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Short Report – Medical nutrition therapy for critically ill patients with COVID-19

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Dear Editor,

We read with great interest the paper from Kaiying and Hanping[1] on nutrition patients hospitalized for COVID-19 in which the authors report evidence issued by the Chinese Society of Parenteral and Enteral Nutrition (CSPEN) of the Chinese Medical Association. The COVID-19 is new β-coronavirus, that can cause acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure and death (~10%) and represents a global health challenge[2,3]. Medical nutritional therapy is among the mainstay of therapeutic principles and one of the core contents of comprehensive treatment measures for patients with COVID-19.

Based on available clinical observations, it is evident that despite people of all ages can become infected, malnourished elderly people, with low immunity and patients with chronic diseases have a worse prognosis and have a higher mortality rates[4]. This phenomenon highlights the importance of nutritional status and the relevance of nutritional therapy that should be regarded as first-line treatment and implemented into standard of practice. Good nutrition not only provides the body with immunity to diseases, including COVID-19, but is also the primary guarantee for promoting disease recovery[4].

We agree that the nutritional indications suggested by Kaiying and Hanping[1], according to the five-step method, diet plus nutrition education, oral nutritional supplementation (ONS), tube feeding, supplementary parenteral nutrition (SPN), and total parenteral nutrition (TPN), are fundamental for the best recovery of the infected patient. Nevertheless, in our opinion, indications for nutrition therapy should be tailored. When the nutritional status is suboptimal, nutritionists should choose the most appropriate artificial nutrition (AN) approach with enteral nutrition (EN) or parenteral nutrition (PN). The first choice treatment should be oral administration with ONS. When ONS is insufficient, nutritionists should prescribe AN with EN or PN. First tier of AN is EN and when insufficient, PN should be selected. The plan, method, route, and formula of nutrition therapy should be adjusted dynamically and timely in accordance with the clinical characteristics of COVID-19 patient. The transition between ONS, EN, and PN should be smooth, following the principle that when the EN can meet the 50% of the target demand, PN can be gradually reduced and subsequently stopped; when the ONS can meet the 50% of target demand, the EN can be progressively reduced and then stopped. Conversely, when 50% of target demand cannot be met

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by ONS, the EN route cannot be reduced[1]. In patients admitted to ICU unable to eat, nutritional medical therapy should be started at the earliest but no more than 72 hours, for a hospitalization that lasts longer than 48 h. COVID-19 has a high demand for Intensive Care Units (ICU), aggravated by long days of hospitalization[5], consequently all critical ill patients need nutritional medical therapy. Therefore, we present the following decalogue based on international guidelines[1,6,7], for COVID-19 treatment:

- In the critical patient in intensive care with respiratory insufficiency, if ICU last longer than 48 hours as expected, the medical nutritional therapy must be started with the following priority (Figure 1): a) early EN must be started within 48 hours, if no contraindications are present; b) PN must be started within 3 to 7 days and must be considered when all strategies for EN have failed to avoid severe malnutrition; b1) in already malnourished patients PN can be started slowly on day 3 and the infusion rate gradually increased up to the 7th day; b2) on day 7, in patients at risk of malnutrition, with stable clinical conditions, PN can be started by changing the fluid therapy; c) overfeeding must be avoided: both EN and PN must be prescribed at increasing speeds to avoid overfeeding and the target speed must be reached in about 3-4 days (in the critical phase, an endogenous production of 2092-5857 kJ/day is present in the first 72 hours)[8]; d) if the necessary requirements are not met with EN, it is possible to start a combined medical nutritional therapy and PN is preferred to administer polyamino acids[9].
- Energy: COVID-19 need more energy than normal. The most correct estimate of caloric needs is functional to avoid overfeeding or underfeeding. It is recommended to supply 84-126 kJ/kg/day (1 kcal = 4.184 kJ). For every 1°C increase in body temperature, the body's energy consumption increases by 10%. With a cumulative energy debt of 33494 kJ, the patient may experience complications; above 41868 kJ, the patient may die[10]. Maintaining the energy balance of patients with COVID-19 is critical. However, considering the increased metabolic load in patients with severe pneumonia, moderately low calories can reduce the metabolic load and excessive energy intake is an independent risk factor for TPN blood-borne infections[11].
- Protein: to reduce the catabolism due to the inflammatory mediators, it is indicated to increase protein supply as top priority. It is recommended 1.3 g/kg/day increasing the supply of branched chain amino acids to 50%, to prevent muscle loss, enhance the strength of respiratory muscles[7,12]. For ICU patients in the anabolic phase, it is suggested not to include protein requirement in the energy expenditure count and in the presence of gastroparesis use NE products with hydrolyzed whey protein.
- Carbohydrates: carbohydrate administration should be limited in the critically COVID-19 patient with respiratory failure. The carbohydrate requirement is 2 g/kg/day and must not exceed 150 g per day. The oxidation of a mole of carbohydrates leads to the production of equal CO_2. In respiratory failure, CO_2 production must be avoided to decrease the respiratory quotients[8].
- Fat: the lipid requirement of the critically ill patient is 1.5 g/kg/day. Generally, the 0.5 g/kg/day of lipids derive from the administration of sedatives in lipid-solution. For example, Propofol can provide 1.1 kcals/mL as fat, similarly to a lipid emulsion at 10% and on average it covers 25% of the energy expenditure in mechanically ventilated sedated patients[13]. Give priority to the use of medium and long chain fatty acids and increase the proportion of ω-3 fatty acids and ω-9 fatty acids. Essential fatty acids play a major role in immune responses by altering the composition of cell membranes and modulating cell signaling. Arachidonic acid, a ω-6 fatty acid, is arguably the most important eicosanoid precursor to prostaglandins and leukotrienes. On the other hand, ω-3 fatty acids dampen inflammatory responses through their effects on eicosanoid production and specific cytokines[14].
- Non-protein energy supply ratio: sugar/lipid is 50-70/50-30; non-protein calorie/nitrogen is (100-150)/1[1].
- Fluid volume: pay attention to maintain neutral fluid balance in critically COVID-19 patients, with particular consideration to renal and prerenal failure[6]. For stable patients in ICU: 30 mL/kg/day of fluid for adult and 28 mL/kg/day for elderly. For large areas of pulmonary consolidation and elderly patients, it is recommended to control the amount of intravenous fluids. For every 1°C increase in body temperature, supplement 3-5 mL/kg (calculated as 4 mL/kg)[1].
- Micronutrients: among routine supplements of multivitamins and minerals, as complex of vitamin B, zinc, and selenium. In ICU patients, the requirements of the micronutrients and the administration must be divided according to the nutritional therapy used. In both EN and PN, Vitamin D deficiency must be assessed and if the level is <12.5 ng/mL (insufficiency), administer Cholecalciferol for EN or i.m. single 100.000 IU solution within a week for a maximum of 500.000 IU[7]. High-dose vitamin C (3-5 g/d), shorten the use time of booster drugs and ventilator, is effective for ARDS and

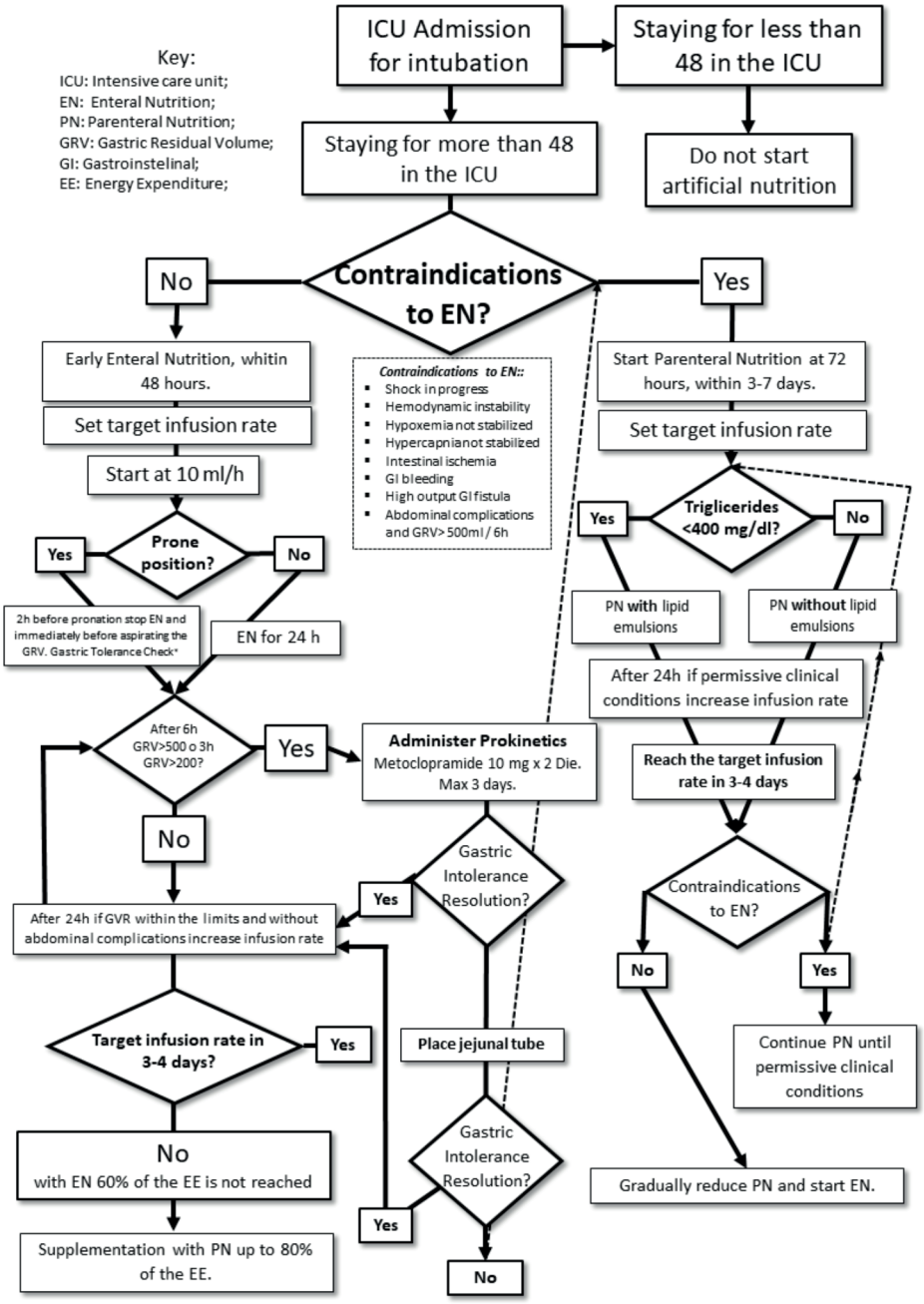

Figure 1. Medical nutrition therapy for critically ill patients.

significantly reduces mortality[15]. The administration of other micronutrients in doses higher than the recommendations should only be carried out if a specific deficiency is present. For example, thiamine, functional to energy metabolism, must be integrated from the 8th-10th day of hospitalization[16]. It can be administered thiamine 100 mg i.m. every 24 hours for 5 days.

- Immunonutrients: these nutrients influence immune system and have shown to have a considerable influence on immune function and improve metabolic and nutritional indices, such as nitrogen balance and serum proteins. There are several types of immunonutrients, such as arginine, nucleotides, glutamine, ω-3 fatty acids, and their functions and mechanisms are different. Immunonutrients can promote patient recovery by inhibiting inflammatory responses and regulating immune function.

Arginine has numerous effects on immune function and wound healing. Arginine availability can affect the immune response in injured states and it is the sole metabolic substrate for the synthesis of nitric oxide (NO). The expression and activity of inducible NOS is triggered by many of the inflammatory stimuli and cytokines, leading to high levels of NO that peak during the early inflammatory phase[17]. On the contrary, glutamine that can modulate and preserve gut function, which is compromised in severe stress, decreasing the production of pro inflammatory cytokines (interleukin [IL]-6 and IL-8) is not indicated in respiratory failure, as in COVID-19.

- Probiotics and polyphenol supplementation: although cytokine mediated effects are an essential part of the response to infection, excessive production of pro-inflammatory cytokines, or production of cytokines in the wrong biological context, increases the risk of a wide range of diseases, including COVID-19. The inflammatory response is activated by the transcription factor NF-kB by a variety of stimuli, including bacterial lipopolysaccharides (LPS), viral trans-activating proteins. Normal inflammation is self-limiting because the production of pro-inflammatory cytokines (TH1 cytokines: e.g., tumor necrosis factor-α [TNF-α], IL-1, IL-6, interferon-γ [IFN-γ]), *via* activation of the transcription factors NF-kB and STAT3, is followed almost immediately by production of anti-inflammatory cytokines (TH2 cytokines; IL-1, IL-4, IL-12, IL-15 IL-10, IL-13, etc). Chronic inflammation results when the initiating factors persist, or there is some sort of failure of the resolution process. Inflammation plays a pivotal role in the pathogenesis of COVID-19: an imbalance between pro-inflammatory and anti-inflammatory cytokines, leading to the storm of cytokines is currently considered to contribute to development and progression of COVID-19[18]. Therefore, the homeostatic equilibrium between TREG cells (IL-10) and Th17 cells (IL-17) is broken in COVID-19. Intestinal epithelial cells (IECs) can secrete and respond to various cytokines, through the expression of CD1d, an MHC-like molecule that after the activation of STAT3 produce the anti-inflammatory IL-10[19].
- Moreover, some commensal bacteria endow resident macrophages (CX3CR1+) T cell differentiation toward regulatory TREG cells and Th2 phenotypes[20,21]. The alteration of the gut-microbiota, consequent to the bacterial translocation, is due to the increase of the gut permeability dependent by endotoxins as lipopolysaccharides (LPS). These contribute to the maintenance of chronic inflammation or upon directly on immune cells. Probiotics and polyphenol supplementation are able to restore innate and adaptive immunity, also correcting alterations of intestinal microbiota which contributes to immune homeostasis, balancing the equilibrium between TREG cells and Th17 cells[18,22]. It is possible to hypothesize that the consumption of probiotics and polyphenols can contribute to extinguish the cytokine storm when recombined with appropriate antiviral treatments. In critically COVID-19 patient, EEN initiated at a low infusion rate nourishes the mucous membrane of the intestinal bacterial flora. Thus, it is possible to avoid intestinal permeability, reduce enterogenic infections, bacterial translocation, and increase in systemic inflammation[23]. In severe pathology with critical clinical conditions, EN, compared to PN alone, is able to reduce serum endotoxin levels by improving intestinal permeability[24]. Even prebiotics, probiotics, postbiotics, and polyphenols can be administered, with EEN or EN, to improve the balance of the microbiota and intestinal epithelium in order to prevent complications of bacterial translocation.

At this time of the COVID-19 pandemic, given the huge sanitary cost and human resource spending, attention to nutritional medical therapy and nutritional status should be considered among the "basic vital signs" as important as blood pressure and pulse oximetry.

The suggestions for a correct evidence-based nutritional therapy here reported are indicated for critically COVID-19 patients and should be included among lifesaving therapies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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