

# Enteral compared with parenteral nutrition: a meta-analysis<sup>1,2</sup>

Carol L Braunschweig, Paul Levy, Patricia M Sheehan, and Xin Wang

## 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. *Am J Clin Nutr* 2001;74:534–42.

**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

<sup>1</sup>From the Department of Human Nutrition and Dietetics and the Division of Epidemiology, University of Illinois at Chicago.

<sup>2</sup>Address reprint requests to CL Braunschweig, University of Illinois at Chicago, Department of Human Nutrition, 1919 W Taylor Street (M/C 517), Chicago, IL 60612. E-mail: braunsch@uic.edu.

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**TABLE 1**  
Criteria met by study populations included in meta-analysis<sup>1</sup>

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

<sup>1</sup>Adapted from reference 1.

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 pre-

sented 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 2**  
Primary outcome categories of meta-analysis

Primary outcome category	Disorder	
Infection	Catheter sepsis	
	Pneumonia	
	Abscess	
	Empyema	
	Infection	
	Blood	
	Urine	
	Wound	
	Intraabdomen	
	Nutrition support complications	Parenteral or enteral nutrition technical problems <sup>1</sup>
		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 <sup>2</sup>		
Vomiting, diarrhea, or constipation <sup>3</sup>		
Fistula at catheter or tube site		
Hyperglycemia <sup>4</sup>		
Other complications	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	
Mortality	—	

<sup>1</sup>Caused by catheter or tube insertion.

<sup>2</sup>Caused by feeding.

<sup>3</sup>Required medical treatment or a feeding that lasted for  $\geq 24$  h.

<sup>4</sup>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 per-

centage of participants with cancer:  $< 50\%$  (low) and  $\geq 50\%$  (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.

RRs 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 pancreatitis (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



**TABLE 3**

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

Reference	Number of subjects		Study-quality score	PEM <sup>1</sup>	Cancer <sup>2</sup>	Outcomes							
	EN	PN				Infection		Nutrition support complications		Other complications		Mortality	
						EN	PN	EN	PN	EN	PN	EN	PN
					%	n (%)							
<b>Tube feeding</b>													
Adams et al, 1986 (32)	23	23	3	0	No	15 (65)	17 (74)	14 (61)	9 (39)	4 (17)	4 (17)	1 (4)	3 (13)
Baigrie et al, 1996 (19)	50	47	2	0	No	2 (4)	10 (21)	10 (20)	14 (30)	15 (30)	23 (49)	4 (8)	6 (13)
Bower et al, 1986 (20)	10	10	3	35	No	0	0	3 (30)	2 (20)	0	0	0	0
Cerra et al, 1988 (36)	33	37	5	0	No	0	0	25 (76)	9 (24)	7 (21)	7 (19)	7 (21)	8 (22)
Dunham et al, 1994 (11)	12	15	5	0	No	0	0	2 (17)	2 (13)	0	0	1 (8)	1 (7)
Gonzalez-Huiz et al, 1993 (18)	23	21	3	39	No	1 (4)	8 (38)	1 (4)	3 (14)	11 (52)	11 (52)	0	0
Greenberg et al, 1998 (10)	19	32	4	0	No	0	0	0	0	0	0	0	0
Hamaoui et al, 1990 (21)	11	8	4	0	Yes	1 (9)	0	1 (9)	1 (13)	0	0	1 (9)	0
Iovinelli et al, 1993 (22)	24	24	3	0	Yes	5 (24)	4 (17)	0	7 (29)	1 (4)	2 (8)	0	0
Kalfarentzos et al, 1997 (15)	18	20	3	0	No	6 (33)	15 (75)	4 (22)	9 (45)	2 (11)	7 (35)	1 (6)	2 (10)
Kudsk et al, 1992 (33)	52	46	5	0	No	9 (17)	18 (39)	1 (2)	0	3 (6)	4 (9)	1 (2)	1 (2)
Kudsk et al, 1994 (34)	34	34	5	0	No	5 (15)	14 (41)	0	0	0	0	1 (3)	0
Lim et al, 1981 (23)	12	12	2	100	Yes	5 (42)	5 (42)	0	1 (8)	7 (58)	3 (25)	2 (17)	1 (8)
McClave et al, 1997 (16)	16	16	4	0	No	2 (12)	2 (12)	5 (31)	5 (31)	0	0	0	0
Moore et al, 1989 (35)	29	30	5	0	No	5 (17)	11 (37)	0	0	6 (21)	7 (23)	0	0
Reynolds et al, 1997 (24)	33	34	4	81	Yes	10 (30)	19 (56)	3 (9)	0	11 (33)	6 (18)	2 (6)	1 (3)
Sako et al, 1981 (25)	33	36	3	38	Yes	3 (9)	2 (6)	0	2 (6)	6 (18)	6 (17)	0	3 (8)
Sand et al, 1997 (26)	13	16	3	0	Yes	3 (23)	5 (31)	0	0	3 (23)	3 (19)	0	1 (6)
Shirabe et al, 1997 (27)	13	13	3	0	Yes	1 (8)	8 (62)	0	0	0	0	0	0
Von Meyenfeldt et al, 1992 (12)	50	51	4	100	Yes	30 (60)	43 (84)	0	2 (4)	10 (20)	10 (20)	4 (8)	2 (4)
<b>Standard care</b>													
Brennan et al, 1994 (28)	57	60	3	0	Yes	20 (35)	36 (60)	0	2 (3)	18 (32)	35 (58)	1 (2)	4 (7)
Holter and Fischer, 1977 (8)	26	30	4	100	Yes	1 (4)	2 (7)	0	0	5 (19)	4 (13)	2 (8)	2 (7)
Muller et al, 1982 (29)	59	66	2	60	Yes	38 (64)	36 (55)	0	2 (3)	0	0	11 (19)	3 (5)
Sandstrom et al, 1993 (30)	150	150	5	22	Yes	57 (38)	91 (61)	9 (6)	12 (8)	89 (59)	95 (63)	10 (7)	12 (8)
Sax et al, 1987 (17)	26	29	3	0	No	1 (4)	3 (10)	0	2 (7)	0	1 (3)	1 (4)	1 (3)
Thompson et al, 1981 (9)	9	12	3	100	Yes	2 (22)	3 (25)	0	1 (8)	0	0	0	0
Wolfson and Smith, 1989 (31)	60	62	5	0	No	4 (7)	7 (11)	22 (37)	16 (26)	4 (7)	6 (10)	8 (13)	8 (13)

<sup>1</sup>PEM, protein-energy malnutrition ≥50%.

<sup>2</sup>Studies in which ≥50% of the study population had cancer.

variables and compared tube feeding with parenteral nutrition ( $n = 508$  tube feeding,  $n = 525$  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)

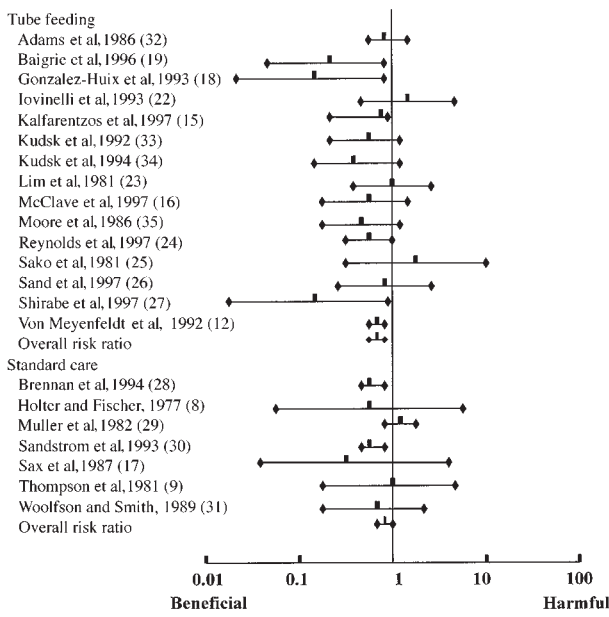
and their subgroup analyses (**Figure 6** and **Figure 7**) were aggregated, they were not significantly different.

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

Seven studies in 798 patients ( $n = 387$  standard care,  $n = 409$  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**).

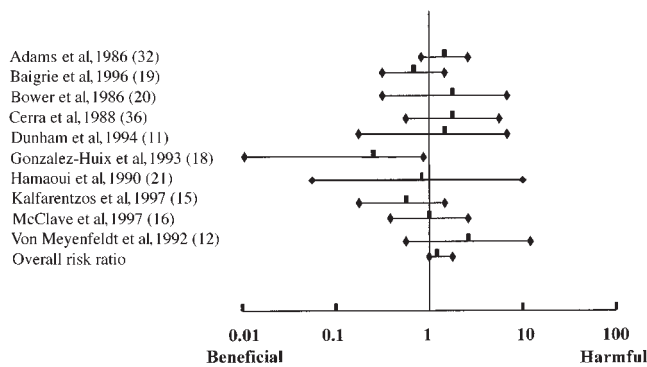




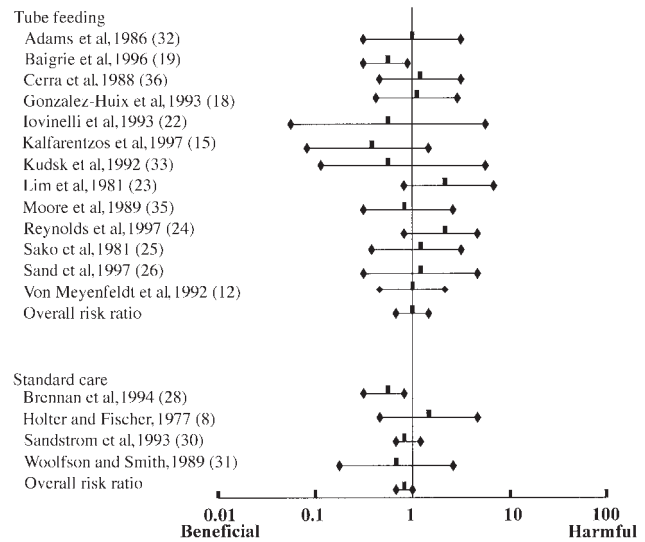


**FIGURE 1.** Risk factors and associated 95% CIs for the effect of enteral nutrition (tube feeding or standard care) compared with that of parenteral nutrition on infection.

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).



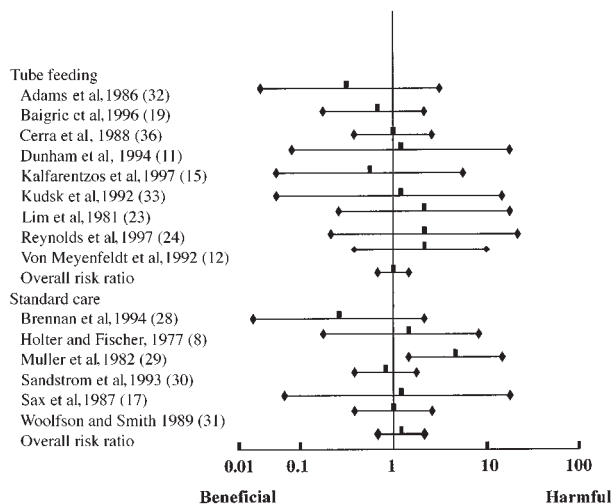
**FIGURE 2.** Risk factors and associated 95% CIs for the effect of enteral nutrition (tube feeding) compared with that of parenteral nutrition on nutrition support complications.



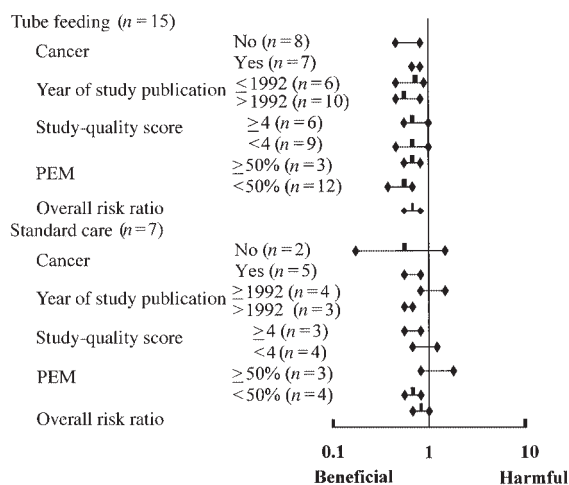
**FIGURE 3.** Risk factors and associated 95% CIs for the effect of enteral nutrition (tube feeding or standard care) compared with that of parenteral nutrition on other complications.

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



**FIGURE 4.** Risk factors and associated 95% CIs for the effect of enteral nutrition (tube feeding or standard care) compared with that of parenteral nutrition on mortality.



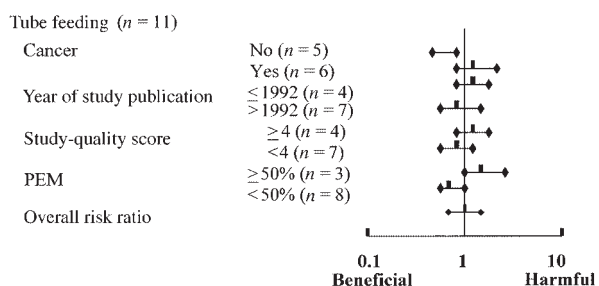
**FIGURE 5.** Results of subgroup analyses of the effect of enteral nutrition (tube feeding or standard care) compared with that of parenteral nutrition on infection. PEM, protein-energy malnutrition.

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).

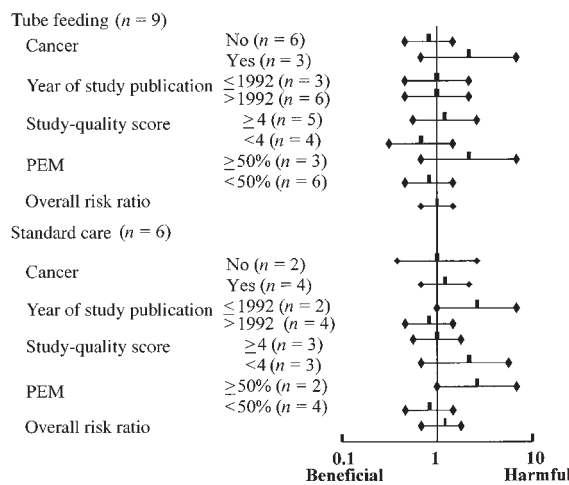
**DISCUSSION**

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 does 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 bac-



**FIGURE 6.** Results of subgroup analyses of the effect of enteral nutrition (tube feeding) compared with that of parenteral nutrition on other complications. PEM, protein-energy malnutrition.



**FIGURE 7.** Results of subgroup analyses of the effect of enteral nutrition (tube feeding or standard care) compared with that of parenteral nutrition on mortality. PEM, protein-energy malnutrition.

teria, 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, 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 caused by a difference in the amounts of energy that were dispensed. 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 glucose production and reduce the capacity to oxidize plasma glucose 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 complications was found to be associated with tube feeding than with parenteral nutrition, although there was significant heterogeneity ( $P = 0.04$ ). 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 abdominal distention) associated with tube feeding occur frequently but are considered to be less severe clinically than are those associated 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 medication or feedings to be stopped for  $\geq 24$  h. Thus, although 8 of the 20 studies that compared tube feeding with parenteral nutrition 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 criteria. The technical risks involved with inserting and maintaining feeding tubes can be significant and are often underrated. Six of the 20 trials that compared tube feeding with parenteral nutrition reported problems with feeding tube placement and maintenance 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 parenteral 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 medically 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 infection 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; however, in the 4 trials of normally nourished populations, it was


associated with a lower risk of infection. These findings illustrate 2 major points: 1) failure to provide adequate nutrition to populations with PEM is associated with untoward consequences, 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 a deterioration in nutritional status, which precipitate poorer outcomes; 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 eating by 14 d had significantly higher mortality rates than did those randomly assigned to the parenteral nutrition group that did not have complications or to the standard care group that had begun eating before 14 d. Sax et al (17) and Brennan et al (28) found that an average of 12 d was required for parenteral nutrition 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  $7.1 \pm 1.1$  d and tube-fed patients required  $5.6 \pm 0.8$  d to begin oral intake. Adams et al (32) reported that 87% of parenteral nutrition patients began oral intake  $10 \pm 6$  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 different 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 complications. 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 conducted 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 selection 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 in both normally nourished and malnourished populations are needed. Finally, studies comparing the costs associated with providing either tube feeding or parenteral nutrition with those of standard care are needed to guide clinicians, hospital administrators, and third-party payers in their decision-making. 

## REFERENCES

- Shils ME, Brown RO. Parenteral nutrition. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern nutrition in health and disease*. 9th ed. Baltimore: Williams & Wilkins, 1999:1658.
- Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. *JPEN J Parenter Enteral Nutr* 1998;22:167–82.
- Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient. *JAMA* 1998;280:2013–9.
- Naber T, Schermer T, de Bree A, et al. Prevalence of malnutrition in nonsurgical hospitalized patients and its association with disease complications. *Am J Clin Nutr* 1997;66:1232–9.
- Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: a prospective study. *JAMA* 1999;281:2013–9.
- Braunschweig C, Gomez S, Sheehan PM. Impact of declines in nutritional status on outcomes in long-term adult hospitalized patients. *J Am Diet Assoc* 2000;100:1316–22.
- Klein S, Koretz RL. Nutrition support in patients with cancer: what do the data really show? *Nutr Clin Pract* 1994;9:91–100.
- Holter AR, Fischer JE. The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. *J Surg Res* 1977;23:31–4.
- Thompson BR, Julian TB, Stremple JF. Perioperative total parenteral nutrition in patients with gastrointestinal cancer. *J Surg Res* 1981;30:497–500.
- Greenberg GR, Fleming CR, Jeejeebhoy KN, Rosenberg IH, Sales D, Tremain WJ. Controlled trial of bowel rest and nutritional support in the management of Crohns disease. *Gut* 1988;29:1309–15.
- Dunham CM, Frankenfield D, Beizberg H, Wiles C, Cushing B, Grant Z. Gut failure—predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994;37:30–4.
- Von Meyenfeldt MF, Meijerink WJHJ, Rouflart MMJ, Builmaassen MTHJ, Soethers PB. Perioperative nutritional support: a randomised clinical trial. *Clin Nutr* 1992;11:180–6.
- Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *JASA* 1963;58:690–700.
- Mantel N, Brown C, Byar DP. Tests for homogeneity of effect in an epidemiologic investigation. *Am J Epidemiol* 1977;106:125–9.
- Kalfarentzos R, 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;84:1665–9.
- McClave SA, Greene LM, Snider HL, et al. Comparison of the safety of early enteral vs. parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enteral Nutr* 1997;21:14–20.
- Sax HC, Warner BW, Talamini MA, et al. Early total parenteral nutrition in acute pancreatitis: lack of beneficial effects. *Am J Surg* 1987;153:117–24.
- Gonzalez-Huix F, Fernandez-Banares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;88:227–32.
- Baigrie RJ, Devitt PG, Watkin DS. Enteral versus parenteral nutrition after oesophagogastric surgery: a prospective randomized comparison. *Aust N Z J Surg* 1996;66:668–70.
- Bower RH, Talamini MA, Sax HC, Hamilton F, Fischer JE. Postoperative enteral vs parenteral nutrition. *Arch Surg* 1986;121:1040–5.
- Hamaoui E, Lefkowitz R, Olender L, et al. Enteral nutrition in the early postoperative period: a new semi-elemental formula versus total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1990;14:501–7.
- Iovinelli G, Marsil I, Varrassi G. Nutrition support after total laryngectomy. *JPEN J Parenter Enteral Nutr* 1993;17:445–8.
- Lim STK, Choa RG, Lam KH, Wong J, Ong GB. Total parenteral nutrition versus gastrostomy in the preoperative preparation of patients with carcinoma of the oesophagus. *Br J Surg* 1981;68:69–72.
- Reynolds JV, Kanwar S, Welsh FKS, et al. Does the route of feeding modify gut barrier function and clinical outcome in patients after major upper gastrointestinal surgery? *JPEN J Parenter Enteral Nutr* 1997;21:196–201.
- Sako K, Lore JM, Kaufman S, Razack M, Bakamjian V, Reese P. Parenteral hyperalimentation in surgical patients with head and neck cancer: a randomized study. *J Surg Oncol* 1981;16:391–402.
- Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomised pilot study. *Eur J Surg* 1997;163:761–6.
- Shirabe K, Matsumata T, Shimada M, et al. A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection—the results of a randomized prospective study. *Hepatogastroenterology* 1997;44:205–9.
- Brennan MF, Pisters PW, Posner M, Quesada O, Hike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Ann Surg* 1994;220:436–44.
- Muller JM, Brenner U, Dienst C, Pichlmaier H. Preoperative parenteral feeding in patients with gastrointestinal carcinoma. *Lancet* 1982;1:68–79.
- Sandstrom R, Drott C, Hyltander A, Arfvidsson B, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993;217:185–95.
- Woolfson AMJ, Smith JAR. Elective nutritional support after major surgery: a prospective randomised trial. *Clin Nutr* 1989;8:15–21.
- 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;26:882–91.
- Kudsk KA, Croce M, Fabian TC, et al. Enteral versus parenteral feeding. *Ann Surg* 1992;215:503–11.
- Kudsk KA, Minard G, Wojtysiak SL, Croce M, Fabian T, Brown RO. Visceral protein response to enteral versus parenteral nutrition and sepsis in patients with trauma. *Surgery* 1994;116:516–23.
- Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma—reduced septic morbidity. *J Trauma* 1986;29:916–22.
- Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM. Enteral nutrition does not prevent multiple organ failure syndrome after sepsis. *Surgery* 1988;104:727–33.
- Levine GN, Derin JJ, Steiger E, Zinno R. Role of oral intake and maintenance of gut mass and disaccharide activity. *Gastroenterology* 1974;67:975–82.
- Purandare S, Offenbartl K, Westerom B, Bengmark S. Increased gut permeability to floresein isothiocyanate-dextran after total parenteral nutrition in the rat. *Scand J Gastroenterol* 1989;24:678–82.



39. Deitch EA, Winterton J, Ma L, Berg R. The gut is a portal of entry for bacteremia: role of protein malnutrition. *Ann Surg* 1987;13:565–71.
40. Lipman TO. Bacterial translocation and enteral nutrition in humans: An outsider looks in. *JPEN J Parenter Enteral Nutr* 1995;19:156–65.
41. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999;22:1404–8.
42. Shaw JH, Wolfe RR. An integrated analysis of glucose, fat and protein metabolism in severely traumatized patients. Studies in the basal state and the response to total parenteral nutrition. *Ann Surg* 1989;209:63–72.
43. Petitti DB. Limitations. In: Petitti DB, ed. *Meta-analysis, decision analysis and cost-effectiveness analysis*. 2nd ed. Oxford, United Kingdom: Oxford University Press, 2000:263–71.

