

The Time for Parenteral Nutrition is Now: 12 Months Caring for Patients with Severe COVID-19

A hora da nutrição parenteral é agora: 12 meses cuidando de pacientes com COVID-19

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Abstract

Keywords

- ▶ covid-19
- ▶ critical care
- ▶ enteral nutrition
- ▶ nutrology
- ▶ parenteral nutrition
- ▶ supplemental parenteral nutrition

The coronavirus disease 2019 (COVID-19) pandemic has brought new challenges to adequate nutrition, especially in critically ill patients. Physicians caring for these patients face great difficulties, including a different pathophysiology compared with other diseases, inadequately trained personnel, pressure from the media and family members, logistical and economic obstacles, and lack of robust medical evidence. Although the literature on COVID-19 is still limited, evidence demonstrates the need to reevaluate the use of effective nutritional support in this unprecedented, challenging clinical context. Supplemental parenteral nutrition must be considered due to the energy expenditure from COVID-19, the difficulty in achieving protein and energy goals in patients under enteral nutrition in prone position, and the worsened gastroparesis related to high doses of sedative/neuromuscular blocking agents.

Resumo

Palavras-chave

- ▶ covid-19
- ▶ cuidados intensivos
- ▶ nutrição enteral
- ▶ nutrologia
- ▶ nutrição parenteral
- ▶ nutrição parenteral suplementar

A pandemia da Covid-19 trouxe novos desafios à nutrição adequada especialmente em pacientes em estado crítico. Grandes dificuldades são impostas aos médicos responsáveis por esses pacientes: fisiopatologia diferente de outras doenças, pessoal inadequadamente treinado, pressão da mídia e de familiares, obstáculos logísticos e econômicos e falta de evidências médicas robustas. Embora a literatura sobre COVID-19 ainda seja limitada as evidências demonstram a necessidade de reavaliar o uso de suporte nutricional eficaz neste contexto clínico desafiador e sem precedentes. A nutrição parenteral suplementar deve ser considerada devido ao gasto energético da COVID-19, à dificuldade em atingir a meta de energia proteica em pacientes em decúbito ventral pela nutrição enteral e pela necessidade de altas doses de sedativos/bloqueadores neuromusculares que pioram a gastroparesia.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has brought new challenges to adequate nutrition, especially in critically ill patients. Physicians caring for these patients face great difficulties, including a different pathophysiology compared with other diseases, inadequately trained personnel, pressure from the media and family members, logistical and economic obstacles, and lack of robust medical evidence.¹

It seems obvious, but one must remember that malnutrition worsens clinical outcomes, including in infectious conditions. The immune system works all the time, and its cells are activated by the presence of pathogens.² This activation results in a significant increase in the demand of the immune system for energetic substrates (glucose, amino acids, and fatty acids). Immune activation induces the production of lipid-derived mediators, such as prostaglandins and leukotrienes, and many different types of proteins, including immunoglobulins, chemokines, cytokines, cytokine receptors, adhesion molecules, and acute phase proteins. This synthesis requires fatty acids and amino acids, respectively, as substrates. The immune response also involves significant cell proliferation, increasing the number of immune cells available for defense, which requires DNA, RNA, protein, and lipid synthesis, as well as the prompt availability of substrates to support it. The metabolic machinery for energy generation and biosynthesis requires many different vitamins and trace elements as cofactors. Amino acids (such as arginine) are precursors to the synthesis of polyamines, which play a role in regulating DNA replication and cell division. Several micronutrients (including iron, folate, zinc, and magnesium) are also involved in nucleic acid synthesis. Some nutrients, such as vitamins A and D, and their metabolites are direct regulators of gene expression in immune cells, playing a pivotal role in the maturation, differentiation, and responsiveness of these cells. In essence, good nutrition creates an environment in which the immune system can respond adequately, regardless of the nature of the offending agent. In contrast, malnutrition creates an environment in which the immune system is not able to respond properly.²

Thus, although the literature on COVID-19 is still limited, evidence demonstrates the need to reassess the use of effective nutritional support in this unprecedented, challenging clinical context.

In March 2020, the Society of Critical Care Medicine (SCCM) released the Surviving Sepsis Campaign guidelines for the management of COVID-19 patients. At the time, however, no nutritional recommendations were made. When the lack of recommendations for nutritional therapy (NT) in this publication was noted, a group of nutrition experts was recruited by the SCCM and the American Society for Parenteral and Enteral Nutrition (ASPEN) to develop specific guidelines for COVID-19 patients. Back then, there was not enough data in the literature to make any specific recommendations about NT in COVID-19. The experts compiled recommendations based on NT principles in critically ill patients and modified them according to COVID-19-spe-

cific restrictions, resulting in the publication of NT guidelines for COVID-19 on April 1, 2020.³

Objectives

This is a literature review on the challenges of properly feeding a critical patient with COVID-19 and the role of parenteral nutrition in this context.

Methodology

We reviewed studies published from December 2019 to September 2020 at the PubMed and Periódicos Capes (from the Brazilian National Department of Education) databases.

Discussion

There are three challenges to the nutrition of critically ill patients with COVID-19 that have raised doubts and disagreements between care teams:

- 1 – The high energy expenditure from COVID-19
- 2 – Enteral nutrition in prone position
- 3 – The need for opioids, sedatives, and neuromuscular blocking agents, usually in higher doses

1-COVID-19-related hypercatabolic state

In a real war, clinical observation and intuition⁴ are important until robust, randomized, double-blinded, and placebo-controlled clinical studies with larger sample sizes are available. Before that, to talk about evidence-based medicine, that is, to define any treatment as beneficial or not, may be hasty.

Therefore, we need to consider that everything that has been published about this new disease has a bias due to the very short time to obtain solid results.

- A study published⁵ at the American Journal of Parenteral and Enteral Nutrition (JPEN) on June 19, 2020 with 7 severely ill patients with COVID-19 under mechanical ventilation evaluated their energy expenditure by indirect calorimetry (IC). This study showed that the median resting energy expenditure (REE) was 4,044 Kcal/day, which was $235.7 \pm 51.7\%$ higher than the REE calculated with a predictive equation. The median carbon dioxide production (VCO_2) was 452 mL/min (range: 295 to 582 mL/min) and the median oxygen consumption (VO_2) was 585 mL/min (range: 416 to 798 mL/min). The authors argued that conditions such as sepsis, polytrauma, and major burns require a lot of energy, but findings from this study are beyond anything previously seen in medicine.

Many COVID-19 patients still present hypercapnia despite ventilation with maximum settings. COVID-19 patients present a dissociation between the degree of lung injury and the severity of hypoxia/hypercapnia.⁶ This fact suggests that the severity of acute respiratory failure (ARF) in COVID-19 patients may not be solely attributable to pulmonary impairment. Acute respiratory failure is associated with the

production of proinflammatory cytokines and with the induction of a hypermetabolic state,⁷ demanding high energy and protein intake.

The absurd increase in oxygen consumption and CO₂ production observed in this cohort of seven patients as a result of their hypermetabolism may explain the high rates of mechanical ventilation failure in patients with severe COVID-19.

These observations suggest the need to increase energy intake above 15 to 20 kcal/kg of current body weight/day, the currently recommended value for critically ill patients with COVID-19 according to the ASPEN/SCCM Guidelines.² The European Society for Clinical Nutrition and Metabolism (ESPEN) Guideline⁸ from March 24, 2020, suggested an acute energy intake of 20 kcal/kg/day, increasing the caloric expenditure predicted by the equation on the 2nd day of intensive care unit (ICU) stay in between 50 and 70% until reaching 80 to 100% on the 4th day. Indirect calorimetry is recommended for optimal calculation; however, this technology is virtually nonexistent in most developed countries, and it is related to an exposure risk of health professionals to Sars-CoV-2. A recent paper advocated for the safety of IC devices as long as teams are properly trained in their use.⁹

Although energy expenditures from acute respiratory discomfort syndrome (ARDS) patients are ~ 30% above the REE, energy expenditures in most COVID-19 patients are 200% greater.

The LEEP-COVID study,¹⁰ performed on 22 critically ill patients with COVID-19 under mechanical ventilation, used a modern IC device and showed progressive hypermetabolism and considerable REE variation during ICU stay. A longer hypermetabolic phase can be independent from organ failure severity and, as previously published, it is minimally affected by interventions such as neuromuscular block.

2–Enteral nutrition in prone positioning

Most recent publications have highlighted that enteral nutrition (EN) in prone positioning is associated with an increased risk of gastroparesis and vomiting; however, since it has been shown to be safe in terms of bulky gastric residue, vomiting, or intolerance,¹¹ prone positioning alone is not a limitation or contraindication for EN, which is recommended by the ESPEN guidelines.¹²

The ESPEN recommends that EN may be instituted in hemodynamically stabilized patients, even in prone position, starting with ~ 30% of the calculated energy expenditure and increasing it progressively.⁸ In contrast, the ASPEN states that most patients tolerate EN with a gastric tube while in prone position, but a postpyloric nasoenteric tube (NET) may be indicated for some subjects. As this procedure increases any potential viral exposure, its use must be limited in COVID-19 patients. For EN delivery in prone position, the ASPEN guidelines dictate that the bed head must be elevated in at least 10 to 25 degrees (reverse Trendelenburg position) to decrease the risk of gastric contents aspiration, facial edema, and intra-abdominal hypertension.

These recommendations clearly demonstrate the confusion and difficulty of consensus at the current practice. We have observed several conducts in our services, including EN

in prone positioning and trophic flow with reverse Trendelenburg, occasionally with the bed head at 0 degrees, or EN in full flow with or without bed head raising in prone patients. Many services are not using EN due to the fear of gastric aspiration, especially due to the administration of opioids, sedatives, and neuromuscular blocking agents.

3–Use of opioids, sedatives, and neuromuscular blocking agents, usually in higher dosages.

Sedation and analgesia to relieve anxiety and pain and to facilitate mechanical ventilation is one of the key roles of intensive care. During the COVID-19 pandemic, an unprecedented number of patients have required ICU sedation due to ventilator dependence.¹³

The current clinical experience witnesses extraordinarily high sedation requirements in a large proportion of COVID-19 patients. These high sedation requirements are probably due to the younger age and good health conditions of many of these subjects, their high respiratory drive, and intense inflammatory responses.¹⁴

This high sedation is achieved with the combined administration of multiple agents (for instance, propofol, ketamine, morphine, dexmedetomidine and midazolam), which increase the potential risks of side effects (such as QT prolongation, hypertriglyceridemia, hypotension, and delirium), requiring high vigilance from the medical team. Administered in combinations, the dosages required to ensure patient comfort and ventilator timing in adult subjects range from 25 to 50 µg/kg/min for propofol, 10 to 20 µg/kg/min for ketamine, 2 to 4 mg/h for morphine, and 2 to 5 mg/h for midazolam. Currently, there are no specific sedation guidelines for this patient population requiring high medication doses for a prolonged time.

Deeper levels of sedation may be required to facilitate ventilator synchrony in patients with severe ARDS and to reduce the risk of self-extubation, which is particularly problematic in this population given the need for emergent reintubation and the risk of coronavirus exposure. After all, COVID-19 patients differ in many aspects from typical critical patients with ARDS in ICUs.¹⁵

Intermittent administration of selected drugs (such as narcotic agents) tailored to the needs of each individual patient are not always feasible when healthcare teams are overloaded (for example, when a nurse needs to care for multiple critically ill patients). In these situations, the continuous infusion of sedatives is favored by its practicality, but it further increases the risk of side effects.

A subset of patients with severe ARDS probably requires prolonged sedation (often for > 2 weeks)¹⁶ to facilitate lung-protective mechanical ventilation or extracorporeal membrane oxygenation therapy (ECMO).

These prolonged periods can lead to drug accumulation (midazolam), tolerance and tachyphylaxis (dexmedetomidine), hypertriglyceridemia (propofol), prolonged QT interval (haloperidol), psychomimetic effects (ketamine), hyperalgesia or opioid dependence (fentanyl and/or morphine), and delirium (midazolam).

Prolonged opioids infusions, often required to facilitate lung-protective ventilation, result in intestinal hypomotility,

leading to intolerance to enteral diet, diet disruption, and malnutrition during protracted ICU stay. These gastrointestinal (GI) side effects from opioids can also result in bloating, which can impair ventilation and/or contribute to nausea/vomiting, increasing the risk of aspiration.¹³

4–Gastrointestinal tract complications

Intensive care unit teams have reported an increased prevalence of GI complications in critically ill patients with COVID-19 compared with other severely ill patients according to a study published in September 2020 by JAMA.¹⁷ A Kaplan-Meier curve reveals a statistically significant difference between both groups regarding these complications, especially after the 3rd day of ICU admission, when critically ill patients with COVID-19 and ARDS presented a higher number of GI complications (► **Figure 1**).

Parenteral Nutrition Indication:

As in other critical patients, NT recommendations are centered on the assumption that the most important aspect of nutrition for critically ill patients with COVID-19 is to nourish the intestinal mucosa with luminal nutrients, to support intestinal barrier defenses, to mitigate systemic inflammation, and to sustain the microbiome.¹⁸ Thus, enteral nutrition would be preferable to parenteral nutrition (PN).

However, due to the difficulties in properly nourishing the patient exclusively per the enteral route, recent publications advocate an earlier reevaluation of PN in these cases, except in contraindications.

According to a study from ASPEN members published in August 2020,¹⁹ the main difference in COVID-19 patients is that doctors should lower the limit to indicate the change from EN to PN. After all, evidence of enteral intolerance may bring a greater danger of complications, such as ischemic bowel syndrome and the need for a postpyloric NET, which would require an additional aerosol-generating procedure.

In addition, the need for noninvasive ventilation may prevent the use of a NET (because of the difficulty in positioning a mask with a NET in place). Therefore, PN is indicated as soon as possible in critically ill patients with COVID-19 for whom EN is contraindicated or not viable:

- High nutritional risk
- Poor nutritional status and malnutrition
- Expectation of prolonged ICU stay
- Gastrointestinal involvement by COVID-19 with significant enteral intolerance

In a retrospective study with 139 patients from five Spanish ICUs (74.8% males, 59.6 ± 13.8 years old, body mass index [BMI] 29.9 ± 5.3 kg/m²), 82.7% of the patients required invasive mechanical ventilation (90.4% of them in prone position), and 3.6% needed ECMO. The length of stay at the ICU was 3.3 ± 4.3 days. As for nutrition, 12.2% of the patients received EN, 29.5% received PN, and 51.8% had both EN and PN. Energy and protein requirements were 1,773 ± 252 and 91.7 ± 17 kcal, respectively. Most patients reached the estimated energy and protein goal between the 4th and 7th day of ICU hospitalization, but PN was required by most cases within the 1st week to reach these goals.²⁰

The fear regarding PN has been overcome after robust studies published in recent years. The CALORIES study, which compared EN with PN with a similar caloric intake, and the NUTRIREA-2 study, which compared EN with PN in patients under mechanical ventilation, reported no differences in mortality rates; as such, EN is no longer considered superior to PN.^{21,22}

In a recent study presented at the ESPEN 2020 Congress, I have confirmed the safety of PN with three-chamber bags, a technique not correlated with mortality and sepsis due to venous access-related bloodstream infection.²³

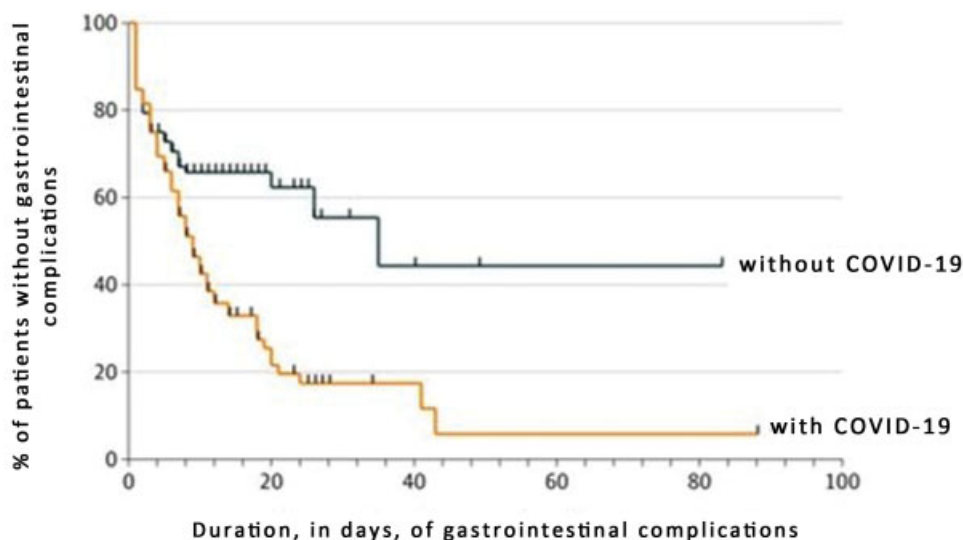


Fig. 1 Kaplan-Meier curve¹⁷ from gastrointestinal complications in patients with acute respiratory distress syndrome related or not to coronavirus disease 2019 (COVID-19). Initially, both curves look similar, but they begin to separate around the 3rd day of hospitalization in an intensive care unit (ICU).

Conclusion

Intensive care teams have been striving to offer the best treatment for critical patients with COVID-19, including NT, but the unprecedented pathophysiology, complications and worsening of these cases, as well as the scarcity of data in the literature, bring a huge challenge. There is a need to advance studies with these patients, but common sense, the experience of well-trained professionals, and teamwork have been fundamental in the victory over this disease. Nutritional therapy is one of the pillars of COVID-19 therapy, and it must be optimized as early as possible, respecting the limits imposed by multiple drug treatment, the need for pronation, and the disease itself.

Highlights

- ✓ COVID-19 results in a high energy expenditure.
- ✓ Prone positioning makes it difficult to achieve the protein and energy goal with enteral diet.
- ✓ High doses of sedatives/neuromuscular blocking agents worsen gastroparesis.
- ✓ Supplemental parenteral nutrition can be useful in these cases.

Conflict of Interests

The authors have no conflict of interests to declare.

References

- 1 Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with Covid-19 in the New York city area. *JAMA* 2020;323(20):2052–2059
- 2 Calder PC. Nutrition, immunity and COVID-19. *BMJ Nutrition. Prevent Health* 2020;3:e000085
- 3 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(07):1174–1184
- 4 Daher W, Godoy MF. *Intuição, Evidência e Caos: Os Sinuosos Caminhos do Fato Científico*. 1ª ed. São José do Rio Preto (SP): Vitrine Literária Editora; 2012
- 5 Yu P-J, et al. Hypermetabolism and COVID-19. *J Parent Enter Nutr* 2019
- 6 Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a “Typical” Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2020;201(10):1299–1300
- 7 Kiiski R, Takala J. Hypermetabolism and efficiency of CO₂ removal in acute respiratory failure. *Chest* 1994;105(04):1198–1203
- 8 Barazzoni R, Bischoff SC, Breda J, et al; endorsed by the ESPEN Council. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr* 2020;39(06):1631–1638
- 9 Singer P, Pichard C, De Waele E. Practical guidance for the use of indirect calorimetry during COVID 19 pandemic. *Clin Nutr Exp* 2020;33:18–23
- 10 Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PELEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. *Crit Care* 2020;24(01):581
- 11 Saez de la Fuente I, Saez de la Fuente J, Quintana Estelles MD, et al. Enteral nutrition in patients receiving mechanical ventilation in a prone position. *JPEN J Parenter Enteral Nutr* 2016;40(02):250–255
- 12 Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;38(01):48–79
- 13 Hanidziar D, Bittner EA. Sedation of Mechanically Ventilated COVID-19 Patients: Challenges and Special Considerations. *Anesth Analg* 2020;131(01):e40–e41
- 14 Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. *N Engl J Med* 2019;380(04):365–378
- 15 COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed [August 15th, 2020] at <https://www.covid19treatment-guidelines.nih.gov/>
- 16 Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382(21):2012–2022
- 17 El Moheb M, Naar L, Christensen MA, et al. Gastrointestinal Complications in Critically Ill Patients With and Without COVID-19. *JAMA* 2020. Doi: 10.1001/jama.2020.19400
- 18 McClave SA, Martindale RG. Why do current strategies for optimal nutritional therapy neglect the microbiome? *Nutrition* 2019; 60:100–105
- 19 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(05):792–799
- 20 Cuerda C, et al. Nutritional treatment in critically ill patients with COVID-19 disease: Spanish experience in a university hospital (extended). *In: ESPEN Virtual Congress on Clinical Nutrition & Metabolism 2020, Lyon. Annals. Clinical Nutrition ESPEN* 2020;(12):629
- 21 Koekkoek KWAC, van Zanten ARH. Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding? *Curr Opin Anaesthesiol* 2018;31(02):136–143
- 22 Reignier J, Boisramé-Helms J, Brisard L, et al; NUTRIREA-2 Trial Investigators Clinical Research in Intensive Care and Sepsis (CRICS) group. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet* 2018;391(10116):133–143
- 23 Barbosa CL, et al. Infectious complications after insertion of peripheral or central venous catheters in patients on parenteral nutrition. *In: ESPEN Virtual Congress on Clinical Nutrition & Metabolism 2020, Lyon. Annals. Clinical Nutrition ESPEN* 2020;(12):629