

Early enteral nutrition in acutely ill patients: A systematic review

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Objective: To evaluate the effect of early enteral nutrition on the outcome of critically ill and injured patients.

Data Sources: MEDLINE, citation review of relevant primary and review articles, personal files, and contact with expert informants.

Study Selection: Randomized, controlled studies that compared early with delayed enteral nutrition in hospitalized adult postoperative, trauma, head-injured, burn, or medical intensive care unit (ICU) patients. From 161 articles screened, 27 were identified as randomized, controlled trials comparing early with delayed enteral nutrition and were included for data extraction. Of these, 12 were excluded. None of the studies included medical ICU patients.

Data Extraction: Fifteen studies containing 753 subjects were analyzed. Descriptive and outcome data were extracted independently from the articles by the two reviewers. Main outcome measures were infections, noninfectious complications, length of hospital stay, and mortality. The meta-analysis was performed using the random effects model.

Data Synthesis: Early enteral nutrition was associated with a significantly lower incidence of infections (relative risk reduction, 0.45; 95% confidence interval, 0.30–0.66; $p = .00006$; test for heterogeneity, $p = .049$) and a reduced length of hospital stay (mean reduction of 2.2 days; 95% confidence interval, 0.81–3.63 days; $p = .004$; test for heterogeneity, $p = .0012$). There were no significant differences in mortality or noninfectious complications between the two groups of patients.

Conclusions: The results of this meta-analysis support the experimental data demonstrating the benefit of the early initiation of enteral nutrition. The results of this meta-analysis must, however, be interpreted with some caution because of the significant heterogeneity between studies. (Crit Care Med 2001; 29:2264–2270)

KEY WORDS: meta-analysis; early enteral nutrition; delayed enteral nutrition; jejunostomy; postoperative; trauma; burns; intensive care unit; critical care

During the last two decades, nutritional support has emerged as a vital component of the management of critically ill patients. Nutrition supplies vital cell substrates, antioxidants, vitamins, and minerals that optimize recovery from illness. The hazards of parenteral nutrition compared with enteral nutrition (i.e., immune compromise, increased infections, increased complications, increased mortality in some patient subsets) are now clearly established and favor the use of enteral nutrition (1–9). Specialized immune-enhancing nutritional formulations have been developed, and these diets have been demonstrated to decrease indexes of inflammation, to improve cell-mediated immunity, to decrease organ failure and intensive care unit (ICU) complications, and to reduce ventilator and ICU days (10–19). The optimal time to start nutritional support is, however, an important and unresolved issue.

Many critically ill, injured, and postoperative patients develop gastroparesis, which limits the ability to tolerate gastric feeding (20, 21). Furthermore, these patients frequently have diminished or absent bowel sounds that are incorrectly interpreted to indicate that the small bowel is “not working.” There is also the fear that early enteral feeding will result in aspiration and worsened clinical outcome. Finally, some believe that patients can tolerate 5–7 days of starvation without detrimental clinical effects. As a result, enteral nutrition is frequently withheld for 5–7 days until the return of gastric emptying and bowel sounds. However, it is now recognized that small-bowel function and the ability to absorb nutrients remains intact, despite critical illness, the presence of gastroparesis, and absent bowel sounds. In patients unable to tolerate gastric feeding, access to the small bowel can be obtained by small-bowel feeding tubes placed at the bedside, during surgery, endoscopically, or percutaneously.

It has been suggested that early enteral feeding may reduce septic and non-septic complications and improve the outcome of the critically ill and injured patient (22, 23). There are several mech-

anisms whereby early enteral nutrition may improve patient outcome. Early enteral nutrition (as opposed to delayed enteral nutrition) has been demonstrated to improve nitrogen balance, wound healing, and host immune function, to augment cellular antioxidant systems, to decrease the hypermetabolic response to tissue injury, and to preserve intestinal mucosal integrity (i.e., maintain mucosal immunity, prevent increased mucosal permeability, and decrease bacterial translocation) (22, 24–29). Although the benefits of early nutritional support have been demonstrated at the cellular and tissue level and in animal studies of critical illness, the effect on patient morbidity and mortality has been less clear. Many studies demonstrated an improvement in one or more outcome variables. However, the studies were underpowered and, hence, the differences between early and delayed feeding groups were not always significant (22, 23). Furthermore, the magnitude of the treatment effect remains unknown (22, 23). We, therefore, performed a meta-analysis of available studies that compared early with delayed enteral nutrition to provide an estimate of the treatment effect of early enteral nutrition on patient outcome.

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METHODS

Identification of Trials. Our aim was to identify all relevant randomized, controlled trials that compared early with delayed enteral nutrition. A randomized, controlled trial was defined as a trial in which subjects were assigned prospectively to one of two interventions by random allocation. We used a multiple-method approach to identify relevant studies for this review. A computerized literature search of the National Library of Medicine's MEDLINE from 1966 to August 2000 was conducted using the following search terms: "enteral nutrition (explode)" and "early or immediate or delayed" and "randomized controlled trials (publication type)" or "controlled clinical trials" or "clinical trials, randomized." Bibliographies of all selected articles and review articles that included information on enteral nutrition were reviewed for other relevant articles. In addition, each author reviewed his personal files and contacted experts in the field. This search strategy was done iteratively, until no new potential, randomized, controlled trial citations were found on review of the reference lists of retrieved articles.

Study Selection and Data Extraction. The following selection criteria were used to identify published studies for inclusion in this analysis: a) study design: randomized clinical trial; b) population: hospitalized adult postoperative, trauma, head-injured, burn, or medical ICU patients; c) intervention: early vs. late/delayed institution of enteral nutrition; and d) outcome variables: at least one of the following primary outcome variables: the number of infections, total number of noninfectious complications, length of hospital stay (LOS), and hospital mortality. For the purposes of this meta-analysis, early enteral nutrition was defined as the initiation of enteral feeds within 36 hrs of admission to the hospital or within 36 hrs of surgery. Delayed enteral nutrition was defined as nutritional support that was initiated after 36 hrs of admission to the hospital or after 36 hrs of surgery. Study selection and data abstraction was conducted independently by the two investigators.

Data Analysis. Infections, complications, and mortality were treated as binary variables. LOS was treated as a continuous variable. The data analysis was performed using the random effects model with meta-analysis software (RevMan 4.1, Cochrane Collaboration, Oxford, UK). The relative risk and continuous data outcomes are presented with 95% confidence intervals. When authors reported standard deviations (SD), we used them directly. When SD were not available, we computed them from the observed mean differences (either differences in changes or absolute readings) and the test statistics. When the tests' statistics were not available, given a p value, we computed the corresponding test statistic from tables for the normal distribution. Subgroup analyses were performed on each of the postoperative,

trauma, head-injured, and burn groups for each outcome variable. We found no studies that met the inclusion criteria for medical ICU patients. These subgroups were chosen because they reflect the main clinical populations included in the trials. We tested heterogeneity between trials with chi-square tests, with $p \leq .05$ indicating significant heterogeneity (30).

RESULTS

From 161 articles screened, 27 were identified as randomized controlled trials comparing early with delayed enteral nutrition, and were included for data extraction. Of these, 12 were excluded; the remaining 15 trials (31–45) were included in this meta-analysis. Articles were excluded for the following reasons: nocturnal protein supplementation was compared with control ($n = 5$) (46–50); enteral nutrition was delayed for >36 hrs in the early feeding group, with feeding delayed for up to 57, 60, and 96 hrs ($n = 3$) (51–53); the control group was not randomized ($n = 1$) (54); pediatric patients were included ($n = 2$) (55, 56); and patients in the treatment group received parenteral nutrition in addition to enteral nutrition ($n = 1$) (26). Overall, 753 patients were enrolled in the included studies. In none of the studies was their crossover to the other arm of the study. It is important to note that no studies of medical ICU patients were found. A summary of the studies, including the differences in caloric intake, is presented in Table 1. The study outcome data are presented in Table 2.

Infections. Information on the incidence of infections was available for 12 of the 15 (80%) studies and included 603 patients. Overall, there was a significantly lower risk of infection in the patients who received early enteral nutrition (relative risk of 0.45; 95% confidence interval [CI], 0.30–0.66; $p = .00006$) (Fig. 1). Infectious complication occurred in 19% of the early nutritional group as compared with 41% in the delayed group. The test for heterogeneity between the studies just reached statistical significance ($p = .049$).

Noninfectious Complications. Information on the incidence of noninfectious complications was available for 9 of the 15 studies (60%). The incidence of noninfectious complications was 33% in the early group compared with 38% in the delayed group; this difference was not significant (relative risk, 0.82; 95% CI, 0.56–1.19) (Fig. 2).

Length of Hospital Stay. Information on LOS was available for 12 of the 15 studies (80%). The LOS was significantly shorter in the early nutrition group ($p = .0012$; mean reduction of 2.2 days; 95% CI, 0.81–3.63 days) (Fig. 3). The reduction in LOS was most marked in the trauma/head injured/burn patients (4.04 days with 95% CI of 1.28–6.81 days; $p = .004$). There was, however, significant heterogeneity between studies (chi-square = 30.7; $p = .0012$).

Mortality. Information on hospital mortality was available for only 6 of the 15 (40%) studies. The mortality was 8% in the early group and 11.5% in the delayed nutrition group; this difference was not significant (relative risk, 0.74; 95% CI, 0.37–1.48) (Fig. 4).

DISCUSSION

This systematic review is stronger than previous overviews of this topic in its adherence to strict methodologic criteria (22, 23). We used explicit inclusion and exclusion criteria, performed a comprehensive literature search, assessed the validity of eligible studies, and conducted a rigorous data analysis. This meta-analysis demonstrates a benefit of early enteral nutrition in reducing episodes of infection and LOS. There was, however, significant heterogeneity among the results of the primary studies. Nevertheless, we proceeded with the meta-analysis despite the presence of heterogeneity, because, short of a large randomized, controlled, and blinded study, our results provide the best guide for clinicians to judge the magnitude of the treatment effect of early enteral nutrition. Although the random effects model results in more conservative 95% CI, because of the significant heterogeneity among the studies, the results of this meta-analysis should be interpreted with some caution. Furthermore, as with any meta-analysis, there may be bias as it is easier to publish a study that shows a difference between the experimental and control group than a negative study (publication bias) (57).

When conducting a systematic review, heterogeneity (major differences in the apparent effect of the interventions across studies) is often found; if present, it should be explained (30). Heterogeneity between studies may be the result of the play of chance, the methodologic quality of the studies, differences in the patient populations, differences in study design, and unconcealed randomization

Table 1. Summary of nutritional support of the studies included in meta-analysis

Date	Author	n	Study Protocol	Formula	Caloric Intake (kcal) or % of Goal; Control vs Intervention (Mean ± SD)	
Abdominal surgery						
1979	Sagar (31)	30	SBT <24 hrs	Elemental diet	Day 2	300 ± 20 vs 1100 ± 100
1991	Schroeder (32)	32	SBT <24 hrs	Standard isocaloric	Days 1–4	382 ± 71 vs 1179 ± 338
1995	Hasse (33)	31	SBT <24 hrs vs oral	Standard isocaloric	Day 3	550 vs 1900
1996	Beier-Holgersen (34)	60	SBT <4 hrs	Nutrition supplement	Day 3 (median)	0 vs 1500
1996	Carr (35)	28	SBT <2 hrs	Standard isocaloric	Days 1–4	377 ± 34 vs 1622 ± 375
1997	Watters (36)	28	Jejun <2 hrs	Standard isocaloric	Day 3	0 vs 1500
1997	Heslin (37)	164	Jejun <24 hrs	Immune enhancing diet	Day 3, % goal	22% vs 58%
1997	Schilder (38)	94	Oral intake <24 hrs	Blenderized liquid diet	—	—
1998	Singh (39)	43	Jejun <12 hrs	Liquid diet	Day 4	406 ± 89 vs 2116 ± 243
Trauma						
1984	Seri (40)	18	Jejun <12 hrs	Blenderized liquid diet	—	—
1986	Moore (41)	63	Jejun <24 hrs	Elemental diet	Day 4, % goal	36 ± 2% vs 156 ± 11%
1998	Kompan (42)	28	OG <6 hrs	Standard isocaloric	Day 4	703 ± 701 vs 1340 ± 473
Head injury						
1989	Graham (43)	32	SBT <36 hrs	Elemental diet	Day 3	411 vs 2499
1999	Taylor (44)	82	OG/STB <24 hrs	Hypercaloric (1.5 kcal/mL)	Day 2, % of goal	20% vs 58%
Burns						
1990	Chiarelli (45)	20	<24 hrs	Blenderized liquid diet	—	—

SBT, small bowel tube; jejun, jejunostomy; OG, orogastric tube; —, data not available.

Table 2. Summary of outcomes data of studies included in meta-analysis

Date	Author	n	Study Protocol Control vs	Outcome Variables (Control vs Intervention)			
				Mean LOS (days)	Infections	Other Complications	Mortality
Abdominal surgery							
1979	Sagar (31)	30	SBT <24 hrs	19 vs 14	5/15 vs 3/15	—	—
1991	Schroeder (32)	32	SBT <24 hrs	15 vs 10	0/16 vs 1/16	7/16 vs 3/16	—
1995	Hasse (33)	31	SBT <24 hrs	18 vs 16	8/17 vs 3/14	—	—
1996	Beier-Holgersen (34)	60	SBT <4 hrs ^a	12 vs 8	14/30 vs 2/30	5/30 vs 6/30	4/30 vs 2/30
1996	Carr (35)	28	SBT <2 hrs	9 vs 10	3/14 vs 0/14	13/14 vs 3/14	1/14 vs 0/14
1997	Watters (36)	28	Jejun <2 hrs	16 vs 17	—	3/15 vs 3/13	—
1997	Heslin (37)	164	Jejun <24 hrs	—	6/83 vs 6/81	23/83 vs 31/81	—
1997	Schilder (38)	94	Oral intake <24 hrs	4 vs 3	—	—	—
1998	Singh (39)	43	Jejun <12 hrs	13 vs 15	22/22 vs 8/21	7/22 vs 8/21	4/22 vs 4/21
Trauma							
1984	Seri (40)	18	Jejun <12 hrs	—	2/8 vs 1/10	—	—
1986	Moore (41)	63	Jejun <24 hrs	29 vs 25	9/31 vs 3/32	15/31 vs 14/32	2/31 vs 1/32
1998	Kompan (42)	28	OG <6 hrs	14 vs 11	—	MOF 3.1 vs 2.5	—
Head injury							
1989	Graham (43)	32	SBT <36 hrs	10 vs 7 ^b	14/15 vs 3/17	—	—
1999	Taylor (44)	82	OG/STB <24 hrs	—	35/41 vs 25/41	25/41 vs 15/41	6/41 vs 5/41
Burns							
1990	Chiarelli (45)	20	<24 hrs	89 vs 69	7/10 vs 3/10 ^c	2/10 vs 2/10	0/10 vs 0/10

LOS, length of stay; SBT, small bowel tube; jejun, jejunostomy; MOF, multiple organ failure score.

^aDouble-blind, placebo-controlled randomized controlled trial.

^bIntensive care unit LOS.

^cPatients with bloodstream infection.

with study investigators being aware of treatment allocation. We believed the latter to be particularly important as blinding of the investigator(s) as to the timing of enteral nutrition is challenging. Only one of the studies included in this meta-

analysis was placebo-controlled (34). Furthermore, the small size of most of the studies included in this meta-analysis and the different types of nutritional formulas used may have contributed to the differences in the treatment effect between

studies. Differences in the underlying risk of patients have also been proposed as an explanation for the differences between the results of studies in a meta-analysis (58, 59). We were unable to control for risk (of infectious or

The results of our analysis of prospective, randomized clinical trials of early vs. delayed enteral nutritional support in critically ill patients indicate that early feeding decreases infectious complications and length of stay.

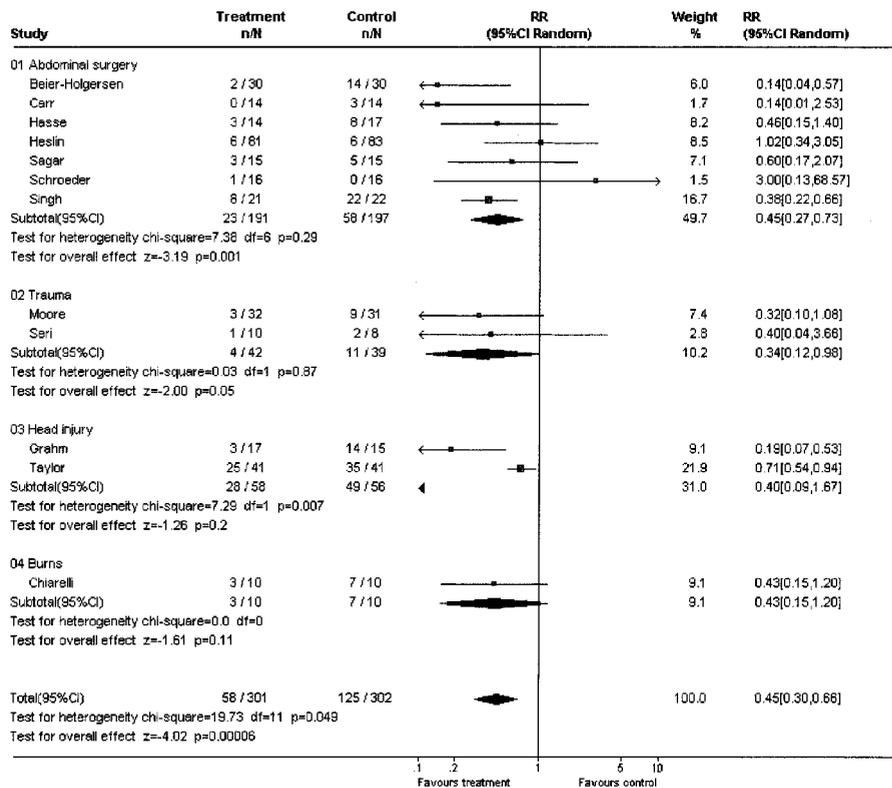


Figure 1. Random effects model of relative risk (RR) (95% confidence interval [CI]) of infectious complications associated with early enteral feeding compared with delayed feeding.

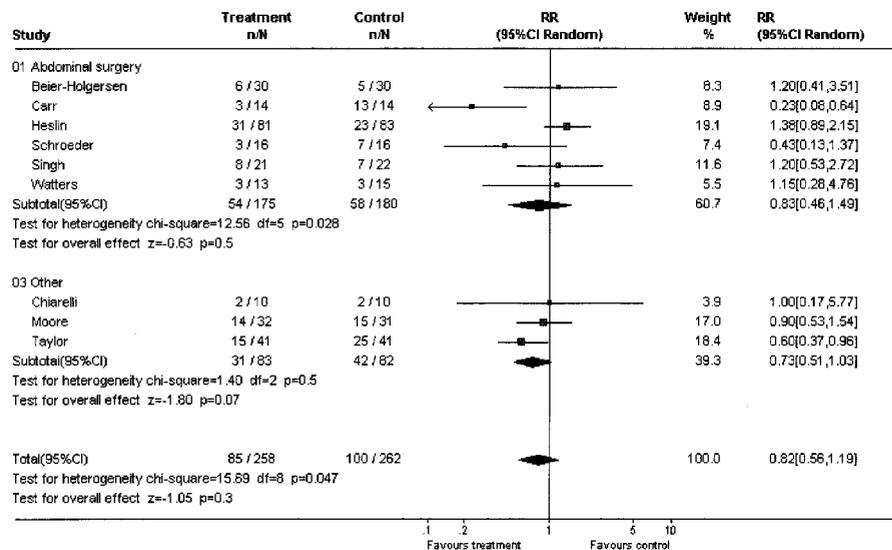


Figure 2. Random effects model of relative risk (RR) (95% confidence interval [CI]) of noninfectious complications associated with early enteral feeding compared with delayed feeding.

noninfectious complications) in this meta-analysis, but, considering the diversity of the patient populations, this factor may have contributed to the heterogeneity between studies. It is noteworthy that the test for heterogeneity just reached statistical significance for infectious complications ($p = .049$), whereas, it was

highly significant for LOS ($p = .0012$); this would suggest that the early initiation of enteral nutrition may directly impact on infectious complications, but that many other factors may determine LOS. The results of this meta-analysis are comparable to those of Beale and colleagues (19), who demonstrated that an immune-

enhancing diet compared with a standard enteral nutritional formula reduced infectious complications and LOS in critically ill patients, with no significant effect on mortality. Considering the complexity of critically ill patients and the multiple factors affecting outcome, only a meta-trial is likely to be able to demonstrate a significant difference in mortality between the early and delayed initiation of enteral nutrition; such a study would be almost impossible to perform (60).

Notwithstanding the limitations of this meta-analysis, the lower risk of infections and LOS in the early nutritional group is supported by findings from previous studies performed over the last two decades. Starvation is well known to cause immune depression and predispose to infections in humans. The effects of starvation are reversed by feeding. However, the benefits of immediate or early feeding after injury or illness compared with a few days' delay in feeding has remained controversial. The effects of nutrition on immune function and infection rates (10–19) led to the discovery of immune-enhancing nutrients and the development of “immune-enhancing” diets enriched in omega-3 long chain fatty acids, arginine, glutamine, nucleotides, and antioxidants. The immune-enhancing diets have been reported to decrease infection rates and improve outcome in critically ill patients (10–19). For example, Braga and colleagues (61) demonstrated that the perioperative administration of an enriched enteral formula significantly improved gut function and positively modulated postsurgical immunosuppressive and inflammatory responses compared

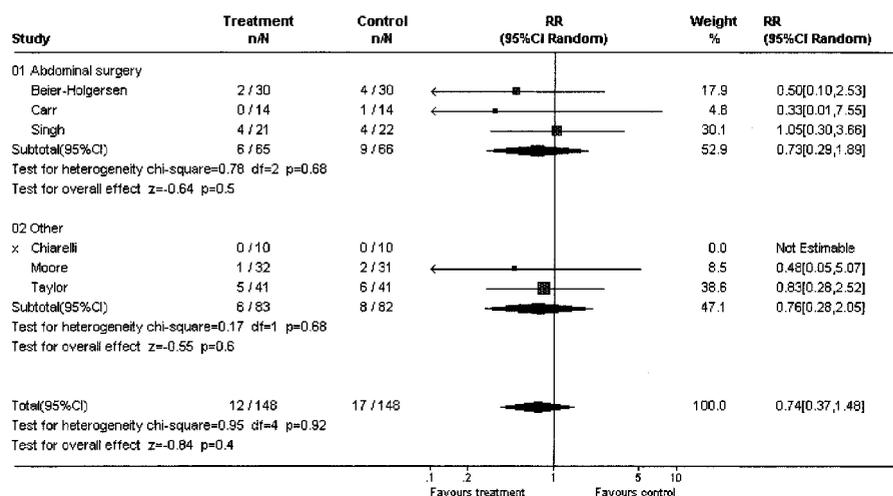


Figure 3. Random effects model of weighted mean difference (95% confidence interval [CI]) of length of stay associated with early enteral feeding compared with delayed feeding. RR, relative risk.

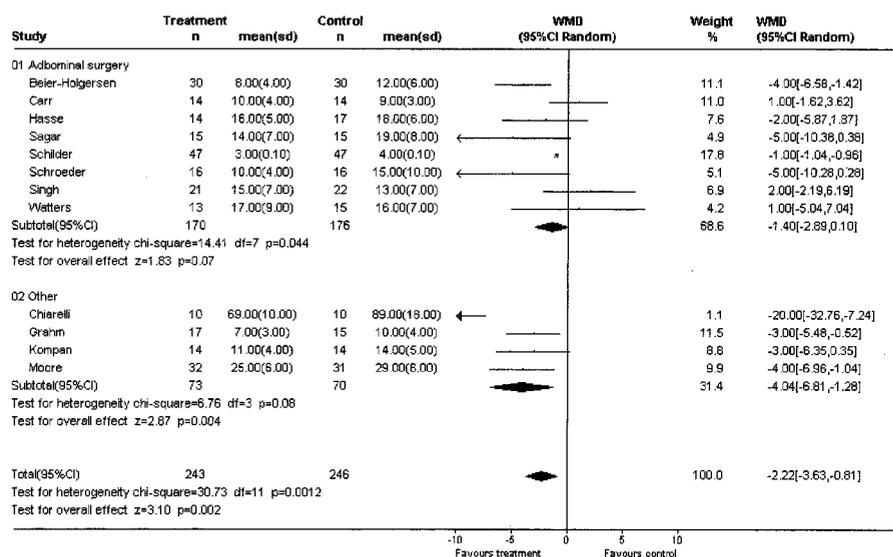


Figure 4. Random effects model of relative risk (95% confidence interval [CI]) of death associated with early enteral feeding compared with delayed feeding. WMD, weighted mean difference.

with a standard formula. Only one of the studies included in our analysis compared early with delayed feeding with an immune-enhancing diet (37). In an additional study, which did not meet our inclusion criteria, Kudsk et al. (54) compared early feeding with an immune-enhancing vs. standard enteral nutritional formula. However, the investigators also compared outcome in these fed patients with a separate group of similar patients who were not started on early nutritional support. The groups receiving early enteral nutrition had lower infection rates, complications, and LOS.

Early enteral feeding has been reported to improve organ function, which

may explain the decreased hospital stay. In a number of landmark studies, Alexander and colleagues (25, 62–65) demonstrated that immediate enteral feeding in burned animals was associated with a decrease in the hypermetabolic state, lower levels of circulating stress hormones (i.e., glucagon, cortisol, and norepinephrine), increased gastrointestinal blood flow, a reduction in bacterial translocation from the intestinal tract, and improved outcome. Tanigawa et al. (27) demonstrated that feeding diminished lipid peroxidation during reperfusion after ischemia in the perfused rat liver. A number of studies demonstrate that starvation for as short as 12 hrs after

injury depletes tissue antioxidant systems whereas early feeding after injury helps maintain tissue antioxidant levels (66–70). Zaloga and colleagues (28, 71) reported that early enteral feeding protected the liver from injury after hemorrhage and endotoxemia and the kidney from damage after rhabdomyolysis. Schroeder et al. (32) and Moss et al. (72) demonstrated that immediate postoperative enteral nutrition improved wound healing. Early enteral nutrition is known to improve protein synthesis (32, 73). Finally, Kompan and colleagues (42) demonstrated that enteral nutrition started within 6 hrs of admission to the ICU preserved intestinal permeability and was associated with a reduction in the incidence of organ failure when compared with trauma patients in whom enteral nutrition was started >24 hrs after admission.

All of the studies included in our analysis of early enteral nutrition were performed in surgical patients. We could find no studies that met our inclusion criteria that were performed in critically ill medical patients. This is clearly an area that requires additional study. However, we believe that medical patients would also receive benefits from early enteral feeding. In support of this statement, early feeding with immune-enhancing vs. standard enteral formulas benefits both surgical and medical critically ill patients (19). In addition, four studies performed in patients with hip fractures indicate that early nutritional support is associated with less complications, decreased hospital stay, and lower mortality (46–50).

The results of our analysis of prospective, randomized clinical trials of early vs. delayed enteral nutritional support in critically ill patients indicate that early feeding decreases infectious complications and LOS. The results of this meta-analysis must, however, be interpreted with some caution because of the significant heterogeneity between studies. A large, multicenter, prospective, double-blind, randomized study would provide more definitive evaluation of the benefits of early enteral feeding. However, until such a study is performed, current data supports the use of early enteral nutritional support in critically ill patients. The studies in this report did not evaluate the use of gastric vs. small-bowel feeding tubes for early feeding. Additional studies addressing the site of feeding would be of clinical value.

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A collective task force of the American College of Chest Physicians, American Association of Respiratory Care, and the Society of Critical Care Medicine have published "Evidence-Based Guidelines for Weaning and Discontinuing Ventilatory Support." They appear in the supplement to the December 2001 issue of *Chest*.