2020

Trophic Enteral Feeds in Mechanically Ventilated Adult Patients with Acute Respiratory Distress Syndrome/Acute Lung Injury and Associated Clinical Outcomes

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TROPHIC ENTERAL FEEDS IN MECHANICALLY VENTILATED ADULT PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME/ACUTE LUNG INJURY AND ASSOCIATED CLINICAL OUTCOMES

by

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A thesis submitted in partial fulfillment of the requirements for the degree of Bachelor of Science in the Department of Nursing at the University of Central Florida
Orlando, Florida

Spring Term, 2020

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Abstract

Enteral nutrition (EN) is often delayed in critically ill patients despite strong evidence to support that early enteral nutrition feeding is beneficial in this population. Adverse outcomes in critically ill patients in which nutrition is delayed include a longer length of stay and time on the ventilator, and a higher incidence of pneumonia and hospital mortality. The purpose of this literature review was to evaluate the current evidence regarding trophic enteral feeds in mechanically ventilated adult patients with acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and associated clinical outcomes. A retrospective literature review was performed to identify articles published on the topic of trophic feeds in mechanically ventilated adult patients with ALI/ARDS, with a focus on associated clinical outcomes. The studies included in this literature review indicated that the dose and timing of enteral nutrition in critically ill patients with ARDS/ALI had an effect on clinical outcomes. It is possible that additional variables such as the level of organ dysfunction and varying definitions for trophic enteral nutrition also influenced clinical outcomes. The United States (U.S.) and Canadian guidelines for nutrition support recommend either trophic or full EN for patients with ARDS/ALI on the basis that these two feeding strategies have similar patient outcomes over the first week of hospitalization. After reviewing the literature, we conclude that caution is warranted when following this recommendation. Regressions suggest full calorie enteral nutrition administered early in the course of critical illness significantly increased the odds of mortality, whereas full calorie enteral nutrition administered later reduced the odds of mortality.

Acknowledgements

Since my nursing education began at the University of Central Florida in 2018, I have been interested in the fields of critical care and nutrition. These two years have passed very quickly, and I am eternally grateful for the knowledge and skills I have gained to care for my community.

I am particularly grateful to my mentor and thesis committee chair, Dr. Brian Peach. His knowledge and love for critical care nursing gave me the courage and guidance necessary to complete this research. None of this work would have been possible without his support, wisdom, and passion for the nursing profession.

Thanks are also due to my other committee members, Professor Joyce DeGennaro and Dr. Sandra Galura. They have provided advice and offered suggestions whenever necessary.

I am also thankful for my parents, Malia and Nicholas Tidwell, who have provided me with the resources and support necessary to pursue my dream of a career in the nursing profession.

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Background

Observational studies of intensive care units demonstrate gaps between nationally recommended nutrition guidelines and bedside practice. Enteral nutrition is often delayed in critically ill patients despite strong evidence to support that early enteral nutrition feeding is beneficial in this population (Cahill, Dhaliwal, Day, Jiang, Heyland, 2010). Barriers to timely receipt of enteral nutrition include nurses addressing nutrition interventions after other priorities have been completed, a lack of resources available such as feeding pumps, enteral formula, and readily available dietitians, and complications with accessing the small bowel (Cahill, Murch, Cook, Heyland, 2012). Moreover, guidelines recommend withholding enteral nutrition in patients that are hypotensive (mean arterial pressure <50 mmHg), receiving catecholamines such as dopamine, norepinephrine, and epinephrine, or displaying early signs of gut ischemia such as abdominal distention, hypoactive bowel sounds, and increasing nasogastric tube output or gastric residual volume (McClave et al., 2016).

Adverse patient outcomes result when enteral nutrition is delayed in critically ill patients. Delayed nutrition results in changes in gut permeability. In healthy patients receiving adequate nutrition, the intestinal epithelium prevents microbes from gaining systemic access to the body. Disruption of this critical gut barrier can result from malnutrition and consequently result in bacterial sepsis, hypercatabolism, and hypermetabolism (Hernandez et al., 1999). Enteral nutrition supports gut integrity by sustaining tight junctions found at epithelial cells, promoting the flow of blood, releasing trophic endogenous agents such as bile salts and cholecystokinin, and maintaining villous height (McClave, et al., 2016). An increase in gut permeability is a time-dependent phenomenon with channels opening within hours of delayed nutrition (McClave et al., 2016). Poor outcomes in critically ill patients in which nutrition is delayed include a longer

length of stay and time on the ventilator, and a higher incidence of pneumonia and hospital mortality (Woo, Finch, Broyles, Wan, Boswell, & Hurdle, 2010). Beneficial clinical outcomes associated with early EN (initiation within 24 to 48 hours of admission to the intensive care unit) prompted nutrition guidelines to recommend the intervention to facilitate favorable gastrointestinal outcomes. (Cerra et al., 1997; Dhaliwal, Cahill, Leumieux, Heyland, 2013; McClave, et al., 2016). New evidence suggests early initiation of nutrition with trophic feed amounts may benefit the gut by preserving intestinal epithelium, mucosa, tight junctions, and microvilli height (McClave et al., 2016) and thus prevent bacterial translocation that has been associated with sepsis, hypercatabolism, hypermetabolism, and multiple organ failure in critically ill patients (Barton and Cerra, 1989; Deitch, 1990; Goris, Nieuwenhuijzen, Jansen, 1996). Trophic amounts range from ~16-57% of estimated caloric needs, as opposed to full-energy enteral feeds which deliver ~40-86% kcal/hour (Rice, Morgan, Hays, Bernard, Jensen, Wheeler, 2011; Rice et al., 2012; Braunschweig et al., 2015; Braunschweig et al., 2017; Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017; Peterson, McKeever, Lateef, Freels, Fantuzzi, Braunschweig, 2019).

Four randomized control studies have investigated the efficacy of trophic enteral nutrition. At the time the American Society for Parenteral and Enteral Nutrition published updated guidelines in 2016, only two of these four randomized control studies were published. The first, a randomized single-center study, investigated the effect of enteral nutrition versus full calorie nutrition on several clinical outcomes including: (a) ventilator-free days (b) intensive care unit (ICU)-free days (c) 60-day mortality (c) organ failure-free days (d) infection and (e) gastrointestinal intolerances. Full calorie nutrition is defined as $\geq$70% of the calculated caloric goal (Rice et al., 2011). While there is not a standard definition of trophic feeding, for the

purposes of this review, it will be defined as ~16-57% of estimated caloric needs administered within the first 24 to 48 hours of ARDS/ALI via the enteral route (Rice, Morgan, Hays, Bernard, Jensen, Wheeler, 2011; Rice et al., 2012; Braunschweig et al., 2015; Braunschweig et al., 2017; Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017; Peterson, McKeever, Lateef, Freels, Fantuzzi, Braunschweig, 2019).

The study found there was a statistically significant trend towards fewer episodes of gastrointestinal intolerance in the trophic group (Rice et al., 2011). The other study, a multi-center trial, demonstrated similar results with less gastrointestinal intolerance and lower residual volumes in the patients receiving trophic enteral nutrition (Rice et al., 2012).

Based on these studies, the Canadian Critical Care Society (CCCS) and The American Society for Parenteral and Enteral Nutrition (ASPEN) deemed trophic feeds a safe and effective method of nutrition to maintain gastrointestinal structure and function in patients who are unsuitable for high volume intragastric feeds (McClave, et al., 2016; Dhaliwal et al., 2013). However, unlike the CCCS, ASPEN recommends both trophic and full-energy feeds for patients with acute respiratory distress syndrome/acute lung injury, who are expected to have a duration of mechanical ventilation greater than or equal to 72 hours (McClave, et al., 2016). Ultimately, the dose of enteral nutrition necessary to support the critically ill patient remains largely unknown, and varying definitions of trophic enteral nutrition among studies remains a barrier to providing optimal nutrition support.

Significance

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are life-threatening diseases in critically ill patients and carry mortality rates of 27-45% (Ragaller and Richter, 2010; Ranieri, et al., 2012). Patients with pulmonary conditions are at increased risk of malnutrition because of the hypermetabolic state of their illness, leading to stress-induced catabolism and accelerated breakdown of protein stores (Bulger, Jurkovich, Farver, Klotz, Mailer, 2004). Therefore, the importance of nutrition therapy in the critically ill patient cannot be overstated (Krzak, Pleva, Napolitano, 2011). Effects of malnutrition in those with pulmonary disease are significant and include reduced respiratory muscle strength, chest wall muscle atrophy post-mechanical ventilation, reduced alveolar-ventilation, and altered surfactant production (Schwartz, 2003).

ARDS is a severe subtype of ALI that describes diffuse injury to the lung parenchyma (Hall, Schmidt, Kress, 2015; Raghavendran and Napolitano, 2011), as a result of an unbridled inflammatory process triggered by etiologies like, but not limited to, non-pulmonary sepsis, noncardiogenic shock, major trauma, inhalation injury, or drowning (Modrykamien and Gupta, 2015). The degree of hypoxemia present is the distinguishing factor between ARDS from ALI, with ARDS established as a more severe form of arterial hypoxemia (Laycock and Rajah, 2010). Diffuse damage of the alveolar-capillary barrier results in leakage of protein-rich fluid within the alveolar space, atelectasis, and compromised pulmonary gas-exchange (Wang, Li, Gu, Liu, Wang, 2019). Consequently, clinical manifestations that characterize ARDS and ALI result, and may include profound respiratory distress, critical refractory hypoxemia, pulmonary hypertension and fibrosis, poor lung compliance, and bilateral pulmonary infiltrates on chest radiograph (Lewis, Bucher, Heitkemper, Kwong, Roberts, 2017; Carlucci, Graf, Simmons, Corbridge, 2014; Gulanick

and Myers, 2017). Furthermore, the release of diffuse pro-inflammatory mediators further insults the critically ill patient.

Despite the recognized importance of nutrition in the critically ill patient, there is a paucity of evidence for guideline-writing organizations to draw from, resulting in inconsistent practice between intensive care units. The optimal guidelines for nutrition support in patients with ARDS and ALI are controversial. There is a need for consensus among existing literature to determine best practices for care that will lead to improved patient outcomes.

Problem Statement

The purpose of this literature review is to evaluate the current evidence regarding trophic enteral feeds in mechanically ventilated adult patients with acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and associated clinical outcomes.

Methodology

A retrospective literature review was performed to identify articles published on the topic of trophic feeds in mechanically ventilated adult patients with ALI/ARDS, with a focus on associated clinical outcomes. CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE were utilized to identify medical and academic journals with the assistance of an experienced nursing librarian. Search terms included acute lung injury OR acute lung injur* OR acute lung injury, transfusion-related OR respiratory distress syndrome, acute OR ARDS or acute respiratory distress syndrome, and enteral nutrition OR enteral feed OR trophic feed OR trickle feed OR hypocaloric feed OR permissive feed OR permissive underfeed. Additional articles were identified through a review of the reference lists of the articles found with the original search terms. Articles found were stored in the University of Central Florida (UCF) library database. Articles were excluded from the search if they were not in the English language, literature reviews, published more than 15 years ago, or pertained to pediatric patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to capture the search strategy and results (see Figure 1). The Critical Appraisal Skills Programme (CASP) Checklists was used to ensure the quality of this systematic review (see Table 2 and Table 3).

Results

In this comprehensive literature review, 179 articles were identified for possible inclusion. After application of the inclusion and exclusion criteria, 8 articles were included in the review. Figure 1 illustrates the details of the literature selection methodology. Of the 8 articles included in this review, 4 were randomized controlled trials, and 4 were cohort studies. Outcomes of interest included: (a) gastrointestinal intolerances (2 articles), (b) mortality (7 articles), (c) ventilator free days (4 articles), (d) ICU and hospital free days (4 articles), (e) organ failure free days (2 articles), (f) infections (3 articles), and (g) various physical and cognitive performance tests (2 articles). See Table 1 for the studies in this review. Appraisal checklists for the articles can be found in Table 2 and Table 3.

A Randomized Trial of Initial Trophic versus Full-Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Respiratory Failure & Initial Trophic vs Full Enteral Feeding in Patients with Acute Lung Injury

Two randomized, open-label trials measured the primary outcome of ventilator-free days through day 28 (Rice et al., 2011; Rice et al., 2012). Secondary outcomes included gastrointestinal intolerances, mortality, ICU-free days, organ failure-free days, and infections. In these trials, full energy nutrition was initiated at 25 mL/hour with feeding rates increased 25 mL/hour every 6 hours until a target rate of 25-30 kcal/kg of nonprotein energy was achieved. Patients of the Early vs. Delayed Enteral Nutrition (EDEN) trial were concurrently randomized into the OMEGA trial that studied a supplement containing omega-3 fatty acids and antioxidants. Trophic energy was initiated at 10 mL/hour in both trials, but the patients in the EDEN trial also consumed omega-3 or control supplements (240 mL volume per day). The data and safety monitoring board stopped the OMEGA portion of the study, and initial trophic feeding rate in the EDEN trial only was increased to 20 mL/hour to estimate the additional calories that had been

administered in the OMEGA study. Patients receiving trophic feeds and still mechanically-ventilated at day 6 were advanced to full energy targets using the same procedure as the full-energy group. The studies reported no statistically significant difference in clinical outcomes in regard to ventilator-free days (Rice et al., 2012:14.9 days trophic feeding vs 15 days full feeding, p=.89; Rice et al., 2011: 23 days trophic feeding vs 23 days full feeding, p=0.9), reduction in mortality (Rice et al., 2012: 23.2% trophic feeding vs 22.2% full feeding, p=0.77; Rice et al., 2011: 22.4% trophic feeding vs 19.6% full feeding, p=0.62), and ICU-free days (Rice et al., 2012: 14.4 days trophic feeding vs 14.7days full feeding, p=0.67; Rice et al., 2011: 21 days trophic feeding vs 21 days full feeding, p=0.64) between trophic and full energy groups for the first 6 days of enteral nutrition therapy. The 2011 trial reported no significant difference in renal-failure-free days (18.4 days ±13.1 trophic feeding vs 18.3 days ± 12.9, p=0.97), hepatic failure-free days (20.0 ± 13.0 days trophic feeding vs 22.0 ± 12.2 days full feeding, p=0.32), or infection (30.6% trophic feeding vs 32.4% full feeding, p=0.79). The 2012 trial reported no significant difference in cardiovascular failure-free days (19.1 days trophic feeding vs 18.9 days full feeding, p=0.75), renal failure-free days (20.0 days trophic feeding vs 19.4 days full feeding, p=0.43), hepatic failure-free days (22.0 days trophic feeding vs 22.6 days full feeding, p=0.37), and ventilator-acquired pneumonia (7.3% trophic feeding vs 6.7% full feeding, p=0.72). However, both studies concluded that the trophic group experienced fewer gastrointestinal intolerances. The full feeding group experienced more vomiting (Rice et al., 2012: 1.7% trophic feeding vs 2.2% full feeding, p=0.05; Rice et al., 2011: 1.8% trophic feeding vs 2.1% full feeding) and elevated gastric residual volumes (Rice et al., 2012: 2.2% trophic feeding vs 4.9% full feeding, p<0.001; Rice et al., 2011: 2% trophic feeding vs 8% full feeding, p<0.001). While constipation was experienced more frequently in the full feeding group in one trial (Rice et al.,

2012: 2.1% trophic feeding vs 3.1% full feeding, p=0.003), constipation was similar in both groups in the other trial (Rice et al., 2011: 6% trophic feeding vs 9.1% full feeding, p=0.10).

Intensive Nutrition in Acute Lung Injury: A Clinical Trial

In another study, the Intensive Nutrition in Acute Lung Injury: Clinical Trial (INTACT), a prospective randomized controlled trial design was used to compare a feeding strategy termed "intensive medical nutrition intervention (IMNT)" to standard care (SC) nutrition. Standard care protocol encompasses nutrition care ordered by the physician after consultation with the registered dietician. IMNT is a more aggressive feeding strategy in which enteral nutrition (EN) tubes were placed more rapidly. EN was initiated within 6 hours of hemodynamic stability. EN rates were increased when feeding interruptions occurred, and oral dietary intake was initiated as soon as swallowing occurred. Those in the IMNT received 25.5 kcal/kg/day, whereas the standard care group received 16.6 kcal/kg. While there were no reported differences among groups for hospital length of stay (14.3% SC vs 18.2% IMNT, P=0.33) and ICU length of stay (11.5% SC vs 12.8% IMNT, p=.83), number of days on mechanical ventilation (6.6% SC vs 8.8% IMNT, p=.17), and infection rates (3-14% SC vs 4-10% IMNT, p=.85), those receiving the more aggressive feeding strategy of IMNT were more likely to die, despite being less sick than the control group at baseline. The trial was stopped due to higher mortality in the intervention group (15.8% SC vs 40% IMNT, p=0.017). The only clinically significant difference between the IMNT and SC groups were the higher energy and protein received in the IMNT group.

Role of Timing and Dose of Energy Received in Patients with Acute Lung Injury on Mortality in The Intensive Nutrition in Acute Lung Injury Trial (INTACT): A Post Hoc Analysis

Furthermore, post hoc analysis of the INTACT trial investigated the role of timing and/or dose of the energy or protein received from diagnosis of ARDS through hospital discharge (Braunschweig et al., 2017). This cohort study was designed to examine if early versus late calorie delivery effects hazards of mortality. Outcome measures explored included overall energy and protein received, and timing of calorie and dose of delivery. Early nutrition was defined as days 1-7 of enteral feeding, and the late nutrition group included patients still enrolled in the trial at day 8 or later. Results indicated that a higher overall energy supply increased the likelihood of death by 14% (OR: 1.14, 95% CI: 1.02, 1.27), and timing of calorie and dose delivery influenced the relationship between energy supply and death. Higher calorie delivery received on days 1-7 increased mortality hazards for death on days 8+ by 17% (HR 1.17, 95% CI: 1.07, 1.28), whereas higher late energy on day 8+ reduced the mortality hazards by 9% (HR 0.91, 95% CI: 0.83, 1.0).

Combination of High-Calorie Delivery and Organ Failure Increases Mortality Among Patients with Acute Respiratory Distress Syndrome

After reviewing the results of the INTACT trial and the post-hoc analysis, Peterson et al. decided to conduct a retrospective observational study to determine if varying levels of organ dysfunction had an impact on clinical outcomes (Peterson, McKeever, Lateef, Freels, Fantuzzi, Braunschweig, 2019). Organ failure was measured upon ICU admission using the Sequential Organ Failure Assessment (SOFA) score. For the purposes of this study, a high SOFA score was

defined as 12, an average SOFA score was 10, and a low SOFA score was 8. High calorie delivery was defined as >/= 12 calories/kg, and low-calorie delivery was <12 calories/kg. Results indicated high calorie delivery and a low SOFA score (OR 1.99, 95% CI, 1.03-3.87; p=0.04), low calorie delivery and a high SOFA score (OR 3.86, 95% CI, 1.78-8.37; p=0.001), and a combination of high calorie delivery and a high SOFA score predicted an incremental increase in the probability of mortality. In comparison, those who received low calorie delivery and had a lower SOFA score had decreased likelihood of mortality. Patients who received a higher calorie delivery and had a higher SOFA score had a 5-fold increase in the odds of death (OR 5.35, 95% CI, 2.55-11.20; p <0.001).

Early Exposure to Recommended Calorie Delivery in the Intensive Care Unit Is Associated with Increased Mortality in Patients with Acute Respiratory Distress Syndrome

In addition to the INTACT trial, another controlled clinical trial reported similar outcomes after studying the effect of calorie delivery on the likelihood of mortality in a larger sample of patients (Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017). The current trial included 298 patients who met the same inclusion criteria as those enrolled in the INTACT trial but excluded patients who actively participated in the INTACT trial. Calorie exposure was divided into categorical tertiles to examine the influence of dose on mortality. The lowest tertile was <11.5 kcal/kg, the intermediate tertile was 11.6-16.5 kcal/kg, and the highest tertile was ≥16.6 kcal/kg. The influence of timing of nutrient delivery was assessed by examining intervals of time (days 1-4, 1-5, 1-6, 1-7) and its subsequent impact on mortality. Compared with the lowest tertile, patients categorized into the intermediate tertile (OR 1.97, 95% CI, 1.02-3.78; P=0.04) and the highest tertile (OR 2.17, 95% CI, 1.02-3.78; p=0.02) had

increased odds of death. Patients receiving ≥16.6 kcal/kg on days 1-4 (OR 2.15, 95% CI, 1.13-4.09; p=0.02), 1-5 (OR 1.70, 95% CI, 0.85-3.37; p=0.133), and 1-7 (OR 1.26, 95% CI, 0.59-2.71; p=.552) had a significantly higher hazard of subsequent death than those who received <11.5 kcal/kg. Moreover, increased calorie delivery after day 7 was associated with a decreased hazard of death, similar to the results of the INTACT trial. Patients who received 11.6-16.5 kcal/kg had a 60% decreased hazard of death on day 7+ (HR 0.40, 95% CI, 0.21-0.77; p=0.006) compared to those who received <11.5 kcal/kg. This relationship was also observed for patients still enrolled 14+ days (HR 0.19, 95% CI, 0.04-0.89; p=0.04).

One Year Outcomes in Patients with Acute Lung Injury Randomised to Initial Trophic or Full Enteral Feeding: Prospective Follow-Up of EDEN Randomised Trial

In addition to short term effects, longer-term outcomes after ALI diagnosis may be important to consider, given the varying number of calories delivered between feeding interventions. A prospective longitudinal follow-up evaluation of the EDEN trial was designed to assess the primary outcome measure of physical function of 525 patients enrolled in the EDEN trial over a longer time frame (Needham et al., 2013). Results indicated that neither initiation of trophic nor full calorie enteral nutrition impacted physical function. Considerable impairments persisted 6 months and 12 months after an acute lung injury. Impairments included physical, cognitive, and psychological deficits, reduced quality of life, an inability to return to work, and a mortality of 36% in the first year after hospital discharge.

Physical and Cognitive Performance of Patients with Acute Lung Injury 1 Year after Initial Trophic versus Full Enteral Feeding

Moreover, another trial that assessed long term outcomes in patients receiving intensive nutritional therapy had similar results (Needham et al., 2013). This prospective, longitudinal study of the EDEN trial was conducted to assess (a) physical and cognitive performance after ALI diagnosis at 6 and 12 months for the entire study sample and (b) the effects of trophic versus full enteral feeding on physical and cognitive performance at 6 and 12 months. A set of physical and cognitive performance tests were conducted. The primary outcome measure utilized to assess physical performance was a 6-minute-walk distance. Cognitive impairment was defined as a cognitive test 2 standard deviations (SD) below population norms, or at least 2 tests greater than or equal to 1.5 SD below norms. Cognitive tests included Hayling Sentence Completion Test, Controlled Oral Word Association (COWA), Logical Memory I and Logical Memory II, Similarities age-adjusted scaled score, and Digit Span age-adjusted scaled score. For the entire study sample, results indicated physical performance below projected values at 6 and 12 months, but with subtle improvement (22% at 6 months vs 25% at 12 months; p=0.001). Cognitive function was significantly below population norms for the entire sample, with 36% displaying cognitive impairment at 6 months and 25% at 12 months, but with substantial improvement between 6 and 12 months (p=0.001). Moreover, there was no significant effect of trophic versus full feeding on physical or cognitive outcomes at 6 or 12 months. There was no significant difference with 6-minute-walk-distance values (25% trophic fed versus 24% full fed; p=0.136) or cognitive function (29% trophic fed versus 20% full fed; p=0.311) at 12 months.

Discussion

In two randomized controlled trials, the trophic (defined as ~15-25% of estimated total caloric need) and full nutrition (defined as ~75-80% of estimated total caloric needs) feeding strategies demonstrated similar clinical outcomes over the first week of hospitalization, but with fewer gastrointestinal intolerances in the trophic group (Rice et al., 2011; Rice et al., 2012). This data suggests that trophic enteral nutrition is not discernably worse than full energy nutrition, and that a less aggressive feeding strategy may result in less gastrointestinal intolerances in critically ill patients. In contrast, in the INTACT clinical trial, patients who received significantly more calories at nationally recommended levels (85% of estimated caloric needs) in an intensive feeding strategy had greater rates of inpatient mortality when compared with patients who received less calories (55% of estimated caloric needs). We suspect the higher caloric intake provided in the INTACT trial when compared to the Rice 2011 and 2012 randomized controlled trials may explain the differing results.

Interestingly, results from the INTACT trial contradicts the feeding strategy endorsed in the U.S. guidelines for nutrition support. Current guidelines recommend that patients with ARDS/ALI and those expected to have a duration of mechanical ventilation ≥72 hours receive either trophic or full enteral nutrition. The guidelines recommend EN be initiated (within 24 to 48 hours) at a rate of 25-30 kcal/kg. (McClave, et al., 2016). However, results from the INTACT trial indicate that providing early enteral nutrition at a rate of 25-30 kcal/kg may be detrimental as higher rates of mortality were recorded with higher energy delivery.

While it is plausible that initiation of the more aggressive feeding strategy, IMNT, is detrimental, it is important to consider that the earliest phases of acute illness are characterized by increased catabolism and muscle wasting, indicating calorie exposure early in the disease

process may differ substantially from calories received later in the disease process (Braunschweig et al., 2017). Interestingly, post hoc analysis of the INTACT clinical trial demonstrated that higher early energy intake resulted in significantly increased odds of mortality, whereas higher late energy intake was significantly protective. Moreover, Peterson et al. conducted a clinical trial similar to the INTACT trial and analysis revealed significantly greater hazards of mortality with increased calorie exposure on ICU days 1-7 and lower hazard of mortality with increased calorie delivery after ICU day 7. These findings are in agreement with those of the INTACT trial, suggesting that nutrition should be withheld in the most acute phase of critical illness. This data indicates patients early in the disease process may require a different feeding strategy than those later in the disease process. It is possible that early (day 1-7) trophic enteral nutrition followed by late (day 8+) full calorie nutrition may more accurately reflect the energy needs of patients with ARDS/ALI. More research is needed to determine the specific caloric requirements during various phases of acute illness.

Moreover, the U.S. guidelines for nutrition support state that trophic enteral nutrition and full enteral nutrition result in similar patient outcomes over the first week of hospitalization. However, results from this literature review suggest that patient outcomes are not similar between these two feeding strategies over the first week of hospitalization. Four studies demonstrate that full enteral nutrition administered early in the course of critical illness (days 1-7) resulted in significantly higher mortality rates (Braunschweig et al., 2015; Braunschweig et al., 2017; Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017; Peterson, McKeever, Lateef, Freels, Fantuzzi, Braunschweig, 2019).

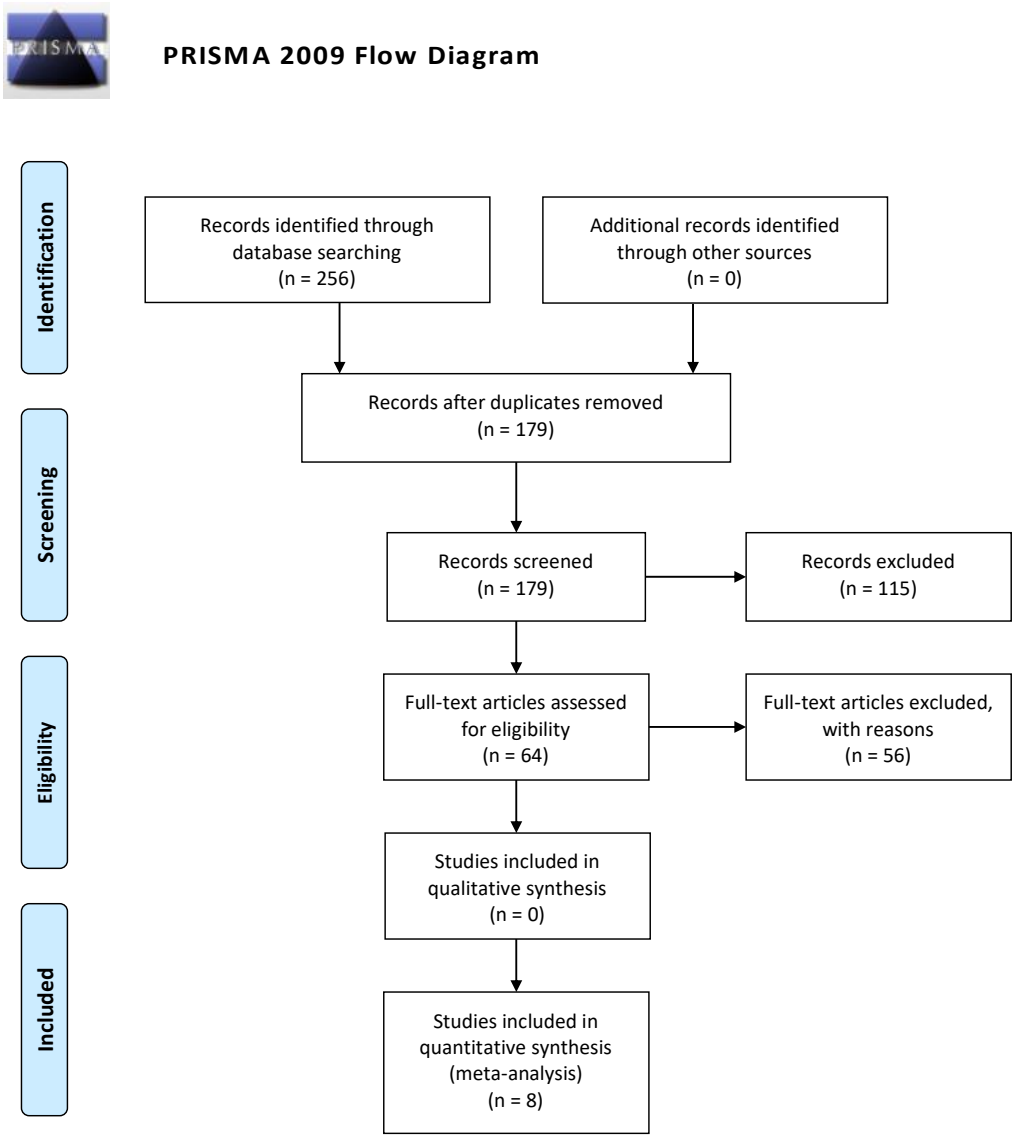
Additionally, the U.S. guidelines for nutrition define initial trophic EN as 10-20 kcal/hour or up to 500 kcal/day (McClave, et al., 2016). However, four studies in this literature review

define trophic as nearly 1,000 kcal/day (Braunschweig et al., 2015; Braunschweig et al., 2017; Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017; Peterson, McKeever, Lateef, Freels, Fantuzzi, Braunschweig, 2019), whereas two studies define trophic as ~300-500 kcal/day (Rice, Morgan, Hays, Bernard, Jensen, Wheeler, 2011; Rice et al., 2012). We hypothesize that the lower calorie delivery in the Rice 2011 and 2012 studies resulted in lower incidence of mortality, whereas a higher calorie delivery in the other four studies resulted in a higher incidence of mortality. There is a need for a universal definition of trophic enteral nutrition to facilitate comparable results among studies.

Limitations of this review of literature included a shortage of randomized controlled trials that evaluate the outcomes of trophic enteral nutrition in patients with ARDS/ALI. Out of the eight articles retrieved on the topic of trophic EN in patients with ARDS/ALI, only four were randomized controlled trials. There is a gap in literature on the topic of trophic enteral nutrition. More research is essential to determine if trophic EN is a safe and reliable method for this population of critically ill patients. Moreover, there is a shortage of studies measuring the same outcome measures. Only two studies in this literature review investigate the efficacy of trophic enteral nutrition on gastrointestinal outcomes. Furthermore, only select outcome measures were investigated in the articles included in this literature review. More research is needed to investigate if trophic enteral nutrition has an effect on additional clinical outcomes that were not accounted for in this literature review.

Conclusion

The studies included in this literature review indicate that the dose and timing of enteral nutrition in critically ill patients with ARDS/ALI has an effect on clinical outcomes. It is possible that additional variables such as the level of organ dysfunction also influence clinical outcomes. Results from the randomized controlled trials included in this review indicate that early trophic enteral nutrition may be a safe and reliable feeding strategy for patients with ARDS/ALI. Moreover, an aggressive feeding strategy that provides a high calorie delivery early in the course of acute lung injuries appears to have detrimental outcomes, such as significantly higher rates of mortality. Two reputable guidelines, the U.S. and Canadian guidelines for nutrition support, recommend that either trophic or full EN is appropriate for patients with ARDS/ALI on the basis that these two feeding strategies have similar patient outcomes over the first week of hospitalization. These recommendations contradict the outcomes of randomized controlled trials that conclude full EN in the first week of hospitalization significantly increases the rate of mortality. Additional research on the topic of trophic and full enteral nutrition in patients with ARDS/ALI is necessary to determine which feeding strategy will best improve clinical outcomes in this select population of critically ill patients.



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For more information, visit www.prisma-statement.org.

Figure 1. PRISMA Flow Diagram

Table 1. Table of Evidence

Source	Design type	Study Outcome Measures	Study population, study setting, study sample size	Study intervention	Key findings
Rice et al., 2012	RCT.	Primary outcome: ventilator-free days through day 28 Secondary outcomes: Gastrointestinal intolerances 60-day mortality ICU free days Organ failure free days Infections	Population: Patients within 48 hours of ALI onset who received mechanical ventilation <72 hours. Sample size: 1000 (508 trophic EN, 492 full calorie nutrition). Setting: 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network	Initial trophic EN for first 6 days followed by advancement to full-energy EN. Trophic: initiated at 10 mL/hr, but later initiated at 20 mL/hr (400 kcal/day). Full energy: initiated at 25 mL/hr (1300 kcal/day)	No statistically significant difference in clinical outcomes (VFDs, 60-day mortality, infection) between trophic and full energy for first 6 days, but less GI intolerances in trophic group.
Rice et al, 2011	RCT.	Primary outcome: ventilator-free days to day 28. Secondary outcomes: ICU free days All-cause hospital mortality Gastrointestinal intolerance Organ failure free days Hospital free days Infection	Population: Patients with acute respiratory failure expected to require mechanical ventilation for at least 72 hours. Sample size: 200 (102 full energy EN, 98 trophic EN). Setting: two ICUs at a single center	Initial trophic EN for first 6 days followed by advancement to full-energy EN. Trophic: initiated at 10 mL/hr, but later initiated at 20 mL/hr (300 kcal/day). Full energy: initiated at 25 mL/hr (1418 kcal/day).	Trophic EN for first 6 days and then advanced to full feed resulted in similar clinical outcomes compared to the full energy groups, but with fewer episodes of GI intolerance in the trophic group.
Peterson, McKeever, Lateef, Freels, Fantuzzi, **Braunschweig, 2019**	Retrospective observational study.	Primary outcome: all-cause hospital mortality Secondary outcomes:	Population: Adults admitted to the ICU with ARDS. Sample size: 298.	SOFA at ICU admit.	Organ failure appears to modify the relationship between calorie

		Duration of mechanical ventilation ICU length of stay Hospital length of stay	Setting: Single center ICU.	Average SOFA for the first 7 days following intubation. The highest SOFA for the first 7 days following intubation. Change in SOFA from intubation to 7 days later.	exposure and ICU outcome.
Braunschweig et al., 2015	RCT.	Primary measure: nosocomial infections Secondary outcomes: Number of days on mechanical ventilation ICU length of stay Hospital length of stay All-cause hospital mortality	Population: Adults with ALI. Sample size: 78 (40 IMNT, 38 SC). Setting: Single center.	A more aggressive feeding strategy termed Intensive Medical Nutrition Intervention (IMNT). SC: 16.6 kcal/kg/day (1221 kcal/day) IMNT: 25.5 kcal/kg/day (1798 kcal/day).	IMNT provided from ALI diagnosis to hospital discharge resulted in greater mortality that SC
Needham et al., 2013	Prospective longitudinal follow-up evaluation of the EDEN trial.	Primary outcome measure: physical function domain of SF-36 instrument, adjusted for age and sex Secondary outcomes: Survival Psychological symptoms Cognition Quality of life Employment status	Population: Adults with ALI. Sample size: 525. Setting: 41 hospitals in the U.S.	Initial trophic EN for first 6 days followed by advancement to full-energy EN. Trophic: initiated at 10 mL/hr, but later initiated at 20 mL/hr (400 kcal/day). Full energy: initiated at 25 mL/hr (1300 kcal/day)	There was no difference in physical function, 12-month survival, or physical, psychological and cognitive function, or employment status at six and 12 months between those randomized to initial trophic versus full enteral feeding.

		Functional activities Fatigue			
Braunschweig et al, 2017	Retrospective cohort study of the INTACT trial.	Primary outcome: All-cause hospital mortality	Population: Adults with ALI. Sample size: 78 (40 IMNT, 38 SC). Setting: Single center.	A more aggressive feeding strategy termed Intensive Medical Nutrition Intervention (IMNT). SC: 16.6 kcal/kg/day (1221 kcal/day) IMNT: 25.5 kcal/kg/day (1798 kcal/day).	Providing kilocalories per kilogram early post-ALI diagnosis at recommended levels was associated with significantly higher hazards of mortality, whereas higher late energy intakes reduced mortality hazards.
Peterson, Lateef, Freels, McKeever, Fantuzzi, Braunschweig, 2017.	Cohort study.	Primary outcome: Mortality; landmark mortality (30-day or 60-day) was not obtained.	Population: Adult patients who met INTACT eligibility but did not participate. Sample size: 298. Setting: Single-center ICU.	Calorie exposure divided into categorical tertiles (<11.5 kcal/kg, 11.6-16.5 kcal/kg, and ≥16.6 kcal/kg) and intervals of time (days 1-4, 1-5, 1-6, 1-7).	Increased overall calorie delivery at ARDS diagnosis is associated with higher likelihood of mortality.
Needham et al, 2013.	Prospective, longitudinal study of the EDEN trial.	Primary outcome: 6-minute walk test Secondary outcomes: 4-m timed walk speed; manual muscle testing; hand grip strength; maximal inspiratory pressure, FEV1, FVC (pulmonary function); BMI; % of fat and	Population: patients who participated in the EDEN trial. Sample size: 174. Setting: 5 of the 12 EDEN study centers, representing 12 hospitals.	Initial trophic EN for first 6 days followed by advancement to full-energy EN. Trophic: initiated at 10 mL/hr, but later initiated at 20 mL/hr (400 kcal/day).	Initial trophic versus full feeding did not affect mean SF-36 physical function at 12 months, survival to 12 months, or nearly all of the secondary outcomes.

		muscle based on upper arm anthropometrics Global muscle strength Cognitive function (based on tests of executive function, language, memory, verbal reasoning/concept formation, and attention	Full energy: initiated at 25 mL/hr (1300 kcal/day)

Note. ALI= acute lung injury; ARDS= acute respiratory distress syndrome; RCT= randomized controlled trial; EN= enteral nutrition; VFD= ventilator-free days; ICU= intensive care unit; GI= gastrointestinal; SOFA=Sequential Organ Failure Assessment; IMNT= intensive medical nutrition intervention; SC=standard care; SF-36= short form-36

Table 2. Critical Appraisal Scores (Cohort Studies)

Authors	1. Does the study address a clearly focused issue?	2. Was the cohort recruited in an acceptable way?	3. Was the exposure accurately measured to minimize bias?	4. Was the outcome accurately measured to minimize bias?	5. (a) Have the authors identified all important cofounding factors? 5. (b) Have they taken account of the cofounding factors in the design and/or analysis?	6. (a) Was the follow up of subjects complete enough? 6. (b) Was the follow up of subjects long enough?	7. What are the results of the study?	8. How precise are the results?	9. Do you believe the results?	10. Can the results be applied to the local population?	11. Do the results of this study fit with other available evidence?	12. What are the implications of this study for practice?
Needham et al., 2013	Yes	Can't tell	Yes	Yes	(a) No (b) Yes	(a) Yes (b) Yes	Primary outcome measure: physical function domain of SF-36 instrument, adjusted for age and sex Secondary outcomes: Survival	Confidence interval reasonably small	Yes	Yes	Can't tell	Factors other than nutrition strategies must be accounted for when considering the substantial physical, psychological, cognitive impairment, and reduced quality of life

							Psychological symptoms Cognition Quality of life Employment status Functional activities Fatigue					reported after acute lung injury.
Needham et al., 2013	Yes	Can't tell	Yes	Yes	(a) No (b) No	(a) Yes (b) Yes	Primary outcome: 6-minute walk test Secondary outcomes: 4-m timed walk speed; manual muscle testing; hand grip strength; maximal inspiratory pressure, FEV1, FVC (pulmonary function); BMI; % of fat and muscle based on upper arm anthropometrics	The confidence intervals are reasonably small	Yes	Can't tell	Can't tell	No

Peterson et al., 2019	Yes	Yes	Yes	Yes	(a) Yes (b) Yes	(a) No (b) No	Primary outcome: all-cause hospital mortality Secondary outcomes: Duration of mechanical ventilation ICU length of stay Hospital length of stay	Confidence intervals are reasonably small	Yes	Yes	Yes	Can't tell
Peterson et al., 2017	Yes	Yes	Yes	Yes	(a) Yes (b) Yes	(a) No (b) No	Primary outcome: Mortality; landmark mortality (30-day or 60-day) was not obtained.	Confidence intervals are reasonably small.	Yes	Can't tell	Yes	Can't tell

Note. SF-36= short form-36; FEV1= forced expiratory volume in 1 second; FVC= forced vital capacity; BMI= body mass index; ICU= intensive care unit

Table 3. Critical Appraisal Scores (Randomized Control Trials)

Authors	1. Did the trial address a clearly focused issue?	2. Was the assignment of treatments randomised?	3. Were all of the patients who entered the trial properly accounted for at its conclusion?	4. Were the patients, healthcare workers, and study personnel 'blind' to treatment?	5. Were the groups similar at the start of the trial?	6. Aside from the experimental intervention, were the groups treated equally?	7. How large was the treatment effect?	8. How precise was the estimate of the treatment effect?	9. Can the results be applied to the local population, or in your context?	10. Were all clinically important outcomes considered?	11. Are the benefits worth the harms and costs?
Rice et al., 2012	Yes	Yes	Yes	No	Can't tell	No	No effect size measure included.	No wide confidence intervals	Can't tell	Yes	Yes
Rice et al., 2011	Yes	Yes	Yes	No	Yes	Yes	No effect side measure included.	No wide confidence intervals.	Can't tell	Yes	Yes
Braunschweig et al., 2015	Yes	Yes	Yes	No	No	No	The hazard of death in the IMNT was 5.67 times (p =0.001) higher than the SC group.	Confidence intervals are wide	Can't tell	No	No
Braunschweig et al., 2017	Yes	Yes	Yes	No	No	Yes	After day 8, the hazards for subsequent death	Confidence intervals are wide	Can't tell	No	No

					were significantly increased by higher mean daily kilocalories per kilogram received during early postrandomization days 1–7 (HR: 1.17) and significantly reduced by the time- varying kilocalories per kilogram received on and after day 8 (HR: 0.91)

Note. IMNT= intensive medical nutrition intervention; SC=standard care; HR= hazard ratio

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