



Lessons Learned in Nutrition Therapy in Patients With Severe COVID-19

Journal of Parenteral and Enteral Nutrition
Volume 44 Number 8
November 2020 1369–1375
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DOI: 10.1002/jpen.2005
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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has reached worldwide, and until a vaccine is found, it will continue to cause significant morbidity and mortality. The clinical presentation of COVID-19 ranges from that of being asymptomatic to developing a fatal illness characterized by multiple organ involvement. Approximately 20% of the patients will require hospitalization; one-quarter of hospitalized patients will develop severe COVID-19 requiring admission to the intensive care unit, most frequently, with acute respiratory failure. An ongoing effort is being made to identify the patients that will develop severe COVID-19. Overall, patients present with 3 different phenotypes of nutrition risk: (1) the frail older patient, (2) the patient with severe ongoing chronic illness, and (3) the patient with severe and morbid obesity. These 3 phenotypes represent different nutrition risks and diverse nutrition interventions. This article explores the different potential approaches to nutrition intervention in patients with COVID-19, evaluating, in this process, the challenges faced in the implementation of guidelines written by different societies. (*JPEN J Parenter Enteral Nutr.* 2020;44:1369–1375)

Keywords

COVID-19; hypocaloric; nutrition; obesity; protein

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First detected as a cause of a typical severe pneumonia in Wuhan, China, at the end of December 2019, SARS-CoV-2 has now become widespread, causing a world pandemic, whose consequences we are only beginning to comprehend. SARS-CoV-2 is a coronavirus that most likely “jumped”

species, readily spreading through droplets among human beings.¹

The incubation period for COVID-19 is around 2 weeks. Patients will, on average, present with clinical manifestations within 4–5 days. A significant number of patients are asymptomatic, an issue that favors the circulation of the virus among populations.² One of the most interesting and important observations of the COVID-19 illness is the widespread range of clinical presentations. Approximately

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Financial disclosure: None declared.

Conflicts of interest: J. B. Ochoa, MD, is a lecturer for Nestlé Health Science, Fresenius Kabi, and Baxter and a past Chief Medical Officer (until July 1, 2018—Nestlé Health Sciences North America). D. Cárdenas, MD, PhD, has no conflicts of interest to declare. M. E. Goiburu, MD, has no conflicts of interest to declare. C. Bermúdez, MD, has no conflicts of interest to declare. F. Carrasco, MD, has no conflicts of interest to declare. M. I. T. D. Correia, MD, PhD, is a lecturer for Abbott Nutrition, Baxter Nutrition, Fresenius Kabi, and Nestlé Health Science.

Received for publication July 9, 2020; accepted for publication August 12, 2020.

This article originally appeared online on September 24, 2020.

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80% of patients will present with a mild disease that can be managed at home, whereas 20% will require hospitalization, and 25% of those hospitalized (5% of the total population of infected patients) will need to be admitted to the intensive care unit (ICU).³⁻⁵

The principal manifestation of patients with severe COVID-19 is respiratory distress and impending respiratory failure. However, other organs/systems are likely to be compromised, including the gastrointestinal tract.⁴ Length of stay in the ICU tends to be prolonged, and recovery may take a significant amount of time, which is often associated with muscle deconditioning and ICU-acquired weakness.

Risk factors for the development of severe illness were identified when the disease first appeared in China and have been confirmed in other countries. Metabolic/nutrition issues including obesity, hyperlipidemia, diabetes, and frailty have been identified as significant risk factors for developing severe COVID-19. We propose that patients with severe COVID-19 fall into 3 distinct, albeit partially overlapping, nutrition phenotypes: (1) the frail older patient, (2) the patient with severe ongoing chronic illness, and (3) the patient with severe and morbid obesity. This article expands on the hypothesis that the different phenotypes predict distinct nutrition risks and demand differential approaches toward providing optimal medical nutrition therapy.

The Frail Older Adult Patient

Published data suggest that older age is the single most important risk factor in determining the severity and mortality risk for COVID-19. This is most likely associated with various comorbidities and polypharmacy. Hypertension and cardiovascular disease, highly prevalent among the older adults, are per se risk factors for worst outcomes.⁶ So is diabetes, which is also commonly found among this group of patients.⁷ COVID-19 has mercilessly attacked the old and is particularly virulent in nursing homes.⁸ Frailty is a uniquely important characteristic of these group of patients and is associated with malnutrition/sarcopenia. In particular, low protein and micronutrient intake are prevalent in this patient population.⁹ On the other hand, owing to another world pandemic—obesity—also commonly prevalent in this group of individuals,¹⁰ malnutrition diagnosis is frequently missed.¹¹

Nutrition assessment in frail older adult patients should thus focus on different clinical variables such as eating habits, nonvolitional weight loss, and assessment of muscle mass. Both anatomic studies such as evaluation of psoas muscle by computed tomography (CT) scan or assessment of quadriceps by ultrasound should be performed. Computerized tomography (CT-scan) assessment is, in general, a convenient method, but under the COVID-19 pandemic, it has been recommended only for symptomatic or hospital-

ized patients.¹² Dynamic studies to assess muscle strength and endurance should also be done, if possible.

Patient With Chronic Debilitating Illness

Debilitating illnesses such as cirrhosis, end-stage renal disease, active cancers, and pulmonary diseases are risks for the development of severe COVID-19, as well as the previously mentioned cardiovascular disease and diabetes. Patients with these diseases commonly present with malnutrition, often also underdiagnosed and untreated. The nutrition status of these patients varies from disease to disease and patient to patient, but classical data have shown prevalence to be as high as 50%.^{13,14}

Patient With Severe and Morbid Obesity

Obesity (body mass index [BMI] > 30 kg/m²) is a risk factor of pejorative evolution of COVID-19, increases the risk of ICU admission, and is independent of age. The US Centers for Disease Control and Prevention (CDC) identifies severe obesity (defined as a BMI > 40 kg/m²) as prominently associated with the development of severe COVID-19¹⁵ and the single most important risk factor in younger patients.¹⁶ Severe obesity is a causative factor for other metabolic diseases including type 2 diabetes mellitus and hyperlipidemia causing target organ damage, including coronary artery disease, hypertension, and chronic kidney disease. Patients with COVID-19 who suffer from severe obesity may also present with decompensated hyperglycemia and elevated lipid, which are also risk factors for the severity of COVID-19.^{15,17} Simonnet et al¹⁸ showed that obesity (BMI > 30 kg/m²) and severe obesity (BMI > 35 kg/m²) were seen in 47.6% and 28.2% of cases, respectively, of their ventilated patients. The authors ran a multivariate statistical model that identified severe obesity as an independent risk factor for disease severity and the need for invasive ventilation. Another short communication from a University Hospital of Lyon, France, observed a significant higher percentage of ventilated patients in those with BMI > 35 kg/m² compared with patients with BMI < 25 kg/m² (81.8% vs 41.9%, $P = .001$).¹⁹

The mechanisms of why morbid obesity is an independent risk factor for the development of severe Covid-19 remain to be confirmed. One of the potential explanations could be associated with the role of epicardial adipose tissue, inflammation, myocardial fibrosis, and reduced angiotensin-converting enzyme 2 (ACE2) expression.^{19,20} In fact, postmortem autopsy heart tissues from 20 individuals who died of COVID-19 showed detectable viral SARS-CoV genome, reduced myocardial ACE2 expression, and increased inflammation and fibrosis.²⁰ Another possible explanation involves the adipose tissue as an actor for viral systemic spread, with a prolonged viral shedding from a tissue already inflamed. Activation of the immune system in

Table 1. Possible hypotheses considered as a cause of severe COVID-19 presentation in obesity.

Hypothesis	Comments
Nutrition deficiency: Vitamin D ω -3 Fatty acids Zinc, selenium	Multiple nutrient deficiencies have been described in MO High prevalence; affects immune function Rarely measured; modulates inflammatory response High prevalence
Altered immune response	Multiple alterations including a proinflammatory milieu May favor a “cytokine storm”
Altered metabolic effects Diabetes mellitus Hyperlipidemia	Multiple end organ effects including altered immune response Risk for hypertension, CAD, stroke
Loss of physiologic reserve: Pulmonary effects	Virtually all organs/systems negatively affected by obesity Sleep apnea, CO ₂ retention, alveolar collapse, acute respiratory distress syndrome, hypoventilation syndrome
Cardiovascular	CAD, increased risk of myocardial infarction Hypertension, risk of ventricular hypertrophy, heart failure
Coagulation	Increased risk of a hypercoagulable state and pulmonary embolism
Renal	Increased risk of CKD
Protein malnutrition	Decompensated morbid obesity may develop sarcopenia Watch for protein malnutrition, difficult to diagnose
Nonbiological aspects	Social inequalities, impaired access to healthcare

CAD, coronary artery disease; CKD, chronic kidney disease; MO, morbid obesity.

patients with obesity and with dysfunction of macrophages and lymphocytes could amplify viral tissue damage, and the adipose tissue in a state of “preactivation,” with increased production of tumor necrosis factor- α , interleukin (IL)-1, and IL-6, could amplify the inflammatory response triggered by SARS-CoV-2 infection.²² Studies in COVID-19 show that IL-6, which is exaggeratedly increased during a cytokine storm, is a strong independent predictor of mortality.²³ Another study conducted in patients undergoing surgical trauma²⁴ showed an exaggerated increase in IL-6 both in plasma and in adipose tissue of patients with severe obesity compared with patients with normal weight, a situation that could be reproduced in other conditions that trigger a large inflammatory response, as is the case of COVID-19.

Increased morbidity and mortality associated with obesity were also observed in SARS, suggesting a common element in both illnesses.²⁰ Additionally, increased susceptibility to severe infection has also been observed in rodent models of obesity.²¹ Table 1 presents a list of possible, causative hypotheses of why obesity is such a high-risk factor for the development of COVID-19. There are multiple possible hypotheses, which are not necessarily exclusive of each other, that deserve at least a discussion and possibly careful testing. Understanding the cause of increased susceptibility to severe COVID-19 in patients with severe obesity may lead to improved mechanisms of prevention and treatment. Furthermore, it will create an increased understanding of the disease of obesity.

Design and Implementation of a Nutrition Intervention Strategy

Several professional nutrition organizations have released COVID-19 guidelines.^{22,23} These guidelines are important, and the reader is urged to follow them. Nonetheless, we have found in our clinical practice with COVID-19 patients that there are unique circumstances that alter how these guidelines are applied. We provide a perspective below.

There are several important characteristics of the COVID-19 pandemic that obligate us to alter our approach to these patients, adapting our practices to better serve their needs. The first one is the need for isolation. This limits access to the patients and eventually reduces the participation of professionals who advise on their nutrition care. In addition, the sheer number of patients that can be seen at any given time may overwhelm the limited healthcare resources of a given institution, including that of specialized nutrition professionals. We may, therefore, have to rely on professionals with little experience, and thus, the nutrition assessment and intervention needs to rely on simplified protocols. Finally, it may be impractical to use sophisticated nutrition assessment tools because of the risk of contamination.

Nutrition Assessment

Owing to the nature of COVID-19, access to the patient for a complete nutrition assessment may be limited. Despite these limitations, the nutrition clinician or any other

Table 2. Suggested key laboratory tests including nutritional related tests to be ordered upon arrival of patients with COVID-19.

Nonspecific studies	Specific studies
Complete white blood cell count and differential: identify the presence of lymphopenia	Vitamin D: identify the presence of vitamin D deficiency and begin treatment
Coagulation status laboratory values including platelet count	Serum albumin: not specific for malnutrition but negatively correlates with inflammation
D dimer: to assess the presence of coagulopathy	Presence of microcytic or macrocytic anemia: aimed at identifying iron and vitamin B deficiencies
C-reactive protein, procalcitonin, to assess the severity of inflammatory response	

Caution—iron levels will be low and ferritin levels will be high in patients with severe inflammatory response and should not prompt iron replacement.

Measure muscle mass and function by anthropometric and dynamic studies, if available.

assistant clinician should try to identify which of the 3 phenotypes described above the patient may fall in. The nutrition clinician should emphasize identifying the presence of malnutrition. Although the diagnosis of malnutrition may require various tools, it has been shown that clinical assessment tools such as subjective global assessment predicts complications.²⁴ However, this method demands training and maybe a critical drawback in times of expert shortage. In cancer populations, unintentional weight loss alone was as good of a predictor for mortality as sophisticated tools, such as CT scans aimed at assessing muscle mass.^{25,26}

Obtaining laboratory samples may be limited in patients with COVID-19 because of, again, the need for isolation and potentially the need to manage resources carefully if the hospital is seeing a very large number of patients at the same time. Upon patient arrival, however, every effort should be made to obtain key laboratory values. There are 2 types of laboratory tests that need to be done. The first involves nonspecific studies, aimed at understanding the severity of illness on presentation, and the second involves laboratory values that may help in the assessment of the nutrition status (Table 2).

Determining the nutrition status of the patients is key, as this will help define the need for immediate nutrition therapy (if the patient is metabolically and hemodynamic stable) or a more conservative approach for the well-nourished patients.

Indirect calorimetry has emerged as the only consistently reliable tool to assess energy needs. The European Society for Clinical Nutrition and Metabolism (ESPEN) suggests in their guidelines that indirect calorimetry is a better way of avoiding excessive delivery of nonprotein energy as compared with standard and widely used formulas.²² Under the best of the circumstances, the adoption of indirect calorimetry has been challenging, making it practically impossible to apply this technology in the middle of a pandemic.²⁷ Indirect calorimetry requires training, a stable patient with specific ventilation parameters such as a low inspired fraction of oxygen, and a significant amount of time at the bedside. In addition, the data obtained are difficult to interpret in patients that have significant ventila-

tion perfusion (V/Q) mismatch, as is seen frequently during COVID-19, with the potential to generate falsely elevated values.²⁸ Besides, indirect calorimetry may increase the risk of breaking the ventilatory circuit, generating aerosols, and exposing the healthcare worker to contamination.²³

Patients with severe COVID-19 exhibit impaired oxygenation and carbon dioxide production, associated with shunting, V/Q mismatch, and potentially increased dead space. Often, patients exhibit a high minute ventilation exacerbated by the hypercapnia and hypoxia observed. From a practical point of view, these physiologic problems may render indirect calorimetry inaccurate and difficult to interpret and/or even contraindicated.^{29,30}

Protein requirements should be in accordance to those suggested for critically ill patients, which vary from 1.3 to 2.0 g/kg/d, respecting the patients renal and hepatic functions.²² Micronutrients must also be delivered according to the established requirements for critically ill patients.²²

Nutrition Intervention

Early enteral nutrition. Initiation of early enteral nutrition, defined as starting nutrition intervention in the first 24–48 hours, is suggested in all guidelines. Although this is ideal, there are significant barriers in the implementation of early oral intake or enteral nutrition for COVID-19 patients.

Impending acute respiratory failure limits the capacity for patients to eat adequately and/or receive oral nutritional supplements. Also, alterations in olfactory and gustatory senses have been described.³¹ Lechien et al assessed the occurrence of these disorders in patients with confirmed COVID-19, in 12 European hospitals, and 85.6% of the patients reported olfactory dysfunctions, whereas 88.0% had gustatory alterations, with females being more affected than males.³¹ Furthermore, noninvasive ventilation, including masks, is frequently used to deliver positive-pressure breathing to these patients. In addition, they may require emergent endotracheal intubation, increasing the risk of aspiration during induction if the patient has just eaten.

We often observe, particularly in the first 48 hours of the patient being admitted to the ICU, a significant degree of multiple-organ system dysfunction and/or failure. These may take significant priority and/or impede the implementation of early enteral nutrition. The so-called rescue phase of critical care illness demands that hemodynamic and respiratory parameters take precedence over other organ functions. Many of these patients will require sophisticated ventilatory management, and most will require the use of vasopressors due to hemodynamic instability. This, again, may limit early initiation of enteral-nutrition therapy.

Parenteral nutrition. Early parenteral-nutrition initiation is a tempting alternative, considering the aforementioned aspects related to the enteral route. Multiple studies involving thousands of patients now have demonstrated that early parenteral nutrition aimed at avoiding the development of an energy deficit is of little value and, in fact, may be associated with significant side effects,^{32–36} particularly when the nutrition status of the patients is not considered, an aspect most studies have not addressed.

Access to an exclusive intravenous port for the delivery of parenteral nutrition may also be limited. Resources may be stretched. Therefore, the authors suggest caution at using parenteral nutrition too liberally. Perhaps the most important exception to this may be the patient with underlying severe protein and energy malnutrition, for whom early parenteral nutrition has a better chance of benefit and lower risks to the patient. This may be particularly useful in the frail, older patient or the patient with chronic underlying conditions.

Achieving Nutrition Goals During the First Week in the ICU

Most patients will remain on a stable dose of vasopressors for several days or even weeks. There are contrasting experiences on the success of achieving nutrition goals using enteral nutrition exclusively in patients with COVID-19. However, the consensus remains that enteral nutrition is the first line of nutrition therapy for patients with severe COVID-19. The suggestion is to start with trickle feeding, limiting volumes initially and slowly ramping up to meet nutrition goals by the end of the first week in the ICU.

Understanding nutrition goals is important. Multiple studies aimed at eliminating an energy deficit through nutrition intervention in the first week in the ICU demonstrate no observable benefit and significant side effects.³² Therefore, the goals should be different. Protein intake should be “ramped up” in the first few days in the ICU and should be aimed at achieving at least 1.3 g protein per kilogram of current body weight per day for nonoverweight patients and per kilogram of ideal body weight for overweight patients by the end of the first week.³⁷ Controversy exists as to

how much higher protein intake should be delivered, and no recommendation regarding COVID-19 patients can be given at this time. Micronutrient deficiencies (identified early on, ideally) should also be treated.

Guidelines suggest that, at least during the first week in the ICU, patients should receive a limited amount of nonprotein energy. In the absence of indirect calorimetry (which occurs in most patients), clinicians should attempt to achieve 50%–70% of energy goal in the first week, considering the estimation based on the quick formula of 25 kcal/kg/d, or <20 kcal per kilogram of ideal weight (<70% of calculated energy needs) for the overweight patient.^{38,39}

Most enteral-nutrition formulas are designed to achieve a protein to energy ratio of 150:1. There is a clear risk of delivering excessive energy if the clinician aims at achieving the protein target suggested. The use of supplemental protein modules has been suggested in the literature. However, these are cumbersome to implement, and in patients with COVID-19 with limited access, they may be impractical. Recently, very high-protein (VHP) formulas with lower nonprotein-energy concentrations have been designed and commercialized by different companies. These formulas contain 35%–37% protein concentrations. Some of these formulas limit the amount of lipid delivered, whereas others limit the amount of carbohydrate. A phase 2 trial using one of these formulas demonstrated that protein goals could be easily achieved with lower volumes, avoiding excess energy delivery. In this study, significant biochemical benefits, including an improvement in glucose control and a potential decrease in CO₂ production, were observed.³⁹ These formulas appear to be beneficial, and further research is badly needed to determine whether there is an advantage in using VHP formulas compared with standard of care in COVID-19.

Beyond the First Week

Average length of stay in the ICU is often limited to <7 days in patients without COVID-19. By 7 days, the inflammatory response associated with illness that prompted transfer of the patient to the ICU may have subsided. There is a paucity of data associated with what nutrition goals should be achieved for those patients that stay longer than 7 days in the ICU. Despite the lack of adequate data, recommendations suggest that liberalizing delivery of energy to achieve 100% of the calculated goals is indicated.²² However, there are 2 issues that prompt us to be cautious of delivering 100% of the energy goals in patients with COVID-19. The first issue is that patients with severe COVID-19 often continue to exhibit an ongoing inflammatory response during the second week and even thereafter for several weeks. The second issue is the fact that many patients, particularly the young, have associated severe or morbid obesity. This cannot be ignored

as we design and implement nutrition intervention for these patients. Furthermore, many of these patients continue to have significant metabolic derangements, including stress hyperglycemia and hyperlipidemia (hypertriglyceridemia). Meeting energy goals only contributes to worsening these problems. All these issues prompt us to continue to be cautious of delivering 100% of the energy goals. The exception to this rule continues to be the patient with severe malnutrition and exhaustion of any energy reserves.

Long-Term Nutrition Care

Little is known as to the best way to provide medical nutrition therapy to any patient that has survived critical illness. There is enormous variation in how quickly and to what degree patients recover. Despite clinicians' best attempt, all patients lose muscle mass and are in negative nitrogen balance during their ICU stay. Muscle weakness is universal and is particularly marked in patients with prolonged ICU stay.⁴⁰

Some key opinion leaders suggest that providing increased protein and energy is indicated for all patients during the recovery phase, aiming to achieve a restoration of muscle mass. This is certainly the case for the patient that can participate in active rehabilitation. The application of a resistance-exercise training program could be a strategy from early stages of the rehabilitation of patients after the critical condition, although the evidence for benefits is insufficient.⁴¹ However, there are risks of advocating for the use of high energy intake for all. These include the following patients:

1. The patient with limited mobility and lower energy expenditure. In these patients, providing increased energy intake would tax metabolic systems and increase cardiopulmonary demands.
2. The patient with severe or morbid obesity, particularly the patient with continued metabolic disease such as diabetes. There is a chance to address obesity in patients recovering after critical illness. In these patients, continued use of nutrition programs including supervised lower energy/higher protein intake may achieve the best results.

Contrasting Practices and Challenges Across Different Countries

In 2019, the Colombian Clinical Nutrition Association (ACNC), working with the associations and schools associated with the Latin American Federation for Nutritional Therapy (FELANPE), published 13 basic principles aimed at protecting the right to nutrition care for all patients, now called the "Cartagena Declaration."⁴¹ These principles, along with national and international guidelines, provide the basis that guides our clinical practices.

The authors of this article practice in different countries with diversity in demographics, nutrition status of the population, degrees of affluence, and political and cultural practices. For example, early realization of the global spread of this pandemic has resulted in widely different governmental stewardship and adoption of public health practices, with countries like Paraguay applying strict measures of isolation, use of face mask, and social distancing but others adopting different approaches.⁴² Nutrition practitioners in different countries are thus facing diverse challenges in applying universal nutrition principles. Sharing differences in practice enriches the scientific discourse, as each country brings unique and highly creative solutions to the nutrition challenges observed.

Conclusions

The COVID-19 pandemic has taxed ICUs worldwide. Severe COVID-19 is a complex disease that we are only beginning to understand. Nutrition societies have used generic guidelines to suggest how the nutrition needs of patients should be addressed. Our article expands beyond this to suggest practical applications, utilizing lessons that we have learned at the bedside.

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