ORIGINAL RESEARCH

Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs

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Purpose: The provision of early enteral (gut) nutrition to critically ill patients, started within 24 hours of injury or intensive care unit admission, is accepted to improve health outcomes. However, not all patients are able to receive early enteral nutrition. The purpose of the economic analysis presented here was to estimate the cost implications of providing early parenteral (intravenous) nutrition to critically ill patients with short-term relative contraindications to early enteral nutrition.

Materials and methods: From the perspective of the US acute care hospital system, a cost-minimization analysis was undertaken based on large-scale Monte Carlo simulation (N = 1,000,000 trials) of a stochastic model developed using clinical outcomes and measures of resource consumption reported in a 1,363-patient multicenter clinical trial combined with cost distributions obtained from the published literature. The mean costs of acute care attributable to each study group (early parenteral nutrition versus pragmatic standard care) and the mean cost difference between groups, along with respective 95% confidence intervals, were obtained using the percentile method.

Results and conclusion: The use of early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition may significantly and meaningfully reduce total costs of acute hospital care by US$3,150 per patient (95% confidence interval US$1,314 to US$4,990). These findings were robust, with all sensitivity analyses demonstrating significant savings attributable to the use of early parenteral nutrition, including sensitivity analysis conducted using European cost data.

Keywords: intensive care, acute hospital care, intravenous nutrition, US acute hospital system

Introduction

The provision of early and appropriate nutrition support to patients during a critical illness is accepted to improve health outcomes,[1] with the preponderance of the clinical evidence suggesting that most benefit can be obtained from the provision of early enteral (gut) feeding.[2–4] Unfortunately, enteral feeding is often difficult to initiate early during critical illness, with multinational observational studies demonstrating that up to 45% of eligible critically ill patients do not have enteral feeding started within the timeframes recommended by international guidelines.[5–7]

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In 2005, we conducted a systematic review of all clinical trials to evaluate the benefits attributable to enteral nutrition compared with parenteral (intravenous) nutrition in critical illness.[8] We concluded that if early parenteral nutrition was provided to critically ill patients in whom early enteral nutrition could not be initiated, lives may be saved. Unfortunately, these same clinical trials also suggested that infectious complications might be increased if early parenteral nutrition was provided. To resolve the discordant results arising from the small trials published on this topic, we initiated a large-scale multicenter clinical trial (the Early Parenteral Nutrition [PN] Trial).

Details regarding the conduct and results of the Early PN Trial have been reported elsewhere.[9,10] The purpose of this current paper is to report a full economic analysis based on the clinical results and measures of resource consumption reported in the Early PN Trial.

Materials and methods
Context
The Early PN Trial was a multicenter randomized controlled trial (RCT) conducted to determine whether adult critically ill patients with short-term relative contraindications to early enteral (gut) nutrition would benefit from the provision of early parenteral (intravenous) nutrition.

Within 24 hours of admission to an intensive care unit (ICU), critically ill patients unable to receive early enteral (gut) feeding due to a short-term relative contraindication were randomized to commence parenteral nutrition immediately or to receive pragmatic standard care. Standard care was defined pragmatically, not by study protocol, and allowed the attending clinician to select the route (gut or intravenous), starting rates, metabolic targets, and composition of nutrition to be provided to patients based on their ICU's current practice.

From October 2006 until June 2011, 1,363 critically ill patients were enrolled and randomized from the ICUs of 31 hospitals throughout Australia and New Zealand.

The provision of early parenteral nutrition did not alter the study's primary outcome, patient mortality at study day 60 (0.0% covariate adjusted risk difference, 95% confidence interval (CI) from −4.2% to 4.3%); however, patients receiving early parenteral nutrition consumed less health care resources, as indicated by a reduction in need for invasive mechanical ventilation (MV; 1.1 fewer days, 95% CI 0.3 to 1.8) and a reduction in duration of ICU stay (0.8 fewer days, 95% CI 0.0 to 1.5 fewer days). Patients randomized to the early parenteral nutrition arm of the clinical trial received a mean of 3.1 days (95% CI 2.4 days to 4.0 days) more parenteral nutrition than standard care patients. There were no differences between randomized groups with regards to any other measures of resource consumption or health states (hospital stay, infection rates, antibiotic use, etc) or any suggestions of harm attributable to the use of early parenteral nutrition. Furthermore, no differential treatment effects were detected in a priori planned subgroup analysis based on nutritional status at baseline.[10]

Type of economic evaluation
In the context of the 95% CIs around the estimate of zero effect on day-60 mortality rates, a cost-minimization analysis (CMA) was undertaken to compare total costs of care associated with the use of early parenteral nutrition with total costs of care associated with pragmatic standard care.

Total costs of care were estimated from measures of resource consumption reported in the Early PN Trial and costs obtained from the published literature using a stochastic model, with a large-scale Monte Carlo simulation undertaken to estimate total cost differences and 95% CIs.

Perspective and time horizon
This CMA was conducted from the perspective of the US acute care hospital system. The time horizon of the study was the period from study enrollment until discharge from acute care hospital.

Discounting/indexing of costs
The US Department of Labor Consumer Price Index for Medical Consumers (CPI) was used to index published US costs to 2012 US funds based on the specific index rate reported for each year.[11] In addition, a sensitivity analysis was conducted using a conservative index rate of 4.0%.[12]

All costs reported in this manuscript are indexed to 2012 US funds using the CPI, unless explicitly reported otherwise.

Details concerning the delivery of the study intervention (early parenteral nutrition)
At all participating sites, Early PN Trial intervention patients received standard parenteral nutrition from a ready-to-mix multi-chamber bag containing amino acids, glucose, lipids and electrolytes (Kabiven® G19%, Fresenius Kabi Australia Pty Limited, Sydney, Australia). Complete product information is available online.[13]

Metabolic targets were set using the Harris–Benedict equation with appropriate adjustment factors (Table S1). Starting rates and daily rate increases were defined by two study PN delivery protocols (A and B), with Protocol B

specifically designed for patients clinically suspected to be malnourished, who are known to be at risk of refeeding syndrome. Protocol B was the default protocol for patients with very low body mass index (<17 kg/m^2). Both PN delivery protocols reminded clinicians to provide vitamins, minerals, and trace elements daily, as clinically indicated. Protocol B made strong recommendations for the daily provision of vitamins, minerals, and trace elements to malnourished patients, who are known to be at risk of refeeding syndrome. See Table S2 for complete details regarding the study PN delivery protocols.

The study parenteral nutrition was a shelf-stable product that did not contain vitamins or trace elements at time of delivery to the study hospital, so it did not require refrigeration for storage. Delivery of the study parenteral nutrition to hospitals participating in the Early PN Trial was received by the nutrition department or study ICU and the product was stored in the ICU's storeroom until use. Pharmacy storage and handling were not required.

Guided by a detailed study protocol, the administration and delivery of the study parenteral nutrition did not require review or supervision by a parenteral nutrition team, nor were any additional biochemical tests required beyond those routinely conducted on a daily basis by the study ICU. Furthermore, only patients who were sick enough to already need a central venous line in situ at time of screening for eligibility into the trial were recruited to participate, thus delivery of early parenteral nutrition did not require de novo placement of a dedicated central line.

Whilst receiving the study intervention, if the patient's clinical team decided the patient required additional vitamins, minerals, or micronutrients (see Table S2), they were delivered via a separate infusion bag and not admixed with the study parenteral nutrition; as such, requirements for preparation of the study parenteral nutrition in a laminar flow environment were avoided. Complete details of the study intervention, such as the identification of eligible patients and calculation of caloric targets, are reported elsewhere.[9,10]

Costs of study intervention (early parenteral nutrition)

In the stochastic model, delivery of the study parenteral nutrition to patients randomized to receive early parenteral nutrition and the delivery of parenteral nutrition to standard care patients was costed at the level of the individual patient.

The cost of delivering 1 day of parenteral nutrition therapy in the US market was obtained from the publication by Turpin et al.[14] Using a transaction level cost database from the Premier Healthcare Alliance, which covers more than 400 hospitals in the USA, Turpin et al identified a total of 44,358 patients from 194 hospitals who had at least one transactional level cost recorded for parenteral nutrition whilst in hospital. The costs for 1 day of parenteral nutrition therapy, including all additives (vitamins, minerals, trace elements, etc) and all fees, were reported as US$186.92 for treatment with a ready-to-mix multi-chamber bag and US$272.40 for a pharmacy compounded bag of parenteral nutrition.

Although the specific intervention delivered in the Early PN Trial involved the use of ready-to-mix multi-chamber bags of parenteral nutrition, to improve generalizability, we elected to blend the costs of a ready-to-mix multi-chamber bag and a pharmacy compounded bag, as blending resulted in a more conservative (higher) estimate of study intervention costs used in the CMA. For the purpose of this simulation, the mean cost of 1 day of parenteral nutrition was estimated at US$229.66, with a standard deviation of US$60.44, indexed from the original publication to 2012 US dollars using the CPI.

Measures of acute care hospital resource consumption

For each of the 1,363 patients enrolled into the Early PN Trial, recorded values for major measures of resource consumption demonstrating marginal differences between randomized groups were abstracted from the Early PN Trial database at the individual patient level. These measures of resource consumption included the patient's ICU length of stay, number of days of parenteral nutrition provided, whether or not the patient received invasive MV during their ICU stay and the primary type of patient population descriptor (ie, medical patient, surgical patient, or trauma patient).

Costs of acute care whilst in the ICU

Cost distributions for acute care whilst admitted to an ICU were obtained from the published literature. Dasta et al reported the mean daily costs of care from the perspective of the acute care hospital for patients admitted to an ICU using an administrative database composed of 51,009 ICU patients from 253 geographically diverse hospitals across the USA.[15] This database, maintained by NDCHealth, contains patient charges recorded by operational billing systems and is regularly audited for accuracy. Costs were estimated using hospital-specific cost-to-charge ratios. Hospitals contributing to this study were considered representative of the larger US hospital population in terms of geographic location, bed number, and teaching status.

Dasta et al's reported costs were significantly higher for the first 2 days of ICU admission compared to subsequent days, with significant differences also existing between major patient groups (medical patient, surgical patient, and trauma patient) and between patients who received invasive MV during their ICU stay compared with patients who did not receive MV. Table 1 presents the relevant cost distribution matrix abstracted from Dasta et al's study.

Structure of the stochastic cost model and large-scale Monte Carlo simulation

Post-randomization costs of care were estimated using a stochastic model based on the sum of daily cost components, modeled using the gamma distribution with mean μ and shape α, where $\alpha = \mu^2/\sigma^2$. For example, the costs of acute care for a trauma patient who received MV, required 3 days of care in an ICU, and received 2 days of parenteral nutrition would be estimated as the sum of five randomly generated gamma distributed costs: Day 1 ICU stay G (US$15,625, US$11,955) plus day 2 ICU stay G (US$7,414, US$6,683) plus day 3 ICU stay G (US$5,880, US$5,750) plus 1 day of parenteral nutrition G (US$229.66, US$60.44) plus day 2 of parenteral nutrition G (US$229.66, US$60.44), where G (mean, standard deviation). If a patient was enrolled into the Early PN Trial on day 2 of their ICU stay, costing was begun with ICU day 2. For those patients enrolled on ICU day 2, day 1 ICU costs would be assigned as zero. Daily costs for each major patient type abstracted from Dasta et al[15] are reported in Table 1.

For each of the 1,363 patients enrolled into the Early PN Trial, costs were estimated for N = 1,000,000 episodes of care to generate stable estimates of costs and CIs. The CMA was based on the net differences in costs between the 1,000,000 simulated clinical trial groups.

All simulations were conducted using PC SAS (v 9.2, SAS Institute Inc, Cary, NC, USA).

Calculation of the mean costs and 95% CIs

The mean costs of acute care attributable to each study group (early parenteral nutrition versus standard care) and the

mean cost difference between groups, along with the respective 95% CIs, were obtained using the percentile method. As opposed to bootstrapping, which requires resampling and typically uses fewer trials (N = 1,000), the percentile method does not require correction for bias when applied to large-scale simulations, which typically use more trials (N >250,000) with no resampling.[16]

Sensitivity analyses

Three sensitivity analyses were planned before conducting the primary CMA:

1. The primary CMA analysis was rerun using normal distributional assumptions for the generated cost data, instead of gamma distributional assumptions.
2. The primary CMA analysis was rerun using a conservative discount of 4% per annum, instead of discounting according to the CPI.
3. The primary CMA analysis was rerun using published daily costs of ICU care and study intervention costs for the European market, instead of published US costs. Based on a micro-costing study conducted in the Netherlands, the average total cost of one ventilated ICU day has been reported as (mean [standard deviation]) €2,644 (€2,502) and for an unventilated ICU day as €2,081 (€1,914), indexed to 2012 Euros at 4% per annum.[17,18] The European costs for the study intervention were obtained from an economic analysis conducted in Belgium.[19] The marginal cost increase attributable to the provision of 1 day of parenteral nutrition to a critically ill ICU patient was reported as €102 per day (indexed to 2012 funds at 4% per annum), which was reported to include acquisition (purchase costs), additional vitamins, minerals, administration of the parenteral nutrition, and the cost of monitoring.

Results

The 1,000,000-trial Monte Carlo simulation required 1 hour 17 minutes to execute on a 5.1 GHz Intel 3930 K processor (Intel, Santa Clara, CA, USA) with 64 GB of memory and six Intel 520 series solid-state drives in RAID 0 on an LSI 9265 SCSI controller. The 1,363 patients in the Early PN Trial

Table 1 Matrix of the distributions of daily costs of care whilst admitted to the intensive care

	Medical patients		Surgical patients		Trauma patients	
	Received MV	**No MV received**	**Received MV**	**No MV received**	**Received MV**	**No MV received**
Day 1	$8,141 ($5,584)	$5,357 ($5,584)	$20,582 ($14,319)	$9,916 ($14,319)	$15,625 ($11,955)	$9,062 ($11,955)
Day 2	$6,535 ($4,678)	$4,783 ($4,678)	$7,726 ($6,977)	$5,050 ($6,977)	$7,414 ($6,683)	$4,968 ($6,683)
Day 3 plus	$5,703 ($4,666)	$4,261 ($4,666)	$6,627 ($5,624)	$4,765 ($5,624)	$5,880 ($5,750)	$4,641 ($5,750)

Notes: Mean costs (standard deviation); indexed to 2012 US dollars. Costs of care whilst admitted to the intensive care unit were abstracted from Dasta JF et al.[15]
Abbreviation: MV, mechanical ventilation.

consumed 11,424 ICU days requiring the stochastic estimation of 11,424,000,000 cost-days (11,424 days × 1,000,000 trials) resulting in a 107 GB data file.

Complete details of the Early PN Trial patient population are reported elsewhere.[10] Specifically relevant to this simulation, 33% (443/1,363) of patients were classified as medical, 64% (880/1,363) as surgical, and 3% (40/1,363) as trauma. Fifteen percent (206/1,363) of patients never received MV during their ICU stay. Forty-four percent (593/1,363) of patients were enrolled into the Early PN Trial on day 1 of their ICU stay, 56% (769/1,363) were enrolled on day 2, and 0.07% (1/1,363) of patients were enrolled on day 3.

To assess the accuracy of the simulation-generated cost structure, Table 2 presents the daily costs of acute care generated by the stochastic model, based on the cost matrix abstracted from Dasta et al[15] (see Table 1) under gamma distributional assumptions by a 250,000-trial Monte Carlo simulation for the first 3 days of ICU stay for each main patient group.

Primary CMA analysis: costs indexed to 2012 US dollars using the CPI, gamma distribution

Using the percentile method, the mean cost of ICU care for patients randomly allocated to receive standard care was US$58,923 per patient, with a 95% CI of US$57,631 to US$60,239, whereas the mean cost of care for patients randomly allocated to receive early parenteral nutrition was US$55,772 per patient, with a 95% CI of US$54,488 to US$57,082.

The simulation-estimated CMA revealed a US$3,150 saving per patient in favor of early parenteral nutrition use, with a 95% CI of US$1,314 to US$4,990 saving per patient.

Sensitivity analyses

1. Under normal distributional assumptions, the mean cost difference was a US$3,150 saving per patient in favor of early parenteral nutrition use, with a 95% CI of US$1,312 to US$4,988 in savings per patient.

2. Indexed at 4% per annum, the mean cost difference was a US$3,036 saving per patient, in favor of early parenteral nutrition use (95% CI US$1,243 to US$4,826 of savings per patient).

3. Using European ICU and study intervention costs, the mean cost difference was a €1,854 saving per patient in favor of early parenteral nutrition use (95% CI €1,103 to €2,605 of savings per patient). At current exchange rates (1 EUR = 1.30140 USD, at mid-market rates on April 24, 2013 at 10.21 pm Coordinated Universal Time), this equates to US$2,412 of savings in favor of early parenteral nutrition use (95% CI US$1,435 to US$3,389).

Discussion

We undertook a full economic analysis to assess the cost implications of providing early parenteral nutrition to adult critically ill patients with short-term relative contraindications to early enteral nutrition. Measures of clinical outcomes and health care resource consumption were obtained from a multicenter clinical trial (the Early PN Trial). Costs of care and costs of providing early parenteral nutrition were obtained from the published literature. Large-scale Monte Carlo simulation of a stochastic cost model revealed the provision of early parenteral nutrition might reduce the overall cost of care by US$3,150 per patient (95% CI US$1,314 to US$4,990). These findings were robust, with all sensitivity analyses demonstrating significant savings attributable to the use of early parenteral nutrition, including the sensitivity analysis conducted using European cost data.

Compared with previous economic analyses assessing the costs of nutrition therapy, which have largely been based on evidence of effectiveness of questionable methodological quality and taken a narrow focus on upfront acquisition costs,[20] our CMA is based on the results of a multicenter clinical trial conducted in a focused patient population[10] using published costs obtained from comprehensive databases with a broad perspective.[14,15] Although our findings of significant and

Table 2 Matrix of the distributions of daily costs of care whilst admitted to the intensive care unit generated by a 250,000-trial Monte Carlo simulation

	Medical patients		Surgical patients		Trauma patients	
	Received MV	**Never MV**	**Received MV**	**Never MV**	**Received MV**	**Never MV**
Day 1	$8,141 ($5,585)	$5,353 ($5,578)	$20,581 ($14,317)	$9,917 ($14,315)	$15,627 ($11,948)	$9,085 ($12,006)
	N = 39,250,000	N = 5,750,000	N = 81,750,000	N = 16,500,000	N = 4,750,000	N = 250,000
Day 2	$6,534 ($4,677)	$4,779 ($4,676)	$7,725 ($6,976)	$5,048 ($6,972)	$7,416 ($6,684)	$4,966 ($6,699)
	N = 90,750,000	N = 14,000,000	N = 175,750,000	N = 31,500,000	N = 9,750,000	N = 250,000
Day 3 plus	$5,702 ($4,665)	$4,262 ($4,668)	$6,627 ($5,624)	$4,764 ($5,625)	$5,882 ($5,750)	$4,626 ($5,739)
	N = 82,500,000	N = 11,750,000	N = 151,500,000	N = 19,750,000	N = 8,250,000	N = 250,000

Notes: Mean costs (standard deviation); 2012 US dollars.
Abbreviations: MV, mechanical ventilation; N, number of cost estimates simulated and pooled (iterations).

substantial cost savings may appear to conflict with a recent economic analysis reporting increased costs attributable to parenteral nutrition,[19] this previously published economic analysis addressed a different clinical indication for parenteral nutrition than did our CMA. That study, by Vanderheyden et al[20], assessed the financial consequences of administering additional parenteral nutrition to critically ill patients who were already able to receive enteral nutrition,[21] whereas our CMA addressed the financial consequences of administering parenteral nutrition to patients who were unable to receive early enteral nutrition due to short-term relative contraindications.[10]

A series of a priori defined sensitivity analyses was undertaken to explore alternate decisions regarding major assumptions behind the primary CMA. Each of these sensitivity analyses concurs with the primary CMA, demonstrating significantly reduced costs associated with early parenteral nutrition use. Use of the CPI to index reported costs to 2012 US funds controlled for realistic cost increases over time, and led to an average index rate of 4.2% per annum, only slightly higher than the conservative sensitivity analysis index rate of 4.0%. Additionally, the results obtained by the sensitivity analysis under normal distributional cost assumptions were essentially identical to the primary CMA results, conducted under the gamma distribution. It is possible that distributional assumptions are more important when conducting smaller simulations but become moot in large-scale simulations (N = 1,000,000 trials). Furthermore, the sensitivity analysis conducted under European cost assumptions also reported significant costs savings, which supports the primary CMA results based on US costs.

Although estimates of savings obtained by the sensitivity analysis conducted with European costs may appear lower than US savings, because the 95% CIs of the two estimates overlap, we cannot claim that estimates of cost savings differ significantly between the two different health care systems. Although it is commonly accepted that the US spends more on health care as a percent of its gross domestic product than any other country (17.9% of gross domestic product in 2011[22]), the apparent difference between estimates of US and European cost savings reported in this CMA may be due to different cost-accounting methods used in the US versus Europe. Whereas the perspective taken by Dasta et al[15] in estimating US costs was broad and included all hospital costs incurred whilst patients were cared for in an ICU, the perspective taken by Tan et al[18] to estimate European costs was slightly narrower. For example, although Tan et al explicitly reported accounting for costs of consultation time for non-ICU clinicians consulting on patients in the ICU, they did not report whether services delivered to critically ill patients by departments outside the ICU (eg, operating theatre expenses) were fully accounted for.

Indeed, many costing studies from Europe report the daily cost of ICU care as considerably lower than US-based studies; however, the European studies often employ a very restricted perspective, frequently reporting only direct costs of ICU care,[23] treating the ICU as a cost center within the acute care hospital. The economic assessment of competing health care alternatives delivered whilst a patient is cared for in an ICU may require a broader perspective. For example, technologies that increase direct costs to the ICU (eg, lease of an air suspension bed to prevent pressure ulcers, paid from the ICU budget) may prove cost-effective only when reduced costs to departments outside the ICU are considered (eg, reduced need for operating theatre time to conduct debridement surgery for Stage 3 and 4 pressure ulcers, paid from the surgery department budget).[24]

Strengths and limitations

In addition to providing costs from the perspective of the acute care hospital, which include services offered by departments outside of the ICU, the cost matrix reported by Dasta et al (Table 1) allows for accurate stochastic modeling because specific cost distributions can be assigned to specific patient groups (ventilated, medical, surgical, trauma) for each ICU day.[15] Furthermore, these US cost estimates, and the cost estimates for parenteral nutrition, were generated from robust databases containing tens of thousands of transactions from hundreds of hospitals.[14,15]

Although the European micro-costing study by Tan et al does provide cost estimates for ventilated and unventilated ICU patient-days, it does not allow for accounting by patient type and was conducted in only one hospital from a narrower perspective.[18] Furthermore, as a consumer price index for medical consumers was not readily available for the Netherlands[25] to allow comparability with the primary US-based CMA, the costs reported by Tan et al[18] were indexed to 2012 funds using the conservative rate of 4%.

Consideration of European financial consequences was not a central objective of this paper. The European-based analysis was undertaken in the context of the primary CMA, as part of a sensitivity analysis. A more thorough analysis, using more comprehensive cost estimates obtained from a broader perspective indexed using a harmonized European consumer price index for medical consumers may be required to draw firm conclusions regarding European costs.

Conclusion

We conducted a CMA based on the clinical outcomes and measures of resource consumption reported in a multicenter

RCT published in the *Journal of the American Medical Association*, with costs obtained from comprehensive and validated databases, reported from the broad perspective of the acute care hospital system. Within the context of the clinical question addressed by the underlying RCT, we found the use of parenteral nutrition in critically ill patients with short-term relative contraindications to enteral nutrition may significantly and meaningfully reduce total cost of care.

Acknowledgments

Disclosure

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Supplementary tables

Table S1 Harris–Benedict equations and adjustment factors used by study website (www.EvidenceBased.net/EarlyPN)

For males

Target metabolic needs (kcals/day) = $[66.5 + (13.75 \times Wt) + (5.003 \times Ht) - (6.775 \times Age)] \times$ adjustment factor

For females

Target metabolic needs (kcals/day) = $[655.1 + (9.563 \times Wt) + (1.85 \times Ht) - (4.676 \times Age)] \times$ adjustment factor

   Wt = weight in kg

   Ht = height in cm

   Age = Age in years

Adjustment factors (most severe was selected)

Other, not listed below <value="1.2">

• Any other problem, not listed below.

Infection, mild <value="1.3">

• Ex mild skin, line or surgical wound infection. Local redness, heat and swelling but no systemic signs.

Operation, minor <value="1.3">

• Any surgical procedure that does not require general anesthesia or respiratory support.

Operation, major <value="1.35">

• Any surgical procedure that does require general anesthesia or respiratory support.

Infection, peritonitis (non-septic) <value="1.35">

• Peritonitis based on visual inspection or culture. Patient does not have systemic signs of sepsis.

Cancer <value="1.35">

• Patient is known to have an active tumor. May or may not be undergoing active or palliative treatment.

Trauma, single fracture (skeletal) <value="1.4">

• Patient has trauma resulting in a single skeletal fracture of any bone except long bones.

Infection, moderate <value="1.45">

• Infections that would normally require ICU admission for treatment. Ex Community acquired pneumonia, Ventilator Associated Pneumonia.

Trauma, single long-bone fracture <value="1.45">

• Trauma with a fracture to a long bone (femur, humerus, tibia, fibula, radius and ulna).

Trauma, multiple fractures <value="1.5">

• Trauma with multiple fractures to any bones, including at least one long bone.

Trauma, blunt with or without fractures <value="1.6">

• Blunt trauma, such as a motor vehicle crash and fall from height. Includes Penetrating trauma.

Infection, severe <value="1.65">

• Any infection, or suspected infection, that expresses itself systemically as sepsis.

Burns, less than or equal to 20% TBSA <value="1.7">

• Chemical or thermal burns to less than 20% of total body surface area.

Malnourished (high risk of refeeding syndrome) <value="0.85">

• Body mass index of less than 17 or history and physical exam consistent with malnourishment or high risk of malnourishment. Based on clinical grounds decided by attending clinician.

Notes: Harris–Benedict calculated targets were capped at 35 kcal/kg/day and obese patients (BMI $\geq$ 30 kg/m²) used ideal body weight (BMI = 21 kg/m²) in all Harris–Benedict calculations.
Abbreviations: kcals, kilocalories; Wt, weight in kilograms; Ht, height in centimeters; kg, kilograms; cm, centimeters; Ex, example; ICU, intensive care unit; TBSA, total burn surface area.

Table S2 PN (parenteral nutrition) Protocols

Study PN Protocol A: all early PN patients except malnourished

Feeding day 1 (first 24 hours of PN)

- Commence Kabiven G19% at 60 mL/hr (or goal rate, whichever is lower).
- Consider trace element, mineral and vitamin needs as clinically appropriate.

Feeding day 2 (second 24 hours of PN)

- Increase Kabiven G19% to 80 mL/hr (or goal rate, whichever is lower).
- Consider trace element, mineral and vitamin needs as clinically appropriate.

Feeding day 3 (next 24 hours)

- Increase Kabiven G19% to goal rate, as appropriate.
- Consider trace element, mineral and vitamin needs, as clinically appropriate.
- Recommend trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Feeding day 4 (next 24 hours) plus all additional days after day 4

- May switch to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- Consider long term needs regarding trace element, mineral and vitamins as clinically appropriate.
- Recommend trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Insulin/glucose protocol: early PN patients

If glucose levels exceed 10 mmol/L an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of <10 mmol/L.

Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at ≥6 units/hr to maintain glucose target:

- Reduce Kabiven G19% to 40 mL/hr for 24 hours.
- At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80 mLs (or original goal rate, whichever is lower) for 24 hours.
- At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.
- If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 mLs/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.

(*Continued*)

Table S2 (*Continued*)

Study PN Protocol B: malnourished early PN patients (ex BMI ≤ 17)

Feeding day 1 (first 24 hr of PN)

• Commence Kabiven G19% at 40 mL/hr (or goal rate, whichever lower).

• Strongly recommend administering 100 mg thiamine, commencing at least 30 minutes prior to initiation of Kabiven G19% infusion, as clinically indicated as per product licensing indications.

• Recommend daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

Feeding day 2 (second 24 hours of PN)

• Increase Kabiven G19% to 60 mL/hr (or goal rate, whichever is lower).

• Recommend daily administration of vitamins, minerals and trace elements, as clinically appropriate.

Feeding day 3 (next 24 hours)

• Increase Kabiven G19% to goal rate, as appropriate.

• Recommend daily administration of vitamins, minerals and trace elements, as clinically appropriate.

• Recommend trialing enteral/oral nutrition, if clinically appropriate.

• Once the patient tolerates ≥475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

• If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Feeding day 4 (next 24 hours) plus all additional days after day 4

• May switch to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.

• Strongly recommend addressing long term needs regarding trace elements, minerals and vitamins as clinically appropriate.

• Recommend trialing enteral/oral nutrition, if clinically appropriate.

• Once the patient tolerates ≥475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

• If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Insulin/glucose protocol: early PN patients

If glucose levels exceed 10 mmol/L an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of <10 mmol/L.

Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at ≥6 units/hr to maintain glucose target:

• Reduce Kabiven G19% to 40 mL/hr for 24 hours.

• At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80 mLs (or original goal rate, whichever is lower) for 24 hours.

• At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.

• If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 mLs/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.

Abbreviations: kcals, kilocalories; EN, enteral; ICU, intensive care unit; BMI, body mass index.