meta-analysis strategy

There was no data on the specific topic covered by this guideline suitable for a formal meta-analytic approach.

## 2.4. Quality of evidence

The classification of the literature into levels of evidence was performed according to the SIGN grading system, as exemplified in Table 1.

## 2.5. Evidence levels and grading of recommendations

Evidence levels were translated into recommendations, taking into account study design and quality as well as consistency and clinical relevance (Table 3) [3]. In particular, the lowest recommendation corresponded to a good practice point (GPP) based on expert opinion and reflecting the consensus views inside the working group experts. As in other ESPEN guidelines [8] this approach reflects the attempt to make the best recommendations possible within the available data and expert clinical experience, mainly because data from RCTs are not available. Recommendations are formulated in terms of a “strong” (“shall”) or “conditional” (“should or can”) and for or against the intervention based on the balance of desirable and undesirable consequences of the intervention (Table 3) [3]. In case of inconsistency, the recommendations were based both on the available evidence and on working group judgment, taking consistency, clinical relevance, and validity of the evidence into account [8]. The recommendations were classified according to the strength of consensus according to Table 4 [3].

## 2.6. Consensus process

The working group prepared a guideline draft with a total of 32 recommendations and eight statements approved by both the working group and the ESPEN Guidelines Editorial Board which was followed by the start of the consensus procedure, by providing the draft to the ESPEN members for the first online voting which took place between 21st February and 15th March 2020. The results of this online voting were a strong consensus (agreement of >90%) for 26 of the recommendations, and seven of the statements, and consensus (agreement of >75–90%) in six of the recommendations and one statement. The feedback obtained in the online voting was used to modify and improve the recommendations to reach a

**Table 1**  
Definition of levels of evidence [3].

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

higher degree of acceptance at the final consensus meeting. Due to the COVID-19 pandemic, a planned Consensus Conference was canceled and replaced by a second online voting where the recommendations and statements with an agreement equal or lower than 90% and those with substantial changes resulting from comments of the first online voting, were voted on again. The second online voting took place between 15th May and 7th June 2020. Nine recommendations and one statement were included in the second online voting. Four recommendations and the statement reached an agreement of >90% (strong consensus), five recommendations reached an agreement of >75–90% (consensus).

## 2.7. Definitions and terminologies

All the definitions and terminologies used in the present guideline are in accordance with the recent ESPEN terminology recommendations [9].

Medical nutrition therapy includes the use of oral nutritional supplements, EN and PN, and replaces the terminology “artificial nutrition”.

Actual body weight is the weight measured during hospitalization; ideal body weight is the weight related to the height to obtain a body mass index (BMI) of 23 kg/m<sup>2</sup>; adjusted body weight is usually used in obese and is calculated as (actual body weight - ideal body weight) × 0.33 + ideal body weight. Through the text, the reference body weight used is the preadmission dry weight for normal and overweight patients. For obese patients, the ideal body weight to reach a BMI = 25 kg/m<sup>2</sup> should be considered.

Iso-caloric nutrition is the administration of energy within 70–110% of the defined target; hypocaloric feeding or underfeeding is an energy administration of <70% of the defined target; overfeeding is an energy administration of >110% of the defined target; trophic feeding is a minimal administration of nutrients to preserve the normal function of the intestinal epithelium, and prevent bacterial translocation.

A low protein diet or conservative nutritional treatment of CKD or AKI/AKD is the administration of ≤0.7 g/kg/d of protein.

The following definitions are presented in detail in Tables 5–7. AKI is a sudden decrease in glomerular filtration rate (GFR) which becomes evident by an increase in serum creatinine or oliguria within 48 h to seven days, with the severity (stage) of AKI determined by the severity of the increase in serum creatinine or oliguria [4]. There are no currently available accepted criteria for markers of kidney damage in the case of AKI, as defined for CKD (e.g. for example proteinuria). It is generally accepted that the urine output criteria for AKI are only applicable in intensive care settings, while ascertainment of AKI and its severity from the timing of serum creatinine level changes alone is generally considered acceptable in

**Table 2**  
Key words used in PICO search.

PICO	Intervention	Control	Key words
1. Indication			
1	Medical nutrition therapy	No medical nutrition therapy	Medical nutrition therapy OR nutritional support AND acute kidney injury OR hemodialysis OR kidney disease OR kidney failure
2. Assessment			
2.1	Screen for malnutrition	No screen	Nutritional screening OR nutritional status AND hospitalized patients AND acute kidney injury OR kidney disease OR kidney failure
2.2	Assess nutritional status		Malnutrition OR nutritional status AND hospitalized patients AND acute kidney injury OR kidney disease OR kidney failure
2.3	Assess lean body mass, muscle mass and function		Acute kidney injury OR kidney disease OR kidney failure AND body composition OR muscle mass OR muscle function OR lean body mass
2.4	Malnutrition definition		Acute kidney injury OR kidney disease OR kidney failure AND malnutrition OR malnutrition diagnosis OR sarcopenia OR cachexia OR protein energy wasting
3. Timing and route of feeding			
3.1	Enteral feeding	Parenteral feeding	Refer to ESPEN guideline in polymorbid hospitalized medical inpatients and critically ill patients [5,26] Refer to ESPEN guideline in critically ill patients [5]
3.2	Parenteral nutrition indication		
3.3 Outcome	Enteral nutrition	Parenteral nutrition	Enteral nutrition or enteral feeding AND parenteral nutrition AND Complications OR aspiration OR hyperglycemia OR infections OR survival OR mortality OR length of stay
3.4 Safety	Enteral nutrition	Parenteral nutrition	Enteral nutrition or enteral feeding AND parenteral nutrition AND Acute kidney injury OR renal failure OR renal insufficiency OR renal dysfunction OR Renal replacement therapy OR hemodialysis
4. Energy requirements			
4.1	Indirect calorimetry	Predictive equations	Rest OR resting AND energy metabolism AND renal insufficiency OR acute kidney injury OR renal failure OR kidney failure
4.2	Optimal energy intake	Under or overfeeding	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND energy intake OR underfeeding OR overfeeding. Also refer to ESPEN guideline in polymorbid hospitalized medical inpatients and critically ill patients [5,26]
4.3	Carbohydrates and lipids based on measure utilization	Standard nutritional composition	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND carbohydrate metabolism OR lipids metabolism AND enteral nutrition AND parenteral nutrition
4.4	Energy balance KRT	Energy balance no KRT	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy OR renal replacement therapy AND energy intake OR energy sources OR overfeeding
4.5	Energy requirements KRT	Energy requirements no KRT	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy AND energy requirements OR indirect calorimetry
5. Protein requirements			
5.1	Protein balance KRT	Protein balance no KRT	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy AND protein needs OR protein catabolic rate
5.2	High protein intake	Standard protein intake	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy AND protein needs OR protein catabolic rate
5.3	Reduce protein intake to delay KRT	No reduction in protein intake	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy AND protein needs OR protein catabolic rate
5.4	Conservative therapy	No conservative therapy	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND protein intake OR low protein AND kidney replacement therapy OR renal replacement therapy
5.5	Maintain conservative therapy in CKD	No conservative therapy CKD	Chronic kidney disease OR kidney failure OR kidney disease AND protein needs OR protein catabolic rate OR low protein diet
6. Micronutrients requirements			
6.1	Supplementation trace elements and vitamins	No supplementation trace elements and vitamins	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND trace elements OR vitamins
7. Disease-specific nutrients			
7.1	Renal-specific formulae (EN or PN)	Standard formulae (EN or PN)	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND standard enteral nutrition OR renal enteral nutrition OR disease-specific enteral nutrition OR standard parenteral nutrition OR renal parenteral nutrition OR disease-specific parenteral nutrition
7.2	Omega-3	No omega-3	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND omega 3 OR omega 3 supplementation OR omega 3 parenteral nutrition
7.3	Glutamine	No glutamine	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND glutamine OR glutamine supplementation
8. Monitoring			
8.1	Normal range glycaemia	Higher range glycaemia	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND glycemic control OR hyperglycemia OR hypoglycemia OR tight glucose control
9. Electrolytes requirements			
9.1	Monitoring electrolytes	No monitoring of electrolytes	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND electrolytes OR electrolytes monitoring OR sodium OR potassium OR phosphorus OR magnesium
9.2	Dialysis/hemofiltration solutions enriched with phosphate, potassium and magnesium	Regular dialysis/hemofiltration solutions	Acute kidney injury OR renal failure OR kidney failure OR kidney disease AND kidney replacement therapy OR renal replacement therapy AND dialysis fluids OR dialysis solutions AND electrolytes

CKD, Chronic kidney disease; EN, Enteral nutrition; KRT, Kidney replacement therapy; PN, parenteral.

**Table 3**  
Definition of grades of recommendation [3].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

**Table 4**  
Classification of the strength of consensus [3].

Strong consensus	Agreement of > 90% of the participants
Consensus	Agreement of > 75–90% of the participants
Majority agreement	Agreement of > 50–75% of the participants
No consensus	Agreement of < 50% of the participants

**Table 5**  
KDIGO definitions for Acute Kidney Injury (AKI), Acute Kidney Disease (AKD) and Chronic Kidney Disease (CKD) [4–6].

Acute kidney injury (AKI)	≤7 days	Abrupt decrease in kidney function that occurs over a period of hours-days (less than seven days) <i>Criteria</i> <ul style="list-style-type: none"> <li>• Increase in sCr by ≥ 0.3 mg/dl (26.5 μmol/l) within 48 h; or</li> <li>• Increase in sCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or</li> <li>• Urine volume &lt; 0.5 ml/kg/h</li> </ul>
Acute kidney disease (AKD)	7-days to 3-months	Acute or subacute damage and/or loss of kidney function occurring for a duration of between 7 and 90 days after exposure to an AKI initiating event
Chronic kidney disease (CKD)	>3-months	Abnormalities in kidney structure or function that persist for ≥ 90 days with or without decreased eGFR <i>Criteria</i> <ul style="list-style-type: none"> <li>• Structural or functional abnormalities of the kidney; with or without decreased glomerular filtration rate (GFR); or</li> <li>• GFR &lt; 60 ml/min/1.73m<sup>2</sup> for ≥ 3 months with or without kidney damage</li> </ul>

AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease; SCR, serum creatinine; GFR, glomerular filtration rate.

all of the other clinical settings. AKI is classified according to three stages (Table 6), based on the KDIGO guidelines [4]. AKD by definition includes AKI but also includes disorders characterized by markers of kidney damage, such as hematuria, pyuria, or urinary tract obstruction, in which the rate of decline in GFR is not as rapid as in AKI. AKD diagnosis includes markers of kidney damage or GFR

reduction to <60 ml/min/1.73 m<sup>2</sup> for ≤3 months, without classification by severity [6]. It appears that AKD without AKI is more common than AKI. CKD is defined based on gradual and progressive loss of kidney function and/or the presence of markers and/or radiological/histological evidence of kidney disease (for example, proteinuria, renal ultrasound suggesting kidney disease, pathological renal biopsy findings, etc.) over months to years. CKD in its initial stages is almost always asymptomatic and is usually detected on routine screening blood work by either an increase in serum creatinine or by the presence of protein/blood in the urine [5]. CKD stages are described in Table 7. KF characterizes stage 5 of CKD, with or without KRT. It is to be understood that in many cases, AKI/AKD can be superimposed to a previous CKD condition (AKI/AKD on CKD).

### 3. General aspects (NON-PICO QUESTIONS)

#### 3.1. What is the impact of AKI/AKD and CKD on substrate metabolism?

##### Statement 1

**Kidney function impairment has negative effects on carbohydrate, protein, and lipid metabolism exerts a pro-inflammatory effect, and has a major impact on the anti-oxidative system.**

##### Strong consensus (100% agreement)

##### Commentary

Severe impairment of renal function (usually to be intended as a loss of glomerular filtration rate) which is peculiar of AKI/AKD and the most advanced stages of CKD up to KF, not only affects water, electrolyte, and acid-base metabolism but also induces global changes in the “milieu interieur”, along with specific alterations in protein, amino acid, carbohydrate and lipid metabolisms [10]. Additionally, it exerts a pro-inflammatory action and has a negative impact on the anti-oxidative system. AKI/AKD, especially in the ICU setting, rarely represent isolated disease processes. Metabolic changes in these patients are also determined by the underlying disease and/or comorbidities, by other organ dysfunction, as well as by the modality and intensity of KRT [10]. Important specific metabolic abnormalities associated with AKI/AKD, are:

- protein catabolism
- alteration of metabolism of specific amino acids
- peripheral insulin resistance
- reduction of lipolysis and impaired fat clearance
- depletion of antioxidant systems
- induction of a pro-inflammatory state
- immunodeficiency

Protein catabolism is the metabolic hallmark of AKI/AKD, especially in the ICU setting. The metabolism of the different amino acids is abnormal, several nonessential amino acids (e.g. tyrosine) become conditionally essential, and there are alterations in the intra- and extra-cellular amino acid pools, as well as in the utilization of exogenously administered amino acids. There is hyperglycemia, caused both by peripheral insulin resistance and the activation of hepatic gluconeogenesis. In contrast to the situation in patients with stable CKD and healthy subjects, the increased glucose formation cannot be suppressed by exogenous nutrient supply. Insulin resistance, defined as hyperglycemia despite high insulin concentrations, may be associated with increased risk of complications in critically ill patients with AKI/AKD; alterations in lipid metabolism are present and are characterized by hypertriglyceridemia due to an inhibition of lipolysis; finally, exogenous

**Table 6**  
KDIGO Classification of acute kidney injury [4, 6].

Acute kidney injury	Serum creatinine	Urine output
Stage 1	1.5–1.9 × baseline or $\geq 0.3$ mg/dl <sup>a</sup> above baseline	<0.5 ml/kg/hr for 6–12 h
Stage 2	2.0–2.9 × baseline	<0.5 ml/kg/hr for >12 h
Stage 3	$\geq 3.0$ × baseline, $\geq 4.0$ mg/dl <sup>a</sup> , or initiation of renal replacement therapy	<0.3 ml/kg/h for $\geq 24$ h of anuria for $\geq 12$ h

<sup>a</sup> To convert values for creatinine to  $\mu\text{mol/L}$ , multiply by 88.4.

**Table 7**  
KDIGO Classification of chronic kidney disease [5, 6].

GFR category	Definition	GFR ml/min/1.73 m <sup>2</sup>
1	Kidney damage with normal GFR	$\geq 90$
2	Kidney damage with mild decrease in GFR	60–89
3A	Mild-to-moderate decrease in GFR	45–59
3B	Moderate-severe decrease in GFR	30–44
4	Severe decrease in GFR	15–29
5	End Stage Renal Disease (ESRD)	

GFR, glomerular filtration rate.

fat particle clearance after parenteral or enteral administration of lipids can be reduced [10].

Additional features include the induction of a pro-inflammatory state and impaired immune competence. The plasma concentrations of water-soluble vitamins are reduced and the activation of vitamin D is impaired, contributing to secondary hyperparathyroidism. Vitamins E and A and selenium levels are low and there is a profound depression of the antioxidant system.

It should be pointed out that pre-existing CKD, especially in its most advanced stages, may already cause various levels of metabolic derangements including systemic oxidative stress and low-grade inflammation. This acutely worsening renal function in CKD patients (i.e., AKI/AKD on CKD) may lead to even worse metabolic alterations and consequent changes in skeletal muscle, adipose tissue, and body composition.

### 3.2. Are AKI/AKD or CKD independent risk factors for malnutrition?

#### Statement 2

**AKI/AKD and/or CKD with or without KF increase the risk for malnutrition by inducing multiple metabolic derangements and, frequently, by reducing nutrient intake**

**Strong consensus (100% agreement)**

#### Commentary

The pathogenesis of malnutrition in hospitalized patients with AKI/AKD and/or CKD with or without KF is complex and involves many different factors and mechanisms in the different patient settings considered [10,11]. In the case of AKI/AKD or AKI/AKD on CKD, especially in the ICU, the acute loss of kidney homeostatic function plays a central role in the worsening of the dysmetabolic status typical of critical illness (Fig. 1) [10]. Central to this process are both insulin resistance [12], which is frequently observed in patients with AKI and is closely associated with increased mortality risk [13], and the release of pro-inflammatory/oxidative stress mediators from the kidney into the systemic circulation [14]. In fact, AKI is now viewed as the consequence of an initially kidney-confined inflammatory process that rapidly spreads to the other organ/systems [15]; protein, carbohydrate, and lipid metabolism alterations, combined to cause a general disruption of the 'internal milieu', could be considered part of the systemic effects of a 'kidney-centered' inflammatory syndrome [16]. Most of the above mechanisms leading to malnutrition can be applied also to acutely ill hospitalized patients with AKI/AKD on CKD or KF not staying in the ICU. In fact, in renal patients with CKD with or without KF,

malnutrition is characterized by loss of protein and energy stores associated with multiple metabolic derangements, most of which are peculiar of the syndrome [17]. Several metabolic and clinical factors (Table 8) may negatively affect nutritional status and lean body mass [18,19], also leading to frailty [20]. Apart from an inadequate spontaneous nutrient intake, several other factors such as metabolic acidosis, insulin resistance, chronic inflammation, intestinal microbiota alterations (intestinal dysbiosis), infection and oxidative stress are also contributive to malnutrition development. In addition, factors related to CKD treatment itself, such as for example inappropriate dietary restrictions or hemodialysis procedures, may play a role. The overall effect is the persistence of a vicious cycle between malnutrition and its complications (Fig. 1) [17].

### 3.3. What is KRT and which modalities are currently used in hospitalized patients with AKI/AKD or CKD with KF?

The term KRT is currently used to include all of the different modalities used to replace kidney function (in particular glomerular or filtration function) in patients with AKI/AKD or CKD with KF. KRT provides clearance of solutes (such for example creatinine, urea, electrolytes, and other so-called "uremic toxins") depending on their molecular weight, removal of fluid excess, and maintenance of acid-base status and electrolyte homeostasis. However, neither the tubular secretive and reabsorptive function nor the endocrine function of the normal kidney is replaced by KRT. Furthermore, solute clearance, even in the case of optimal KRT, is significantly lower than that achieved by the normal kidney, since it is only about 10–20% of the physiological clearance of index substances such as urea or creatinine, and even less in case of higher molecular weight solutes. Finally, some beneficial substances, and in particular some low molecular weight macronutrients or micronutrients, like amino acids or water-soluble vitamins can be lost as well, since they are easily removed during KRT. The basic principles of solute removal by KRT are diffusion and convection (Fig. 2). Diffusion is the movement of solutes from an area of high concentration to an area of low concentration across a semipermeable membrane. The movement continues until equilibrium is reached. In the case of convection, the solvent (i.e. water) carries the solutes across the membrane (solvent drag); fluid is thus removed (a process called ultrafiltration) together with solutes, removed by convection. The semipermeable membrane can be artificial, so that the blood of the patient is to be sent by a machine in an external filter in an extracorporeal circuit, or natural. In the latter case the only membrane available to this purpose is the peritoneal membrane, and blood flow is granted by the peritoneal microcirculation. Peritoneal dialysis fluids are removed by the creation of an osmotic gradient vs the peritoneal capillaries through the instillation of osmotic solutions (hypertonic glucose or icodextrin) in the peritoneal cavity. Based on these principles KRT can be divided into extracorporeal KRT (hemodialysis and/or hemofiltration) and intracorporeal KRT (peritoneal dialysis, PD). Diffusion and convection are usually combined and proceed simultaneously both in hemodialysis and in PD. Hemodialysis (usually lasting 4 h thrice a week) represents the standard

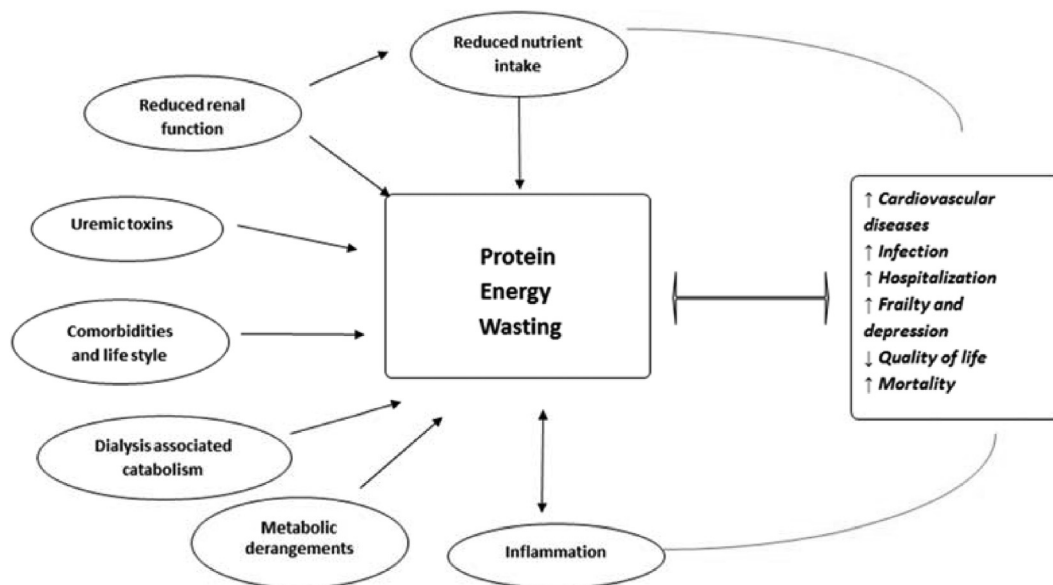


Fig. 1. Vicious circle of malnutrition in CKD [17].

**Table 8**  
Causes and mechanisms of Protein energy wasting in CKD patients [17].

1. Reduced protein and energy intake	a. Anorexia: <ol style="list-style-type: none"> <li>i. Dysregulation of appetite mediators</li> <li>ii. Amino acid stimuli in the hypothalamus</li> <li>iii. Uremic toxins</li> </ol> b. Inappropriate dietary restrictions c. Gastrointestinal diseases d. Depression e. Difficulties in food preparation f. Socio-economic difficulties
2. Hypercatabolism	a. Increase in energy expenditure: <ol style="list-style-type: none"> <li>i. Chronic inflammation</li> <li>ii. Increase in pro-inflammatory cytokines</li> <li>iii. Altered metabolism of adiponectin and resistin</li> </ol> b. Hormonal changes: <ol style="list-style-type: none"> <li>i. Insulin resistance</li> <li>ii. Increased glucocorticoid activity</li> </ol>
3. Metabolic acidosis	Increased protein breakdown, increased BCAA oxidation, insulin and IGF-1 resistance
4. Reduced physical activity	Reduced muscle trophism, reduced self-sufficiency, reduced performance
5. Reduced anabolism	a. Reduced uptake of nutrients b. Resistance to insulin, GH/IGF-1 c. Testosterone deficiency d. Reduced levels of thyroid hormones
6. Comorbidities and life style	a. Comorbidities (diabetes, heart failure, ischemic heart disease, peripheral vascular disease) b. Sedentary lifestyle
7. Dialytic treatment	a. Loss of amino acids and proteins in the dialysate b. Inflammatory processes related to dialysis c. Hypermetabolism related to dialysis d. Loss of residual renal function

CKD, chronic kidney disease; GH, growth hormone; IGF, insulin-like growth factor.

treatment for patients with CKD in the KF stage on chronic KRT, being only a minority of these patients on PD. Many different modalities are instead currently available in critically ill patients with AKI/AKD. All of them are based on diffusion or convection or a combination of both, but they can be significantly different for what concerns the efficiency (clearance) and duration. The choice of treatment thus depends on this case from the characteristics of patients and is mainly based on an integrated clinical judgment on depurative needs (for example the rate of catabolism), fluid removal needs, and hemodynamic status of the patient. Only a few critically ill patients with AKI/AKD can tolerate the relatively short duration of treatments typical of the conventional hemodialysis

schedule routinely used for patients with KF. As far as hemodynamic status is concerned, more prolonged KRT modalities (from eight to 12 h a day up to 24 h a day, i.e. continuously) are usually more adequate. In Western countries and the US, PD is not routinely utilized for critically ill adult patients in the ICU. Thus, in this clinical setting, extracorporeal KRT represents the gold standard, and in the case of acutely/critically ill, AKI/AKD patients are usually classified based on its duration [21]. Each of the principal modalities of KRT used in the ICU (intermittent, prolonged intermittent, and continuous) carries advantages and disadvantages in this specific patient setting. In the case of AKI/AKD patients outside

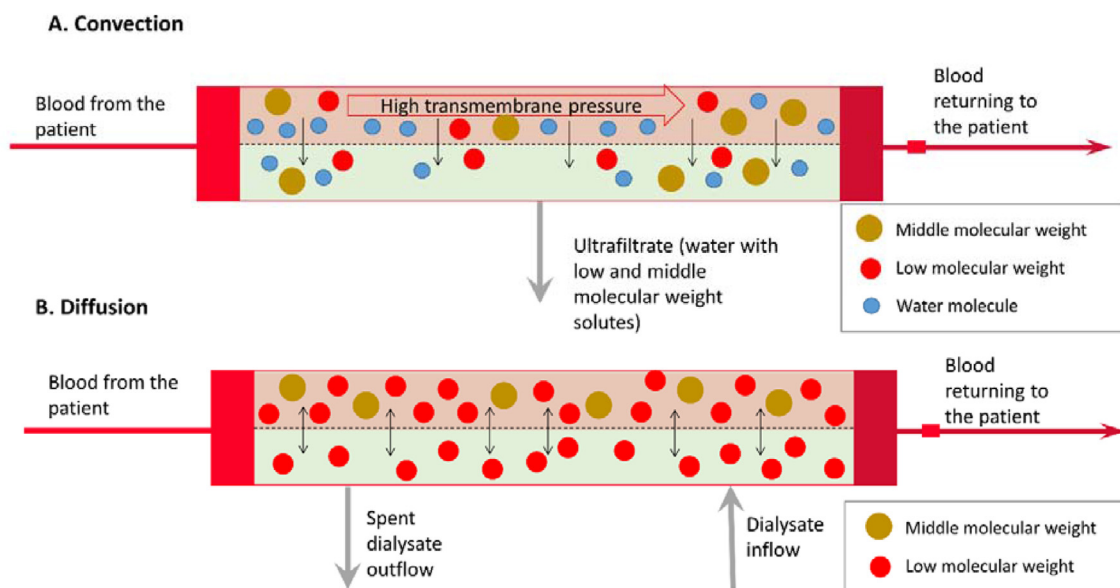


Fig. 2. Principles of solute removal in KRT (diffusion and convection).

the ICUs, intermittent conventional hemodialysis represents the most commonly used modality of KRT.

### 3.4. Modalities of KRT

Intermittent hemodialysis is the most commonly used extracorporeal KRT modality in patients with advanced CKD in the KF stage, but it can be used also in patients with AKI/AKD or AKI on CKD provided they are not hemodynamically unstable. Intermittent hemodialysis is usually performed three times a week for three to 4 h. Intermittent hemofiltration can be also used in patients with KF on chronic KRT in hypotension-prone subjects. In this case, clearance is achieved by convection. However, in most of these cases, hemodialysis and hemofiltration are combined in the same KRT session (hemodiafiltration). In the ICU, the more prolonged modalities are preferred, such as CKRT or Prolonged Intermittent Kidney Replacement (PIKRT). This latter term encompasses the group of the so-called "hybrid" therapies since it combines the characteristics of intermittent and continuous KRT concerning the prolonged duration and increased frequency of treatment, along with the main advantages of both [21].

The use of more prolonged KRT modalities such as CKRT and PIKRT in critically ill patients has the advantage of better hemodynamic stability, slower and reduced solute shifts, and better tolerance of fluid removal, and are therefore preferentially used in patients with AKI and hemodynamic instability [22]. No clear advantage has been demonstrated so far for CKRT over PIKRT.

### 3.5. Peritoneal dialysis

In addition to the above mentioned extracorporeal treatments, some hospitalized patients are treated with PD. The use of PD in the adult ICU setting is quite rare in Western countries, while it can be more frequent in the case of hospitalized patients previously on continuous ambulatory peritoneal dialysis (CAPD, a PD modality based on daily manual exchanges by the patient at home) or automated peritoneal dialysis (APD, a PD modality where exchanges are by a simplified machine, usually at home and by night). PD is based on the exchange of solutes between the blood in the peritoneal capillaries and the dialysis fluid is introduced in the

peritoneal cavity and subsequently drained. PD solutions contain glucose or another sugar to achieve fluid removal. However, dextrose is absorbed over time, and this may cause a positive glucose balance of about 400 kcal/d.

## 4. Recommendations

### 4.1. Indication

4.1.1. Does nutritional treatment (based on screening and/or assessment versus no screening and/or assessment) improve outcomes and which patients would benefit from it?

#### Recommendation 1

**Medical nutrition therapy may be considered for any patient with AKI/AKD, AKI on CKD, CKD with or without KF requiring hospitalization.**

**Grade of recommendation GPP – Strong consensus (100% agreement)**

#### Recommendation 2

**Medical nutrition therapy should be provided to any patient with AKI/AKD, AKI on CKD, CKD with or without KF staying in the ICU for more than 48 h.**

**Grade of recommendation GPP – Strong consensus (100% agreement)**

#### Commentary to recommendations 1 and 2

Patients with CKD, especially in those in the KF stage undergoing or not chronic dialysis, are at high risk of developing nutritional disorders [11]. Progressive depletion of protein and/or energy stores is often observed [23], with prevalence rates that increase along with the decline in kidney function [23]. In a global meta-analysis, the prevalence of malnutrition as defined by subjective global assessment (SGA) or malnutrition-inflammation score was found to range from 11% to 54% in patients with non-dialysis CKD stages 3–5, and between 28 and 54% in patients undergoing chronic hemodialysis [24]. Given this high prevalence, we find it justified to suggest that all patients admitted to the hospital should be considered at risk of malnutrition.

For ethical reasons, there are no studies directly addressing the effects of starvation of hospitalized patients with KF. The scientific literature regarding nutritional support in AKI is scarce and



mainly represented by low-quality studies from the 1980s that have been summarized in more recent reviews [10,25,26]. Given that even kidney impairment per se does not cause major modifications on energy needs [1], and important alterations in energy expenditure are usually better explained by acute comorbidities and complications, recommendations for medical nutrition therapy in patients with AKI and critically-ill patients with CKD with KF should be the same as for any other ICU patient (see ref. [8]). Since the publication of the earlier ESPEN recommendations [1,2], a cut-off of 48h for the initiation of early nutrition has been established for critically ill patients [8,27], and we feel this is also adequate in patients with AKI/AKD or CKD with KF in the ICU.

### Recommendation 3

**In malnourished non-critically ill hospitalized patients with AKI/AKD or CKD with or without KF and those patients at risk for malnutrition who can safely feed orally but cannot reach their nutritional requirements with a regular diet alone, ONS shall be offered.**

**Grade of recommendation A – Strong consensus (100% agreement)**

#### Commentary

In stable, non-critically ill hospitalized patients with AKI/AKD or CKD with or without KF, nutritional support is indicated in patients with malnutrition or patients at risk of malnutrition [1,28,29]. ONS, and especially those with higher energy and protein content, can add up to 10–12 kcal/kg and 0.3–0.5 g of protein/kg daily over the spontaneous intake in a 70 kg patient if provided two times a day at least 1 h after a meal, thus facilitating the achievement of nutritional targets [23]. To our knowledge, there are no published studies on this topic in non-critically ill hospitalized patients with AKI/AKD or CKD with or without KF. However, evidence in polymorbid (defined as two or more chronic comorbidities) inpatients suggests that ONS may improve nutritional status, and we speculate that this evidence may also extend to the polymorbid inpatient with AKI/AKD or CKD with or without KF. In a large RCT with 200 inpatients from internal medicine wards, ONS combined with physiotherapy increased energy and protein intake without negatively affecting hospital food consumption, while preserving lean body mass during recovery and until three months after discharge [30]. In another large (n = 445) RCT of hospitalized patients, ONS provision significantly improved nutritional status, as assessed by serum albumin, red-cell folate, and vitamin B12 concentration, and reduced the number of non-elective readmissions in the following six months after discharge [31]. Similar results were found in other RCTs in which ONS resulted in improved nutritional status (as assessed by the difference in body weight and functional status) [32,33], reduced complications [32], and mortality [34,35].

Besides, there is rich evidence from RCTs in non-hospitalized patients with KF suggesting that ONS may rapidly improve nutritional status as well as some aspects of quality of life and physical functioning [28,36–46]. In an observational study that enrolled CKD patients on hemodialysis with low serum albumin, the provision of ONS was associated with improved survival rates [43]. A large trial of undernourished CKD patients on hemodialysis showed that standard ONS is capable of inducing a sustained improvement of serum albumin and transthyretin independently from inflammatory status, and the increase in transthyretin during ONS was associated with better survival [47].

### Recommendation 4

**Intradialytic parenteral nutrition (IDPN) shall be applied in malnourished non-critically ill hospitalized patients with CKD and KF on hemodialysis, or the same patients if at risk of malnutrition that fail to respond or do not tolerate ONS or EN.**

**Grade of recommendation A – Strong consensus (91.7% agreement)**

### Commentary

IDPN is a specific modality of PN that can be applied only to patients with KF on chronic hemodialysis. It is based on the administration of macro- and micronutrients in the extracorporeal circuit of hemodialysis, three times a week for three to 4 h [48]. Although the gastrointestinal route is the preferred choice for nutritional supplementation, parenteral provision of nutrients during hemodialysis is a safe and convenient approach for individuals who cannot tolerate oral or enteral administration of nutrients. Multiple studies, including several RCTs, showed evidence for nutritional improvements with the use of IDPN in patients with KF on hemodialysis with overt protein-energy wasting [1,47,49–51]. Because of its non-superiority to ONS, and its time limitation (hemodialysis is usually 4 h three times a week), IDPN may be a reasonable treatment option for patients who fail to respond or cannot receive recommended treatments, but the widespread use of IDPN before trying counseling and ONS does not appear warranted [52].

### Recommendation 5

**EN, PN, or EN and PN shall be given to critically and non-critically ill hospitalized patients with AKI/AKD, CKD, CKD with KF unable to achieve at least 70% of macronutrient requirements with oral nutrition.**

**Grade of recommendation A – Strong consensus (95.7% agreement)**

#### Commentary to recommendations 1–5

EN is indicated if oral intake (with or without ONS) is not sufficient to meet at least 70% of daily requirements [1,8]. Reaching nutritional intake goals is important to prevent weight loss and loss of muscle mass. However, in the hospital care setting, many conditions may interfere with the patient's spontaneous oral intake [53]. These conditions may include loss of appetite, delayed gastric emptying, and dysphagia among others. In these cases, the use of EN or PN may help increase nutritional intake [54,55]. No study has specifically investigated the effect of nutritional support or compared EN and PN in non-critically ill hospitalized patients with AKI/AKD, CKD, or CKD with KF. Several RCTs compared the effects of nutritional support on the outcome of patients hospitalized in internal medicine wards. A recent meta-analysis of 27 trials found increased energy and protein intake with beneficial effects on weight in patients receiving EN when comparing to the control group [56]. There is some observational evidence comparing EN and PN effects on the outcome of non-critically ill internal medicine patients [57]. In this large observational study (n = 1831), the authors found a significantly lower risk of overall complications and infections associated with medical nutritional therapy. Particularly, patients receiving EN had significantly lower infectious and non-infectious complications than those receiving PN [57]. Regarding the critical care setting, there is some evidence demonstrating that EN compared to PN results in lower complication risk [8]. Besides, one study in non-malnourished critically-ill patients with AKI described potential advantages in delaying PN if EN is not possible/tolerated [58,59]. A careful and progressive re-introduction of nutrition may prevent the risk of refeeding syndrome, particularly in patients who are severely malnourished or report reduced food intake before or during admission [8].

## 4.2. Assessment

4.2.1. *Should all hospitalized patients with AKI/AKD, and/or CKD be screened for malnutrition?*

### Recommendation 6

**Any hospitalized patient with AKI/AKD and/or CKD with or without KF, and especially those staying for more than 48 h in the ICU, should be screened for malnutrition.**

### Grade of recommendation GPP – Strong consensus (95.7% agreement)

#### Commentary

Few existing screening tools have been evaluated in hospitalized patients with AKI/AKD and/or CKD. The malnutrition universal screening tool (MUST) score was found to have low sensitivity in these patients [60], perhaps due to the complex and multifactorial nature of malnutrition in patients with kidney diseases. MUST screening acknowledges acute starvation but omits some KF-specific risk factors such as anorexia and nutritional deficit [61,62]. The nutritional risk screening (NRS) 2002 tool [63,64] has been reported to adequately identify patients considered malnourished by SGA and predicted worse clinical outcomes [65,66]. We are not aware of studies comparing the reliability of existing screening tools in these patients. Therefore, we conclude that until such studies are conducted all screening tools ought to be considered equally valuable. Nutrition-related symptoms have been shown to have an important role in predicting malnutrition risk in kidney patients, and among those, appetite loss conveyed the highest prognostic power [67,68]. Recently, a new renal inpatient nutritional screening tool (Renal iNUT) was specifically developed for hospitalized patients with AKI/AKD and/or CKD, or CKD with KF on KRT [60], showing a good sensitivity, specificity, and positive predictive value against the SGA. In addition to the components of MUST, the renal iNUT includes questions on appetite, dietary intake, use of nutritional supplements, and kidney-specific details on weight (dry-weight target or edema free target weight). However, whether the renal iNUT may be an adequate tool to screen hospitalized patients with kidney diseases requires external validation.

#### 4.2.2. How to assess nutritional status in hospitalized patients with AKI/AKD and/or CKD?

##### Recommendation 7

**Until a specific tool has been validated, a general nutritional assessment should be performed to any hospitalized patient with AKI/AKD or CKD with or without KF at risk of malnutrition.**

**Grade of recommendation GPP – Strong consensus (91.3% agreement)**

#### Commentary

A general nutritional assessment should include patient history, report of unintentional weight loss or decrease in physical performance before hospital or ICU admission, physical examination, general assessment of body composition, muscle mass, and strength.

In the absence of consensus in defining one single tool for the assessment of nutritional status, the diagnosis of malnutrition should be made by clinical observations and complementary examinations [3]. Many tools have been suggested to assess malnutrition in hospitalized patients, however, most of them suffer from major limitations, especially when applied to patients with kidney disease [69] and especially to those in the ICU [10].

Body weight and BMI, unless very low (e.g. BMI <18 kg/m<sup>2</sup>), are poor nutritional assessment tools in hospitalized patients with AKI/AKD and/or CKD or CKD with KF. This is because body size measures cannot take into account the frequent presence of fluid overload in these patients, and cannot distinguish fat from muscle stores [10]. Overweight/obesity is not uncommon in AKI or CKD with KF, and conditions of low lean body mass or skeletal muscle mass loss may exist in these patients despite appearing as having a normal or overweight BMI (e.g. sarcopenic obesity) [70,71].

The SGA has been used in AKI patients to diagnose nutritional derangements, and it has been shown to predict poor outcomes at the population level [72]. The SGA has also been used to identify malnourished hospitalized KF patients on chronic hemodialysis

[73]. Severe malnutrition by SGA at ICU admission was also associated with late mortality (until six months after discharge) in AKI patients [74]. This being said, the SGA is not widely employed and can be difficult to apply in the ICU setting.

Despite its sensitivity as a screening and prognostic tool, serum albumin provides limited information about the complex nature of the underlying nutritional problem in the setting of AKI and CKD. The albumin concentration is the net result of its synthesis, breakdown, the volume of distribution, and exchange between intra- and extra-vascular spaces, as well as losses [75]. Besides, it is a negative acute phase reactant, i.e., during acute illness its synthesis is reduced, resulting in low serum levels. Albumin level values should not be interpreted alone, and the appropriate nutritional assessment should also include a thorough physical exam and clinical judgment [76].

#### 4.2.3. How to assess lean body mass, muscle mass, and function?

##### Recommendation 8

**Body composition assessment should be preferred to anthropometry measurements when diagnosing and monitoring malnutrition in hospitalized patients with AKI/AKD and/or CKD or CKD with KF.**

**Grade of recommendation B – Strong consensus (95.7% agreement)**

#### Commentary

Because critically ill patients suffer an important and accelerated skeletal muscle loss already occurring in the first few days at the ICU [8,77,78], body composition monitoring during hospital stay appears of major importance. Identifying early muscle loss is important since it could represent a major cause of delayed weaning from mechanical ventilation, and a well-known predictor of both in-hospital mortality and morbidity [79], functional recovery [80,81], and disability after discharge [82,83]. Key problems in this regard are however the lack of reliable bedside tools able to assess muscle mass and the interference of fluid overload and rapid fluid shifts when using conventional methods for muscle mass evaluation. Because of such drawbacks, the literature investigating the role of body composition in hospitalized patients with kidney disease is scarce. A study on 31 critically-ill patients with AKI used bioelectric impedance analysis (BIA) and observed that measurements performed after KRT reported a reduction in the estimated fat free mass of almost 5% in comparison to measurements performed before KRT, showing how unreliable BIA can be when patients are overhydrated [84]. In another study, BIA analysis only suggested the presence of excess total body water and body fat, thus hampering the possibility to separately detect any change in lean body mass [85]. While dual energy X-ray absorptiometry (DEXA), computed tomography scan (CT), and magnetic resonance imaging (MRI) are considered the reference standard techniques for the assessment of skeletal muscle mass and body composition [86], however, they cannot be used routinely for nutritional status assessment in ICU or more in general in hospitalized patients [86]. As a potential alternative method, the use of ultrasound for the assessment of muscle mass has been recently investigated in hospitalized patients with AKI and CKD patients with KF on hemodialysis, with good reliability [87,88]. Muscle ultrasound is a noninvasive technique easily applicable even in non-collaborative patients, it appears economically viable, safe and does not require specialized staff nor X-ray exposure [87,89–91]. Besides, muscle ultrasound measures seem to be scarcely influenced by rapid fluid shifts both in patients with AKI and in patients with CKD and KF on chronic hemodialysis [87,92]. Validations studies against CT in critically ill patients with AKI disclosed an absence in differential and proportional bias, with a minor loss of precision [88]. Because of the

lack of cutoff values to identify low muscle mass using ultrasound, we suggest that ultrasound may be valuable for monitoring of muscle mass during recovery and for assessing the effectiveness of physical and nutritional interventions. CT scan has also been used in the ICU to assess skeletal muscle mass (at the L3 vertebra level), but obviously may be useful only for patients already undergoing abdominal CT for other clinical reasons [93]. Low muscle mass by CT scan at admission predicted a higher length of stay and the risk of mortality [94], while it associated with the risk of complications and 30-day mortality in ICU patients when measured at the time of extubation [95]. However, at the present time its use is confined to research purposes.

In summary, amongst the currently validating techniques, ultrasound appears promising and easy to implement in the ICU and the hospital wards. For those patients undergoing abdominal CT, the assessment of skeletal muscle mass at the level of the third lumbar vertebra can be a valuable prognostic and diagnostic tool.

#### Recommendation 9

**In collaborative patients with AKI/AKD and/or CKD or CKD with KF, muscle function should be assessed by hand-grip strength.**

**Grade of recommendation B – Strong consensus (95.7% agreement)**

#### Commentary to recommendations 8 and 9

Besides malnutrition, other conditions such as critical illness polyneuropathy, critical illness myopathy, and disuse atrophy caused by immobilization may increase the risk of developing a specific neuromuscular dysfunction syndrome during and after an ICU stay, including a form of severe weakness typical of critically ill patients, currently known as ICU-acquired weakness [96]. Decreased functional capacity before hospital admission is associated with increased hospital mortality regardless of age, comorbidities, disease severity, and type of ICU admission [97]. In individuals aged 70 years or older [98], the pre-ICU functional trajectory strongly influences post-ICU functional status. Pre-morbid health status, the functional decline in the ICU, and post-ICU functional status are likely determined by the complexity of different factors over time.

In the ICU the recommended tool to assess muscle strength is the six-point Medical Research Council (MRC) score. An MRC sum score of less than 48 for 12 muscle groups (or a mean MRC of less than four per muscle group) is used as the cutoff for defining ICU-acquired weakness [99–101]. However, assessing the MRC score in ICU patients is time-consuming and requires adequate training. Handgrip strength dynamometry has been proposed as a simple and easy diagnostic method for ICU-acquired weakness and can identify disorders even before the changes in body composition parameters are identified, allowing nutritional interventions to be made earlier, and possibly influencing the prognosis of the patient [101,102]. There are no studies available regarding the use of MRC score in critically ill patients with KF. On the other hand, handgrip strength has been used in this clinical setting to assess muscle strength. In a cohort of hospitalized patients with KF and at risk of malnutrition, handgrip strength values were shown to be in the sarcopenic range [60]. In another study, handgrip strength lower than 10 kg at the time of discharge and lower than 15 kg one month after hospital discharge were associated with the risk of death [74]. In patients with KF on hemodialysis, handgrip strength correlates with the number of comorbidities and the malnutrition inflammation score [92,103]. Despite these promising applications, we do not recommend handgrip strength to be used in isolation as it also has some limitations. One important limitation is that cooperation by the subject is always required. Besides, there is still no absolute consensus on the measurement protocols for handgrip

strength, the handheld dynamometer must be well-calibrated and adjusted for hand size for accurate measurements and finally, standard reference values for handgrip strength are also lacking [104].

#### 4.2.4. How to define malnutrition in patients with AKI/AKD and/or CKD or CKD with KF?

##### Statement 3

**There is no uniform and validated criteria to define malnutrition in hospitalized patients with AKI/AKD and/or CKD or CKD with KF. Studies to validate the ESPEN endorsed GLIM criteria in patients with kidney disease should be performed.**

**Strong consensus (100% agreement)**

##### Commentary

The pathophysiology of nutritional disorders in patients with kidney disease is complex, involving both reduced food intake or deranged assimilation of nutrients, and disease-associated and comorbidity-associated hypercatabolism. There is no clear consensus on how to define these derangements, and available definitions are based on studies of stable patients with CKD managed in outpatient care. We will argue here that some of these definitions may not apply for diagnostic purposes in inpatient settings and especially in AKI.

The International Society of Renal Nutrition and Metabolism (ISRNM) [28], introduced the term “protein-energy wasting” to indicate “a condition of decreased body stores of protein and energy fuel (i.e. lean body mass and fat stores), which can occur in either AKI or CKD, regardless of the cause, and can be associated with diminished functional capacity related to metabolic stresses” [28]. Although this definition corresponds to what occurs physiologically in hospitalized patients, the recommended criteria to diagnose it may not be entirely suitable for the setting of hospitalized KF and we refer to sections 2.2 and 2.3 above regarding limitations of diagnostic tools. Furthermore, the criteria of diagnosis of protein-energy wasting by derangements in three out of four subsets of nutritional indicators still lacks internal or external validation, despite having been shown to strongly predict long-term mortality, at least in chronic hemodialysis patients [105].

Major clinical nutrition societies worldwide joined in the Global Leadership Initiative on Malnutrition (GLIM) and established a consensus definition for an etiology-independent diagnosis of malnutrition in adults from different clinical care settings [76]. The GLIM criteria consist of a two-step model for risk screening (with tools such as NRS-2002, MUST, and the short form of the mini-nutrition assessment (MNA-SF)) and diagnostic assessment. Assessment includes five criteria: three phenotypic criteria, i.e. non-volitional weight loss, low BMI (<20 kg/m<sup>2</sup> if < 70 years old or < 22 kg/m<sup>2</sup> if > 70 years old), and reduced muscle mass (by DEXA, BIA, CT or MRI using their corresponding standards), and two etiological criteria, i.e., reduced food intake or assimilation, and disease burden/inflammation (acute illness or chronic disease-related). Diagnosis of malnutrition requires at least one phenotypic and one etiological criterion. No study has validated so far the application of these criteria in hospitalized patients with kidney disease. Limitations of BMI use in overhydrated patients may also lead to underestimating malnutrition in this setting, and special attention should therefore be paid to the use of this criterion in potential applications of the GLIM approach to hospitalized subjects with AKI/AKD and/or CKD or CKD with KF.

The term cachexia is used to describe a syndrome associated with chronic conditions, including CKD and CKD with KF, and is characterized mainly by the loss of muscle mass. Loss of fat can also be present but is not a requisite for its diagnosis [106]. The clinical manifestations of cachexia include weight loss corrected for fluid retention and anorexia. Its pathophysiology is thus similar to the

ISRNM definition of protein-energy wasting, in which cachexia is suggested for most severe stages of protein-energy wasting [28,107]. Diagnostic criteria proposed by the Society on Sarcopenia, Cachexia and Wasting Disorders are similar to those of protein-energy wasting, since both rely on serum chemistry, measures of body and muscle mass, and nutritional intake, with thresholds being lower for cachexia than for protein-energy wasting. However, as mentioned above, these criteria may not be fully suitable for the acute care setting, especially in the ICU.

Sarcopenia is a complex geriatric syndrome associated with the loss of muscle mass and function [76]. Sarcopenia can be defined as primary or secondary. In the first case, it is a sole consequence of aging, while secondary sarcopenia has a multifactorial etiology, and includes as possible causes the decline in physical activity, alterations of the endocrine system, presence of chronic or acute illnesses, inflammation, insulin resistance, and nutritional inadequacy [108]. Many operational definitions for sarcopenia have been proposed during the last decade [76,108–111]. In any case, reliable assessments of muscle strength and function may be difficult to obtain in the inpatient setting, especially in critically ill patients.

#### 4.3. Timing and route of feeding

##### 4.3.1. Which is the most appropriate route of feeding and when it should be started?

For this PICO question, we refer to recommendation 8.1 of the ESPEN guideline for polymorbid hospitalized medical patients [29] and recommendations 4 and 5 of the ESPEN guideline for critically ill patients [8].

**Early nutritional support (i.e. provided in less than 48 h from hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved.**

**Grade of recommendation B – strong consensus (95% agreement) [29]**

**If oral intake is not possible, early EN (within 48 h) in critically ill adult patients should be performed/initiated rather than delaying EN.**

**Grade of recommendation B – strong consensus (100% agreement) [8]**

**If oral intake is not possible, early EN (within 48 h) shall be performed/initiated in critically ill adult patients rather than early PN.**

**Grade of recommendation A – strong consensus (100% agreement) [8]**

##### Commentary

As discussed above in section 1, non-critically ill patients with AKI/AKD and/or CKD, or CKD with KF are a high-risk population for developing malnutrition and muscle loss and should receive nutritional therapy when needed. There are no published studies, to our knowledge, on non-critically ill hospitalized patients with kidney diseases that investigated the timing for initiation of such therapy. However, evidence in polymorbid (defined as two or more chronic comorbidities) inpatients shows that this population could benefit from early nutritional support during hospital admission to avoid worsening of nutritional status with subsequent negative outcomes [29]. In one RCT on 200 elderly inpatients [30], early nutritional support and physical rehabilitation were able to attenuate muscle loss during the hospital stay and helped to regain lean body mass back to its original value within 12 months after discharge. In another study [112], early EN was related to reduced infection rates and better self-sufficiency.

The timing of initiation and the best route of feeding in critically ill patients has been a matter of debate for years. In comparing early EN vs. delayed EN (including six studies in ICU patients [113–118] and four studies including non-ICU patients [119–122] and early EN vs PN (including six studies in ICU patients [123–128] and seven studies with also non-ICU patients included [129–135] the ESPEN guideline in critically ill patients reports a reduction in infectious complications when using early EN. Besides, in comparison to early PN, early EN was also related to shorter hospital and ICU stays [8].

In line with the ESPEN and ESICM guidelines [8,27], we suggest to withhold EN in critically ill patients with AKI/AKD and/or CKD, or CKD with KF when there is uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate volume > 500 ml/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access.

##### 4.3.2. When is PN indicated?

For this PICO question, we refer to the recommendations 6 and 7 of the ESPEN guideline for critically ill patients [8].

**In case of contraindications to oral and EN, PN should be implemented within three to seven days.**

**Grade of recommendation B – consensus (89% agreement) [8].**

**Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.**

**Grade of Recommendation 0 – strong consensus (95% agreement) [8].**

##### Commentary

A meta-analysis of studies comparing enteral and parenteral routes independent of timing [136], found an important reduction in infectious episodes with EN as compared to PN (RR 0.64, 95% CI 0.48, 0.87, P ¼ 0.004, I2 ¼ 47%). This difference did not occur when the calories administered by PN and EN were similar (most recent studies), suggesting that caloric overfeeding may play a role in the infectious complications of PN. However, considering the negative consequences of malnutrition and muscle wasting, and based on expert consensus, also in the case of AKI/AKD and/or CKD or CKD with KF, when a patient is likely to be at high nutritional risk or severely malnourished, and EN is not possible, the initiation of PN should be carefully considered and balanced against the risks of overfeeding and refeeding.

##### 4.3.3. Is EN associated with improved outcomes as compared to PN?

##### Statement 4

**As in other clinical settings (polymorbid hospitalized patients, ICU patients) EN is the most physiologic route of feeding in comparison to PN, and in general has been linked to lower infection rates, shorter ICU and hospital stay.**

**Strong consensus (100% agreement)**

##### Commentary

As in other clinical settings, the route of feeding depends more on gastrointestinal tract function than on the presence of renal function impairment itself. In the past, critically ill patients with AKI/AKD were mostly fed via the parenteral route, while now the enteral route is the first choice for medical nutrition therapy. Safety and efficacy of nutritional support administered solely via EN were evaluated in an observational study on 182 critically ill patients with AKI, there was no evidence that AKI is associated with a consistent increase in gastrointestinal, mechanical, or metabolic complications during EN [137]. In other clinical settings, the evidence favoring EN instead of PN is more consolidated. In a meta-analysis of studies comparing EN and PN in the ICU independent of timing, EN was able to reduce dramatically the risk for ICU

acquired infections [136]. While other studies in critically ill [123–128] and non-ICU patients [129–133] showed a reduction in infectious complications, shorter ICU and hospital stay with early EN versus PN.

#### 4.3.4. Is EN safe in hospitalized patients with AKI/AKD or CKD/CKD with KF as compared to PN when renal function is reduced?

##### Statement 5

**There is no evidence linking a reduced renal function with an increase of either gastrointestinal, mechanical, or metabolic complications during EN in patients with AKI/AKD and/or CKD or CKD with KF.**

##### Strong consensus (100% agreement)

##### Commentary

EN represents the first and most important measure to support and restore gastrointestinal function, especially in the critically ill [8]. However, it is frequently impossible to meet the nutrient requirements exclusively by EN, making supplementation of one or more nutrients by the parenteral route necessary. EN should start at low rates and should be increased slowly (over days) until requirements are met. Clear evidence concerning the incidence and severity of refeeding syndrome in hospitalized patients with kidney disease is not available at present: however, plasma electrolyte and phosphorus levels must be strictly monitored [1].

Few systematic clinical trials of EN in hospitalized patients with kidney disease are currently available. The largest observational study to date has evaluated the safety and efficacy of nutritional support administered solely via nasogastric tubes using either a standard formula or a disease-specific formula for patients with KF on hemodialysis in 182 patients with AKI, [137]. No evidence was found that AKI is associated with a serious increase of either gastrointestinal, mechanical, or metabolic complications when EN was chosen. High gastric residuals were more frequent in patients with AKI compared to those with normal renal function, but in general, EN was safe and effective [137].

#### 4.4. Energy requirements

##### 4.4.1. How to define energy requirements?

##### Recommendation 10

**In hospitalized patients with AKI/AKD and/or CKD or CKD with KF needing medical nutrition therapy, indirect calorimetry should be used to assess energy expenditure to guide nutritional therapy (caloric dosing) and avoid under- or overfeeding.**

**Grade of recommendation B – Strong consensus (95.7% agreement)**

*Bearing in mind that predictive equations and weight-based formulae are subject to significant bias and imprecision especially in kidney patients, in the absence of IC, for non-critically ill patients with AKI/AKD and/or CKD or CKD with KF staying in a medical ward and not on a low protein diet, we refer to the recommendations 4.2 and 4.3a and b of the ESPEN guideline for polymorbid internal medicine patients [29].*

*For non-critically ill CKD patients with KF (without KRT) staying in a medical/nephrology ward with no stress factors, and continuing previously established low protein diet regimens during the hospital stay, the 30–35 kcal/kg/d amount already indicated in the past ESPEN guidelines [1,2] can be confirmed.*

##### Commentary

Accurate determination of protein and energy needs is important in this clinical setting because both over- and underfeeding may occur and are likely to be associated with poor outcomes [10,138].

The gold standard for measuring individual caloric needs is represented by indirect calorimetry, a noninvasive method allowing resting energy expenditure (REE) assessment based on oxygen consumption and carbon dioxide production measurements in the exhaled air [139]. In critically ill patients, REE measured by indirect calorimetry is generally considered for a nutritional prescription. Unfortunately, indirect calorimetry measurements are not widely used in daily hospital routine [139].

The knowledge of metabolic rate provided by indirect calorimetry is clinically relevant as a clinical study on 124 ICU patients with severe AKI revealed a hypermetabolic state in 62% and a hypometabolic state in 14% [140].

Global consensus exists on the importance of indirect calorimetry use to evaluate REE. Both the European [8] and the US [141] guidelines state recommendations to support the use of indirect calorimetry as a gold standard tool. This is largely supported by the fact that equations and formulations aiming at REE estimation are largely inadequate, thus carrying the risk of clinically significant under- and overfeeding, which is well proven even in the context of AKI and KRT [140,142,143].

A prospective interventional study on ICU patients with AKI on KRT as CKRT demonstrated that a metabolic cart can improve energy provision also increasing protein intake [144]. When a positive effect on nitrogen balance has reached the probability of survival is likely to be increased [145].

While published prediction equations and weight-based formulae provide valid estimates of energy requirements at the population level, both methods are subject to significant bias and imprecision when applied to individual patients [142,143,146,147], requiring the clinician to exercise a considerable degree of clinical judgment, to individualize energy prescription. Therefore, clinicians need to be aware of the limitations of using such predictive tools to obtain REE values.

Past guidelines on ICU patients with AKI have recommended 20–30 kcal/kg/d of non-protein calories [1,2,148], or 20–30 kcal/kg/d total calories [4,149,150]. These indications reasonably include the mean energy needs at the population level and can be used as a general starting point when indirect calorimetry is not available. However, in many cases, it is not mentioned if the actual, pre-admission, or ideal body weight should be considered for calculations. Considering that patients with AKI frequently have fluid overload and suffer sudden fluid shifts related to KRT, it is even more difficult to define the reference body weight to be used to estimate energy expenditure using predictive equations. In this regard, a recent study on 205 critically ill patients in which REE measured by indirect calorimetry was compared to the Harris–Benedict equation calculated with three different reference weights (actual, ideal, and predicted body weight), concluded that the number of calories calculated by the Harris–Benedict equation, regardless of the reference body weight used, cannot replace indirect calorimetry results [151]. Only two observational studies were performed in critically ill patients with AKI comparing indirect calorimetry determination of energy expenditure and energy expenditure estimated with weight-based formulae or predictive equations, including Harris–Benedict equation [142,143]. Both studies agree that these methods of energy expenditure calculation have low precision, wide limits of agreement, and can often under- or overestimate the real energy expenditure, depending on the BW used for the calculations. Thus, despite being a very simple way to predict energy expenditure, this approach is likely to increase the risk of both over- and underfeeding in ICU patients with AKI.

From the review of the literature, at present, it is not possible to determine, and therefore recommend, which method for predicting energy needs is the best in terms of promoting better outcomes

in hospitalized patients with AKI/AKD and/or CKD or CKD with KF. Given the absence of robust evidence, referring to the recent ESPEN guidelines on critically ill patients [8] and on polymorbid internal medicine patients [29] could facilitate the daily practice of clinicians because these guidelines do not exclude patients with kidney disease.

#### Recommendation 11

**Indirect calorimetry can be performed during CKRT, bearing in mind the intrinsic limitations of the method. A minimum interval of 2 h after an intermittent dialysis session should be preferred to improve the precision of the measurement.**

**Grade of recommendation 0 – Consensus (78.3% agreement) Commentary**

Currently available recommendations from experts suggest that indirect calorimetry measurements should not be performed during KRT, due to possible interferences by KRT on CO<sub>2</sub> balance [139]. However, more recently, studies investigating the use of indirect calorimetry in patients receiving or not CKRT suggested no difference in REE [144,152–154]. The MECCIAS trial recently showed that the influence of CO<sub>2</sub> changes during CKRT on REE is minimal and that indirect calorimetry during CKRT should be preferred because of its effects on energy expenditure [154]. In indirect calorimetry, the REE value is calculated from O<sub>2</sub> consumption and CO<sub>2</sub> production (Weir equation), and both gases are also exchanged in the extracorporeal circulation [155]. However, during KRT, a substantial amount of CO<sub>2</sub> (26 ml/min) is removed in the effluent in the course of CKRT, which represented 14% of the average expired VCO<sub>2</sub> [155], thus VCO<sub>2</sub> measurement could not exactly reflect the endogenously produced CO<sub>2</sub>, limiting the correct interpretation of IC-based measured REE.

#### Recommendation 12

**Whenever the clinical condition of the patient is changing, indirect calorimetry shall be repeated.**

**Grade of recommendation GPP – Strong consensus (100% agreement)**

#### Commentary to recommendation 12

Whether only one indirect calorimetry measurement at the beginning of recovery is enough to tailor nutritional prescriptions during ICU stay is still an open question. In one study on patients with AKI, no differences were observed between energy measurements performed at the beginning of ICU stay and within one week, nor within 48 h, despite in the vast majority of patients (68%) variations greater than ±10% was measured, which could be clinically relevant [142]. A retrospective study on 1171 critically ill patients found a statistically significant between-day difference, however, the difference lost significance after excluding the first two days of hospitalization [156]. An expert position paper on indirect calorimetry in critically ill patients [139] states that the energy expenditure of critically ill patients is very dynamic and depends on the phase and the severity of illness, treatment, and extended bed rest. The same concept reasonably holds for AKI patients [1,2]. Thus, it is recommended that, whenever the clinical condition of the patient is changing, indirect calorimetry should be repeated. If indirect calorimetry is not available, the calculation of REE from VCO<sub>2</sub> only obtained from ventilators has been demonstrated to be more accurate than equations in critically ill patients not on CKRT [157] but less than indirect calorimetry [139]. However, no such study has been made up to now in critically ill patients with AKI.

Overall, we refer to Statement 2 from the ESPEN GL on clinical nutrition in the intensive care unit [8].

**If calorimetry is not available, using VO<sub>2</sub> (oxygen consumption) from pulmonary arterial catheter or VCO<sub>2</sub> (carbon dioxide production) derived from the ventilator will give a better evaluation on energy expenditure than predictive equations.**

#### Consensus (82% agreement)

#### Commentary

If indirect calorimetry is not available, the calculation of REE only from VCO<sub>2</sub> values obtained from ventilators (REE – VCO<sub>2</sub> × 8.19) has been demonstrated to be more accurate than equations [157], but less than indirect calorimetry [139]. Also, VO<sub>2</sub> calculated from a pulmonary artery catheter is another available option [158].

#### 4.4.2. What is the optimal energy intake to avoid under- or overfeeding?

Since no major modifications of energy metabolism are associated with AKI per se, as the more relevant effects on energy expenditure are usually due to chronic (such as diabetes, severe hyperparathyroidism, and inflammation) or acute catabolic comorbidities and complications [8,159,160], and since there are no high-quality studies that investigated energy provision in hospitalized patients with AKI/AKD and/or CKD or CKD with KF, we refer to the recommendation 11.1 of the ESPEN guideline for polymorbid hospitalized medical patients [29] and the recommendations 8 and 16–19 of the ESPEN guideline for critically ill patients [8].

**In polymorbid medical inpatients with reduced food intake and hampered nutritional status at least 75% of calculated energy and protein requirements should be achieved in order to reduce the risk of adverse outcomes.**

**Grade of recommendation B – strong consensus (100% agreement) [29]**

**Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.**

**Grade of recommendation B - strong consensus (100% agreement) [8]**

**After day three, caloric delivery can be increased up to 80–100% of measured energy expenditure.**

**Grade of recommendation 0 - strong consensus (100% agreement) [8]**

**To avoid overfeeding, early full EN and PN shall not be used in critically ill patients but shall be prescribed within three to seven days.**

**Grade of recommendation A - strong consensus (100% agreement) [8]**

**If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness.**

**Grade of recommendation 0 - strong consensus (95% agreement) [8]**

**If predictive equations are used to estimate the energy need, hypocaloric nutrition (below 70% estimated needs) should be preferred over isocaloric nutrition for the first week of ICU stay.**

**Grade of recommendation B - strong consensus (95% agreement) [8]**

#### Commentary

The optimal energy to nitrogen ratio has not been determined during AKI. A prospective study investigating the effect of increasing calorie to nitrogen ratio in critically ill patients with AKI (40 kcal/kg/d vs. 30 kcal/kg/d) found that this approach is not associated with improved nitrogen balance; instead, more severe metabolic complications of medical nutrition therapy (hyperglycemia, hypertriglyceridemia) and more positive fluid balance were observed [161].

There are three RCTs performed in critically ill patients looking at the effects of different levels of energy provision in other organs as a secondary outcome [162–164]. No study found any positive effect on KF free days or other renal outcomes, apart from an increase in fluid balance during the full feed protocol [162].

An RCT designed to study different levels of protein intake in critically ill patients with AKI on CKRT that provided an average of 89% of measured energy requirements during the whole study period found that patients that achieved a positive nitrogen balance during the study had a better hospital outcome, suggesting that the impact of protein intake could have been more important than that of energy intake; however, no data on metabolic complications were made available [145]. In the same study, EN was also related to better outcomes in comparison to PN. In another more recent RCT, full feeding, calculated using 25–35 kcal/corrected ideal body weight/d given through PN, no benefit in kidney function recovery or AKI incidence was demonstrated; instead, delayed recovery in patients with stage two AKI was likely [59]. Besides, no improvement in nitrogen balance was found, while urea formation increased, which probably prolonged the duration of KRT [59].

In critically ill patients, actual energy expenditure should not be the target during the first 72 h. Because in the early phase of critical illness there is an endogenous energy production of 500–1400 kcal/d, early full feeding adding up to this amount may cause overfeeding [165]. Unfortunately, it is still not possible to assess this endogenous nutrient production, which would be very helpful to adjust early medical nutrition and to prevent the deleterious effects of overnutrition (increased length of stay, ventilation duration, and infection rates), likely to be observed when exogenous nutrients are administered on top of the endogenous production [166]. On the other hand, an intake below 50%, may lead to severe calorie debt and energy reserves depletion, lean body mass reduction, and infectious complication increase [167,168]. Recently, a large observational study including 1171 patients [156] confirmed that both under- and overfeeding were deleterious and that the optimal calorie amount is between 70 and 100% of measured energy expenditure.

Taken together, timing, route, and caloric/protein target should no longer be considered as three different issues, but should rather be integrated into a more comprehensive approach. After defining the timing and the route, the energy/protein goal should be achieved progressively and not before the first 48 h to avoid overnutrition. This progression should be ordered according to a local protocol preventing sharp and too rapid increases. Full targeted medical nutrition therapy is considered to achieve more than 70% of the REE, but not more than 100% [8]. Key points for the initiation of medical nutrition are the following:

- 1. Oral nutrition as early as possible while considering the risks of complications (e.g. aspiration);
- 2. Early EN at a low rate and progressive increase within 48 h if oral nutrition is not possible while considering the risk of complications;
- 3. Determination of the optimal starting point and the dose of (supplemental) PN based on the risk of complications from oral or EN, state of acute illness, and presence of previous under/malnutrition.

#### 4.4.3. What are the optimal combinations of carbohydrate and lipid calories for medical nutrition?

##### Recommendation 13

**In hospitalized patients with AKI/AKD and/or CKD or CKD with KF needing medical nutrition the amount of lipids and carbohydrates may be combined to increase lipid intake and reduce carbohydrate provision based on real substrate utilization assessed by indirect calorimetry.**

**Grade of recommendation 0 – Strong consensus (91.3% agreement)**

##### Commentary

Hospitalized patients with AKI/AKD and/or CKD or CKD with KF may show a hypermetabolic state. The kidney has an important role in gluconeogenesis, insulin clearance, and glucose uptake [10,138]. Therefore, decreased glucose oxidation is to be expected in AKI patients, especially those critically ill patients with an unbalanced release of catabolic hormones and excessive release of proinflammatory cytokines. Lipid metabolism derangements in AKI are more complex. Impaired lipolysis is a known phenomenon in AKI, a condition characterized by a decrease in lipoprotein lipase and hepatic triglyceride lipase activity and slowed down fat emulsions clearance from the blood [10]. The most recent available evidence suggests that critically ill patients with AKI oxidize much fewer carbohydrates (56.7%) and much more lipids (150.7%) than expected [169]. A similar finding was described in an earlier study [170].

Almost all of the standard EN and PN formulas available today contain a high percentage of calories from carbohydrates, even in lipid-based all-in-one formulas. This non-protein macronutrient distribution may not be appropriate for hospitalized patients with KF. However, the possible impact of this imbalance in nutritional status, morbidity, and mortality remain ill-defined.

#### 4.4.4. How KRT might impact on energy balance by the potential delivery of energy substrates (citrate, lactate, glucose)?

##### Recommendation 14

**For patients undergoing KRT, the total energy provision by additional calories given in the form of citrate, lactate, and glucose from dialysis/hemofiltration solutions should be included in the calculations to determine the total daily energy provision to avoid overfeeding.**

**Grade of recommendation B – Strong consensus (100% agreement)**

##### Commentary

Some of the solutions commonly used in the dialysis/hemofiltration procedures (dialysate and replacement fluids) may provide energy substrates in the form of:

1. Citrate (3 kcal/g) from regional circuit anticoagulation using ACD-A (2.2% citrate), TSC (4% trisodium citrate), or the more recent diluted citrate solutions (citrate 12 or 18 mmol/l)
2. Glucose (3.4 kcal/g) from ACD-A (2.45% dextrose) and replacement and dialysate fluids (0–110 mg/dl)
3. Lactate (3.62 kcal/g), used as a buffer

In recent years, anticoagulation with citrate during KRT has proved to be a safe and efficient alternative compared to conventional protocols of anticoagulation, most often based on unfractionated heparin [22,171,172]. Citrate is partially removed from the blood by KRT, and the citrate load to the patients depends on the balance between the total dose administered in the extracorporeal circulation and the amount of citrate removed through the filter during KRT [173]. Citrate reaching the systemic circulation is metabolized primarily in the liver, as well as in the kidney and skeletal muscle [171]. Citrate is the anion of a tricarboxylic acid (citric acid), which is an intermediate metabolite of the Krebs cycle. As such, citrate does not require insulin to enter the cells, where it can be metabolized yielding energy and bicarbonate (0.59 kcal/mmol and 3 mmol of bicarbonate/mmol of citrate, respectively).

Energy gain can be substantial, depending on the type and rate of fluids used, with one study reporting up to 1300 kcal/d using high lactate replacement fluids and anticoagulation with ACD-A [174]. High variability in energy gain was noted in the three available studies on this matter, depending on the lactate content of replacement fluids and type of anticoagulation (115–1300 kcal/d) [174–176]. The most recent study published on this topic confirmed

the potential for significant caloric contribution, specifically with the use of continuous veno-venous hemo-diafiltration (CVVH) as the KRT modality. By using citrate anticoagulation as ACD-A and bicarbonate based replacement fluids with glucose 110 mg/dl, the study reported an average daily delivery of 513 kcal (citrate 218 kcal, glucose 295 kcal). On the other hand, the use of glucose-free replacement fluids should also be taken into account, since it may contribute to increased net glucose loss because effluent losses of glucose are left unreplaced [177].

Energy excess provided by KRT could be partially avoided by using protocols based on lower citrate concentration solutions, bicarbonate as a buffer, and citrate solutions other than ACD-A in lower doses and without glucose [21]. Alternatively, diffusive PIKRT modalities, such as sustained low-efficiency dialysis (SLED), easily allow increased citrate removal by the treatment itself [22,171], with only a limited amount of energy (100–300 kcal/d) to be factored in the patient's prescribed energy intake.

4.4.5. *What are the energy requirements in AKI/AKD and/or CKD or CKD with KF patients not started on KRT as compared to those patients on KRT?*

#### Recommendation 15

**No factor should be applied to the measured REE to compensate for KRT since there is no difference between patients not on KRT as compared to those on KRT.**

**Grade of recommendation B – Strong consensus (100% agreement)**

#### Commentary

No major modifications of energy metabolism are associated with AKI per se, as the more relevant effects on energy expenditure are usually due to acute comorbidities and complications [8,170]. In mechanically ventilated patients, no differences were found in REE due to the presence of AKI [178]. Even in multiple organ failure, the energy expenditure of critically ill patients amounts to not more than 130% of predicted energy expenditure [2]. The scarce available evidence suggests that not even KRT is responsible for increasing energy needs in patients with KF. One observational study in CKD with KF patients found no difference in REE in the same cohort of patients before the beginning of dialysis (hemodialysis and PD) and one month after hemodialysis or PD initiation [179]; in the same way, critically ill patients with AKI undergoing KRT had similar REE measured by indirect calorimetry than AKI patients not on KRT [142]. Only one observational study found a difference between REE of patients with AKI before the initiation of KRT and after five days on dialysis [180]. However, the study had a high dropout rate (24 patients evaluated at five days out of 124 enrolled).

#### 4.5. Protein requirements

4.5.1. *What is the potential impact of KRT on protein balance in patients with AKI or AKI on CKD or CKD with KF as compared to that of similar patients, not on KRT? Does KRT increase protein needs?*

#### Statement 6

**KRT can exert a negative influence on protein balance by inducing amino acid and peptide/protein losses. As a consequence, protein requirements can be increased in patients undergoing KRT.**

**Strong consensus (100% agreement)**

#### Commentary

Kidney replacement therapies as CKRT or PIKRT such as SLED have become the treatment modality of choice in critically ill patients with AKI. These modalities of intensive KRT, due to their prolonged schedules and the type of membranes used, can exert a negative influence on protein balance by inducing amino acid and peptide/protein losses (up to 15–20 g/d and 5–10 g/d, respectively)

[10,144,181–187]. The factors related to the KRT prescription that will determine how many amino acids will be lost include the modality of KRT (continuous or intermittent and convection, diffusion or both), the blood and dialysis fluid flow rate, effluent rate, as well as membrane properties of the filter used [144,188]. Besides, since amino acids are low molecular weight substances with a sieving coefficient near 1.0, many amino acids such as cysteine, arginine, alanine, and glutamine can be readily filtered from the blood into effluent [183,184]. Currently, with the increased efficiency of the available KRT modalities, allowing higher blood flow rates and increased effluent removal, it is possible to estimate that the actual amino acid losses of patients on CKRT are much more than those reported in the earlier studies [181–184]. A study that enrolled eight patients (four with cardiogenic shock and four with septicemia) reported a mean daily loss of 3.8 g/d of amino acids in septic patients and 7.4 g/d in patients with cardiogenic shock during CVVH [182], while a more recent study in critically ill patients on CVVH reported a median amino acid loss of 13.4 g/d, ranging from 11.8 to 17.4 g/d [189].

4.5.2. *How to define protein requirements in patients with kidney disease? Does high protein intake lead to improved outcomes as compared to standard protein intake?*

#### Statement 7

**Protein requirements are mainly determined by baseline illness, however, prolonged KRT can exert a negative influence on protein balance.**

**Strong consensus (100% agreement)**

#### Statement 8

**There are no substantial differences in terms of protein requirements between ICU, surgical, and medical acutely ill patients with AKI/AKD and/or CKD or CKD with KF since all these conditions are characterized by protein catabolism.**

**Strong consensus (91.3% agreement)**

#### Recommendation 16

**In hospitalized patients with AKI/AKD and/or CKD or CKD with KF receiving medical nutrition, protein prescription may be preferably guided by protein catabolic rate instead of only using predictor factors normalized by body weight (see recommendation 18).**

**Grade of recommendation GPP – Consensus (86.4% agreement)**

#### Recommendation 17

**Overfeeding should be avoided in order to achieve a positive nitrogen balance or minimize an existing negative nitrogen balance.**

**Grade of recommendation B – Strong consensus (95.7% agreement)**

#### Recommendation 18

**The following protein intakes may be prescribed:**

- Hospitalized patient with CKD without acute/critical illness: 0.6–0.8 g/kg BW/d
- Hospitalized patient with CKD and KF on conventional intermittent chronic KRT without acute/critical illness:  $\geq$  1.2 g/kg BW/d
- Hospitalized patient with AKI, AKI on CKD without acute/critical illness: 0.8–1.0 g/kg BW/d
- Hospitalized patient with AKI, AKI on CKD, CKD, with acute/critical illness, not on KRT: start with 1 g/kg BW/day, and gradually increase up to 1.3 g/kg BW/d if tolerated
- Critically ill patients with AKI or AKI on CKD or CKD with KF on conventional intermittent KRT: 1.3–1.5 g/kg/d
- Critically ill patients with AKI or AKI on CKD or CKD with KF on CKRT or PIKRT: 1.5 g/kg/d up to 1.7 g/kg/d



**If available, the pre-hospitalization body weight or usual body weight may be preferred over the ideal BW. Actual BW should not be considered for a protein prescription.**

**Grade of recommendation 0 – Consensus (82.6% agreement)  
Commentary to statements 7 and 8, and recommendations 16–18**

The protein requirement is determined by the inflammatory stress of the acute/critical illness. Critically ill patients with systemic inflammation and immobilization are strongly catabolic and are characterized by extensive muscle protein breakdown and impaired protein synthesis, leading to negative nitrogen balance [10]. Consequently, the protein requirement can be largely increased. Providing increased protein intake can limit nitrogen losses, even though it cannot reverse the catabolic condition [145,161,186].

Instead, a difference exists with those medical patients who have non-complicated AKI due for example to urinary tract obstruction or nephrotoxic drugs or contrast-induced nephropathy, in the absence of underlying acute/critical illness. In these non-catabolic conditions, patients could be metabolically stable and do not require increased protein regimes. Nevertheless, the estimation of the protein catabolic rate could provide a better understanding of the patients' catabolic status and help guide nutrient prescription.

The optimal protein intake in hospitalized patients on KRT, especially in critically ill patients with AKI is still unclear. It should be quantitatively sufficient to blunt skeletal muscle wasting while providing the amino acids needed for the acute-phase response. Protein requirement in hospitalized patients with AKI or AKI on CKD or CKD not started on KRT are likely to depend mainly on the underlying disease, acute comorbidities, and complications than on the presence of reduced renal function per se. Considering the increased loss of amino acids, patients on KRT may require higher protein intakes [10,190].

Total nitrogen loss in a typical CKRT patient can be about 25 g/d [184,186] further worsening negative nitrogen balance. Normalized protein catabolic rate values of 1.2–2.1 g/kg/d have been obtained by the urea kinetic method in small groups of patients with AKI on different modalities of KRT and medical nutrition (prolonged, continuous, and intermittent modalities) [142,161,191–195]. Few data are currently available on the effects of high protein intakes on nitrogen balance in patients on KRT. Protein intakes up to 2.5 g/kg/d, at least in nonrandomized studies, led to near positive or slightly positive nitrogen balance [145,186]. In a nonrandomized study of AKI patients on CKRT comparing a higher dose of dietary protein supplementation 2.5 g/kg/d to a group of patients receiving standard of care 1.2 g/kg/d with both receiving equal amount of calories [185], patients receiving the higher dose of protein were more likely to achieve a positive nitrogen balance at any time during follow-up (53.6% vs. 36.7%;  $p < 0.05$ ) and trended towards having less overall negative nitrogen balance, but required increased CKRT dose due to increased blood urea nitrogen production. In a detailed metabolic study [193], it was reported that AKI patients that received 2.0 g protein/kg had improved nitrogen balance compared to those receiving 1.5 g protein/kg. Interestingly, increasing calorie intake from 10 to 15 kcal/kg to 30 kcal/kg benefited those patients with lower protein intake (0.6–0.8 g/kg) but not ones receiving increased protein. Patients that were overfed (40–60 total kcal/kg) had increased normalized protein catabolic rate and worsened nitrogen balance. A positive nitrogen balance is associated with improved patient survival in AKI with critical illness [144]. Supplementing protein to a target of 2.0 g/kg/d may be desirable in patients on prolonged CKRT or PIKRT with negative nitrogen

balance. One important consideration regarding protein prescription is that it is frequently normalized using the body weight of patients. Considering that critically ill patients with AKI frequently have fluid overload, the determination of the reference body weight to be used for protein prescription is a delicate issue. Different body weights will lead to different protein needs estimation, which may in part explain the wide range of normalized protein catabolic rate values found in previous studies. A recent study found that estimation of protein needs based on body weight in critically ill patients with AKI overestimated protein requirements in patients undergoing KRT, while it underestimated it in patients not on KRT [142]. While the first situation may increase urea production and the need for KRT, the second one may contribute to the intensification of muscle wasting. Despite technical difficulties that may occur during 24 h urine and dialysis fluid collection, it is very important to calculate the protein catabolic rate in hospitalized patients on KRT.

*4.5.3. Should protein prescription be reduced in critically ill hospitalized patients with AKI and/or CKD or CKD with KF to delay KRT start?*

#### **Recommendation 19**

**Protein prescription shall not be reduced in order to avoid or delay KRT start in critically ill patients with AKI, AKI on CKD, or CKD with KF.**

**Grade of recommendation A – Strong consensus (95.5% agreement)**

#### **Commentary**

In the presence of increased protein catabolism associated with reduced nitrogen waste product clearance due to decreased renal function, excessive protein supplementation may result in further accumulation of end products of protein and amino acid metabolism, and consequently, blood urea nitrogen values increase. However, protein catabolism in patients with AKI is only quite partially influenced by protein intake, i.e. lowering protein intake does not influence the protein catabolic rate [85]. A recent meta-analysis found no difference in outcome between the timing of KRT initiation (early versus late) [196]. Thus, protein prescription in this clinical setting should be guided by the catabolic state of patients, and protein intake should not be reduced to delay KRT initiation.

Considering the relatively low content of protein present in standard enteral formulas (40–60g of protein/L), more concentrated disease-specific (renal) formulas containing 70–80 g of protein/L may be preferred, mainly to reduce fluid overload; in some cases, parenteral supplementation of amino acids is recommended to achieve protein need goals by enteral nutrition [1,2,137].

*4.5.4. Should a conservative approach (protein reduction) be considered in any situation?*

#### **Recommendation 20**

**A medical conservative approach consisting of moderately restricted protein regimens, may be considered only in the case of metabolically stable patients with AKI or CKD, without any catabolic condition/critical illness and not undergoing KRT (see recommendation 18).**

**Grade of recommendation GPP – Consensus (87.0% agreement)**

#### **Commentary**

In selected non-catabolic conditions with acutely reduced renal function (such as drug-induced isolated AKI, contrast-associated AKI, and some conditions of post-renal AKI) or in metabolically stable CKD patients, medical conservative treatment can help to correct phosphate, sodium, potassium acid-base alterations, also

reducing the accumulation of nitrogen waste products, such as urea. Instead, when catabolic status exists, a conservative approach might only partially correct electrolytes, fluids or acid-base unbalances but invariably worsens nitrogen balance; in most of such cases, KRT start is advised.

4.5.5. *Should CKD patients on conservative treatment be maintained on lower protein diets during hospitalization?*

#### Recommendation 21

**CKD patients previously maintained on controlled protein intake (the so-called “low protein diet”) should not be maintained on this regimen during hospitalization if acute illness is the reason for hospitalization.**

**Grade of recommendation GPP – Strong consensus (100% agreement)**

#### Commentary

As discussed above, hospitalization due to critical or acute illness or major surgery is often characterized by a pro-inflammatory status and increased protein catabolism, thus continuing the dietary protein restriction is not appropriate. The protein need in hospitalized patients must be oriented by the baseline illness that caused hospital admission more than by the underlying CKD condition per se. Conversely, CKD patients can continue on controlled protein intake regimens during hospitalization provided the absence of a pro-catabolic state. Besides, the nutrient intake must fully cover the essential amino acids and the energy requirement [197], and metabolic acidosis must be prevented or adequately corrected [198]. If this not the case, the CKD patients will be at high risk of negative nitrogen balance and hence of muscle wasting, even in metabolically stable non-catabolic conditions. Last but not least, optimal control of glucose metabolism is needed to implement a nutritionally safe protein restriction [199].

#### 4.6. Micronutrient requirements

4.6.1. *Should trace elements and vitamins be supplemented?*

#### Recommendation 22

**Because of increased requirements during KF and critical illness, and large effluent losses during KRT, trace elements should be monitored and supplemented. Increased attention should be given to selenium, zinc, and copper.**

**Grade of recommendation B – Strong consensus (100% agreement)**

#### Recommendation 23

**Because of increased requirements during KF and critical illness, and large effluent losses during KRT, water-soluble vitamins should be monitored and supplemented. Special attention should be given to vitamin C, folate, and thiamine.**

**Grade of recommendation B – Strong consensus (100% agreement)**

#### Commentary to recommendations 22 and 23

During critical illnesses, vitamins, and trace elements may impact on immunomodulation, wound healing and may have antioxidant properties [200,201]. Even though optimal dosing of micronutrients in critically ill patients is still a matter of debate, it appears quite clear that the start of KRT as CKRT in patients with AKI or AKI on CKD or CKD with KF represents an additional variable negatively affecting serum micronutrient levels [202,203]. The depurative mechanisms at the basis of dialysis modalities along with a variable amount of hemofilter adsorption may increase the risk of vitamin and trace element deficiency, but dedicated and specific nutritional approaches are still lacking [204]. In patients on CKRT, a reduction in serum levels of folate, vitamins C, E, thiamine, zinc, and selenium have been described, probably as a consequence

of increased utilization in critical illness and losses secondary to CKRT [202,205–207]. Specifically, a daily loss in the effluent of about 68 mg of vitamin C, 0.3 mg of folate, and 4 mg of vitamin B1 (thiamine) have been reported [206,207]. In an observational study on 77 patients with CKD with KF on chronic hemodialysis, zinc, thiamin, and vitamin B6 were the most deficient micronutrients (44.1%, 24.7%, and 35.1% respectively) [208]. In a randomized trial of chronic hemodialysis patients [209], serum levels of selenium and zinc in 150 chronic hemodialysis patients were not normalized by giving a moderate supplementation (up to 75 µg/d of selenium and 50 mg/d of zinc), suggesting increased requirements in these patients. The current recommendation is that the losses of selenium and other micronutrients in the effluent fluid should be replaced [210,211] and that these patients would need an additional amount beyond that provided by standard PN [207,212]. The optimal dose remains unknown, but a dosage of 100 mg/d has been suggested for vitamin C [213]. Large effluent losses of several trace elements, but particularly of copper were shown to far exceed nutritional intakes [207]. Recently a fatal case of copper deficiency was published [212]. When CKRT is required for more than two weeks, blood copper determination should probably be recommended. It has been suggested to intravenously administer about 3 mg/d of copper to prevent deficiencies (based on repeated determinations in patients on hemodialysis) [214]. In conclusion, given the blood assay limitations and the lack of evidence of clinical advantages derived from micronutrients supplementation, supplementation of micronutrients should be guided by their serum levels and KRT losses.

#### 4.7. Disease-specific nutrients

4.7.1. *Would the use of renal disease-specific formulae (EN or PN) lead to reduced complication rate and improved nutrient delivery as compared to standard formulae?*

#### Recommendation 24

**No disease-specific enteral nor parenteral formula oriented for patients with reduced kidney function should be routinely utilized in every patient with AKI, AKI on CKD, or CKD with KF in comparison to conventional formulas. Instead, their use is to be individualized (see recommendation 26).**

**Grade of recommendation B – Consensus (87.5% agreement)**

#### Recommendation 25

**The choice of the most appropriate EN or PN formula should be made based on the calorie and protein ratio to provide the most accurate dosing in clinical practice.**

**Grade of recommendation B – Strong consensus (91.3% agreement)**

#### Recommendation 26

**In selected patients with electrolyte and fluid imbalances, concentrated “renal” EN or PN formulas with lower electrolyte content may be preferred over standard formulas.**

**Grade of recommendation GPP – Strong consensus (95.7% agreement)**

#### Commentary to recommendations 24 to 26

The most recent review on this subject, which included literature up to December 2013, did not suggest any proven benefit in using disease-specific enteral formulas in critically ill patients [141]. However, formulas designed for patients with KF are more concentrated and all of them have lower sodium, potassium, and phosphorus content. Thus they could be advantageous for reaching the protein target of patients with higher protein needs, but also in patients presenting electrolyte disturbances (for example hyperkalemia) and/or fluid overload.

4.7.2. *Would adding omega-3 supplements or PN solutions enriched with omega-3 lipids lead to improved outcomes?*

#### Recommendation 27

**There is not enough evidence to support the routine use of omega-3 polyunsaturated fatty acids (PUFA) supplements or PN solutions enriched with omega-3 PUFA in hospitalized patients with AKI, AKI on CKD or CKD with KF.**

**Grade of recommendation GPP – Strong consensus (95.8% agreement)**

#### Commentary

The role of omega-3 PUFA in hospitalized patients with kidney disease and reduced kidney function is at this time point unknown. Even though interesting experimental data exist [215,216], no RCT is currently available to support the recommendation of its use in hospitalized patients with AKI/AKD and/or CKD with or without KF [10]. However, intravenous lipid emulsions with omega-3 PUFA are recommended by ESPEN for critically ill patients due to their anti-inflammatory and immune-modulating effects and these recommendations do not exclude patients with AKI [8].

4.7.3. *Would adding glutamine supplements lead to improved outcomes?*

#### Recommendation 28

**In critically ill patients with AKI, AKI on CKD, or CKD with KF, additional high dose parenteral glutamine shall not be administered.**

**Grade of recommendation A – Strong consensus (100% agreement)**

#### Commentary

Even though glutamine losses of about 1.2 g/d have been documented during CKRT [217], and earlier underpowered studies showed some benefit of intravenous L-glutamine only when summarized in a meta-analysis [218], the most important evidence regarding glutamine, the REDOX study [219,220], shows that high doses intravenously or via EN of alanyl-glutamine seem to be harmful in the subgroup of critically ill patients with KF. Besides, another important trial, the MetaPlus trial [221] showed similar results in a population of critically ill patients.

### 4.8. Monitoring

4.8.1. *Would reaching and maintaining serum glucose levels in the normal range (80–110 mg) lead to improved outcomes?*

#### Recommendation 29

**Serum glucose levels shall be maintained between 140–180 mg/dl in hospitalized patients with AKI, AKI on CKD, or CKD with KF.**

**Grade of recommendation A – Strong consensus (95.5% agreement)**

#### Recommendation 30

**Tight glucose control (80–110 mg/dl) shall not be pursued because of the increased risk of hypoglycemia.**

**Grade of recommendation A – Strong consensus (100% agreement)**

#### Commentary to recommendations 29 and 30

In this clinical setting, patients are at increased risk of both hyper- and hypoglycemia [138]. Insulin resistance is highly prevalent among patients with AKI and is associated with increased mortality risk [222]. High blood glucose concentration can be considered one of the best independent predictors of mortality in this clinical setting [222]. On the other hand, since insulin is metabolized also by the kidney, renal function impairment may act as a predisposing factor for hypoglycemia. An observational study in critically ill patients with trauma treated with insulin to achieve a target of 70–149 mg/dl, showed hypoglycemia (<60 mg/dl) in 76%

of cases with concomitant KF (either AKI or CKD with KF), as compared with 35% in patients with normal renal function [223]. In the case of severe hypoglycemia (<40 mg/dl) the corresponding percentages were 29% and 0%, respectively [223]. Similarly, glycemic variability was increased in patients with KF [223].

In this regard, the use of specific protocols targeting higher glycemic values for patients with AKI, AKI on CKD, or CKD with KF, independently of KRT, could contribute to the reduction of the incidence of hypoglycemia in this category of patients [224]. Furthermore, the contribution of renal gluconeogenesis is also very important, being responsible for approximately 30% of glucose systemic appearance [225,226]. The relevance of the kidney in insulin metabolism and glucose regulation explains the increased incidence of hypoglycemia in the presence of AKI or CKD with KF, the reduced insulin need of diabetic patients with CKD, as well as the increased risk of hypoglycemia during AKI [138]. As an additional factor complicating glycemic control in patients with AKI in the ICU, some of the solutions commonly used in the dialysis/hemofiltration procedures (dialysate and replacement fluids) may provide energy substrates in the form of citrate, glucose and lactate) as already discussed. Regarding possible favorable effects renal outcome, strategies aiming at a tighter glycemic control are not supported [227–231].

### 4.9. Electrolytes requirements

4.9.1. *In hospitalized patients with AKI, AKI on CKD, or CKD with KF undergoing KRT, would monitoring of electrolytes (mainly phosphate, potassium, and magnesium) improve clinical outcome?*

#### Recommendation 31

**Electrolytes abnormalities are common in patients with AKI, AKI on CKD, or CKD with KF receiving KRT and shall be closely monitored.**

**Grade of recommendation A – Strong consensus (100% agreement)**

#### Commentary

Electrolyte disorders are common among hospitalized patients and, despite the exact incidence remaining still unclear, a cumulative incidence of up to 65% has been reported, especially among critically ill patients [232]. In the clinical setting considered in the present guideline, the most commonly reported electrolyte disorders are hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, and most of them normally improve when KRT is started. However, KRT, and especially the most intensive KRT modalities such as CKRT and PIKRT commonly used in the ICU, may add other electrolyte derangements, due to the high intrinsic efficiency of the treatments in electrolyte removal [233,234].

Common laboratory abnormalities associated with intensive/prolonged KRTs include hypophosphatemia, hypokalemia, and hypomagnesemia [235,236]. Hypophosphatemia, defined as serum phosphate levels <0.81 mmol/l and commonly classified as mild, moderate, and severe (respectively < 0.81, 0.61 and 0.32 mmol/l), has a reported prevalence up to 60–80% among ICU patients [237,238]. Given the association of hypophosphatemia with worsening respiratory failure and increased risk of prolonged weaning from mechanical ventilation, cardiac arrhythmias, and prolonged hospitalization and a global negative impact on patients' outcome hypophosphatemia is particularly important in critically ill patients [239–241]. Phosphate balance is maintained through a complex interaction between phosphate uptake and phosphate excretion; in hospitalized patients, the mechanisms regulating this interaction are frequently disrupted, leading to an increased risk for hypophosphatemia by three main mechanisms: inadequate intake and/or decreased intestinal absorption, redistribution, and loss of phosphate [242]. In patients with KF, the start of KRT may represent

a further significant risk factor for hypophosphatemia [232]. Finally, in this clinical setting, the parallel initiation of medical nutrition, especially when calories from carbohydrates are privileged, may add another component to the development of hypophosphatemia as a part of the refeeding syndrome, a complex constellation of symptoms and blood electrolyte derangements associated with reintroduction of oral or (par)enteral nutrition after deprivation of caloric intake, either acute or chronic [243]. In course of prolonged KRT modalities, the prevalence of hypophosphatemia can rise to 80%, especially when intensive dialysis strategy is applied and standard phosphate-free KRT solutions are adopted [235,244–249] 2017]. Hypokalemia is another usual complication observed among hospitalized patients, with a prevalence ranging from 12 to 20% [250,251], with reported values increasing up to around 25% in patients with KF started on prolonged modalities of KRT [235]. The risk of hypokalemia is proportional to the delivered dialysis dose and may be further augmented by the use of low-concentration potassium dialysis or replacement solutions, as well as by the coexistence of inadequate potassium intake or patients' comorbidities (e.g. diarrhea, metabolic alkalosis, diuretic therapy) [235,244]. Finally, hypomagnesemia, generally defined as serum magnesium levels <0.70 mmol/l and commonly classified as mild, moderate, and severe (respectively between 0.76 and 0.64, between 0.63 and 0.40 and <0.40 mmol/l), has been reported in up to 12% of hospitalized patients with an incidence around 60–65% among critically ill patients [252,253]. In addition to the most common causes (such as diarrhea, malabsorption syndrome, chronic use of proton pump inhibitors and diuretics, hypercalcemia, and volume expansion), increased attention has recently been directed to the increased magnesium removal in course of KRT [254]. In particular, the onset and the exacerbation of hypomagnesemia in course of CKRT have been associated not only to the depurative mechanism at the basis of dialysis treatment (diffusive or convective clearance) but also to the amount of ionized magnesium chelated by citrate when regional citrate anticoagulation is utilized and magnesium is lost in the effluent under the form of magnesium–citrate complexes [246,255–258].

4.9.2. *Are hypophosphatemia, hypokalemia, and hypomagnesemia in course of KRT in patients with AKI, AKI on CKD, or CKD with KF preventable by using dialysis/hemofiltration solutions enriched with phosphate, potassium, and magnesium?*

#### Recommendation 32

**Dialysis solutions containing potassium, phosphate, and magnesium should be used to prevent electrolyte disorders during KRT.**

**Grade of recommendation B – Strong consensus (100% agreement)**

#### Commentary

An intravenous supplementation of electrolytes in patients undergoing CKRT is not recommended. In this regard, given the possibly severe clinical implications and the risks associated with exogenous supplementation, prevention of KRT-related electrolyte derangements by modulating KRT fluid composition may represent the most appropriate, and easier, therapeutic strategy [259–261]. Nowadays, commercial KRT solutions enriched with phosphate, potassium, and magnesium, which can be safely used as dialysis and replacement fluids, are widely available and they can also be used in the setting of regional citrate anticoagulation. This approach could prevent the onset of hypophosphatemia, hypokalemia, and hypomagnesemia. The adoption of phosphate-containing KRT solutions has been reported as a safe and effective strategy to prevent CKRT-related hypophosphatemia, limiting the need for exogenous supplementations [242,262–264]. In the same way, the onset of hypokalemia in course of CKRT has been

successfully minimized by using replacement and/or dialysate solutions with a potassium concentration of 4 mEq/l [265]. Concerning magnesium, despite the majority of the originally KRT solutions were characterized by a low magnesium concentration to correct the KF-related hypermagnesemia, with the diffusion of regional citrate anticoagulation, the use of dialysis and replacement fluids with increased magnesium concentration may be indicated to prevent KRT-related hypomagnesemia [255,263].

## 5. Conclusions

The presence of AKI/AKD or CKD with or without KF in hospitalized patients identifies a highly heterogeneous group of subjects with widely varying nutrient needs and intakes. However, since all of these patients are at high risk for malnutrition, nutritional status should be thoroughly assessed. Also, nutritional requirements should be frequently evaluated in their quantitative and qualitative aspects, individualized, and carefully integrated with KRT, to avoid both underfeeding and overfeeding. Despite the high degree of heterogeneity in the patient population considered, the methodological difficulties encountered and the paucity of high-quality evidence data, literature was reviewed aiming to define the most relevant important aspects of nutritional support in different clinical settings of hospitalized patients with AKI/AKD or CKD with or without KF. Practical recommendations and statements were developed, aiming at defining suggestions for everyday clinical practice in the individualization of nutritional support in this patient setting. Literature areas with scarce or without evidence were also identified, thus requiring further basic or clinical research.

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None declared.

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