Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

Yaseen M. Arabi, M.D., Abdulaziz S. Aldawood, M.D., Samir H. Haddad, M.D., Hasan M. Al-Dorzi, M.D., Hani M. Tamim, M.P.H., Ph.D., Gwynne Jones, M.D., Sangeeta Mehta, M.D., Lauralyn McIntyre, M.D., Othman Solaiman, M.D., Maram H. Sakkijha, R.D., Musharaf Sadat, M.B., B.S., and Lara Afesh, M.S.N., for the PermiT Trial Group*

BACKGROUND
The appropriate caloric goal for critically ill adults is unclear. We evaluated the effect of restriction of nonprotein calories (permissive underfeeding), as compared with standard enteral feeding, on 90-day mortality among critically ill adults, with maintenance of the full recommended amount of protein in both groups.

METHODS
At seven centers, we randomly assigned 894 critically ill adults with a medical, surgical, or trauma admission category to permissive underfeeding (40 to 60% of calculated caloric requirements) or standard enteral feeding (70 to 100%) for up to 14 days while maintaining a similar protein intake in the two groups. The primary outcome was 90-day mortality.

RESULTS
Baseline characteristics were similar in the two groups; 96.8% of the patients were receiving mechanical ventilation. During the intervention period, the permissive-underfeeding group received fewer mean (±SD) calories than did the standard-feeding group (835±297 kcal per day vs. 1299±467 kcal per day, P<0.001; 46±14% vs. 71±22% of caloric requirements, P=0.001). Protein intake was similar in the two groups (57±24 g per day and 59±25 g per day, respectively; P=0.29). The 90-day mortality was similar: 121 of 445 patients (27.2%) in the permissive-underfeeding group and 127 of 440 patients (28.9%) in the standard-feeding group died (relative risk with permissive underfeeding, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P=0.58). No serious adverse events were reported; there were no significant between-group differences with respect to feeding intolerance, diarrhea, infections acquired in the intensive care unit (ICU), or ICU or hospital length of stay.

CONCLUSIONS
Enteral feeding to deliver a moderate amount of nonprotein calories to critically ill adults was not associated with lower mortality than that associated with planned delivery of a full amount of nonprotein calories. (Funded by the King Abdullah International Medical Research Center; PermiT Current Controlled Trials number, ISRCTN68144998.)

* A complete list of investigators in the Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

From King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center (Y.M.A., A.S.A., S.H.H., H.M.A.-D., H.M.T., M.H.S., M.S., L.A.); and King Faisal Specialist Hospital and Research Center (O.S.) — all in Riyadh, Saudi Arabia; the Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon (H.M.T.); and the Department of Medicine, Division of Critical Care Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa (G.J., L.M.); and the Interdepartmental Division of Critical Care Medicine, Department of Medicine, Division of Respiratory, University of Toronto, and Mount Sinai Hospital, Toronto (S.M.) — all in Canada. Address reprint requests to Dr. Arabi at the Intensive Care Department, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, ICU 1425, P.O. Box 22490, Riyadh 11426, Saudi Arabia, or at arabi@ngha.med.sa.

This article was published on May 20, 2015, at NEJM.org.
DOI: 10.1056/NEJMoaa1502826
Copyright © 2015 Massachusetts Medical Society.
NUTRITIONAL SUPPORT IS AN ESSENTIAL component of the care of critically ill adults. Achieving caloric targets has been recommended with the premise that attenuating malnutrition and protein catabolism, which are associated with increased morbidity and mortality, will improve outcomes. Observational studies examining various doses of enteral feeding have yielded conflicting results. Two cluster-randomized, controlled trials comparing higher enteral nutritional delivery with usual care in critically ill patients showed no reduction in mortality with the higher enteral nutrition. Augmenting energy intake with early parenteral nutrition has been shown to result in no change in mortality and in an increased time to discharge from the intensive care unit (ICU).

Conversely, caloric restriction may be beneficial; it has been shown to prolong life span in several species, promote mammalian cell survival, and improve longevity biomarkers in humans, possibly through its effects on metabolic, hormonal, and inflammatory pathways. Among critically ill patients receiving parenteral nutrition, lower morbidity was observed with hypocaloric nutrition than with standard nutritional support. Two randomized, controlled trials involving patients with acute lung injury or acute respiratory failure evaluated minimal or trophic enteral feeding (15 to 25% of estimated caloric requirements) with no protein supplementation for up to 6 days and showed outcomes that were similar to those with standard enteral feeding. Whether restricting nonprotein calories (permissive underfeeding) in conjunction with meeting full protein requirements improves outcomes is unclear, although reviews of the existing evidence recommend a level of protein intake during early critical illness that is sufficient to satisfy full protein requirements, regardless of the simultaneous caloric intake. A study in rats showed that protein refeeding, but not glucose refeeding, restores mitochondrial function that has been reduced by malnutrition. Therefore, it has been suggested that caloric restriction may be beneficial only if adequate dietary protein is provided.

Such findings prompt the question of whether moderate caloric restriction while protein intake is preserved would improve the outcomes in critically ill adults. In a single-center, randomized, controlled trial of moderate caloric intake (60 to 70% of the estimated caloric requirement) versus standard caloric intake (90 to 100%), with maintenance of the full targeted protein intake in both groups, we observed that the lower caloric intake was associated with a reduction in inhospital mortality, which was a secondary end point. We hypothesized that a permissive-underfeeding strategy that restricts nonprotein calories but preserves protein intake, as compared with a standard feeding strategy, would reduce 90-day mortality among critically ill adults.

STUDY DESIGN
The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial was an unblinded, pragmatic, randomized, controlled trial conducted at seven tertiary care centers in Saudi Arabia and Canada between November 2009 and September 2014. The institutional review board at each participating center approved the study. Written informed consent was obtained from all the patients or their legal representatives. The study was sponsored by the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, and the investigators designed, managed, and analyzed the study independently. Patients were eligible for the trial if they were fed enterally within 48 hours after ICU admission. Inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study protocol is also available at NEJM.org.

INTERVENTIONS
Enrolled patients were randomly assigned to the permissive-underfeeding group or the standard-feeding group with the use of opaque, sealed, sequentially numbered envelopes. The randomization list was computer-generated. Randomization was performed in random permuted blocks and was stratified according to center. The feeding strategy was unblinded because of the need for adjustment of the nutritional support according to feeding tolerance and gastric residual volumes. ICU dietitians estimated patients’ standard caloric requirements using the equation developed by investigators at Pennsylvania State University.

METHODS

STUDY DESIGN
The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial was an unblinded, pragmatic, randomized, controlled trial conducted at seven tertiary care centers in Saudi Arabia and Canada between November 2009 and September 2014. The institutional review board at each participating center approved the study. Written informed consent was obtained from all the patients or their legal representatives. The study was sponsored by the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, and the investigators designed, managed, and analyzed the study independently. Patients were eligible for the trial if they were fed enterally within 48 hours after ICU admission. Inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study protocol is also available at NEJM.org.

INTERVENTIONS
Enrolled patients were randomly assigned to the permissive-underfeeding group or the standard-feeding group with the use of opaque, sealed, sequentially numbered envelopes. The randomization list was computer-generated. Randomization was performed in random permuted blocks and was stratified according to center. The feeding strategy was unblinded because of the need for adjustment of the nutritional support according to feeding tolerance and gastric residual volumes. ICU dietitians estimated patients’ standard caloric requirements using the equation developed by investigators at Pennsylvania State University.
University (the Penn State equation) for mechanically ventilated patients who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 30 and using the 1992 Ireton-Jones equation for mechanically ventilated patients who had a BMI of 30 or higher and for spontaneously breathing patients (Table S2 in the Supplementary Appendix).

The caloric goal was 40 to 60% of caloric requirements in the permissive-underfeeding group and 70 to 100% of caloric requirements in the standard-feeding group. We set the caloric goal in the permissive-underfeeding group at a lower level than we did in the earlier trial, with the premise that a larger separation in caloric intake between the two groups would lead to a larger treatment effect. The assigned intervention was continued for up to 14 days or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition as part of palliation. Participating centers used their own protocols to guide delivery of enteral feeding. Daily caloric targets were established to achieve the prescribed nutritional delivery, and if caloric intake was below the target on a given day, intake was increased the following day to compensate. Calculation of actual intake included calories received from propofol, intravenous dextrose, and parenteral nutrition. Additional details of the interventions have been published previously and are also provided in the Supplementary Appendix.

Cointerventions
Protein requirements were calculated at 1.2 to 1.5 g per kilogram of body weight per day, in accordance with clinical practice guidelines. To ensure that enteral protein and volume delivery in the permissive-underfeeding group would be similar to those in the standard-feeding group, the permissive-underfeeding group received additional protein (Beneprotein, Nestlé Nutrition) and normal saline or water at a dose of 2 ml per kilogram every 4 hours unless otherwise specified by the clinical team. The study protocol provided suggestions on the selection of enteral formulas on the basis of published guidelines; however, the decision was left to the clinical team (Table S3 in the Supplementary Appendix).

Study centers used their own insulin protocols, with a target blood glucose level of 4.4 to 10 mmol per liter (80 to 180 mg per deciliter) in both groups. The study protocol recommended daily enteral multivitamins for all patients (Table S4 in the Supplementary Appendix). All other cointerventions were left to the discretion of the treating team.

Data Collection
At baseline, we collected data on patient demographics, diabetes history, admission category (medical, surgical, or trauma), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and use of mechanical ventilation, vasopressors, or renal-replacement therapy. We also measured levels of blood glucose, creatinine, bilirubin, hemoglobin, platelets, glycated hemoglobin, C-reactive protein, serum lipids (triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein), albumin, prealbumin, and transferrin. In addition, we assessed the international normalized ratio, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and 24-hour urinary nitrogen excretion.

Daily during the intervention period, we obtained nutritional data (total calories and calories from enteral feeding, propofol, intravenous dextrose, and parenteral nutrition), laboratory data (levels of blood glucose, hemoglobin, creatinine, potassium, magnesium, and phosphate), and information on insulin dose, fluid intake and output, use of prokinetic agents, stool frequency and consistency, and duration of interruption in feeding. On a weekly basis, we recorded body weight; levels of lipids, prealbumin, and transferrin; and 24-hour urinary nitrogen excretion. We also recorded the use of selected medications during the ICU stay. Information on the monitoring of serious adverse events is provided in Table S5 in the Supplementary Appendix.

Outcomes
The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality in the ICU, 28-day mortality, in-hospital mortality, 180-day mortality, and serial SOFA scores. Tertiary outcomes included days free from mechanical ventilation, ICU-free days, hospital length of stay, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusions of packed
red cells, ICU-associated infections (documented by the research coordinator according to published definitions), feeding intolerance (vomiting, abdominal distention, or a gastric residual volume of more than 200 ml), and diarrhea.

**STATISTICAL ANALYSIS**

On the basis of the findings of our previous randomized, controlled trial, we estimated that permissive underfeeding would be associated with an absolute risk reduction in mortality of 8 percentage points. Assuming an estimated 90-day mortality of 25% with standard feeding, we calculated that enrollment of 432 patients in each group would give the study 80% power to detect the 8-percentage-point difference in mortality. With an estimated 3% loss to follow-up, the final calculated sample size was 892 patients. The primary outcome was compared between the two groups with use of the chi-square test; the results were reported as relative risks and 95% confidence intervals. We performed an unadjusted Cox proportional-hazards analysis as well as an analysis adjusted for BMI, APACHE II score, and baseline vasopressor use, with the results reported as hazard ratios and 95% confidence intervals.

For serial measurements, we tested the change over time and the difference between the two groups over time using a repeated-measures analysis of variance, with no imputation for missing values. The primary outcome was compared between the two study groups in the following prespecified subgroups: nonsurgical patients versus surgical patients, patients with diabetes versus patients without diabetes, patients with an APACHE II score of 18 or lower versus those with a score higher than 18, patients with a specific admission diagnosis (severe sepsis or traumatic brain injury) versus patients without either of those diagnoses, patients using vasopressors at baseline versus those not using them, and patients with a blood glucose level of no more than the median value at randomization versus those with a level higher than the median value. Tests were two-sided and at the 5% significance level. For serial measurements, we used a Bonferroni correction to account for multiple comparisons. To account for alpha spending by the interim analyses, we used the O’Brien–Fleming method. A final P value of less than 0.045 was considered to indicate statistical significance for the primary outcome. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

**RESULTS**

**PATIENTS**

A total of 894 patients underwent randomization (Fig. S1 in the Supplementary Appendix). At baseline, the two groups were similar with respect to demographic, physiological, and nutritional characteristics (Table 1, and Table S6 in the Supplementary Appendix). A total of 96.8% of the patients were receiving mechanical ventilation.

**INTERVENTIONS AND COINTERVENTIONS**

Throughout the intervention period, patients in the permissive-underfeeding group had a lower caloric intake than did patients in the standard-feeding group (Table 2 and Fig. 1, and Fig. S2 in the Supplementary Appendix); the average caloric intake during the intervention period was 46±14% versus 71±22% of daily requirements (P<0.001). Protein intake and the enteral formulas used did not differ significantly between the two groups (Table 2, and Table S7 and Fig. S3 in the Supplementary Appendix). Patients in the permissive-underfeeding group had lower glucose levels, required less insulin, and had lower daily fluid balance on several study days (Table 2 and Fig. 1). Other cointerventions and nutrition-related data are shown in Table 2 and Figure 1, and Figure S4 in the Supplementary Appendix.

**OUTCOMES**

**Mortality**

The 90-day mortality (primary end point) was 27.2% (121 of 445 patients) in the permissive-underfeeding group and 28.9% (127 of 440 patients) in the standard-feeding group (relative risk, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P = 0.58) (Table 3). Unadjusted and adjusted hazard ratios were also nonsignificant (unadjusted hazard ratio, 0.92; 95% CI, 0.72 to 1.18; P = 0.51; adjusted hazard ratio, 0.91; 95% CI, 0.71 to 1.17; P = 0.48). Similarly, there were no significant between-group differences with respect to mortality in the ICU, in-hospital mortality, 28-day mortality, or 180-day mortality. Kaplan–Meier survival estimates showed no significant differ-
Permissive Underfeeding in Critically Ill Adults

Other End Points
Serial SOFA scores, nitrogen balance, body weight, and levels of C-reactive protein, prealbumin, creatinine, bilirubin, partial pressure of arterial carbon dioxide, hemoglobin, lipids, potassium, magnesium, phosphate, transferrin, and urinary nitrogen excretion did not differ significantly between the two groups (Fig. 1, and Fig. S5 through S10 in the Supplementary Appendix). The number of days free from mechanical ventilation and the number of ICU-free
Table 2. Study Interventions and Cointerventions.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Permissive Underfeeding (N=448)</th>
<th>Standard Feeding (N=446)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated caloric requirement — kcal/day</td>
<td>1822±377</td>
<td>1842±370</td>
<td>0.51†</td>
</tr>
<tr>
<td>Caloric target for the trial — kcal/day</td>
<td>1036±262</td>
<td>1826±375</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Daily caloric intake for duration of intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of kilocalories</td>
<td>835±297</td>
<td>1299±467</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Percent of requirement</td>
<td>46±14</td>
<td>71±22</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Caloric source for duration of intervention — kcal/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral</td>
<td>740±294</td>
<td>1198±470</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Propofol</td>
<td>63±88</td>
<td>65±89</td>
<td>0.84†</td>
</tr>
<tr>
<td>Intravenous dextrose</td>
<td>32±59</td>
<td>35±60</td>
<td>0.23†</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>3±32</td>
<td>5±59</td>
<td>0.38†</td>
</tr>
<tr>
<td>Calculated protein requirement — g/day</td>
<td>85±21</td>
<td>88±23</td>
<td>0.18†</td>
</tr>
<tr>
<td>Daily protein intake for duration of intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of grams</td>
<td>57±24</td>
<td>59±25</td>
<td>0.29†</td>
</tr>
<tr>
<td>Percent of requirement</td>
<td>68±24</td>
<td>69±25</td>
<td>0.56†</td>
</tr>
<tr>
<td>Protein source — g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main enteral formula</td>
<td>30±13</td>
<td>54±22</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Supplemental enteral protein</td>
<td>27±16</td>
<td>6±10</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Parenteral protein</td>
<td>0.2±2.6</td>
<td>0.2±2.7</td>
<td>0.79†</td>
</tr>
<tr>
<td>Duration of intervention — days</td>
<td>9.1±4.6</td>
<td>9.4±4.4</td>
<td>0.36†</td>
</tr>
<tr>
<td>Cointerventions during study period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use — no. (%)</td>
<td>205 (45.8)</td>
<td>235 (52.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dose — units/day</td>
<td>15±27</td>
<td>22±40</td>
<td>0.02†</td>
</tr>
<tr>
<td>Enteral formulas on day 1 — no./total no. (%)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With a specific disease indication</td>
<td>263/441 (59.6)</td>
<td>240/443 (54.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Without a specific disease indication</td>
<td>178/441 (40.4)</td>
<td>203/443 (45.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prokinetics — no. (%)¶</td>
<td>120 (26.8)</td>
<td>127 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Blood glucose — mmol/liter</td>
<td>9.1±5.3</td>
<td>9.4±5.0</td>
<td>0.04†</td>
</tr>
<tr>
<td>Fluid balance — ml/day</td>
<td>490±1408</td>
<td>688±1196</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.
† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.
‡ P values were calculated with the use of the independent Student’s t-test.
§ Information on formulas with a specific disease indication and those without a specific disease indication is provided in Tables S3 and S7 in the Supplementary Appendix.
¶ Prokinetics included metoclopramide, erythromycin, domperidone, and any combination of these.

Figure 1 (facing page). Serial Measurements of the Intervention, Cointerventions, and Selected Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.

The values shown are means; I bars indicate 95% confidence intervals. Asterisks denote statistical significance, after Bonferroni correction, for the difference between the two groups on each day, with the use of the independent Student’s t-test (for daily caloric intake) and Wilcoxon–Mann–Whitney test (for all other variables). P values for the change over time for both groups combined and for the difference between the two groups over time were calculated with the use of repeated-measures analysis of variance. Total scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Nitrogen balance was calculated as [total protein intake in grams ÷ 6.25] – [(urinary nitrogen excretion in millimoles ÷ 35.7) + 4 g]. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.
days did not differ significantly between the two groups (Table 3, and Table S8 in the Supplementary Appendix). In addition, there were no significant between-group differences with respect to hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusion of packed red cells, ICU-acquired infections, diarrhea, or feeding intolerance. Post hoc analysis showed
The New England Journal of Medicine

Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups. *

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Permissive Underfeeding (N = 448)</th>
<th>Standard Feeding (N = 446)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by 90 days — no./total no. (%)</td>
<td>121/445 (27.2)</td>
<td>127/440 (28.9)</td>
<td>0.94 (0.76–1.16)</td>
<td>0.58</td>
</tr>
<tr>
<td>Death in the ICU — no. (%)</td>
<td>72 (16.1)</td>
<td>85 (19.1)</td>
<td>0.84 (0.63–1.12)</td>
<td>0.24</td>
</tr>
<tr>
<td>Death by 28 days — no./total no. (%)</td>
<td>93/447 (20.8)</td>
<td>97/444 (21.8)</td>
<td>0.95 (0.74–1.23)</td>
<td>0.7</td>
</tr>
<tr>
<td>Death in the hospital — no./total no. (%)</td>
<td>108/447 (24.2)</td>
<td>123/445 (27.6)</td>
<td>0.87 (0.70–1.09)</td>
<td>0.24</td>
</tr>
<tr>
<td>Death by 180 days — no./total no. (%)</td>
<td>111/438 (29.9)</td>
<td>140/436 (32.1)</td>
<td>0.93 (0.76–1.14)</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of mechanical ventilation — days</td>
<td>Median 9</td>
<td>10</td>
<td>0.49†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interquartile range 5–15</td>
<td>5–16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days free from mechanical ventilation</td>
<td>Median 77</td>
<td>75</td>
<td>0.48†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interquartile range 0–84</td>
<td>0–84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU length of stay — days</td>
<td>Median 13</td>
<td>13</td>
<td>0.46†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interquartile range 8–21</td>
<td>8–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU-free days</td>
<td>Median 72</td>
<td>71</td>
<td>0.28†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interquartile range 0–81</td>
<td>0–79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay — days</td>
<td>Median 28</td>
<td>30</td>
<td>0.24†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interquartile range 15–54</td>
<td>14–63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia — no. (%)</td>
<td>6 (1.3)</td>
<td>7 (1.6)</td>
<td>0.85 (0.29–2.52)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypokalemia — no. (%)</td>
<td>101 (22.5)</td>
<td>91 (20.4)</td>
<td>1.10 (0.86–1.42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypomagnesemia — no. (%)</td>
<td>127 (28.3)</td>
<td>131 (29.4)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypophosphatemia — no. (%)</td>
<td>267 (59.6)</td>
<td>261 (58.5)</td>
<td>1.01 (0.91–1.14)</td>
<td>0.74</td>
</tr>
<tr>
<td>Transfusion of packed red cells — no. (%)</td>
<td>141 (31.5)</td>
<td>142 (31.8)</td>
<td>0.99 (0.82–1.20)</td>
<td>0.91</td>
</tr>
<tr>
<td>Incident renal-replacement therapy — no./total no. (%)</td>
<td>29/406 (7.1)</td>
<td>45/396 (11.4)</td>
<td>0.63 (0.40–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>ICU-associated infection — no. (%)</td>
<td>161 (35.9)</td>
<td>169 (37.9)</td>
<td>0.95 (0.80–1.13)</td>
<td>0.54</td>
</tr>
<tr>
<td>Urinary tract infection — no. (%)</td>
<td>45 (10.0)</td>
<td>48 (10.8)</td>
<td>0.93 (0.64–1.37)</td>
<td>0.73</td>
</tr>
<tr>
<td>Catheter-related infection — no. (%)</td>
<td>11 (2.5)</td>
<td>19 (4.3)</td>
<td>0.58 (0.28–1.20)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia — no. (%)</td>
<td>81 (18.1)</td>
<td>90 (20.2)</td>
<td>0.90 (0.68–1.17)</td>
<td>0.43</td>
</tr>
<tr>
<td>ICU-associated severe sepsis or septic shock — no. (%)</td>
<td>61 (13.6)</td>
<td>58 (13.0)</td>
<td>1.05 (0.75–1.46)</td>
<td>0.79</td>
</tr>
<tr>
<td>Feeding intolerance — no. (%)</td>
<td>67 (15.0)</td>
<td>79 (17.7)</td>
<td>0.84 (0.63–1.14)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diarrhea — no. (%)</td>
<td>97 (21.7)</td>
<td>117 (26.2)</td>
<td>0.83 (0.65–1.04)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* The number of days free from mechanical ventilation and the number of intensive care unit (ICU)–free days were calculated for the first 90 study days and were considered to be 0 for patients who died on or before day 90. Hypoglycemia was defined as a blood glucose level of less than 2.2 mmol per liter (40 mg per deciliter), hypokalemia as a potassium level of less than 2.8 mmol per liter, hypomagnesemia as a magnesium level of less than 0.60 mmol per liter, and hypophosphatemia as a phosphate level of less than 0.70 mmol per liter. Feeding intolerance was defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml. Diarrhea was defined as three or more loose or liquid stools per day for 2 consecutive days.

† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.
that incident renal-replacement therapy was re-
quired less frequently in the permissive-under-
feeding group than in the standard-feeding group
(29 of 406 patients [7.1%] vs. 45 of 396 patients
[11.4%]; relative risk, 0.63; 95% CI, 0.40 to 0.98;
P = 0.04). No serious adverse events were reported.

Prespecified Subgroup Analyses
There were no significant differences in 90-day
mortality between the two study groups in any
of the prespecified subgroups (Table S9 in the
Supplementary Appendix). Tests of interactions
were not significant for any of the subgroups.

DISCUSSION
In our study, a strategy of enteral feeding for
critically ill adults in which patients received a
moderate amount of nonprotein calories (40 to
60% of estimated caloric requirements), along
with the full recommended amount of protein,
had no significant effect on mortality, as com-
pared with a strategy in which patients received
70 to 100% of estimated caloric requirements.
These findings are similar to those of two previ-
ous randomized, controlled trials that evaluated
minimal or trophic feeding (15 to 25% of caloric
requirements for up to 6 days) in patients with
acute lung injury or acute respiratory failure.19,20

Our trial has several important differences
from the two earlier trials. First, the degree of
caloric restriction in our trial was more modera-
t but the duration was more prolonged. Second,
we administered supplemental protein in the
permissive-underfeeding group, thus eliminating
the confounding effect of differential and re-
duced protein intake. Third, we administered
enteral normal saline or water to minimize the
differences in delivered enteral volume, which
may explain the lack of difference in the inci-
dence of feeding intolerance between the study
groups in our trial, a difference that was ob-
erved in the other two trials. Fourth, we esti-
mated caloric requirements as total calories and
not, as in the other two studies, as nonprotein
calories. Although there is no evidence to sup-
port the superiority of our approach, we assumed
that in the catabolic state of our severely ill pa-
tients, protein does contribute to energy require-
ments. Most commercial formulas list protein as
a caloric component, accounting for 15 to 20%
of calories (Table S3 in the Supplementary Ap-
pendix); therefore, not including calories from
protein may lead to overfeeding.33 Despite these
differences, however, the collective results of our
study and the two previous trials add to a grow-
ing body of research that suggests that standard
feeding goals in critically ill patients do not
improve clinical outcomes.

Permissive underfeeding was associated with
lower blood glucose levels and reduced insulin
requirements, findings that are consistent with
those of other studies.20,25 Our study does not
support the premise that higher caloric intake
attenuates protein catabolism in critically ill pa-
tients, because the two groups had similar clin-
ical indexes of protein status, including nitrogen
balance and levels of prealbumin, transferrin, and
urinary nitrogen excretion. However, the limita-
tions of these indexes in assessing protein status
in ICU patients must be noted.21 Prealbumin and
transferrin levels are influenced by nonnutri-
tional factors such as the level of inflammation,
fluid status, and iron depletion. Nitrogen bal-
ance studies that are based on the measurement
of urinary nitrogen excretion are subject to day-
to-day variation and do not take into account
nonurinary nitrogen losses such as those that
occur as a result of diarrhea or fistulas.21 We
also found no significant between-group differ-
ce with respect to ICU-acquired infections, a
finding that is consistent with the results of
other studies.19,20,25,34

Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.
Could caloric intake matter in certain subpopulations? One randomized, controlled trial involving 82 patients with traumatic brain injury showed better 3-month neurologic outcomes with a higher caloric intake but no significant differences in 6-month outcomes or mortality.35 Similarly, we found no effect of feeding strategy on mortality among 118 patients with traumatic brain injury. The lack of significance in tests of interaction suggests that permissive underfeeding, as compared with standard feeding, has no differential effect in prespecified subgroups. However, some of these subgroup analyses may have been underpowered owing to the small size of the subgroup.

The lower requirement for incident renal-replacement therapy in the permissive-underfeeding group was a finding in a post hoc analysis and should therefore be interpreted cautiously. However, our finding supports the notion that higher caloric intake may be associated with kidney injury. Caloric restriction has been shown to be renoprotective in animal models of acute kidney injury,36–38 through several mechanisms, including improved insulin sensitivity.38 In contrast to our study, previous randomized, controlled trials did not show significant differences in the rates of renal-replacement therapy or in the number of days free from renal failure between patients assigned to caloric restriction and those assigned to full caloric intake.19,20,25 However, those studies varied in the degree and duration of caloric restriction,28,29 and some may have been underpowered.25,39 Reductions in the rate of acute renal impairment and in the rate of the need for renal-replacement therapy were reported with intensive insulin therapy as compared with standard insulin therapy,30 which suggests that hyperglycemia may contribute to kidney injury. A higher fluid balance in the standard-feeding group may correlate with the observed higher requirement for renal-replacement therapy. Clinical practice guidelines recommend standard caloric and protein intake in patients with acute kidney injury and increasing protein intake during renal-replacement therapy,31 but further research is required.

Strengths of this study include the multicenter design and the pragmatic inclusion of critically ill adults with a medical, surgical, or trauma admission category; these features increase the generalizability of the results. The inclusion of patients in whom enteral feeding was initiated early during critical illness avoided the confounding effect of the timing of feeding.

The study also had limitations. First, only 14% of the patients who were admitted to the ICU and screened were included in the study; therefore, the results may not be generalizable to other patients, such as those in whom enteral feeding was initiated late. Second, the target caloric intake was not reached in some patients, particularly in the standard-feeding group. This is not unusual in critically ill patients, given that feeding intolerance and feeding interruptions are common. Nevertheless, there was significant separation in caloric intake between the two groups. Third, blinding of the intervention was not possible, but important nutritional interventions were standardized and the primary outcome was objective. Fourth, the duration of intervention in our study was fixed; therefore, the effect of permissive underfeeding for a duration that is individualized on the basis of the critical illness remains to be studied. Fifth, we did not monitor adherence to multivitamin supplementation and did not have a formal adjudication process for the secondary outcome of infections. Finally, our study was powered to detect an absolute risk reduction of 8 percentage points in 90-day mortality; thus, we cannot rule out a smaller treatment effect.

In conclusion, a strategy of enteral feeding to provide a moderate amount of calories to critically ill adults in the presence of full protein intake was not associated with lower mortality than a strategy aimed at providing a full amount of calories.
PERMISSIVE UNDERFEEDING IN CRITICALLY ILL ADULTS

REFERENCES


Copyright © 2015 Massachusetts Medical Society.