Journal of Intensive Care Medicine
1-12

DOI: 10.1177/0885066619843782
journals.sagepub.com/home/jic
SAGE

The Benefits of Parenteral Nutrition (PN) Versus Enteral Nutrition (EN) Among Adult Critically Ill Patients: What is the Evidence? A Literature Review

Angel Joel Cadena, MD[1], Sara Habib, MD[1], Fred Rincon, MD, MSc FACP, FCCP, FCCM[1], and Stephanie Dobak, MS, RD, LDN, CNSC[2]

Abstract

Malnutrition is frequently seen among patients in the intensive care unit. Evidence shows that optimal nutritional support can lead to better clinical outcomes. Recent clinical trials debate over the efficacy of enteral nutrition (EN) over parenteral nutrition (PN). Multiple trials have studied the impact of EN versus PN in terms of health-care cost and clinical outcomes (including functional status, cost, infectious complications, mortality risk, length of hospital and intensive care unit stay, and mechanical ventilation duration). The aim of this review is to address the question: In critically ill adult patients requiring nutrition support, does EN compared to PN favorably impact clinical outcomes and health-care costs?

Keywords

nutrition, enteral nutrition, parenteral nutrition, intensive care unit, critical care, critically ill patients, literature review

Introduction

The main aim of nutritional support in the critically ill patients is to avoid malnutrition. Malnutrition can cause impaired immunity, respiratory drive, and functional status and potentially result in prolonged dependence on mechanical ventilation, increased morbidity and mortality, and higher health-care costs.[1,2] There is evidence that enhanced nutritional support can lead to better clinical outcomes.[2-6] The optimal nutrition delivery route has been debated over the years. Multiple studies have compared the impact of enteral nutrition (EN) versus parenteral nutrition (PN) on injury response,[7,8] gastrointestinal (GI) permeability mitigation[9,10] and clinical outcomes such as mortality risk, infection rate, functional status, and hospital and intensive care unit (ICU) length of stay (LOS), among others.

The most recent nutrition guidelines for critically ill adult patients were created by The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) in 2016.[11] Overall, these guidelines favor the use of EN (when feasible) over PN. However, the results of more recent large randomized control trials (RCT)[12,13] and meta-analyses[14] question the efficacy of EN use over PN use. This leaves practitioners in a dilemma as to which is the preferred route of nutritional support. The aim of this review is to address the question, in critically ill adult patients requiring nutrition support, does EN compared to PN favorably impact clinical outcomes and healthcare costs?

Methodology

In order to answer our questions, we conducted a review of the literature. Relevant studies published between 1980 and May 2018 were independently searched by the authors in different databases including the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Medline using the following MeSH headings and key words: "total parenteral nutrition versus enteral nutrition" or "TPN versus EN" or "TPN and EN" or "total parenteral nutrition and enteral nutrition" and "intensive care unit" or "critical care" or "ICU." Language restrictions were not applied. If there was any disagreement as to whether or not to include an article, the researchers resolved it by discussion and arrived at a consensus.

[1] Division of Neurocritical Care, Departments of Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA
[2] Department of Nutrition and Dietetics, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Received January 15, 2019. Received revised March 6, 2019. Accepted March 25, 2019.

Corresponding Author:
Angel Joel Cadena, Departments of Neurosurgery and Neuro-critical Care, Thomas Jefferson University, 909 Walnut Street, 3rd Floor, Philadelphia, PA 19107, USA.
Email: angel.cadena@jefferson.edu

Table 1. Randomized Controlled Trials Conducted Among Critically Ill Patients Comparing Enteral to Parenteral Nutrition.

Study Name		Sample Size, N		Sample Characteristics	Methods	
		EN	PN		Randomized	Blinded
Adams et al, 1980	1980	23	23	Patients with trauma, critically ill	Yes	No
Rapp et al, 1983	1983	18	20	Head-injured patients	Yes	No
Young et al, 1987	1987	28	23	Head-injured patients	Yes	No
Peterson et al, 1988	1988	21	25	Abdominal trauma	Yes	No
Cerra et al, 1988	1988	33	37	Critical state	Yes	No
Moore et al, 1989	1989	29	30	Abdominal trauma	Yes	No
Kudsk et al, 1992	1992	52	46	Abdominal trauma	Yes	No
Dunham et al, 1994	1994	12	15	Blunt trauma injury	Yes	No
Borzotta et al, 1994	1994	27	21	Closed head injury	Yes	No
Kalfarentzos et al, 1997	1997	18	20	Severe acute pancreatitis	Yes	No
Woodcock et al, 2001	2001	32	32	All patients who required adjuvant nutritional support	Yes	single
Casas et al, 2007	2007	11	11	Severe acute pancreatitis	Yes	No
Chen et al, 2007	2007	10	9	Severe burn patients	Yes	No
Justo Meirelles et al, 2011	2011	12	10	Traumatic brain injury	Yes	No
Wang et al, 2013	2013	61	60	Severe acute pancreatitis	Yes	double
Sun et al, 2013	2013	30	30	Severe acute pancreatitis	Yes	No
Harvey et al, 2016	2016	1197	1191	Medical and Surgical	Yes	No
Reigner et al, 2018	2018	1202	1208	Patients in shock on vasopressors	Yes	No

Abbreviations: PN, Parenteral Nutrition; EN, Enteral Nutrition (EN).

Articles that met the following characteristic were included in this review: 1. *Population*: critically ill patients who are ≥18 years old. 2. *Intervention*: EN versus PN. 3. *Comparison*: RCTs, retrospective studies, reviews, observational studies, systematic reviews and/or meta-analyses in comparison with EN and PN groups. 4. *Outcomes*: At least one of the clinically relevant variables such as mortality, infectious complications, mechanical ventilation-free days, cost, hospital, and ICU length of stay (LOS).

Results

In total, 49 studies in the English Literature were reviewed, of which 27 were randomized controlled trials (RCT), eight meta-analyses, 11 observational studies, and 3 nonsystematic reviews. The sample characteristics and most outcomes from the principal RCTs used for the results are shown in Tables 1–3. The findings of these were used to answer the following questions:

1. Do Baseline Diseases or Conditions Dictate the Need for PN or EN?

It was once thought that particular clinical scenarios dictated the need for PN over EN. Obviously, certain diagnoses such as complete mechanical bowel obstruction inhibit EN delivery. However, early EN has now been found to be safe in many complex situations (although nutrition management must be individualized for each particular case). For example, in meta-analyses of patients with pancreatitis, EN was associated with significant reduction in overall mortality, decreased multiple organ failure rate, lower incidence of infections, reduced surgical interventions to control pancreatitis, and a reduced length of hospital stay when compared to PN.[15,16] In the secondary analysis of the prospective, randomized-controlled, multicenter "Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis (VISEP)" trial including patients with severe sepsis, EN alone (compared to EN + PN) was associated with lower overall mortality and morbidity (less infectious complication rates and renal-replacement therapy rates; more ventilator-free days), despite these patients receiving significantly less calories and protein.[17] In an RCT of 78 patients with postoperative enterocutaneous (EC) fistulas following Whipple procedure, early EN increased the likelihood of fistula closure when compared to PN.[18] Feeding within 24 hours of GI surgery helps reduce postoperative ileus, attenuate dysmotility, and prevent bowel wall edema.[11] Studies have also determined the safety and efficacy of enterally feeding the patient receiving vasopressor agents.[19] Khalid et al[19] prospectively collected and retrospectively analyzed data from a multi-institutional medical ICU database and divided patients into 2 groups based on starting EN within 48 hours of mechanical ventilation initiation. The study included 1174 patients who required mechanical ventilation for more than 2 days and were treated with vasopressor agents to support blood pressure. Intensive care unit and hospital mortality were lower for patients receiving early EN (22.5% vs 28.3%; $P = .03$; and 34.0% vs 44.0%; $P < .001$, respectively), and the beneficial effect was more pronounced in patients treated with multiple vasopressors (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.15-0.85). Given these findings, a recent, large (n = 2410) RCT hypothesized that outcomes were better with early EN than with early PN in patients being treated for shock (NUTRIREA-2).[13] In this study, groups receiving early normocaloric EN (17.8 kcal/kg/day) or PN (19.6 kcal/kg/day) had no significant differences in 28-day mortality, frequency of infectious complications,

Table 2. Mortality and Complications Observed in Randomized Controlled Trials Conducted Among Critically Ill Patients Comparing Enteral to Parenteral Nutrition

	Mortality, n (%)		Infectious Complications, n (%)		Noninfectious Complications, n (%)			
					GI		Non-GI	
Study Name	EN	PN	EN	PN	EN	PN	EN	PN
Adams et al, 1980	1/23 (4.35)	3/23 (13)	15/13 (65)	15/13 (65)	Diarrhea 11 (48), bloating 19 (83)	Diarrhea 6 (26), bloating/cramps 16 (70)	–	Air embolism 1 (4.34), pneumothorax 1 (4.34)
Rapp et al, 1983	9/18 (50)	3/20 (15)	–	–	–	–	–	–
Young et al, 1987	10/28 (35.7)	10/23 (43.5)	5/28 (18)	4/23 (17)	Diarrhea 12/28 (43)	Diarrhea 13/23 (57)	–	Pneumothorax 5/23 (21.7)
Peterson et al, 1988	–	–	2/21 (10)	8/25 (32)	–	–	–	–
Cerra et al, 1988	7/31 (22)	8/35 (23)	–	–	–	–	–	–
Moore et al, 1989	–	–	5/29 (17)	11/30 (37%)	7 patients: pancreatitis, partial small bowel obstruction, biliary fistula.	–	–	6 patients developed atelectasis, pneumothorax, CSF leak
Kudsk et al, 1992	1[a]	1[a]	9/51 (15.7)	18/45 (40)	Diarrhea 11/51 (21.6) Abdominal distention 2/51 (3.92)	Diarrhea 7/45 (15.6)	Delirium tremens 1/51 (1.96)	–
Dunham et al, 1994	1/12 (8.3)	1/15 (6.6)	–	–	Tube occlusion (2), Failed duodenal intubation (1), Patient extubation of feeding tube (1), Gastric reflux (2), Abdominal distension (2)	–		
Borzotta et al, 1994	5/27 (18.5)	1/21 (4.7)	51/27, 1.89 episodes per patient	39/21 1.86 episodes per patient	Diarrhea 8 (29.6)	Diarrhea 13 (61.9)	Pneumothorax 1 (3.7), Dehiscence 2 (7.4), Aspiration 3 (10.7)	Aspiration 2 (9.5)
Kalfarentzos et al, 1997	1/18 (5.6)	2/20 (10)	5/18 (28)	0/20 (50)	Diarrhea 6	Diarrhea 3		Catheter-related sepsis 2

(continued)

Table 2. (continued)

	Mortality, n (%)		Infectious Complications, n (%)		Noninfectious Complications, n (%)			
					GI		Non-GI	
Study Name	EN	PN	EN	PN	EN	PN	EN	PN
Woodcock et al, 2001	12/32 (37.5)	7/32 (7)	10/32 (31.3)	16/32 (50)	Diarrhea 2/32 (6.3), large volume NG aspirates 7/32 (21.9), tube dislodgement 14/32 (43.8)			Hyperkalemia, hyperglycemia, abnormal liver test 3/32 (9.4), fluid overload 1/32 (3.1)
Casas et al 2007	0/11 (0)	2/11 (18.2)	1/11 (9)	5/11 (45.5)	Portal venous thrombosis 1		SIRS 2, Lower UTI 1	SIRS 2
Chen et al, 2007	0/10 (0)	0/9 (0)	–	–	Diarrhea 2 (20)	–	–	–
Justo Meirelles et al, 2011	1/12 (8.3)	1/10 (10)	2/12 (16.7)	4/10 (40)	–	–	–	–
Wang et al, 2013	3/61 (4.9)	7/60 (11.7)	Pancreatic sepsis 13/61 (21) Multi-Organ Dysfunction Syndrome 15/61 (24.6)	Pancreatic sepsis 24/60 (40), Multi-Organ Dysfunction Syndrome 22/60 (36.7)				
Sun et al, 2013	2/30 (6.7)	1/30 (3.3)	Multi-Organ Dysfunction Syndrome 5/30 (17), SIRS 12/30 (40)	Pancreatic sepsis 10/30 (33), Multi-Organ Dysfunction Syndrome 13/30 (43), SIRS 22/30 (73)				
Harvey et al, 2016	30 day: 409/1195 (34.2%); 90 day: 464/1188 (39.1); ICU: 352/1197 (29.4), Hosp: 450/1186 (37.9)	30 day: 393/1188 (33.1); 90 day: 442/1184 (37.3); ICU: 317/1190 (26.6), Hosp: 431/1185 (36.4)	Number of infections no reported	Number of infections no reported	Nausea: 53/1197 (4.4), Vomiting: 194/1197 (16.2), Abdominal distention: 99/1197 (8.3), Increase liver enzymes: 179/1197 (15)	Nausea: 44/1191 (3.7), Vomiting: 100/1191 (8.4), Abdominal distention: 78/1191 (6.5), increase liver enzymes: 212/1191 (17.8)	Pressure ulcers: 179/1195 (15)	Pressure ulcers: 181/1190 (15.2)
Reigner et al, 2018	28 day: 443/1202 (37); 90 day: 530/1185 (45); ICU: 429 (33), Hosp: 498 (36)	28 day: 422/1208 (35); 90 day: 507/1192 (43); ICU: 405 (31), Hosp: 479 (34)	383/1202 (31.8)	437/1208 (36)	Vomiting: 406 (34), diarrhea 432 (36), bowel ischemia 19 (2), pseudo-obstruction 11 (1)	Vomiting: 246 (24), diarrhea 393 (33), bowel ischemia 5 (<1), pseudo-obstruction 3 (<1)		

Abbreviations: PN, Parenteral Nutrition; EN, Enteral Nutrition; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; CSF, cerebrospinal fluid; GI, gastrointestinal; UTI, urinary tract infection.
[a]Excluded from analysis.

Table 3. Length of Stay, Ventilator-Free Days, Calorie Intake, Cost, and Glycemic Status From Randomized Controlled Trials Conducted Among Critically Ill Patients Comparing Enteral to Parenteral Nutrition.[a]

	LOS, days		Ventilator-Free Days		Calorie Intake		Cost		Glycemic Status	
Study name	EN	PN	EN	PN	EN	PN	EN	PN	EN, n (%)	PN, n (%)
Adams et al, 1980	ICU: 13 ± 10, Hosp.: 30 ± 21	ICU: 10 ± 10, Hosp.: 31 ± 29	12 ± 11	10 ± 110	2088 kcal/kg	2572 kcal/kg	US$ 1346 (23-day cost)	US$ 3729 (23-day cost)	–	–
Rapp et al, 1983	Hosp.: 49.4	Hosp.: 52.6	On Vent.10.3	On Vent.10.4	685 kcal/kg	1750 kcal/kg	–	–	–	–
Young et al, 1987	–	–	–	–	1671 kcal/kg	2299 kcal/kg	–	–	–	–
Peterson et al, 1988	ICU: 3.7, Hosp.13.2	ICU: 4.6, Hosp.14.6	–	–	2204 kcal/kg	2548 kcal/kg	–	–	–	–
Cerra et al, 1988	–	–	–	–	1684 kcal/kg	2000 kcal/kg	–	–	–	–
Moore et al, 1989	–	–	–	–	1847 ± 123 kcal/kg by day 5	2261 ± 60 kcal/kg by day 5	–	–	–	–
Kudsk et al, 1992	Hosp.: 20.5 ± 2.8	Hosp.: 19.6 ± 2.8	2.8 ± 7	3.2 ± 1	15.7 kcal/kg	19.1 kcal/kg	–	–	–	–
Dunham et al, 1994	–	–	–	–	–	–	–	–	–	–
Borzotta et al, 1994	39± 23.1	36.9± 14	–	–	2097 not significant	1961	EN endoscopic $4815 Surgical $ 6336	PN + NG $9697 PN+PEG$9707 PN+both $10654	12 (44.4)	16 (76.2)
Kalfarentzos et al, 1997	ICU 11(5-21), Hospital 40(25-83)		on vent 15(6-16)	on vent 11(7-31)	Non-protein kcal/kg/day 24.1 not significant	24 significant	£30 per patient per day	£100 per patient per day	4 (22)	9 (45)
Woodcock et al, 2001	33.2± 43 (16)	27.3 ± 18.7 (18)			54.1% significant	96.7%significant	–	–	Hyperglycemia included among metabolic complications, numbers not reported separately	
Casas et al 2007	30.2	30.7	–	–	kcal/kg/d 20.1 not significant	20.8	–	–		
Chen et al 2007	–	–	–	–	–	–	–	–	–	–

(continued)

Table 3. (continued)

	LOS, days		Ventilator-Free Days		Calorie Intake		Cost		Glycemic Status	
Study name	EN	PN	EN	PN	EN	PN	EN	PN	EN, n (%)	PN, n (%)
Justo Meirelles et al, 2011	ICU 14 (5-26)	ICU 14 (6-24)	–	–	Cumulative kcal over 5 days, 5958, not significant	6586	–	–	102.4; CI 95% = 91.6-113.2mg/dL ($P <$ .001)	134.4; CI 95% = 122.6-146.2mg/dL (P .01)
Sun et al, 2013	ICU 9 (5-14)	ICU 12 (8-21)	–	–	–	–	–	–	–	–
Harvey et al, 2016	ICU: 7.3 (3.9-14.3), Hosp.: 16 (8-33)	ICU: 8.1 (4-15.8), Hosp.: 17 (8-34)	14.3 ($\pm$ 12.2)	14.3 ($\pm$ 12.1)	74 kcal/kg	89 kcal/kg	–	–	Hypoglycemia: 74/1197 (6.2),	Hypoglycemia: 44/1191 (3.7),
Reigner et al, 2018	ICU: 9 (5-16), Hosp.: 17 (8-32)	ICU: 10 (5-17), Hosp.: 18 (9-33)	11 (0-23)	12 (0-23)	113.4 kcal/kg	125.7 kcal/kg	–	–	Hypoglycemia:29 (2)	Hypoglycemia:13 (1)

Abbreviations: PN, Parenteral Nutrition; EN, Enteral Nutrition; ICU, intensive care unit; CI, confidence interval.
[a]Wang et al 2013 did not report data on LOS, ventilator days, calorie intake, cost, and glycemic status, hence not included in the table.

organ failure severity or duration, ventilator-free days, ICU and hospital stay lengths, or ICU, hospital, or 90-day mortality. Compared with PN, EN use was associated with significantly higher frequencies of hypoglycemia, bowel ischemia, and colonic pseudo-obstruction. In summary, studies support the use of EN over PN during severe and/or acute pancreatitis, severe sepsis, EC fistula, vasopressor requirements, and shock.

Does Baseline Nutritional Risk Impact the Optimal Timing of Nutrition Support Initiation?

Different factors play in determining a patient's baseline nutritional risk, including recent weight loss, recent reduced dietary intake, critical illness, age, APACHE II score, SOFA score, number of comorbidities, and days from hospital to ICU admission.[20] Higher nutrition risk is associated with increased hospital and ICU length of stay, less mechanical ventilation-free days, and higher 28-day mortality.[21,22] Almost half of the patients included in critical care nutrition studies are at high nutrition risk.[21,22]However, few studies compare the impact of EN versus PN as they relate to nutrition risk. One isocaloric study concluded that early EN when compared to PN significantly reduced the complication rate and duration of postoperative stay of malnourished (high nutrition risk) patients undergoing surgery for GI cancer.[23]

Regarding EN and nutrition risk, Heyland et al's[5] large observational study noted that higher provision of estimated calorie and protein needs from EN reduces 28-day mortality risk for patients at high nutrition risk (but not for those at low nutrition risk).

Casaer et al[24] conducted a multicenter RCT comparing early (ICU day 3) and late (ICU day 8) PN initiation to supplement inadequate EN in previously well-nourished patients. Patients in the late PN initiation group had a relative increase of 6.3% in the likelihood of being discharged alive earlier from the ICU (hazard ratio [HR], 1.06; 95% CI, 1.00-1.13; $P = .04$) and from the hospital (HR, 1.06; 95% CI, 1.00-1.13; $P = .04$). The late PN initiation group also had fewer ICU infections (22.8% vs 26.2%, $P = .008$), a lower incidence of cholestasis ($P < .001$), a relative reduction (9.7%) in the proportion of patients requiring more than 2 days of mechanical ventilation ($P = .006$), a median reduction of 3 days in the duration of renal-replacement therapy ($P = .008$), and a mean reduction in health care costs of €1,110 (about $1,600) ($P = .04$).Conversely, in Heyland et al's meta-analysis, early PN initiation in malnourished (high nutrition risk) ICU patients was associated with significantly fewer overall complications (risk ratio [RR], 0.52; 95% CI, 0.30-0.91;$P< .05$)[25] compared to standard care (STD; oral diet plus intravenous dextrose).Braunschweig et al[26] noted similar findings in their meta-analysis: In malnourished ICU patients, STD (vs PN) was associated with a significantly higher risk for mortality (RR, 3.0; 95% CI, 1.09-8.56) and a trend toward higher rate of infection (RR, 1.17; 95% CI, 0.88-1.56).

While supplemental PN provides additional calories and protein, it is a costly therapy that may or may not provide additional benefits when initiated within the first week of the ICU stay.[27]In an international multicenter observational study, initiation of supplemental PN early in the ICU stay was associated with slower recovery, more ICU infections, and increased cost.[28]There was no significant potential benefit even for patients at risk for iatrogenic malnutrition. Conversely, Wischmeyer et al's,[27] more recent pilot study, albeit underpowered for clinical outcomes, noted encouraging trends in mortality, quality of life, and functional end points with the use of supplemental PN. The pilot also showed signals of reduced mortality with the use of supplemental PN in high nutrition risk patients.

More studies are needed comparing the use of EN versus PN in patients of varying nutrition risk. At this time, evidence supports initiating EN (if feasible) prior to PN initiation, regardless of nutrition risk.

3. What Are the Most Common Noninfectious Complications Associated With EN Versus PN?

In studies comparing EN versus PN, the most common complications are divided into categories of infectious and noninfectious. Noninfectious complications include compartment syndrome, fluid overload, heart failure, and GI complications. Infectious and GI complications are discussed in another section.

In their retrospective study of ICU patients with acute mesenteric ischemia, Yang et al[29] divided patients into 2 groups based on the route of nutrition support during the first week: EN (n = 95) and PN (n = 88). Compared to the PN group, the EN group had fewer infectious complications (7.4% vs 20.5%, $P = .01$), a lower incidence of acute respiratory distress syndrome (4.2% vs 13.6%, $P < 0.01$), and a higher 1-year survival rate (88.4% vs 78.4%; $P = .031$) compared to the PN group. Enteral nutrition was also associated with earlier bowel continuity restoration ($P < .01$) and lower 30-day mortality (7.3% vs 26.1%, $P = .01$) and for patients without initial bowel resection (n = 82) significantly shorter ICU LOS and hospital LOS. These outcomes may be related to the PN catheterization and chemical composition that becomes a good nidus of bacteria to grow. There were no significant differences between groups regarding noninfectious complications (acute compartment syndrome, cardiac failure, and liver dysfunction).

Two larger and more recent RCTs comparing the use of early EN versus PN found no differences in the rates of secondary infections between the groups.[12,13] The CALORIES trial[12] randomized 2388 ICU patients to receive early EN or PN. Caloric intake was similar in the 2 groups although the target intake was not achieved in most patients. When compared to the EN group, the PN group had significant reductions in rates of hypoglycemia (44 patients [3.7%] vs 74 patients [6.2%]; $P = .006$) and vomiting (100 patients [8.4%] vs 194 patients [16.2%]; $P < .001$).

The meta-analysis by Elke et al,[14] which included the CALORIES trial[12] and other studies,[10,30-44] reported that early EN was associated with shorter ICU LOS and fewer infectious

complications compared to early PN. However, subgroup analyses suggested that these results might be affected by trials in which the energy intake was lower with EN than with PN.[12,13]

4. Is There Any Difference in Infectious Complications when Comparing the Use of EN Versus PN in Critically Ill Patients?

The majority of the studies we reviewed reported infection complications as one of the outcomes. Several of those trials[31,33,36,39-43,45] reported increased rates of infections in the PN group compared to the EN group. Elke et al[14] also reported in their meta-analysis that EN-fed patients had significantly fewer infections rates than their PN-fed counterparts (RR, 0.64; 95% CI 0.48-0.87, $P = .004$). This difference was maintained in subgroup analysis when the caloric intake was higher in the PN group (RR, 0.55; 95% CI 0.37-0.82, $P = .003$) but not when the caloric intake was similar between groups. The larger, more recent trials do not note differences in infection rates between the groups. In the CALORIES trial,[12] the number of treated infectious complications per patient was not significantly different between PN and EN groups. Similarly, the NUTRIREA-2 trial[13] saw no significant differences in the rates of ICU-acquired infection, ventilator-associated pneumonia, bacteremia, central line infection, urinary tract infection, soft tissue infection, or other infections between groups (although rates were higher in the PN group for the majority of these infections).

Multiple meta-analyses and systematic reviews have documented significant reductions in infectious morbidity with the use of EN (mainly pneumonia and central line infections).[14,16,26,33,35,46-49]

In summary, meta-analyses note an increased infection risk with PN although this finding is not supported by recent large RCTs.[12,13] This may be a result of increased calorie provision with PN. To quote Elke et al.'s conclusion in their meta-analysis, "Different treatment effect concerning infectious morbidity favoring EN must be interpreted in light of the observed differences in caloric intake."[14]

5. Is There a Significantly Increased Risk for Hyperglycemia With the Use of PN Versus EN?

The stress response leads to impaired glucose utilization and increased insulin resistance with resulting hyperglycemia.[50] Hyperglycemia superimposed on the stress response may lead to an impaired immune response and higher infection risk.[26] Meta-analyses and RCTs including critically ill patients with acute pancreatitis or other GI complications have noted increased rates of hyperglycemia with PN when compared to EN.[26,39,51] Increased PN caloric intake (36 kcal/kg/day) has been noted to be an independent risk factor for bloodstream infections.[52]

It was believed that the increased calorie and dextrose load from PN resulted in the increased hyperglycemia risk. Standard PN solutions contain 60% to 75% of energy as dextrose, whereas standard EN solutions contain 40% to 55% of energy as dextrose. In a subgroup meta-analysis of the Gramlich et al,[46] there was no difference in treatment effect between those studies in which the PN groups received more calories or had a higher incidence of hyperglycemia. An older meta-analysis evaluating studies from 1966 to 1999 noted increased hyperglycemia rates with PN compared to EN.[51] The authors, believing the increased hyperglycemia rates may be caused by increased calorie delivery from PN, more closely evaluated the calorie provision in 6 RCTs. In 1 RCT, patients randomly assigned to receive PN received less energy than EN patients; in 4 RCTs, PN and EN groups received approximately equal amounts of energy; and in another RCT, the PN group received greater calorie amounts than the EN group. In another study, McCowen et al.[53] compared hypocaloric PN (1 L of fat-free TPN to provide 1000 kcal, 70 g of protein, and 210 g of dextrose) with a standard weight-based PN (3-in-1 solution aiming to provide 25 kcal/kg/day with 1.5 g/kg/day protein). The authors noted that the treatment group received significantly less calories (daily average 14 $\pm$ 3 kcal/kg vs 18 $\pm$ 4 kcal/kg) and dextrose (daily average 187 $\pm$ 26 g/day vs 225 $\pm$ 41 g/day), yet the incidence of hyperglycemia in both groups was similar. However, the difference in provided dextrose, although statistically significant, may not have been clinically significant enough to impact serum glucose levels. On the other side, the NUTRIREA-2 trial[13] noted slightly lower calorie and protein intakes and higher frequencies of hypoglycemia in critically ill patients fed EN versus PN (HR, 2.26; 95% CI, 1.18-4.33).

At this time, it appears that hyperglycemia is not dependent on the amount of dextrose dispensed but instead may be attributed to the physiological disturbances in the release of biochemical mediators in response to PN.

6. Does EN Cause More GI Complications Versus PN?

The presence of appropriate nutrients within the GI lumen is necessary to maintain structural and functional gut integrity.[36,47] Exclusive PN use results in the absence of these nutrients in the gut's lumen. A possible physiological mechanism is that PN (and/or lack of enteral stimulation) leads to a breakdown of GI mucosal integrity, translocation of bacteria, and production of endotoxin leading to multi-organ failure and sepsis.[54]

Hadfield et al[10] conducted a trial with the aim to measure the effect of EN versus PN on gut mucosal permeability in adult ICU patients. All patients enrolled experienced reduced GI absorption and increased gut permeability. However, institution of EN decreased the rate of further gut permeability, whereas PN use perpetuated loss of mucosal integrity.

The more recent CALORIES trial[12] studying mixed populations of critically ill patients noted increased rates of nausea, vomiting, and abdominal distention with EN when compared to PN use, although this was not significant. Conversely, NUTRIREA-2[13] noted a significant increase in GI complications (vomiting [$P < .0001$], diarrhea [$P = .009$], bowel

ischemia [$P = .007$], and acute colonic pseudo-obstruction [$P = .004$]) with the use of EN compared to PN during shock. Therefore, the NUTRIREA-2 study findings support the ASPEN/SCCM recommendations[11] to postpone full EN until hemodynamic stability is restored and to prefer PN or no nutrition in patients at the worst end of the severity spectrum.

In view of recent findings, both EN and PN can cause GI complications. While EN is more associated with GI intolerance (nausea, vomiting), exclusive PN use is associated with increased gut permeability and associated infectious complications.

7. Is EN Use Associated With Decreased ICU and Hospital LOS When Compared to PN?

Multiple RCTs have not noted any difference between feeding routes on ICU LOS.[12,13,31,33,39,42] Recent studies have also not showed any difference in hospital LOS between EN and PN groups.[12,13,30,31,38-41] The 2 most recent and largest trials support these findings. Both the CALORIES[12] and the NUTRIREA[13] trials found no significant difference in the median days of ICU or hospital LOS between groups.

Several meta-analyses and systematic reviews expressed different point of views regarding this outcome.[14,16,46,48,55] Elke et al[14] found that EN was associated with a significant reduction in ICU LOS when compared to PN (95% CI, 1.23-0.37, $P = .0003$), but in subgroup analysis when the caloric intake was similar between the groups, the difference was not observed. In the same review, the hospital LOS was not different between the groups. Marik and Zaloga[16] reported significantly shorter hospital LOS in the EN group ($P < .001$) although with significant heterogeneity amongst studies. Peter et al found that hospital LOS and ICU LOS were significantly reduced in patients who received EN ($P < .004$ and $P = .008$, respectively). Other authors support the conclusion that no difference in ICU or hospital LOS exists between EN and PN groups.[46,48]

Based on the latest evidence available from trials with rigorous methodologies such as CALORIES and NUTRIREA and several meta-analyses, including the one done by Elke et al, which performed subgroup analysis, we state that there is no difference in the ICU or hospital LOS when the EN and PN are compared. None of the routes of nutritional support provides a significant benefit over the other regarding this outcome.

8. In Critically Ill Patients, Is EN or PN Superior in Reducing Mortality Risk?

Of the trials[30,31,37,39,42-45] included in the meta-analysis by Elke et al[14] that reported mortality rate as an outcome, no significant difference in mortality risk was seen between EN and PN groups. The CALORIES[12] and NUTRIREA-2[13] trials support this finding. The CALORIES trial[12] did not show any significant difference in 30-day mortality between the groups, even after subgroup analysis was performed. (Subgroups were defined according to age quartiles, the presence or absence of malnutrition, quartiles of APACHE II and ICNARC model, the presence or absence of mechanical ventilation, the presence or absence of cancer, and the time from ICU admission to the initiation of nutritional support [<24 hours or ≥24 hours]). Similar outcomes were presented in NUTRIREA-2[13]: There was no significant 28-day or 90-day mortality risk difference between PN and EN groups. When stratified by ICU and hospital mortality, the data were similar among groups and no variation was found.

In a recent meta-analysis with 16 RCTs,[14] no significant difference in overall mortality was seen between EN and PN groups. A subgroup analysis aggregating trials according to caloric intake also noted no significant mortality effect between groups provided similar calories or when the PN group received significantly more calories than the EN group. Another meta-analysis[46] looked at a subgroup of studies in which the PN group received more calories than the EN group and noted that the EN group was associated with a trend toward higher mortality rates (RR,1.58, 95%; CI, 0.75-3.35, $P = .2$). After aggregating trials in which EN and PN groups were fed isocalorically, the difference in mortality rate was no longer noted. The majority of similar meta-analyses also noted no significant mortality benefit with the use of EN versus PN,[16,26,48,55] while others found a mortality benefit in the use of PN (OR, 0.51, 95%; CI, 0.27-0.97, $P = .04$)[49] or EN (RR, 0.36, 95%; CI, 0.20-0.65, $P = .001$).[15] In summary, the mode of nutrition support does not seem to impact mortality risk.

9. Do Ventilator-Free Days Differ Between Patients Fed With EN Versus PN?

Of the RCTs we reviewed, seven reported data on mechanical ventilation days.[12,13,30,31,36,39,56] The trials failed to demonstrate any significant difference in the length of duration or ventilator support free days between EN group and PN groups. Previous meta-analyses also support this finding.[14,16,39] At this time, it seems that the route of nutritional support does not affect the time the critically ill patients spend on mechanical ventilation.

10. What Is the Effect of PN Versus EN on the Functional Status of Patients at Time of Hospital Discharge?

There are limited trials with mixed results on the impact of nutritional adequacy on the functional status and long-term outcomes of ICU patients. Even fewer studies exist comparing the effect of PN versus EN on functional outcomes. Greater provision of prescribed calories during the first week in the ICU has been associated with longer survival time and accelerated physical and neurological recovery 3 months (although not 6 months) post ICU discharge.[3,4] Conversely in acute lung injury patients, the EDEN trial[57] noted no difference in long-term outcomes between adequately fed and permissively underfed EN patients. Parenteral nutrition nutrient provision often surpasses EN provision within the first week of ICU stay due to EN intolerance or withholding for procedures. An older

study[32] noted that PN may be associated with better outcomes (such as higher Glasgow coma scores) after hospital discharge when compared to EN. However, this was thought to not necessarily be related to route of nutrition but rather the heightened nutritional adequacy from PN. Of note, although PN was initiated within 48 hours of admission in this study, it is unclear as to when EN was initiated. Enteral nutrition was only initiated after low gastric wall suction (an outdated routine practice) was no longer required. At this time, it is believed that *early* EN may have the greatest impact on postdischarge functional outcomes (although EN amount remains debatable).

11. How Cost-Effective Is PN Versus EN?

There are a few studies comparing the cost effectiveness of EN versus PN among the critically ill adult population. The critically ill population in these studies included patients with severe head injury leading to metabolic complications,[38] acute mesenteric ischemia,[29] multiorgan failure,[39] acute pancreatitis,[16] and upper GI malignancy requiring post-operative nutritional support.[58] The majority of these studies noted decreased health-care costs with EN related to decreases in complications, hospital LOS, and ICU LOS. However, one of these studies[58] evaluated the cost-effectiveness in more detail. The cost analysis of this study considered the instrumentation, monitoring evaluations, formulations of nutritional support, and sanitary personnel (physicians, nurses, technicians, pharmacists) needed for each mode of nutrition support. This study concluded that the mean daily cost of EN was 4-fold lesser than PN ($25 vs $90.60; $P < .001$). By using EN instead of PN, the daily savings was $65, and the mean saving for the entire duration of nutritional support (13 days) was $845 per patient. Although this study did not calculate the costs of complications or ICU and hospital LOS, the costs would definitely have been lower with the use of EN versus PN, since there was a 40% reduction in complications with the use of EN.

So far, EN can be recommended in terms of cost-effectiveness, although more research is needed to analyze daily costs among critically ill patients requiring nutritional support. The following variables should be considered in future studies analyzing cost differences between groups: cost of formulations of nutritional support, personnel required in a situation when complications arise (physician, consults, and consulting physicians such as anesthesiologists, surgeons, and infectious diseases specialists), additional drugs apart from antibiotics, mechanical ventilation, nurses, pharmacists, instrumentation, ICU LOS, and hospital LOS.

Conclusions

When not contraindicated, EN has been found to be safe and beneficial in many complex situations including pancreatitis, severe sepsis, postoperative EC fistulas following Whipple procedure, recent GI surgery, and in the setting of low, stable vasopressor doses. However, for patients receiving treatment for shock, the more recent NUTRIREA-2 trial noted that early EN did not reduce mortality or secondary infection risk but was associated with greater risk of digestive complications when compared to early PN. Malnourished patients are more likely to benefit from receiving goal rate EN within 24 to 48 hours of ICU admission or early PN (when EN is contraindicated) compared to patients at low nutrition risk. In regard to secondary infection rates, many recent RCTs found no differences between EN and PN groups, although the CALORIES trial noted significant reductions in hypoglycemia rates and vomiting episodes with PN. Regarding hyperglycemia, EN is associated with a lower risk than PN. While EN is associated with more GI intolerance (nausea and vomiting), exclusive PN use is associated with increased risk of gut permeability and associated infectious complications. Differences in hospital and ICU LOS between PN and EN use vary among studies; some note no difference, whereas other note decreased LOS with EN. Meta-analyses note an increased infection risk with PN although this finding is not supported by more recent large RCTs; the increased infection risk may be a result of increased calorie provision with PN. Regarding mortality risk, mode of nutrition support does not appear to impact risk. Length of ventilation duration (or ventilator support-free days) also does not appear to be associated with nutrition route. It is believed that *early* EN may have the greatest impact on postdischarge functional outcomes (although EN amount remains debatable). Enteral nutrition is typically more cost effective overall than PN.

Authors' Note

Angel Joel Cadena, MD, and Sara Habib, MD, contributed same effort to the development of this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Corkins MR, Guenter P, DiMaria-Ghalili RA, et al. Malnutrition diagnoses in hospitalized patients: United States, 2010. *JPEN J Parenter Enteral Nutr*. 2014;38(2):186-195.
2. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med*. 2009;35(10):1728-1737.
3. Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The Association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. *Crit Care Med*. 2015;43(8):1569-1579.
4. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated

patients suffering head injury. *Crit Care Med*. 1999;27(11): 2525-2531.
5. Heyland DK, Stephens KE, Day AG, McClave SA. The success of enteral nutrition and ICU-acquired infections: a multicenter observational study. *Clin Nutr*. 2011;30(2):148-155.
6. Elke G, Wang M, Weiler N, Day AG, Heyland DK. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. *Crit Care*. 2014;18(1):R29.
7. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and american society for parenteral and enteral nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2009;33(3):277-316.
8. Mochizuki H, Trocki O, Dominioni L, Brackett KA, Joffe SN, Alexander JW. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg*. 1984; 200(3):297-310.
9. Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? *JPEN J Parenter Enteral Nutr*. 2007;31(3):246-258.
10. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med*. 1995;152(5 Pt 1): 1545-1548.
11. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and american society for parenteral and enteral nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
12. Harvey SE, Parrott F, Harrison DA, et al. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). *Health Technol Assess*. 2016;20(28):1-144.
13. Reignier J, Boisrame-Helms J, Brisard L, et al. 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.
14. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1):117.
15. Yao H, He C, Deng L, Liao G. Enteral versus parenteral nutrition in critically ill patients with severe pancreatitis: a meta-analysis. *Eur J Clin Nutr*. 2018;72(1):66-68.
16. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*. 2004;328(7453):1407.
17. Elke G, Kuhnt E, Ragaller M, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. *Med Klin Intensivmed Notfmed*. 2013;108(3):223-233.
18. Klek S, Sierzega M, Turczynowski L, Szybinski P, Szczepanek K, Kulig J. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. *Gastroenterology*. 2011;141(1):157-163, 163 e151.
19. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care*. 2010;19(3):261-268.
20. Lee ZY, Heyland DK. Determination of nutrition risk and status in critically ill patients: what are our considerations? *Nutr Clin Pract*. 2019;34(1):96-111.
21. Kalaiselvan MS, Renuka MK, Arunkumar AS. Use of nutrition risk in critically ill (nutric) score to assess nutritional risk in mechanically ventilated patients: a prospective observational study. *Indian J Crit Care Med*. 2017;21(5):253-256.
22. Mendes R, Policarpo S, Fortuna P, et al. Nutritional risk assessment and cultural validation of the modified NUTRIC score in critically ill patients-A multicenter prospective cohort study. *J Crit Care*. 2017;37:249.
23. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet*. 2001;358(9292):1487-1492.
24. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011; 365(6):506-517.
25. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA*. 1998; 280(23):2013-2019.
26. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr*. 2001;74(4):534-542.
27. Wischmeyer PE, Hasselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. *Crit Care*. 2017;21(1):142.
28. Kutsogiannis J, Alberda C, Gramlich L, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. *Crit Care Med*. 2011;39(12):2691-2699.
29. Yang S, Guo J, Ni Q, et al. Enteral nutrition improves clinical outcome and reduces costs of acute mesenteric ischaemia after recanalisation in the intensive care unit. *Clin Nutr*. 2019;38(1): 398-406.
30. Rapp RP, Young B, Twyman D, et al. The favorable effect of early parenteral feeding on survival in head-injured patients. *J Neurosurg*. 1983;58(6):906-912.
31. Adams S, Dellinger EP, Wertz MJ, Oreskovich MR, Simonowitz D, Johansen K. Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. *J Trauma*. 1986;26(10):882-891.
32. Young B, Ott L, Twyman D, et al. The effect of nutritional support on outcome from severe head injury. *J Neurosurg*. 1987; 67(5):668-676.
33. Peterson VM, Moore EE, Jones TN, et al. Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic protein reprioritization. *Surgery*. 1988;104(2): 199-207.

34. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM. Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. *Surgery*. 1988;104(4): 727-733.
35. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma–reduced septic morbidity. *J Trauma*. 1989;29(7):916-922. discussion 922-913.
36. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg.* 1992;215(5):503-511. discussion 511-503.
37. Dunham CM, Frankenfield D, Belzberg H, Wiles C, Cushing B, Grant Z. Gut failure–predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma*. 1994; 37(1):30-34.
38. Borzotta AP, Pennings J, Papasadero B, et al. Enteral versus parenteral nutrition after severe closed head injury. *J Trauma*. 1994;37(3):459-468.
39. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg*. 1997;84(12):1665-1669.
40. Woodcock NP, Zeigler D, Palmer MD, Buckley P, Mitchell CJ, MacFie J. Enteral versus parenteral nutrition: a pragmatic study. *Nutrition*. 2001;17(1):1-12.
41. Casas M, Mora J, Fort E, et al.Total enteral nutrition vs. total parenteral nutrition in patients with severe acute pancreatitis. *Rev Esp Enferm Dig*. 2007;99(5):264-269.
42. Justo Meirelles CM, de Aguilar-Nascimento JE. Enteral or parenteral nutrition in traumatic brain injury: a prospective randomised trial. *Nutr Hosp*. 2011;26(5):1120-1124.
43. Wang G, Wen J, Xu L, et al. Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. *J Surg Res*. 2013;183(2):592-597.
44. Sun JK, Mu XW, Li WQ, Tong ZH, Li J, Zheng SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol*. 2013;19(6):917-922.
45. Sun B, Gao Y, Xu J, et al. Role of individually staged nutritional support in the management of severe acute pancreatitis. *Hepatobiliary Pancreat Dis Int*. 2004;3(3):458-463.
46. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition*.2004;20(10):843-848.
47. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. *Crit Care Med*. 2014;42(12):2600-2610.
48. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines C. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27(5):355-373.
49. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med*. 2005;31(1):12-23.
50. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care Med*. 2013;41(6):e93-e94.
51. Petrov MS, Whelan K. Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. *Br J Nutr*. 2010; 103(9):1287-1295.
52. Dissanaike S, Shelton M, Warner K, O'Keefe GE. The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care*. 2007;11(5):R114.
53. McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications–a randomized clinical trial. *Crit Care Med*. 2000;28(11):3606-3611.
54. Alverdy J, Stern E. Effect of immunonutrition on virulence strategies in bacteria. *Nutrition*. 1998;14(7-8):580-584.
55. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Crit Care Med*. 2005;33(1):213-220.discussion 260-211.
56. Chen Z, Wang S, Yu B, Li A. A comparison study between early enteral nutrition and parenteral nutrition in severe burn patients. *Burns*. 2007;33(6):708-712.
57. Needham DM, Dinglas VD, Bienvenu OJ, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *BMJ*. 2013;346:f1532.
58. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med*. 2001;29(2):242-248.