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Special report

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

Riccardo Caccialanza M.D. [a,*], Alessandro Laviano M.D. [b], Federica Lobascio M.D. [a], Elisabetta Montagna R,D [a], Raffaele Bruno M.D. [c,d], Serena Ludovisi M.D. [c,d], Angelo Guido Corsico M.D., Ph.D. [e,f], Antonio Di Sabatino M.D. [g], Mirko Belliato M.D. [h], Monica Calvi Pharm.D. [i], Isabella Iacona Pharm.D. [i], Giuseppina Grugnetti R.N. [j], Elisa Bonadeo M.D. [k], Alba Muzzi M.D. [k], Emanuele Cereda M.D. Ph.D. [a]

[a] *Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[b] *Department of Translational and Precision Medicine, La Sapienza University, Rome, Italy*
[c] *Division of Infectious Diseases Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[d] *Department of Medical, Surgical, Diagnostic and Paediatric Science, University of Pavia, Pavia, Italy*
[e] *Pneumology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[f] *Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy*
[g] *First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy*
[h] *UOS Advanced Respiratory Intensive Care Unit, UOC Anestesia e Rianimazione 1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[i] *Pharmacy Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[j] *Nursing Technical and Rehabilitation Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[k] *UOC Direzione Medica di Presidio, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

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ABSTRACT

Objectives: Beginning in December 2019, the 2019 novel coronavirus disease (COVID-19) has caused a pneumonia epidemic that began in Wuhan, China, and is rapidly spreading throughout the whole world. Italy is the hardest hit country after China. Considering the deleterious consequences of malnutrition, which certainly can affect patients with COVID-19, the aim of this article is to present a pragmatic protocol for early nutritional supplementation of non-critically ill patients hospitalized for COVID-19 disease. It is based on the observation that most patients present at admission with severe inflammation and anorexia leading to a drastic reduction of food intake, and that a substantial percentage develops respiratory failure requiring non-invasive ventilation or even continuous positive airway pressure.
Methods: High-calorie dense diets in a variety of different consistencies with highly digestible foods and snacks are available for all patients. Oral supplementation of whey proteins as well as intravenous infusion of multivitamin, multimineral trace elements solutions are implemented at admission. In the presence of 25-hydroxyvitamin D deficit, cholecalciferol is promptly supplied. If nutritional risk is detected, two to three bottles of protein-calorie oral nutritional supplements (ONS) are provided. If <2 bottles/d of ONS are consumed for 2 consecutive days and/or respiratory conditions are worsening, supplemental/total parenteral nutrition is prescribed.
Conclusion: We are aware that our straight approach may be debatable. However, to cope with the current emergency crisis, its aim is to promptly and pragmatically implement nutritional care in patients with COVID-19, which might be overlooked despite being potentially beneficial to clinical outcomes and effective in preventing the consequences of malnutrition in this patient population.

Introduction

Beginning in December 2019, the 2019 novel coronavirus disease (COVID-19) has caused a pneumonia epidemic in Wuhan,

*Corresponding author: Tel.: +39 0382 501615; Fax: + 39 0382 502801.
E-mail address: r.caccialanza@smatteo.pv.it (R. Caccialanza).

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China, and as of this writing is rapidly spreading throughout the whole world, particularly in Italy and the United States.

The clinical spectrum of COVID-19 disease appears wide, encompassing asymptomatic infection, mild upper respiratory tract infection, and severe pneumonia with respiratory failure, with many patients being hospitalized and requiring subintensive or intensive care [1–3].

The majority of severe complications and deaths are reported among older patients with evidence of underlying illness such as cardiovascular, liver, kidney disease, or cancer [1–4]. Several factors leading to the progression of COVID-19 pneumonia have been identified [5]. In addition to age, smoking status, maximum body temperature, respiratory failure, C-reactive protein, and serum albumin have been shown to be independent prognostic markers [5]. Although albumin is not exclusively dependent on nutritional status, it is part of several nutritional screening indices and is associated with nutritional conditions [6]. Interestingly, low prealbumin levels, another marker of malnutrition, have been demonstrated to predict the progression to respiratory failure and mechanical ventilation [7]. This evidence strengthens the concept that nutritional derangements should be systematically and urgently managed in patients affected by COVID-19, also considering that the immune response has been shown to be weakened by inadequate nutrition [8,9].

The few available articles that mentioned supportive care in COVID-19 recommend that nutritional status should be evaluated in all infected patients at hospital admission [10,11] and patients at nutritional risk should receive nutritional support as early as possible, particularly increasing protein intake by oral nutritional supplements (ONS) [11]. They also underline that even patients with COVID-19 who are not at risk for malnutrition should maintain adequate protein (1.5 g/d) and calorie (25–30 kcal/d) intake [11] and that several vitamins and nutrients may have the potential to benefit infected patients due to their anti-inflammatory and antioxidants properties [10].

Given the above and considering the well-known deleterious consequences of malnutrition [12], which can be prevented or contained by prompt nutritional support [13], and having in mind the peculiarities of the intensive care unit (ICU) setting, we are presenting our shared pragmatic protocol for early nutritional supplementation of non-ICU patients hospitalized for COVID-19.

We are aware that our simplified and direct approach may be debatable, as it may not appear to be in complete agreement with the current guidelines on clinical nutrition [14]. However, to cope with the current emergency crisis, its principal aim is to promptly and pragmatically implement nutritional care in hospitalized non-ICU COVID-19 patients, which might be overlooked despite being potentially beneficial to clinical outcomes and effective in preventing the consequences of malnutrition in this patient population. Guidelines are based on the best available scientific evidence. Therefore, our protocol should not be considered as guidelines, but rather as the practical implementation of the need to provide nutritional care given the current clinical and organizational situations.

Protocol descritpion and rationale

The early nutritional supplementation protocol is summarized in Figure 1. It is based on the observation that almost all hospitalized patients present at admission with severe inflammation and anorexia leading to a major reduction of food intake, and that a substantial percentage of them develops respiratory failure requiring non-invasive ventilation (NIV) or even continuous positive airway pressure (CPAP) in a few days.

Specific high-calorie–dense diets in a variety of different textures and consistencies with highly digestible foods and snacks (yogurt, custard, fruit mousse, sliced fruit, soft cheese, etc.) are available for all hospitalized patients, to favor the maintenance/increase of protein-calorie intake. However, we are unfortunately recording a significant number of patients reporting severe eating difficulties as a consequence of the symptoms. Hence, beyond a simplified nutritional risk screening procedure and biochemical nutritional markers (Fig. 1), we decided to start with a systematic supplementation of oral whey proteins (20 g/d) and intravenous multivitamin, multimineral, trace elements solutions (target: satisfaction of recommended dietary allowance [RDA]) upon admission). The choice of whey proteins is based on their anabolic and antioxidant properties combined with high digestibility [15,16]. Their potential clinical benefits have been underlined in cancer cachexia [17] and have been recently shown in a randomized controlled trial with malnourished advanced cancer patients conducted by our group [18]. Whey proteins also have immunomodulatory properties [19] and potential antiviral activity [20]. Furthermore, whey protein supplementation has been associated with improved immune recovery in patients with HIV during the first 3 mo of antiretroviral treatment (ART) [21].

The straight intravenous supplementation of multivitamin, multimineral, trace element solutions aimed at satisfying RDA is due to the consideration of their antioxidant properties and that specific vitamin and micronutrient deficits have been shown to be harmful during viral infections [22–36]. Although we are aware that this approach is not precise, as it should be ideally guided by singular vitamin and micronutrient assessment, we think that it may be beneficial, with very limited risk for harm secondary to overdosing in consideration of the dosages used.

In the presence of 25-hydroxyvitamin D (25[OH]D) deficit, cholecalciferol is promptly supplied according to blood tests results (50 000 UI/wk if 25(OH)D $<$20 ng/mL; 25 000 UI/wk if 25(OH)D $\geq$20 to $<$30 ng/mL). The particular focus on vitamin D is justified by the increasing evidence that its supplementation and restoration to normal values in infected patients may improve immunologic recovery during ART, reduce levels of inflammation and immune activation, and increase immunity against pathogens [37–41].

If nutritional risk is detected by the simplified screening procedure (Fig. 1), two to three bottles (125/200 mL/d) of protein-calorie ONS (600–900 kcal/d; 35–55 g/d of proteins) are provided to patients, to be consumed between or immediately after meals. If ONS are not tolerated (i.e., $<$2 bottles/d are consumed for 2 consecutive days) and/or respiratory conditions are worsening (i.e.: NIV or CPAP are expected to be necessary), supplemental/total parenteral nutrition (PN) is prescribed by the Clinical Nutrition and Dietetics Unit, which plans blood tests and glucose monitoring.

The preference of PN over enteral nutrition (EN), which may certainly be debatable, is due to the consideration that the presence of a nasogastric tube (NGT) may result in air leakage and compromise the effectiveness of NIV or CPAP and that, particularly in this emergency scenario, special NIV masks with a port for NGT are rarely available [42]. Positive pressure ventilation through a face mask may also result in gastric distention, which may adversely affect diaphragmatic function, further compromising the respiratory conditions. Receiving EN during NIV was associated with a significantly higher rate of airway complications and longer NIV duration compared with patients who did not receive EN [43] and there is currently no validated strategy to reduce the critical complications of EN among patients with NIV or CPAP [44]. Moreover, in a randomized trial conducted in an ICU setting, which compared early PN with EN in critically ill shocked patients, the EN group had

AT ADMISSION

Record:
- Body weight and height*
- Relevant biochemical parameters†

Start systematic supplementation with:
- Whey proteins 20 g/d (in once or twice, preferably during meals)
- Daily infusion of RDA tailored multivitamin, multimineral and trace elements solutions (e.g., in 100/250 mL of physiological saline solution)
- Cholecalciferol - 50 000 UI or 25 000 UI/wk if 25-hydroxyvitamin D is <20 or ≥20<30 ng/mL, respectively.

	Simplified nutritional risk screening‡	Yes	No
1	Is BMI <22 kg/m^2?		
2	Did the patient loose weight in the past 3 mo?		
3	Did the patient reduce food intake or is expected to reduce it in the next few days?		

Monitor food/supplement intake with the aid of local health care professionals.

DURING HOSPITAL STAY

If patient does not tolerate ONS (i.e., <2 bottles/d are consumed for 2 consecutive days) or respiratory conditions worsen, contact the Clinical Nutrition and Dietetics Unit for the prescription of parenteral nutrition or start it implementing strict biochemical monitoring†

* Use referred or estimated values if scales are not available or cannot be used due to hygiene reasons.

** Albumin, transferrin, prealbumin, glucose, kidney (creatinine and blood urea nitrogen) and liver (cholinesterase, aspartate amino-transferase, alanine amino-transferase, γ-glutamyl transferase) function, electrolytes (sodium, potassium, chlorine, calcium, phosphorus, magnesium), TG , folic acid, vitamina B_{12}, 25-hydroxyvitamin D, C-reactive protein.

‡If any answer is "Yes," start supplementation (between or immediately after meals) with high-protein, high-calorie ONS (2–3 bottles [125/200 mL each] providing 600–900 kcal and 35–55 g of proteins).

Fig. 1. Protocol for early nutritional supplementation in non-critically ill COVID-19 patients. ONS, oral nutritional supplements; RDA, recommended dietary allowance; TG, triacylglyceride.

higher cumulative incidences of vomiting, diarrhea, and other gastrointestinal complications, whereas no differences in mortality rates were detected [45]. A further consideration regarding the choice of PN is that patients receiving ART, which is currently being used in COVID-19 disease, are frequently likely to experience diarrhea that can contribute to treatment interruption [46,47] and further worsen nutrient absorption. Finally, it has been shown that gastrointestinal symptoms are frequently reported in COVID-19, particularly by patients with rapid progression and worse outcome [48], which may increase the risk for EN intolerance.

Regarding PN, treatment consists of multichamber bags containing glucose, amino acids with or without lipids, and electrolytes, and supplemented with multivitamin and multimineral trace elements, which are infused via either central (when available) or peripheral infusion lines for 18 to 24 h/d, according to clinical conditions and biochemical data (Fig. 1). In particular, PN bags without lipids are prescribed in the presence of basal triglyceride levels >200 mg/dL.

Energy needs, in the obvious absence of indirect calorimeters outside the ICU setting, are estimated multiplying the resting energy expenditure calculated by the Harris–Benedict equation by a correction factor of 1.5 (in obese patients [body mass index {BMI} > 30 kg/m^2], ideal body weight [i.e., with BMI 23 kg/m^2] was used in the equation), whereas amino acid requirements are set to 1.5 g/kg actual body weight (in obese patients [BMI >30 kg/m^2] = 1.5 g/kg ideal body weight [i.e., with BMI 23 kg/m^2]).

Discussion

The principal aim of this empirical protocol is to promptly and pragmatically implement nutritional care in hospitalized non-ICU COVID-19 patients, which would risk being overlooked as a consequence of the current emergency crisis. A clear example of this risk is given by the recent guidelines issued by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, which do not address the issue of nutritional support in critically ill COVID-19 patients [49]. We are aware of the possible limitations of this approach, but we believe that action is much more important than methodological subtlety, given the tragic situation we are living in our hospitals.

Systematic weight and height measurement can be difficult or even impossible to perform owing to the lack of scales and in consideration of the hygienic precautions required. Similarly, body composition assessment cannot be regularly performed during the peak of epidemics with many patients admitted to the wards and the associated safety concerns. This can obviously limit the accuracy of nutritional assessment and support, but it is seems very difficult to us to find a valid alternative to relying on estimated or referred anthropometric values.

Likewise, we acknowledge that underfeeding occurs in patients hospitalized for COVID-19 for several reasons. Owing to the emergency scenario and the constantly increasing number of admitted patients, assisting even the oldest and most fragile ones during meals is time consuming and distracts health care professionals from taking care of other important procedures. Also, patients' relatives are not admitted to the wards. Hence, the accurate monitoring of food intake may be extremely difficult, if feasible at all, which we believe justifies our straight approach. Also the PN support may only partially fit the needs of pre-ICU COVID-19 patients, as central infusion lines may be rarely available outside the ICU wards and energy requirements are likely to be elevated, considering the concurrent severe acute inflammatory state and that the average BMI of COVID-19 patients is high (>27 kg/m^2 in our preliminary case histories) upon admission. Furthermore, the cardiovascular and pulmonary compliance may limit the infused volume of PN. Also, clinical nutrition units are not widespread in Italian hospitals, thus specific competences in nutritional care of patients are not available for all Italian patients. Finally, also the timely provision and availability of ONS, EN formulas, PN bags, and enteral and infusion pumps could be problematic in the current scenario.

Nonetheless, we believe that every effort should be made to try to avoid or at least limit underfeeding, even if it means struggling against objective and often insurmountable difficulties. Regarding specific nutritional support issues, the peculiarity of COVID-19 is that it can suddenly require intensive care measures, including intubation. Also in the ICU setting, nutritional support could become very problematic, as new ICU wards are progressively being created in emergency circumstances and EN tolerance may be incomplete because of gastric distention and erosive gastritis. Hence, different strategies should be considered, like the use of supplemental PN or specific high protein-calorie, highly digestible enteral formulas enriched in ω-3 fatty acids or other anti-inflammatory or immunomodulatory nutrients. The use of ω-3 fatty acids may be relevant because of their recognized anti-inflammatory properties [50]. However, their use should be cautiously considered on a case-by-case approach, keeping in mind their potential effect on the immune response [51], which may interfere with the currently tested treatments for COVID-19 [1,4]. Clinical research focused on the aforementioned nutritional issues could be decisive for this purpose, but the present emergency scenario renders it extremely difficult if not impossible to perform.

Conclusion

Implementing prompt and appropriate nutritional care in COVID-19 disease management is a difficult challenge owing to the current dramatic emergency circumstances. However, all efforts should be made to try to guarantee adequate nutritional support to hospitalized patients, as it may be potentially beneficial to clinical outcomes and effective in reducing or preventing the deleterious consequences of malnutrition in this patient population.

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Conflict of interest

The authors have no conflicts of interest to declare.

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