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Enteral Nutritional Supplementation With Key Nutrients in Patients With Critical Illness and Cancer

A Meta-Analysis of Randomized Controlled Clinical Trials

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Objective
To conduct a meta-analysis of 11 randomized controlled trials comparing enteral nutritional support supplemented with key nutrients *versus* standard enteral nutritional support to determine effects on morbidity and mortality rates and hospital stay.

Background Data
Recent studies have shown that malnutrition occurs in up to 30% of patients undergoing gastrointestinal surgery, resulting in an increased risk of postoperative complications and death. With the realization that key nutrients can modulate inflammatory, metabolic, and immune processes, enteral nutritional regimens (supplemented with large amounts of key nutrients) have been developed for clinical use.

Methods
Eleven prospective, randomized controlled trials evaluating 1009 patients treated with combinations of key nutrients (Impact, Immun-Aid) were evaluated. Outcome measures examined were the incidences of pneumonia, infectious complications, and death, and length of hospital stay. Meta-analyses were undertaken to obtain the odds ratio and 95% confidence interval for incidences of infectious complications, pneumonia, and death, and the weighted mean difference and 95% confidence interval for length of hospital stay.

Results
The provision of nutritional support supplemented with key nutrients to patients with critical illness resulted in a decrease in infectious complications when compared with patients receiving standard nutritional support and a significant reduction in overall hospital stay. Similar results were documented in patients with gastrointestinal cancer. However, there were no differences between patient groups for either pneumonia or death.

Conclusions
This meta-analysis has demonstrated that nutritional support supplemented with key nutrients results in a significant reduction in the risk of developing infectious complications and reduces the overall hospital stay in patients with critical illness and in patients with gastrointestinal cancer. However, there is no effect on death. These data have important implications for the management of such patients.

Enteral nutritional support has been provided to patients with critical illnesses using a variety of nutritional regimens. However, there has been a growing recognition that certain key nutrients can modulate a variety of inflammatory, metabolic, and immune processes when ingested in excess of the normal daily requirements.[1] For example, the amino acids L-arginine and L-glutamine can stimulate a variety of host defenses,[2–4] modulate tumor cell metabolism,[5] increase wound healing,[6] and reduce nitrogen losses after trauma.[7,8] Further, L-glutamine may have beneficial effects in maintaining the integrity of the intestinal barrier function in preventing the translocation of bacteria and endotoxins from the bowel lumen into the systemic circulation.[9]

RNA or synthetic polyribonucleotides also enhance a variety of host defenses in patients with cancer.[10–12] The n-3 essential fatty acids (EFAs) were initially thought to enhance host defenses through the increased production of

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prostaglandin E_3, which is less immunosuppressive than the normally produced prostaglandin E_2.[13] However, subsequent studies have shown that both the n-3 and n-6 EFAs inhibit a variety of host defense mechanisms (cellular and humoral), both in healthy volunteers and patients with cancer.[14–17] The effects of these nutrients on immune, metabolic, and inflammatory processes have been reviewed in detail elsewhere.[1,18]

Although these and other studies have demonstrated significant and substantial effects on the immune system, metabolic processes, and wound healing, clinically beneficial effects by supplementation with a *single* nutrient have been more difficult to demonstrate. However, Ziegler et al[19] reported that L-glutamine supplementation reduced the risk of infectious complications and reduced hospital stay in patients who had undergone bone marrow transplantation. Further, in a double-blind, randomized controlled trial, it was documented that "priming" of a breast cancer with L-arginine, given for 3 days before chemotherapy, resulted in a better response to chemotherapy (assessed histologically) when compared with patients receiving placebo.[20]

An alternative approach has been to combine three or more specific nutrients; for example, amino acids (L-arginine, L-glutamine, or branched-chain amino acids), n-3 EFAs, and RNA. The effects of such an approach on the immune system were reported by Cerra et al[21] in 1990. In a randomized controlled study, a combination of nutrients was shown to enhance host defenses significantly. On the basis of these results, clinical trials have been undertaken to determine if not only immunologic changes but also clinical benefits can be achieved by using nutritional support supplemented with key nutrients in patients who are critically ill—specifically, those undergoing surgery for gastrointestinal (GI) cancer.

This article analyzes the results of randomized, controlled studies of enteral nutrition supplemented with combinations of key nutrients *versus* standard enteral diets on clinical outcome—complications (infectious complications, pneumonia), death, and length of stay in the intensive therapy unit or hospital.

METHODS

Data Acquisition

We identified 11 randomized, controlled trials (published in peer-reviewed journals) evaluating the use of enteral nutritional support supplemented with combinations of key nutrients *versus* standard enteral nutrition, in a total of 1009 patients with a critical illness. These were obtained by reviewing reference lists in relevant publications and by manual and computer (Medline) searches of published articles from January 1990 to February 1998. In addition, two more studies were identified[21,22] that focused on the effects on immunologic functions and not clinical outcome; they were therefore not included in the analysis.

The nutritional regimens evaluated varied among the different studies. In patients undergoing surgery, the nutrition was given in the postoperative period only. However, the key nutrients used in the various combinations were L-arginine, L-glutamine, branched-chain amino acids, EFAs, and RNA. These are listed for each of the studies in Table 1. Impact (enriched with L-arginine, n-3 EFAs, and RNA) was most commonly used.

Clinical Outcome Measures

The clinical outcome measures evaluated for each of these studies were the incidence of major infectious complications (wound infection, intraabdominal abscess, pneumonia, septicemia), nosocomial pneumonia alone (in view of the common occurrence and importance of hospital-acquired respiratory tract infections), and death. For the definition of infectious complications in the papers studied, either clear criteria were detailed or the authors referred to definitions previously published.[23,24] For the purposes of this meta-analysis, these were comparable between the different studies examined.

In addition, the effects of the enteral nutritional support on rehabilitation time (time spent in the hospital or intensive therapy unit) were also documented, if this information was provided. Two reviewers independently abstracted the data from the publications, and differences were agreed by consensus. Intention-to-treat analyses for these outcome measures were undertaken.

These analyses were carried out for all the studies. In addition, because six of the studies had studied only patients undergoing surgery for GI cancer, a further analysis of these six studies was also undertaken separately.

Statistical Methods

For each trial, the patients allocated to the nutritional support group and those allocated to the control nutritional group were compared with each other and not with patients in any other trial. Mathematically, the odds ratio (OR) was calculated using the following formula:

OR = (number of patients who experienced the event in the treatment group/number who did not experience the event)/(number of patients in the control group who experienced the event/number of patients in the control group who did not experience the event).

The OR and 95% confidence interval (CI) for all studies pooled together was then calculated for the effects of nutrient combinations on major infectious complications, pneumonia, and death.[25,26] Homogeneity of effects was assessed using the chi square test, and a fixed-effect model was used.[27] In addition, each study's contribution to the sum of the products of the measured variables was weighted by the precision of that study's estimate of effect (weight). The weight given to each study was the inverse of the vari-

Table 1. STUDIES OF SUPPLEMENTED NUTRITIONAL SUPPORT

Study Ref. No.	Patient Numbers	Patient Group Studied	Time of Starting Feeding	Supplemented Nutrients	Power Calculations
31	85	Surgery for upper GI cancer	Within 24 hours of surgery	L-arginine, n-3 EFAs, RNA	To detect a difference in hospital stay of 4 days
32	105	Trauma (ISS 16–45)	Within 24 hours of admission	L-arginine, L-glutamine, branched chain amino acids, n-3 EFAs	Not given
33	247	Trauma, sepsis, or surgery	Within 48 hours of event	L-arginine, n-3 EFAs, RNA	To detect a 20% difference in hospital stay
34	50	Surgery for upper GI cancer	Within 12 hours of surgery	L-arginine, n-3 EFAs, RNA	Not given
35	60	Surgery for upper GI cancer	Within 24 hours of surgery	L-arginine, n-3 EFAs, RNA	To detect 50% change in complications
39	35	Trauma (ISS > 21) and laparotomy	Within 24 hours of surgery	L-arginine, L-glutamine, branched-chain amino acids, n-3 EFAs	Not given
36	28	Surgery for upper and lower GI cancer	"As early as possible"	L-arginine, n-3 EFAs, RNA	To detect hospital stay difference of 4 days
43	49	Burns (2.5% to 83% of body surface area)	Within 48 hours of admission	L-arginine, n-3 EFAs, RNA	Not given
38	43	Trauma (ISS > 13)	Within 72 hours of admission	L-arginine, L-glutamine	Not given
45	154	Surgery for upper GI cancer	Within 12 hours of surgery	L-arginine, n-3 EFAs, RNA	Not given
37	110	Surgery for upper GI cancer	Within 12 hours of surgery	L-arginine, n-3 EFAs, RNA	Not given

GI = gastrointestinal; EFA = essential fatty acid; RNA = ribonucleic acid; ISS = injury severity score.

ance—in other words, more precise estimates (from larger studies with more events) were given more weight.[28]

Assessment of Validity of Studies

An assessment of validity of each trial was derived using a three-point scale, taking into account sources of systematic errors of bias: selection, performance, attrition, and detection biases, as previously described.[29] These were categorized as A (low risk of bias), B (moderate risk of bias), or C (high risk of bias).[29] The value for each study was obtained by two independent observers, and any differences were agreed by consensus. The rating given to each study is shown in Table 2, but this was not taken into account in the meta-analysis.[30]

RESULTS

Patient Groups Studied

Patients with a range of critical illnesses were evaluated; these are listed in Table 1, as are the numbers of patients in each study. Details of power calculations given for the outcome variables are also listed in Table 1.

Nutritional Regimens

The different nutritional regimens used and the time when they were administered (in relation to the onset of critical illness) are shown in Table 1. Most of the studies evaluated the effects of Impact *versus* a standard diet.[31–37] Two evaluated Immun-Aid[32,39] (enriched with L-arginine, L-glutamine, branched-chain amino acids, n-3 EFAs, and RNA), and in one study the experimental diet was enriched with L-arginine and L-glutamine.[38]

The experimental and control diets were isonitrogenous and isocaloric in seven of the studies, but in three studies the nitrogen content of the experimental diet was substantially higher than that of the control.[31–33] In one study, the nitrogen intake in the experimental group was more than twice that of the control group (80 g *vs.* 38 g of protein/day).[32] In another study, the daily nitrogen intake was 15.6 g in the experimental group and 9 g/day in the control group.[31]

Table 2. NUTRITIONAL GOALS, ACHIEVEMENTS, AND WEIGHT LOSS IN PATIENTS STUDIED

Study (Validity Assessment)	Stated Nutritional Goals	Nutritional Intake Achieved (supplemented *vs.* nonsupplemented groups)	Weight Loss Before Study
31(A)	25 kcal/kg/d by 4th postoperative day	1421 *vs.* 1285 kcal/d 15.6 g *vs.* 9 g N/d	27 patients had > 10% loss body weight, stratified between groups
32(B)	35 kcal/kg/d within 72 h	26 *vs.* 24 kcal/kg/d 0.38 *vs.* 0.16 g N/kg/d	Not reported
33(B)	65 g N/d and 1500 kcal/d within 96 h	> 75% of patients achieved nutritional goal	Not reported
34(B)	25 kcal/kg/d and 0.25 g/kg/d within 96 h	96% achieved nutritional goals	27 patients has lost > 10% body weight, stratified between groups
35(A)	25 kcal/kg/d within 72 h	1067 *vs.* 1234 kcal/d 12 g N *vs.* 10 g N/d	22 patients with > 10% body weight loss, stratified between groups
39(A)	0.32 to 0.38 g N/kg/d	Mean intake in both groups: 18 kcal/kg/d 0.23 g N/kg/d	Not reported
36(B)	25 kcal/kg/d	Mean intake was 18 kcal/kg/d after 96 h	Not reported
43(A)	35 kcal/kg/d	32 *vs.* 33 kcal/kg/d 1.7 *vs.* 1.5 g protein/kg/d	Not reported
38(A)	30 kcal/kg/d 1.5 g protein/kg/d	85% of patients achieved nutritional goal	Not reported
45(A)	25 kcal/kg/d by 5 d	"Most" achieved nutritional goals	Not reported
37(A)	25 kcal/kg/d and 0.25 g N/kg/d by 4 d	4.5% of patients had "delayed" achievement of goal and 1.8% had interrupted feeding	Not reported

Another study also had an increased daily nitrogen intake in the experimental group.[33] In addition, in some of the studies it is documented that the experimental diet also contained increased amounts of micronutrients (*e.g.*, selenium, vitamins A and E), which are known to enhance immune function.[32,33,35,38] The presence or absence of these micronutrients is not stated in the other studies.

Effect of Supplemented Nutrition on Major Infectious Complications

All Patients

The effects of supplemented nutritional support on major infectious complications (pneumonia, intraabdominal abscess, major wound infections, septicemia) is shown in Figure 1 and is expressed as OR and 95% CI. Nine of these studies reported such effects, with only one showing a significant reduction in "infectious complications" in patients receiving supplemented nutrition compared with controls.[35] However, this study, as published, included a wide range of infectious complications (*e.g.*, gastric necrosis, perforation, bile leak, "patchy bowel necrosis") not included in this meta-analysis.

In the study by Bower et al,[33] the findings were evaluated according to different patient subgroups. These authors presented information on infectious complications for "surviving patients" and intention-to-treat analysis of experimental and control groups of patients. However, when the results of all nine studies were combined, the overall OR for the risks of developing major infectious complications was 0.47 (95% CI 0.32 to 0.70; chi square test for heterogeneity 7.50, p = NS). Therefore, from this analysis the use of supplemented nutritional support was associated with a significant and substantial decrease in the risk of developing infectious complications.

Patients With GI Cancer

The results for the 497 patients with GI cancer are shown in Figure 2. The overall OR for the risk of developing major infectious complications was again 0.47 (95% CI 0.30 to 0.73; chi square test for heterogeneity 3.55, p = NS). Therefore, the use of supplemented nutritional support in the postoperative period in patients undergoing surgery for GI cancer was associated with a significant decrease in the risk of developing infectious complications.

Effect of Supplemented Nutrition on Nosocomial Pneumonia

All Patients

In view of the high risk of nosocomial pneumonia in patients who are critically ill, a separate analysis of the

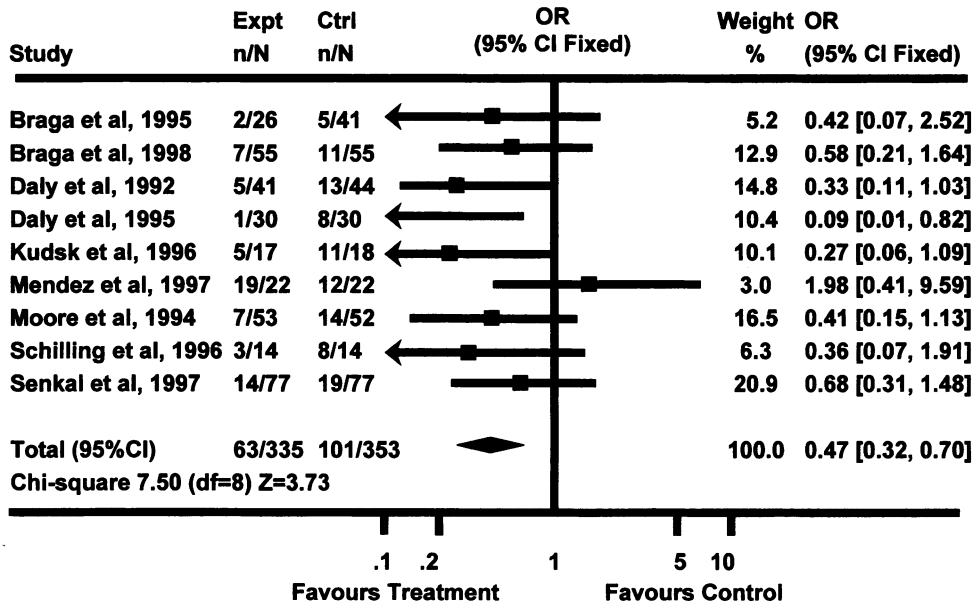

Figure 1. Effect of targeted nutritional support on the incidence of major infective complications (wound infections, intraabdominal abscess, pneumonia, septicemia) in all patients. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis.

effects of supplemented nutrition was carried out, focusing on the incidence of hospital-acquired pneumonia. The results for this analysis are shown in Figure 3 for the eight studies in which this was reported. No individual study found a significant reduction in the risk of developing nosocomial pneumonia with supplemented nutritional support. When the results of all studies were combined, the overall OR for the risk of developing nosocomial pneumonia was 0.91 (95% CI 0.53 to 1.56; chi square test for heterogeneity 7.50, p = NS). Therefore, the use of supplemented nutritional support was not associated with a significant decrease in the risk of developing nosocomial pneumonia.

Patients With GI Cancer

The results for the patients with upper GI cancer are shown in Figure 4. The overall OR for the risk of developing nosocomial pneumonia was 0.71 (95% CI 0.32 to 1.60; chi square test for heterogeneity 6.100, p = NS). Therefore, the use of supplemented nutritional support in the postoperative period in patients undergoing surgery for GI cancer was not associated with a significant decrease in the risk of developing nosocomial pneumonia.

Effect of Supplemented Nutrition on Death Rate

All Patients

Eleven studies examined what effect supplemented nutrition had on the death rate in critically ill patients; these results are shown in Figure 5. In four of the investigations, there were no deaths in either the experimental or control group.[34,36,37,39] Of the other seven studies, only one[33] dem-

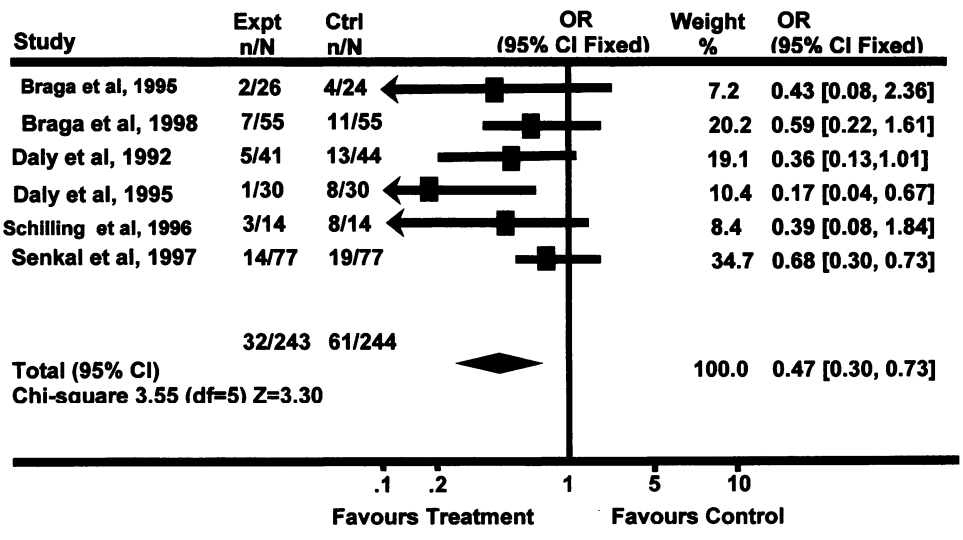

Figure 2. Effect of targeted nutritional support on the incidence of major infective complications in patients with GI cancer. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis.

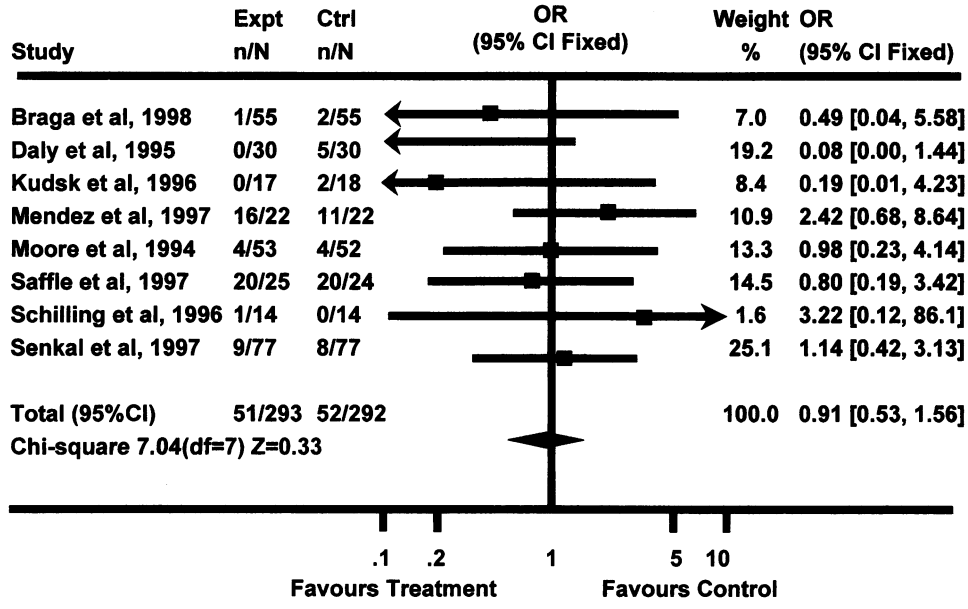

Figure 3. Effect of targeted nutritional support on the incidence of pneumonia in all patients. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis.

onstrated a significant difference in the risk of death between the two groups. There was an increased risk of death in patients who had received targeted nutrition, with an OR of 2.26 (95% CI 1.03 to 4.95). However, a randomization error occurred in this study: there was a significantly higher APACHE II score in patients receiving supplemented nutritional support when compared with standard nutritional support.

When the results of all studies were combined, the overall OR for death was 1.77 (95% CI 1.00 to 3.12; chi square test for heterogeneity 3.32, p = NS). Therefore, the use of supplemented nutritional support was not associated with a significant decrease in the risk of death.

Patients With Upper GI Cancer

The results for the patients with GI cancer are shown in Figure 6. When the results of all studies were combined, the overall OR for death was 1.53 (95% CI 0.440 to 5.372; chi square test for heterogeneity 2.28, p = NS). Therefore, the use of supplemented nutritional support was not associated with a significant decrease in the risk of death.

Effects on Hospital Stay

All Patients

Eight of the studies compared overall length of hospital stay between the patients in the experimental and control groups. Although there were no significant differences in six of these, there was a reduction in hospital stay in two studies.[35,39] In one of these studies, patients had undergone surgery for upper GI cancer and had a 28% reduction in hospital stay.[35] In the second study, involving 43 patients with major trauma, there was a 44% reduction in overall

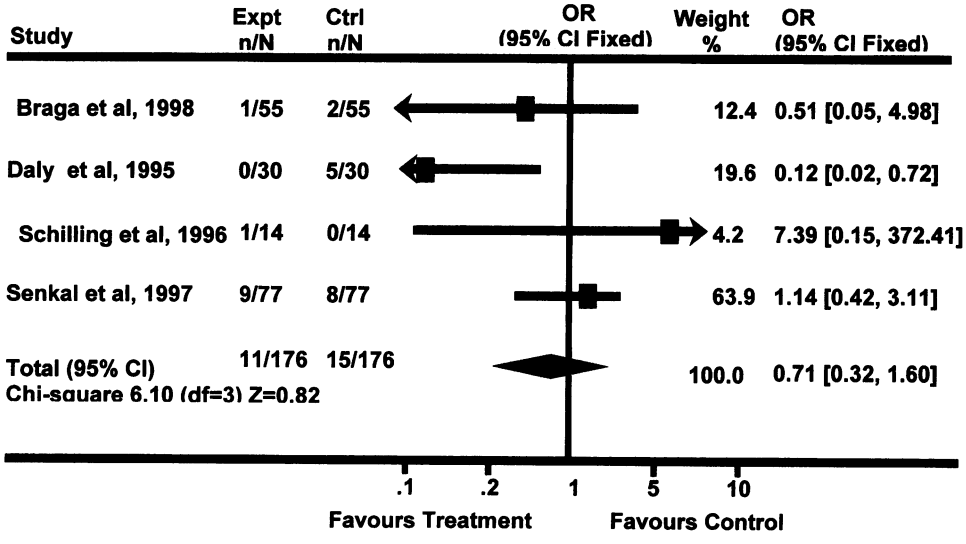

Figure 4. Effect of targeted nutritional support on the incidence of pneumonia in patients with GI cancer. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis.

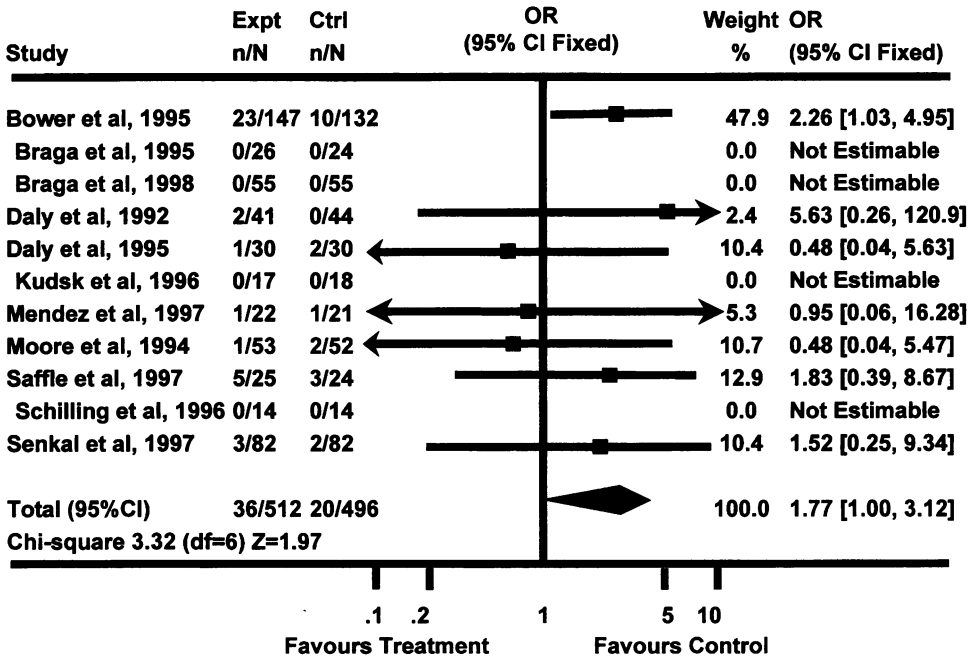

Figure 5. Effect of targeted nutritional support on mortality rate in all patients. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis; x = not estimable.

hospital stay in the group receiving the experimental diet when compared with the control group.[39]

Bower et al[33] also reported that there was a significant reduction in overall hospital stay in patients receiving an experimental diet. However, this was based on a subgroup analysis (85 of 247 patients) determined by the pattern of feeding the patients received and whether the patients were septic. Of importance was the intention-to-treat analysis, which stated that there was no significant difference between hospital stay in patients receiving experimental or control diets (actual lengths of stay were not reported). The weighted mean differences in the length of hospital stay for these studies are shown in Figure 7. The mean difference in hospital stay for all studies combined was a significant reduction for patients receiving targeted nutrition. This was a reduction of 2.5 days (95% CI 4.0 to 1.0 days; chi square test for heterogeneity 4.73, p = NS).

Only four studies reported effects on length of stay in the intensive therapy unit, with none of these reporting a significant reduction in time spent there.[32,36,38,39] The combined weighted difference is shown in Figure 8 (inadequate data were provided in reference 36 to allow inclusion in the analysis). There was no significant difference between patients receiving targeted nutrition or standard nutrition.

Patients With GI Cancer

The effects on overall hospital stay in patients with GI cancer are shown in Figure 9. The mean difference in hospital stay for all studies combined was a significant reduction for patients receiving targeted nutrition. This was

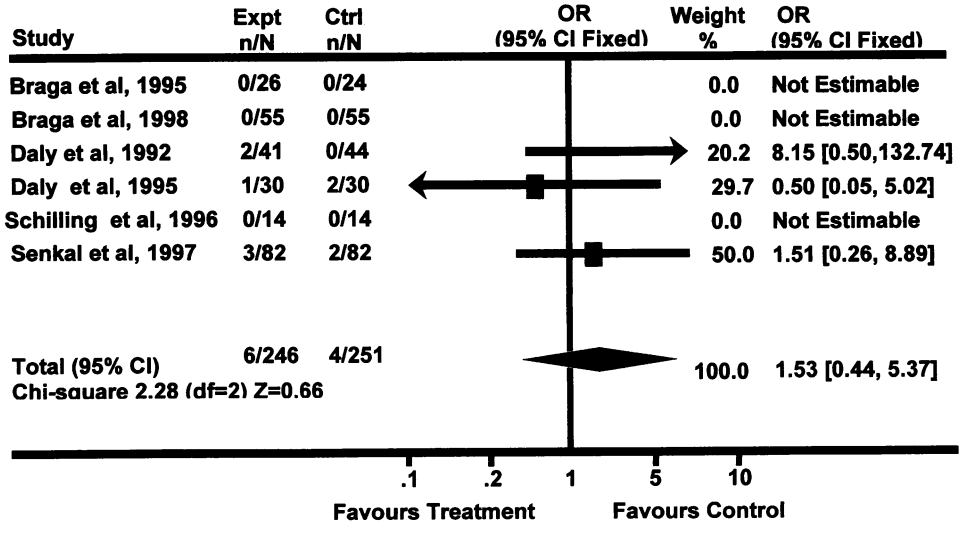

Figure 6. Effect of targeted nutritional support on mortality rate in patients with GI cancer. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of events; N = number of patients in each group on intention-to-treat basis; x = not estimable.

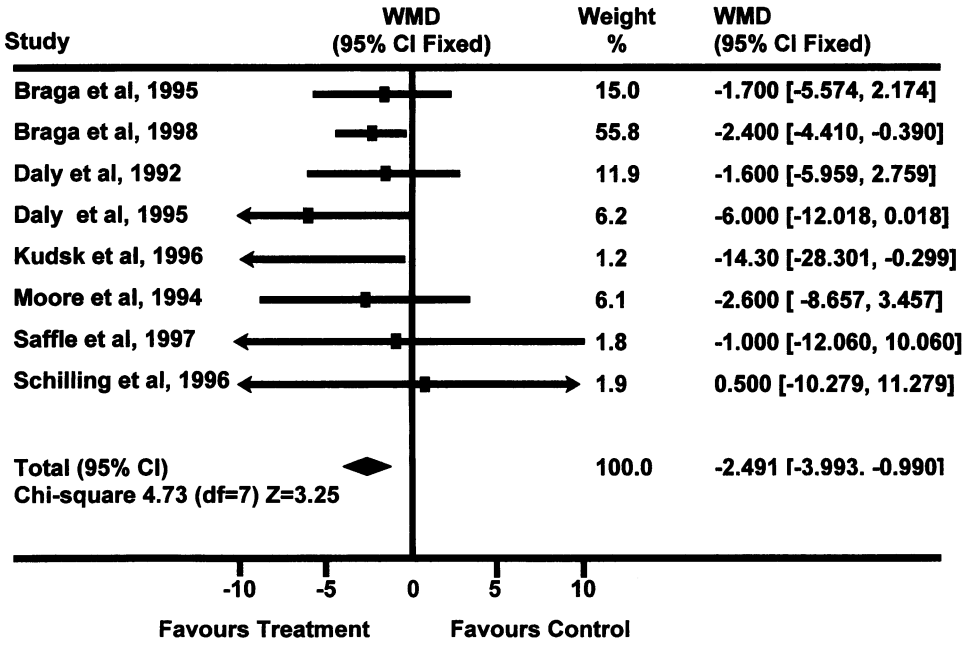

Figure 7. Effect of targeted nutritional support on the length of hospital stay in all critically ill patients. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of patients in each group on intention-to-treat basis. Values shown are means ± standard deviations; WMD = weighted mean difference.

a reduction of 2.4 days (95% CI 4.0 to 0.8 days; chi square test for heterogeneity 1.91, p = NS). However, only one study reported the effects on intensive therapy unit stay, and this demonstrated no difference between the two groups.[36]

DISCUSSION

There are an increasing number of enteral nutritional products available for use in clinical practice. Moreover, there has been an increasing emphasis on the use of enteral nutritional regimens enriched with specific nutrients known to modulate immune, inflammatory, and metabolic processes. In view of this, the time was opportune to carry out an analysis of the published data available to the clinician. We focused on the 11 randomized, controlled studies that have evaluated the effects of enteral nutritional support supplemented with key nutrients published between 1990 and 1998. In particular, we concentrated on the clinical outcome of all critically ill patients documented in the published studies. We also carried out a separate analysis of the six studies that evaluated patients with GI cancer, a homogeneous group.

Our analysis showed that the administration of enteral nutritional support supplemented with key nutrients to critically ill patients significantly reduces the incidence of major infectious complications (major wound infections, pneumonia, intraabdominal abscess, septicemia). A similar reduction was also demonstrated in patients with GI cancer who received the nutritional support in the postoperative

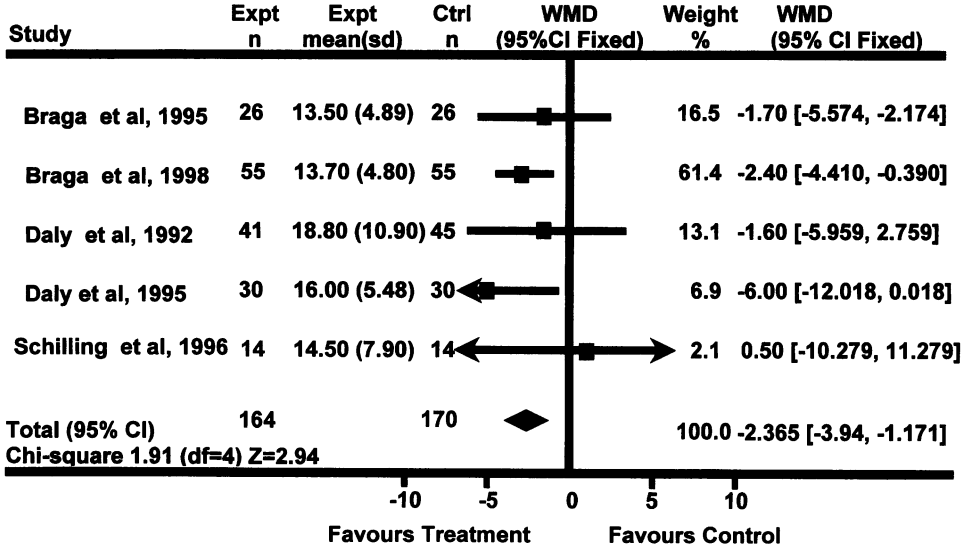

Figure 8. Effect of targeted nutritional support on the length of hospital stay in patients with GI cancer. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of patients in each group on intention-to-treat basis. Values shown are means ± standard deviations; WMD = weighted mean difference.

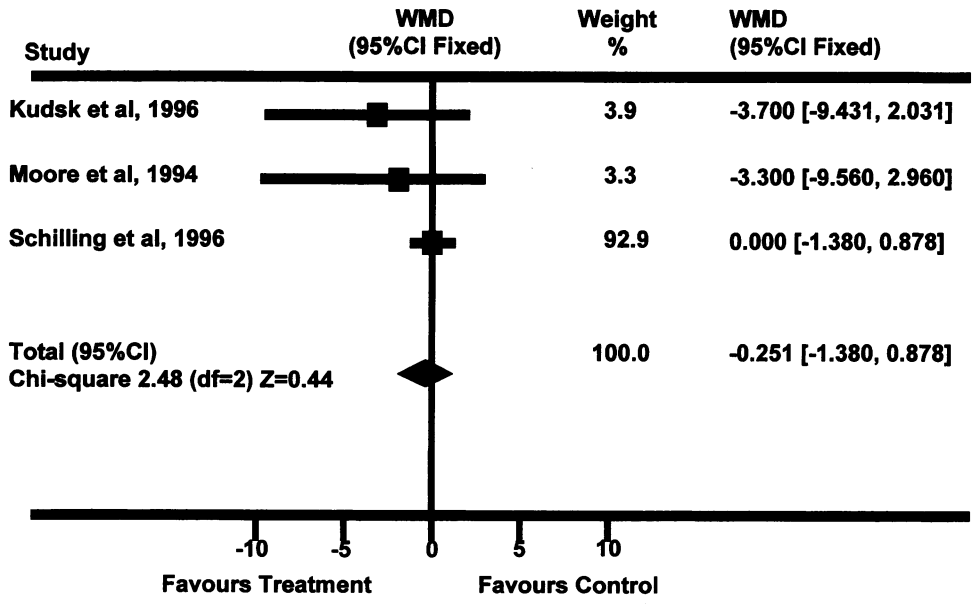

Figure 9. Effect of targeted nutritional support on the length of stay in the intensive therapy unit of all critically ill patients. Expt = patients receiving targeted nutrition; Ctrl = patients receiving standard nutrition; n = number of patients in each group on intention-to-treat basis. Values shown are means ± standard deviations; WMD = weighted mean difference.

period. However, when the risk of developing pneumonia alone was examined, there was no significant benefit in patients receiving supplemented nutritional support.

When the effects of supplemented nutritional support on death were examined, no significant difference was detected in patients receiving this or a standard nutritional regimen, although there was a trend toward an increased risk of death in patients receiving supplemented nutrition. However, a major part of the weighting for this analysis was from the study by Bower et al,[33] where there were more than twice as many deaths in patients receiving supplemented nutritional support. In this study, patients were randomized and stratified according to age and disease (whether septic or systemic inflammatory response syndrome), with the randomization process designed by an independent team. However, the patients in the supplemented nutrition group had a significantly higher APACHE II score than the patients receiving standard enteral nutrition. Although there was a low mortality rate in both groups, this difference in APACHE II scores may have contributed to the differing mortality rates.

It is also important to consider the nutritional status of patients given nutritional support in the perioperative period. It has been shown that it is the "malnourished" patients who are most likely to benefit from nutritional support, in terms of reduced complications.[40] However, in many of these studies information on the nutritional status of patients before study entry was not given. Further data regarding the effects of nutritional supplementation in the subgroups of patients identified as malnourished were not available, or patient numbers were too small to allow a robust statistical analysis.

The timing of administration of nutritional support is another important consideration. Previous analyses of perioperative nutritional support have demonstrated that it should be given for 7 to 10 days before surgery to reduce postoperative complications.[41] However, there may also be evidence to suggest that shorter periods of preoperative nutritional support may also reduce these complication rates. In studies involving patients undergoing surgery, all patients were given nutritional support after surgery, not before. Therefore, the questions of whether malnourished patients benefit most and whether preoperative nutritional support is beneficial remain unanswered from these studies.

Recently, concern has been expressed about the provision and availability of beds in intensive care units, and also of the economic costs and benefits of treating patients in this setting. Moreover, interest has focused on the availability of hospital beds and of possible reductions, with an increasing emphasis on primary care. It is not surprising, therefore, that the effects of supplemented nutrition on length of stay in the intensive therapy unit and overall hospital stay need to be examined carefully. This is a difficult area to assess and to obtain accurate information about because a variety of factors can affect the duration of stay. For example, the acute physiology score, age, coexisting diseases, primary reason for admission to the intensive therapy unit, nature of surgery (elective or emergency), and a variety of other hospital- or clinician-determined factors can affect these times.[42] Nevertheless, taking all these limitations into account, the length of time spent in the intensive therapy unit was reported to be unaffected by the provision of supplemented nutritional support in all four studies where it was reported in all types of critical illness.

When considering length of overall hospital stay, the combined results of all the studies (see Figs. 7 and 8) demonstrated a significant reduction when all patients were analyzed together, and also when patients with GI cancer were examined separately. This could have major financial implications. However, a cost/benefit analysis comparing total costs for all patients needs to be done in this context. Another important point to consider when interpreting anal-

yses such as these is that the censoring effects of death may not be accommodated appropriately; this is because the reduction in infectious complications and hospital stay may be influenced by the patient's dying. To overcome this problem, survival analysis methodology requiring data on the event times for every patient would be necessary for this calculation, and this is not provided in these studies.

The supplemented nutritional regimens used were Impact in six of the trials (used in all studies of patients with GI cancer) and Immun-Aid in two. In the remaining study, the diet was enriched with L-arginine and L-glutamine. However, in three of these studies,[32,33,36] the patients in the control group received a substantially lower nitrogen intake than did those in the experimental group. Further, in four studies the experimental diet also contained increased amounts of trace elements and vitamins, many of which have been shown also to enhance the immune response.[32,33,38,43]

In conclusion, supplemented nutritional support may result in a reduction in major infectious complications and reduce the length of hospital stay in all patients with critical illness and in those with GI cancer. However, further well-designed studies (with adequate statistical power), focusing on defined patient groups, with a clearly defined supplemented nutritional regimen, appropriate control nutritional supplement, and precise outcome measures are now urgently required to confirm that supplemented nutritional supplementation has beneficial effects on clinical outcome in critically ill patients. Lastly, when reporting the results of randomized studies, the guidelines described in the CONSORT statement should be followed to allow better interpretation of trial results.[44]

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