Enteral compared with parenteral nutrition: a meta-analysis1,2

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ABSTRACT

Background: The difference in outcomes in patients is unclear when 2 types of enteral nutrition, ie, tube feeding and conventional oral diets with intravenous dextrose (standard care), are compared with parenteral nutrition.

Objective: We reviewed systematically and aggregated statistically the results of prospective randomized clinical trials (PRCTs) to examine the relations among the nutrition interventions, complications, and mortality rates.

Design: We conducted a MEDLINE search for PRCTs comparing the effects of enteral and parenteral nutrition in adults. Two different people abstracted data for the method and outcomes separately. We used fixed-effects meta-analysis technique to combine the relative risks (RRs) of the outcomes of infection, nutrition support complications, other complications, and mortality.

Results: Twenty-seven studies in 1828 patients met the study criteria. Aggregated results showed a significantly lower RR of infection with tube feeding (0.64; 95% CI: 0.54, 0.76) and standard care (0.77; 95% CI: 0.65, 0.91). A priori hypotheses showed a lower RR of infection with tube feeding than with parenteral nutrition, regardless of nutritional status, presence of cancer, year of study publication, or quality of the study method. In studies in which participants had high rates of protein-energy malnutrition, there was a significantly higher risk of mortality (3.0; 95% CI: 10.9, 8.56) and a trend toward a higher risk of infection with standard care than with parenteral nutrition (1.17; 95% CI: 0.88, 1.56). Conclusions: Tube feeding and standard care are associated with a lower risk of infection than is parenteral nutrition; however, mortality is higher and the risk of infection tends to be higher with standard care than with parenteral nutrition in malnourished populations.

KEY WORDS Meta-analysis, enteral nutrition, parenteral nutrition, prospective randomized clinical trials, tube feeding, oral diets, intravenous dextrose, MEDLINE

INTRODUCTION

Parenteral nutrition is an invasive therapy that provides nutrition support for persons who do not have adequate gastrointestinal functions; however, it does have inherent risks (1). Enteral nutrition, specifically tube feeding, is the preferred method of feeding because it is cheaper, has fewer complications, and has better outcomes than does parenteral nutrition. A review of the prospective randomized clinical trials (PRCTs) that compared tube feeding with parenteral nutrition cast doubt on some of these generally accepted benefits (2). The review, although comprehensive, did not systematically compile results or evaluate the quality of the studies’ methods, and it also included many studies conducted in populations that would not be considered candidates for parenteral nutrition by today’s standards. Heyland et al (3) conducted a meta-analysis of PRCTs that evaluated the outcomes of parenteral nutrition compared with those of standard care (conventional oral diets with intravenous dextrose) in surgical or critically ill patients. They found that parenteral nutrition did not influence mortality rates; however, a trend toward fewer complications, particularly in populations that had protein-energy malnutrition (PEM), was reported. Their analysis included studies that provided parenteral nutrition in amounts less than the estimated energy and protein needs of the patients and trials conducted in populations with functional gastrointestinal tracts. Both of these factors could have reduced the influence of parenteral nutrition on outcomes. Also, they did not include investigations that compared parenteral nutrition with tube feeding. The purpose of this paper was to review systematically and aggregate statistically the PRCTs that were conducted in populations appropriate for random assignment to parenteral nutrition and to compare the effects of parenteral nutrition with those of aggressive enteral nutrition (tube feeding) and limited nutritional intervention (standard care) on outcomes in which parenteral nutrition was provided at or above estimated energy needs.

METHODS

Sources and criteria of PRCT selection

MEDLINE (National Library of Medicine, Bethesda, MD) was searched for PRCTs that evaluated the effects of parenteral nutrition compared with tube feeding or standard care and that were conducted from 1966 to November 1999. Only PRCTs that evaluated the effect of parenteral nutrition administered at or above estimated energy needs compared with those of tube feeding or standard care on outcomes with clinical significance (morbidity and mortality) were reviewed; studies that evaluated only...
the effect on nutritional outcomes (eg, nitrogen balance and serum protein) were not included because these were considered surrogate endpoints. Studies were limited to the ones that involved English-speaking adult patients. Reference lists from studies found by the search were reviewed for additional reports. Also, Ronald Koretz provided a list of all the studies published about nutrition support that he had compiled for >20 y; some of these were found in his manual search of the literature that was completed for the Cochrane Collaboration, which publishes electronically the COCHRANE DATABASE OF SYSTEMATIC REVIEWS (The Cochrane Library, Oxford, United Kingdom).

Nutritional interventions

Parenteral nutrition is designed to provide nutrition to patients who cannot be nourished adequately by enteral nutrition for a critical period of time. Because of the inherent risk and higher cost of parenteral nutrition, it should not be used as a substitute for enteral nutrition if either standard care or tube feeding is feasible. Also, because of physiologic changes that are caused by gastrointestinal tract dysfunction, outcomes observed in populations with functional gastrointestinal tracts might be different from those observed in populations without adequate gastrointestinal function. The criteria met by populations included in the meta-analysis are listed in Table 1. Tube feeding was defined as either surgical or nonsurgical placement of a small flexible tube into the gastrointestinal tract to provide required nutrients. Standard care was defined as the gradual reintroduction of an oral diet as tolerated after its interruption was caused by a disease or a surgical procedure that resulted in several days of inadequate nutrient intake and the use of intravenous dextrose or fluids for hydration.

Outcome descriptions and data extraction

The primary outcomes assessed were infection, nutrition support complications, other complications, and mortality. Only deaths that occurred during a patient’s hospitalization were included. The specific disorders included within each outcome category are shown in Table 2. “Other complications” included any reported major or minor complication that developed during hospitalization but were not included as an infection or nutrition support complication. The definitions of the variables given by the authors were used unless they indicated otherwise. All data were generated on a per-patient basis. Unclear data and data presented as total complications instead of complications per patient were not included. Patients recruited into the study were recorded as the total number included in each treatment arm. Thus, all of our relative risks (RRs) were calculated on the basis of intent-to-treat numbers. Two of the meta-analysis investigators, whose ratings for study-quality scores and outcomes were blinded to one another, reviewed and extracted data with the use of preset criteria. Disagreements among ratings in study evaluations were resolved by consensus.

Study-quality score and subgroup analysis

Because differences in study populations and design might cause variations in results, 4 sources for heterogeneity were defined a priori: 1) study-quality score, 2) year of study publication, 3) nutritional status of patients, and 4) percentage of patients with cancer.

The method used in each study was evaluated for the quality of these characteristics: concealed randomization, comparability of groups at baseline, endpoints (blinded to staff or not), well-described treatment protocols, well-defined outcomes, and analysis by intent to treat. One point was given for each of these traits and a study-quality score that ranged from 0 to 6 for each investigation was calculated. Studies were categorized into those with low study-quality score (<4 points) and those with a high study-quality score (≥4 points), and separate subgroup analyses were performed for each category.

PEM in hospitalized patients has been associated with high rates of morbidity and mortality (4–6). To address this possible source of heterogeneity, the nutritional status of patients at the time of enrollment was examined. Each investigator’s definition of PEM was used when possible. When this was not specifically stated, an unplanned body weight loss of ≥15% of normal body weight was used as the cutoff for PEM classification. Studies were categorized into 2 groups on the basis of the percentage of participants with PEM (% PEM) those with <50% (low) and those with ≥50% (high), and the subgroups were analyzed separately.

The skill with which specialized nutrition support is provided has improved since it was first used in patient care. To assess whether time-induced changes led to discrepant results, studies were divided into equal groups of those that were relatively recent (1992 or later) and those that were not recent (earlier than 1992) publications, and separate subgroup analyses were performed for each category.

### Table 1

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorptive syndromes with severe food, electrolyte, and fluid losses not adequately managed by oral or enteral nutrition</td>
<td>Severe short-bowel syndrome</td>
</tr>
<tr>
<td>Motility disorders</td>
<td>Those induced by infection, inflammatory, and immunologic disorders, drugs, or radiation</td>
</tr>
<tr>
<td>Mechanical intestinal obstruction not immediately remedied by surgery</td>
<td>High-output gastrointestinal fistulas that enteral intubation cannot bypass</td>
</tr>
<tr>
<td>Perioperative state with severe undernutrition</td>
<td>Severe renal tubular defects with large fluid and ion losses</td>
</tr>
<tr>
<td>Critically ill patients, especially those with hypermetabolism, who are not appropriate for enteral nutrition because it was contraindicated or failed</td>
<td>Persistent ileus (postoperative or disease related)</td>
</tr>
<tr>
<td>—</td>
<td>Severe intestinal pseudoobstruction</td>
</tr>
<tr>
<td>—</td>
<td>Severe persistent vomiting caused by medication, brain tumor, or other disorder (eg, hyperemesis gravidarum)</td>
</tr>
</tbody>
</table>

Adapted from reference 1.
TABLE 2
Primary outcome categories of meta-analysis

<table>
<thead>
<tr>
<th>Primary outcome category</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Catheter sepsis, Pneumonia, Abscess, Empyema, Infection, Blood, Urine, Wound, Intraabdominal</td>
</tr>
<tr>
<td>Nutrition support</td>
<td>Parenteral or enteral nutrition technical problems, Pneumothorax, Hemothorax, Subclavian artery puncture, Cardiac perforation and tamponade, Brachial plexus injury, Innominate or subclavian vein laceration, Carotid artery injury, Thromboembolism, Catheter embolism, Catheter malposition, Thoracic duct laceration, Subclavian hematoma, Subclavian air embolism, Mechanical problems, Dislodged or occluded tube or catheter, Aspiration, Vomiting, diarrhea, or constipation, Fistula at catheter or tube site, Hyperglycemia, Deep vein thrombosis, Laryngeal nerve palsy, Fistulas, Intestinal obstruction, Hemorrhage, Aspiration, Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Other complications</td>
<td>Organ failure, Hepatic, Renal, Respiratory, Cardiac, Reoperation, Pancreatitis, Anastomotic leak, Pulmonary emboli, Myocardial infarct or arrhythmia, Coronary vascular accident, Gastric outlet obstruction, Aortic aneurysm, Deep vein thrombosis, Laryngeal nerve palsy, Fistulas, Intestinal obstruction, Hemorrhage, Aspiration, Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Mortality</td>
<td>—</td>
</tr>
</tbody>
</table>

1\(^{a}\) Caused by catheter or tube insertion.
2\(^{a}\) Caused by feeding.
3\(^{a}\) Required medical treatment or a feeding that lasted for ≥24 h.
4\(^{a}\) Hyperglycemia: glucose >11 mmol/L (>200 mg/dL).

Finally, because previous investigations reported little or no effect of specialized nutrition support on outcomes in cancer patients (7), we speculated that differences in outcomes might be caused by the presence of cancer in the patients. Therefore, the studies were categorized into 2 groups on the basis of the percentage of participants with cancer: <50\% (low) and ≥50\% (high), and the subgroups were analyzed separately.

Analysis

The PRCTs were divided into 2 categories: 1) tube feeding compared with parenteral nutrition and 2) standard care compared with parenteral nutrition. This categorization allowed for the examination of aggregated differences observed in outcomes when the route of aggressive nutrition support varied (tube feeding compared with parenteral nutrition) and when aggressive intravenous nutrition support was compared with little or no nutritional intervention (standard care compared with parenteral nutrition). To avoid the loss of each group's independence, meta-analysis techniques were used to prevent any group from being compared with more than one other group. For example, a parenteral nutrition group could not be compared with a tube-fed group and then with a standard care group because it would then not be an independent comparison. Hence, 5 investigations used a method to randomly assign patients that resulted in some of the groups being eliminated from our analysis. Holter and Fischer (8) and Thompson et al (9) randomly assigned patients to normally nourished standard care control, malnourished parenteral nutrition, and malnourished standard care groups; only the malnourished parenteral nutrition and standard care groups were included in the analysis. Greenberg et al (10) randomly assigned patients to parenteral nutrition, tube-fed, partial parenteral nutrition, and partial standard care groups; only those in the parenteral nutrition and tube-fed groups were included in the analysis. Dunham et al (11) randomly assigned patients to parenteral nutrition, tube-fed, partial parenteral nutrition, and partial enteral nutrition groups; only those randomly assigned to the parenteral nutrition and tube-fed groups were included in the analysis. Von Meyenfeldt et al (12) randomly assigned patients to 4 groups: malnourished parenteral nutrition, malnourished tube-fed, malnourished standard care, and normally nourished standard care groups; only the malnourished parenteral nutrition and tube-fed groups were included. RR\(s\) and 95\% CIs were calculated for each investigation and for each outcome variable. A fixed-effects meta-analysis technique modeled after the Mantel-Haenszel method was used to estimate summary RRs and their 95\% CIs (13). CIs for the common RR that did not include unity were considered significant. To determine whether the investigations within each group for each outcome had widely discrepant RRs, a test for heterogeneity was done (14). We considered \(P < 0.05\) to be statistically significant.

RESULTS

Seventy-six citations were identified in the MEDLINE search and 22 additional studies were obtained from Koretz’ list. Of these studies, 27 met our inclusion criteria and included a total of 1829 patients (\(n = 895\) enteral nutrition, \(n = 934\) parenteral nutrition) with compromised gastrointestinal function caused by pancreaticitis (15–17), ulcerative colitis (18), Crohn disease (10), surgery (8–9, 12, 19–31), trauma (11, 32–35), or multisystem organ failure (36). The 27 PRCTs are referenced in Table 3, including information on study-quality scores, PEM, and outcomes.

Effect of tube feeding compared with parenteral nutrition on risk of outcomes

Twenty studies in 1033 patients had information that allowed the calculation of the RRs of the primary outcome...
variables and compared tube feeding with parenteral nutrition \((n = 508 \text{ tube feeding}, n = 525 \text{ parenteral nutrition})\). When the results of these trials were aggregated, tube feeding was associated with a significantly lower risk of infection (Figure 1) (RR: 0.66; 95% CI: 0.56, 0.79). The test for heterogeneity was not significant. Risk of nutrition support complications was higher for tube feeding than for parenteral nutrition (Figure 2) (RR: 1.36; 95% CI: 0.96, 1.83); however, the strength of this association is questionable because the test for heterogeneity was significant \(P = 0.03\). No treatment effect for tube feeding was observed for other complications (Figure 3) (RR: 0.92; 95% CI: 0.71, 1.22) or for mortality (Figure 4) (RR: 0.96; 95% CI: 0.55, 1.65).

Tube feeding was associated with a lower risk of infection in all subgroup categories (Figure 5). A significantly higher risk of nutrition support complications was seen for tube feeding in studies published in 1992 or earlier (RR: 2.12; 95% CI: 1.43, 3.14) and in studies with higher study-quality scores (RR: 2.22; 95% CI: 1.4, 3.53) than for parenteral nutrition. When the results of the risk of other complications and mortality (Figures 3 and 4) and their subgroup analyses (Figure 6 and Figure 7) were aggregated, they were not significantly different.

**Effect of standard care compared with parenteral nutrition on risk of outcomes**

Seven studies in 798 patients \((n = 387 \text{ standard care}, n = 409 \text{ parenteral nutrition})\) compared standard care with parenteral nutrition and had information that allowed the calculation of the RRs of the primary outcome variables. When the results of these trials were aggregated, a significantly lower risk of infection (RR: 0.77; 95% CI: 0.65, 0.91; Figure 1) and a trend toward fewer other complications (RR: 0.87; 95% CI: 0.74, 1.03; Figure 3) were found for those randomly assigned to standard care than for those assigned to parenteral nutrition. The test for heterogeneity for the aggregated RR of infection was significant \(P = 0.03\). Only 2 studies reported data that allowed for the calculations of the RRs of nutrition support complications. Thus, this outcome could not be aggregated meaningfully. There were no significant differences in aggregated risk of mortality (RR: 1.14; 95% CI: 0.69, 1.88; Figure 4).

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**Table 3**

Prospective randomized clinical trials of enteral nutrition (EN; tube feeding or standard care) compared with parenteral nutrition (PN)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of subjects</th>
<th>Study-quality score</th>
<th>PEM(^1) Cancer(^2)</th>
<th>Infection</th>
<th>Nutrition support complications</th>
<th>Other complications</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EN</td>
<td>PN</td>
<td>EN</td>
<td>PN</td>
<td>EN</td>
<td>PN</td>
<td>EN</td>
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<tr>
<td>Tube feeding</td>
<td>23</td>
<td>23</td>
<td>3</td>
<td>0</td>
<td>No</td>
<td>15 (65)</td>
<td>17 (74)</td>
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<tr>
<td>Adams et al, 1986</td>
<td>50</td>
<td>47</td>
<td>2</td>
<td>0</td>
<td>No</td>
<td>2 (4)</td>
<td>10 (21)</td>
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<tr>
<td>Baigrie et al, 1996</td>
<td>33</td>
<td>37</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sako et al, 1981</td>
<td>33</td>
<td>36</td>
<td>3</td>
<td>0</td>
<td>No</td>
<td>1 (9)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Greenberg et al, 1998</td>
<td>19</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hamaoui et al, 1990</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>Yes</td>
<td>1 (9)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Ioivinelli et al, 1993</td>
<td>24</td>
<td>24</td>
<td>3</td>
<td>0</td>
<td>Yes</td>
<td>5 (241)</td>
<td>4 (17)</td>
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<td>Kalfarentzos et al, 1997</td>
<td>18</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>No</td>
<td>6 (33)</td>
<td>15 (75)</td>
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<td>Kudsk et al, 1992</td>
<td>52</td>
<td>46</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>9 (17)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>Kudsk et al, 1994</td>
<td>34</td>
<td>34</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>5 (15)</td>
<td>14 (41)</td>
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<td>12</td>
<td>12</td>
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<tr>
<td>Clavell et al, 1997</td>
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<td>4</td>
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<td>Moore et al, 1989</td>
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<td>30</td>
<td>5</td>
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<td>5 (17)</td>
<td>11 (37)</td>
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<tr>
<td>Reynolds et al, 1997</td>
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<td>4</td>
<td>81</td>
<td>Yes</td>
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<td>33</td>
<td>36</td>
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<td>8</td>
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<td>Sand et al, 1997</td>
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<td>0</td>
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<td>Shirabe et al, 1997</td>
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<td>3</td>
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<td>8 (62)</td>
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<tr>
<td>Von Meyenfeldt et al, 1992</td>
<td>50</td>
<td>51</td>
<td>4</td>
<td>100</td>
<td>Yes</td>
<td>30 (60)</td>
<td>43 (84)</td>
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<tr>
<td>Standard care</td>
<td>57</td>
<td>60</td>
<td>3</td>
<td>0</td>
<td>Yes</td>
<td>20 (35)</td>
<td>36 (60)</td>
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<tr>
<td>Brennan et al, 1994</td>
<td>26</td>
<td>30</td>
<td>4</td>
<td>100</td>
<td>Yes</td>
<td>1 (4)</td>
<td>2 (7)</td>
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<td>Holter and Fischer, 1977</td>
<td>59</td>
<td>66</td>
<td>2</td>
<td>60</td>
<td>Yes</td>
<td>38 (64)</td>
<td>36 (55)</td>
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<td>Muller et al, 1993</td>
<td>150</td>
<td>150</td>
<td>5</td>
<td>22</td>
<td>Yes</td>
<td>57 (38)</td>
<td>91 (61)</td>
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<td>Sandstrom et al, 1993</td>
<td>26</td>
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<td>3</td>
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<td>9</td>
<td>12</td>
<td>3</td>
<td>100</td>
<td>Yes</td>
<td>2 (22)</td>
<td>3 (25)</td>
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<td>Thompson et al, 1981</td>
<td>60</td>
<td>62</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>4 (7)</td>
<td>7 (11)</td>
</tr>
</tbody>
</table>

\(^1\)PEM, protein-energy malnutrition ≥ 50%.

\(^2\)Studies in which ≥ 50% of the study population had cancer.
In studies in populations with high percentages of PEM, standard care was associated with a significantly higher risk of mortality (RR: 3.0; 95% CI: 1.09, 8.56; Figure 7) and a trend toward a higher risk of infection (RR: 1.17, 95% CI: 0.88, 1.56; Figure 5) than was parenteral nutrition. The risk of infection was found to be lower for standard care than for parenteral nutrition in the relatively recent studies (RR: 0.62; 95% CI: 0.50, 0.76), studies with low rates of PEM (RR: 0.61; 95% CI: 0.50, 0.76), studies with a high percentage of patients with higher study-quality scores (RR: 0.63; 95% CI: 0.49, 0.80), and studies with a high percentage of patients with cancer (RR: 0.78; 95% CI: 0.65, 0.92; Figure 5). Subgroup analyses could not be completed for nutrition support complications because of the insufficient number of studies that reported this information. The risk of other complications was lower for standard care than for parenteral nutrition in studies with lower study-quality scores (RR: 0.61; 95% CI: 0.4, 0.91).

Additional analysis for other complications could not be completed because of the inadequate numbers in the different categories.

To determine whether the lower risk of infection observed with enteral nutrition was due to the categorization of catheter sepsis as an infection instead of a nutritional support complication, these events were removed. The RRs and 95% CIs were recalculated for studies that reported them, and new aggregated RRs were calculated. There were a total of 36 reported events of catheter sepsis (n = 2 tube feeding compared with n = 23 parenteral nutrition; n = 1 standard care compared with n = 10 parenteral nutrition). The risk of infection remained significantly lower in a comparison of parenteral nutrition for both tube feeding and standard care (RR: 0.70; 95% CI: 0.58, 0.83) and standard care (RR: 0.79; 95% CI: 0.67, 0.94). To determine whether the higher risk of nutrition support complications in tube-fed populations was due to the exclusion of catheter sepsis from the analysis.
this category, this event was categorized as a nutrition support complication. The RRs and 95% CIs were recalculated for studies that reported them, and new aggregated RRs were calculated. The risk of nutrition support complications was reduced from 1.35 to 1.05, and the CI included unity (95% CI: 0.79, 1.4).

**DISCUSSION**

Our primary objective was to determine whether aggregated results of PRCTs supported the use of tube feeding instead of parenteral nutrition. An additional objective was to determine whether the risk of infection, nutrition support complications, other complications, and mortality were greater with standard care or with parenteral nutrition. We found that both tube feeding and standard care were associated with a lower risk of infection than was parenteral nutrition, and this lower risk was not an artifact of whether catheter sepsis was included in our analysis. For tube feeding, this lower risk remained regardless of the presence of cancer, nutritional status, year of study publication, or study-quality score.

It was reported in animals that enteral nutrition more so than parenteral nutrition lowers the risk of infection by preserving the gastrointestinal tract’s integrity and enhancing its ability to provide an immunocompetent barrier to endogenous gut bacteria, which prevents the occurrence of bacterial translocation (37–39); however, the role that enteral nutrition plays in preventing bacterial translocation in human investigations is still debated (40). We cannot suggest that our findings support the hypothesis of a protective role for aggressive enteral nutrition (tube feeding) in preventing bacterial translocation because there are several aspects of our meta-analysis design that prohibited this. Specifically, none of the studies included in our analysis investigated bacterial translocation as a primary hypothesis, and all types of infection were grouped together within our infection category, which further limited interpretation. Also, we cannot determine from our results whether aggressive enteral nutrition reduced the risk of infection or whether parenteral nutrition led to a higher risk of infection. Our finding of fewer infections associated with both tube feeding and standard care than with parenteral nutrition in normally nourished populations suggests that it is not that enteral nutrition does not result in a lower risk of infection but rather that parenteral nutrition results in a higher risk of infection.

The higher risk of infection associated with parenteral nutrition may be partially explained by the higher number of patients with hyperglycemia in this population. Elevated glucose concentrations reduce neutrophil chemotaxis and phagocytosis and were found to be an independent risk factor for short-term infection in patients undergoing coronary artery surgery (41). Of the 20 trials that compared tube feeding with parenteral nutrition, 16 included data on infection (12, 15, 16, 18, 19, 21–27, 32–35) and 7 reported data on hyperglycemia (15, 16, 18, 20, 21, 22, 23), 6 of which reported data on both infection and hyperglycemia (15, 16, 18, 19, 21, 22, 23). In all of these investigations, hyperglycemia occurred more frequently in patients who received parenteral nutrition than in those who were tube fed; however, because of the way the data were presented, it was not possible to discern whether persons with infection were also those with hyperglycemia. To be included in this meta-analysis, feeding protocols for both tube feeding and parenteral nutrition had to provide energy at or above estimated needs; however, tube-fed patients frequently receive less than the amount prescribed because of feeding intolerance and interruptions. To
determine whether the hyperglycemia reported was caused by
the greater energy infusion received by parenteral nutrition than
by tube feeding, the 5 investigations that reported both infection
and hyperglycemia were reviewed. Patients randomly assigned
to receive parenteral nutrition received less energy than did the
tube-fed patients in one investigation (18), approximately equal
amounts in 4 investigations (15, 16, 22, 23), and greater amounts
in one investigation (21). Thus, the hyperglycemia was not
called by a difference in the amounts of energy that were dis-
pensed. Standard parenteral nutrition solutions contain 60–75%
of energy as dextrose, whereas standard tube feeding solutions
contain 40–55% of energy as dextrose. Metabolic alterations
that accompany the stress response result in more endogenous
insulin resistance and reduced capacity to oxidize plasma
insulin directly (42). The higher incidence of hyperglycemia
caused by excessive glucose loads that are superimposed on
the stress response in parenteral nutrition may lead to an
impaired immune response that contributes to the observed
higher risk of infection.

Overall, a significantly higher risk of nutrition support com-
plications was found to be associated with tube feeding than
with parenteral nutrition, although there was significant hetero-
genosity ($P = 0.04$). When separated into the a priori categories,
these results remained, and heterogeneity was not significant in
the relatively recent studies or in those with higher study-quality
score. Many of the complications (eg, diarrhea and abdomi-
nal distention) associated with tube feeding occur frequently but
are considered to be less severe clinically than are those associ-
ated with parenteral nutrition. To address this, the less severe
complications of tube feeding, such as diarrhea, vomiting, and
ileus, were limited to the instances in which they required med-
ication or feedings to be stopped for ≥24 h. Thus, although 8
of the 20 studies that compared tube feeding with parenteral nutri-
tion reported diarrhea, our definitions restricted its inclusion as
a nutrition support complication to just 3 studies, and there were
no instances of vomiting or ileus with use of the modified crite-
ria. The technical risks involved with inserting and maintaining
feeding tubes can be significant and are often underestimated.
Six of the 20 trials that compared tube feeding with parenteral nutri-
tion reported problems with feeding tube placement and main-
tenance and accounted for 14% (9 of 66) of the reported nutrition
support complications. As previously discussed, catheter
sepsis, a severe complication associated with parenteral nutrition,
was categorized as an infection instead of as a nutrition
support complication. When catheter sepsis was categorized as
a nutrition support complication, the differences in the risk of
nutrition support complications between tube feeding and par-
tenteral nutrition were eliminated (RR: 1.05; 95% CI: 0.79, 1.4).

Our findings of a substantial risk of these various untoward
events caused by both tube feeding and parenteral nutrition
were based on definitions that minimized the inclusion of med-
ically insignificant events. They illustrate the need to weigh
these risks against the potential benefits before the initiation of
either type of nutrition support.

The nutritional status of patients influenced the risk of infec-
tion and mortality in trials that compared standard care with
parenteral nutrition but not in trials that compared tube feeding
with parenteral nutrition. When aggregated, standard care was
associated with a higher risk of infection and mortality in the 3
trials of populations that had high percentages of PEM; how-
ever, in the 4 trials of normally nourished populations, it was
associated with a lower risk of infection. These findings illus-
strate 2 major points: 1) failure to provide adequate nutrition to
populations with PEM is associated with untoward conse-
quences, and 2) parenteral nutrition should not be initiated in
normally nourished populations, unless there is a good reason
to do so.

The issue of the number of days to wait before initiating
enteral or parenteral nutrition in normally nourished populations
is complex and frequently discussed. The goal is to prevent
deterioration in nutritional status, which precipitate poorer out-
comes; however, it must be determined whether the benefit of the
intervention exceeds its risk. Ascertaining the number of days to
wait before the initiation of aggressive nutrition support was not
one of our selected objectives; however, several of the PRCTs
reviewed in this meta-analysis addressed this issue. Sandstrom
et al (30) reported that 60% of their patients began eating on
their own 8–9 d after surgery, and those that had not begun eat-
ing by 14 d had significantly higher mortality rates than those
randomly assigned to the parenteral nutrition group that
did not have complications or to the standard care group that had
debegan eating before 14 d. Sax et al (17) and Brennan et al (28)
found that an average of 12 d was required for parenteral nutri-
tion patients to consume adequate energy orally. Several of the
trials that compared tube feeding with parenteral nutrition
reported the number of days required for adequate oral intake.
McClave et al (16) found that patients who received parenteral
nutrition required 7.1 ± 1.1 d and tube-fed patients required
5.6 ± 0.8 d to begin oral intake. Adams et al (32) reported that
87% of parenteral nutrition patients began oral intake 10 ± 6 d
after injury, and Sako et al (25) found that a mean of 20 d was
required for parenteral nutrition patients to resume an adequate
oral intake. Collectively, these results suggest that most normally
nourished patients begin to eat 6–10 d after surgery or a hospital
admission for a disease that necessitates bowel rest can achieve
an adequate oral intake within 6–20 d. Our findings suggest that
7–10 d is a reasonable amount of time to wait before initiating
parenteral nutrition in normally nourished patients who have not
begun eating spontaneously.

The limitations of our study were similar to those for any
meta-analysis of PRCTs. For example, each author used differ-
ent definitions for the outcome variables evaluated. Thus, there
was a concern that we were comparing “apples with oranges.” A
meta-analysis of small trials may overestimate treatment effects
(43), and only 5 of the 27 studies reviewed had >50 patients
per treatment group. Other concerns were the paucity of PRCTs
in populations with PEM and the scarcity of PRCTs that
compared standard care with parenteral nutrition and that
reported nutritional support complications and other complica-
tions. These concerns limited our ability to make generalized
practice recommendations.

A goal of this meta-analysis was to provide an interim guide
for clinical decision-making until the results of large trials con-
ducted in populations with marginal gastrointestinal function
are available. A comprehensive search of the literature was done
with the use of clinically relevant criteria for both study selec-
tion and assessed outcomes. In a broad spectrum of patients
with compromised gastrointestinal function with tube feeding,
we found fewer infections in those who were tube-fed than in
those who received parenteral nutrition. These findings were
similar, although not as strong, in a comparison of standard care
with parenteral nutrition in normally nourished patients. We
also found a higher risk of nutrition support complications with tube feeding than with parenteral nutrition. Collectively, these results suggest that waiting 7–10 d to initiate any form of aggressive nutrition intervention may be prudent for normally nourished populations with compromised gastrointestinal function. Studies that compare outcomes of tube feeding with those of standard care are needed to guide clinicians, hospital administrators, and third-party payers in their decision-making.

REFERENCES