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ESPEN Guideline

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

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SUMMARY

Background and aims: Hospitalized patients often have acute kidney disease (AKD) or chronic kidney disease (CKD), with important metabolic and nutritional consequences. Moreover, in case kidney replacement therapy (KRT) is started, the possible impact on nutritional requirements cannot be neglected.

On this regard, the present guideline aims to provide evidence-based recommendations for clinical nutrition in hospitalized patients with KD.

Methods: The standard operating procedure for ESPEN guidelines was used. Clinical questions were defined in both the PICO format, and organized in subtopics when needed, and in non-PICO questions for the more general topics. The literature search was from January 1st, 1999 until January 1st, 2020. Each question led to one or more recommendation/statement and related commentaries. Existing evidence was graded, as well as recommendations and statements were developed and agreed upon in a multi-stage consensus process.

Results: The present guideline provides 32 evidence-based recommendations and 8 statements, defining how to assess nutritional status, how to define patients at risk, how to choose the route of feeding, and how to integrate nutrition with KRT. In the final online voting, a strong consensus was reached in 84% at least of recommendations and 100% of statements.

Conclusion: The presence of KD in hospitalized patients identifies a highly heterogeneous group of subjects with widely varying nutrient needs and intakes. Considering the high nutritional risk related with this clinical condition, an individualized approach consisting of nutritional status evaluation and monitoring, frequent evaluation of nutritional requirements, and careful integration with KRT should be planned to avoid both underfeeding and overfeeding. 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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Abbreviations

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

1. Introduction

Abnormal kidney function is highly prevalent among hospitalized patients in different clinical settings, including nephrology and internal medicine wards, surgery wards, and intensive care units (ICU). It can be characterized by acute kidney injury/acute kidney disease (AKI/AKD), or by chronic kidney disease (CKD) with or without kidney failure (KF). As far as nutrition is concerned, the approach to these patients is highly complex since they represent a very heterogeneous group of subjects, with widely differing metabolic characteristics and nutritional needs.

In all of these clinical settings, AKI/AKD and CKD with or without KF, 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, its impact on nutritional profile, substrate balance, and nutritional treatment processes cannot be neglected.

The present guideline aims to provide 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.

2. Methods

The present practical guideline consists of 37 recommendations and eight statements and is based on the aforementioned ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease [1]. The original guideline was shortened by focusing the commentaries on the evidence and literature on which the recommendations are based on. The recommendations were not changed, but the presentation of the content was transformed into a graphical presentation. The original guideline was developed according to the standard operating procedure for ESPEN guidelines and consensus papers [2].

A comprehensive, systematic literature search was performed the PubMed and Cochrane Library databases for studies and systematic reviews published until January 1st, 2020 based on 26 clinical questions in PICO (population of interest, interventions, comparisons, outcomes) format. Existing evidence was graded according to the SIGN (Scottish Intercollegiate Guidelines Network) grading system. Recommendations were developed and graded into four classes (A/B/0/GPP) [2].

All recommendations were agreed in a multistage consensus process, which resulted in a percentage of agreement (%). The guideline process was funded exclusively by the ESPEN society. For further details on methodology, see the full version of the ESPEN guideline [1] and the ESPEN standard operating procedure [2].

1. General aspects.

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.

(S1, strong consensus 100%)

Commentary.

Severe loss of glomerular filtration rate not only affects water, electrolyte, and acid-base metabolism but also induces specific alterations in protein, amino acid, carbohydrate and lipid metabolisms [3]. Additionally, it exerts a pro-inflammatory action and has a negative impact on the anti-oxidative system. AKI/AKD, especially in the ICU setting, are rarely isolated disease processes. Metabolic changes in these patients are also determined by the underlying disease and/or co-morbidities, by other organ dysfunctions, as well as by the modality and intensity of KRT(3).

Protein catabolism is the metabolic hallmark of AKI/AKD, especially in the ICU setting. The metabolism of 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. Insulin resistance 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 fat particle clearance after parenteral or enteral administration of lipids can be reduced [3].

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. Vitamins E and A and selenium levels are low and there is a profound depression of the antioxidant system.

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.

(S2, strong consensus 100%)

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 different patient settings [3,4]. In the case of AKI/AKD, 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 [3]. Central to this process are both insulin resistance [5], which is frequently observed in patients with AKI [6], and the release of pro-inflammatory/oxidative stress mediators from the kidney into the systemic circulation [7]. Protein, carbohydrate, and lipid metabolism alterations could be considered part of the systemic effects of a 'kidney-centered' inflammatory syndrome [8]. Most of the 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 [9]. Apart from an inadequate spontaneous nutrient intake, several other factors such as metabolic acidosis, insulin resistance, chronic inflammation, intestinal dysbiosis, infection and oxidative stress are also contributive to malnutrition development. In addition, factors related to CKD treatment itself, such as 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 [9].

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.

(S3, strong consensus 100%)

Commentary.

The International Society of Renal Nutrition and Metabolism (ISRNM) [10], introduced the term "protein-energy wasting" to indicate "a condition of decreased body stores of protein and energy fuel stores (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" (10). Although this definition corresponds to what occurs physiologically in hospitalized patients, the recommended criteria to diagnose it may not be entirely suitable for the hospital setting.

Major clinical nutrition societies worldwide joined in the Global Leadership Initiative on Malnutrition (GLIM) and established a consensus definition for the diagnosis of malnutrition in adults from different clinical care settings [11]. The GLIM criteria consist of a two-step model for risk screening and diagnostic assessment. Assessment includes five criteria: three phenotypic criteria, i.e. non-volitional weight loss, low BMI, and reduced muscle mass, and two etiological criteria, i.e., reduced food intake or assimilation, and disease burden/inflammation. Diagnosis of malnutrition requires at least one phenotypic and one etiological criterion. So far, no study has validated 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.

3. Indication for medical nutrition treatment

3.1. Which patients?

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

(R1, Grade GPP, strong consensus 100%)

Commentary.

Patients with CKD, especially in those in the KF stage undergoing or not chronic dialysis, are at high risk of developing nutritional disorders [4]. Progressive depletion of protein and/or energy stores is often observed [12], with prevalence rates that increase along with the decline in kidney function [12]. 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 [13]. Given this high prevalence, we find it justified to suggest that all patients admitted to the hospital should be considered at risk of malnutrition.

5) 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.

(R2, Grade GPP, strong consensus 100%)

Commentary.

For ethical reasons, there are no studies directly addressing the effects of starvation on 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 [3,14,15]. Given that even kidney impairment per se does not cause major modifications on energy needs [16], 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. [17]). Since the publication of the earlier ESPEN recommendations [16,18], a cut-off of 48 h for the initiation of early nutrition has been established for critically ill patients [17,19], and we feel this is also adequate in patients with AKI/AKD or CKD with KF in the ICU.

3.2. What type of nutritional treatment?

6) 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.

(R3, Grade A, strong consensus 100%)

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 [10,16,20]. 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 [12]. 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 [21]. In another large (n = 445) RCT of hospitalized patients, ONS provision significantly improved nutritional status, and reduced the number of non-elective readmissions in the following six months after discharge [22]. 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) [23,24], reduced complications [23], and mortality [25,26].

7) 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.

(R4, Grade A, strong consensus 100%)

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 [27]. 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 [16,28–31]. 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 the first choice recommended treatment options (i.e., ONS) does not appear warranted [32].

8) 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.

(R5, Grade Am strong consensus 96%)

Commentary.

EN is indicated if oral intake is not sufficient to meet at least 70% of daily requirements [16,17]. Reaching nutritional intake goals is important to prevent weight loss and muscle wasting. However, many conditions may interfere with patient's spontaneous intake [33]. These conditions may include loss of appetite, delayed gastric emptying, dysphagia, among others. In these cases, the use of artificial nutrition may increase nutritional intake [34,35]. 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 [36]. There is some observational evidence comparing EN and PN effects on the outcome of non-critically ill internal medicine patients [37]. 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(37). Regarding the critical care setting, there is some evidence demonstrating that EN compared to PN results in lower complication risk [17]. Besides, one study in non-malnourished critically-ill patients with AKI described potential advantages in delaying PN if EN is not possible/tolerated [38,39]. 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 [17].

4. Screening and assessment

4.1. Screening for malnutrition

9) 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.

(R6, Grade GPP, strong consensus).

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 [40], 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 [41,42]. The nutritional risk screening (NRS) 2002 tool [43,44] has also been reported to adequately identify patients considered malnourished by SGA and predicted worse clinical outcomes [45,46]. 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 [47,48]. 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(40), 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. Assessment tools

10) 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.

(R7, grade GPP, strong consensus 91%)

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 [2].

Body weight and BMI, unless very low (e.g. BMI <18 kg/m^2), 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 presence of fluid overload, and cannot distinguish fat from muscle stores [3]. 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) [49,50].

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 [51]. The SGA has also been used to identify malnourished hospitalized KF patients on chronic hemodialysis [52]. Severe malnutrition by SGA at ICU admission was also associated with late mortality (until six months after discharge) in AKI patients [53]. 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. 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 [11].

4.3. Assessment of body composition and muscle function

11) 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.

(R8, grade B, strong consensus 96%)

Commentary.

In this clinical setting, muscle loss should be identified early, since it has been linked to complications and worse prognosis [54–58]. Studies using bioelectric impedance analysis (BIA) show that this method is unreliable in patients with AKI and fluid overload, providing inaccurate values of fat free mass [59], and total body water [60]. Imaging techniques are considered the reference standard techniques for the assessment of skeletal muscle mass and body composition [61]. In this regard, the use of ultrasound for the assessment of muscle mass has been recently investigated in this clinical setting with good reliability [62,63]. An important advantage of US is that measures seem to be scarcely influenced by rapid fluid shifts [62,64]. Validation studies against CT in critically ill patients with AKI disclosed an absence in differential and proportional bias, with a minor loss of precision [63]. Because of the lack of cutoff values to identify low muscle mass using ultrasound, we suggest that ultrasound may be used as a monitoring tool. The opportunistic use of CT scans performed for clinical reasons is a valuable tool to evaluate skeletal muscle mass (at the L3 vertebra level) [65]. Low muscle mass by CT scan at admission predicted a higher length of stay and increased risk of mortality [66], while it was associated with the risk of complications and 30-day mortality in ICU patients when measured at the time of extubation [67].

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

(R9, grade B, strong consensus 96%)

Commentary.

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 [68–70]. 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 [70,71]. There are no studies available regarding the use of MRC score in critically ill patients with KF. On the other hand, in a cohort of hospitalized patients with KF and at risk of malnutrition, handgrip strength values were shown to be in the sarcopenic range [40]. 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 [53]. In patients with KF on hemodialysis, handgrip strength correlates with the number of comorbidities and the malnutrition inflammation score [64,72]. Despite these promising applications, we do not recommend handgrip strength to be used in isolation since cooperation by the subject is required, and standard reference values for handgrip strength are lacking [73].

5. Timing and route of feeding

5.1. Timing of medical nutrition

For this PICO question, we refer to recommendation 8.1 of the ESPEN guideline for polymorbid hospitalized medical patients [20] and recommendations 4 and 5 of the ESPEN guideline for critically ill patients [17].

13) 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.

(R8.1 [Polymorbid Guideline(20)], grade B, strong consensus 95%)

Commentary.

As discussed above, 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 [20]. In one RCT on 200 elderly inpatients [21], 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 [74], early EN was related to reduced infection rates and better self-sufficiency.

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

(R4 [ICU Guideline(17)], grade B, strong consensus 100%)

Commentary.

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 [75–80] and four studies including non-ICU patients [81–84] the ESPEN guideline in critically ill patients reports a reduction in infectious complications when using early EN.

5.2. Route of feeding

5.2.1. Enteral nutrition if the gastrointestinal tract is available

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

(R5 [ICU Guideline(17)], grade A, strong consensus 100%)

Commentary.

When comparing early EN to early PN (including six studies in ICU patients [85–90] and seven studies with also non-ICU patients included [91–97], the ESPEN guideline in critically ill patients reports a protection against infections when starting early EN instead

of PN. Early EN was also related to shorter hospital and ICU stays in comparison to early PN(17).

In line with the ESPEN and ESICM guidelines [17,19], 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.

16) 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.

(S4, strong consensus 100%)

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 [98]. 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 [99]. While other studies in critically ill [85–90] and non-ICU patients [91–95] showed a reduction in infectious complications, shorter ICU and hospital stay with early EN *versus* PN.

17) 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.

(S5, strong consensus 100%)

Commentary.

EN represents the first and most important measure to support and restore gastrointestinal function, especially in the critically ill [17]. 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 [16].

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, [98]. 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 [98].

5.2.2. Parenteral nutrition if the gastrointestinal tract is not available

For this PICO question, we refer to the recommendations 6 and 7 of the ESPEN guideline for critically ill patients [17].

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

(R6 [ICU Guideline(17)], grade B, consensus 89%)

Commentary.

A meta-analysis of studies comparing enteral and parenteral routes independent of timing [99], found an important reduction in infectious episodes with EN as compared to PN (RR 0.64, 95% CI 0.48, 0.87, P = 0.004, I^2 = 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.

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

(R7 [ICU Guideline(17)], grade 0, strong consensus 95%)

Commentary.

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 low-dose PN should be carefully considered and balanced against the risks of overfeeding and refeeding.

6. Energy requirements

6.1. Definition of energy requirements?

20) 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.

(R10, grade B, strong consensus 96%)

Commentary.

To avoid over- and underfeeding, accurate determination of protein and energy needs is important [3,100]. The gold standard for measuring energy needs is the indirect calorimetry (IC) [101]. The knowledge of metabolic rate provided by IC is clinically relevant since critically ill patients with AKI can be either in a hypermetabolic state or in a hypometabolic state [102].

Although more practical than IC, equations aiming at REE estimation are largely inadequate, carrying the risk of under- and overfeeding [102–104].

A prospective interventional study on ICU patients with AKI on KRT demonstrated that a metabolic cart can improve energy provision also increasing protein intake [105].

Past guidelines on ICU patients with AKI have recommended 20–30 kcal/kg/d of non-protein calories [16,18,106], or 20–30 kcal/kg/d total calories [107–109]. 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, 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. Only two observational studies were performed in critically ill patients with AKI comparing IC with weight-based formulae or predictive equations [103,104]. Both studies agree that these methods 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.

21) 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.

(R11, grade 0, consensus 78%)

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_2 balance [101]. However, more recently, studies investigating the use of indirect calorimetry in patients receiving or not CKRT suggested no difference in REE [105,110–112]. The MECCIAS trial recently showed that the influence of CO_2 changes during CKRT on REE is minimal and that indirect calorimetry during CKRT should be preferred because of its effects on energy expenditure [112]. In indirect calorimetry, the REE value is calculated from O_2 consumption and CO_2 production (Weir equation), and both gases are also exchanged in the extracorporeal circulation [113]. However, during KRT, a substantial amount of CO_2 (26 ml/min) is removed in the effluent in the course of CKRT, which represented 14% of the average expired $VCO_{2(114)}$, thus VCO_2 measurement could not exactly reflect the endogenously produced CO_2, limiting the correct interpretation of IC-based measured REE.

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

(R12, grade GPP, strong consensus 100%)

Commentary.

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 [103]. 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 [114]. An expert position paper on indirect calorimetry in critically ill patients [101] 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 [16,18]. 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_2 only obtained from ventilators has been demonstrated to be more accurate than equations in critically ill patients not on CKRT [115] but less than indirect calorimetry [101]. However, no such study has been made up to now in critically ill patients with AKI.

23) If calorimetry is not available, using VO2 (oxygen consumption) from pulmonary arterial catheter or VCO2 (carbon dioxide production) derived from the ventilator will give a better evaluation on energy expenditure than predictive equations.

(S2 [ICU Guideline(17)], consensus 82%)

Consensus (82% agreement).

Commentary.

If indirect calorimetry is not available, the calculation of REE only from VCO_2 values obtained from ventilators (REE = VCO_2 x 8.19) has been demonstrated to be more accurate than equations [115], but less than indirect calorimetry [101]. Also, VO_2 calculated from a pulmonary artery catheter is another available option [116].

6.2. Optimal energy intake

Since no major modifications of energy metabolism are associated with AKI per se, 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 recommendations from the ESPEN guideline for polymorbid hospitalized medical patients [20] and the ESPEN guideline for critically ill patients [17].

24) 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.

(R11 [Polymorbid Guideline(20)], grade B, 100%)

Commentary.

In polymorbid medical inpatients reduced food intake is associated with increased mortality and complications [117–120]. The EFFORT trial has demonstrated that reaching ≥75% of estimated nutrition goals versus lower achievements led to significant lower risk of adverse events and mortality [26]. Supporting this finding in a meta-analysis from 2019, Gomes et al. [36] stratified trials by adherence to nutrition protocol and found that high adherence led to a more pronounced survival benefit. Whether the impact would be more pronounced if the interventional group had achieved 100% cannot be answered by the data. Achieving 100% of the targets should be strived for but is usually not realistic when patients are hospitalized and have either an exacerbation of one of their conditions or a current complication.

A prospective observational study [121], reported that patients with reduced food intake had a higher in-hospital mortality as well as 90-day mortality. Similar results were observed in a supportive study conducted in the critically ill population [122]. In a trial Li et al. found nutritional intake to be higher in patients with LOS of less than twelve days compared to patients with higher LOS [123]. However, a small sample size (n = 40) pilot RCT could not find a difference in readmissions within 30 days between the interventional group that reached 75% of their nutritional goals and the control group that did not [124].

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

(R8 [ICU Guideline(17)], grade B, 100%)

Commentary.

A larger database analysis suggested that energy intake is associated with significantly improved survival when it is close to measured EE [125] or between 70 and 100% of the repeatedly measured resting EE (115). Undernutrition or over-nutrition is deleterious to outcome according to these large observational studies. If there is consensus stating that overfeeding should be avoided, it remains difficult to define which calorie targets should be proposed in the different phases of critical illness. Actual EE should not be the target during the first 72 h of acute critical illness. Early full feeding causes overfeeding as it adds to the endogenous energy production which amounts to 500–1400 kcal/d and can lead to deleterious effects such as increased length of stay, ventilation duration and infection rates [126]. Early full feeding also increases the risk of refeeding. On the other hand, a too low intake, below 50%, was associated in retrospective studies with a worse clinical outcome, may lead to severe calorie debt and empty the energy reserves, reduce lean body mass and may increase infectious complications [127,128]. In a 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 [39]. Besides, no improvement in nitrogen balance was found, while urea formation increased, which probably prolonged the duration of KRT(39).

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

(R16 [ICU Guideline(17)], grade 0, 100%)

Commentary.

Recently the analysis of a large data base including 1171 patients with indirect calorimetry data [114] confirmed that under- and overfeeding were both deleterious, and that the optimal amount appeared to be between 70 and 100% of measured EE. Prospective randomized studies comparing the delivery of 70–80% of the measured EE to another regimen may improve our knowledge.

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 over-nutrition. This progression should be ordered according to a local protocol preventing sharp and too rapid increases.

27) 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.

(R17 [ICU Guideline(17)], grade A, 100%)

Commentary.

A meta-analysis of studies comparing enteral and parenteral routes independent of timing [99], 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. The energy/protein goal should be achieved progressively and not before the first 48–72 h to avoid over-nutrition. 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 to exceed 100% of measured EE. Provision of excessive amounts of nutrients by any route should be avoided in the early phase of critical illness, which is associated with relevant endogenous energy production.

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

(R18 [ICU Guideline(17)], grade 0, 95%)

Commentary.

This guideline focused only on studies using indirect calorimetry and the meta-analysis performed found a trend (RR 1.28, 95%CI 0.98–1.67, p = 0.07) to improved short-term mortality when using indirect calorimetry to identify the energy target, compared to hypocaloric regimens but there were no significant differences in long term mortality, infection or length of stay [17]. Four RCTs have based their energy targets on indirect calorimetry. The pilot TICACOS study [129] showed that such a strategy was associated with an improvement in 60-day survival in the per protocol study, but also to an increase in length of ventilation, infections and length of stay related to the calorie overload and positive energy balance due to non-nutritional energy intakes. Petros et al. [130]showed a reduction in infection rate in the study group. Heidegger et al. [131] measured EE at day 3 and adapted the energy intake accordingly, comparing supplemental PN from day four to an EN only group. The intervention group had a lower late nosocomial infection rate after day 9. The recent EAT-ICU study compared the goal-directed group, receiving the EE measured with indirect calorimetry as a caloric target to reach within 24 h to patients receiving standard therapy. The study group also received protein according to urinary nitrogen loss. No advantages or harm were observed in terms of functional outcome, morbidity, or mortality in this RCT [132].

29) 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.

(R19 [ICU Guideline(17)], grade B, 95%)

Commentary.

Studies using predictive equations and observational studies were analyzed [17]. If predictive equations are used, we suggest using hypocaloric nutrition (up to 70% estimated needs), over isocaloric nutrition (70% or greater of estimated needs), in the early phase of acute illness (RR 0.92, 95%CI 0.86–0.99, p = 0.02). Various studies have compared energy intake based on predictive equations to reduced calorie intake achieving even trophic enteral feeding concluding that there was no difference between normocaloric versus hypocaloric diets in critically ill patients [17]. Berger & Pichard observed an increase in mortality in the group of patients receiving energy close to the prescribed recommended energy intake [133]. Conversely, Reignier et al. observed a better outcome in patients receiving low energy and proteins over 7 days (Nutrirea 3) [134]. Large observational series including hundreds to thousands of patients have observed that the optimal calorie load associated with the best survival is around 80% of predicted energy needs [135], whereas others suggested no relation between intake and outcome or better outcome with lower energy intakes [136]. However, in all these studies, calorie delivery was lower than recommended/prescribed or the studies were not targeted to this parameter.

6.3. *Influencing factors*

30) 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.

(R13, grade 0, strong consensus 91%)

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 [3,100]. 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 [3]. 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 [137]. A similar finding was described in an earlier study [138].

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.

31) 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.

(R14, grade B, strong consensus 100%)

Commentary.

Some of the solutions commonly used in the KRT procedures may provide energy substrates in the form of citrate (3 kcal/g) from regional circuit anticoagulation, glucose (3.4 kcal/g) from dialysis fluids, and lactate (3.62 kcal/g) that might be used as a buffer.

Although citrate is partially removed from the blood by KRT, some of it may reach the systemic circulation and get metabolized

in the liver, kidneys and skeletal muscle [139,140]. Since citrate is an intermediate metabolite of the Krebs cycle, it does not require insulin to enter the cells, where it can be metabolized yielding energy and bicarbonate.

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 (143). 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) [141–143].

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 [144]. Alternatively, diffusive PIKRT modalities, such as sustained low-efficiency dialysis (SLED), easily allow increased citrate removal by the treatment itself [139,145], with only a limited amount of energy (100–300 kcal/d) to be factored in the patient's prescribed energy intake.

32) 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.

(R15, grade B, strong consensus 100%)

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 co-morbidities and complications [17,138]. In mechanically ventilated patients, no differences were found in REE due to the presence of AKI [146]. Even in multiple organ failure, the energy expenditure of critically ill patients amounts to not more than 130% of predicted energy expenditure [18]. 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 [147]; in the same way, critically ill patients with AKI undergoing KRT had similar REE measured by indirect calorimetry than AKI patients not on KRT(104). Only one observational study found a difference between REE of patients with AKI before the initiation of KRT and after five days on dialysis [148]. However, the study had a high dropout rate (24 patients evaluated at five days out of 124 enrolled).

7. Protein requirements

7.1. KRT impact

33) 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.

(S6, strong consensus 100%)

Commentary.

Intensive modalities of KRT (such as CKRT or PKRT), 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) [3,105,149–155]. 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 [105,156]. Besides, since amino acids are low molecular weight substances with a sieving coefficient near 1.0, many amino acids can be readily filtered from the blood into effluent [151,152]. 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 [149–152]. 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(152), 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 [157].

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

(S7, strong consensus 100%)

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 [3]. Consequently, the protein requirement can be largely increased. Providing increased protein intake can limit nitrogen losses, even though it cannot reverse the catabolic condition [154,158,159].

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 patients' catabolic status and help guide nutrient prescription.

7.2. Defining protein requirements

35) 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).

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 [3,160].

36) 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).

(R16, grade GPP, consensus 86%)

Commentary.

Total nitrogen loss in a typical CKRT patient can be about 25 g/d [152,154] 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) [103,158,161–165]. Considering the wide range of protein catabolism in different clinical conditions, it is recommended to perform

protein catabolic rate of patients to guide medical nutrition implementation.

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

(R17, grade B, strong consensus 96%)

Commentary.

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 [154,159]. 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 [153], 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 [163], 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 [105]. 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.

38) 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: ≥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.

(R18, grade 0, consensus 83%)

Commentary.

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(104). 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.

7.3. Protein reduction?

39) 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.

(R19, grade A, strong consensus 96%)

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 [60]. A recent meta-analysis found no difference in outcome between the timing of KRT initiation (early versus late) [166]. 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 (40-60 g 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 [16,18,98].

40) 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).

(R20, grade GPP, consensus 87%)

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.

41) 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.

(R21, grade GPP, strong consensus 100%)

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 [167], and metabolic acidosis must be

prevented or adequately corrected [168]. 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 [169].

8. Micronutrient requirements

8.1. Trace elements and vitamins

42) 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.

(R22, grade B, strong consensus 100%)

Commentary.

During critical illnesses, vitamins, and trace elements may impact on immunomodulation, wound healing and may have antioxidant properties [170,171]. 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 [172,173]. 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 [174].

In patients on CKRT, a reduction in serum levels of zinc, and selenium have been described, probably as a consequence of increased utilization in critical illness and losses secondary to CKRT [172,175–177]. In a randomized trial of chronic hemodialysis patients [178], a moderate supplementation with zinc and selenium (respectively 50 mg/d and 75 μg/d) was not able to correct deficiencies in patient on chronic KRT suggesting increased requirements in these patients.

Large effluent losses of several trace elements, but particularly of copper were shown to far exceed nutritional intakes [177]. 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) [179].

43) 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.

(R23, grade B, strong consensus 100%)

Commentary.

In patients on CKRT, a reduction in serum levels of folate, vitamins C, E, and thiamine have been described, probably as a consequence of increased utilization in critical illness and losses secondary to CKRT(174, 177–179). 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 [176,177]. 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) [180]. The current recommendation is that the losses of micronutrients in the effluent fluid should be replaced [181,182] and that these patients would need an additional amount beyond that provided by standard PN [177,183]. However, 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.

8.2. Electrolytes

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

(R31, grade A, strong consensus 100%)

Commentary.

Electrolyte disorders are common among hospitalized patients [184]. Kidney failure is often characterized by hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, and most of them normally improve when KRT is started. However, intensive KRT, is often associated to electrolytes deficiency [185,186,187].

Common laboratory abnormalities associated with intensive/prolonged KRTs include hypophosphatemia, hypokalemia, and hypomagnesemia [188,189]. Hypophosphatemia (serum phosphate levels <0.81 mmoL/l) has a high reported prevalence (60–80%) in the ICU [190,191] and is associated with a global negative impact on patients' outcome [192–194]. The initiation of KRT is a major risk factor for the development of hypophosphatemia ([188,195–200] 2017).

Hypokalemia is another usual complication observed among hospitalized patients, with a prevalence ranging from 12 to 20% [201,202], with reported values increasing up to around 25% in patients with KF started on prolonged modalities of KRT(189). Finally, hypomagnesemia, generally defined as serum magnesium levels <0.70 mmol/l has been reported in up to 12% of hospitalized patients with an incidence around 60–65% among critically ill patients [203,204]. Increased attention has recently been directed to the increased magnesium removal in course of KRT(206). 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 [197,205–208].

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

(R32, grade B, strong consensus 100%)

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 electrolytes derangements by modulating KRT fluid composition may represent the most appropriate, and easier, therapeutic strategy [209–211]. 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 [212–215]. 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 (218). 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 [205,216,213].

9. Disease-specific nutrients

9.1. Renal disease-specific formulae?

46) 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).

(R24, grade B, consensus 88%)

Commentary.

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 [217].

47) 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.

(R25, grade B, strong consensus 91%)

Commentary.

Formulas designed for patients with KF are more concentrated and provide an advantageous calorie and protein ration in patients with high protein needs and when fluid restriction is needed.

48) In selected patients with electrolyte and fluid imbalances, concentrated "renal" EN or PN formulas with lower electrolyte content may be preferred over standard formulas.

(R26, grade GPP, strong consensus 96%)

Commentary.

Formulas designed for patients with KF have lower amounts of fluids, sodium, potassium, and phosphorus. Thus they could be advantageous in patients presenting electrolyte disturbances (for example hyperkalemia) and/or fluid overload.

9.2. Omega-3 fatty acids?

49) 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.

(R27, grade GPP, szrong consensus 96%)

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 [218,219], 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(3). 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(17).

9.3. Glutamine?

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

(R50, grade A, strong consensus 100%)

Commentary.

Even though glutamine losses of about 1.2 g/d have been documented during CKRT [220], and earlier underpowered studies showed some benefit of intravenous L-glutamine only when summarized in a meta-analysis [221], the most important evidence regarding glutamine, the REDOX study [222,223], 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 [224] showed similar results in a population of critically ill patients.

9.4. Glucose monitoring

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

(R29, grade A, szrong consensus 96%)

Commentary.

In this clinical setting, patients are at increased risk of both hyper- and hypoglycemia [100]. Insulin resistance is highly prevalent among patients with AKI and is associated with increased mortality risk [6]. High blood glucose concentration can be considered one of the best independent predictors of mortality in this clinical setting [6]. On the other hand, since insulin is metabolized also by the kidney, renal function impairment may act as a predisposing factor for hypoglycemia. 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 [225].

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

(R30, grade A, strong consensus 100%)

Commentary.

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(101).

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 [226]. In the case of severe hypoglycemia (<40 mg/dl) the corresponding percentages were 29% and 0%, respectively [226]. Similarly, glycemic variability was increased in patients with KF(229). Regarding possible favorable effects on renal outcome, strategies aiming at a tighter glycemic control are not supported [227–231].

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Disclaimer

This guideline has been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using this guideline shall do so only after consultation with a health professional and shall not mistake this guideline as professional medical advice. This guideline must not substitute seeking professional medical and health advice from a health professional.

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Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

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