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Review

Nutritional therapy for hospitalized patients with COVID-19: A narrative and integrative review

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ABSTRACT

Hospitalized patients affected by coronavirus disease 19 (COVID-19) have a sustained pro-inflammatory state and recurrent gastrointestinal symptoms that correlate with a decline in the nutritional status, which is directly related to poor immune response and clinical evolution. Nutritional therapy has proven crucial in COVID-19 treatment through the provision of adequate amounts of nutrients. Since the beginning of the pandemic, medical societies have mobilized to provide practical nutritional guidelines to support decision-making; despite this, there are only a few studies dedicated to compiling the most relevant recommendations. In this narrative review, we aimed to summarize and stratify the current scientific literature on nutritional support for hospitalized COVID-19 patients. We carried out a literature review from three databases between January 2020 and July 2021, using nutrition therapy (or medical nutrition or enteral nutrition or parental nutrition or nutritional support) and COVID-19 (SARS-CoV-2 infection) as the search terms. Only those studies that evaluated adult hospitalized patients with admissions to wards, specific clinics, or intensive care units were included. The nutritional intervention considered was that of specific nutritional support via oral, enteral, or parenteral modes. A total of 37 articles were included. In general, the nutritional care provided to COVID-19 patients follows the same premises as for other patients, i.e., it opts for the most physiological route and meets nutritional demands based on the clinical condition. However, some protocols that minimize the risk of contamination exposure for the health team have to be considered. Energy requirements varied from 15 kcal/kg/day to 30 kcal/kg/day and protein goals from 1.2 g/kg/day to 2 g/kg/day. In both cases, the ramp protocol for increased supply should be considered. In cases of enteral therapy, ready-to-use diet and continuous mode are recommended. Attention to refeeding syndrome is essential when parenteral nutrition is used.

Introduction

Coronavirus disease 19 (COVID-19) is characterized by an inflammatory syndrome that results from decompensated stimulation of the host's immune system in response to the SARS-CoV-2 virus, leading to a condition of inflammation sustained by high concentrations of cytokines.[1] This pro-inflammatory state may be associated with hypermetabolism and nitrogen losses, culminating in increased energy demand and high muscle catabolism. Furthermore, COVID-19 can lead to a reduction in food intake due to decreased appetite, nausea, and other gastrointestinal discomforts.[2,3] Both factors are related to a high risk of malnutrition in affected patients.[4]

Literature published thus far indicates that malnutrition and nutritional risk are related to worse disease prognosis, especially in critically ill patients.[5] In this context, a recent study showed that sarcopenia may be related to a worsening of clinical prognosis and increased mortality.[6] Zhao et al.[7] observed a positive correlation between high nutritional risk and adverse effects resulting from COVID-19.

Adequate nutritional screening, with subsequent assessment of the nutritional state and assertive diagnosis with risk stratification, is important while treating COVID-19.[8] Most importantly, the provision of adequate nutrition with adequate energy and macro and micronutrients supply is crucial for the maintenance and/or recovery of nutritional status, an adequate

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immune response, and prevention of muscle wasting. Therefore, this narrative review aimed to summarize current scientific literature about nutritional therapy in hospitalized patients with COVID-19. This summary will help guide healthcare professionals in their decision-making with well-founded arguments and a more robust body of evidence that could be incorporated into frontline COVID-19 care.

Literature Review

Literature search methods

We carried out a literature review from three databases between January 2020 and July 2021, namely PubMed, Web of Science, and Virtual Health Library. The search was performed using the Boolean technique with the descriptors created by using Medical Subject Headings (MESH) terms with the following generated terms: nutrition therapy (or medical nutrition or enteral nutrition or parental nutrition or nutritional support) and COVID-19 (SARS-CoV-2 infection). In view of the broader scope, additional studies were included after a website search from governmental and non-governmental institutions to include guidelines, practical protocols, and expert consensus.

The eligibility criteria were defined according to the acronym PICOS (Population, Intervention, Comparator, Outcomes, and Study design). Studies that evaluated hospitalized patients of both sexes, aged >19 years old and with admissions to wards, specific clinics, or intensive care units (ICUs) were included. The nutritional intervention considered is that of specific nutritional support via oral, enteral, or parenteral modes. Studies without nutritional guidance or description of the diet, post-hospitalization patients, those that analyzed specific micronutrient supplements, or studies that do not specifically address COVID-19 were excluded. Filters for language were not applied.

After the first search step, the Rayyan Software (Qatar Foundation, https://rayyan.qcri.org/welcome) was used for the selection of articles and removal of duplicates. Based on the eligibility criteria, studies were independently screened by titles and abstracts. Data extraction was conducted using a digital file with information collected including (1) name of the authors or entity; (2) publication year; (3) publication classification (including consensus, randomized clinical trial, and observational); (4) population characteristics (mean age, sex, clinical conditions); (5) place of admission (i.e., ward, specialty clinics, or ICU); (6) type of nutrition therapy (oral, enteral, or parenteral); (7) extended nutrition therapy data (i.e., quantities and percentages of macro and micronutrients recommended); and (8) specific conditions contemplated (e.g., prone position, intubation, mechanical ventilation [MV] support).

Literature search results

The initial literature search identified 181 articles (165 after removing duplicates), of which 122 were excluded according to the eligibility criteria. A total of 43 articles were selected for full-text review; of these, only 31 contained sufficient information on nutritional recommendations or covered information on nutritional care. Subsequently, 6 publications from national and international associations and societies were manually included. A flow diagram of the literature search and study selection is presented in Figure 1. From the final sample of 37 articles, 19 publications were from the year 2020 and 18 from 2021. In total, guidelines, practical protocols, review articles, expert consensus, and observational studies were included.

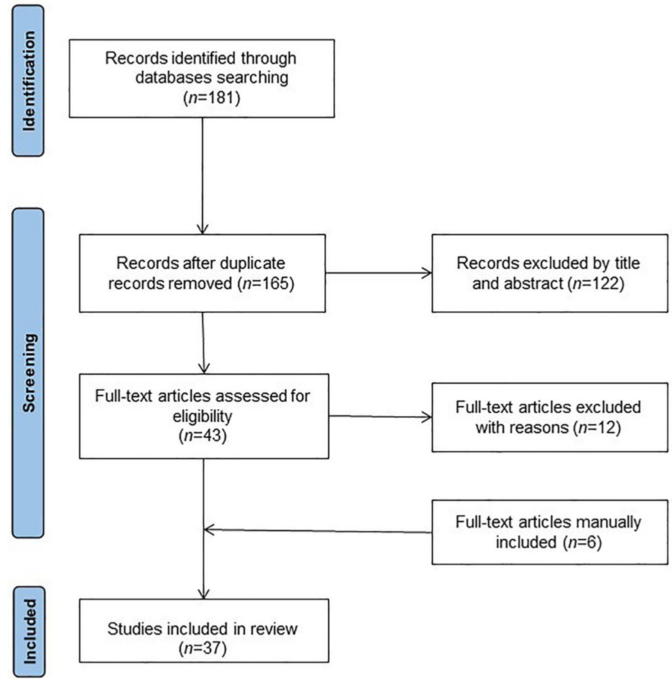

Figure 1. Flow diagram of the literature search and studies selection.

The included study population includes adults and older individuals with and without comorbidities. Regarding the severity of the disease, mild, moderate, severe, and critical cases were reported, with a predominance of patients hospitalized in ICUs, with or without MV, in addition to other forms of non-invasive ventilatory support.

Nutrient Requirements

Energy requirements

There was no consensus in the literature regarding the mode and time taken to reach the energy goal in COVID-19 patients. Multiple factors such as disease severity, phase of the pathogenic period, significant metabolic disturbances, tolerance of the organs involved in the digestive process, and prolonged permanence of an inflammatory response must be considered, especially while dealing with critically ill patients.[9]

Literature differs on how to estimate the energy expenditure and energy requirement of individuals affected by the disease. Although indirect calorimetry (IC) is the gold standard for measuring real energy expenditure in humans — and studies nearly unanimously agree with this fact — there are other factors that influence its use in the midst of the pandemic. The American Society of Parenteral and Enteral Nutrition (ASPEN) and the Brazilian Society of Parenteral and Enteral Nutrition (BRASPEN) claim that the use of this technology involves additional risks to the health team and contamination of equipment and, therefore, its use has been contraindicated.[10,11] This position is also endorsed by the Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) in a practical protocol published by Chapple et al. [12]. The European Society of Parenteral and Enteral Nutrition (ESPEN) reiterates that its use is possible if done safely.[13,14]

Some considerations are made in the case of critically ill patients. According to Thibault et al.[15], the use of IC is indicated only in patients with a stay of >10 days in the ICU and in those using total parenteral nutrition, to avoid overfeeding. Furthermore, Micic et al.[16] indicated the use of IC in case of prolonged intubation (>7 days) for patients admitted to the ICU. An interesting solution was proposed by Stachowska et al.[17], who supported IC as the first line and, in case of impossibility of use, suggested the calculation of caloric needs by expired volume translated into carbon dioxide release (VCO_2), which in turn can be obtained through MV, using a specific formula: resting energy expenditure (REE, kcal) = $VCO_2 \times 8.19$. A similar strategy was proposed by ESPEN, which recommends that critically intubated and MV patients receiving enteral nutrition should have their energy supply measured by oxygen consumption (VO_2), coming from the central pulmonary artery access, or from VCO_2 on the ventilator.[16] Both Micic et al.[16] and ESPEN[13] recommend predictive formulas as the last option.

The severe inflammation observed in critically ill patients with COVID-19 remains exacerbated for a longer period than in normal conditions, which delays this endocrine-metabolic phase, thereby altering the REE. In addition, complications such as multiple organ failure, use of MV, and use of sedative drugs or neuroblockers also interfere with REE.[18,19] A longitudinal study that used IC in patients who were positive for COVID-19 for a period of 3 weeks showed that REE was higher than what would be indicated by the predictive equations; after a period of 10–14 days in the ICU, this value increased even more.[20] Lakenman et al.[18] conducted a single-center observational study in which they measured the REE via IC of 21 patients admitted to the ICU and observed that a hypermetabolic state was present in both acute and late phases in 65% of patients.

BRASPEN proposed an amount between 15 kcal/kg and 20 kcal/kg of energy to be offered daily to patients with COVID-19.[11,21] ESPEN indicates 27 kcal/kg/day and makes a reservation for severely malnourished patients, who should receive 30 kcal/kg/day.[13,14] Similarly, a Chinese expert statement proposed a value of 25–30 kcal/kg/day for critically ill patients in the ICU.[22] Some studies point out that hypocaloric nutrition is preferable to isocaloric nutrition in the first few days in the ICU, specifically, when it is not possible to use IC owing to a high risk of overestimating energy expenditure through predictive formulas. The argument is based on the metabolic and systemic conditions characteristic of the disease and the patients' previous nutritional status. According to some studies, by providing calories equivalent to 100% or more of a patient's energy requirement, important signs and symptoms would be perpetuated and the necessary autophagy would be inhibited, worsening the outcome of critically ill patients.[18,23,24]

The biggest difference among the studies analyzed is the variation in the timepoint when the energy supply should be increased. Ochoa et al.[23] recommend to start nutritional therapy with 24 kcal/kg of the current weight, or up to 20 kcal/kg of the ideal weight in the first days, progressing in a staggered manner up to 50–70% of the goal at the end of the first week of hospitalization in the ICU. This ramp-up strategy is also reported in two studies by the same group, in which they present a hypocaloric or trophic enteral nutritional therapy strategy with goal achievement on the 7th day.[25,26] A review suggests an "initial permissive hyponutrition," in which 20 kcal/kg /day is prescribed for the entire first week, and only after the acute inflammatory phase has ceased, energy supply should be increased to 25–30 kcal/kg/day. [9] This study also states that patients on MV should receive fewer calories, around 10–15 kcal/kg/day. By contrast, some authors believe that the advancement of nutritional therapy should be done in stages, in this case, in days. Thibault et al. [15] stated that enteral or parenteral nutrition should be started at 10 kcal/kg/day on the first day and increased by 5 kcal/day over the course of 4 days, reaching the goal of 25 kcal/kg/day-. Micic et al. [16] suggested a hypocaloric intake until the 5th day, increasing the intake on the following day. This strategy of starting with a low caloric dose was also reported by Wu et al. [27] after evaluating critical patients.

Protein goals

Hospitalized patients with COVID-19 often face progressive loss of muscle mass due to hypermetabolic state and increased energy catabolism. Protein depletion can negatively impact the clinical outcome of these individuals; hence, ensuring adequate protein supply is crucial for coping with the disease, both in the acute and rehabilitative phases.[28] Recently published opinions and consensuses by the entities include recommendations on the optimal protein content for individuals who tested positive for SARS-CoV-2. Values for non-obese patients are in the range of 1.2–2.0 g of protein/kg of current weight/day. In addition to the optimal amount of protein, it is also relevant to consider the severity of the disease, the timing of reaching the proposed goal, and the expected results with long-term high-protein nutrition.[24,28]

Recent literature studies[9,15,16,23,25,26,29] showed that the protein value indicated for infected patients with mild-to-moderate symptoms may be different from that recommended for patients with more severe conditions. In a recent review, Aguila et al.[29] proposed that patients in wards receive absolute values of 75–100 g of daily protein; whereas those admitted to ICUs should receive an amount relative to their body weight (1.2–2.0 g/kg/day). By contrast, practical guidance suggests that mild-to-moderate patients receive 1.2–2.0 g/kg/day and critical patients receive similar values, but at a more restricted threshold of 1.5–2.0 g/kg/day.[15] Other studies with critically ill patients proposed that reaching the protein goal should be in a ramp protocol, with a gradual increase. [9,16,23,25,26] The treatment should be started with normoproteic values of 0.8 g/kg/day, which can be gradually increased to amounts close to 1.2 g/kg/day at the end of the first week. Protein content can be increased after decreasing exacerbated inflammation, as this period appears to enjoy the benefits of high-protein nutritional therapy.[9,16,23,25,26]

Considering some particularities, Cervantes-Pérez et al.[30] reported that geriatric patients should receive 1.0 g/kg/day and those with more than one comorbidity should receive >1.0 g/kg/day. These values are similar to those proposed by Fernández-Quintela et al.[31], for patients with the same characteristics, but hospitalized in ICUs. The authors also suggest supplementation of branched-chain amino acids (BCAA) in addition to the recommended values of 1.3 g/kg/day for patients with polymorbidities.[31] However, despite the literature recommending certain values, in practice, it is observed that one of the most difficult nutritional therapy indicators to achieve is protein intake, especially for critically ill patients. This may be because of some factors such as caution in offering high caloric intake in the acute phase; nutritional inadequacy of the hospital oral diet; inappetence; symptoms of gastrointestinal intolerance; enteral nutrition break periods; prolonged fasting; and composition of enteral formulas.[32–35] Cereda et al.[36] conducted a study during the first wave of COVID-19 in two Italian hospitals, and followed the nutritional evolution of 222 MV patients admitted to ICUs. The researchers followed the ESPEN recommendations for energy and protein values (25 kcal/kg/day and 1.3 g/kg/day, respectively) and attempted to achieve the goals over the course of the first week. Among the survivors, 36.4% and 46.6% of patients achieved satisfactory protein intake on the 4th day and 7th day, respectively. Further, 65.2% and 77% of patients reached caloric adequacy on days 4 and 7, respectively. The study's multifactorial analysis showed an association between reaching the energy goal on day 4 and lower mortality (hazzard ratio = 0.46, 95% confidence interval: 0.42–0.50, $P < 0.001$), providing evidence for the positive impact of prevention of the caloric deficit to improve the clinical outcomes.[36] With regard to protein supply, one study provided evidence that prescribed and administered amounts of protein were greater in the late phase compared to the early phase of the disease.[18] However, the mean urinary protein loss was 110 g (1.5 g/kg/day) in the acute phase and 161 g (1.9 g/kg/day) in the late phase, and the urinary nitrogen loss was 18 ± 11 g/day and 26 ± 13 g/day, in each of the phases, which results in a significantly more negative urinary protein balance ($P = 0.003$). Considering the protein prescription in the acute and late phases was 1.0 ± 0.4 g/kg/day and 1.3 ± 0.3 g/kg/day ($P = 0.053$), respectively, the authors considered that this supply was lower than optimal to ensure nitrogen balance.[18]

Non-protein calorie requirements

Carbohydrate and lipid requirements were low according to studies presented in this review. Only a third of the reviews had specifications on carbohydrates and lipids. Some studies state that due to the higher rate of production of carbon dioxide (CO_2), patients in respiratory decompensation should receive a lower percentage of carbohydrates.[14,22,31] The objective would be to promote favorable conditions for weaning from MV, by providing energy without exceeding the respiratory system's capacity to eliminate CO_2. The ratio of lipids and carbohydrates, in these cases, should be 50:50, different from the usual (70:30).[14,22,31] However, BRASPEN disagrees with this and suggests not trying to manipulate the respiratory coefficient with high-fat, low-carbohydrate formulas.[11] Formisano et al.[37] reported that carbohydrate intake was reduced in critical and non-critical patients aimed at non-aggravation of acute respiratory distress syndrome (ARDS) and consequent hypercapnia. Martindale et al.[25] suggested that the volume of dextrose in parenteral solutions should be conservative in the initial phase of critical illness, advancing slowly until the goal is reached. Another review gave similar advice, recommending to maintain glucose infusion up to 5 mg/kg/min initially.[17]

With regard to lipid goals, one study proposed to use 1.5 g/kg daily, prioritizing medium-chain triglycerides (MCT) and long-chain triglycerides (LCT).[31] However, two studies advised limiting the use of exclusively soy-based lipid emulsions in parenteral nutrition during the first week of ICU stay and suggested using a mix of less inflammatory oils instead such as olive oil, fish oil, and MCT.[10,25] Furthermore, with the aim of attenuating, or not aggravating, the inflammatory response, Thibault et al.[15] pointed out that enteral formulas enriched with omega-3 and intravenous emulsions supplemented with fish oil are preferable to patients with ARDS. In agreement, Stachowska et al.[17] proposed supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for the same purpose. In contrast, BRASPEN states that the use of enteral formula with omega-3 and antioxidants in patients with ARDS does not seem to bring clinical benefits.[11]

Nutritional Therapy Route

Oral therapy

In a cohort of patients with COVID-19, the most frequent nutritional problems described were inadequate oral intake (46.7%), inadequate energy intake (18.9%), and malnutrition (18.4%).[38] Considering that the oral route is the most direct physiological route possible, it is preferable in patients who were positive for COVID-19 with mild-to-moderate conditions,[11,29,39] and oral feeding must meet at least 70% of the patient's energy needs. [17] According to some authors, the consistency of the diet should preferably be pasty or liquid.[30,40] Moreover, the use of oral nutritional supplements may be interesting in some cases.[30,40]

Studies about nutritional therapy by oral feeding almost unanimously agree that professionals should consider oral supplements when the standard diet alone does not meet nutritional goals.[11-13,21,29,41] Stachowska et al.[17] reported that oral supplements should provide 400–600 kcal/day. Chapple et al.[12] stated that supplements should be hypercaloric, with 1.5 kcal/mL or 2 kcal/mL. In a study conducted by Formisano et al.[37], non-critical patients ingested a high-protein, high-calorie, soft-based diet divided throughout the day, aiming to reduce the duration and volume of the meal. If the nutritional risk was detected, 2–3 bottles of oral supplements were provided. The supplements were tasteless, due to dysgeusia and/or anosmia upon hospital admission. Of the 94 patients, 35 received only the basic hospital diet; 18 consumed increased portions of meals and/or oral supplement in addition to the diet; 9 patients were fed exclusively with the supplements; and 7 patients admitted to the semi-intensive unit received the basic diet or oral supplement, in addition to supplemental peripheral parenteral nutrition. As a preliminary result, the authors observed that patients who did not meet their energy and protein requirements had a lower hospital discharge value than those patients who had their requirements met (63.2% *vs*. 92.9%, respectively) and higher mortality (36.8% *vs*. 7.1%, respectively) ($P < 0.001$). [37]

Regarding extubated patients, return to oral feeding should consider the risk of dysphagia, adapt the texture, and observe acceptance of a given diet. In addition, there is the indication to maintain enteral nutrition until it is possible to satisfy needs only through food.[13,15] This is due to the fact that orotracheal intubation (OTI) and MV procedures have become routine in critically ill patients. Although crucial for patient care, these interventions can lead to dysphagia, because of iatrogenic reasons such as laryngeal damage at the time of intubation or factors underlying the respiratory disease itself such as a prolonged period of OTI.[13,15] A multicenter prospective cohort that included 11 hospitals and 100 patients with a positive COVID-19 test result showed that the mean intubation time was 14 days. After extubation, 90% of patients required adaptation to the oral diet, and 36% did not have oral return based on speech-language assessment. [42]

Ventilatory support is frequently used in patients with COVID-19, and there are a considerable number of publications that provide notes on nutrition in these circumstances. Oral feeding can still be used in patients using a high-flow catheter or intermittent non-invasive ventilation (NIV); however, it is recommended that patients using these supports receive an in-depth investigation of food ingestion, considering that there is a possibility of inadequate oral feeding and an indication of enteral therapy. [11]

Enteral nutritional therapy

During this literature review, it was noted that enteral nutrition is the most discussed topic among the included studies. Thirteen of the 15 reviews suggested enteral nutrition in patients with COVID-19. A noteworthy point is a fact that most reviews (76.9%) provide recommendations for enteral nutrition in critically ill patients. It can be assumed that most patients admitted to ICUs are unable to eat orally and that the enteral route is preferred to the parenteral route. [11] The suggestion of some researchers is that in case of unfeasible oral feeding for >3 days, or if consumption is <50% of the target for a period of 1 week, enteral nutrition should be chosen.[14,30] For critically ill patients, early enteral nutrition (i.e., within 48 h of ICU admission) is beneficial and should be used.[10,11,15,21-23,25]

The literature is not unanimous about the caloric value offered by enteral nutrition for COVID-19 hospitalized patients. There are more conservative recommendations of 15–20 kcal/kg/day or 1.25–1.5 kcal/mL with an infusion rate of 40–50 mL/h;[12,29] however, there are also strong indications of diets with high caloric density, [21] even if in low volume (20 mL/h). [11] When water restriction is required, hypercaloric formulas are indicated.[11,22] In accordance with the previously mentioned protein indications, enteral solutions must contain at least 20% of the total energy value in proteins [10] or they must constitute solutions with a high protein content.[11,16] The addition of a protein module can be interesting to achieve the protein goal and is endorsed by some entities.[10,22] Ochoa et al.[23] suggested that modules may be less affordable than hyper-protein ready-made formulas. However, despite being a potential facilitator, the handling of the open system may lead to a greater risk of contamination by the nursing team.[11,23] Some studies included in this review cite the lipid composition in enteral nutrition, of which two proposed formulas are enriched with omega-3 acids in cases of ARDS:[17,40] one study indicates this same supplementation with caution,[9] although two other studies contraindicate this finding.[11,21]

According to some authors, the enteral diet during the hospitalization period should be low in fiber content.[9,25] However, a review published by Martindale et al. [25] showed that as soon as the patient shows improvement in clinical signs, stability of the vasopressor dose and improvement of abdominal dysfunction, the addition of fibers can be considered in critically ill patients. Conversely, a retrospective study analyzed data from critically ill subjects with COVID-19 receiving tumor-specific enteral preparation (composition 1.3 kcal/mL, 0.045 g protein/kcal), which was rich in dietary fiber, and found that this formula had a light reduction in blood glucose levels.[43]

Considering enteral nutrition administration, most studies described that the continuous mode is preferable to the bolus mode, either because of gastrointestinal tolerance or because of the greater risk of contamination.[10,11,17,25,26] Furthermore, the catheter can be positioned in the patient's mouth or nose. [24] Although Osuna-Padilla et al. [44] proposed that orogastric positioning is more recommended to avoid epistaxis and sinus infection, gastric position in patients with COVID-19 receiving an enteral diet is supported by some researchers for the ease of early initiation of enteral nutrition and for representing the most physiological pathway. [12,15,17,26,30] ESPEN reiterates that the nasogastric tube is advised for critically ill patients with OTI and under MV.[13,14] Shang et al. [22] pointed out that the gastric position is preferable, but only for patients without a high risk of aspiration. The risk of regurgitation of gastric contents causes fear while administering food to the stomach; thus, there is also the indication of a post-pyloric position.[14,17,22]

Considering gastrointestinal complications, some authors demonstrated that 35% of patients under enteral therapy experienced symptoms such as nausea, diarrhea, gastroparesis, and abdominal distention. In some cases, this intolerance was the reason for temporarily ceasing nutrition. [44] In these cases, management is possible by decreasing the infusion rate, volume, type of diet, or tube position (post-pyloric position).[22,29] One study proposed that, in principle, a prokinetic drug should be administered before moving to the intestinal position. [26] However, Chappel et al. [12] recommended that the first alternative should be the post-pyloric position; however, if this measure does not cure the intolerance and the discomfort continues for 5–7 days, parenteral nutrition is indicated. In addition, Shang et al. [22] suggested that the jejunal position should be used for prone patients. Jiang et al. [9] described that all patients on an enteral diet should receive jejunal nutrition.

According to some studies, the recommendation for trophic enteral nutrition for patients with COVID-19 is 10–20 mL/h or 10–20 kcal/h, progressing slowly over the first week of ICU stay or for non-severe patients with signs of intolerance such as bloating and uncontrollable diarrhea.[11,17,22,29,30] Another factor that may be related to digestive tolerance is osmolality; however, only four studies make specific statements about this.[10,16,25,26] For these authors, the diet must be a polymeric standard (intact) and isosmotic.[10,16,25,26]

According to Micic et al. [16], it is of clinical value to monitor daily signs of gastrointestinal dysfunction in patients receiving enteral nutrition. Measurement of gastric residual volume is a parameter that can indicate gastrointestinal motility disorders and delayed gastric emptying. [45] The retrospective study by Liu et al. [46] reported that 56.0% of patients admitted to ICUs developed food intolerance, 83.9% had large gastric residual volume, 67.2% had abdominal distention, and 63.9% had vomiting. [46] ESPEN states that patients with COVID-19 should have the feeding tube relocated to the intestinal position if the residual gastric volume is elevated (>500 mL). [14] Another review suggests postponing enteral nutrition when the volume is high. [17] However, some authors advise against gastric residual volume measurement in these patients because of the potential for contamination of the medical team.[10,25]

Considering ventilation support, patients under NIV may present a higher risk of bronchoaspiration while using the digestive tract, in addition to the insertion of the tube being a potential generator of aerosols, thereby exposing professionals to a greater risk of infection. Therefore, there may be contraindications for the use of enteral nutrition under these circumstances.[14,25] In the case of individuals with OTI undergoing MV, enteral nutrition is indicated and should be started immediately (up to 12 h).[14,25,26] Another life support technique used in patients with COVID-19 in cardiovascular or pulmonary failure is extracorporeal membrane oxygenation (ECMO). Under these circumstances, the indication is for trophic intragastric enteral nutrition with slow and gradual advancement during the first week.[25,26]

Parenteral nutritional therapy

The indication of parenteral nutrition in patients with COVID-19 is similar to those given to other patients. The studies included in this review indicate the parenteral therapy (total or partial): (1) when there is an infeasibility of providing nutrients satisfactorily by other routes;[14,16,46] (2) when enteral nutrition is not indicated or tolerated;[25,26,40,46] and (3) when patients present with severe malnutrition.[23,41] In these cases, partial or supplemental parenteral nutrition is preferable compared to total parenteral nutrition.[12,37] Early complementation is not indicated before the 4th day [40] or before the 5th day or 7th day[11] since the premature use of this resource can cause secondary damages because of the increase in volume provided.[16]

In an intensive care setting, some studies state that parenteral nutrition should be considered in individuals who cannot tolerate full-dose enteral nutrition at the end of the first week or up to the 10th day in the ICU.[25,26] As stated earlier, patients with COVID-19 often experience digestive dysfunction; however, parenteral nutrition should not necessarily be initiated with the onset of these symptoms, being reserved only after all strategies to maximize gastrointestinal tolerance have been tried. [14]

In some cases of ventilatory support such as a high-flow nasal catheter or NIV, the indication of parenteral therapy may precede the use of enteral therapy. [40] Caccialanza et al. [47] presented an empirical protocol applied to patients affected with coronavirus, in which they opted for parenteral nutrition over enteral nutrition. This choice was because of the nasogastric tube potentially compromising the effectiveness of the NIV mask, in addition to the possibility of gastric distention caused by positive pressure ventilation, which can worsen respiratory parameters. [47] A review by Thibault et al. [40] stated that if the oxygen volume is >9 L/min or the inspired oxygen fraction (FiO_2) >60%, total or partial parenteral therapy is recommended. In addition, critically ill patients may not have intravenous access exclusively to nutrition, making it even more difficult to implement this form of nutritional therapy. [23] The insertion of an access, whether central or peripheral, is an invasive process that must consider the clinical condition of the patient, nutritional demand, availability of venous access, and the time of use. [37] Central parenteral nutrition usually makes total parenteral nutrition feasible, as it is indicated for patients who will depend on its use for a period longer than 14 days and who need great nutritional support with a restricted volume. Moreover, most studies have stated no preference regarding the location of the access.[36,47,48] Only a study by Formisano et al.[37] mentions the use of partial parenteral nutrition only for peripheral access.

Infectious, mechanical, and metabolic complications can occur while administering parenteral nutrition. Considering that COVID-19 patients often have significant endocrine dysfunction, [49] additional care should be considered, especially in the first few days, to avoid overfeeding and the development of refeeding syndrome.[17,40]

Discussion Points

This narrative review described and discussed important aspects of nutritional therapy applied to patients with COVID-19 in the context of hospital and ICU admissions [Figure 2]. The method employed allowed the combination of empirical and theoretical data that did not aim to exhaustively answer the central question of the theme, but rather to present the vastness of the literature and analyze it predominantly in a qualitative way.

A broad discussion about caloric and macronutrient requirements, supplementation, feeding route, and some special considerations about the prone position and respiratory support were compiled. Of note, some of the guidelines showed many specificities which can make it difficult to summarize the recommendations in addition to choosing a single suitable measure. In this sense, customization of treatment, mainly considering the previous and current nutritional status is essential in the decision-making process. General recommendations concerning energy and protein requirements range from 15 kcal/kg/day to 30 kcal/kg/day and 1.2 g/kg/day to 2.0 g/kg/day, respectively; however, nutritional status, ICU hospitalization, need for MV, and presence of comorbidities should be considered in the choice of nutritional supply. Moreover, the ramp protocol for increased energy and protein supply also differs from the literature, and the NT team has to evaluate the best choice for each patient.

In this review, we have discussed some critical phases of nutritional management of COVID-19 hospitalized patients. The extubation phase may represent an important challenge for patients in MV because a certain degree of dysphagia may occur. The choice of the NT route is crucial for all follow-ups of NT. Moreover, the definition of energy supply is also a critical stage. There is no consensus regarding the use of IC, and predictive formulas may be an alternative choice. However, predictive formulas should be used with caution, because they were developed in a unique patient population. [50] Energy supply should be discussed with the NT team to avoid under or overfeeding. Finally, the carbohydrate content of the diet is another discussed point. While some evidence supports high-carbohydrate content as a factor for the worsening of ARDS symptoms, [36] other authors suggested not trying to manipulate the respiratory coefficient. [13] It is important to assess and discuss individual cases with the NT team.

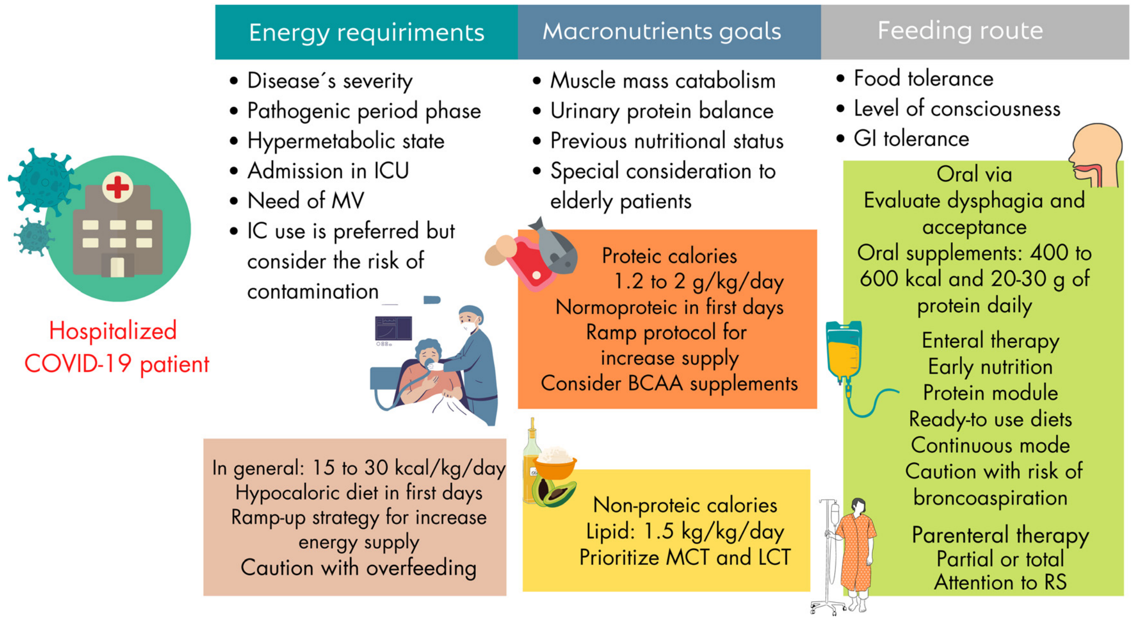

Figure 2. Practical recommendations of nutritional support for hospitalized COVID-19 patients.
BCAA: Brainched-chain amino acids; COVID-19: Coronavirus disease 19; GI: Gastrointestinal tract; IC: Indirect calorimetry; ICU: Intensive care units; LCT: Long-chain triglycerides; MCT: Medium-chain triglycerides; MV: Mechanical ventilation; RS: Refeeding syndrome.

The establishment of a specific protocol for COVID-19 treatment was difficult at the beginning of the pandemic when the disease's physiological effects were not yet elucidated. The results point to the importance of nutritional intervention as an integral part of patient care therapy. It can be said that proper nutritional care is essential to ensure adequate means to enable possible recovery. Improved education of health professionals involved in the nutritional support of patients infected by COVID-19 is essential and should be actively incorporated into the hospital environment. At present, a considerable number of published studies on COVID-19 are available, which allows clinicians on the front line to guide their decision-making with well-founded arguments and a more robust body of evidence.

The limitations of this narrative review should be acknowledged. The lack of systematic criteria for the search and analysis of the literature and a certain subjectivity in the selection of articles may have led to potential biases.

Conclusions

In this study, hypothetical and experimental recommendations were summarized that allow extensive insight into various segments of nutritional therapy for hospitalized patients with COVID-19. In general terms, the nutritional care provided to this group of patients follows the same premises as the other patients: (1) always opts for the most physiological route; and (2) meets nutritional demands considering the clinical condition. However, there are special considerations that must be taken into account in the pandemic situation, which do not relate solely to the best interest of the patient, such as the choice of protocols that minimize the risk of contamination exposure to the health team.

It can be said that the results obtained illustrate the reality experienced in most health services, wherein patients who require specific nutritional therapy are those in very severe or critical medical conditions. Although the literature has not been homogeneous in some aspects, these data are not negative, since patients with COVID-19 experience different aggravations during the period of hospitalization, manifest different symptoms, and thus need nutritional therapy adaptations according to the severity of the disease, the systems affected, and the overall health condition.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Rabaan AA, Al-Ahmed SH, Muhammad J, Khan A, Sule AA, Tirupathi R, et al. Role of inflammatory cytokines in COVID-19 patients: a review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. Vaccines (Basel) 2021;9(5):436–58. doi:10.3390/vaccines9050436.
[2] Sun JK, Liu Y, Zou L, Zhang WH, Li JJ, Wang Y, et al. Acute gastrointestinal injury in critically ill patients with COVID-19 in Wuhan. China. World J Gastroenterol 2020;26(39):6087–97. doi:10.3748/wjg.v26.i39.6087.
[3] Kaafarani H, El Moheb M, Hwabejire JO, Naar L, Christensen MA, Breen K, et al. Gastrointestinal complications in critically ill patients with COVID-19. Ann Surg 2020;272(2) e61–61. doi:10.1097/SLA.0000000000004004.
[4] Haraj NE, El Aziz S, Chadli A, Dafir A, Mjabber A, Aissaoui O, et al. Nutritional status assessment in patients with Covid-19 after discharge from the intensive care unit. Clin Nutr ESPEN 2021;41:423–8. doi:10.1016/j.clnesp.2020.09.214.
[5] Sharma K, Mogensen KM, Robinson MK. Pathophysiology of critical illness and role of nutrition. Nutr Clin Pract 2019;34(1):12–22. doi:10.1002/ncp.10232.
[6] Wang PY, Li Y, Wang Q. Sarcopenia: an underlying treatment target during the COVID-19 pandemic. Nutrition 2021;84:111104. doi:10.1016/j.nut.2020.111104.

[7] Zhao X, Li Y, Ge Y, Shi Y, Lv P, Zhang J, et al. Evaluation of nutrition risk and its association with mortality risk in severely and critically Ill COVID-19 patients. JPEN J Parenter Enteral Nutr 2021;45(1):32–42. doi:10.1002/jpen.1953.

[8] Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. Clin Nutr 2019;38(1):1–9. doi:10.1016/j.clnu.2018.08.002.

[9] Jiang H, Zhang JC, Zeng J, Wang L, Wang Y, Lu CD, et al. Gut, metabolism and nutritional Support for COVID-19: experiences from China. Burns Trauma 2020;8 tkaa048. doi. doi:10.1093/burnst/tkaa048.

[10] Wells Mulherin D, Walker R, Holcombe B, Guenter P. ASPEN report on nutrition support practice processes with COVID-19: the first response. Nutr Clin Pract 2020;35(5):783–91. doi:10.1002/ncp.10553.

[11] Campos L, Barreto P, Ceniccola G, Gonçalves R, Nunes de Matos L. Parecer BRASPEN/AMIB para o Enfrentamento do COVID-19 em Pacientes Hospitalizados. BRASPEN J 2020;35(1):3–5.

[12] Chapple LS, Fetterplace K, Asrani V, Burrell A, Cheng AC, Collins P, et al. Nutrition management for critically and acutely unwell hospitalised patients with coronavirus disease 2019 (COVID-19) in Australia and New Zealand. Aust Crit Care 2020;33(5):399–406. doi:10.1016/j.aucc.2020.06.002.

[13] Barazzoni R, Bischoff SC, Busetto L, Cederholm T, Chourdakis M, Cuerda C, et al. Nutritional management of individuals with obesity and COVID-19: ESPEN expert statements and practical guidance. Clin Nutr 2021 S0261-5614(21)00248-X. doi:10.1016/j.clnu.2021.05.006.

[14] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr 2020;39(6):1631–8. doi:10.1016/j.clnu.2020.03.022.

[15] Thibault R, Seguin P, Tamion F, Pichard C, Singer P. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. Crit Care 2020;24(1):447. doi:10.1186/s13054-020-03159-z.

[16] Micic D, Wall E, Semrad C. Nutrition support in the ICU-A refresher in the era of COVID-19. Am J Gastroenterol 2020;115(9):1367–70. doi:10.14309/ajg.0000000000000761.

[17] Stachowska E, Folwarski M, Jamioł-Milc D, Maciejewska D, Skonieczna-Żydecka K. Nutritional support in coronavirus 2019 disease. Medicina (Kaunas) 2020;56(6) 289-101. doi:10.3390/medicina56060289.

[18] Lakenman P, van der Hoven B, Schuijs JM, Eveleens RD, van Bommel J, Olieman JF, et al. Energy expenditure and feeding practices and tolerance during the acute and late phase of critically ill COVID-19 patients. Clin Nutr ESPEN 2021;43:383–9. doi:10.1016/j.clnesp.2021.03.019.

[19] Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201(11):1430–4. doi:10.1164/rccm.202003-0736LE.

[20] Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020;24(1):581. doi:10.1186/s13054-020-03286-7.

[21] Campos LF, Barreto PAGDC, Gonçalves RC, de Matos LBN, Zambelli CMSF, Castro MG. Revisão do parecer BRASPEN de terapia nutricional em pacientes hospitalizados com COVID-19. BRASPEN J 2021;36:122–6.

[22] Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan. China. Ann Intensive Care 2020;10(1):73. doi:10.1186/s13613-020-00689-1.

[23] Ochoa JB, Cárdenas D, Goiburu ME, Bermúdez C, Carrasco F, Correia M. Lessons learned in nutrition therapy in patients with severe COVID-19. JPEN J Parenter Enteral Nutr 2020;44(8):1369–75. doi:10.1002/jpen.2005.

[24] Van Aanholt DPJ, Dias MCG, Marin MLM, Silva MFB, Cruz MELF, Fusco SRG, et al. Diretriz Brasileira de Terapia Nutricional Domiciliar. BRASPEN J 2018;33(Supl 1):37–46.

[25] Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically Ill patients with Coronavirus Disease 2019. JPEN J Parenter Enteral Nutr 2020;44(7):1174–84. doi:10.1002/jpen.1930.

[26] Patel JJ, Martindale RG, McClave SA. Relevant nutrition therapy in COVID-19 and the constraints on its delivery by a unique disease process. Nutr Clin Pract 2020;35(5):792–9. doi:10.1002/ncp.10566.

[27] Wu S, Lou J, Xu P, Luo R, Li L. Early enteral nutrition improves the outcome of critically ill patients with COVID-19: a retrospective study. Asia Pac J Clin Nutr 2021;30(2):192–8. doi:10.6133/apjcn.202106_30(2)0.0002.

[28] Silvah J, Nicoletti C, Lima C, Welle A, Marchini J. Necessidade de módulo proteico para pacientes em estado grave: estudo das fórmulas enterais em sistema fechado disponíveis no mercado. BRASPEN J 2020;35(2):130–8. doi:10.37111/braspenj.2020352005.

[29] Aguila E, Cua I, Fontanilla J, Yabut V, Causing M. Gastrointestinal manifestations of COVID-19: impact on nutrition practices. Nutr Clin Pract 2020;35(5):800–5. doi:10.1002/ncp.10554.

[30] Cervantes-Pérez E, Cervantes-Guevara G, Martínez-Soto Holguín MC, Cervantes-Pérez LA, Cervantes-Pérez G, Cervantes-Cardona GA, et al. Medical nutrition therapy in hospitalized patients with SARS-CoV-2 (COVID-19) infection in a non-critical care setting: knowledge in progress. Curr Nutr Rep 2020;9(4):309–15. doi:10.1007/s13668-020-00337-x.

[31] Fernández-Quintela A, Milton-Laskibar I, Trepiana J, Gómez-Zorita S, Kajarabille N, Léniz A, et al. Key aspects in nutritional management of COVID-19 patients. J Clin Med 2020;9(8):2589 2612. doi:10.3390/jcm9082589.

[32] Minnelli N, Gibbs L, Larrivee J, Sahu KK. Challenges of maintaining optimal nutrition status in COVID-19 patients in intensive care settings. JPEN J Parenter Enteral Nutr 2020;44(8):1439–46. doi:10.1002/jpen.1996.

[33] Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, et al. Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: a retrospective study. Clin Nutr 2011;30(2):209–14. doi:10.1016/j.clnu.2010.09.003.

[34] Vallejo KP, Martínez CM, Matos Adames AA, Fuchs-Tarlovsky V, Nogales G, Paz R, et al. Current clinical nutrition practices in critically ill patients in Latin America: a multinational observational study. Crit Care 2017;21(1):227. doi:10.1186/s13054-017-1805-z.

[35] Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care 2014;18(6):701. doi:10.1186/s13054-014-0701-z.

[36] Cereda E, Guzzardella A, Klersy C, Belliato M, Pellegrini A, Sciutti F, et al. Early caloric deficit is associated with a higher risk of death in invasive ventilated COVID-19 patients. Clin Nutr 2021 S0261-5614(21)00094-7. doi:10.1016/j.clnu.2021.02.020.

[37] Formisano E, Di Maio P, Ivaldi C, Sferrazzo E, Arieta L, Bongiovanni S, et al. Nutritional therapy for patients with coronavirus disease 2019 (COVID-19): practical protocol from a single center highly affected by an outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Nutrition 2021;82:111048. doi:10.1016/j.nut.2020.111048.

[38] Ansu V, Papoutsakis C, Gletsu-Miller N, Spence LA, Kelley K, Woodcock L, et al. Nutrition care practice patterns for patients with COVID-19-A preliminary report. JPEN J Parenter Enteral Nutr 2021;45(8):1774–8. doi:10.1002/jpen.2106.

[39] Aguila E, Cua I, Dumagpi J, Francisco C, Raymundo N, Sy-Janairo M, et al. COVID-19 and its effects on the digestive system and endoscopy practice. JGH Open 2020;4(3):324–31. doi:10.1002/jgh3.12358.

[40] Thibault R, Coëffier M, Joly F, Bohé J, Schneider SM, Déchelotte P. How the Covid-19 epidemic is challenging our practice in clinical nutrition-feedback from the field. Eur J Clin Nutr 2021;75(3):407–16. doi:10.1038/s41430-020-00757-6.

[41] Behrens S, Kozeniecki M, Knapp N, Martindale RG. Nutrition support during prone positioning: an old technique reawakened by COVID-19. Nutr Clin Pract 2021;36(1):105–9. doi:10.1002/ncp.10592.

[42] Regan J, Walshe M, Lavan S, Horan E, Gillivan Murphy P, Healy A, et al. Post-extubation dysphagia and dysphonia amongst adults with COVID-19 in the Republic of Ireland: a prospective multi-site observational cohort study. Clin Otolaryngol 2021;46(6):1290–9. doi:10.1111/coa.13832.

[43] Yue X, Li M, Wang Y, Zhang J, Wang X, Kan L, et al. Nutritional support and clinical outcome of severe and critical patients with COVID-19 pneumonia. Front Nutr 2020;7:581679. doi:10.3389/fnut.2020.581679.

[44] Osuna-Padilla I, Rodríguez-Moguel NC, Aguilar-Vargas A, Rodríguez-Llamazares S. Safety and tolerance of enteral nutrition in COVID-19 critically ill patients, a retrospective study. Clin Nutr ESPEN 2021;43:495–500. doi:10.1016/j.clnesp.2021.02.015.

[45] Elke G, Felbinger TW, Heyland DK. Gastric residual volume in critically ill patients: a dead marker or still alive. Nutr Clin Pract 2015;30(1):59–71. doi:10.1177/0884533614562841.

[46] Liu R, Paz M, Siraj L, Boyd T, Salamone S, Lite TV, et al. Feeding intolerance in critically ill patients with COVID-19. Clin Nutr 2021 S0261-5614(21)00180-1. doi. doi:10.1016/j.clnu.2021.03.033.

[47] Caccialanza R, Laviano A, Lobascio F, Montagna E, Bruno R, Ludovisi S, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): rationale and feasibility of a shared pragmatic protocol. Nutrition 2020;74:110835. doi:10.1016/j.nut.2020.110835.

[48] Lin J, Ke L, Doig GS, Ye B, Jiang Z, Liu Z, et al. Nutritional practice in critically ill COVID-19 patients: a multicenter ambidirectional cohort study in Wuhan and Jingzhou. Asia Pac J Clin Nutr 2021;30(1):15–21. doi:10.6133/apjcn.202103_30(1)0.0003.

[49] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26(7):1017–32. doi:10.1038/s41591-020-0968-3.

[50] Wichansawakun S, Meddings L, Alberda C, Robbins S, Gramlich L. Energy requirements and the use of predictive equations versus indirect calorimetry in critically ill patients. Appl Physiol Nutr Metab 2015;40(2):207–10. doi:10.1139/apnm-2014-0276.