Efficacy and Safety of Glutamine-supplemented Parenteral Nutrition in Surgical ICU Patients

An American Multicenter Randomized Controlled Trial

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Objective: To determine whether glutamine (GLN)-supplemented parenteral nutrition (PN) improves clinical outcomes in surgical intensive care unit (SICU) patients.

Summary Background Data: GLN requirements may increase with critical illness. GLN-supplemented PN may improve clinical outcomes in SICU patients.

Methods: A parallel-group, multicenter, double-blind, randomized, controlled clinical trial in 150 adults after gastrointestinal, vascular, or cardiac surgery requiring PN and SICU care. Patients were without significant renal or hepatic failure or shock at entry. All received isonitrogenous, isocaloric PN.

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The 6-month cumulative mortality was 31.4% in the GLN-PN group (17.3%; difference, 23.7%; 95% confidence interval, 9.0% to 37.8%; P = 0.03). Other clinical outcomes and adverse events were similar. Conclusions: PN supplemented with GLN dipeptide was safe, but did not alter clinical outcomes among SICU patients.

Keywords: critical care, critical illness, glutamine, hospital-acquired infection, nutrition support, parenteral nutrition

Over the past several decades, numerous studies in animal models of catabolic and critical illness indicate that parenteral nutrition (PN) supplemented with the nonessential amino acid (AA) glutamine (GLN) may enhance protein anabolism, gut-associated barrier functions, systemic immunity, and gut mucosal repair, potentially via GLN use as an important fuel substrate and via upregulation of cytoprotective pathways. Concomitantly, small randomized controlled trials (RCTs) in postoperative and/or critically ill medical and surgical patients demonstrated that PN supplemented with L-GLN (or water-soluble and heat-stable GLN dipeptides) improved nitrogen balance, gut barrier function, indexes of immunity, and clinical outcomes (including reduced hospital-acquired infections, length of stay (LOS), and mortality).

Earlier experimental data showed that organ GLN uptake was increased during catabolic states by the splanchnic bed, immune cells, and other tissues. GLN levels in human skeletal muscle decreased markedly after major surgery and in critically ill patients admitted to intensive care units (ICU). In addition, low GLN levels early in the ICU course were associated with adverse clinical outcomes. Relatively small RCTs of GLN-supplemented PN in patients after major operation and/or critical illness suggest beneficial effects on hospital infections, length of hospital stay, and 6-month mortality. However, other prospective trials in postoperative...
patients showed no significant clinical outcome benefits with intravenous GLN.\textsuperscript{20–22} Furthermore, intent-to-treat analysis of several recently published, double-blind, multicenter RCTs in mixed ICU patients showed no benefit on clinical outcomes with GLN-supplemented PN.\textsuperscript{23–25} Most RCTs have not focused on specific types of critically ill medical or surgical patients; thus, characteristics of those who may benefit (and the effective GLN dose) remain an area of uncertainty.\textsuperscript{26–30} This is reflected in the results of several meta-analyses on efficacy of GLN-supplemented PN in critical illness, which often have shown improved specific clinical outcome parameters, but with trial heterogeneity and data uncertainty.\textsuperscript{31–35}

No RCT of GLN-supplemented PN to date has suggested any adverse effects because of GLN supplementation. However, the recently published large REDOXS RCT enrolled primarily medical ICU patients with multiple organ failure and shock, who were given a high dose of combined enteral and parenteral GLN, with or without antioxidants, beginning on the day of ICU admission and independent of enteral or PN support.\textsuperscript{36} The study showed no effects of GLN on organ failure or overall infection rates; however, the GLN-treated arms demonstrated a modest, but statistically significant, increase in hospital and 6-month mortality.\textsuperscript{37} This was particularly true in patients with early renal failure.\textsuperscript{38} Therefore, it is important to define the safety of parenteral GLN in ICU settings and in specific subgroups of patients who potentially may benefit from GLN supplementation.

This RCT (the “GLND” trial) was a prospective, randomized, controlled, double-blind, parallel-group, intent-to-treat, multicenter investigator-initiated Phase III study designed to define the safety and clinical efficacy of GLN dipeptide-supplemented PN in surgical ICU (SICU) patients after cardiac, vascular, or intestinal surgery. The study design and power was determined by an earlier single-center trial in which GLN dipeptide-supplemented PN significantly decreased nosocomial infections in the subgroup of patients following cardiac, vascular, and colonic surgery (17). We hypothesized that the current trial would decrease hospital mortality and new hospital-acquired infections (primary endpoints).

METHODS

Informed Consent

The Institutional Review Boards of Emory University (Atlanta, GA), Vanderbilt University (Nashville, TN), Miriam Hospital (Providence, RI), University of Wisconsin-Madison (Madison, WI), and University of Colorado (Aurora, CO) approved this study (Clinicaltrials.gov identifier: NCT00248638). All patients or their legally authorized representatives signed site-specific approved consent forms before randomization.

Study Coordination and Oversight

The GLND Steering Committee included the overall Principal Investigator (TRZ), the National Institute of Diabetes and Digestive and Kidney Diseases U01 grant Project Scientist (MEE), the Data Coordinating Center (DCC) Director (KAE), and the site Principal Investigators (AKM, HCS, KAK, and PEW), and was the main oversight body of the study responsible for the implementation, coordination, and management of the trial. The Steering Committee reviewed and analyzed progress of the trial, monitored performance at individual clinical centers, and responded to recommendations from the National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK)-convened Data and Safety Monitoring Board (DSMB).

The GLND DCC, located at the Emory University Rollins School of Public Health, Department of Biostatistics and Bioinformatics, was responsible for data management and quality control, case report form (CRF) generation, and statistical analysis. The DCC also prepared interim and final analyses blinded and open semiannual DSMB reports.

An independent DSMB, established by the NIDDK, consisted of 4 experts in SICU nutrition support and a biostatistician. The DSMB met twice yearly with the Emory-based study leadership and the NIDDK Program Official.

Patient Eligibility for Enrollment and Recruitment

Adult patients were screened for enrollment if the following criteria were met: (1) patient required admission to the SICU following cardiac, nonneurologic vascular, or complete or partial esophageal, gastric, or intestinal surgery or after exploratory laparotomy to identify a source of peritonitis when evidence of a bowel perforation was present; and (2) patient deemed by the investigator team (each led by an expert in SICU nutrition support) and attending physician to likely require PN for ≥7 subsequent days. Informed consent was obtained from all study participants or their legally authorized representative.

Inclusion criteria were: (1) age 18 to 90 years; (2) body mass index (BMI) <40 kg/m² before surgery; (3) requires current SICU care and is <14 days postoperative from the following open (nonlaparoscopic) surgical procedures: coronary artery bypass grafting (CABG), cardiac valve, vascular (nonneurological), complete or partial esophageal, gastric, small bowel, colon, and/or rectal resection or exploratory laparotomy to identify a source of peritonitis when evidence of a bowel perforation was present; (4) deemed to require central venous PN for ≥7 subsequent days after entry; (5) central venous access for administration of the study PN in place by entry; and (6) patient’s primary physician(s) will allow the investigative team to manage the study PN and enteral feedings during the current hospitalization.

Exclusion criteria were: (1) pregnancy; (2) current clinical sepsis, defined as an unstable blood pressure despite vasopressor agent support and mean arterial pressure <60 mm Hg on at least 3 consecutive readings within a 3-hour period during the 24 hours before study entry; (3) current malignancy requiring surgery as the study qualifying operation or receiving an active regimen of chemotherapy and/or radiotherapy to treat a previously diagnosed malignancy; (4) history of seizures or preexisting seizure disorder; (5) current encephalopathy; (6) known history of cirrhosis or a serum total bilirubin level ≥10.0 mg/dL; (7) history of chronic renal failure requiring dialysis, or significant renal dysfunction (defined as serum creatinine >2.5 mg/dL and not receiving continuous renal replacement therapy or the patient requires acute hemodialysis postoperatively); (8) concomitant burn or trauma injury; (9) previously organ transplant(10) history of HIV/AIDS; (11) administration of any investigational drug within 60 days before study entry; (12) administration of enteral or parenteral enteral feedings enriched in arginine and/or GLN within 30 days before study entry; and (13) patient unable or unwilling to participate in study procedures such as longitudinal blood draws and outpatient follow-up visits. The most recent available blood renal and hepatic function test results in the medical record were used to determine eligibility. The primary diagnosis leading to the index cardiac, vascular, or intestinal surgery was also recorded.

Randomization of Study Subjects

Following informed consent, the study team at each site calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.\textsuperscript{38} Treatment assignments were stratified according to clinical center and on the illness severity (APACHE II score dichotomized as ≤15 or >15). The APACHE II score CRF was received at the DCC by the DataFax data management system using optical character recognition software to create data records from the
CRFs (www.datafax.com). Treatment assignments were generated using a pseudo-random-number generator with randomly permuted blocks. The unblinded PN pharmacist manager at each clinical center maintained 2 color-coded sets of sealed, sequenced, opaque envelopes containing the treatment assignment (APACHE II stratum \( \leq 15 \) or \( > 15 \)). Each envelope uniquely identified the clinical center and illness severity stratum and the sequence number. All other individuals involved in the study were blinded to the randomization, with the exception of DCC biostatisticians (TL, GAC, ESR) who prepared biannual closed reports to the DSMB. TL served as the unblinded DCC biostatistician during the closed session of each DSMB meeting.

### Baseline Data Collection

Baseline clinical data were obtained on the day of randomization and before initiation of study PN. These data included demographic data, dates of initial hospitalization and specific index operation, APACHE II score upon admission to the SICU, indication for PN, days in SICU before study entry, entry day Sepsis-related Organ Failure Assessment (SOFA) score,\(^4\) preoperative body weight, height, BMI [weight (kg)/height (m\(^2\)], nutritional status as estimated by the Subjective Global Assessment method,\(^5\) prescence of acute respiratory distress syndrome (ARDS), current requirement for mechanical ventilation, and evidence of nosocomial infection postoperatively (before study entry), based on Centers for Disease Control and Prevention (CDC) definitions for healthcare associated infections.\(^6\) Based on medical records and discussions with the primary care team, the primary indication(s) for use of PN was also recorded in the CRF by the coordinators (eg, ileus, hemodynamic instability, ischemic bowel, intolerance to EN, bowel obstruction). Use of PN and/or enteral tube feedings within the 30-day period before entry and the number of days of these nutritional interventions were also recorded. Test results available in the electronic medical record were recorded: white blood cell count, serum renal function tests [blood urea nitrogen (BUN) and creatinine concentrations], and hepatic function tests [total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)].

Blood was collected in the \( \text{AM} \) (08:00–10:00 hours) and serum and plasma aliquots stored at \(-80^\circ\text{C}\) for later batch analysis of serial study samples within individual subjects for GLN and glutamate concentrations and blood chemistry levels from all clinical centers at Emory University. Serum was also obtained for later batch analysis for concentrations of glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, ALT, and AST, performed using standard chemical analyzer methods at Emory University Hospital, Atlanta, GA. AA analysis was performed using a Beckman System 6300 High Performance Amino Acid Analyzer (Beckman Instruments, Inc, Palo Alto, CA) at the Emory Genetics Laboratory. In the latter 3 years of the study, AAs were analyzed using a Biochrom 30 Amino Acid Analyzer (Biochrom US, Holliston, MA).

Baseline (entry day) blood glucose (BG) was recorded from the electronic medical record at 3 predefined time points (between 4 and 6 AM using the hospital laboratory value if obtained), and subsequent representative laboratory or hospital floor point-of-care BG level obtained between 2 and 4 PM and again between 10 PM and 12 AM. If a BG value was not recorded for the specified time intervals, the most recent to the outside time point was recorded.

### Study PN Formulations

After randomization, PN calorie (kcal), AA, dextrose, and fat emulsion composition for both control (STD-PN) and experimental (GLN-PN) formulas was calculated by the blinded study team. This data was faxed to the PN pharmacist manager at each clinical center for preparation of the appropriate study PN solution.

Study PN was given for a maximal time of 28 days after entry. Conventional methods for PN administration and daily composition adjustment for critically ill patients were used.\(^4,22,23\) Patients who received GLN-free standard PN before and/or after surgery were eligible.

The overall total daily kcal intake goal after entry was 1.3 times basal energy expenditure from study PN, plus any kcal provided by dextrose-containing IV fluids (when \( > 500 \text{mL/d}\), propofol and clevidipine, and enteral nutrition (EN). Basal energy expenditure was calculated via the Harris–Benedict equation.\(^44\) The initial total AA intake goal from study PN was 1.5 gm/kg/d.\(^4,22\) A conventional GLN-free complete PN AA formula (15% Clinisol Baxter Inc, Deerfield, IL) was used in STD-PN (1.5 gm/kg/d). In GLN-PN, a 20% alanyl-GLN dipeptide solution (Dipeptiven, Fresenius-Kabi, Bad Homburg, Germany) was admixed to provide alanyl-GLN dipeptide at 0.5 gm/kg/d and thus 15% Clinisol at 1.0 gm/kg/d was used such that the 2 formulas provided the same total PN AA dose/kg body weight. If the patient was \( > 125\%\) of ideal body weight (IBW), adjusted body weight \( \text{ABW} = \text{IBW} \times \text{weight/IBW} \times 0.25\) was used to calculate energy and AA requirements.\(^22\) In both STD-PN and GLN-PN, dextrose initially comprised 70% of study PN non-AA kcal and a standard soybean oil-based fat emulsion (20% Intralipid, Fresenius Kabi, Uppsala, Sweden) initially comprised 30% of study PN non-AA kcal daily. Conventional formulations of vitamins (10 mL of MVI Adult, Mayne Pharma, Paramus, NJ) and trace elements (1 mL of Multitrace-5 Concentrate, American Regent, Shirley, NY) were added to both STD-PN and GLN-PN daily.\(^33\)

The study PN was continued after the patient was discharged from the SICU to the regular floor if PN was deemed to be indicated by the investigators and attending physician. If the study PN was initially discontinued before the 28-day time point from entry, but later reinitiated on clinical grounds, the patient was placed on the same study PN type as previously administered (ie, STD-PN or GLN-PN), until 28 days of study PN administration, after which nonstudy PN was administered as indicated, at the discretion of the attending physicians.

Enteral tube feeding, using conventional formulas that were not GLN- or arginine-enriched, was initiated and advanced at each site via feeding tube as clinically indicated. The amount of study PN administered was proportionally decreased as a function of EN (tube feeding and oral diet) intake to maintain the daily kcal and AA/protein goals. Study PN was discontinued when the patient received \( > 50\%\) of their caloric intake goal enterally for a consecutive 48-hour period.

### Study Procedures Overview

Patients were followed for a total of 6 months after entry. Blood sampling for GLN, glutamate, glucose, renal function, and hepatic function was performed at entry (day 1, before initiation of study PN) and serially, when possible, on study days 3, 7, 14, 21, and 28 after entry. Patients were contacted via telephone 2, 4, and 6 months after randomization to determine vital status and whether they had been rehospitalized or readmitted to the SICU. The overall study schema is shown in Figure, Supplemental Digital Content 1, http://links.lww.com/SLA/A864.

### Procedures for Insulin Administration and BG Management

The BG goal range for the trial was 80 to 130 mg/dL. Conventional SICU methods were used to achieve BG goal levels over time.\(^45\)

### Longitudinal Data Collection

Daily energy and AA intake from study PN and EN were determined daily during the 28 days after enrollment or until hospital discharge, whichever came later. Daily BG data obtained from
baseline to day 28 were determined. Patients were monitored for clinical outcomes while hospitalized, including the incidence of new nosocomial infections, daily SOFA score while in the SICU, body weight, concomitant medication use, SICU, and hospital LOS, presence or absence of ARDS, and ventilator free days, defined as the number of days within the first 28 days after enrollment on which the patient was alive and breathing without ventilator assistance for ≥48 hours. Conventional methods for mechanical ventilation and sedation were used at all clinical study sites.47–49

Assessment and Surveillance for Hospital-acquired Infections

Hospital-acquired infections were diagnosed based on standardized CDC criteria (www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInf-Definitions.pdf).41 Incident nosocomial infections were not diagnosed until ≥48 hours after day 1 study PN initiation to minimize the chance that the infection was actually prevalent (but undiagnosed) before study PN entry. All prevalent and incident infections were adjudicated by review of the required pertinent data from all clinical sites in a blinded fashion by an infectious disease specialist coinvestigator (HMB) at Emory University.

In addition to total new (incident) hospital-acquired infections (second primary endpoint), secondary hospital infection endpoints monitored included: (1) rate of new bloodstream infections and other site-specific infections; (2) rate of new hospital infections attributed to gram-positive microorganisms; (3) rate of new hospital infections attributed to gram-negative microorganisms; and (4) rate of new infections attributed to fungal pathogens.

Six-month Mortality Determination

Six-month mortality was determined via telephone contact with the patient’s home at 2, 4, and 6 months after enrollment.

Adverse Event and Serious Adverse Event Monitoring and Reporting

All serious adverse events (SAEs) and unexpected and expected adverse events (AEs), as well as significant clinical or surgical events as narrative data, were recorded in the CRF. SAEs and AEs were reported up to and including 30 days after study PN discontinuation.

Sample Size and Power Considerations

Our pilot RCT in SICU patients following cardiac, vascular, or colonic surgery showed that the hospital mortality rate was 22% (6 deaths) for the combined 27 patients: STD-PN 5/12 (42%) and GLN-PN 1/15 (7%), respectively; P = 0.06 (17). GLN goal enrollment was determined to be 150 patients (75 patients in each arm) to provide 90% statistical power to detect a 25% difference in hospital mortality (42% vs 17%) with a 2-sided Fisher exact test and type I error rate of 5%. Our pilot RCT showed that 83% of the STD-PN and 64% of the GLN-PN group developed new hospital-acquired infections after entry.21 GLN group sample sizes of 75 patients in the STD-PN group and 75 patients in the GLN-PN for GLN achieved 90% power to detect a 25% difference between study groups in the percentage of patients with new infections (83% vs 58%).

Statistical Analysis

The primary analyses of the data were performed according to patients’ original treatment assignment [ie, intention-to-treat (ITT) analyses] and the inclusion of all data from all patients randomized in the final analysis. Hospital mortality was compared between treatment groups using a χ2 test. Confidence intervals (CIs) (95%) were calculated for hospital mortality rates within each study cohort and for the observed difference in hospital mortality rates.

Hospital-acquired infection rates per 1000 hospital days were estimated and compared between treatment groups, using exact methods based on the Poisson distribution. Cumulative mortality was estimated with the Kaplan–Meier method and compared between treatment groups with the log-rank test.

Repeated-measures analyses of daily SOFA scores, daily BG concentrations and serial GLN, glutamate, and blood chemistry concentrations were analyzed with a means model with SAS Proc Mixed (version 9, mixed linear models, SAS Institute Inc., Cary, NC) providing separate estimates of the means by time on study (daily for SOFA scores, baseline and days 3, 7, 14, 21, and 28 for GLN, glutamate, and blood chemistry concentrations; daily with morning, afternoon, and evening measurements of BG concentrations) and treatment group. A compound-symmetric variance–covariance form among the repeated measurements was assumed for each outcome, and robust estimates of the standard errors of parameters were used to perform statistical tests and construct 95% CIs. The model-based means are unbiased with unbalanced and missing data, so long as the missing data are noninformative (missing at random). Reported P values are 2-sided.

The primary outcomes were hospital mortality and incident total hospital-acquired infections. Relative risks were calculated to measure the degree of association between APACHE II score at SICU admission (quartiles) and hospital mortality. In addition, the relative risk for hospital mortality was estimated with treatment as a covariate stratified by Apache II quartiles, using the methods described by Zou.50 The potential association between clinical outcomes (hospital mortality; incident infection) and the entry plasma GLN concentration was evaluated with a χ2 test. Other secondary clinical outcomes (ventilator-free days, ICU and hospital LOS after entry) were compared between treatment groups with the Wilcoxon rank-sum test.

The hyperglycemia and hypoglycemia rates (episodes per 1000 hospital days) by treatment group were estimated and compared by performing a generalized estimating equation Poisson regression analysis of the daily counts, implemented using SAS Proc Genmod, using an exchangeable correlation structure for the repeated daily counts within patient. Each SAE and each adverse event was counted once per patient when first identified and compared between treatment groups with a χ2 or Fisher exact test.

One planned interim analysis for all-cause mortality was performed before the final analysis. A Lan-DeMets spending function was used, with stopping boundaries corresponding to the O’Brien–Fleming stopping rule. The DSMB regularly reviewed accrual, quality control, safety, and efficacy, and approved the interim analysis plan proposed by the DCC.

Additional details on Methods are provided in the online Material, Supplemental Digital Content, http://links.lww.com/SLA/A864.

RESULTS

Subjects

A total of 1247 patients were assessed for eligibility (Fig. 1). A total of 150 patients were randomized to receive either STD-PN (n = 75) or GLN-PN (n = 75). Demographic and clinical characteristics were comparable between the 2 study groups (Table 1). Estimated nutritional status at entry (using the Subjective Global Assessment method) did not differ by study group; no evidence of malnutrition [GLN-PN 32 (42.6%), STD-PN 28 (37.3%)]; mild-to-moderate malnutrition [GLN-PN 31 (41.3%), STD-PN 37 (49.3%)]; or severe malnutrition [GLN-PN 12 (16.0%), STD-PN 10 (13.3%)]. The indications for use of PN were similar between the 2 study groups (Supplemental Table 1, http://links.lww.com/SLA/A864).

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One hundred patients completed 6-months of follow-up. Forty-five patients died. One patient withdrew consent on day 7 and 4 were lost to follow-up at days 39, 59, 64, and 121. The primary diagnosis leading to the index cardiac, vascular, or intestinal surgery was recorded at study entry. A total of 35 specific conditions were reported, which were similar between groups (not shown). The most common events leading to intestinal surgery were, in order, intestinal fistula/stricture/adhesion (GLN-PN 8.0%, STD-PN 10.7%), intestinal ischemia (GLN-PN 6.7%, STD-PN 17.3%), and intestinal perforation (GLN-PN 8.0%, STD-PN 10.7%). The most common events leading to vascular surgery were vascular aneurysm (GLN-PN 16.0%, STD-PN 10.6%) and to cardiac surgery were coronary artery disease (GLN-PN 4.0%, STD-PN 2.7%) and cardiac valve malfunction (GLN-PN 4.0%, STD-PN 2.7%).

AA/Protein and Caloric Intake From Study PN and EN

Nonstudy PN was administered within 30 days before enrollment in 122/150 (81%) patients for a median of 3 days. The average number of days patients received study PN was similar between the groups (STD-PN, 10.6 ± 5.2 d; GLN-PN, 11.0 ± 5.0 d, respectively). The mean GLN dose administered during study PN days was 22.7 g/d (0.30 ± 0.04 g/kg/d) in the GLN-PN group.

Overall, pre hoc goal AA + protein and caloric intakes were achieved in both study groups (Supplemental Fig. 2A, B, http://links.lww.com/SLA/A864). The median (25th and 75th percentile) intake for combined AA/protein intake during the 28 days after entry was 1.5 (1.4–1.5) g/kg/d in both study groups. Caloric intake was also similar; the STD-PN group received 26.7 (23.8–29.6) kcal/kg/d and the GLN-PN group 26.7 (23.9–29.5) kcal/kg/d, respectively.

Study PN AA and kcal administration was similar between the STD-PN and GLN-PN groups for the first 14 study days (Fig. 2A, B) and also for the entire 28-day period of observation (not shown). The advance of EN-derived protein and kcal during the initial 14 days was also similar between groups and is shown in Supplemental Figure 3A, B, http://links.lww.com/SLA/A864.

Plasma GLN and Glutamate Concentrations

Mean plasma GLN concentrations were in the low to low-normal range at entry in both groups (Fig. 3).31 Plasma GLN levels rose significantly (=33%) by day 3 with GLN-PN compared with plasma GLN levels the STD-PN group. Plasma GLN concentrations remained in this range and were significantly higher than in STD-PN patients through day 14. With STD-PN, plasma GLN levels rose slowly and modestly over time. Plasma GLN concentrations were similar between the 2 study groups at the days 21 and 28 time points, reflecting transition from study PN to EN (Fig. 3). Plasma glutamate concentrations rose slightly from baseline on days 3 and 7 and were similar in both groups over time (data not shown).

BG Concentrations

Mean BG levels remained within the target GLND range (80–130 mg/dL) and were similar in both the STD-PN and GLN-PN groups over time at the morning, afternoon, and evening time points (Supplemental Fig. 4, panels A, B, and C, http://links.lww.com/SLA/A864). As shown in Supplemental Table 2, panel A, http://links.lww.com/SLA/A864, the rate of hyperglycemic episodes (BG >200 mg/dL/1000 hospital study days (mean and 95% CI) was significantly lower in the GLN-PN group compared with the STD-PN group (P = 0.04). Rates of BG >180 mg/dL/1000 hospital days and hypoglycemia (<50 mg/dL/1000 hospital days) were similar between groups (Supplemental Table 2, panels B and C, http://links.lww.com/SLA/A864).

SICU Illness Severity

There were no differences between the 2 study groups for changes in SICU illness severity over time by sequential SOFA scores (Supplemental Fig. 5, http://links.lww.com/SLA/A864).

Healthcare-associated Infection Rates

Thirty-six patients (24.0%) had a prevalent infection at entry and 56 patients (37.3%) had an incident healthcare-associated infection after entry. Incident infections included 35 patients with gram-positive bacterial infections, 29 patients with gram-negative bacterial infections, and 24 patients with fungal pathogen as the putative causal microorganism. There were no differences between the STD-PN and GLN-PN groups for total number of new (incident) healthcare-associated infections after entry, infection rates/1000 hospital days, site-specific infections, or causative microorganism class (Table 2).

Mortality

A total of 45 patients died during 6-month follow-up. There were no differences between the groups for any index of mortality (Fig. 4). Total hospital mortality was 13/75 (17.3%) with STD-PN compared with 11/75 (14.7%) with GLN-PN (P = 0.66). Mortality at 28 days after entry was also similar [STD-PN, 12/75 (16.0%) vs GLN-PN, 11/75 (14.7%); P = 0.82]. The 6-month cumulative all-cause mortality was 31.4% in the GLN-PN group and 29.7% in the STD-PN group (P = 0.88; Fig. 4), and the estimated hazard ratio for treatment was 1.05 (95% CI, 0.58–1.88; P = 0.88). Hospital mortality rates between groups did not differ by Apache II score at SICU admission, although as expected admission Apache II score did predict hospital mortality (Supplemental Table 3, http://links.lww.com/SLA/A864). Similarly,
hospital mortality did not differ by group in patients with an SICU admission Apache II score at or below the median score of 23 (not shown). In patients with an SICU admission Apache II score of ≥24, 8/34 (23.5%) of patients in the STD-PN group died in the hospital compared with 6/37 (16.2%) of patients randomized to GLN-PN [relative risk = 0.69 (0.27–1.78), P = 0.44].

Other Clinical Outcomes

There were no differences between the study groups for median ventilator free days [STD-PN 26.0 (12.0–28.0), GLN-PN 24.0 (6.0–28.0)], ICU LOS [STD-PN 6.0 (3.0–13.0), GLN-PN 8.0 (3.0–18.0)], or hospital LOS [STD-PN 17.0 (10.0–28.0), GLN-PN 19.0 (14.0–28.0)].

### TABLE 1. Baseline Demographic and Clinical Characteristics by Treatment

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<tbody>
<tr>
<td>Age</td>
<td>60.2 ± 13.6</td>
<td>60.4 ± 13.0</td>
</tr>
<tr>
<td>Male sex</td>
<td>35 (46.7)</td>
<td>45 (60.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>60 (80.0)</td>
<td>71 (94.7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>15 (20.0)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 ± 5.9</td>
<td>26.4 ± 6.3</td>
</tr>
<tr>
<td>APACHE II score at study entry</td>
<td>16.2 ± 5.7</td>
<td>15.7 ± 7.3</td>
</tr>
<tr>
<td>Apache ≤ 15</td>
<td>33 (44.0)</td>
<td>38 (50.7)</td>
</tr>
<tr>
<td>APACHE II score on first day in SICU†</td>
<td>22.9 ± 7.6</td>
<td>22.0 ± 7.6</td>
</tr>
<tr>
<td>SOFA score at entry‡</td>
<td>7.1 ± 4.7</td>
<td>6.2 ± 4.8</td>
</tr>
<tr>
<td>Index surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal resection</td>
<td>50 (66.7)</td>
<td>52 (69.5)</td>
</tr>
<tr>
<td>Vascular</td>
<td>17 (22.7)</td>
<td>14 (18.7)</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>3 (4.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Cardiac valve</td>
<td>3 (4.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Esophageal/gastric resection</td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Days from index surgery to randomization</td>
<td>4.5 ± 3.0</td>
<td>4.3 ± 2.9</td>
</tr>
<tr>
<td>On mechanical ventilation at entry</td>
<td>54 (72.0)</td>
<td>44 (58.7)</td>
</tr>
<tr>
<td>ARDS at entry</td>
<td>11 (14.7)</td>
<td>6 (8.0)</td>
</tr>
<tr>
<td>Received any enteral tube feedings within 30 d before entry†</td>
<td>13 (17.5)</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>Received any PN within 30 d before entry†</td>
<td>59 (78.7)</td>
<td>63 (84.0)</td>
</tr>
<tr>
<td>Morning blood glucose at entry, mg/dL‡</td>
<td>136 ± 41</td>
<td>143 ± 41</td>
</tr>
<tr>
<td>WBC at entry, 10⁹/L‡</td>
<td>14.3 ± 7.3</td>
<td>14.2 ± 8.8</td>
</tr>
<tr>
<td>Plasma glutamate and glutamine concentrations at entry, μM§</td>
<td>48 ± 35</td>
<td>53 ± 32</td>
</tr>
<tr>
<td>Glutamate</td>
<td>438 ± 161</td>
<td>427 ± 206</td>
</tr>
<tr>
<td>Glutamine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Continuous variables are reported as mean ± SD and categorical variables are reported as no. (%).
- Sample size is 74 in the GLN-PN group and 75 in the STD-PN group.
- Sample size is 75 in the GLN-PN group and 72 in the STD-PN group.
- Sample size is 74 in the GLN-PN group and 72 in the STD-PN group.
- APACHE II indicates Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; PN, parenteral nutrition; SOFA, Sepsis-related Organ Failure Assessment; WBC, white blood cell.

FIGURE 2. A, Administration of amino acids (AAs; g/kg/d) from study PN, shown as median and 25th and 75th percentiles, during the initial 14 days after entry. Intake was similar between the STD-PN and GLN-PN groups, and also for the entire 28-day period of observation (not shown). B, Study PN kcal intake, shown as median and 25th and 75th percentiles. Intake was similar between the STD-PN and GLN-PN groups during the initial 14 days and also for the entire 28-day period of observation (not shown). The steady decrease in study PN AA and kcal over time reflected the GLND standard of care protocol for weaning from PN to EN as tolerated.
Relationship of Plasma GLN Levels to Mortality and Infection Endpoints

There was no relationship between entry (day 1) plasma GLN concentrations and hospital mortality or development of any new infection when examined by GLN concentration quartile or dichotomized as GLN concentration <420 or ≥420 μM (Supplemental Table 4a, http://links.lww.com/SLA/A864). Supplemental Table 4b, http://links.lww.com/SLA/A864, summarizes hospital mortality data by treatment group and baseline plasma GLN concentration quartile. Treatment effects on hospital mortality did not vary by level of baseline GLN (P = 0.81, test for interaction between treatment and GLN quartile).

Safety of GLN-PN

Serum Renal and Liver Function Tests

There were no significant effects of treatment (study PN) or an interaction between treatment and time (blood chemistry values from entry, days 3, 7, 14, 21, and 28) on renal function tests (serum BUN and creatinine concentrations, respectively; Supplemental Fig. 6, panels A and B, and Supplemental Table 5, http://links.lww.com/SLA/A864) or on liver function tests (serum total bilirubin, alkaline phosphatase, AST, and ALT concentrations, respectively; Supplemental Fig. 7, panels A, B, C, and D, http://links.lww.com/SLA/A864).

SAEs

No SAE was reported to be possibly or definitely related to study PN treatment. SAEs were similar between the STD-PN and GLN-PN groups, except for a higher incidence of cardiopulmonary arrest in the STD-PN group (Supplemental Table 6, http://links.lww.com/SLA/A864).

AEs

Overall, AEs were similar between the STD-PN and GLN-PN groups (Supplemental Table 7, http://links.lww.com/SLA/A864). Additional details on Results are provided in Supplemental Material, http://links.lww.com/SLA/A864.

DISCUSSION

The results of this Phase III, double-blind RCT of GLN dipeptide-supplemented PN demonstrate that this approach is safe, but did not improve clinical outcomes in SICU patients requiring PN after gastrointestinal, vascular, or cardiac surgery in comparison to conventional GLN-free PN. The results do not confirm our previous double-blind pilot RCT study, in which patients receiving GLN dipeptide-supplemented PN demonstrated decreased new hospital infection rates compared with patients receiving GLN-free PN after colonic, vascular, or colonic surgery.17 These results are also in contrast to a number of multicenter European RCTs, indicating that complete PN supplemented with GLN decreased hospital-acquired infections in adult mixed medical/surgical ICU patient populations,15,16,19 as well as beneficial clinical effects with GLN-PN observed in several previous RCTs in other types of critically ill medical and surgical patients.8,10–12,20

Despite an initial PN GLN dose similar to 2009 European recommended guidelines for ICU patients (0.33 g/kg/d L-GLN),52 we found no significant differences in new healthcare-associated infections, SICU illness severity, mortality indexes, LOS indexes, or use of mechanical ventilation after entry vs STD-PN controls who received no GLN in PN. In addition, plasma GLN levels at entry did not correlate with increased hospital mortality, as suggested in some studies in which GLN levels were determined on the day of ICU

### TABLE 2. Incident Hospital-acquired Infection Rates by Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLN-PN n (%), rate (95% CI)</th>
<th>STD-PN n (%), rate (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>52 (32, 43)</td>
<td>28 [21–37]</td>
<td>39 (24, 32)</td>
</tr>
<tr>
<td>Specific site infections</td>
<td></td>
<td></td>
<td>39 (24, 32)</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>18 (17, 23)</td>
<td>9.6 [6.1–15.1]</td>
<td>13 (11, 15)</td>
</tr>
<tr>
<td>Lower respiratory§</td>
<td>10 (10, 13)</td>
<td>5.3 [3.0–9.3]</td>
<td>12 (12, 16)</td>
</tr>
<tr>
<td>Surgical site</td>
<td>9 (8, 11)</td>
<td>4.8 [2.6–8.8]</td>
<td>9 (8, 11)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>7 (7, 9)</td>
<td>3.7 [1.8–7.9]</td>
<td>3 (2, 3)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>5 (5, 7)</td>
<td>2.7 [1.2–5.8]</td>
<td>1 (1, 1%)</td>
</tr>
<tr>
<td>Any fungal species</td>
<td>21 (16, 21)</td>
<td>11.1 [6.7–18.4]</td>
<td>13 (8, 11)</td>
</tr>
<tr>
<td>Any gram-negative bacteria</td>
<td>33 (16, 21)</td>
<td>17.5 [12–26.8]</td>
<td>18 (13, 17)</td>
</tr>
<tr>
<td>Any gram-positive bacteria</td>
<td>35 (18, 24)</td>
<td>18.6 [12.0–28.7]</td>
<td>32 (17, 23)</td>
</tr>
</tbody>
</table>

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§Lower respiratory infections include pneumonia.
However, GLND patients were enrolled a median of 3 to 4 days after SICU admission, thus our results are not strictly comparable to these previous reports.14,51 We rigorously assessed the safety of GLN dipeptide-supplemented PN using strict inclusion/exclusion criteria (which excluded those patients in shock or with severe, acute renal, or hepatic failure at entry), site performance monitoring, serial monitoring of AEs and SAEs up to 30 days after study PN discontinuation, and regularly evaluating potential adverse events over time by both a central Medical Monitor and an active DSMB with expertise in ICU nutrition support. Our data clearly demonstrate the safety of the approaches we used for administration of GLN-supplemented PN in patients with moderately severe critical illness.

Strengths of the GLND study included performance of the trial in 5 major independent medical centers located in different regions of the United States, rigorous concealment of random treatment allocation, appropriate blinding implementation, and the ITT design. The study was also unusual among prior studies of GLN-PN in ICU patients in that it focused on a subset of SICU patients after specific major types of surgery, excluded cancer as a primary diagnosis, and was informed by the results of a similar pilot study. Other strengths include the clinically matched study groups at entry (eg, demographic criteria, index operations, underlying illness severity, entry GLN concentrations, presence of ARDS, and need for mechanical ventilation) and the similar tight BG control between groups. Study procedures ensured double-blind and adequate intake of conventional PN and EN, which provided nearly identical amounts of calories, protein/AA, and micronutrients between groups up to 28 days, initially as study PN, with subsequent transition to EN in a pragmatic manner. Also, all healthcare-associated infections were adjudicated by an infectious disease specialist using well-defined pre hoc CDC criteria.

To minimize heterogeneity in clinical outcomes, we also excluded patients with malignancy, burns, and trauma as in the pilot study, but it is unclear whether such patients may benefit from GLN administration.71,22,25 GLND was designed to study the efficacy of PN GLN supplementation alone (ie, it was not a study of PN timing, non-GLN macronutrient doses, or route of feeding). The investigators’ practices were to initiate PN several days after SICU admission, but to generally continue PN immediately postoperatively in patients receiving PN preoperatively. Thus, the GLND enrollment window was a 2- to 14-day period after the index surgical operation.

Although entry after the index surgery and duration of study PN were similar between the study groups, it is unclear whether the wide enrollment window after the index surgery may have introduced variation.

Similar to our results, recently a number of double-blind RCTs also have not shown consistent clinical benefits of GLN-supplemented PN in ICU patients via ITT analysis.23–25 Grau et al23 studied 127 primarily surgical ICU patients in 12 Spanish hospitals receiving 0.5 g/kg/d alanyl-GLN dipeptide in complete PN vs GLN-free complete PN, similar to our regimen. GLN-PN was administered for a median of 6 (5–8) days, but by ITT analysis, no infectious or other clinical outcome was affected, other than decreased urinary tract infections/1000 catheter days in GLN-PN cohort.23 The Scandinavian GLN trial was a multicenter double-blind RCT in which intravenous alanyl-GLN dipeptide was given independent of EN and/or PN, as indicated, to 413 medical/surgical ICU patients for a median of 6 (3–11) days in ITT analysis and 9 (5–14) days in per-protocol analysis (>3 d of administration).24 No impact of GLN administration on serial SOFA scores or mortality was observed with ITT analysis, although decreased ICU mortality with GLN dipeptide was observed in per-protocol analysis.23 The SIGNET study was a 2 × 2 factorial multicenter double-blind RCT in 502 mixed medical/surgical patients from 10 Scottish ICUs that examined PN supplemented with 20.2 g L-GLN/d ± 500 μg selenium vs a control group with neither supplement.25 No significant effect of L-GLN-supplemented PN on hospital infection, SOFA scores, LOS, or mortality indexes was observed.25 The SIGNET study has been criticized because exact dosing of GLN in g/kg body weight was not reported and GLN-containing PN was administered for an average of only 5 days.25 In GLND, our GLN dosing regimen achieved significantly increased and sustained plasma GLN levels well above control values for 14 days and study PN was given for ≈11 days in each group (GLN dose = 0.30 ± 0.04 g/kg/d, in the GLN-PN group). Thus, it cannot be argued that GLND provided an inadequate dose of GLN, given for an inadequate period of time, based on 2009 European recommendations.52 Nonetheless, our protocol called for weaning of study PN

FIGURE 4. Kaplan–Meier cumulative mortality curve through 6 months after entry. There were no differences in mortality between the STD-PN and the GLN-PN groups over time. The estimated hazard ratio for treatment was 1.05 [95% CI: 0.38–1.88, \( P = 0.88 \)] for GLN-PN relative to STD-PN.

Although entry after the index surgery and duration of study PN were similar between the study groups, it is unclear whether the wide enrollment window after the index surgery may have introduced variation.

Similar to our results, recently a number of double-blind RCTs also have not shown consistent clinical benefits of GLN-supplemented PN in ICU patients via ITT analysis.23–25 Grau et al23 studied 127 primarily surgical ICU patients in 12 Spanish hospitals receiving 0.5 g/kg/d alanyl-GLN dipeptide in complete PN vs GLN-free complete PN, similar to our regimen. GLN-PN was administered for a median of 6 (5–8) days, but by ITT analysis, no infectious or other clinical outcome was affected, other than decreased urinary tract infections/1000 catheter days in GLN-PN cohort.23 The Scandinavian GLN trial was a multicenter double-blind RCT in which intravenous alanyl-GLN dipeptide was given independent of EN and/or PN, as indicated, to 413 medical/surgical ICU patients for a median of 6 (3–11) days in ITT analysis and 9 (5–14) days in per-protocol analysis (>3 d of administration).24 No impact of GLN administration on serial SOFA scores or mortality was observed with ITT analysis, although decreased ICU mortality with GLN dipeptide was observed in per-protocol analysis.23 The SIGNET study was a 2 × 2 factorial multicenter double-blind RCT in 502 mixed medical/surgical patients from 10 Scottish ICUs that examined PN supplemented with 20.2 g L-GLN/d ± 500 μg selenium vs a control group with neither supplement.25 No significant effect of L-GLN-supplemented PN on hospital infection, SOFA scores, LOS, or mortality indexes was observed.25 The SIGNET study has been criticized because exact dosing of GLN in g/kg body weight was not reported and GLN-containing PN was administered for an average of only 5 days.25 In GLND, our GLN dosing regimen achieved significantly increased and sustained plasma GLN levels well above control values for 14 days and study PN was given for ≈11 days in each group (GLN dose = 0.30 ± 0.04 g/kg/d, in the GLN-PN group). Thus, it cannot be argued that GLND provided an inadequate dose of GLN, given for an inadequate period of time, based on 2009 European recommendations.52 Nonetheless, our protocol called for weaning of study PN as EN was able to be advanced clinically (pragmatic); thus, GLN administration was steadily decreased over time, particularly after the first 2 weeks after entry. It is unknown whether weaning enteral GLN during (or after) hospitalization after a period of largely parenteral GLN in the ICU setting can impact clinical outcomes.

Recently, the 1223-subject REDOX trial, conducted in predominantly medical ICU patients with shock and multiple organ failure, demonstrated a slight but statistically significant increase in hospital and 6-month mortality in patients given high-dose alanyl-GLN dipeptide (0.35 g/kg/d intravenously, plus 30 g/d enterally, independent of EN/PN delivery), started during the first 24 hours after ICU admission.56 Post hoc analysis of REDOX data suggested that the presence of multiorgan failure that included renal dysfunction at study entry was most strongly associated with the mortality signal with GLN administration.52 However, the current GLND trial differs from the REDOX trial in that it was conducted exclusively in postoperative SICU patients, excluded those in shock or with significant renal/hepatic dysfunction at entry, and provided a lower, more conventionally used GLN dose,55 in conjuction with complete PN ± EN support, with GLN-PN started several days after ICU admission in resuscitated patients.

Given several decades of published RCTs and numerous meta-analyses suggesting the clinical and metabolic benefits of GLN-supplemented PN,6–12,16–20,32–36 it remains unclear why we were unable to observe a signal of benefit in this or recent RCTs of GLN-supplemented PN.23–25 Since our pilot study,17 the index operations we included (vascular, intestinal, and cardiac procedures) have increasingly been performed using minimally invasive surgical

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techniques, which are less catabolic than previous open procedures, whereas ICUs have incorporated increasing use of standardized operating procedures and clinical decision support tools. However, the impact of these changes in the clinical ICU setting on GLN utilization/requirements and clinical impact of GLN administration is unknown.

In conclusion, in a rigorous, multicenter, Phase III American trial, complete PN supplemented with alanyl-GLN dipeptide at a dose of 0.5 g/kg/d was safe, but did not impact clinical outcomes in SICU patients deemed to require PN after intestinal, vascular, or cardiac surgery.

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REFERENCES


