Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial1–5

Eric J Charles, Robin T Petroze, Rosemarie Metzger, Tjasa Hranjec, Laura H Rosenberger, Lin M Riccio, Matthew D McLeod, Christopher A Guidry, George J Stukenborg, Brian R Swenson, Kate F Willcutts, Kelly B O’Donnell, and Robert G Sawyer

ABSTRACT

Background: Proper caloric intake goals in critically ill surgical patients are unclear. It is possible that overnutrition can lead to hyperglycemia and an increased risk of infection.

Objective: This study was conducted to determine whether surgical infection outcomes in the intensive care unit (ICU) could be improved with the use of hypocaloric nutritional support.

Design: Eighty-three critically ill patients were randomly allocated to receive either the standard calculated daily caloric requirement of 25–30 kcal · kg$^{-1}$ · d$^{-1}$ (eucaloric) or 50% of that value (hypocaloric) via enteral tube feeds or parenteral nutrition, with an equal protein allocation in each group (1.5 g · kg$^{-1}$ · d$^{-1}$).

Results: There were 82 infections in the hypocaloric group and 66 in the eucaloric group, with no significant difference in the mean (±SE) number of infections per patient (2.0 ± 0.6 and 1.6 ± 0.2, respectively; \( P = 0.50 \)), percentage of patients acquiring infection [70.7% (29 of 41) and 76.2% (32 of 42), respectively; \( P = 0.57 \)], mean ICU length of stay (16.7 ± 2.7 and 13.5 ± 1.1 d, respectively; \( P = 0.28 \)), mean hospital length of stay (35.2 ± 4.9 and 31.0 ± 2.5 d, respectively; \( P = 0.45 \)), mean 0600 glucose concentration (132 ± 2.9 and 135 ± 3.1 mg/dL, respectively; \( P = 0.63 \)), or number of mortalities [3 (7.3%) and 4 (9.5%), respectively; \( P = 0.72 \)]. Further analyses revealed no differences when analyzed by sex, admission diagnosis, site of infection, or causative organism.

Conclusions: Among critically ill surgical patients, caloric provision across a wide acceptable range does not appear to be associated with major outcomes, including infectious complications. The optimum target for caloric provision remains elusive. Am J Clin Nutr 2014;100:1337–43.

INTRODUCTION

Appropriate nutrition intake in critically ill surgical patients is a crucial aspect of care. Nutritional support is needed to overcome stress-induced metabolic responses, prevent excessive cellular injury, and favorably modulate the immune response (1–3). Malnutrition is associated with impaired immune function, reduced ventilatory drive, weakened respiratory muscles, prolonged ventilator dependence, and increased infectious complications in critically ill patients (4, 5). Nutritional support is believed to improve wound healing and gastrointestinal structure and function, as well as reduce catabolism, complication rates, and length of stay (1).

Despite its attributes, nutritional support does have adverse effects, suggesting a delicate balance between overfeeding and underfeeding. Feeding intolerance is a less frequent occurrence when patients receive trophic enteral feedings (6). However, when goal enteral feeding is attempted and leads to high gastric residual volumes, patients are at an increased risk of hospital-acquired pneumonia, longer intensive care unit (ICU) stays, and increased ICU mortality (7). When enteral nutrition is not possible, patients may receive supplemental parenteral nutrition, although the appropriate timing of initiation and its role continue to be debated (8–10). Parenteral nutrition is known to be associated with increased infections, gut mucosal atrophy, hyperglycemia, and overall increased mortality in critically ill patients (9, 11).

Current guidelines detail the optimal delivery of nutritional support and recommend providing 25–30 kcal · kg$^{-1}$ · d$^{-1}$ with 1.2–2 g protein · kg$^{-1}$ · d$^{-1}$. Yet, no published data have validated these standard daily caloric intake targets (2, 12, 13). Although there is general consensus that excessive hypocaloric (=25% recommended daily caloric intake) or hypercaloric (=125%) feeding should be avoided, controversy still exists over what feeding targets should be (14). Particularly in patients with a high severity of illness, attempting to provide full nutritional support may correlate with adverse outcomes (15, 16). New evidence suggests that outcomes may be improved in patients who are “underfed.” Nevertheless, to our knowledge, no study has yet randomly allocated critically ill patients to

1 From the Department of Surgery, University of Virginia Health System, Charlottesville, VA (EJC, RTP, RM, TH, LHR, LMR, MDM, CAG, BRS, KFW, KBO, and RGS), and the Department of Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA (GJS).
2 EJC and RTP share first authorship on this article.
3 The work presented here is the original work of the aforementioned authors and represents the authors’ views and not those of the institution where the work was completed or that of any funding source.
4 Supported by grant 5-T32-AI-078875-03 from the NIH (principal investigator: RGS).
5 Address correspondence to EJ Charles, Department of Surgery, University of Virginia Health System, PO Box 800679, Charlottesville, VA 22908-0679. E-mail: cc4wx@virginia.edu.

Received March 21, 2014. Accepted for publication August 11, 2014. First published online September 3, 2014; doi: 10.3945/ajcn.114.088609.
The hypocaloric target was 50% (12.5–15 kcal
support. Inclusion criteria were age
to the surgical ICU and were deemed appropriate for nutritional
Patients granted to continue the study.
reviewed by the independent data and safety monitoring officer
study procedures. After 50 patients were enrolled, the study was
representative provided written informed consent before any
treatment of human subjects. Each patient or legally authorized
accordance with the Declaration of Helsinki and the ethical
13183) approved the study after ensuring that its design was in
2011 (initial recruitment date 1 March 2008) in the surgical ICU
Study design
This randomized controlled trial was conducted from 2008 to
11 (initial recruitment date 1 March 2008) in the surgical ICU
at a tertiary care hospital. The Institutional Review Board for
Human Subjects Research at the University of Virginia (Protocol
13183) approved the study after ensuring that its design was in
accordance with the Declaration of Helsinki and the ethical
treatment of human subjects. Each patient or legally authorized
representative provided written informed consent before any
study procedures. After 50 patients were enrolled, the study was
reviewed by the independent data and safety monitoring officer
(Timothy L Pruell, University of Minnesota), and approval was
granted to continue the study.

Patients
We enrolled adult patients older than 18 y who were admitted
to the surgical ICU and were deemed appropriate for nutritional
support. Inclusion criteria were age ≥18 y, projected need for
artificial nutrition >48 h, and projected need for intensive care
stay >48 h as judged by the attending intensivist. Typical patients
admitted to the surgical ICU included operative and nonoperative trauma patients, as well as abdominal, vascular, liver transplant, and orthopedic nontrauma surgical patients. Exclusion criteria included age <18 y, patients who had an expected death or ICU discharge within 48 h, pregnancy, and patients with a primary burn diagnosis.

Randomization
Patients were randomly allocated 1:1 by using a random
number sequence. Investigators were blinded to the preparation
of the randomization envelopes, and the randomization assign-
ment was determined by opening sequential opaque security
envelopes containing the randomization assignment.

Procedures
Before initiating nutritional support, daily caloric re-
quirements were calculated for each patient by using actual body
weight, unless the patient’s weight was greater than 130% of
ideal body weight, in which case an adjusted body weight was
used. For the purpose of this study, the eucaloric goal was 100% of
the calculated daily caloric requirement (25–30 kcal · kg⁻¹ · d⁻¹). The hypocaloric target was 50% (12.5–15 kcal · kg⁻¹ · d⁻¹) of the
calculated daily caloric requirement. Both groups had a protein
intake goal of 1.5 g · kg⁻¹ · d⁻¹.

All patients were evaluated before the initiation of nutritional
support to determine their risk for refeeding syndrome. Patients
were considered at risk if they had a history of significant alcohol
abuse, a 5% weight loss in the preceding 30 d or 10% loss in the
preceding 6 mo, or poor caloric intake for at least 7 d before
initiation of nutritional support or if their premorbid diet/weight
history was unavailable. Patients at risk for refeeding syndrome
who were randomly allocated to the eucaloric group had initial
goals set at 12.5–15 kcal · kg⁻¹ · d⁻¹ and 1.5 g protein · kg⁻¹ · d⁻¹ for at least 2 d. Electrolytes were closely monitored and
replaced. According to institutional protocol for all patients re-
ceiving nutritional support, advancement to full feeding did not
occur until electrolyte abnormalities resolved.

Enteral nutrition was initiated at 25 mL/h and advanced by
25-mL increments 3 times daily until the desired goal rate was
achieved. For patients fed into the stomach, gastric residuals were
checked 4 times a day. Prokinetic agents were permitted. Post-
pyloric rather than gastric feeding tubes were used at the dis-
cretion of the attending intensivist. No immune-enhancing
enteral formulas were used to limit confounding variables.

In accordance with institutional policy and American Society
for Parenteral and Enteral Nutrition standards, patients were
considered for parenteral nutrition if they were severely mal-
nourished and could not receive enteral feeding. Otherwise, all
other patients were started on enteral feeds. Any patient who
demonstrated continued intolerance of enteral feeds after 5–7 d
was started on parenteral nutrition. It is not routine at our
institution to supplement enteral nutrition with parenteral nu-
trition to meet caloric goals. Adequacy of nutritional support
was determined by measurement of nitrogen balance.

An insulin infusion was initiated for any patient with blood
glucose greater than 150 mg/dL and adjusted in accordance to the
ICU treatment protocol. For those patients receiving continuous
infusion therapy, the number of units of insulin received per day
was determined by reviewing nursing records.

Data were abstracted from the electronic medical record.
Glucose data were reported as mean overall glucose for the study
inclusion dates and mean glucose at 0600, reported as the glucose
value nearest 0600 on every day of the study. Infection data were
abstracted from a previously described prospectively collected
ICU infections database from the general surgery, trauma, and
transplantation services. US Centers for Disease Control and
Prevention criteria were used to define infections (17, 18). For
example, to diagnose pneumonia, the following were necessary:
a properly collected specimen with isolation of a predominant
organism, production of purulent sputum, a new or changed
infiltrate on chest radiograph, and a quantitative endotracheal
suction specimen with ≥10⁶ colony-forming units/mL.

Study endpoints
The primary study endpoint was the development of a hospital-
acquired infection. Secondary outcomes included glucose con-
trol, as defined by morning glucose values and daily insulin
requirements, ICU length of stay, hospital length of stay, and all-
cause in-hospital mortality.

Statistical analysis
Preliminary data from 309 ICU patients showed a 67% in-
festation rate. Therefore, by using a conservative estimate of at
least a 50% infection rate in the control group, we estimated
a sample size of 58 patients in each study arm (a total of 116 patients) to detect a 50% reduction in infection rate. Because this is a pilot study, it was not designed or powered to detect a mortality difference.

Differences in demographic characteristics between the hypocaloric and eucaloric groups were compared by using a Student’s t test and Wilcoxon rank-sum test for continuous variables, as well as the Wald χ² test and Fisher exact test for categorical variables. Bivariable logistic regression analysis and the Wald χ² test were used to estimate the relative odds of hospital-acquired infection and associated 95% CIs for the ORs. Adjusted ORs for the primary outcome were calculated by using multivariate logistic regression to control for risk of refeeding, which showed a statistically significant difference between the 2 groups, and the percentage of goal calories received. Statistical significance was indicated by using an α level of 0.05.

Differences in mean values for glucose control variables (mean glucose values and mean insulin requirements), hospital length of stay, and ICU length of stay were assessed by using bivariable linear regression. The difference in the relative odds of in-hospital death between the 2 groups was also assessed by using bivariable logistic regression and the Wald χ² test. To determine the efficacy of treatment randomization, we compared several treatment characteristics. Group means were compared by using a Wilcoxon rank-sum test. Subgroup analysis of the primary and secondary outcomes was completed comparing the trauma with the nontrauma population and men with women. All calculations were performed with SAS 9.3 (SAS Institute Inc).

RESULTS

Of 2892 admissions to the surgical/trauma ICU between March 2008 and November 2011, a total of 83 patients were enrolled and randomized, 41 to hypocaloric and 42 to eucaloric feeding. As shown in Figure 1, details of the randomization of patients, as well as the reasons for exclusion and reasons for study end, are presented. Analysis for all patients was completed on an intention-to-treat basis. Because of slow enrollment, this study was closed before the full planned enrollment of 116 patients.

FIGURE 1. Participant flow diagram. ICU, intensive care unit.
There were no statistically significant differences between the 2 groups in terms of Acute Physiology and Chronic Health Evaluation II score, age, sex, height, weight, admission diagnosis (trauma compared with nontrauma), or the number of comorbidities (Table 1). The percentage of patients at risk for refeeding syndrome was higher in the eucaloric group, and thus we controlled for refeeding risk when describing our primary outcome.

The treatment characteristics of patients in both arms of the study are summarized in Table 2. There was a statistically significant difference in the mean (±SE) amount of nutritional support provided to each group, 12.3 ± 0.7 compared with 17.1 ± 1.1 kcal · kg⁻¹ · d⁻¹, P = 0.0002. The mean protein received daily by each group was not significantly different (1.1 g/kg for each group). There were no statistically significant differences identified between the 2 groups when analyzed for percentage of days of key ICU treatment interventions that may influence nutrition such as renal replacement therapy, mechanical ventilation, insulin infusion, or total parenteral nutrition.

As shown in Table 3, details of the primary infectious outcomes between both groups are presented. There were 82 infections in the hypocaloric group and 66 in the eucaloric group, with no statistically significant difference in the mean number of infections per patient (2.0 ± 0.6 and 1.6 ± 0.2, respectively; P = 0.50) or the percentage of patients acquiring infection [70.7% (29 of 41) and 76.2% (32 of 42); P = 0.57; adjusted OR: 0.82 (95% CI: 0.28, 2.39)]. There were also no statistically significant differences between the hypocaloric and eucaloric groups in the percentage distributions of infection types or types of causative organism.

As shown in Table 3, details of the primary infectious outcomes between both groups are presented. There were 82 infections in the hypocaloric group and 66 in the eucaloric group, with no statistically significant difference in the mean number of infections per patient (2.0 ± 0.6 and 1.6 ± 0.2, respectively; P = 0.50) or the percentage of patients acquiring infection [70.7% (29 of 41) and 76.2% (32 of 42); P = 0.57; adjusted OR: 0.82 (95% CI: 0.28, 2.39)]. There were also no statistically significant differences between the hypocaloric and eucaloric groups in the percentage distributions of infection types or types of causative organism.

The results of secondary outcomes are summarized in Table 4. No statistically significant differences occurred between groups in mean ICU length of stay (16.7 ± 2.7 and 13.5 ± 1.1 d, respectively; P = 0.28), mean hospital length of stay (35.2 ± 4.9 and 31.0 ± 2.5 d, respectively; P = 0.45), or inpatient mortality [7.3% (3 of 41) and 9.5% (4 of 42), respectively; P = 0.72]. Glucose values and insulin usage were not different between groups. Further subgroup analyses revealed no differences when analyzed by sex (men compared with women) and trauma compared with nontrauma (data not shown).

When patients who developed an infection were compared with patients who did not develop an infection, there was no statistically significant difference between the mean percentage of goal kilocalories received (P = 0.21; 79% goal kcal for any infection; 70% goal kcal for no infection). Again comparing patients who did and did not develop an infection, there was no statistically significant difference between the percentage of days with primary parenteral nutrition (P = 0.12; 25% compared with 13%, respectively) or the percentage of days receiving enteral nutrition (P = 0.99; 67% compared with 67%, respectively). In univariate analysis, patients who received less than 80% of their goal kcal were not at increased risk of developing an infection compared with those who received 80% or more of their goal (P = 0.13; OR: 0.47; 95% CI: 0.18, 1.26).

**DISCUSSION**

Few studies have been conducted to challenge the notion that critically ill patients benefit from receiving the same caloric intake recommended for patients in the acute care setting. Since its publication in 1997, many clinicians have referred to the consensus statement by the American College of Chest Physicians to determine caloric goals for critically ill patients. “Administering 25 total kilocalories per kilogram usual body weight per day appears to be adequate for most patients” (12). It is unknown from current literature what effect this level of caloric

| TABLE 1 | Demographic characteristics | Hypocaloric | Eucaloric | P value |
| Variable | (n = 41) | (n = 42) | |
| Age (y) | 50.4 ± 2.8 | 53.4 ± 2.7 | 0.45 |
| Age (y) | 51.0 (38–63) | 52.5 (45–61) | 0.58 |
| Male sex [% (n)] | 68.3 (28) | 73.8 (31) | 1.00 |
| White race [% (n)] | 90.2 (37) | 90.2 (37) | 0.09 |
| Height (cm) | 174.0 ± 1.6 | 176.5 ± 1.4 | 0.10 |
| Actual body weight (kg) | 97.9 ± 4.6 | 88.0 ± 3.4 | 0.18 |
| BMI (kg/m²) | 32.9 ± 2.0 | 28.1 ± 0.9 | 0.23 |
| Ideal body weight (kg) | 69.9 ± 1.9 | 72.4 ± 1.8 | 0.03 |
| Refeeding risk at admission [% (n)] | 31.7 (13) | 54.8 (25) | 0.41 |
| Trauma admission [% (n)] | 68.3 (28) | 59.5 (25) | 0.58 |
| APACHE II score | 16.6 ± 0.9 | 17.3 ± 0.8 | 0.39 |
| APACHE II score | 17 (13–20) | 17 (14–20) | 0.50 |
| Total comorbidities | 2.2 ± 0.3 | 2.5 ± 0.3 | 0.53 |
| Coronary artery disease [% (n)] | 17.1 (7) | 11.9 (5) | — |
| Diabetes mellitus [% (n)] | 19.5 (8) | 14.3 (6) | 0.29 |
| Ventilator dependence [% (n)] | 68.3 (28) | 57.1 (24) | 0.02 |

1 Continuous variables were compared by using Student’s t test and the Wilcoxon rank-sum test. Categorical variables were compared by using the Wald χ² test and Fisher exact test. APACHE II, Acute Physiology and Chronic Health Evaluation II.

2 Mean ± SE (all such values).

3 Median; IQR in parentheses (all such values).
support might have on glucose control and infectious outcomes, particularly during critical illness. To address this issue, we conducted a single-institution pilot study to evaluate the differences in infectious outcomes between critically ill patients randomly allocated to receive either the standard daily recommendation of 25–30 kcal·kg⁻¹·d⁻¹ or 50% of that amount. These results failed to identify any difference in outcomes between critically ill surgical patients enrolled to each group.

Current literature supports the following recommendations for providing nutritional support to critically ill adults: the enteral route is preferred; nutrition should be initiated as soon as possible, ideally within 24–48 h of ICU admission; and postpyloric feeding should be considered (2, 12, 13). Patients should be in the semirecumbent position, have their tube feeds titrated up to 80% of goal rate within 72 h, and have gastric residuals monitored (19). Motility agents should be used and enteral nutrition should be continued unless residuals >500 mL are encountered (2, 13). There is also literature that supports providing increased protein for patients receiving continuous renal replacement therapy or hemodialysis, as well as monitoring and controlling glucose levels closely (2, 20).

Of those that have addressed the issue of proper dosing of nutritional support in the recent past, results are inconclusive, but a push toward less is more has garnered some recent attention. Arabi et al (21) published their results of a cohort study to determine whether morbidity and mortality are affected by caloric intake and concluded that increased hospital mortality, ICU and hospital lengths of stay, infection rates, and mechanical ventilation duration were associated with near-target caloric intake (>64.6% of goal). These findings are consistent with a study published by Krishnan et al (16), which found that caloric intake between 33% and 66% of recommended was beneficial to

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypocaloric (n = 41)</th>
<th>Eucaloric (n = 42)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of infections</td>
<td>82</td>
<td>66</td>
<td>0.72</td>
<td>—</td>
</tr>
<tr>
<td>Infections per patient (n)</td>
<td>2.0 ± 0.6²</td>
<td>1.6 ± 0.2</td>
<td>0.50</td>
<td>—</td>
</tr>
<tr>
<td>Any infection [% (n)]</td>
<td>70.7 (29)</td>
<td>76.2 (32)</td>
<td>0.57</td>
<td>0.76 (0.28, 2.01)</td>
</tr>
<tr>
<td>ICU-acquired infection [% (n)]</td>
<td>56.1 (23)</td>
<td>57.1 (24)</td>
<td>0.92</td>
<td>0.96 (0.40, 2.28)</td>
</tr>
<tr>
<td>Infection site [% (n)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>43.9 (18)</td>
<td>47.6 (20)</td>
<td>0.73</td>
<td>0.86 (0.36, 2.04)</td>
</tr>
<tr>
<td>Central line</td>
<td>4.9 (2)</td>
<td>4.8 (2)</td>
<td>0.98</td>
<td>1.03 (0.14, 7.65)</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>24.4 (10)</td>
<td>19.1 (8)</td>
<td>0.56</td>
<td>1.37 (0.48, 3.92)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>14.6 (6)</td>
<td>14.3 (6)</td>
<td>0.96</td>
<td>1.03 (0.30, 3.50)</td>
</tr>
<tr>
<td>Wound</td>
<td>12.2 (5)</td>
<td>7.3 (3)</td>
<td>0.44</td>
<td>1.81 (0.40, 8.10)</td>
</tr>
<tr>
<td>Causative organism [% (n)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>53.7 (22)</td>
<td>42.9 (18)</td>
<td>0.33</td>
<td>1.54 (0.65, 3.67)</td>
</tr>
<tr>
<td>MRSA</td>
<td>2.4 (1)</td>
<td>4.8 (2)</td>
<td>0.58</td>
<td>0.50 (0.04, 5.74)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>7.3 (3)</td>
<td>7.1 (3)</td>
<td>0.98</td>
<td>1.03 (0.20, 5.41)</td>
</tr>
<tr>
<td>Anaerobe</td>
<td>12.2 (5)</td>
<td>9.5 (4)</td>
<td>0.7</td>
<td>1.32 (0.33, 5.31)</td>
</tr>
<tr>
<td>Fungus</td>
<td>14.6 (6)</td>
<td>14.3 (6)</td>
<td>0.96</td>
<td>1.03 (0.30, 3.50)</td>
</tr>
</tbody>
</table>

¹ Continuous variables were compared by using Student’s t test and the Wilcoxon rank-sum test. Categorical variables were compared by using the Wald χ² test and Fisher exact test. Bivariable logistic regression and the Wald χ² test were used to estimate the relative odds of hospital-acquired infection and associated 95% CIs. ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

² Mean ± SE (all such values).

³ Adjusted ORs for the primary outcome were calculated by using multivariate logistic regression to control for risk of refeeding and the percentage of goal calories received.

⁴ Adjusted P = 0.41; OR: 0.82; 95% CI: 0.28, 2.39.

⁵ Adjusted P = 0.61; OR: 0.78; 95% CI: 0.31, 2.00.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypocaloric (n = 41)</th>
<th>Eucaloric (n = 42)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU² length of stay (d)</td>
<td>16.7 ± 2.7³</td>
<td>13.5 ± 1.1</td>
<td>0.28</td>
<td>—</td>
</tr>
<tr>
<td>Hospital length of stay (d)</td>
<td>35.2 ± 4.9</td>
<td>31.0 ± 2.5</td>
<td>0.45</td>
<td>—</td>
</tr>
<tr>
<td>Mortality [% (n)]</td>
<td>7.3 (3)</td>
<td>9.5 (4)</td>
<td>0.72</td>
<td>0.75 (0.16, 3.58)</td>
</tr>
<tr>
<td>Glucose control variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean overall glucose (mg/dL)</td>
<td>133 ± 2.8</td>
<td>138 ± 2.7</td>
<td>0.22</td>
<td>—</td>
</tr>
<tr>
<td>Mean 0600 glucose (mg/dL)</td>
<td>132 ± 2.9</td>
<td>135 ± 3.1</td>
<td>0.63</td>
<td>—</td>
</tr>
<tr>
<td>Mean insulin (units/d)</td>
<td>36.9 ± 8.3</td>
<td>39.3 ± 12.2</td>
<td>0.87</td>
<td>—</td>
</tr>
</tbody>
</table>

¹ Bivariable linear regression was used to compare differences in mean values. Relative odds of in-hospital mortality was assessed by using bivariable linear regression and the Wald χ² test.

² ICU, intensive care unit.

³ Mean ± SE (all such values).
clinical outcomes. Permissive underfeeding is currently recommended for critically ill obese patients and may be associated with lower mortality rates (22). And although limited to parenteral nutrition alone, a randomized controlled trial published in 2000 by McCowen et al (23) found that hypocaloric parenteral nutrition can help avoid overfeeding, hyperglycemia, and infectious complications. For enteral nutrition, a goal of only 15 kcal · kg⁻¹ · d⁻¹ has been described as beneficial in nonobese multiple-trauma patients (24).

The EDEN Randomized Trial compared initial trophic feeding with full enteral feeding for the first 6 d of nutritional support in patients with acute lung injury. Outcomes of that study showed no differences between groups in terms of ventilator-free days, 60-d mortality, or infectious complications (6). A previous randomized controlled trial by Rice and colleagues (25) also concluded that no clinical benefit existed from initial trophic feeds other than fewer incidences of gastrointestinal intolerance. A 1-y follow-up study to the EDEN trial analyzing physical and cognitive functioning and quality of life failed to demonstrate any difference between patients who received initial trophic or full enteral feeding (26). In the Tight Caloric Control Study, when indirect calorimetry was used to calculate energy targets, compared with using the consensus statement from the American College of Chest Physicians, there was a statistically significant increase in total infection rate, length of time on mechanical ventilation, and ICU length of stay (27).

The results of our study failed to find any significant differences between treatment arms. The optimum target remains undetermined, and future studies are needed to identify outcome differences. Even when the caloric goal is set at 25–30 kcal · kg⁻¹ · d⁻¹, many patients do not actually achieve this amount, especially within the first 7 d of ICU admission. This may be attributable to interruptions in feeding for procedures or to rate titration. In the absence of any complicating factors such as refeeding risk, patients can be started at their target feeding goal rate. This is an option supported by the findings of a study by Desachy et al (28), which would improve total caloric intake. The fact that 54.8% (25 of 42) of patients in the eucaloric arm were determined to be at risk for refeeding syndrome definitely influenced the mean daily caloric intake for that group, causing them to fall short of their goal. Supplementing enteral nutrition with parenteral nutrition sooner than 5–7 d is an option to increase the percentage of goal calories received, although this practice is not supported by outcomes in the Early Parenteral Nutrition to Supplement Insufficient Enteral Nutrition in Intensive Care trial (29). Results of that study demonstrated that allowing hypocaloric feeding in the ICU during the first 7 d of admission decreased the rate of new infections and increased the likelihood of early alive-discharge. A post hoc analysis of this study again concluded that combining early parenteral nutrition with enteral nutrition to reach caloric intake goals delays recovery (30). In contrast, however, the findings of a study by Petros et al (31) concluded that hypocaloric feeding was associated with more nosocomial infections in medical ICU patients during the first 7 d. The interpretation of these results in comparison to our study is complicated by the differences in the delivery of nutritional support, such as the addition of parenteral nutrition by day 3 in the Petros et al study, the cohort of patients (surgical/trauma ICU compared with medical ICU), and the overall infection and mortality rates. The outcomes of both studies validate the notion that future studies are needed to determine whether hypocaloric feeding may be appropriate for certain cohorts of critically ill patients.

To focus our analysis on caloric intake, we had protein provision goals the same for both groups. Although our data failed to reveal any statistically significant outcome differences between patients with hypocaloric feeding goals and those with eucaloric feeding goals, it may be that optimizing nutritional support is not so much a factor of caloric intake but of protein provision.

Several limitations should be noted for this study. First, all patient enrollment and data collection occurred in a single surgical ICU. Set up as a pilot study, this allowed for feasibility of enrollment, data gathering, and analysis. Second, the sample size of the study was small. Although we achieved adequate patient randomization, opening the study to multiple institutions could improve enrollment and the generalizability of the findings. Third, the study was closed before the targeted enrollment was completed, because of low volume, increasing the possibility that type II error may result from lack of power. A difference in the number of infections may have been seen with full enrollment. Unfortunately, with limited prior research on hypocaloric feeding, there was a misconception held by family members signing consent that patients would be intentionally starved if randomly allocated to the hypocaloric arm. Overcoming this fear was challenging, and consent was often difficult to obtain. Despite these limitations, the results of the study can inform the design of future multicenter studies that would have larger enrollments. Patients and their family members now have data to review showing that hypocaloric feeding is a reasonable alternative to eucaloric feeding and should not imply intentional starvation. Subsequent studies could also allow for diagnosis-specific subgroup analyses and the identification of patients with certain illnesses who might benefit from varying levels of hypocaloric nutritional support.

In conclusion, we performed a randomized controlled trial to evaluate the benefit of hypocaloric nutritional support in the treatment of critically ill surgical patients. Although limited by a small sample size, we failed to show significant differences in outcome between patients with eucaloric or hypocaloric feeding goals in terms of glucose control, infection rates, ICU and hospital lengths of stay, and mortality. Further research is necessary to determine whether specific subsets of critically ill patients might benefit from different levels of caloric provision.

We thank the NIH; the Department of Surgery at the University of Virginia Health System, Charlottesville, VA; and the entire staff of the Surgical, Trauma, Burn Intensive Care Unit for their hard work and dedication to the successful completion of this project.

The authors’ responsibilities were as follows—RM, TH, LHR, GJS, BRS, and RGS: designed the research; RM, TH, LHR, LMR, MDM, CAG, KFW, KBO, and RGS: conducted the research; EJC, RTP, LHR, CAG, GJS, BRS, KFW, KBO, and RGS: analyzed data; EJC, RTP, and RGS: wrote the manuscript; and EJC: had primary responsibility for the final content. All authors read, revised, and approved the final manuscript. No conflicts of interest were reported.

REFERENCES


