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SYSTEMATIC REVIEW

Benefits of Early Implementation of Enteral Feeding in Ventilated COVID-19 Patients: A Systematic Review of Current Literature

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Abstract:

Introduction:

COVID-19 (SARS-CoV-2) has swept destruction across the world and continues to cause significant morbidity and mortality. For critically ill patients requiring mechanical ventilation enteral feeding is typically required for nutritional support.

Method:

Due to the novelty of this virus, protocols have been aimed to mimic Acute Respiratory Distress Syndrome (ARDS) patient nutritional support. There is limited data around the benefits of early enteral nutritional support for mechanically ventilated patients.

Result:

Data from two studies evaluated the use of enteral nutrition protocols in critically ill COVID-19 patients and revealed only minor significant differences in hospital course between early and late enteral feeding. There were better outcomes overall for COVID-19 patients who were able to tolerate enteral feeding compared to patients who were intolerant of enteral feeding.

Conclusion:

Future studies involving a baseline nutritional assessment may help clinicians better understand the role of early enteral nutrition support among mechanically ventilated COVID-19 patients.

Keywords: COVID-19, Enteral, Nutrition, Mechanical, Ventilation, ARDS.

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1. INTRODUCTION

The Coronavirus (COVID-19) related death rate as of May 20, 2022, in the US, is 1,002,067 [1]. COVID-19's increasing death toll can be attributed to its development of Acute Respiratory Distress Syndrome (ARDS) in patients due to a cytokine storm of inflammatory cells and chemokines [2]. Specifically deemed a potential cytokine release syndrome-like (CRSL), a small study revealed the presence of lymphopenia with a decrease in CD4, CD8, and NK cells in the lung parenchyma with an increase of IL-6 (an interleukin responsible for general inflammation) – this combination is reported to be an indicator for the development of CRSL in infected COVID-19 patients [2]. Upon development of CRSL, which increases the chances of ARDS development, mechanical ventilation is required due to alveolar destruction [3]. Most patients have fever, cough, nasal congestion, fatigue, GI symptoms, and a hyper-inflammatory response which

further causes deterioration of health [4, 5]. Globally, 33% of patients develop ARDS and 26% of those patients are transferred to the Intensive Care Unit (ICU) [6]. Approximately 63% of these ICU patients will need mechanical ventilation and 75% have a diagnosis of ARDS [6].

Treatment protocols for COVID-19 are changing constantly as new information is evolved about the virus. The majority of patients who develop COVID-19-related ARDS will require intubation. Although ventilation should not be delayed, “early” intubation has not been clearly defined for this virus [7]. Treatment with COVID-19 parallels the ARDS standard of care [7]. These include mechanical ventilation, sedatives, neuromuscular blockade, nutrition, management of glucose levels and hemodynamics, and prevention of deep vein thrombosis (DVT), gastrointestinal (GI) bleeding, and nosocomial pneumonia [8].

Nutritional support from enteral feeding through orogastric or nasogastric tubing is the most common method used in critically ill patients on mechanical ventilation, using sump

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tubing (larger and stiffer) or feeding tubes (small and flexible) when compared to post-pyloric feeding [9]. Although there are hundreds of enteral formulas to choose from, they are categorized into five basic groups: standard, polymeric, elemental, whole food-based (blenderized tube feeding), disease-specific, and immune-modulating products [10]. These formulas differ amongst macronutrients (carbohydrates, protein, fat), micronutrients (electrolytes, vitamins, and minerals), caloric density, and osmolarity [10]. Critically ill patients may be placed on any of these formulas, although studies have not clearly revealed improved patient outcomes with specialty formulas. Because of this, critically ill patients with ARDS are placed on standard polymeric formulas unless there is an indication to use a more specific formula [10].

Recommendations for nutrition are based on enteral trophic feeding which are low initial volumes between 10 and 30mL/hour and increased gradually after six days [9]. Low initial volumes are suggested to reduce GI side effects while also replenishing nutrients due to patients with ARDS having high catabolic rates [9]. However, clinical trials of trophic feeding versus full initial feeding have rendered equivocal results. The EDEN trial reviewed ARDS patients with trophic feeding (~400 kcal/day) versus full feeding (~1300 kcal/day) with little difference in infectious outcomes, ventilator-free days, organ failure-free days, and mortality [10]. Treatment protocols of COVID-19 parallel ARDS treatment and enteral feeding standards [7, 9]. Typical recommendations in practice include starting critically ill patients on early trophic feed between 25 and 30% of their estimated goal rate [9]. Indirect calorimetry (IC) is recommended for determining the energy/kcal needs of critically ill tube-fed patients; however, estimation equations are used when IC is not available. For patients with a BMI between 18.5 kg/m² and 29.9 kg/m², clinicians will use the patient's current weight and account for the estimated peripheral edema to calculate the estimated goal rate [9]. Obese patients (BMI ≥ 30.0) estimated goal rates can be determined using the Penn State University 2010 predictive equation or the Mifflin-St Jeor equation [11]. The recommendation of early enteral feeding in critically ill medical patients is a Grade 2C recommendation – meaning it is a weak recommendation, and the benefits and risks are equivocal due to the lack of consistent evidence [12]. Consequently, clinical expertise and patient monitoring are fundamental for determining tube feed initiation rate and formula selection.

Several clinical trials have shown decreased infectious complications in patients that received early enteral nutrition (EN) compared to delayed enteral nutrition or intravenous fluids only [12]. Although current protocols do not specifically call for early implementation, it is suggested that there are benefits of reduced complications and preservation of gut lining and function [12]. Although there is novelty surrounding the treatment of COVID-19, there are several observational studies on early EN versus later EN in ventilated COVID-19 patients [13]. The results showed no difference in length of stay between later enteral feeding and early enteral feeding (within 24 hours of mechanical ventilation) [13]. However, the study acknowledged the recommendation of starting EN within twelve hours of mechanical ventilation, and patients who received later EN have not been followed long enough to observe outcomes [13]. The increased catabolic rate in patients with severe respiratory infections is acknowledged along with

the identified increase in energy expenditure from mechanical ventilation;– ultimately leaving the patient in a nutrient deficient state with metabolism superseding that of nutritional intake under infectious circumstances [14]. As acknowledged by Emer Delaney, the current protocol of International enteral feeding guidelines for ICU patients is directed toward non-COVID-19 patients, which further encourages the discussion of early enteral feeding in COVID-19 patients [14].

Due to COVID-19's lack of clarity and overwhelming distribution across the world, formulating treatment strategies is urgent to reduce mortality worldwide. In studying effective but novel treatments for ARDS, there is potential to discover a new approach to treating the virus before ARDS possibly sets in. Specifically, studies may focus on combating the inflammatory process by implementing enteral feeding early during treatment compared to current treatment protocols. Developing universal protocols for COVID-19 treatment requires a swift but careful investigation into the potential benefits that have been presented in previous critically ill medical patients with early enteral nutrition and the possible benefits that COVID-19-related ARDS patients could reap from the same treatment course.

2. METHODS

Data was collected using Samford University's Library Databases, specifically UpToDate, along with Google Scholar, PubMed, Cochrane, and ASPEN. COVID-19's novelty limited the amount of data surrounding treatment protocols for enteral feeding as very few studies have been conducted and most of them were observational or retrospective. Searches included the words "COVID-19" AND "Enteral Nutrition, Mechanical Ventilation". For studies analyzing COVID-19 and enteral feeding, the publication range was 2019-2022. No internal or external funding was utilized for this research collection.

Data was collected by the primary author and University Librarian staff. The tertiary author (Dr. Teresa Johnson) also assisted with primary data collection. Data was initially analyzed by the primary author and University Librarian staff and then reviewed by all secondary authors after the initial manuscript was completed.

2.1. Inclusion Criteria

- Studies published in English
- Studies published between 2016 and 2022
- Studies analyzing enteral nutrition implementation and outcomes
- Studies analyzing critically ill medical patients
- Studies define early enteral feeding as no later than within 36 hours of ICU admission or 12 hours of mechanical ventilation

2.2. Exclusion Criteria

- Studies were not in English
- Studies published before 2016
- Studies including surgical patients
- Studies define early enteral feeding as within 48 hours

3. RESULTS

Two studies resulted from a research that provided insight into early EN versus late EN implementation. A retrospective, observational study conducted at a tertiary academic medical center in Michigan compared 155 patients (Table 1) who received EN within 24 hours of mechanical ventilation *versus* patients who received EN later than 24 hours (within 48 hours) [13]. Patients administered early EN received more weight-based calories (P = 0.015) and protein (P = 0.003).¹³ SOFA (sepsis criteria) scores were lower in patients who received early EN (P = 0.006).¹³ Length of stay (LOS) was the primary observed outcome. There was no difference in LOS between the groups (18.5 vs. 23.5 days, P = 0.37) [13]. No harm was detected in nutritional implementation timing.¹³ There was also no difference in days alive, ventilation-free days, inpatient mortality, discharge(s) to home, hyperglycemia, and hypophosphatemia [13].

Table 1. Comparison of patients receiving EN within first 24 hours of mechanical ventilation and patients receiving EN >24 hours of mechanical ventilation [13].

N=155	Early Enteral Feeds (First 24 hours) n=60	Late Enteral Feeds (After 24 hours) n=95
Daily weight-based calories kcal/kg/d, mean (SD)	17.5 (4.7)	15.2 (5.8)
Daily protein, g/kg/d, mean (SD)	1.04 (0.34)	0.85 (0.39)
Inpatient length of stay, d, median	18.5 (24.4)	23.5 (21.5)
Mortality, n (%)	17 (28.3)	23.5 (26.3)

Table 2. Comparison of COVID-19 patients who were tolerant vs. intolerant to early enteral nutrition [15].

N=323	Feeding Intolerance (n=180)	No Feeding Intolerance (n=143)
Length of ICU admission, median, days	21.5 (14-30)	15 (9-22)
ICU readmission	13 (7.2)	8 (5.6)
Length of overall hospitalization, median, days	30.5 (19-42)	24 (15-35)
Length of intubation, median, days	19 (13.5-28)	13 (7.5-18.8)
Died	61 (33.9)	23 (16.1)

Massachusetts General Hospital (MGH), a tertiary medical facility, studied 323 patients admitted to ICU with COVID-19 who received early EN (Table 2) [15]. Data reported that 180 (56%) patients experienced feeding intolerance to EN [15]. These patients were more likely to be male (69.4%) and had higher Sequential Organ Failure Assessment (SOFA) scores on admission [15]. Other demographics did not vary significantly. [15] The most common EN intolerant symptoms include large gastric residual volumes, abdominal distention, vomiting, and diarrhea.¹⁵ A decreased risk of EN intolerance was associated with extreme obesity and one or more GI symptoms at presentation [15]. Length of intubation and overall hospitalization was 6 days longer in EN intolerant patients

[15]. Mortality rates in EN intolerance (33.9%) versus EN tolerance (16.1%) were statistically significant (p < 0.001).¹⁵ From the accumulated results, this study associated EN intolerance with the severe illness of COVID-19 infection and an increase in poor outcomes [15].

4. DISCUSSION

Although COVID-19 and ARDS treatment protocols run parallel to each other, small studies reveal the possible need for adjusting EN implementation, nutrition assessment, and potential combination of therapies concomitant with EN therapy. A study in Michigan resulted in no clinical improvement in patients who received early EN versus late EN.¹³ The Massachusetts study revealed EN intolerance in ventilated COVID-19 patients, increasing the risk of mortality and possibly indicating severe infection [15]. However, both studies lacked a defined nutritional status of patients prior to intubation. The Michigan study stated one limitation as the lack of nutrition-focused physical assessment of patients along with unclear oral intake prior to admission [15]. Prior to intubation, 72.9% of patients scored greater than five in the NUTRIC assessment, categorizing them as high nutrition risk during admission [13]. The Massachusetts study did not list the nutritional status of patients on admission or prior to intubation.

The Massachusetts study used standard polymeric feeding, following current recommendations, at a trophic rate of 10cc/hr days 1-3 with slow advancement starting at day 4.¹⁵ Patients with at least one GI symptom were started at 10cc/hr days 1-5 with slow advancement based on clinical judgment.¹⁵ The Michigan study reported a mean of 16.1 +/- 5.5 kcal/kg/d and a mean protein of 0.93 +/-0.38 g/kg/d with an aggressive introduction of nutrition. Aggressive introduction, or aggressive nutritional therapy, is defined as rapid nutrition therapy initiation within six hours of hemodynamic stabilization and receiving approximately 80% of estimated energy needs starting day one [16]. It may be difficult to tell if future modifications of the regimen will give patients early EN advantages due to the ambiguity in the Michigan study's methodologies. ICU COVID-19 patients often have reduced oral intake 5-10 days prior to admission [17]. Lack of nutritional status may have obscured the outcomes and side effects of EN nutrition. With unknown nutritional status at admission, the patient's energy needs and expenditure were not fully accounted for to order appropriate feeding volumes. There is currently very limited data available due to the novelty of COVID-19, which does limit the overall impact of this review. Data from both studies allows for better construction of future trials to ensure more well-rounded data of nutritional status and outcomes when implementing early EN. There are known benefits for ARDS patients receiving early EN, and given the similarities of the two disease processes further trials utilizing early EN for COVID-19 patients requiring nutritional support should be conducted.

CONCLUSION

Although both studies lacked information in certain areas, the studies offered a foundation for future trials. Given the novelty of COVID-19, it is challenging to determine the true efficacy of early EN, but even this limited analysis provides some indication of the possible advantages. Given the

usefulness of early EN in patients suffering from ARDS it would be beneficial to conduct larger trials on COVID ICU patients requiring nutritional support. Nutritional assessment should be performed prior to intubation and applied to feeding volumes appropriate for each patient along with the time of initiation. Having a baseline nutritional assessment would provide a better study foundation for future enteral feeding studies. Although early EN may not be beneficial in every patient, it may offer gut protection and immune support for those at nutritional risk who are able to tolerate EN. Future studies should also include an analysis of different formulas with COVID-19 high catabolic rate, specifically observing the effects of high protein formulas versus standard formulas. With COVID-19's increasing catabolic state occurring later in infectious progression, calories may not be the initial nutritional need of patients. COVID-19 changes the nutritional status of patients, so early EN may be beneficial depending on the formulas administered to patients. This also needs to be analyzed in future research and further multi-center trials would be beneficial. This information can be applied to COVID-19 clinical trials for analyzing EN initiation post-intubation, formula and volume, and overall outcomes.

LIST OF ABBREVIATIONS

ARDS	=	Acute Respiratory Distress Syndrome
CRSL	=	Cytokine Release Syndrome-like
ICU	=	Intensive Care Unit
DVT	=	Deep Vein Thrombosis
GI	=	Gastrointestinal

AUTHORS' CONTRIBUTIONS

All authors contributed equally in the preparation of this manuscript.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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