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Should Immunonutrition Become Routine in Critically Ill Patients?

A Systematic Review of the Evidence

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NOSOCOMIAL INFECTION IN critically ill patients is associated with higher morbidity and mortality, prolonged intensive care unit (ICU) and hospital stay, and increased health care costs.¹⁻³ Among seriously ill patients, malnutrition has been associated with increased infectious morbidity and prolonged hospital stay.⁴ Providing nutrition support has become the standard of care for critically ill patients. Enteral nutrition is preferred to parenteral nutrition for meeting the nutritional needs of critically ill patients with functioning alimentary tracts.⁵

Several specific nutrients such as arginine, glutamine, nucleotides, and omega-3 fatty acids, either alone or in combination, have been shown in laboratory and clinical studies to influence nutritional, immunological, and inflammatory parameters.⁶⁻¹¹ To date, there have been several randomized trials that have evaluated the effect of these immunonutrients on clinically important outcomes. To our knowledge, 2 systematic reviews have already statistically aggregated the results of these randomized clinical trials in critically ill patients.^{12,13} However, methodological limitations of

Context Several nutrients have been shown to influence immunologic and inflammatory responses in humans. Whether these effects translate into an improvement in clinical outcomes in critically ill patients remains unclear.

Objective To examine the relationship between enteral nutrition supplemented with immune-enhancing nutrients and infectious complications and mortality rates in critically ill patients.

Data Sources The databases of MEDLINE, EMBASE, Biosis, and CINAHL were searched for articles published from 1990 to 2000. Additional data sources included the Cochrane Controlled Trials Register from 1990 to 2000, personal files, abstract proceedings, and relevant reference lists of articles identified by database review.

Study Selection A total of 326 titles, abstracts, and articles were reviewed. Primary studies were included if they were randomized trials of critically ill or surgical patients that evaluated the effect of enteral nutrition supplemented with some combination of arginine, glutamine, nucleotides, and omega-3 fatty acids on infectious complication and mortality rates compared with standard enteral nutrition, and included clinically important outcomes, such as mortality.

Data Extraction Methodological quality of individual studies was scored and necessary data were abstracted in duplicate and independently.

Data Synthesis Twenty-two randomized trials with a total of 2419 patients compared the use of immunonutrition with standard enteral nutrition in surgical and critically ill patients. With respect to mortality, immunonutrition was associated with a pooled risk ratio (RR) of 1.10 (95% confidence interval [CI], 0.93-1.31). Immunonutrition was associated with lower infectious complications (RR, 0.66; 95% CI, 0.54-0.80). Since there was significant heterogeneity across studies, we examined several a priori subgroup analyses. We found that studies using commercial formulas with high arginine content were associated with a significant reduction in infectious complications and a trend toward a lower mortality rate compared with other immune-enhancing diets. Studies of surgical patients were associated with a significant reduction in infectious complication rates compared with studies of critically ill patients. In studies of critically ill patients, studies with a high-quality score were associated with increased mortality and a significant reduction in infectious complication rates compared with studies with a low-quality score.

Conclusion Immunonutrition may decrease infectious complication rates but it is not associated with an overall mortality advantage. However, the treatment effect varies depending on the intervention, the patient population, and the methodological quality of the study.

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the previous reviews weaken the inferences that can be drawn from them. These reviews included a limited data set since the authors of each study searched MEDLINE, included articles published in English,¹⁴ and included studies available before January 1998. One of the meta-analyses¹² did not include some of the key studies on the topic^{15,16} and included duplicate data.¹⁷ The other meta-analysis¹³ aggregated studies of only 2 commercially produced formulas without providing justification for not including other formulations. Given that several studies are available in languages other than English and that new studies have been published subsequent to the previous reviews, we undertook a third meta-analysis of immunonutrition.

The purpose of this article is to systematically review, critically appraise, and synthesize randomized clinical trial data evaluating the effect of enteral immunonutrients in critically ill patients.

METHODS

Study Identification

Using text word or MeSH terms *randomized, blind, clinical trial, nutrition, arginine, glutamine, omega-3 fatty acids, fish oil, nucleotides, immune, and immunonutrition*, we performed computerized searches for relevant articles on MEDLINE, EMBASE, Biosis, and CINAHL electronic databases from 1990 to 2000 and the Cochrane Controlled Trials Register from 1990 to 2000. We contacted the major manufacturers of “immune-enhanced” formulas and asked for additional published and unpublished studies. We also searched reference lists of review and original articles, personal files, and abstract proceedings of recent scientific meetings.

Study Selection Criteria

Two of us (D.K.H. and F.N.) screened all citations and classified them as primary studies, review articles, or other. All primary studies were retrieved and reviewed independently. We included

Table 1. Methodological Quality Assessment Criteria

| Criterion | Score | | |
|-------------------------------------|-------------------------------------|-------------------------------------|------------------------------|
| | 0 | 1 | 2 |
| Randomization | Not applicable | Not concealed or not sure | Concealed randomization |
| Analysis | Other | Not applicable | Intention-to-treat |
| Blinding | Not blinded | Single blind | Double blind |
| Patient selection | Selected patients or unable to tell | Consecutive eligible patients | Not applicable |
| Comparability of groups at baseline | No or not sure | Yes | Not applicable |
| Extent of follow-up | <100% | 100% | Not applicable |
| Treatment protocol | Poorly described | Reproducibly described | Not applicable |
| Cointerventions* | Not described | Described but not equal or not sure | Well described and all equal |
| Outcomes | Not described | Partially described | Objectively defined |

*The extent to which antibiotics, nutritional support, ventilation, oxygen, and transfusions were applied equally across groups.

primary studies if they (1) were randomized clinical trials; (2) studied critically ill or surgical patients; (3) compared enteral nutrition supplemented with any combination of arginine, glutamine, omega-3 fatty acids, or nucleotides compared with standard enteral nutrition; and (4) included clinically important outcomes, such as mortality, infectious complications, and length of hospital stay.

To select studies with the greatest validity in terms of relative treatment effect, we included only randomized clinical trials.¹⁸ We excluded the studies reporting only nutritional or immunological outcomes.¹⁹ We defined critically ill patients as being routinely cared for in a critical care environment. Although patients after major surgery are not necessarily cared for in a critical care environment, we included studies of elective surgical patients because their response to illness resembles the hypercatabolic state in critical illness.²⁰ In addition, previous meta-analyses combined data from both surgical and critically ill patients.^{12,13}

Immune-enhancing nutrients are a group of chemically heterogeneous substances. Only a small number of clinical trials evaluate the efficacy of a single agent; most of the studies examine various combinations of these nutrients. We included studies that compared enteral nutrition containing at least 2 or

more of the 4 most frequently used immune-enhancing nutrients (arginine, glutamine, omega-3 fatty acids, or nucleotides) vs standard enteral nutrition only.

Data Extraction and Assessment of Methodological Quality of Primary Studies

We assessed study method quality by using 9 parameters that influence the ability of the study to provide a true estimate of treatment effect (TABLE 1). Using a system⁵ that we have used in previous analyses, we scored the methodological quality of individual studies (range, 0-14) and abstracted necessary data in duplicate and independently. Disagreement was resolved by consensus. We attempted to contact the authors of included studies and requested further information not contained in published articles.

Prior Hypotheses Regarding Sources of Heterogeneity

The presence of heterogeneity (or between-study differences in treatment effect) is a major threat to the validity of meta-analyses. Heterogeneity weakens, if not invalidates, the overall results obtained from the aggregated analysis of randomized trials. If present, heterogeneity may be due to differences across studies in their methods, study populations, interventions,

outcomes, or due to chance. A priori, we postulated that heterogeneity may be explained by the following hypotheses, which we formally tested in the form of subgroup analyses.

First, the methodological quality of the primary randomized trials included in a meta-analysis influences the aggregated results.¹⁸ Therefore, we planned to compare studies with higher methodological score (≥ 8) to those with a lower score (< 8 ; median score, 8).

Second, there is an increasing number of commercially produced formulations available on the market. Two of

the most frequently studied formulas (Immun-Aid, McGaw, Irvine, Calif; Impact, Novartis Nutrition, Minneapolis, Minn), which are similar in arginine content, were compared with the other formulations (which contain less arginine). We hypothesized that there could be an adverse effect caused by immunonutrition in critically ill patients with ongoing infection and sepsis. This may be due to increased production of nitric oxide as a consequence of arginine supplementation.²¹

Third, since a previous meta-analysis suggested that the treatment effect may

vary across subgroups of patients,⁵ we planned a separate analysis comparing studies of elective surgical patients with studies of critically ill patients. In the subset of studies of critically ill patients, we explored whether the treatment effect varied in studies of differing methodological quality and different products.

Data Synthesis

The primary outcomes of interest were mortality (ICU and hospital) and number of patients with new infectious complications. Although no standard definition was used in all studies, infectious

Table 2. Randomized Studies Evaluating Immunonutrition in Elective Surgical and Critically Ill Patients*

| Source, y | Methods Score† | Blinding | No. of Patients | Type of Experimental Diet | Isonitrogenous Diets | No./Total (%) | | |
|---|----------------|----------|-----------------|---------------------------|----------------------|---------------|--------------|---------------|
| | | | | | | Mortality | | Infectious |
| | | | | | | Experiment | Control | Experiment |
| Elective Surgical Patients | | | | | | | | |
| Daly et al, ³¹ 1992 | 10 | No | 85 | Impact‡ | No | 2/41 (4.9) | 0/44 (0) | 5/41 (12.2) |
| Daly et al, ³² 1995 | 9 | Yes | 60 | Impact‡ | Yes | 1/30 (3.3) | 2/30 (6.7) | 1/30 (3.3) |
| Braga et al, ²⁹ 1996 | 9 | Yes | 40 | Impact‡ | Yes | 0/20 (0) | 0/20 (0) | 2/20 (10) |
| Schilling et al, ²⁸ 1996 | 6 | No | 28 | Impact‡ | No | 0/14 (0) | 0/14 (0) | 3/14 (21.4) |
| Gianotti et al, ²⁷ 1997 | 8 | No | 174 | Impact‡ | Yes | 1/87 (1.1) | 2/87 (1.3) | 13/87 (14.9) |
| Senkal et al, ³³ 1997 | 8 | Yes | 154 | Impact§ | Yes | 3/77 (3.9) | 2/77 (2.6) | 17/77 (22.1) |
| Braga et al, ³⁴ 1999 | 12 | Yes | 206 | Impact | Yes | 0/102 (0) | 1/104 (1) | 14/102 (13.7) |
| Senkal et al, ³⁵ 1999 | 11 | Yes | 154 | Impact§ | Yes | 0/78 (0) | 0/76 (0) | 10/78 (12.8) |
| Snyderman et al, ³⁶ 1999 | 8 | Yes | 129 | Impact§ | No | 0/82 (0) | 0/47 (0) | 19/82 (23.2) |
| Critically Ill Patients | | | | | | | | |
| Cerra et al, ⁴⁴ 1990¶ | 8 | Yes | 20 | Impact | No | 1/11 (9.1) | 1/9 (11.1) | NA |
| Gottschlich et al, ³⁷ 1990 | 10 | Yes | 31 | Experimental formula# | Yes | 2/17 (11.8) | 1/14 (7.1) | NA |
| Brown et al, ³⁸ 1994 | 5 | No | 37 | Experimental formula# | Yes | 0/19 (0) | 0/18 (0) | 3/19 (15.8) |
| Moore et al, ³⁹ 1994 | 5 | No | 98 | Immun-Aid | No | 1/51 (2) | 2/47 (4.3) | 9/51 (17.6) |
| Bower et al, ⁴⁵ 1995¶ | 9 | Yes | 296 | Impact | Yes | 24/153 (15.7) | 12/143 (8.4) | 86/153 (56.3) |
| Kudsk et al, ⁴⁰ 1996 | 8 | Yes | 33 | Immun-Aid | Yes | 1/16 (6.3) | 1/17 (5.9) | 5/16 (31.3) |
| Ross Products Division of Abbott Laboratories, 1996** | 11 | Yes | 170 | Experimental formula# | Yes | 20/87 (23) | 8/83 (9.6) | 57/87 (65.5) |
| Engel et al, ⁴¹ 1997 | 6 | No | 36 | Impact | No | 7/18 (38.9) | 5/18 (27.8) | 6/18 (33.3) |
| Mendez et al, ⁴² 1997 | 6 | Yes | 43 | Experimental formula# | Yes | 1/22 (4.5) | 1/21 (4.8) | 19/22 (86.4) |
| Rodrigo and Garcia, ⁴⁶ 1997¶ | 7 | No | 30 | Impact | Yes | 2/16 (12.5) | 1/14 (7.1) | 5/16 (31.3) |
| Weimann et al, ⁴³ 1998 | 9 | Yes | 29 | Impact | Yes | 2/16 (12.5) | 4/13 (30.8) | NA |
| Atkinson et al, ¹⁵ 1998¶ | 11 | Yes | 390 | Impact | Yes | 95/197 (48.2) | 85/193 (44) | NA |
| Galban et al, ¹⁶ 2000¶ | 6 | No | 176 | Impact | Yes | 17/89 (19.1) | 28/87 (32.2) | 39/89 (43.8) |

*NA indicates data not available.
 †The range of the methods score was 0 to 14.
 ‡Intervention was administered after surgery.
 §Intervention was administered before and after surgery.
 ||Intervention was administered prior to surgery.
 ¶Baseline infections not excluded.
 #Consisted of L-arginine and omega-3 fatty acids.
 **Unpublished data.

complications included pneumonia, intra-abdominal abscess, sepsis, line sepsis, wound infection, and urinary tract infection. The secondary outcomes included length of hospital and ICU stay and duration of mechanical ventilation. We combined data from all studies to estimate the common risk ratio (RR) and associated 95% confidence intervals (CIs) for death and infectious complications. To avoid the problem with bias and instability associated with RR estimation in sparse data, we added half to each cell.²² In the meta-analysis, we used maximum likelihood methods of combining

RRs across all trials and examined the data for evidence of heterogeneity within groups.^{5,23} The Mantel-Haenszel method was used to test the significance of treatment effect.²⁴ We used a random-effects model to estimate the overall relative risk.^{25,26} Three studies²⁷⁻²⁹ randomized patients to 3 groups (immune-enhanced enteral formula, standard formula, and standard total parenteral nutrition). We only included data from the immune-enhanced enteral and standard enteral groups. For the length of stay analysis, the effect size (ES) was used to describe the standardized difference between 2 means from treatment and placebo. Hedges method³⁰ was used for estimating the individual ES and the pooled effect size between 2 treatments. We considered pooled ES to be more robust than pooled differences in means because it weights individual studies according to their sample variance. Since pooled ES is dimensionless, when we found a statistically significant result using ES, we reported the pooled-simple differences between 2 group means to provide the estimate of treatment effect in days. We used the *t* test for the differences across subgroups. We considered *P* < .05 to be statistically significant.

There were 12 articles and abstracts published by a group of authors from Milan, Italy.* We contacted the authors and excluded preliminary reports† of 3 studies published later.^{27,29,34} We also excluded 1 article that was in press⁶⁴ because data from the majority of patients had already been published in another article²⁷ together with data of other patients.

Effect of Enteral Immunonutrition on Mortality, Infectious Complication Rates, and Hospital Stay

There were 22 randomized trials involving 2419 patients that compared the use of immune-enhanced enteral formula with standard formulas. These studies included evaluations of the experimental enteral formula in patients undergoing elective surgery,^{27-29,31-36} critically ill patients with severe trauma,³⁸⁻⁴³ critically ill patients in an ICU (Ross Products Division of Abbott Laboratories, unpublished data; 1996),^{15,16,44-46} and critically ill patients with severe burns.³⁷ The details of each study, including the methodological quality score, are described in Table 2 and TABLE 3.

When the results of these trials were aggregated, with respect to mortality, immunonutrition was associated with no mortality advantage (RR, 1.10; 95% CI, 0.93-1.31; FIGURE 1). The test for heterogeneity was not significant (*P* = .54), although a visual inspection of Figure 1 suggests that the treatment effects were variable.

Eighteen studies reported infectious complications in study patients. The aggregated results of these studies suggest that immunonutrition was associated with fewer patients with infectious complications compared with standard formulas (RR, 0.66; 95% CI, 0.54-0.80; FIGURE 2). The test for heterogeneity was significant (*P* < .001).

We aggregated results of 17 studies reporting on length of hospital stay. Overall, patients receiving immunonu-

| Complications | Mean (SD) | |
|---------------|------------------|-------------|
| | Hospital Stay, d | |
| | Experiment | Control |
| 13/44 (29.5) | 18.8 (11.1) | 20.4 (9.6) |
| 9/30 (30) | 16 (0.9) | 22 (2.9) |
| 3/20 (15) | 13.2 (6.1) | 15.5 (3.5) |
| 6/14 (42.9) | 14.7 (4) | 20.3 (13) |
| 20/87 (23) | 16.1 (6.2) | 19.2 (7.9) |
| 24/77 (31.2) | 27 (2.3) | 30.6 (3.1) |
| 31/104 (29.8) | 11.1 (4.4) | 12.9 (4.6) |
| 18/76 (23.7) | 22.2 (4.1) | 25.8 (3.8) |
| 19/47 (40.4) | 15.3 (9.1) | 17.4 (11.9) |
| NA | 36.7 (8.5) | 54.7 (10.5) |
| NA | NA | NA |
| 10/18 (55.6) | NA | NA |
| 10/47 (21.3) | 14.6 (1.3) | 17.2 (2.8) |
| 90/143 (62.9) | 27.6 (23) | 30.9 (26.2) |
| 11/17 (64.7) | 18.3 (2.8) | 32.6 (6.6) |
| 52/83 (62.7) | 25.4 (26.1) | 20.9 (17.3) |
| 5/18 (27.8) | NA | NA |
| 12/21 (57.1) | 34 (21.2) | 21.9 (11.3) |
| 3/14 (21.4) | NA | NA |
| NA | 70.2 (52.9) | 58.1 (30.1) |
| NA | 20.6 (26.3) | 23.1 (31.6) |
| 44/87 (50.6) | NA | NA |

RESULTS

Study Identification and Selection

We identified a total of 326 citations. Initial eligibility screening resulted in 60 original articles describing human randomized trials of immunonutrition selected for further evaluation. Of these, 22 studies met all inclusion criteria (TABLE 2).

We reached 100% agreement on the inclusion of articles for this systematic review. Other randomized studies were excluded because the study evaluated immune-enhanced formula vs oral diet plus intravenous fluids only,⁴⁷ 2 different formulas both containing immune-enhancing nutrients,⁴⁸ formulas containing only one of the most frequently used immune-enhancing nutrients,⁴⁹⁻⁵⁶ the study results were duplicated in other publications,⁵⁷⁻⁶⁵ or the studies were available in abstract form only.⁶⁶⁻⁶⁸

*References 17, 27, 29, 34, 57, 59, 62-64, 69-71.
 †References 17, 57, 59, 62, 63, 69-71.

trition had a shorter length of hospital stay (ES, -0.63; 95% CI, -0.94 to -0.32; FIGURE 3). The test for heterogeneity was significant ($P < .001$). Using pooled

difference between 2 group means, we also found a shorter length of hospital stay (-3.33 days; 95% CI, -5.63 to -1.02 days).

Subgroup Analyses

As there was significant heterogeneity across the studies, we examined our a priori hypotheses. We compared the trials that used high-arginine-content formulas (Impact or Immun-Aid) with other formulas of relatively low-arginine content. There was no difference in mortality for high-arginine-content studies (RR, 1.05; 95% CI, 0.88-1.25), but we found a higher mortality in patients receiving immunonutrition in the subgroup of studies using formulas other than those of high arginine content (RR, 2.13; 95% CI, 1.08-4.21). The P value for the difference between these 2 subgroups was not statistically significant ($P = .06$). The rate of infectious complications was significantly lower in patients receiving formulas with high arginine content (RR, 0.55; 95% CI, 0.46-0.67) and there was no difference in the subgroup of formulas other than formulas with high arginine content (RR, 1.27; 95% CI, 0.74-2.22). The difference in infectious complications between these subgroups was statistically significant ($P = .01$). In addition, the subgroup of studies evaluating formulas with high arginine content was associated with significantly shorter length of hospital stay (ES, -0.77; 95% CI, -1.09 to -0.45) in the experimental group; using pooled difference between 2 group means, -4.19 days; 95% CI, -5.52 to -2.86 days. On the contrary, studies of other formulas showed a trend toward longer hospital stays (ES, 0.37; 95% CI, -0.09 to 0.83; $P = .11$). The P value for the difference between these 2 subgroups was .008.

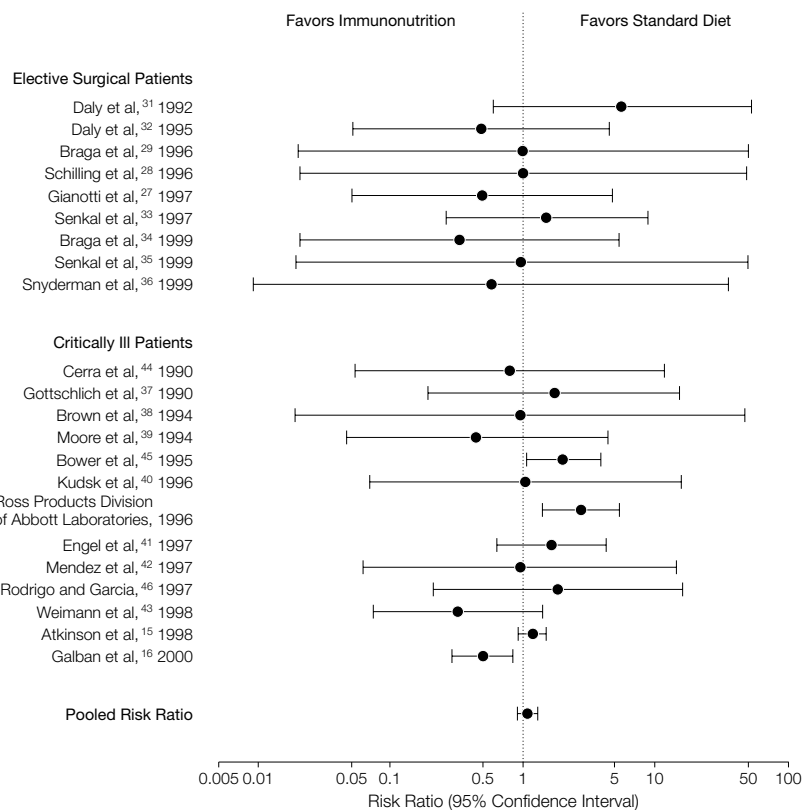
We then compared studies of critically ill patients with studies of elective surgical patients. In studies of critically ill patients (RR, 1.18; 95% CI, 0.88-1.58) and studies of surgical patients (RR, 0.99; 95% CI, 0.42-2.34), there was no difference in mortality (difference between subgroups, $P = .70$). In studies of critically ill patients, immunonutrition had no effect on infectious complications (RR, 0.96; 95% CI, 0.77-1.20). In studies of elective surgical patients, the number of patients with an infec-

Table 3. Randomized Studies of Critically Ill Patients Evaluating Effect of Immunonutrition on Intensive Care Unit (ICU) Length of Stay and Ventilator Use*

| Source, y | Mean (SD), d | | | |
|--|--------------------|-------------|----------------|-------------|
| | ICU Length of Stay | | Ventilator Use | |
| | Experiment | Control | Experiment | Control |
| Gottschlich et al, ³⁷ 1990 | NA | NA | 9 (4.5) | 10 (2.5) |
| Moore et al, ³⁹ 1994 | 5.3 (0.8) | 8.6 (3.1) | 1.9 (0.9) | 5.3 (3.1) |
| Kudsk et al, ⁴⁰ 1996 | 5.8 (1.8) | 9.5 (2.3) | 2.4 (1.3) | 5.4 (2) |
| Ross Products Division of Abbott Laboratories, 1996† | 14.8 (19.6) | 12 (10.9) | 14.3 (22.4) | 10.8 (12.8) |
| Engel et al, ⁴¹ 1997 | 19 (7.4) | 20.5 (5.3) | 14.8 (5.6) | 16 (5.6) |
| Mendez et al, ⁴² 1997 | 18.9 (20.7) | 11.1 (6.7) | 16.5 (19.4) | 9.3 (6) |
| Rodrigo and Garcia, ⁴⁶ 1997 | 8 (7.3) | 10 (2.7) | NA | NA |
| Weimann et al, ⁴³ 1998 | 31.4 (23.1) | 47.4 (32.8) | 21.4 (10.8) | 27.8 (14.6) |
| Atkinson et al, ¹⁵ 1998 | 10.5 (13.1) | 12.2 (23.2) | 8 (11.1) | 9.4 (17.7) |
| Galban et al, ¹⁶ 2000 | 18.2 (12.6) | 16.6 (12.9) | 12.4 (10.4) | 12.2 (10.3) |

*NA indicates data not available. †Unpublished data.

Figure 1. Effect of Immunonutrition on Mortality in 22 Trials



P value for homogeneity is .54. The study by the Ross Products Division of Abbott Laboratories has not been published.

tious complication was significantly lower (RR, 0.53; 95% CI, 0.42-0.68). The difference between these subgroups was statistically significant ($P = .002$). There was a significant decrease in length of hospital stay in studies of elective surgical patients (ES, -0.76; 95% CI, -1.14 to -0.37); using pooled difference between 2 group means, -3.39 days; 95% CI, -4.55 to -2.23 days. In addition, there was a significant reduction in length of hospital stay in studies of critically ill patients (ES, -0.47; 95% CI, -0.93 to -0.01; $P = .047$); using pooled difference between 2 group means, -3.34 days; 95% CI, -8.27 to 1.45 days. The P value for the difference between studies of elective surgery and critically ill patients was .95.

We also compared studies with a methodological quality score of less than 8 with trials with a score of 8 or more. Trials with a higher methods score suggested an increase in mortality (RR, 1.19; 95% CI, 0.99-1.43). We found a trend toward a lower mortality rate in studies with a lower methods score (RR, 0.74; 95% CI, 0.49-1.14). The difference between these 2 subgroups was not statistically significant ($P = .06$). There were fewer patients with infectious complications in studies with a higher methodological quality score (RR, 0.53; 95% CI, 0.42-0.68). Studies with lower quality scores did not show a difference in infectious complications (RR, 1.01; 95% CI, 0.68-1.50). The difference between these subgroups was significant ($P = .01$). There was a significant decrease in length of hospital stay in studies with a higher quality score (ES, -0.67; 95% CI -1.00 to -0.35); using pooled difference between 2 group means, -3.87 days; 95% CI, -6.63 to -1.12 days. However, there was no effect on length of hospital stay in studies with a lower quality score (ES, -0.37; 95% CI, -1.56 to 0.82). The P value for the difference between high-quality and low-quality studies was .30.

Effect of Enteral Immunonutrition on Critically Ill Patients

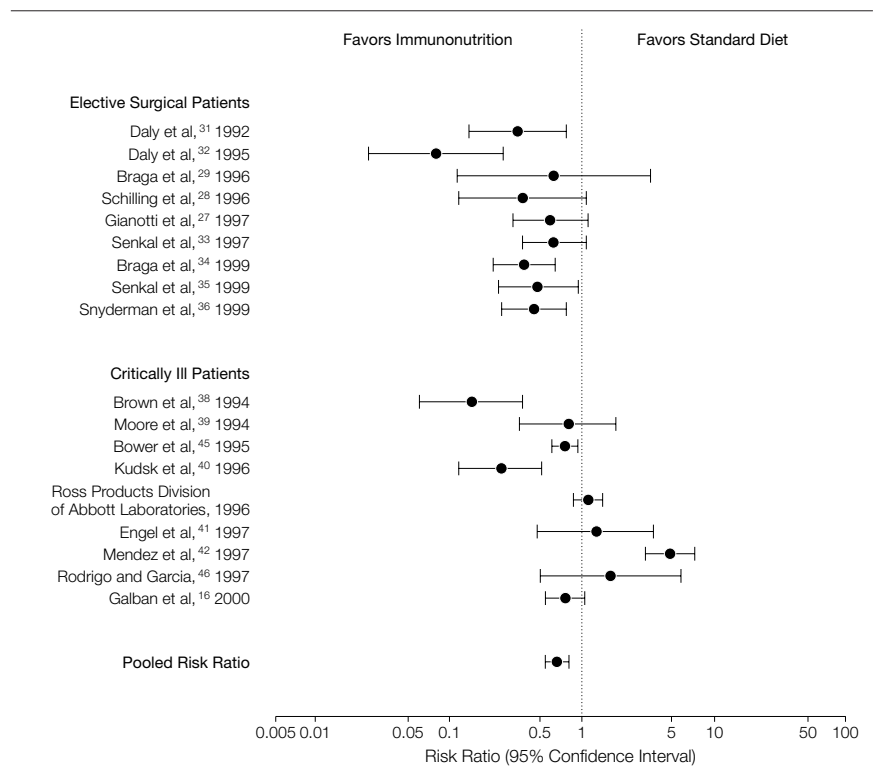
Within the subgroup of studies of critically ill patients, we further examined the

effect of immunonutrition on mortality, infectious complications, and duration of ICU stay and mechanical ventilator use. The overall effect of immunonutrition in critically ill patients is consistent with no treatment effect on mortality (RR, 1.18; 95% CI, 0.88-1.58) or rate of infectious complications (RR, 0.96; 95% CI, 0.77-1.20). However, immunonutrition was associated with a reduction in length of hospital stay (ES, -0.47; 95% CI, -0.93 to -0.01). In the subgroup analyses, we again found higher mortality in studies with formulas other than those high in arginine (RR, 2.13; 95% CI, 1.08-4.21) compared with no effect on mortality in studies with formulas of high arginine content (RR, 1.03; 95% CI, 0.75-1.41). The between-subgroup difference was not statistically significant ($P = .08$). With respect to infectious complications, there was no effect in studies evaluating formulas other than formulas of high arginine content (RR,

1.28; 95% CI, 0.74-2.22) and there was a trend toward a lower number of infectious complications in high-arginine-content studies (RR, 0.87; 95% CI, 0.75-1.02). The P value for the difference between subgroups was .20. With respect to length of hospital stay, those studies evaluating formulas of high arginine content were associated with a significantly shorter length of hospital stay (ES, -0.81; 95% CI, -1.38 to -0.24); using pooled difference between 2 group means, -7.19 days; 95% CI, -13.25 to -1.08 days. Studies of other formulas showed a trend toward a longer length of hospital stay (ES, 0.37; 95% CI, -0.09 to 0.83; $P = .11$); using pooled difference between 2 group means, 6.51 days; 95% CI, -0.06 to 13.10 days. The difference between formulas with high arginine content and other products was statistically significant ($P = .02$).

Trials of critically ill patients with higher methodological scores (≥ 8)

Figure 2. Effect of Immunonutrition on Infectious Complications in 18 Trials



P value for homogeneity is $<.001$. The study by the Ross Products Division of Abbott Laboratories has not been published.

demonstrated a significantly higher mortality associated with use of immunonutrition (RR, 1.46; 95% CI, 1.01-2.11). There was a trend to decreased mortality in studies with a lower methodological score (RR, 0.74; 95% CI, 0.49-1.14). The difference between subgroups was statistically significant ($P = .04$). There were fewer patients with infectious complications in trials with a higher methods score (RR, 0.80; 95% CI, 0.64-1.01). In studies with a lower methods score, immunonutrition was associated with no effect on complication rates (RR, 1.12; 95% CI, 0.74-1.70). The P value for the difference between subgroups was .20.

With respect to length of hospital stay, those studies with a higher methodological score were associated with a significantly shorter length of hospital stay (ES, -0.48; 95% CI, -0.95 to -0.01); using pooled differences between 2 group means, -5.35 days; 95%

CI, -14.90 to 1.21 days. Studies with a lower methodological score showed no difference in length of hospital stay (ES, 0.27; 95% CI, -2.12 to 1.60). The difference between these 2 groups was not statistically significant ($P = .28$).

We also aggregated studies of critically ill patients reporting on number of days of ventilator use and length of ICU stay. Immunonutrition was associated with a trend toward a shorter length of ICU stay (ES, -0.36; 95% CI, -0.76 to 0.04) and fewer days of mechanical ventilator use (ES, -0.35; 95% CI, -0.75 to 0.04). In both cases, the test for heterogeneity was statistically significant ($P < .001$).

COMMENT

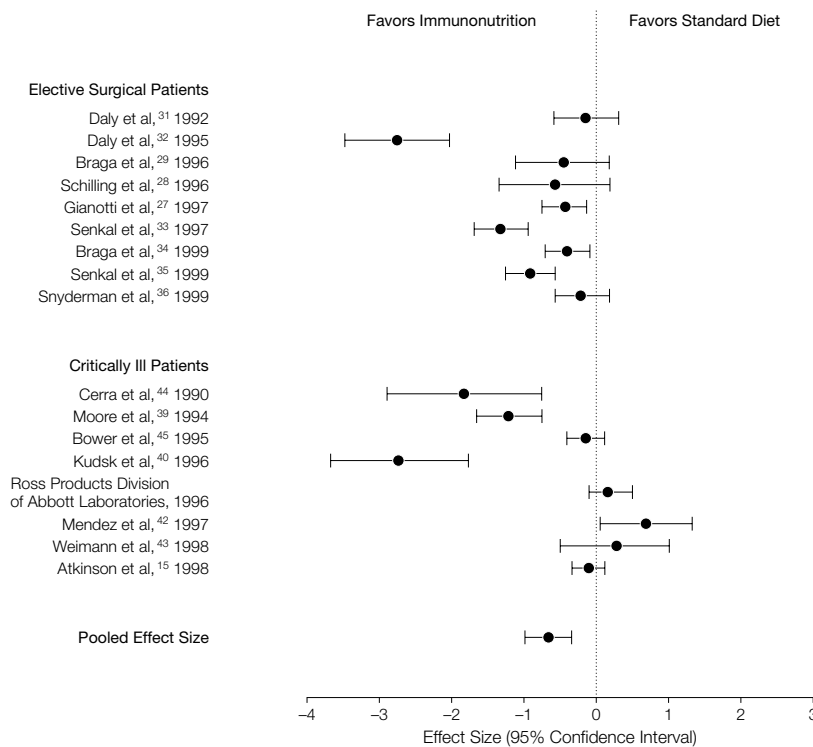
In this systematic review, we included studies that were recently published, indexed on databases other than MEDLINE, and published in non-English journals that were not in-

cluded in previous meta-analyses.^{12,13} When the results of the 22 randomized trials were aggregated, we did not find a statistically significant benefit of immunonutrition on mortality. Immunonutrition was associated with a statistically significant decrease in the number of patients with infectious complications and shorter length of hospital stay. However, the level of heterogeneity of the results across the studies was significant, precluding us from making strong inferences from the pooled overall results. Therefore, we performed several a priori-defined subgroup analyses trying to explain the heterogeneity across the trials. This exercise can be best viewed as hypothesis-generating rather than hypothesis-confirming.

In contrast to studies evaluating other products, studies evaluating formulas high in arginine were not associated with an increase in mortality and were associated with a significant reduction in infectious complications. Since all studies combined more than 1 specific nutrient, we can only speculate whether these differences might be due to a different dose of arginine or other specific nutrients. There is some suggestion from animal studies that arginine may have a variable response depending on the dose, underlying disease process, and timing of administration.^{72,73}

The effect of immunonutrition in critically ill patients may be systematically different from the treatment effect in elective surgical patients. Immunonutrition was associated with significantly fewer infectious complications in elective surgical patients, but there was no such effect in critically ill patients. There was a trend toward higher mortality in studies of critically ill patients, while there was no effect on mortality in elective surgical patients. These findings are supported by a previous meta-analysis of total parenteral nutrition⁵ that also demonstrated significant differences in treatment effect in elective surgical and critically ill patients. Perhaps these differences are due to differences in underlying pathophysiology, popula-

Figure 3. Effect of Immunonutrition on Length of Hospital Stay in 17 Trials



P value for homogeneity is $< .001$. The study by the Ross Products Division of Abbott Laboratories has not been published.

tions studied, other cointerventions, or outcomes.

Generally, elective surgical patients are at a much lower risk of adverse outcomes (complications and/or death) than critically ill patients. Following surgical stress, patients experience some degree of immunosuppression,^{74,75} increasing their risk for acquired infectious morbidity and mortality. It follows that immunostimulation in elective surgical patients may reduce infectious complications. In critically ill patients, the associated changes to the immune system accompanying critical illness are complex, variable, and poorly defined. Novel therapies that have been shown to be effective in critical illness decrease the inflammatory response rather than stimulate it. We suggest that the results of studies of elective surgical patients should not be generalized to critically ill patients.

Focusing on the results of the studies of critically ill patients, our meta-analysis suggests that there is no overall effect of immunonutrition on mortality, infectious complications, length of ICU stay, or duration of mechanical ventilation. Immunonutrition is associated with an overall reduction in length of hospital stay. However, in the subgroup analysis, there is some evidence that immunonutrition may do more harm than good. Studies using products other than those high in arginine seem to be associated with an increased mortality rate and a trend toward increased complications. In addition, studies of high quality are associated with a significant increase in mortality and a significant reduction in infectious complications. One possible explanation for fewer infectious complications and shorter length of hospital stay is that more patients die and die early in the course of their illness so that they have a lower chance of becoming infected. This can be supported to some extent by the largest randomized trial of critically ill patients (contributing to 45.8% of all deaths in this meta-analysis). In this study, Atkinson et al¹⁵ compared an immune-enhancing formula with a stan-

dard formula in 398 critically ill patients. On an intention-to-treat basis, 48% of the patients who received the immune-enhancing formula died compared with 44% in the control group ($P = .36$). There was no significant difference in length of hospital or ICU stay. When the data analysis was restricted to the 25% of the randomized patients who received a specific amount of enteral nutrition within the first 72 hours, they found a significant reduction in duration of mechanical ventilation use and length of ICU stay in patients receiving the immune-enhancing formula. However, patients receiving immunonutrition also tended to have an increased mortality rate ($P = .16$) and to die earlier, which may explain why length of stay was reduced.

The methodological quality of individual randomized trials has been shown to influence the overall treatment effect in meta-analyses.^{5,18} Using a tool that we have used in previous meta-analyses,⁵ we evaluated each individual study for its methodological strengths and weaknesses, weighing the presence of concealed randomization, double-blinding, and intention-to-treat analysis more than other criteria. The median score was 8. Post-hoc, we found that studies that scored 8 or above also had at least 2 of the 3 key criteria (concealed randomization, double-blinding, and intention-to-treat analysis). If we accept that the highest-quality studies of critically ill patients offer the most valid estimate of treatment effect in critically ill patients, this meta-analysis raises concerns that immunonutrition may do more harm than good in this population.

Is it plausible that immunonutrition may do more harm than good in critically ill patients? This hypothesis is consistent with examining individually the results of 2 large randomized trials of critically ill patients. The first study, conducted by Bower et al,⁴⁵ demonstrated that significantly more patients who received immunonutrition died (RR, 2.00; 95% CI, 1.01-3.75; $P = .04$). Overall infectious episodes were similar between both groups. In

the subgroup of patients stratified at baseline as septic, there was a shorter length of hospital stay. However, mortality in this subgroup receiving immunonutrition was 3 times higher than that of septic patients who received standard enteral nutrition (11/44 [25%] vs 4/45 [8.9%]; $P = .05$). The second study was an unpublished randomized trial that also demonstrates that immunonutrition is associated with increased mortality (Ross Products Division of Abbott Laboratories, unpublished data, 1996). One hundred seventy critically ill patients were randomized to receive either an experimental diet consisting of supplemental arginine, omega-3 fatty acids, and vitamins A and E, and β carotene or isonitrogenous enteral nutrition. There were significantly more deaths in the group that received the experimental formula (20/87 [23.0%]) compared with the control group (8/83 [9.6%]; $P = .03$). However, there were more patients with pneumonia at baseline in the group that received the experimental formula compared with patients in the control group. It was in this subgroup (patients with pneumonia at baseline who received an experimental diet), in which the excess deaths occurred in the experimental group (10/26 [38.5%]) compared with control group (0/9 [0%]). Therefore, we can only speculate as to whether stimulating the immune system of infected critically ill patients may be harmful.

These findings contradict a recently published study by Galban et al.¹⁶ This study included 181 critically ill patients who presented with laboratory or clinical signs of infection on admission to the ICU and who were randomized to receive Impact or standard enteral nutrition. The overall results demonstrated that Impact was associated with a significantly lower ICU mortality (RR, 0.50; 95% CI, 0.25-1.00), but no significant change in overall ICU acquired infectious morbidity and length of ICU stay. However, the treatment effect of immunonutrition was only evident in the least sick group of patients (baseline Acute Physiology and Chronic

Health Evaluation [APACHE] II score, 10-15). There was no mortality advantage among the patients with the highest baseline APACHE II score who received immunonutrition. This study was not blinded, did not report on cointerventions, and dropped randomized patients from the analysis. Among 13 randomized trials of critically ill patients, there are no other studies, apart from that of Galban et al,¹⁶ which demonstrate a clear improvement in mortality associated with immunonutrition.

Our study has several limitations. First, as we excluded studies of single immune-enhancing agents,⁴⁹⁻⁵⁶ the results of our meta-analysis are not applicable to single interventions. Second, our method of scoring the quality of each trial did not allow us to determine which component of quality was most important. Third, we did not apply meta-regression techniques to determine if there are confounding effects between different variables explaining the heterogeneity.

In conclusion, immunonutrition may decrease infectious complication rates. However, the treatment effect varies depending on the patient population, the intervention, and the methodological quality of the study. In elective surgical patients, immunonutrition is associated with a reduction in infectious complication rates and a shorter length of hospital stay without any adverse effect on mortality. However, in critically ill patients, immunonutrition is not associated with any apparent clinical benefits and it may be harmful in some subgroups of patients. Given the methodological weaknesses of the primary studies, their sample size, and the suggestion that immunonutrition may be associated with an increased mortality in critically ill patients (as evidenced by the studies with a higher methods score), we cannot recommend immunonutrition to all critically ill patients. Further research needs to define the underlying mechanism by which immunonutrition may be harmful and to identify which products and which patients are associated with clinical benefit.

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Study supervision: Heyland, Drover, Jain.

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