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Original article

Supplemental parenteral nutrition in intensive care patients: A cost saving strategy

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SUMMARY

Background & aims: The Swiss supplemental parenteral nutrition (SPN) study demonstrated that optimised energy provision combining enteral nutrition (EN) and SPN reduces nosocomial infections in critically ill adults who fail to achieve targeted energy delivery with EN alone. To assess the economic impact of this strategy, we performed a cost-effectiveness analysis using data from the SPN study.
Methods: Multivariable regression analyses were performed to characterise the relationships between SPN, cumulative energy deficit, nosocomial infection, and resource consumption. The results were used as inputs for a deterministic simulation model evaluating the cost-effectiveness of SPN administered on days 4–8 in patients who fail to achieve ≥60% of targeted energy delivery with EN by day 3. Cost data were derived primarily from Swiss diagnosis-related case costs and official labour statistics.
Results: Provision of SPN on days 4–8 was associated with a mean decrease of 2320 ± 338 kcal in cumulative energy deficit compared with EN alone ($p < 0.001$). Logistic regression analysis showed that each 1000 kcal decrease in cumulative energy deficit was associated with a 10% reduction in the risk of nosocomial infection (odds ratio 0.90; 95% confidence interval 0.83–0.99; $p < 0.05$). The incremental cost per avoided infection was −63,048 CHF, indicating that the reduction in infection was achieved at a lower cost.
Conclusion: Optimisation of energy provision using SPN is a cost-saving strategy in critically ill adults for whom EN is insufficient to meet energy requirements.

1. Introduction

Adequate nutrition support is vitally important in the management of patients in the intensive care unit (ICU) [1–3]. Due to the persistent metabolic demands and the difficulty of initiating feeding in ICU patients, energy deficits accumulate rapidly during the first week following admission to the ICU [4], leading to an increased risk of infection, prolonged duration on mechanical ventilation, longer stay in the ICU, and increased mortality [5–9]. To prevent such complications, clinical practice guidelines recommend early initiation of enteral nutrition (EN) in haemodynamically stable critically ill patients who are unable to maintain volitional intake [1–4]. However, EN alone is often insufficient to meet energy and protein requirements [10–15]. As a result, a significant proportion of critically ill patients fail to achieve adequate nutritional intake [12].

Supplemental parenteral nutrition (SPN) has been shown to improve the cumulative energy balance and reduce infectious morbidity in ICU patients who fail to achieve energy and protein goals with EN alone [16]. Nonetheless, parenteral nutrition (PN) is often withheld in practice due to cost and perceived risks [17–21]. In the Swiss SPN study, we tested the hypothesis that individually optimised energy provision using EN plus SPN would improve clinical outcomes in critically ill patients who fail to achieve ≥60% of energy goals with EN alone by day 3. The findings showed that supplemental administration of PN on days 4–8 resulted in a 35% reduction in the adjusted risk of nosocomial infection compared with continued administration of EN alone (hazard ratio 0.65; 95% confidence interval [CI] 0.43–0.97; $p = 0.03$) [16]. To assess the economic impact of this strategy, we performed a cost-effectiveness analysis using modelled outcomes derived from the Swiss SPN study.

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2. Materials and methods

The primary objective of the study was to evaluate the cost-effectiveness of SPN in critically ill adult ICU patients who fail to achieve ≥60% of calculated energy targets with EN alone. A deterministic model-based analysis integrated clinical data from the SPN trial with cost data derived from other sources to simulate clinical outcomes and resource utilisation in the target population. Data from the SPN study were analysed using multivariable regression models to sequentially characterise the relationships between nutritional intervention, cumulative energy deficit, and nosocomial infection. Linear multiple regression analysis was then used to estimate the effect of nosocomial infection on resource consumption parameters such as antibiotic use, duration of mechanical ventilation, and length of stay in the ICU and hospital. Finally, effect size estimates from the multivariable analyses and cost estimates derived primarily from Swiss diagnosis-related case costs were used as model inputs for a pharmacoeconomic analysis to evaluate the cost-effectiveness of SPN.

2.1. Source data—clinical outcomes

The source population for the analysis of clinical outcomes included all patients enrolled in the Swiss SPN Study (N = 305; ClinicalTrials.gov registration number, NCT00802503) [16]. Study design and enrolment criteria have been previously described [16]. Briefly, eligible patients were critically ill adults with a functional gastrointestinal tract who failed to achieve ≥60% of targeted energy delivery with EN by day 3 following ICU admission. Patients were randomised to receive continued EN alone or EN plus SPN on days 4–8 with the aim of delivering 100 percent of the energy expenditure measured by indirect calorimetry. There was no catch-up feeding of the previous deficit. The primary study endpoint was the occurrence of nosocomial infections between days 9 and 28, defined according to the Centers for Disease Control and Prevention [22].

2.2. Source data—cost analysis

Unit costs for medical resources were derived primarily from the Swiss Federal Statistical Office 2013 diagnosis-related case costs for a sample population of 7614 mechanically ventilated adult ICU patients with a Simplified Acute Physiology II (SAPS II) score >30 and an ICU stay ≥3 days. The cost of SPN was calculated as the acquisition cost of a representative PN product (StructoKabiven®, Fresenius Kabi GmbH; 1 bag per day administered for 4 days) plus the cost of medical staff to prescribe and administer PN. The latter was estimated based on gross wages for medical and nursing staff obtained from the Swiss Federal Statistical Office and the mean PN administration times reported in a previous time-and-motion study [23]. Daily costs for standard doses of antimicrobial therapy for nosocomial infection were obtained via interviews with experts from two Swiss university hospitals (interviews conducted by Polynomics AG, Olten, Switzerland, August 2015).

2.3. Statistical analysis—clinical outcomes and resource utilisation

Linear multivariable regression analysis was used to characterise the relationship between potential explanatory variables and cumulative energy deficit during days 1–8 in the SPN trial. Logistic multivariable analysis was used to examine the relationship between potential explanatory variables and nosocomial infection from day 9 to day 28. Additionally, the effect of nosocomial infection on medical resource consumption (antibiotic days, hours on mechanical ventilation, length of stay in the ICU, and length of stay in the ward) was estimated using linear multivariable regression analysis. Potential explanatory variables included age, gender, height, weight, body mass index (BMI), diagnosis, institution, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, baseline infection status, duration of prophylactic antibiotic therapy, cumulative energy deficit during days 1–8, mean percentage of energy target achievement on days 1–8, and mean energy delivery on days 1–8. Independent variables were selected for the initial models based on the strength of associations in unadjusted univariable analyses. Multi-collinearity was evaluated using the variance inflation factor (VIF). Among coupled variables with a VIF >2.50, the variable with the weaker association was eliminated from the model. Parameter estimates for the linear regression analyses were evaluated using the Student t-test. The fully specified multivariable model was evaluated using Fisher's exact test. The logistic regression model was evaluated using the z-test. All analyses were performed using R statistical software, version 3.1.2 (R Foundation, Vienna, Austria).

Analyses evaluating resource consumption parameters as the response variable were based on the full dataset from the intent-to-treat population in the Swiss SPN study (N = 305). Analyses evaluating cumulative energy deficit and nosocomial infection as the response variable were based on the per protocol population (N = 275) due to missing data for cumulative energy deficit (N = 30).

2.4. Cost-effectiveness analysis

The cost-effectiveness analysis was conducted from the perspective of Swiss hospitals. Effect size estimates derived from the Swiss SPN study were used as model inputs for a pharmacoeconomic model evaluating the cost-effectiveness of SPN compared with continued EN in critically ill patients who fail to achieve targeted energy delivery with EN. Discrete event simulation was used to model patient outcomes following ICU admission in two cohorts (Fig. 1) [24]. The time horizon of the model corresponds with the observation period in the clinical trial. The initial step in the model was the decision to either continue EN therapy alone or add SPN. Patients receiving EN alone were assigned a cumulative energy deficit based on the observed cumulative energy deficit for days 1–8 in the corresponding treatment group in the SPN trial. For those receiving SPN, the cumulative energy deficit was determined by applying the estimated nutritional advantage attributed to SPN in the multivariable analysis to the observed cumulative energy deficit in the EN group. The occurrence of infection in patients receiving EN was determined based on the observed probability of nosocomial infection between days 9 and 28 in the EN group during the SPN study. In patients receiving SPN, the occurrence of infection was based on the adjusted odds ratio (OR) for nosocomial infection in the logistic regression analysis. For patients without infection, values for resource utilisation parameters were based on the observed mean values for non-infected patients in the SPN trial; for patients with infection, adjusted estimates from the multivariable analyses were used.

The primary outcome of the pharmacoeconomic analysis was the incremental cost per infection avoided, reported in Swiss francs (CHF). All direct hospital costs from the time of admission until discharge were included in the model and assigned to one of the following categories: ICU stay, ward stay, mechanical ventilation, antimicrobial therapy, and SPN administration. Because the time horizon was limited to the hospital stay, future costs and outcomes were not discounted.

A probabilistic sensitivity analysis was conducted to assess the effect of uncertainty surrounding parameter estimates. Additionally, a one-way deterministic sensitivity analysis was performed to

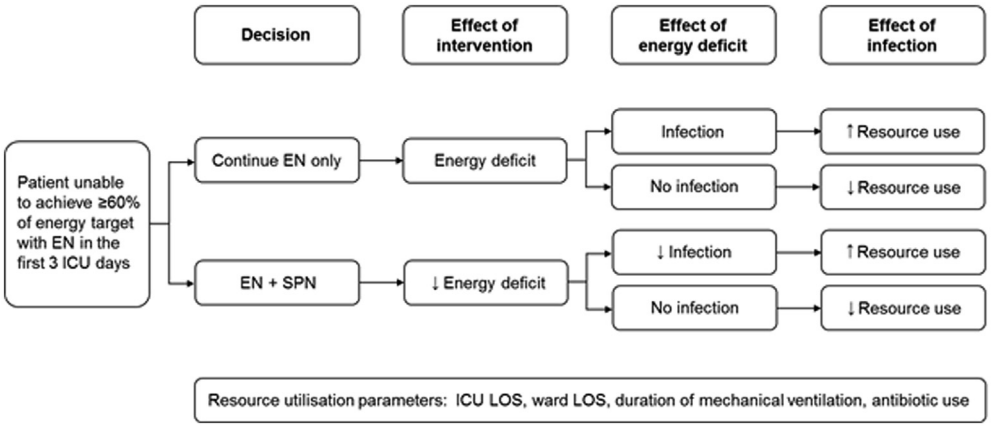

Fig. 1. Schematic representation of the pharmacoeconomic model. *Abbreviations*: *EN*, enteral nutrition; *ICU*, intensive care unit; *LOS*, length of stay; *SPN*, supplemental parenteral nutrition.

assess the sensitivity of the estimated cost difference between interventions to variations in estimated values for each model parameter.

3. Results

3.1. Clinical outcomes

Model-derived estimates for clinical outcomes and resource utilisation parameters are presented in Table 1 (see Data Supplement for the fully specified models). Multivariable analysis of data from the SPN study showed a statistically significant association between the provision of SPN on days 4–8 and cumulative energy deficit during days 1–8. A statistically significant association was also observed between cumulative energy deficit during days 1–8 and the risk of nosocomial infection from day 9 to day 28. After adjustment for covariates, provision of SPN on days 4–8 was associated with a mean (SD) difference of 2320 kcal (338) in cumulative energy deficit compared with EN alone ($p < 0.001$). Logistic regression analysis showed that each 1000 kcal decrease in cumulative energy deficit was associated with a 10% relative reduction in the risk of nosocomial infection (OR 0.90; 95% CI 0.83–0.99; $p < 0.05$) between day 9 and day 28. Based on the adjusted mean difference in cumulative energy deficit between the two treatment groups, an adjusted OR of 0.80 (95% CI 0.63–0.98) was used to determine the incidence of infection in the SPN cohort in the pharmacoeconomic model.

Linear multivariable regression analyses evaluating predictors of hospital resource utilisation showed statistically significant associations between nosocomial infection and antibiotic use (mean increase, 8.3 days [standard error, 0.7], $p < 0.001$), duration of mechanical ventilation (mean increase, 64.8 h [11.6], $p < 0.001$), and length of stay in both the ICU (mean increase, 7.7 days [1.2], $p < 0.001$) and the ward (mean increase, 11.9 days [3.1], $p < 0.001$; Table 1).

3.2. Cost-effectiveness evaluation

Unit costs for the resource utilisation parameters in the pharmacoeconomic model are summarised in Table 2. Deterministic simulation analysis using the mean values for clinical and resource utilisation parameters yielded total hospitalisation costs of 112,338 CHF and 108,999 CHF per patient in the EN and SPN groups, respectively, resulting in an estimated net cost reduction of 3339 CHF per patient with the SPN strategy (Table 3). Based on the 5.3% absolute reduction in nosocomial infections in patients receiving

Table 1
Model-derived estimates for clinical outcomes and resource utilisation parameters.[a]

Effect of SPN on cumulative energy deficit[b]				
	EN	SPN	Mean difference	p-value
Mean cumulative energy deficit, kcal	6702 (296)[c]	4383 (363)	−2320 (338)	<0.001
Effect of cumulative energy deficit on risk of infection[d]				
	EN	SPN	Odds ratio (95% CI)	p-value
Nosocomial infection	38.0%[c]	32.7%	0.80 (0.63–0.98)[e]	<0.05
Effect of infection on mean resource utilisation[f]				
	New infection	No new infection[c]	Mean difference	p-value
Antibiotic use, days	11.1 (1.0)	2.75 (0.4)	8.34 (0.7)	<0.001
Mechanical ventilation, hours	94.5 (13.0)	29.7 (5.1)	64.8 (11.6)	<0.001
ICU length of stay, days	18.1 (1.4)	10.4 (0.6)	7.72 (1.2)	<0.001
Ward length of stay, days	28.3 (3.6)	16.4 (1.4)	11.9 (3.1)	<0.001

Abbreviations: *APACHE*, Acute Physiology and Chronic Health Evaluation; *CI*, confidence interval; *EN*, enteral nutrition; *ICU*, intensive care unit; *SD*, standard deviation; *SE*, standard error; *SPN*, supplemental parenteral nutrition.

[a] Based on data from the Swiss SPN study [16].

[b] Linear regression analysis, adjusted for sex, institution, and patient type (medical vs. surgical); data are presented as mean (SD).

[c] Observed result, Swiss SPN study.

[d] Logistic regression analysis, adjusted for age, APACHE II score, and cumulative energy balance for days 1–8.

[e] Derived from the adjusted risk of nosocomial infection per 1000 kcal decrease in energy deficit (OR 0.90; 95% CI 0.83–0.99) and the adjusted mean difference in cumulative energy deficit between treatment groups.

[f] Linear regression analysis, adjusted for relevant baseline covariates (see appendix in data supplement); data are presented as mean (SE).

Table 2
Unit costs for medical resource utilisation parameters.[a]

	Mean unit cost (CHF)	SD or 95% CI
ICU stay, day[b]	5055	SD, 2167
Ward stay, day[b]	1900	SD, 1182
Mechanical ventilation, hour[b]	85.4	95% CI, 77–94
Antimicrobial therapy, day[c]	65.0	95% CI, 60–70
Intervention[d]	247	SD, 49

Abbreviations: *CI*, confidence interval; *ICU*, intensive care unit; *SD*, standard deviation.

[a] Conversion: 1 CHF = €0.92 = US$1.02 (based on published exchange rates on 1 November 2016).

[b] Derived from Swiss Federal Statistical Office 2013 diagnosis-related case costs for a sample population of 7614 mechanically ventilated adult ICU patients with a SAPS II score >30 and an ICU stay ≥3 days.

[c] Based on the average cost of standard doses of piperacillin/tazobactam or daptomycin reported by medical administration staff from two Swiss university hospitals.

[d] Includes acquisition cost for 4 parenteral nutrition bags (139.6 CHF), physician salary (7.34 CHF for 0.1 h), and nurse salary for 0.5 h/day for 4 days (100.6 CHF). Medical staff costs based on 2013 average gross wages reported by the Swiss Federal Statistics Office and a prior time-and-motion study in Swiss university hospitals [23].

SPN, the estimated number of patients needed to nourish to avoid one infection was 19. The estimated incremental cost per infection avoided was −63,048 CHF, indicating that the cost of the intervention is more than offset by the cost savings associated with the reduction in nosocomial infections.

The probabilistic sensitivity analysis confirmed the robustness of the main findings (Fig. 2a). Consistent with the original model, the probabilistic analysis showed an estimated 5.2% absolute reduction in nosocomial infections and an expected mean cost reduction of 3296 CHF per patient with the SPN strategy. Model-derived probabilities of observing reductions in infections and total hospital costs with SPN were 98.4% and 97.6%, respectively.

Results of the one-way deterministic sensitivity analysis are depicted in the tornado diagram in Fig. 2b. A mean overall cost reduction with SPN remained evident when each parameter value varied within the extremes of the probability distribution, further confirming the robustness of the main findings. The magnitude of reduction in the risk of nosocomial infection had the largest effect on the estimated cost savings; however, even the lower limit of the estimated reduction in nosocomial infections resulted in a net cost savings with SPN.

4. Discussion

The Swiss SPN study was the first randomised controlled trial to demonstrate that individually optimised energy supplementation with SPN confers meaningful clinical benefits to ICU patients who fail to achieve targeted energy delivery with EN alone [16]. In the present analysis, we used data from the SPN study to sequentially characterise the relationships between SPN, cumulative energy deficit, nosocomial infection, and medical resource consumption. A significant cost reduction was found with SPN, suggesting that optimisation of energy provision using SPN is a cost-effective strategy in selected critically ill adults.

Comprehensive analysis of data from the SPN study yielded several important observations. First, SPN significantly improved energy delivery and prevented further progression of energy deficits during the initial days following ICU admission without causing overfeeding. In the multivariable analysis of cumulative energy deficit during days 1–8, SPN administration was the strongest independent predictor of energy target attainment, resulting in a mean improvement of 2320 kcal in cumulative energy balance. Second, a negative cumulative energy balance was independently associated with the risk of nosocomial infection. After adjustment for model covariates, the risk of nosocomial infection was reduced by 10% for each 1000 kcal decrease in cumulative energy deficit. While previous studies have evaluated the effect of both underfeeding and overfeeding on clinical outcomes in critically ill populations [7,25–27], this finding confirms a direct quantitative association between cumulative energy target and an objective clinical outcome. Finally, linear regression analyses demonstrated a statistically significant association between nosocomial infection and medical resource consumption, including antibiotic use, duration of mechanical ventilation, and length of stay in the ICU and hospital.

The pharmacoeconomic evaluation showed that the total costs associated with SPN were exceeded by the savings accrued due to the reduction in resource consumption, most of which was attributable to a reduction in infectious morbidity. Providing SPN to patients who failed to achieve the targeted energy delivery by day 3 resulted in a savings of 3339 CHF per patient compared with EN alone. Based on the estimated number of patients needed to nourish to avoid one infection (n = 19), SPN would be expected to result in an incremental cost of −63,048 CHF for each infection avoided. In contrast to the typical scenario in which providing treatment to the number of patients required to prevent a single clinical event imposes an additional cost, the negative incremental cost observed in our analysis indicates that the cost of SPN is more than offset by the savings associated with the corresponding reduction in nosocomial infections. Notably, our findings therefore show that supplemental administration of PN to critically ill patients for whom EN is insufficient confers both a meaningful clinical benefit and a clear cost advantage.

Table 3
Medical costs and clinical outcomes based on the deterministic simulation model.

	Clinical outcomes			Cost (CHF)		
	EN	SPN	Difference	EN	SPN	Difference
Infections/100 patients, n	38.0	32.7	−5.30	–	–	–
ICU LOS, d	13.4	12.9	−0.41	67,491	65,424	−2067
Ward LOS, d	21.0	20.3	−0.63	39,825	38,627	−1198
Mechanical ventilation, h	54.3	50.9	−3.43	4637	4344	−293
Antimicrobial therapy, d	5.92	5.48	−0.44	385	356	−29
Intervention	–	–	–	–	247	247
Total	–	–	–	**112,338**	**108,999**	**−3339**
Incremental cost effectiveness						
Cost per infection avoided, CHF				**−63048**[a]		

Abbreviations: *CHF*, Swiss francs; *EN*, enteral nutrition; *ICU*, intensive care unit; *LOS*, length of stay; *SPN*, supplemental parenteral nutrition.

[a] Calculated using the formula (EN cost − SPN cost)/(infections with EN − infections with SPN); a negative incremental cost indicates pharmacoeconomic dominance, defined as an incremental cost savings for each unit of benefit due to the intervention.

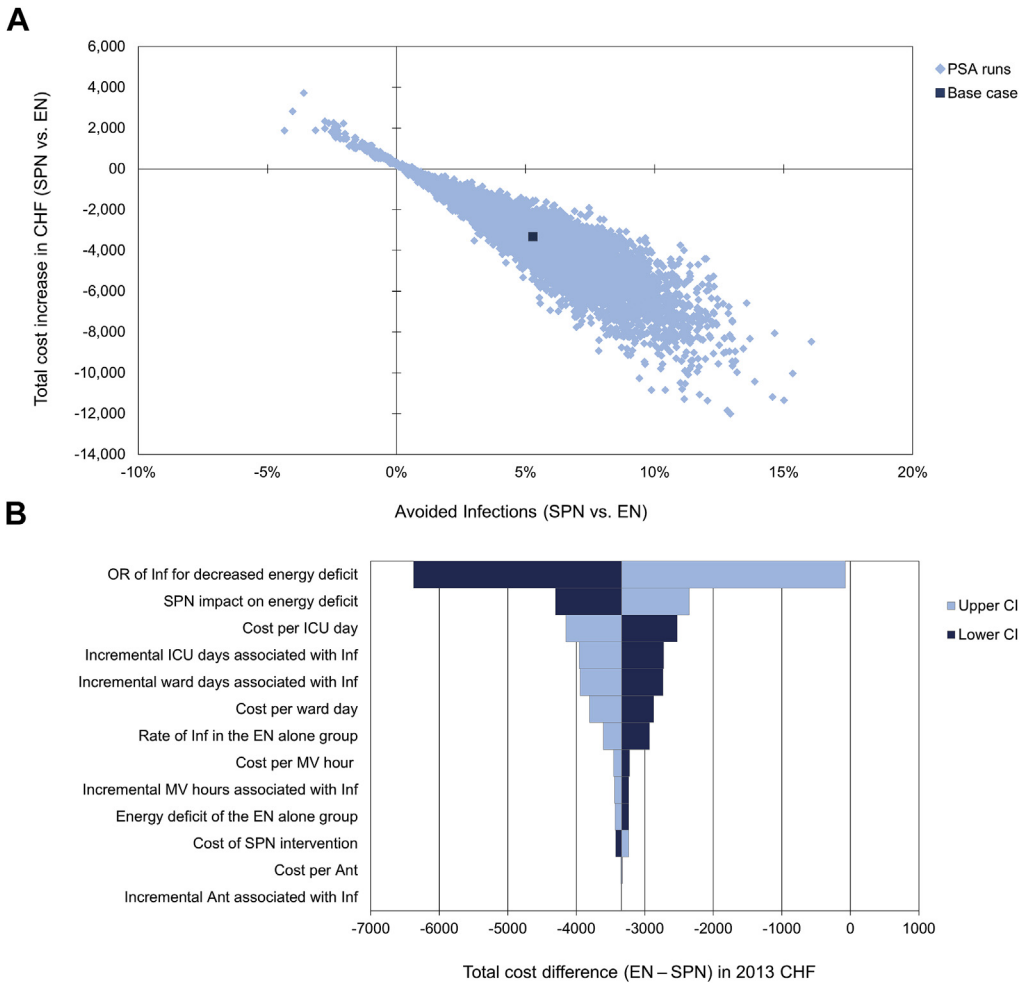

Fig. 2. A. Scatterplot of 10,000 probabilistic sensitivity analysis runs. The results demonstrate a 98.4% probability of a reduction in nosocomial infection and a 97.6% probability of reduced hospital costs with the use of SPN compared with EN alone. **B**. Tornado diagram depicting the results of the one-way deterministic sensitivity analysis. The x-axis represents the difference in total hospital costs for SPN compared with EN; the y-axis lists the clinical and resource utilisation parameters in decreasing order of their effect on the difference in total hospital cost. Values were varied by one parameter at a time within the extremes of the 95% CI. The 95% CI was taken directly from the multivariable regression analyses for clinical and resource utilisation parameters; for cost estimates, the 95% CI was calculated assuming a SD equal to 20% of the mean value. *Abbreviations*: *Ant*, antibiotic; *CI*, confidence interval; *EN*, enteral nutrition; *ICU*, intensive care unit; *Inf*, infection; *MV*, mechanical ventilation; *PSA*, probabilistic sensitivity analysis; *SD*, standard deviation; *SPN*, supplemental parenteral nutrition.

The 2009 European guidelines indicate that all ICU patients receiving less than the targeted enteral feeding after two days should be considered for supplementary PN [1]. To date, however, no study has formally evaluated the cost-effectiveness of this strategy in critically ill patients with an indication for artificial nutrition. In a cost analysis based on data from a Belgian study (EPaNIC) [28], Vanderheyden et al. [29] reported that early initiation of SPN (day 2) following ICU admission resulted in higher overall costs compared with late SPN (day 8). In contrast to the study upon which our economic model was based, the EPaNIC trial included a large proportion of patients without a firm indication for PN and a shorter median stay in the ICU. Additionally, the early hypertonic glucose load during the acute phase coupled with slight overfeeding in the early PN group likely contributed to a higher infection rate [30], thereby influencing overall cost. The economic evaluation of the CALORIES trial, which found no difference in clinical outcome between PN and EN, yielded inconclusive results [31]. Conversely, the Swiss SPN study demonstrated that initiating SPN on day 4 in critically ill patients for whom artificial nutrition is indicated but EN is insufficient and carefully adjusting energy delivery to avoid overfeeding reduces energy deficits and decreases metabolic complications [16]. Our findings further demonstrate that the lower energy deficit is associated with a reduced risk of infection, which results in decreased resource consumption and lower overall cost. Consistent with this latter finding, Doig and colleagues [32] reported significant cost savings attributable to the use of early PN in critically ill patients with short-term relative contraindications to EN. We note, however, that the analysis differed from the present study in two significant respects. First, the clinical trial upon which the economic analysis was based evaluated a separate clinical indication for PN (contraindication to EN) and showed no statistically significant effect on clinical outcomes [33]. Second, the pharmacoeconomic evaluation was based on a cost-minimisation analysis, which—unlike the cost-effectiveness model used in our study—assumes equivalent clinical outcomes for the interventions under consideration. Nonetheless, the cost benefit attributable to the use of early PN is generally consistent with our results.

Certain limitations of our study should be considered. The cost-effectiveness model was based on clinical outcomes in a trial conducted in two Swiss university hospitals with a dedicated nutrition support team and cost estimates derived from cost data for the Swiss healthcare system. The extent to which the findings are generalizable to hospitals with limited nutrition support

resources and different cost structures is unknown. The model-based approach was selected because the original study protocol did not include an economic analysis; therefore, not all relevant cost and resource consumption parameters were measured. The use of modelling techniques was considered the most appropriate method to integrate clinical study outcomes with cost data from separate sources to facilitate evaluation of economic outcomes. Moreover, because the model-based analysis employs stochastic techniques to balance the uncertainty of the effect size estimates used in the model, the generalisability of the findings to other clinical settings is improved [34]. Comparison of model predictions with observed data from the SPN trial suggest that the model results represent conservative estimates, with more modest reductions in nosocomial infections compared with estimates based on observed data. The apparent underestimation of the benefits associated with SPN in our model might be explained in part by the possibility that not all of the effect of SPN on nosocomial infection is mediated through an improvement in energy balance. Similarly, the effect of SPN on the length of stay might be due not only to the reduction in nosocomial infections, but also to an improvement in general clinical status. Finally, while several PN products were used in the SPN study, the acquisition cost for PN products in the cost-effectiveness analysis was based on a single representative product. However, given the marginal differences in cost between products used in the SPN study, our analysis would be expected to yield similar results for each product. It's important to note that these cost-savings apply and are limited to a very sick ICU subpopulation of long-stayers (median length of ICU stay = 11 days), which constitute the potentially chronic critically ill patients.

In conclusion, a pharmacoeconomic analysis based on Swiss healthcare costs demonstrated that the savings accrued due to reduced resource consumption, in particular length of hospital stay, should more than offset the initial costs for SPN. Collectively, these findings demonstrate that optimisation of energy provision using SPN in selected ICU patients results in both a meaningful clinical benefit and a clear cost advantage.

Statement of authorship

LP, SG, CP, and MMB were responsible for study design, data acquisition, and data analysis and interpretation. LP performed the statistical analyses. LP, CP and MMB were responsible for preparation of the manuscript. All authors critically reviewed the manuscript for intellectual content and approved the final draft.

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Conflict of interests

LP has received research grants from Fresenius Kabi for the work under consideration, and received research grants and consulting fees from Fresenius Kabi, Amgen, GSK, Roche, Jannsen Cilag, Novartis, and Livanova, among others, outside of the submitted work. MMB has received research grants and consulting fees from Baxter and Fresenius Kabi. CP has received research grants and consulting fees from Abbott, Baxter, B Braun, Cosmed, Fresenius Kabi, Nestle Medical Nutrition, Novartis, Nutricia-Numico, Pfizer, and Solvay. SG reports no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.01.009.

References

[1] Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009;28:387–400.
[2] Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al., DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C, ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 2006;25:210–23.
[3] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al., Society of Critical Care Medicine, American Society for Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr 2016;40:159–211.
[4] Singer P, Hiesmayr M, Biolo G, Felbinger TW, Berger MM, Goeters C, et al. Pragmatic approach to nutrition in the ICU: expert opinion regarding which calorie protein target. Clin Nutr 2014;33:246–51.
[5] Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr 2006;25:37–44.
[6] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35:1728–37.
[7] Faisy C, Candela Llerena M, Savalle M, Mainardi JL, Fagon JY. Early ICU energy deficit is a risk factor for *Staphylococcus aureus* ventilator-associated pneumonia. Chest 2011;140:1254–60.
[8] Petros S, Horbach M, Seidel F, Weidhase L. Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized pilot trial. J Parenter Enter Nutr 2016;40:242–9.
[9] Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux MC, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24:502–9.
[10] Heyland DK, Dhaliwal R, Wag M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: results of an international, multicenter, prospective study. Clin Nutr 2015;34:659–66.
[11] Petros S, Engelmann L. Enteral nutrition delivery and energy expenditure in medical intensive care patients. Clin Nutr 2006;25:51–9.
[12] Genton L, Dupertuis YM, Romand JA, Simonet ML, Jolliet P, Huber O, et al. Higher calorie prescription improves nutrient delivery during the first 5 days of enteral nutrition. Clin Nutr 2004;23:307–15.
[13] Oshima T, Heidegger CP, Pichard C. Supplemental parenteral nutrition is the key to prevent energy deficits in critically ill patients. Nutr Clin Pract 2016;31:432–7.
[14] Oshima T, Deutz NE, Doig G, Wischmeyer PE, Pichard C. Protein-energy nutrition in the ICU is the power couple: a hypothesis forming analysis. Clin Nutr 2016;35:968–74.
[15] Pichard C, Oshima T, Berger MM. Energy deficit is clinically relevant for critically ill patients: yes. Intensive Care Med 2015;41:335–8.
[16] Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385–93.
[17] Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004;20:843–8.
[18] Evans RA, Strauss BJ. Cost and benefit of hospital, hospital-in-the-home and ambulatory care nutrition support services. Asia Pac J Clin Nutr 1998;7:241–4.

[19] Kalfarentzos F, Kehiagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg 1997;84:1665–9.
[20] Borzotta AP, Pennings J, Papasadero B, Paxton J, Mardesic S, Borzotta R, et al. Enteral versus parenteral nutrition after severe closed head injury. J Trauma 1994;37:459–68.
[21] Adams S, Dellinger EP, Wertz MJ. Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. J Trauma 1986;26:882–91.
[22] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309–32.
[23] Pichard C, Schwarz G, Frei A, Kyle U, Jolliet P, Morel P, et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. Clin Nutr 2000;19:245–51.
[24] Caro JJ, Briggs AH, Siebert U, Kuntz KM. ISPOR-SMDM modeling good research practices task force. Modeling good research practices—overview: a report of the ISPOR-SMDM modeling good research practices task force-1. Value Health 2012;15:796–803.
[25] Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. Crit Care Med 2015;43:1569–79.
[26] Reignier J, Darmon M, Sonneville R, Borel AL, Garrouste-Orgeas M, Ruckly S, et al. Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study. Intensive Care Med 2015;41:875–86.
[27] Ekpe K, Novara A, Mainardi JL, Fagon JY, Faisy C. Methicillin-resistant *Staphylococcus aureus* bloodstream infections are associated with a higher energy deficit than other ICU-acquired bacteremia. Intensive Care Med 2014;40:1878–87.
[28] Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–17.
[29] Vanderheyden S, Casaer MP, Kesteloot K, Simoens S, De Rijdt T, Peers G, et al. Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. Crit Care 2012;16:R96.
[30] Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.
[31] Harvey SE, Parrott F, Harrison DA, Sadique MZ, Grieve RD, Canter RR, et al. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). Health Technol Assess 2016;20:1–144.
[32] Doig GS, Simpson F. 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. Clin Outcomes Res 2013;5:369–79.
[33] Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early PN Investigators of the ANZICS Clinical Trials Group. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130–8.
[34] Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. Value Health 2012;15:835–42.