CORRESPONDENCE

Trial of the Route of Early Nutritional Support in Critically Ill Adults

TO THE EDITOR: In reporting the results of the CALORIES trial, Harvey and colleagues (Oct. 30 issue)[1] indicate that the route of delivery of early nutritional support in the intensive care unit (ICU) does not alter patient outcomes. This message contradicts the widely held belief that the enteral route, which is more physiological, is to be preferred. However, we think that there is another implicit message: this study suggests that the role of nutritional support in the ICU should be reconsidered. Past evidence has led researchers to implement an overzealous approach to nutritional support in patients in the ICU. Given the results from the present study, we should probably take a step backward. There is still an unanswered question regarding which critically ill patients should receive early nutritional support. Some recent trials[1-3] suggest that such patients may be those with depleted body stores due to malnutrition rather than all those who are at nutritional risk as a consequence of critical illness. We believe that targeting early nutritional support to the right patients constitutes a key point that should be addressed.

Once that question is addressed, we could focus again on timing, the route of delivery, protein and caloric targets, and nutrients that have putative pharmacologic activity.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1414479

TO THE EDITOR: The external validity of the study by Harvey et al. is questionable in our view. The inclusion criteria do not adhere to standards of care[1,2] based on updated literature (see www.criticalcarenutrition.com). These standards call for the preferential use of enteral nutrition in patients who are able to receive it. The area in which experts and guidelines disagree is the timing of supplemental parenteral nutrition in patients who are unable to receive sufficient enteral nutrition without unacceptable side effects.[3,4] The lack of advantage of early parenteral nutrition in the CALORIES study is not surprising, given that some patients may not have needed any nutritional support and the most appropriate route was not assessed in other patients in this trial. Both the low protein intake and the low caloric intake, as well as the low number of patients per center, are other major concerns. In our view, the primary outcome, all-cause mortality at 30 days, was also unlikely to be related to the efficacy of

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the therapeutic interventions. The contribution of this study would have been much more valuable after a selection of patients in whom the adequacy of nutrition mattered and could be properly evaluated.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1414479

TO THE EDITOR: In my view, the CALORIES trial fails to support the hypothesis that the parenteral route is superior to the enteral route for the delivery of early nutritional support in adults. According to the trial design, even patients who were assigned to the parenteral group received the benefits of enteral nutrition. A significant number of patients in the parenteral group received enteral nutrition both during the 120-hour period and after it. Among 700 patients in the parenteral group, only 13 patients (1.9%) exclusively received parenteral nutrition after the intervention. Extrapolation of such a short duration of parenteral nutrition with or without enteral nutritional support to estimate the effect on mortality at 30 days is not ideal. Data about coexisting diseases such as diabetes mellitus, hypertension, congestive heart failure, and chronic obstructive pulmonary disease — all of which may have an important effect on secondary outcome measures — are not mentioned. The summary of the original protocol (available with the full text of the article at NEJM.org) mentions a primary objective to estimate the incremental cost-effectiveness of early parenteral nutrition as compared with early enteral nutrition at 1 year. I do not find mention of this in the article.

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No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1414479

THE AUTHORS REPLY: CALORIES was a pragmatic trial evaluating the effectiveness of the parenteral route as compared with the enteral route for early nutritional support in critically ill adults. Nutritional support was initiated within 36 hours after unplanned admission to one of a representative sample of ICUs in England and was used exclusively for 120 hours.

The suggestion by Cereda and Caccialanza that critically ill patients should receive early nutritional support only if they are malnourished is interesting but not directly relevant to our trial. Therefore, we do not believe that our data can be interpreted either to support or to refute their hypothesis, which we agree merits further consideration.

Preiser and colleagues appear to advocate opinion-based guidelines and a meta-analysis of small, older, and methodologically compromised studies, rather than evidence from a large, rigorous, randomized, controlled trial. We disagree with such an approach. Contrary to their assertion, all patients recruited into the CALORIES trial met standard criteria to receive nutritional support, as our article made clear. Moreover, effectiveness, not efficacy, was tested in our pragmatic trial. Despite their belief that mortality was unlikely to be affected by the route of nutritional support, the meta-analysis by Simpson and Doig[1] suggested otherwise. The energy intake and protein intake in our pragmatic trial were similar to or greater than those in other studies of nutritional support in clinical practice.[2] In addition, the number of eligible patients recruited per center was greater than that in another recent, large, multicenter trial of nutritional support in intensive care.[3]

Ramamurthy's statement that benefits are associated with the use of the enteral route rather

than the parenteral route is not supported by our trial. Our aim was to evaluate the effect of the route for the delivery of early nutritional support, and the number of patients in the parenteral group who were fed enterally during the 120-hour intervention period was small. Baseline characteristics, including coexisting conditions, were well balanced between the groups and were summarized in Table 1 of our article. A 1-year follow-up study is under way to assess longer-term outcomes and to provide an integrated economic evaluation.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1414479

Etanercept Tapering in Rheumatoid Arthritis

TO THE EDITOR: The study by Emery et al. (Nov. 6 issue)[1] contravenes the recommendations not to use biologic agents as first-line treatment for rheumatoid arthritis. Furthermore, the study uses biased control groups (methotrexate monotherapy and placebo) and does not compare the combination treatment (etanercept plus methotrexate) with a balanced combination of disease-modifying antirheumatic drugs (DMARDs). Several studies have shown that such a combination is as effective as biologic treatment, especially when combined with a short-term initial course of glucocorticoids.[2-4]

Owing to a lack of comparison with DMARD combination therapy, the conclusion of the study is inappropriately biased in favor of etanercept. The correct first-line treatment algorithm for rheumatoid arthritis includes DMARD monotherapy and combination therapy. Biologic agents should be reserved as second-line therapy for patients with rheumatoid arthritis who have an insufficient response to combination DMARD treatment.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1414787

THE AUTHORS REPLY: Graudal and Jürgens contend that our study contravenes recommendations not to use biologic agents as first-line therapy for rheumatoid arthritis. The recommendations of the European League against Rheumatism (EULAR) in 2010,[1] when the study started, stated that biologic agents could be used first in the case of severe disease. In 2013, the recommendations[2] were modified (not by unanimous decision) to suggest that conventional synthetic DMARDs be used first. Graudal and Jürgens also indicate that a comparison with methotrexate monotherapy rather than with combination DMARDs biased the study. However, the 2013 EULAR recommendations do not endorse initial triple therapy but suggest initial methotrexate monotherapy, albeit plus glucocorticoids.