Parenteral nutrition in the critically-ill patient: more harm than good?

D. K. Heyland
Department of Medicine and Department of Community Health and Epidemiology, Queen’s University Faculty of Health Sciences, Kingston, Ontario K7L 2V7, Canada

While many studies have reported that providing parenteral nutrition (PN) can change nutritional outcomes, there are limited data that demonstrate that PN influences clinically-important end points in critically-ill patients. The purpose of the present paper is to systematically review and critically appraise the literature to examine the relationship between PN and morbidity and mortality in the critically-ill patient. Studies comparing enteral nutrition (EN) with PN and studies comparing PN with no PN were reviewed. The results suggest that EN is associated with reduced infectious complications in some critically-ill subgroups. PN, on the other hand, is associated with increased morbidity and mortality in critically-ill patients. When nutritional support is indicated, EN should be used preferentially over PN. Further studies are needed to define the optimal timing and composition of PN in patients not tolerating sufficient EN. Strategies to optimize EN delivery and minimize PN utilization in critically-ill patients are indicated.

Parenteral nutrition: Enteral nutrition: Critically-ill

Amongst seriously-ill hospitalized patients malnutrition has been associated with increased infectious morbidity, prolonged hospital stay and increased mortality (Reinhardt et al. 1980; Chandra, 1983; Windsor & Hill, 1988; Herrmann et al. 1992; Galanos et al. 1997). In critically-ill patients malnutrition results in impaired immunological function, impaired ventilatory drive and weakened respiratory muscles, leading to prolonged ventilatory dependence and increased infectious morbidity and mortality (Dark & Pingleton, 1993). Furthermore, the metabolic response to critical illness (or hypercatabolism) can lead to severe wasting of the lean body mass, impairment of visceral organ function and a decrease in the body’s reparative and immune function (Barton, 1994). Finally, beyond its digestive and absorptive capacities, the gastrointestinal tract is recognized for its immunological role and barrier function. Awareness of these associations and observations has led to the practice of providing nutritional support, either enterally (EN) or parenterally (PN), to critically-ill patients.

The administration of PN can clearly prevent the effects of starvation in patients with a non-functioning gastrointestinal tract (Dudrick et al. 1968). However, it is unclear whether PN can modulate the catabolic response to critical illness and reduce complications associated with hypercatabolism (Dempsey et al. 1988). In other terms, the administration of PN may result in significant improvement in weight, N balance, pre-albumin levels and other nutritional end points, but the effect on clinically-important end points in critically-ill patients, such as mortality and complications, is less certain. However, some patients with an intact gastrointestinal tract do not tolerate enteral feeds or do not receive sufficient intake enterally or orally to meet their energy and protein requirements. PN is used as a supplement or as the only source of nutrition in these patients (American Society for Parenteral and Enteral Nutrition Board of Directors, 1993; Cerra et al. 1997).

Evidence supporting this practice seems to be lacking (Deegan et al. 1999). The purpose of the present paper is to systematically review, critically appraise and statistically aggregate all studies evaluating the effect of PN on complication and mortality rates in critically-ill patients.

Critical appraisal of the evidence allows us to put forward clinical recommendations based on rules of evidence (Sackett, 1989). Strong clinical recommendations can be made (i.e. grade A recommendations) when supported by rigorous randomized trials in critically-ill patients with a low chance of error (level I evidence). Moderately-strong recommendations (grade B) can be made from randomized trials in critically-ill patients with a high risk of error (level II evidence). Weaker recommendations (grade C) are based on less-rigorous studies, or randomized trials in different patient populations, or randomized trials focusing on

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition; RR, risk ratio.
Corresponding author: Dr D. K. Heyland, fax +1 613 548 2577, email dkh2@post.queensu.ca

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surrogate outcomes. Finally, no recommendations are made in the present paper from evidence that comes from non-randomized studies in non-critically-ill patients, animal studies or studies based on biological rationale. This relationship between levels of evidence and grades of recommendations is outlined in Table 1.

### Methods

#### Search strategy

A computerized bibliographic search of Medline (including pre-Medline) from 1980 to 1999 to locate all relevant articles was conducted. The terms ‘randomized controlled trial’, ‘double-blind method’, ‘clinical trial’, ‘placebo’ and ‘comparative study’ were combined with ‘exp parenteral nutrition’, ‘total’, ‘enteral nutrition’, ‘intensive care units’ and ‘critical care’. Citations were limited to English-language studies reporting on adult patients. Reference lists of relevant review articles and personal files were also searched.

#### Study selection criteria

Primary studies were selected for inclusion in the present review article if they met the following criteria:

1. research design (randomized clinical trials);
2. population (surgical or critically-ill adult human subjects);
3. intervention (EN compared with PN, PN compared with no PN);
4. outcome (infectious morbidity, length of stay and mortality).

As studies in which treatment is allocated by any other method than randomization tend to show larger (and frequently ‘false-positive’) treatment effects than do randomized trials (Sacks et al. 1983), only randomized trials were included in the present review. Patients undergoing major surgery may not be cared for in a critical care environment in all cases, but share sufficient similarities in their response to illness that studies of surgical patients and critically-ill patients were combined. Studies of pediatric patients or neonates and studies of non-operative cancer patients were excluded. As the scope of the present review was defined by the research question, studies that only evaluated the impact of nutritional support on nutritional outcomes (i.e. N balance, amino acid profile etc.) were not included in the present paper. These end points were considered as surrogate end points (Fleming & DeMets, 1996); only papers that reported on clinically-important outcomes (morbidity and mortality) were included in the present review.

Ineligible studies were included in the introduction of each section to provide supportive evidence, but were not used to derive treatment recommendations.

#### Methodological quality of primary studies

The methodological quality of all selected articles was assessed by considering the extent to which blinding was present, consecutive patients were enrolled in the trial, whether groups were equal at baseline, if co-intervention was adequately described, whether objective definitions of infectious outcomes were employed and whether all patients were properly accounted for in the analysis (intention-to-treat analysis).

#### Data extraction

Data on methodological quality and outcomes were extracted from the primary papers. When data were missing or unclear, the primary investigators were contacted and requested to provide further information.

### Results

#### What is the effect of enteral nutrition compared with parenteral nutrition with respect to clinically-important outcomes?

There have been a number of randomized trials in human populations comparing EN with PN. Studies in patients undergoing head and neck surgery (Sako et al. 1981), liver transplantation (Wicks et al. 1994), major upper gastrointestinal surgery (Lim et al. 1981; Bower et al. 1986; Hamaoui et al. 1990; Baigrie et al. 1996) and patients with multiple organ dysfunction (Cerra et al. 1988) have demonstrated that enteral feeding is feasible, safe, cheaper and results in similar nutritional outcomes compared with PN. Compared with PN, critically-ill patients receiving EN have demonstrated better wound healing (Schröder et al. 1991) and a decrease in gastrointestinal tract mucosal permeability (Hadfield et al. 1995).

There are only a few studies that evaluate the relative merits of EN and PN in critically-ill patients and report on clinically-important outcomes. In trauma patients there were two small studies that found no difference between EN and PN (Adams et al. 1986; Dunham et al. 1994). Moore et al. (1989) found that enteral feeding resulted in similar N

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**Table 1. Levels of evidence and grades of recommendations**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Randomized trial in seriously-ill patients with low risk of error, i.e. blinded, objective criteria, intention-to-treat analysis</td>
<td>Grade A: Supported by level I evidence</td>
</tr>
<tr>
<td>Level 2: Randomized trial in seriously-ill patients with high risk of error, i.e. not blinded, objective criteria not used, non-intention-to-treat analysis</td>
<td>Grade B: Supported by at least one level II study</td>
</tr>
<tr>
<td>Level 3: Non-randomized trial of seriously-ill patients or randomized trial of non-seriously-ill patients or randomized trial of seriously-ill patients measuring surrogate outcomes</td>
<td>Grade C: No support from level I or II studies</td>
</tr>
<tr>
<td>Level IV: Non-randomized trial in non-seriously-ill patients or animal studies or biological rationale</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>
balance and energy intake compared with PN. However, they also found a lower incidence of major septic morbidity in the enterally-fed group. Seventy-five patients undergoing emergent laparotomy for blunt trauma were randomized to PN or EN. Objective criteria were used to define infectious outcomes, although investigators and clinicians were not blinded to treatment group allocation. Sixteen patients were excluded after randomization, leaving fifty-nine evaluable subjects. Five of twenty-nine (17 %) from the PN group compared with eleven of thirty (37 %) from the PN group (P > 0·05) developed septic complications. However, only one patient (3 %) in the EN group developed an intra-abdominal abscess compared with six patients (20 %) in the PN group who developed major septic complications (two had abdominal abscess, six had pneumonia, in the six patients; P = 0·03).

Kudsk et al. (1992) repeated the latter study in trauma patients with a broader range of severity of illness. In this randomized unblinded study using objective criteria to define outcomes, ninety-eight patients with abdominal trauma were allocated to enteral or parenteral feeding within 24 h of injury. Nine of fifty-one (18 %) patients who received EN developed septic complications compared with eighteen of forty-five (40 %) of the patients receiving PN (P < 0·02).

Moore et al. (1992) aggregated the results of eight studies, including six unpublished trials to evaluate EN compared with PN in surgical and trauma patients. The unpublished trials were not blinded, and septic complications were determined by a retrospective chart review without explicit criteria. Studies also varied in the nutritional formula used and the time of initiating nutritional support. When analysed according to the intention-to-treat method, the overall results showed that nineteen of 118 (16 %) patients receiving EN developed infectious complications compared with thirty-nine of 112 (35 %) receiving PN (P = 0·03).

In head-injured patients, the benefits of EN over PN are not as apparent. Two small studies of patients with head trauma did not detect a difference in nutritional and clinical outcomes between PN and EN (Hadley et al. 1986; Borzotta et al. 1994). Rapp et al. (1983) conducted a trial of thirty-eight head-injured patients who were randomly allocated to receive PN within 48 h or EN when bowel sounds were present. There was a significant difference in the N intake between the two groups, resulting in an improved N balance in those patients who received PN. Infectious outcomes were not reported. Nine of eighteen (50 %) patients fed enterally died, primarily of infectious causes, compared with three of thirty (10 %) patients who received PN. Later, this same research group repeated this study in fifty-one head-injured patients (Young et al. 1987). In this study, they again demonstrated a difference in nutritional outcomes, but there was no difference in overall infections and mortality between the two groups. However, patients fed enterally had a much higher incidence of aspiration pneumonia (nine of twenty-eight patients, 32 %) compared with patients receiving PN (three of twenty-three, 13 %; P = 0·11). It is hypothesized that head-injured patients have impaired gastric emptying (Ott et al. 1991) and lower oesophageal sphincter dysfunction (Saxe et al. 1994), placing them at high risk for aspiration pneumonia. In both studies patients with better nutritional variables had a better neurological recovery. Thus, the differences in clinical outcome could be ascribed to differences in energy and protein intake rather than differences in route of administration of nutrients. However, in another study of forty-five patients with head trauma, despite better energy intake and a more positive N balance associated with PN, there was no difference in clinical outcomes.

There are three small randomized controlled trials that compare the safety and efficacy of EN and PN in patients with acute pancreatitis. McClave et al. (1997) found nasojejunal feedings to be equally as safe and significantly less costly than PN, but were unable to demonstrate differences in complication rates or length of stay. Windsor et al. (1998) demonstrated that EN favourably modifies the inflammatory response associated with pancreatitis and results in a reduction in the requirement for intensive care and incidence in organ failure. Finally, Kalfarentzos et al. (1997) demonstrated that patients with acute severe pancreatitis fed enterally experienced fewer total complications (44 % v. 75 %; P < 0·05) and fewer septic complications (25 % v. 50 %; P < 0·01).

Summary. Randomized trials demonstrate that EN is associated with lower costs, improved nutritional outcomes, less mucosal permeability and greater wound healing than patients fed with PN (level III evidence). Small unblinded studies show a decrease in septic morbidity in enterally-fed patients with abdominal trauma and patients with pancreatitis (level II evidence).

In patients with pancreatitis or abdominal trauma, where possible, EN should be used preferentially over PN to meet the nutritional requirements of critically-ill patients (grade B recommendation). In head-injured patients either EN or PN would be an acceptable method of providing nutritional support (grade B recommendation). In all other critically-ill patients EN is the preferred method of providing nutritional support (grade C recommendation).

Impact of parenteral nutrition compared with no parenteral nutrition on mortality and complications rates

There are twenty-six randomized trials involving 2211 patients that compare the use of PN with standard care (usual oral diet plus intravenous fluids) in patients undergoing surgery (Abel et al. 1976; Holter & Fischer, 1977; Freund et al. 1979; Lim et al. 1981; Thompson et al. 1981; Yamada et al. 1983; Askanzki et al. 1986; Bower et al. 1986; Bellatone et al. 1988; Cerra et al. 1988; Meguid et al. 1988; Smith & Hartemink, 1988; Woolfson & Smith, 1989; Gys et al. 1990; Hamaoui et al. 1990; Schroeder et al. 1991; Von Meyenfeldt et al. 1992; Brennan et al. 1994; Fan et al. 1994; Hadfield et al. 1995; Jimenez et al. 1995; Baigrie et al. 1996), patients with pancreatitis (Sax et al. 1987), patients in an intensive care unit (Chiarelli et al. 1996) and patients with severe burns (Herdon et al. 1989). The details of individual studies, including the methodological quality score of each study, are described in Table 2. When the results of these trials were aggregated (Heyland et al. 1998), PN had no effect on mortality (risk ratio (RR) 1·03, 95 % CI 0·81, 1·31; see Fig. 1). The test for heterogeneity was not

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Table 2. Randomized studies evaluating total parenteral nutrition (PN) in critically-ill patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods score* (maximum 14)</th>
<th>Patients</th>
<th>Intervention</th>
<th>Major complications†</th>
<th>Mortality†</th>
<th>Hospital stay (d)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Veteran's Affairs Total Parenteral Nutrition Cooperative Study Group (1991)</td>
<td>10</td>
<td>100 % malnourished thoraco-abdo surgery (n 395); 7–15 d pre-op; lipids</td>
<td>49 of 192 (25-5)</td>
<td>31 of 231 (13-4)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Fan et al. (1989)</td>
<td>10</td>
<td>Surgery for oesophageal CA (n 40); 75 % malnourished</td>
<td>17 of 20 (85-0)</td>
<td>16 of 20 (30-0)</td>
<td>15 (No range specified)</td>
<td></td>
</tr>
<tr>
<td>Figueras et al. (1988)</td>
<td>7</td>
<td>GI surgery (n 49); 0 % malnourished</td>
<td>4 of 25 (16-0)</td>
<td>0 of 25 (0)</td>
<td>13 (SD 6)</td>
<td></td>
</tr>
<tr>
<td>Sandstrom et al. (1988)</td>
<td>10</td>
<td>Major surgery or trauma (n 300); 22 % malnourished</td>
<td>na</td>
<td>0 of 8 (0)</td>
<td>67 (SD 29)</td>
<td></td>
</tr>
<tr>
<td>Hwang et al. (1993)</td>
<td>5</td>
<td>Gastric surgery (n 42); 100 % malnourished</td>
<td>0 of 12 (0)</td>
<td>0 of 12 (0)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Müller et al. (1982)</td>
<td>3</td>
<td>GI surgery (n 125); 60 % malnourished</td>
<td>11 of 66 (16-6)</td>
<td>3 of 66 (4-5)</td>
<td>9 (SD 6)</td>
<td></td>
</tr>
<tr>
<td>Müller et al. (1986)</td>
<td>4</td>
<td>GI surgery (n 105); 100 % malnourished</td>
<td>17 of 46 (37-0)</td>
<td>10 of 46 (21-7)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Jimenez et al. (1995)</td>
<td>5</td>
<td>GI surgery (n 75); 100 % malnourished</td>
<td>6 of 60 (10-0)</td>
<td>4 of 60 (6-7)</td>
<td>16 (7–12)</td>
<td></td>
</tr>
<tr>
<td>Brennan et al. (1994)</td>
<td>8</td>
<td>Pancreatic resection (n 117); 58 % malnourished</td>
<td>27 of 60 (45-0)</td>
<td>4 of 60 (6-7)</td>
<td>17 (4–88)</td>
<td></td>
</tr>
<tr>
<td>Askanazi et al. (1986)</td>
<td>3</td>
<td>Radical cystectomy (n 35); 53 % malnourished</td>
<td>1 of 22 (4-5)</td>
<td>0 of 22 (0)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Thompson et al. (1981)</td>
<td>4</td>
<td>GI surgery (n 21); 100 % malnourished</td>
<td>2 of 12 (16-7)</td>
<td>0 of 12 (0)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Fan et al. (1994)</td>
<td>7</td>
<td>Surgery for hepatocellular CA (n 124); 26 % malnourished</td>
<td>22 of 64 (34-4)</td>
<td>5 of 64 (7-8)</td>
<td>19 (SD 6)</td>
<td></td>
</tr>
<tr>
<td>Abel et al. (1976)</td>
<td>4</td>
<td>Cardiac surgery (n 44); 100 % malnourished</td>
<td>1 of 20 (0)</td>
<td>0 of 15 (0)</td>
<td>18 (SD 6)</td>
<td></td>
</tr>
<tr>
<td>Bellantone et al. (1988)</td>
<td>6</td>
<td>GI surgery (n 100); 7 d pre-op; lipids</td>
<td>8 of 54 (14-8)</td>
<td>1 of 54 (1-9)</td>
<td>na (22466)</td>
<td></td>
</tr>
<tr>
<td>Smith &amp; Hartemirk (1988)</td>
<td>7</td>
<td>GI surgery (n 34); 100 % malnourished</td>
<td>3 of 17 (17-6)</td>
<td>1 of 17 (5-9)</td>
<td>44 (SD 13)</td>
<td></td>
</tr>
<tr>
<td>Holter &amp; Fischer (1977)</td>
<td>5</td>
<td>GI surgery (n 56); 100 % malnourished</td>
<td>4 of 30 (13-3)</td>
<td>2 of 30 (6-7)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Meguid et al. (1988)</td>
<td>4</td>
<td>GI surgery (n 64); 100 % malnourished</td>
<td>1 of 32 (3-1)</td>
<td>0 of 34 (0)</td>
<td>10 (6–30)</td>
<td></td>
</tr>
<tr>
<td>Woolfson &amp; Smith (1989)</td>
<td>10</td>
<td>Thoracic or abdominal surgery (n 122); 26 % malnourished</td>
<td>6 of 62 (9-7)</td>
<td>8 of 62 (12-9)</td>
<td>14 (9–64)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Methods score* (maximum 14)</td>
<td>Patients</td>
<td>Intervention</td>
<td>PN group</td>
<td>Control group</td>
<td>PN group</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td>Von Meyenfeldt et al. (1992)</td>
<td>7</td>
<td>GI surgery (n 101); 29 % malnourished</td>
<td>10 d pre-op; lipids</td>
<td>6 of 51 (11·8)</td>
<td>7 of 50 (14·0)</td>
<td>2 of 51 (3·9)</td>
</tr>
<tr>
<td>Yamada et al. (1983)</td>
<td>3</td>
<td>Gastric surgery (n 62); 0 % malnourished</td>
<td>Post-op; lipids</td>
<td>0 of 29 (0)</td>
<td>5 of 28 (17·9)</td>
<td>0 of 29 (0)</td>
</tr>
<tr>
<td>Gys et al. (1990)</td>
<td>7</td>
<td>Colo-rectal surgery (n 20); 0 % malnourished</td>
<td>Post-op; lipids</td>
<td>1 of 10 (10·0)</td>
<td>1 of 10 (10·0)</td>
<td>0 of 10 (0)</td>
</tr>
<tr>
<td>Freund et al. (1979)</td>
<td>8</td>
<td>GI surgery (n 35); 0 % malnourished</td>
<td>Post-op; no lipids</td>
<td>0 of 25 (0)</td>
<td>0 of 10 (0)</td>
<td>0 of 25 (0)</td>
</tr>
<tr>
<td>Sax et al. (1987)</td>
<td>8</td>
<td>Pancreatitis (n 54); 0 % malnourished</td>
<td>Post-admission; lipids</td>
<td>4 of 29 (13·8)</td>
<td>1 of 29 (3·4)</td>
<td>1 of 29 (3·4)</td>
</tr>
<tr>
<td>Chiarelli et al. (1996)</td>
<td>6</td>
<td>Neuro ICU patients (n 24); 0 % malnourished</td>
<td>Post-admission; both groups received EN</td>
<td>6 of 12 (50·0)</td>
<td>3 of 12 (25·0)</td>
<td>3 of 12 (25·0)</td>
</tr>
<tr>
<td>Herndon et al. (1989)</td>
<td>7</td>
<td>Burns &gt; 50 % (n 49); 0 % malnourished</td>
<td>Post-admission; no lipids; both groups received EN</td>
<td>na</td>
<td>10 of 16 (62·5)</td>
<td>6 of 23 (26·1)</td>
</tr>
</tbody>
</table>
significant ($P = 0.59$), although a visual inspection of Fig. 1 suggests that the treatment effects are variable.

Twenty-two studies reported major complications in study patients. When these results were aggregated there was a trend towards a reduction in complication rates in patients receiving PN (RR 0.84, 95% CI 0.64, 1.09; Fig. 2). The test for heterogeneity was significant ($P = 0.003$).

To better understand these findings, several *a priori* hypotheses were explored. First, those trials that included only malnourished patients were compared with other trials. There was no difference in mortality (see Fig. 3) between studies of malnourished patients (RR 1.13, 95% CI 0.75, 1.71) and studies that included adequately-nourished patients (RR 1.00, 95% CI 0.71, 1.39; for differences between subgroups $P = 0.64$). The rate of major complications was significantly lower among malnourished patients receiving PN (RR 0.52, 95% CI 0.30, 0.91). There was no difference in complication rates among studies of adequately-nourished patients (RR 1.02, 95% CI 0.75, 1.40). The difference in complication rates between these subgroups was significant ($P = 0.05$).

Next, trials with a methodological quality score of < 7 were compared with trials with a score of ≥ 7 (see Fig. 3). Trials with the higher score demonstrated no effect of PN on mortality (RR 1.17, 95% CI 0.88, 1.56). There was a trend towards a lower mortality rate in studies with a lower methodological quality score (RR 0.76, 95% CI 0.49, 1.19). The difference between these two subgroups was not within conventional levels of significance ($P = 0.12$). With respect to complication rates, studies with a higher score demonstrated no treatment effect (RR 1.18, 95% CI 0.89, 1.57). Studies with a lower score showed a significant reduction in complication rates associated with PN (RR 0.54, 95% CI 0.33, 0.87). The difference in complication rates between these subgroups was significant ($P = 0.02$).

Trials published before 1989 were then compared with trials published in 1989 or later (see Fig. 3). Trials published in 1988 or earlier demonstrated a trend towards a lower mortality associated with PN (RR 0.70, 95% CI 0.44, 1.13). Trials published since 1989 demonstrated no treatment effect (RR 1.18, 95% CI 0.89, 1.57). Differences between these two subgroups were not within conventional levels of statistical significance ($P = 0.07$). With respect to complication rates, in studies published in 1988 or earlier there were significantly fewer major complications associated with PN (RR 0.49, 95% CI 0.29, 0.81), while the studies published since 1989 showed no effect of PN on complication rates (RR 1.19, 95% CI 0.93, 1.53). The difference between these subgroups was significant ($P = 0.005$).

Studies that provided intravenous lipids as a component of PN administration were also compared with those studies

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**Fig. 1.** Risk ratios and associated 95% CI, represented by horizontal bars, for the effect of total parenteral nutrition (TPN) on mortality in critically-ill patients. Veterans Affairs (1991). The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group (1991). (From Heyland et al. 1998.)
that did not include lipids. In studies that used lipids (RR 1·03, 95% CI 0·78, 1·36) compared with those studies that did not (RR 0·98, 95% CI 0·49, 1·95) there was no difference in mortality (for the difference between subgroups \( P = 0·89 \)). With respect to complication rates, studies that used lipids compared with standard care demonstrated no effect (RR 0·96, 95% CI 0·69, 1·34). In studies of PN that did not contain lipids, the complication rate was significantly lower (RR 0·59, 95% CI 0·38, 0·90). The difference between these subgroups was just outside conventional levels of significance (\( P = 0·09 \)).

Finally, studies of critically-ill patients (patients cared for in a critical care environment) were compared with studies of primarily surgical patients. With respect to mortality, there was a higher mortality in critically-ill patients receiving PN (RR 1·78, 95% CI 1·11, 2·85), while studies of surgical patients showed no treatment effect (RR 0·91, 95% CI 0·68, 1·21). The differences between these groups was statistically significant (\( P = 0·03 \)). With respect to complication rates, there was a trend towards an increase in complication rate in the studies of critically-ill patients (only two studies reported complication rates; RR 2·40, 95% CI 0·88, 6·58), while studies of surgical patients were associated with lower complication rates (RR 0·76, 95% CI 0·48, 1·0). The difference between these subgroups was significant (\( P = 0·05 \)).

Only fourteen studies reported the impact of PN on duration of stay in hospital; five reporting median stay, nine reporting mean stay. In eight studies the duration of stay in hospital was shorter in the control group. Due to the variability in duration of stay and variability of reporting methods, we did not statistically aggregate these results but they are displayed in Table 2.

**Summary.** A meta-analysis of several level I and level II randomized trials fails to demonstrate any significant difference in morbidity and mortality associated with the supplemental use of PN. There may be a reduction in complication rates in malnourished patients, but this reduction is not supported by recent trials or trials with higher methodological quality scores. The results of the subgroup analysis suggest that both mortality and complication rates may be increased in critically-ill patients receiving PN, and these treatment effects may differ from the results in surgical patients. Thus, there are no data from randomized trials to support the use of PN in patients with an intact gastrointestinal tract (grade A recommendation).

![Fig. 2. Risk ratios and associated 95% CI, represented by horizontal bars, for the effect of total parenteral nutrition (TPN) on rate of major complications in critically-ill patients, Veterans Affairs (1991), The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group (1991). (From Heyland et al. 1998.)](https://doi.org/10.1017/S002966510000063X)
Timing and Composition of PN in Patients Who Do Not Routine Use.

Further studies are needed to clarify the optimal intact gastrointestinal PN is not recommended for and mortality in critically-ill patients. For the patient with an suggest that PN may be associated with increased morbidity and pancreatitis. In other patient populations data are insufficient to make strong conclusions about the benefits of EN over PN. However, the studies that compare the use of PN with no PN (standard care plus intravenous fluids) suggest that PN may be associated with increased morbidity and mortality in critically-ill patients. For the patient with an intact gastrointestinal tract PN is not recommended for routine use. Further studies are needed to clarify the optimal timing and composition of PN in patients who do not tolerate sufficient energy enterally. Consistent with findings of the present review, there are some experimental and clinical data that suggest that intravenously-administered lipid emulsions may have an adverse effect on immune function and clinical outcomes (Seidner et al. 1989; Bastitstella et al. 1997).

In the absence of further data clarifying the role of PN in critically-ill patients, strategies to optimize the use of EN and minimize the use of PN need to be further evaluated. Up to 60 % of patients receiving nutrition support in intensive care units across Europe are receiving PN (Preiser et al. 1999). There is tremendous cross country (and probably cross hospital) variation in utilization of PN. In one hospital, using a multi-disciplinary multifaceted approach to providing nutrition support, clinicians were able to reduce the use of PN from 61 % of critically-ill patients receiving nutrition support in 1992 to 11 % in 1998 (Keefe et al. 2000). Aligning the provision of nutrition support to critically-ill patients with the ‘best evidence’ available currently will probably result in improved clinical outcomes and significant cost savings.

Conclusion

The pioneering work of many investigators has led us to understand the important role that malnutrition and nutrition plays in critical illness. While providing nutritional support to seriously-ill patients can alter nutritional outcomes, there are few randomized controlled trials demonstrating that any form of nutritional support improves the morbidity and mortality of such patients. Moreover, the majority of studies demonstrating any benefit to nutritional support are in surgical or severely-traumatized patients. Yet, in practice, we generalize this data to all types of critically-ill patients.

It would appear that EN is associated with a reduction in infectious complications, especially in patients with trauma and pancreatitis. In other patient populations data are insufficient to make strong conclusions about the benefits of EN over PN. However, the studies that compare the use of PN with no PN (standard care plus intravenous fluids) suggest that PN may be associated with increased morbidity and mortality in critically-ill patients. For the patient with an intact gastrointestinal tract PN is not recommended for routine use. Further studies are needed to clarify the optimal timing and composition of PN in patients who do not tolerate sufficient energy enterally. Consistent with findings of the present review, there are some experimental and clinical data that suggest that intravenously-administered lipid emulsions may have an adverse effect on immune function and clinical outcomes (Seidner et al. 1989; Bastitstella et al. 1997).

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