Does Enteral Nutrition Compared to Parenteral Nutrition Result in Better Outcomes in Critically Ill Adult Patients? A Systematic Review of the Literature

Leah Gramlich, MD, Krikor Kichian, MD, Jaime Pinilla, MD, Nadia J. Rodych, RD, Rupinder Dhaliwal, RD, and Daren K. Heyland, MD, MSc

From the Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; the Department of Surgery, Royal University Hospital, Saskatoon, Saskatchewan, Canada; and the Department of Medicine, Queens University, Kingston, Ontario, Canada

OBJECTIVE: Nutritional support is part of the standard of care for the critically ill adult patient. In the average patient in the intensive care unit who has no contraindications to enteral nutrition (EN) or parenteral nutrition (PN), the choice of route for nutritional support may be influenced by several factors. Because EN and PN are associated with risks and benefits, we systematically reviewed and critically appraised the literature to compare EN with PN the critically ill patient.

METHODS: We searched computerized bibliographic databases, personal files, and relevant reference lists to identify potentially eligible studies. Only randomized clinical trials that compared EN with PN in critically ill patients with respect to clinically important outcomes were included in this review. In an independent fashion, relevant data on the methodology and outcomes of primary studies were abstracted in duplicate. The studies were subsequently aggregated statistically.

RESULTS: There were 13 studies that met the inclusion criteria and, hence, were included in our meta-analysis. The use of EN as opposed to PN was associated with a significant decrease in infectious complications (relative risk = 0.64, 95% confidence interval = 0.47 to 0.87, $P = 0.004$) but not with any difference in mortality rate (relative risk = 1.08, 95% confidence interval = 0.70 to 1.65, $P = 0.7$). There was no difference in the number of days on a ventilator or length of stay in the hospital between groups receiving EN or PN (Standardized Mean Difference [SMD] = 0.07, 95% confidence interval = −0.2 to 0.33, $P = 0.6$). PN was associated with a higher incidence of hyperglycemia. Data that compared days on a ventilator and the development of diarrhea in patients who received EN versus PN were inconclusive. In the EN and PN groups, complications with enteral and parenteral access were seen. Four studies documented cost savings with EN as opposed to PN.

CONCLUSION: The use of EN as opposed to PN results in an important decrease in the incidence of infectious complications in the critically ill and may be less costly. EN should be the first choice for nutritional support in the critically ill. *Nutrition* 2004;20:843–848. ©Elsevier Inc. 2004

KEY WORDS: enteral nutrition, parenteral nutrition, critical illness, meta-analysis

INTRODUCTION

In the critically ill patient, malnutrition results in impaired immunologic function, impaired ventilatory drive, and weakened respiratory muscles leading to prolonged ventilator dependence and increased infectious morbidity and mortality rates.[1] Malnutrition is prevalent in patients in the intensive care unit (ICU), and its prevalence has been reported to be as high as 40% and is associated with poor outcome.[2] Recent reviews have documented evidence that nutritional support influences morbidity and mortality rates in critically ill patients[3]. Parenteral nutrition (PN) is used in 12% to 71% and enteral nutrition (EN) is used in 33% to 92% of critically ill patients who receive nutritional support.[4–9]

The general benefits of nutritional support include improved wound healing,[3] a decreased catabolic response to injury,[10] improved gastrointestinal permeability,[11] decreased bacterial translocation,[12] and improved clinical outcomes, including a decrease in complication rates and length of stay with accompanying cost savings.[13–16] However, nutritional support is not without adverse effects and risks. Early EN may be associated with high gastric residuals,[17] bacterial colonization of the stomach, and increased risk of aspiration pneumonia.[18] PN has been associated with gut mucosal atrophy, overfeeding, hyperglycemia, an increased risk of infectious complications[16] and increased mortality rates[19] in critically ill patients. Both forms of nutritional support can affect cost and workload.

Various factors influence the choice of EN or PN, one of which is the estimate of treatment benefit and risk of harm.

Braunschweig et al.[20] conducted a meta-analysis to review prospective, randomized, controlled trials that randomly assigned patients to EN or PN and in which PN was provided at or above

Dr. Heyland is a Career Scientist for the Ontario Ministry of Health in Ontario, Canada.

Correspondence to: Daren K. Heyland, MD, MSc, Angada 3, Kingston General Hospital, 76 Stuart Street, Kingston ON K7L 2V7, Canada. E-mail: dkh2@post.queensu.ca

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estimated needs. Studies included patients identified as having compromised gastrointestinal function (pancreatitis, ulcerative colitis, or Crohn's disease), surgery, trauma, or multisystem organ failure. When the results of the trials were aggregated, tube feeding was associated with a lower risk of infection but a higher risk of complications associated with nutritional support. The strength of this association was questioned because of a significant test for heterogeneity ($P = 0.03$). There was no treatment effect for EN on other complications or mortality rate. Koretz et al., in the AGA Technical Review on Parenteral Nutrition[21], performed a global meta-analysis on 82 randomized, controlled trials to assess the clinical efficacy of PN, including perioperative trials, oncologic therapy trials, alcoholic hepatitis trials, and trials in low-birth-weight infants. They also tried to distinguish whether or not malnutrition was present in patient populations. They identified that PN did not influence mortality or overall complication rates but that it was associated with an increased risk for infection.

One of the limitations of these previous reviews is the heterogeneity of the patient populations included in the meta-analyses. The treatment effect of nutritional support differs depending on the population studied. Heyland et al.[19] compared PN with standard care (oral diet plus intravenous dextrose) in surgical and critically ill patients and found that, overall, PN did not influence overall mortality rate, but that there was a trend toward decreased complication rates in malnourished patients. They identified that study results were influenced by patient populations. Patients undergoing major surgery were more likely to achieve a positive outcome with PN, whereas critically ill patients were more likely to have a complication and die. The differences in treatment effect across these groups were statistically significant. This suggests that the results of studies in patients who are not critically ill are not generalizable to those who are.

Because there have been several small clinical studies that have compared EN with PN in specific populations of patients with critical illness,[22–34] we systematically reviewed and statistically aggregated all studies that compared EN with PN in the critically ill to allow a more precise estimation of the treatment effect and to increase the power to identify a treatment effect that may not be apparent in smaller individual studies.

MATERIALS AND METHODS

Search Strategy

We conducted a computerized bibliographic search of Medline, Embase, Cinahl, and Cochrane Library for studies from 1980 to August 2002 to locate all relevant articles. Search terms included *nutritional support*, *dietary supplementation*, *enteral nutrition*, *parenteral nutrition*, *peripheral nutrition*, *total parenteral nutrition*, *nutritional support team*, *nutrition requirements*, *nutritional assessment*, *parenteral nutrition solutions*, *critical care*, *critical illness*, and *intensive care units*. In addition, personal files and relevant review articles were searched for additional studies.

Study Selection Criteria

Studies were selected for inclusion in the review process it they met the following criteria:

1. Study design: randomized clinical trial and meta-analysis of randomized controlled trials (pseudo-randomized trials were excluded).
2. Population: critically ill, human adult patients (patients who underwent elective surgery were excluded).
3. Intervention: any form of EN or PN.
4. Outcomes: primary outcomes of interest were mortality rate (ICU, hospital, or long term) and infectious complications. Secondary endpoints included length of stay, quality of life, functional recovery, complications, and cost.

We elected to include only randomized trials in this review. The trials evaluated the effect of PN administered at or above estimated energy needs compared with the effect of EN in the critically ill. We defined critically ill patients as those who would be routinely cared for in the critical care environment. We excluded studies of pediatric or neonatal patients. Studies were not limited to those that involved English-speaking adult patients. Studies that evaluated the effect of PN or EN on nutritional outcomes (i.e., nitrogen balance, amino acid profile) were not included in this review.

Methodologic Quality of Primary Studies

Each randomized trial was critically appraised according to an explicit procedure. The two appraisers (L.G. and J.P.) appraised the following descriptors: intervention, study population, nature of allocation, co-intervention, exclusion after randomization, double blinding, event rates, relative risk (RR), and other outcomes. Clinical trials were assigned "level 1" if they reported information on concealed randomization, blinded outcome adjudication, and an intent-to-treat analysis. Trials were assigned "level 2" if any one of those characteristics was unfulfilled. For the one meta-analysis included in the review process, the following descriptors were abstracted: intervention, number of trials, population selection criteria, search strategy, independent validity assessment, method of pooling results, assessment of homogeneity, pooled event rates, and other outcomes. Disagreement between appraisers was resolved by consensus. When data were missing, unclear, or not reported on a per-patient basis, we attempted to contact the primary investigator and request further information. One investigator[27] provided data on a subset of critically ill patients who were randomized to received EN or PN, and these data were included in the analysis. A priori, we considered that the harmful effect of PN might be associated with relative overfeeding and hyperglycemia. Accordingly, we conducted a subgroup analysis to determine the effect of excess calories (PN versus EN) and higher glucose levels (across groups).

The primary outcomes were mortality rate and infectious complications. Data from all relevant studies were combined to estimate the common risk ratio and associated 95% confidence intervals (95% CIs). The common risk ratios and their confidence intervals were estimated by using the random effect model of DerSimonian and Laird[35] as implemented in RevMan 4.1.[36] We considered $P < 0.25$ to be supportive of a trend and $P < 0.05$ to be statistically significant. A test for heterogeneity was considered significant if $P < 0.05$, indicating heterogeneity among studies, thereby weakening the estimate of overall treatment.

RESULTS

Study Identification and Selection

Twenty-seven citations of randomized controlled trials were identified in the bibliographic search, our personal files, and review of references. Of these studies, there were 12 level 2 studies[5,11,16,22–26] and one level 1 study[27] that met the inclusion criteria[28–32] and described a total of 856 critically ill patients. The 13 studies are presented in Table I, which lists study populations, designs, interventions, and outcomes (mortality rate, infections, length of stay in the ICU, days on a ventilator, and cost). Reasons for exclusions were studies[20,33,34,37–48] that examined a mix of patients who and were not critically ill or that examined patients who underwent elective surgery. The 13 studies included reflected a heterogeneous population of ICU patients who had head trauma and injuries, abdominal trauma, sepsis, cardiac bypass, or severe acute pancreatitis. In the study by Woodcock et al.,[27] we abstracted data concerning only ICU patients, and 11 of 38 patients moved between groups after randomization. The data on mortality rate

TABLE I.

RANDOMIZED CLINICAL TRIALS THAT COMPARED EN WITH PN IN CRITICALLY ILL PATIENTS

	Subjects			Infection		Mortality		LOS		VD	
References	EN	PN	Population	EN	PN	EN	PN	EN	PN	EN	PN
29	23	23	Trauma and laparotomy	15 (65)	17 (74)	1 (4)	3 (13)	30	31	12	10
22	28	21	Closed-head injury	N/A	N/A	5 (18)	1 (5)	39	37	N/A	N/A
23	31	35	Post sepsis	N/A	N/A	7 (22)	8 (23)	N/A	N/A	N/A	N/A
28	12	15	Blunt trauma	N/A	N/A	1 (7)	1 (8)	N/A	N/A	N/A	N/A
11	13	11	Cardiac bypass	N/A	N/A	2 (15)	6 (55)	N/A	N/A	N/A	N/A
24	21	24	Head trauma	17 (80)	15 (63)	3 (14)	2 (8)	N/A	N/A	N/A	N/A
32	18	20	Acute pancreatitis	5 (28)	10 (50)	1 (6)	2 (10)	11	12	15	11
16	51	45	Abdominal trauma	9 (16)	18 (40)	1	1	20.5	19.6	2.8	3.2
26	29	30	Abdominal trauma	5 (17)	11 (37)	0	0	N/A	N/A	N/A	N/A
25	118	112	High-risk surgical	19 (16)	39 (35)	8 (7)	11 (10)	17	22	N/A	N/A
30	18	20	Head injury	N/A	N/A	9 (50)	3 (15)	49.4	52.6	10.3	10.4
27	17	21	Malnutrition	6 (38)	11 (52)	9 (53)	5 (24)	33.2	27.3	N/A	N/A
31	28	23	Brain injury	5 (18)	4 (17)	10 (36)	10 (43)	N/A	N/A	N/A	N/A

EN, enteral nutrition; N/A, not available; PN, parenteral nutrition

and infectious complications from the 1989 study by Moore et al.[26] were included in their 1992 meta-analysis,[25] whereas data on caloric intake, blood sugars, and non-septic complications were not and, hence, appeared in the tables of the 1989 study.[26]

Effect of EN Versus PN on Clinical Outcomes

Nine of the 13 studies reported data on infectious complications with EN versus PN. The nature of the infectious complications varied with the particular patient population and included pneumonia, aspiration pneumonia, urinary tract infections, bacteremia, wound infection, abdominal abscess, and line sepsis. When the data were aggregated from these studies (Figure 1), there was a significant decrease in the number of patients with infectious complications who had received EN rather than PN (RR = 0.64, 95% CI = 0.47 to 0.87). The test for heterogeneity of this aggregate was not statistically significant ($P = 0.22$). All 13 studies reported mortality rate as an outcome. The result of this analysis (Figure 2) demonstrated no difference in mortality rate in critically ill patients on EN versus PN (RR = 1.08, 95% CI = 0.70 to 1.65), with a non-significant test for heterogeneity of 0.2.

When a subgroup of studies in which the PN group was fed more calories than the EN group (non-isocaloric dosing across groups) were aggregated[16,26,27,30,31] (Figure 3), EN was associated with a trend toward an excessive mortality rate (RR = 1.58, 95% CI = 0.75 to 3.35, $P = 0.2$) compared with PN. When the trials in which EN and PN were fed isocalorically were aggregated, there was no effect between EN and PN (RR = 1.08, 95% CI = 0.56 to 2.06, $P = 0.8$). Mortality rate in the subgroup analysis that compared patients who received PN and had higher levels of blood sugar with those who received EN showed no effect (RR = .093, 95% CI = .021 to 4.15, $P = 0.90$) when compared with studies in which patients' levels of blood sugar were similar across groups.

There was no difference in length of stay[16,22,25,27,29,30,32] or days on ventilation[16,29,30,32] between groups receiving EN or PN, but the information was not aggregated statistically due to insufficient data.

Only three studies reported on baseline nutritional status, and data regarding the relation of nutritional status to outcome were not available.

Of the studies that reported on nutritional intake, 5 of 11 associated PN with a larger caloric intake.[16,25,27,30,31] Three studies associated EN with an increase in diarrhea,[16,23,31] and one reported decreased diarrhea.[22]

Four studies reported cost savings with the use of EN rather than PN.[22,23,29,32]

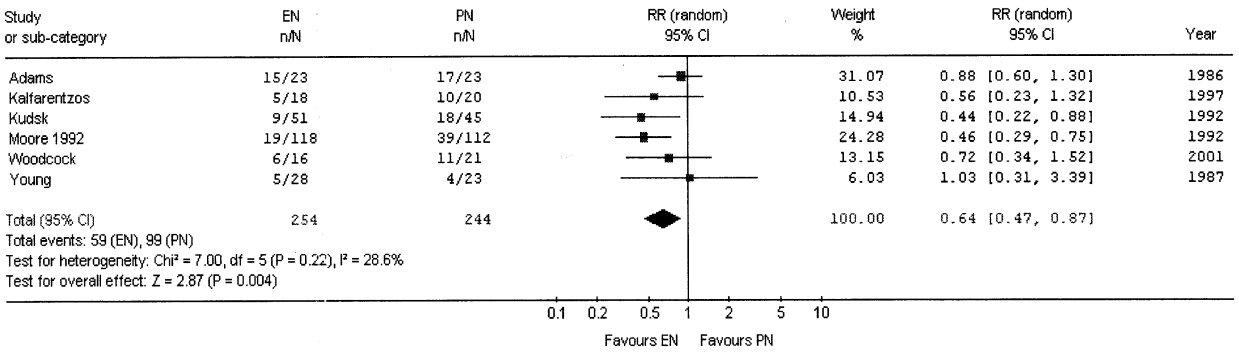

FIG. 1. EN is associated with fewer infectious complications than is PN (RR = 0.64, $P = 0.004$). 95% CI, 95% confidence interval; EN, enteral nutrition; PN parenteral nutrition; RR, relative risk.

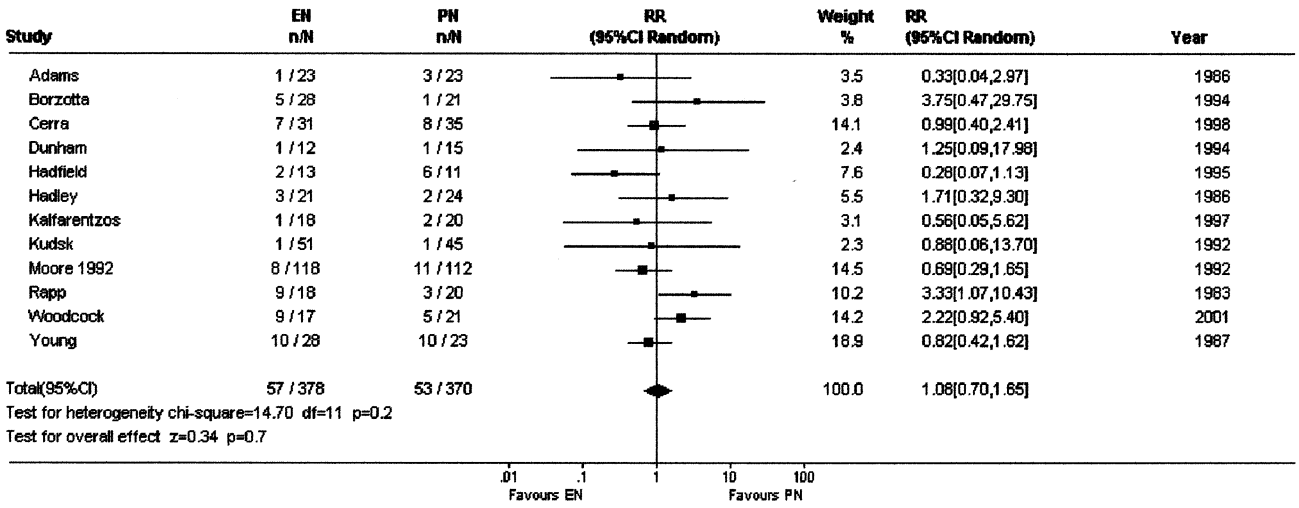

FIG. 2. EN does not differ from PN with respect to mortality rate (RR = 1.08, $P = 0.7$). 95% CI, 95% confidence interval; EN, enteral nutrition; PN parenteral nutrition; RR, relative risk.

DISCUSSION

The body of literature regarding nutritional support in critically ill patients continues to grow, but, because of methodic limitations and the small size of many of the studies, making inferences and generalizing results from individual trials are problematic. Because the treatment effects of EN and PN vary depending on the patient population, in contrast to previous reviews, we systematically examined all randomized trials that compared EN with PN specifically in critically ill patients. The data, when aggregated, demonstrated that patients on EN developed fewer infectious complications. Further, neither EN nor PN was associated with a survival advantage. Complications were seen with both forms of therapy.

Although a meta-analysis does not replace a large, multicenter, randomized, controlled trial that compares EN with PN in the critically ill patient, it does provide useful information and can guide us in the development of such a trial to specifically assess treatment effects of EN versus PN. This would also require a change in how the nutrition community performs such studies, so that larger multicenter, randomized, controlled trials could be performed in this patient population. Among the limitations, we acknowledge the heterogeneity in the formulations and amount of energy provided by nutritional support in patients receiving EN and PN. We also recognize the difficulty of conducting studies in severely ill patients who often have an unpredictable course in the ICU and determining the effect of that course on outcome. Other important considerations for inclusion in future studies investigating nutritional support in critical illness would be a quantifiable assessment of disease severity (Injury Severity Score and Second Acute Physiology and Chronic Health Evaluation) and baseline nutritional status.

The main clinical implication of our data concerns the use of nutritional support in critically ill patients who can tolerate some EN. Our findings suggest that EN is the preferred method to provide nutritional support to critically ill patients. Although we did not find any difference in mortality rate between patients administered EN and PN, the meta-analysis lacked power to detect a small but meaningful treatment effect. Moreover, a difference in infectious complications alone warrants a preferential recommendation of EN. Acquired infection, in particular ventilator-associated pneumonia, is a major problem for critically ill patients, which results in increased morbidity and mortality rates and health care costs.[49–51] Perceived barriers to using EN for nutritional support include concerns over the risk of aspiration pneumonia, high gastric residuals and bowel irregularities, and an inability to reach targeted nutritional goal rates. In those patients on pressors, there is the added concern of the potential to increase the oxygen demand of the gastrointestinal tract in those who are fed with EN.[52]

Recent guidelines that address decreasing the risks and maximizing the benefits of EN have been published.[53] These guidelines include an evidence-based evaluation of nutritional support in the

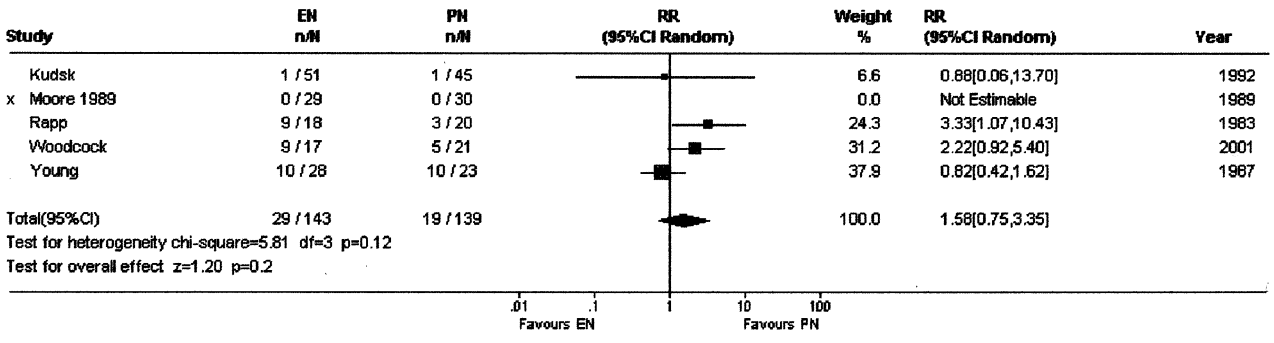

FIG. 3. EN in non-isocaloric studies (in which the PN group received more calories than the EN group) is associated with a trend toward an excessive mortality rate. 95% CI, 95% confidence interval; EN, enteral nutrition; PN parenteral nutrition; RR, relative risk.

ventilated, critically ill patient and review EN versus PN compositions of nutritional support. Several measures have been shown to decrease the risk of aspiration pneumonia in critically ill patients on EN.[54–57] Gastrointestinal promorbidity agents in the ICU have been systematically reviewed recently;[58] although no study demonstrated a positive effect on clinical outcomes, promorbidity agents as a class appear to increase indexes of gastrointestinal transit and "tolerance" of feeding. Small bowel feeding, beyond the pylorus, may also be associated with a decrease in gastroesophageal regurgitation, an increase in nutrient delivery, and a lower rate of ventilator-associated pneumonia.[59] The use of an EN feeding protocol with a gastric residual threshold volume of 250 mL may also positively affect tolerance of tube feeds and achievement of goal rates.[60]

Why is there an increased risk of infection associated with PN in the critically ill patient? Although perhaps controversial,[16,61] the adverse effects of PN have been attributed to hyperglycemia and subsequent increased infectious complications.[61] This attribution has been supported by Van den berghe et al.[62] who reported that intensive insulin therapy and tight control (glucose 4.4 to 6.1 mM/L) decrease morbidity and mortality rates in critically ill patients. All patients in this study received 200 to 300 g of glucose on day 1 and 60% went on to receive PN. An alternative explanation of this study's findings is that high glucose loading, as one would see with PN, with inadequate glycemic control is associated with *increased* morbidity and mortality rates. In our subgroup analysis, we found no difference in treatment effect between those studies in which the PN groups received more calories or had a higher incidence of hyperglycemia.

McCowan et al.[61] compared hypocaloric PN (1000 kcal, 70 g of protein, and no lipid) with standard PN (25 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} with lipid, 1.5 g/kg) and found a trend toward fewer infections (P = 0.2) in the hypocalorically fed group. Interestingly, the incidence of hyperglycemia in both groups was similar. Another hypothesis, not proved in human subjects, is that bacterial translocation in the setting of gut atrophy, secondary to its disuse with PN, is responsible for the increased risk of infection seen with PN.[63]

There will be critically ill patients in whom EN is not possible, such as patients with bowel obstruction, short bowel syndrome, or abdominal compartment syndrome or those who could not tolerate EN over a prolonged period[64] and who may be at increased risk for mortality and morbidity. As such, it is imperative to consider strategies to optimize PN,[53] which would include optimization of glycemic control.[62] PN without lipid has been associated with fewer infections.[61,65] The addition of parenteral glutamine to PN may also be associated with decreased complication and mortality rates.[66–71] Although the combination of EN and PN does not confer a significant advantage over PN alone to satisfy patients' needs,[53] it is reasonable to continue attempts at EN in patients who require PN.

In conclusion, when EN and PN are compared in the critically ill patient, EN is associated with fewer infectious complications and, if possible, should be the chosen route for nutritional support. It is fundamental that, in the provision of EN and PN, strategies be adopted to optimize benefit and minimize potential harm.

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