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Angaben zur Veröffentlichung / Publication details:

Pradelli, Lorenzo, Stanislaw Klek, Konstantin Mayer, Abdul Jabbar Omar Alsaleh, Martin D. Rosenthal, Axel R. Heller, and Maurizio Muscaritoli. 2021. "Cost effectiveness of parenteral nutrition containing ω 3 fatty acids in hospitalized adult patients from 5 European countries and the US." *Journal of Parenteral and Enteral Nutrition* 45 (5): 999–1008. <https://doi.org/10.1002/jpen.1972>.

Cost-Effectiveness of Parenteral Nutrition Containing ω -3 Fatty Acids in Hospitalized Adult Patients From 5 European Countries and the US

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Journal of Parenteral and Enteral Nutrition
Volume 45 Number 5
July 2021 999–1008
© 2020 The Authors. *Journal of Parenteral and Enteral Nutrition* published by Wiley Periodicals, Inc. on behalf of American Society for Parenteral and Enteral Nutrition.
DOI: 10.1002/jpen.1972
wileyonlinelibrary.com

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Abstract

Background: ω -3 Fatty acid (FA)-containing parenteral nutrition (PN) is associated with improvements in patient outcomes and with reductions in hospital length of stay (HLOS) vs standard PN regimens (containing non- ω -3 FA lipid emulsions). We present a cost-effectiveness analysis of ω -3 FA-containing PN vs standard PN in 5 European countries (France, Germany, Italy, Spain, UK) and the US. **Methods:** This pharmacoeconomic model was based on estimates of ω -3 efficacy reported in a recent meta-analysis and data from country-specific sources. It utilized a probabilistic discrete event simulation model to compare ω -3 FA-containing PN with standard PN in a population of critically ill and general ward patients. The influence of model parameters was evaluated using probabilistic and deterministic sensitivity analyses. **Results:** Overall costs were reduced with ω -3 FA-containing PN in all 6 countries compared with standard PN, ranging from €1741 (\pm €1284) in Italy to €5576 (\pm €4193) in the US. Expenses for infections and HLOS were lower in all countries for ω -3 FA-containing PN vs standard PN, with the largest cost differences for both in the US (infection: €825 \pm €4001; HLOS: €4879 \pm €1208) and the smallest savings in the UK for infections and in Spain for HLOS (€63 \pm €426 and €1636 \pm €372, respectively). **Conclusion:** This cost-effectiveness analysis in 6 countries demonstrates that the superior clinical efficacy of ω -3 FA-containing PN translates into significant decreases in mean treatment cost, rendering it an attractive cost-saving alternative to standard PN across different healthcare systems. (*JPEN J Parenter Enteral Nutr.* 2021;45:999–1008)

Keywords

cost-effectiveness; fish oil; intravenous lipid emulsions; meta-analysis; omega-3 fatty acids; parenteral nutrition

Clinical relevancy statement

A recent meta-analysis showed that ω -3 fatty acid (FA)-containing parenteral nutrition (PN) is associated with statistically and clinically significant reductions in the rates of infection and sepsis as well as in the duration of hospitalization and length of stay in the intensive care unit. This cost-effectiveness analysis for 6 countries (France, Germany, Italy, Spain, UK, and US) demonstrates that these outcomes translate into significant decreases in mean hospital costs with ω -3 FA-containing PN in comparison with PN not containing ω -3 FAs.

Background

Hospitalized critically ill and surgical patients typically receive parenteral nutrition (PN) if oral or enteral nutrition is contraindicated or insufficient. A complete all-in-one PN admixture comprises amino acids/protein, glucose, elec-

trolytes (depending on patient condition), lipid, micronutrients (such as vitamins), and trace elements to sustain or improve patient nutrition status and clinical outcomes. Lipid is an integral part of PN, as it is a dense source of energy and supplies the building blocks for cell membranes and essential fatty acids (FAs) in PN to prevent deficiencies.¹

Traditionally, the lipid added to PN in the form of a lipid emulsion was derived from soybean oil.² Soybean oil emulsions, however, contain high concentrations of linoleic acid and other ω -6 polyunsaturated FAs, which may have detrimental properties.¹ Following concerns that ω -6 FA may promote inflammation and immunosuppression, lipid emulsions with balanced mixtures of different oil sources, such as soybean oil, medium-chain triglycerides, olive oil, and fish oil, were developed for use in PN.¹ There is a strong body of evidence that ω -3 FAs derived from fish oil, especially eicosapentaenoic acid, docosahexaenoic acid, and their respective metabolites, possess beneficial anti-inflammatory and immunomodulatory properties and play

a key role in the resolution of inflammation across a wide range of patient groups, including surgical, critically ill, and cancer groups.^{1,3} This attenuation of proinflammatory processes could contribute to the trend observed across several studies and meta-analyses that report decreases in hospital and intensive care unit (ICU) length of stay (LOS) when using PN regimens containing ω -3 FA-containing lipid emulsions.⁴⁻¹⁰

In general, decreases in hospital LOS (HLOS) are associated with a lower risk of infection,¹¹ and a shorter ICU LOS reduces general deconditioning due to prolonged bed rest, sedation, and immobilization, with overall improvements in patient quality of life.¹² A number of clinical trials and meta-analyses in hospitalized patients demonstrated that PN containing ω -3 FA is associated with better clinical outcomes than standard PN regimens (PN with lipid emulsions not containing ω -3 FA; ie, derived from sources such as soybean oil and/or olive oil), including decreases in morbidity and mortality,^{6,13} shortened HLOS^{4-9,14} and ICU LOS,¹⁵ and reduced infection rates.^{4,5,8,9}

In a previously published clinical meta-analysis and subsequent pharmacoeconomic analysis, ω -3 FA-containing PN was shown to be more clinically effective and more cost-effective than standard PN in both ICU and non-ICU patients.^{16,17} Based on Italian outcome data, this pharmacoeconomic analysis modeled the cost-effectiveness of PN with and without ω -3 FA in 4 countries (France, Germany, Italy, UK) and found that infection rates, overall LOS, and total cost per patient were reduced with the use of ω -3 FA-containing PN. The higher treatment costs for ω -3 FA-containing PN were completely offset by the lower overall costs, demonstrating that PN containing ω -3 FA was cost-effective in French, German, Italian, and UK hospitals.

A more recent meta-analysis,⁴ which included 49 randomized controlled trials and a total of 3641 patients, re-

ported a significantly lower relative risk of infection (40%), a 56% reduced risk of sepsis, and a nonsignificant 16% reduction in mortality in patients receiving PN containing ω -3 FA compared with standard PN. In addition to decreases in mean length of ICU and hospital stays, the analysis also showed significant reductions in the relative risk of infection and sepsis.⁴ Whereas the positive clinical effects of ω -3 FA-containing PN found in a previous analysis¹⁷ were confirmed in the recent analysis adhering to current study quality standards, the evaluation of the economic impact of ω -3 FA-containing PN remains to be updated.

The aim of the present study was to investigate the cost-effectiveness of ω -3 FA-containing PN compared with standard PN without fish oil based on a recent meta-analysis.⁴ Here, we present the results of 6 country-specific cost-effectiveness models comparing the utilization of ω -3 FA-containing PN with standard PN from the perspective of a hospital in France, Germany, Italy, Spain, the UK, and the US.

Methods

This analysis modeled the cost-effectiveness of ω -3 FA-containing and standard PN based on country-specific data sources for 6 countries (France, Germany, Italy, Spain, UK, and the US).

Model Structure

Six separate cost-effectiveness models comparing ω -3 FA-containing PN with standard PN without fish oil were developed and simulated for hospitals in France, Germany, Italy, Spain, the UK, and the US. Overall, the model generation included the following steps: (1) conceptualization of a logical structure for both patient cohorts (critically ill cohort [CR] and acute general ward cohort [GE]); (2) identification

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Financial disclosure: Research activities and medical writing were funded by Fresenius Kabi Deutschland GmbH.

Conflicts of interest: L. Pradelli is director and employee of AdRes, which has received project funding from Fresenius; S. Klek reports having received speakers honoraria from Baxter, B. Braun, Fresenius, Nestlé, and Nutricia; K. Mayer reports having received fees from Abbott, Astra Zeneca, Baxter, B. Braun, Fresenius Kabi, MSD, Nestlé, Novartis, and Pfizer; A. J. Omar Alsaleh reports no conflicts of interest; M. D. Rosenthal reports no conflicts of interest; A. R. Heller reports having received project funding by Fresenius Kabi and speaker honoraria by CSL-Behring; M. Muscaritoli reports having received speaker's fees from Fresenius Kabi.

Received for publication June 4, 2020; accepted for publication July 20, 2020.

This article originally appeared online on August 18, 2020.

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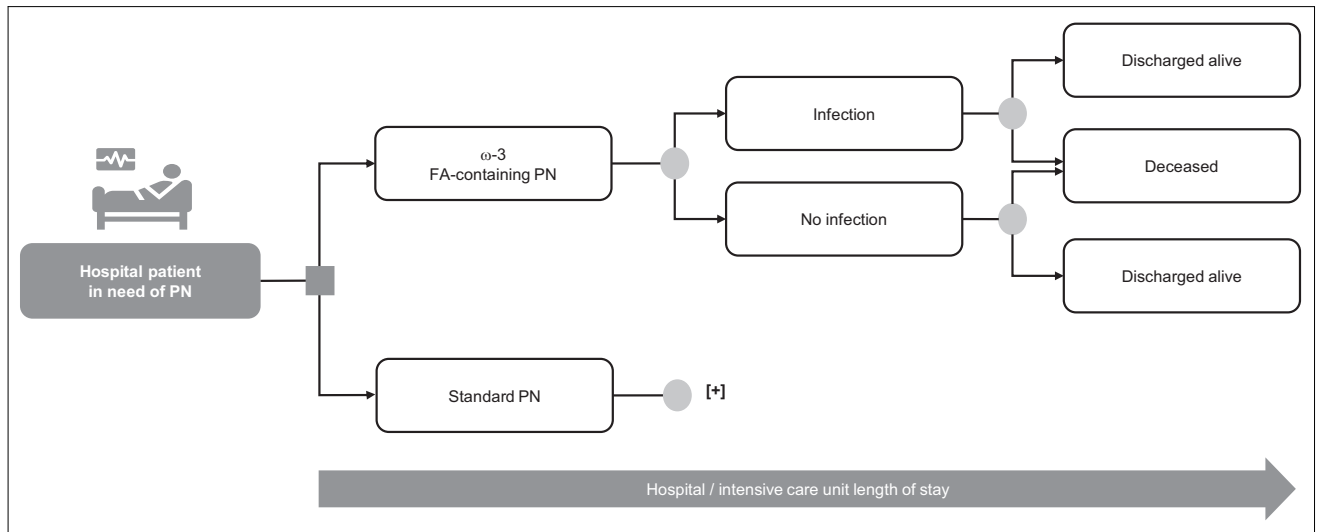


Figure 1. Simplified model structure including 2 treatment arms, each with critically ill and acute general ward patients. FA, fatty acid; PN, parenteral nutrition.

of country-specific clinical outcomes for patients receiving standard PN in both cohorts; (3) identification of country-specific sources for drug acquisition and hospital service costs; (4) simulation of country-specific clinical outcomes for patients receiving ω -3 FA-containing PN by applying the ω -3 efficacy estimates from the recent meta-analysis to (2); (5) calculation of the country-specific total cost per simulated patient; (6) analysis of the result's sensitivity to input parameter uncertainty via deterministic and probabilistic sensitivity analyses (PSAs).

The models were based on a probabilistic discrete event simulation technique and developed in Excel (Microsoft Corporation, Redmond, WA, USA). Simulations were run over 10,000 iterations, with each iteration representing 1 patient.

Patient Population and Epidemiological Data

On the patient level, all models included 2 treatment arms (ω -3 FA-containing PN and standard PN) with each patient passing simultaneously through both arms, thus enabling both alternative simulations to run on the same cohort (Figure 1). The simulated hospitalized patients were sent to CR and GE pathways and could receive either PN treatment option (ω -3 FA-containing PN or standard PN). In the present pharmacoeconomic analysis, patients from both settings (CR and GE) were combined to evaluate the cost-effectiveness of ω -3 FA-containing PN in a mixed adult population of CR and GE patients.

Model Inputs and Data Sources

Relative treatment effects for patients receiving ω -3 FA-containing PN were derived from a recent meta-analysis.⁴

Economic data such as daily costs, costs per infection, and costs for PN treatment were extracted from published sources for each country and treatment arm (Table 1).^{4,18-47} The models also included inputs on the clinical outcomes nosocomial infections, HLOS, and mortality. The latter 2 parameters defined the end of the patient pathway, whereas the first reflected only costs. Mean HLOS and mean incidence of infection with ω -3 FA-containing PN and standard PN without ω -3 FA varied widely between countries (Table 2), with the shortest mean HLOS and the lowest incidence of infection for both treatment groups in the US and Germany, respectively. For inclusion of time-to-event parameters, such as HLOS, in the model, a Weibull distribution fitting was performed, with population parameters estimated using the method of moments.

For the 5 European countries, the daily costs of PN were estimated based on current market shares, the daily number of PN bags per patient, and current market prices. For the estimation of daily costs in the US, a model was created to approximate daily lipid requirements based on patient age distribution⁴³ and patient weight in gender- and age-specific groups.⁴⁸ The cost of lipid emulsions was based on the lowest cost for standard PN while using the manufacturer price for ω -3 FA-containing PN, thus leading to a conservative estimate of the latter. Costs were modeled according to local currencies in each country but converted into euros (EUR) to facilitate comparability. Pound sterling (GBP) and US dollar (USD) were converted to EUR using the mean exchange rates for January 2020: GBP-EUR: 1.1759; USD-EUR: 0.9005. Exchange rates were derived from <https://www.oanda.com/>. No discount rate was applied to the costs, because of the short time frame of the simulation.

Table 1. Country- and Patient Cohort–Specific Model Inputs, Including Clinical and Economic Data As Well As Overall Efficacy Estimates and Their Respective Sources.

Model inputs	France	Germany	Italy	Spain	UK ^a	US ^a
CR patients, %				45 ⁴		
GE patients, %				55 ⁴		
Clinical input parameters						
Mean HLOS; CR, d	31.2 ± 18.5 ¹⁸	29.1 ± 18.7 ²²	36.8 ± 28.5 ²⁷	45.9 ± 23.9 ³⁵	19.65 ± 19.3 ³⁹	20.1 ± 15.5 ⁴³
Mean HLOS ± SD; GE, d	23.6 ± 16.0 ¹⁹	15.2 ± 9.7 ²³	29.75 ± 19.0 ²⁸	33.6 ± 26.7 ³⁶	29.75 ± 19.0 ²⁸	14.3 ± 16.3 ^{44, b}
Infection; CR, %	47 ¹⁸	18 ²⁴	45 ²⁹	46 ³⁵	19 ³⁹	34 ⁴³
Infection; GE, %	42 ¹⁹	12 ²³	27 ³⁰	19 ³⁶	15 ⁴⁰	27 ^{44, b}
Mean PN duration ± SD, CR, d	14 ± 8 ¹⁸	8 ± 8 ²²	7 ± 6 ³¹	19 ± 15 ³⁵	9 ± 5 ³⁹	7 ± 7 ⁴³
Mean PN duration ± SD, GE, d	14 ± 14 ¹⁹	8 ± 5 ²³	15 ± 10 ²⁸	13 ± 11 ³⁶	15 ± 10 ²⁸	6 ± 4 ^{44, b}
Mortality, CR, %	28 ¹⁸	19 ²²	15 ²⁷	46 ³⁵	36 ³⁹	21 ⁴³
Mortality, GE, %	3 ¹⁹	9 ²³	11 ³⁰	29 ³⁶	30 ⁴⁰	11 ^{44, b}
Economic input parameters						
Mean cost, CR/d, € (\$)	1136 (1262) ²⁰	1556 (1728) ²⁵	1108 (1230) ³²	981 (1089) ³⁷	1912 (2123) ⁴¹	2914 (3236) ⁴³
Mean cost, GE/d, € (\$)	785 (872) ²⁰	581 (645) ²⁵	654 (726) ³³	610 (677) ³⁷	962 (1068) ⁴¹	1777 (1973) ⁴⁵
Mean cost of infection, € (\$)	1162 (1290) ²¹	2006 (2228) ²⁶	1855 (2060) ³⁴	2085 (2315) ³⁸	872 (968) ⁴²	6641 (7375) ⁴⁶
Mean cost of PN/d, € (\$)	28 (31) ^c	117 (130) ^c	96 (107) ^c	14 (16) ^c	69 (77) ^c	8 (9) ^c
Mean cost of ω -3	26 (29) ^c	130 (144) ^c	154 (171) ^c	22 (24) ^c	77 (86) ^c	30 (33) ^c
FA-containing PN/d, € (\$)						
ω -3 FA-containing PN efficacy, mean ± SD	HLOS mean difference, d −2.14 ± 0.54 ⁴			Infection relative risk 0.60 ± 0.06 ⁴		

CR, critically ill cohort; FA, fatty acid; GE, acute general ward cohort; HLOS, hospital length of stay; PN, parenteral nutrition; SD, standard deviation.

^aPound sterling (GBP) and US dollar (USD) converted to euro (EUR) using the average exchange rates of January 2020: GBP-EUR: 1.1759, USD-EUR: 0.9005.

^bData combined from 2 groups according to the Cochrane handbook.⁴⁷

^cSee methods section for basis of calculations; Fresenius Kabi data on file.

Table 2. Country-Specific Efficacy Estimates: HLOS and Incidence of Infections With ω -3 FA-Containing PN and Standard PN.

Mean efficacy		HLOS, d	Incidence of infections, %
France	ω -3 FA-containing PN	25.2	26
	Standard PN	27.3	44
Germany	ω -3 FA-containing PN	20.4	9
	Standard PN	22.6	15
Italy	ω -3 FA-containing PN	31.2	21
	Standard PN	33.3	35
Spain	ω -3 FA-containing PN	37.3	19
	Standard PN	39.5	35
UK	ω -3 FA-containing PN	23.1	10
	Standard PN	25.2	16
US	ω -3 FA-containing PN	14.9	18
	Standard PN	17.1	31

FA, fatty acid; HLOS, hospital length of stay; PN, parenteral nutrition.

Sensitivity Analysis

The influence of model parameters on calculated estimates was evaluated using probabilistic and deterministic sensitivity approaches.

In the PSA, 1000 sets of unique parameter combinations are created, drawing each model parameter within the extremes of its probability distribution. In case of missing data on uncertainty, a 20% standard deviation of the mean value was used and an appropriate probability distribution according to the shape of the data was chosen.

In the deterministic sensitivity analyses, simulations were repeated with variations of parameter values to the lower and upper confidence interval limits, while keeping the remaining parameter values constant.

Results

Costs in the 6 Countries Analyzed

A recent meta-analysis⁴ showed that PN containing ω -3 FA was associated with a significant increase in clinical effectiveness: Mean HLOS was reduced by 2.14 ± 0.54 days and the relative risk of infection was 0.60 ± 0.06 with ω -3 FA-containing PN vs standard PN (Table 1). This increase in clinical effectiveness with ω -3 FA-containing PN leads to a significant decrease in mean cost per adult patient in all of the European and US hospital settings investigated. Total costs were reduced in all 6 countries and amounted to €2244 ± €848 (\$2492 ± \$942) in France, €2228 ± €1389

(\$2474 ± \$1542) in Germany, €1741 ± €1284 in Italy (\$1933 ± \$1426), €1782 ± €1307 (\$1979 ± \$1451) in Spain, €2973 ± €1108 (£2528 ± £942 or \$3300 ± \$1230) in the UK, and €5576 ± €4193 (\$6192 ± \$4657) in the US. Expenses for infections and HLOS were lower in all 6 countries for ω -3 FA-containing PN compared with standard PN, with the US accruing the largest savings for both (infection: €825 ± €4001 [\$916 ± \$4443]; HLOS: €4879 ± €1208 [\$5418 ± \$1342]). The lowest cost differences were observed in the UK for infection (€63 ± €426 [£54 ± £362, \$70 ± \$473]) and in Spain for HLOS (€1636 ± €372 [\$1817 ± \$413]). Detailed results regarding the cost of PN, infections, HLOS, and total costs are reported in Table 3.

In summary, ω -3 FA-containing PN demonstrated superior efficacy with a concurrent overall cost reduction in all countries compared with standard PN without ω -3 FA via reductions in mean length of ICU and hospital stays, as well as lower incidences of infection and sepsis.

Sensitivity Analyses

Sensitivity analyses demonstrated the stability and robustness of the outcomes in this pharmacoeconomic assessment to parameter changes. For all 6 countries, ω -3 FA-containing PN was associated with cost savings compared with standard PN in 100% of the simulations. Our analyses showed that in order to achieve an average cost saving of €0 with ω -3 FA-containing PN per treated patient compared with standard PN, the daily cost of ω -3 FA-containing PN would have to be equal to €224.77 (\$ 249.61) in France, €476.99 (\$ 529.69) in Germany, €438.70 (\$ 487.17) in Italy, €145.96 (\$ 162.09) in Spain, €492.98 (£419.23, \$ 547.45) in the UK, and €974.48 (\$1082.2) in the US. The incremental cost-effectiveness ratio (ICER) plots in Figure 2 display the results of 1000 ICER estimates and thus the cost required to avoid 1 case of infection using the most effective strategy. For all 6 countries, the incremental costs for avoided infections were negative, including the entirety of the 95% confidence interval ellipses. Hence, each avoided infection with ω -3 FA-containing PN was associated with a reduction in total cost, which is referred to as dominance in pharmacoeconomic terms (ie, better clinical outcomes at a lower cost).

The results of the deterministic sensitivity analyses are displayed as tornado diagrams, which show the influence of variations in key parameters on cost savings per patient (Figure 3). These graphs indicate that for both treatment options (ω -3 FA-containing PN and standard PN), the most influential parameter for cost savings across all 6 countries was mean difference of HLOS (topmost bars). In France, Germany, the UK, and the US, the second most influential factor was the cost of caring for critically ill patients, whereas in Italy and Spain the cost of ω -3 FA-containing PN was ranked second.

On average, the use of ω -3 FA-containing PN was demonstrated to be a cost-saving strategy under the circumstances and conditions of the model.

Discussion

According to the US guidelines on the provision and assessment of nutrition support therapy in adult critically ill patients, PN has evolved from mere nutrition support to nutrition therapy.⁴⁹ Adequately fed patients are thought to benefit from improvements in a range of clinical factors, such as attenuation of the metabolic response to stress, prevention of oxidative cellular injury, and favorable modulation of immune responses.⁴⁹ ω -3 FA-containing PN in particular has been associated with significantly improved patient outcomes^{4-9,13,14,50} and, as shown in the present pharmacoeconomic analysis, concurrent cost savings.

This cost-effectiveness analysis builds on a previously published model¹⁶ but includes a wider country scope, country-specific analyses, and a more sophisticated source selection. Using a robust model and country-specific data from 6 countries (France, Germany, Italy, Spain, UK, US), we demonstrate that PN containing ω -3 FA is, with very great likelihood, a dominant alternative to standard PN for a mixed population of CR and GE patients in terms of treatment cost. Despite the higher acquisition cost of ω -3 FA-containing PN in comparison with standard PN in nearly all of the countries analyzed, the superior efficacy with regard to patient outcomes renders it a cost-saving alternative to standard PN.

Since economic models are built on data from various sources with the objective of creating an accurate cost estimate, their results are limited by the availability of valid data inputs and the overall assumptions upon which the models are built. The limitations of the presented models are mainly centered around input data sources. Although some data were available, more research evaluating clinical outcomes, particularly in CR patients, would be indicated. The literature, at least for some countries, was incomplete (none for GE patients in the UK) and, in part, outdated. Specifically, some of the data sources for CR patients in France, Germany, Italy, and Spain were more than a decade old.

Accurate economic inputs are just as important as clinical information to achieve accurate cost estimates. Updated and valid sources for hospital cost data are not easily available, especially at the desired level of detail in the breakdown by components. Some data elaboration and assumptions were necessary also in this study; nevertheless, we are confident in the main conclusions, for 2 main reasons. Firstly, when there was the need for an assumption, we have always adopted the most conservative. Secondly, sensitivity analyses consistently show expected savings across countries and assumptions.

Table 3. Country-Specific Costs for PN, Infections, and HLOS Based on Model Simulations for ω -3 FA–Containing PN, Standard PN, and the Difference Thereof.

Mean costs ± SD in 2020 € (USD)		PN	Infection	HLOS	Total
France	ω -3 FA–containing PN	288 ± 142 (320 ± 158)	307 ± 512 (341 ± 569)	24135 ± 18560 (26802 ± 20611)	24729 ± 18622 (27461 ± 20680)
	Standard PN	328 ± 158 (364 ± 175)	513 ± 577 (570 ± 641)	26131 ± 18718 (29018 ± 20786)	26973 ± 18770 (29953 ± 20844)
	Δ	−40 ± 28 (−44 ± 31)	−206 ± 768 (−229 ± 853)	−1996 ± 354 (−2217 ± 393)	−2244 ± 848 (−2492 ± 942)
Germany	ω -3 FA–containing PN	837 ± 458 (929 ± 509)	180 ± 573 (200 ± 636)	24700 ± 27701 (27429 ± 30762)	25717 ± 27798 (28559 ± 30870)
	Standard PN	775 ± 439 (861 ± 488)	304 ± 720 (338 ± 800)	26866 ± 28428 (29835 ± 31569)	27945 ± 28511 (31033 ± 31661)
	Δ	62 ± 67 (69 ± 74)	−124 ± 915 (−138 ± 1016)	−2166 ± 1036 (−2405 ± 1150)	−2228 ± 1389 (−2474 ± 1542)
Italy	ω -3 FA–containing PN	938 ± 523 (1042 ± 581)	396 ± 760 (440 ± 844)	27549 ± 25442 (30593 ± 28253)	28883 ± 25533 (32074 ± 28354)
	Standard PN	589 ± 338 (654 ± 375)	657 ± 887 (730 ± 985)	29378 ± 25647 (32624 ± 28481)	30624 ± 25741 (34008 ± 28585)
	Δ	349 ± 189 (388 ± 210)	−261 ± 1152 (−290 ± 1279)	−1829 ± 483 (−2031 ± 536)	−1741 ± 1284 (−1933 ± 1426)
Spain	ω -3 FA–containing PN	322 ± 224 (358 ± 249)	397 ± 818 (441 ± 908)	29686 ± 22701 (32966 ± 25209)	30405 ± 22876 (33765 ± 25404)
	Standard PN	209 ± 143 (232 ± 159)	656 ± 968 (728 ± 1075)	31322 ± 22895 (34783 ± 25425)	32187 ± 23099 (35743 ± 25651)
	Δ	113 ± 83 (125 ± 92)	−259 ± 1223 (−288 ± 1358)	−1636 ± 372 (−1817 ± 413)	−1782 ± 1307 (−1979 ± 1451)
UK ^a	ω -3 FA–containing PN	554 ± 272 (615 ± 302)	91 ± 266 (101 ± 295)	30010 ± 28498 (33326 ± 31647)	30655 ± 28535 (34042 ± 31688)
	Standard PN	514 ± 256 (571 ± 284)	154 ± 333 (171 ± 370)	32960 ± 28648 (36602 ± 31813)	33627 ± 28666 (37343 ± 31833)
	Δ	40 ± 48 (44 ± 53)	−63 ± 426 (−70 ± 473)	−2949 ± 1001 (−3276 ± 1112)	−2973 ± 1108 (−3300 ± 1230)
US ^a	ω -3 FA–containing PN	178 ± 99 (198 ± 110)	1226 ± 2576 (1361 ± 2861)	35781 ± 40023 (39736 ± 44447)	37186 ± 40248 (41296 ± 44697)
	Standard PN	50 ± 28 (56 ± 31)	2050 ± 3068 (2277 ± 3407)	40660 ± 40520 (45154 ± 44999)	42761 ± 40703 (47488 ± 45202)
	Δ	128 ± 74 (142 ± 82)	−825 ± 4001 (−916 ± 4443)	−4879 ± 1208 (−5418 ± 1342)	−5576 ± 4193 (−6192 ± 4657)

FA, fatty acid; HLOS, hospital length of stay; PN, parenteral nutrition; SD, standard deviation.

^aPound sterling (GBP) and US dollar (USD) converted to euro (EUR) using the average exchange rates of January 2020: GBP-EUR: 1.1759, USD-EUR: 0.9005.

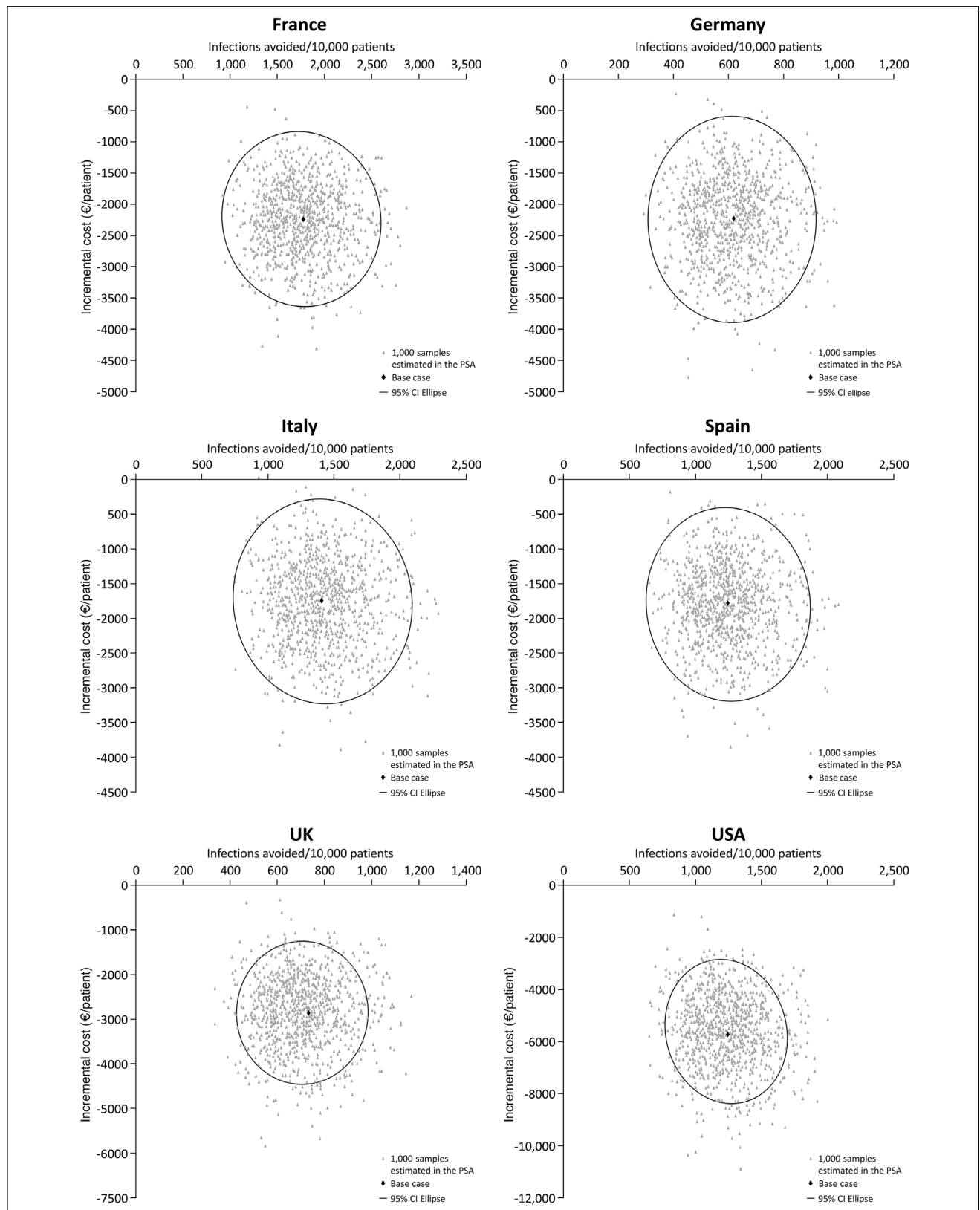


Figure 2. Scatterplots of 1000 incremental cost-effectiveness ratio estimates in PSAs for all 6 countries. CI, confidence interval; PSA, probabilistic sensitivity analysis.

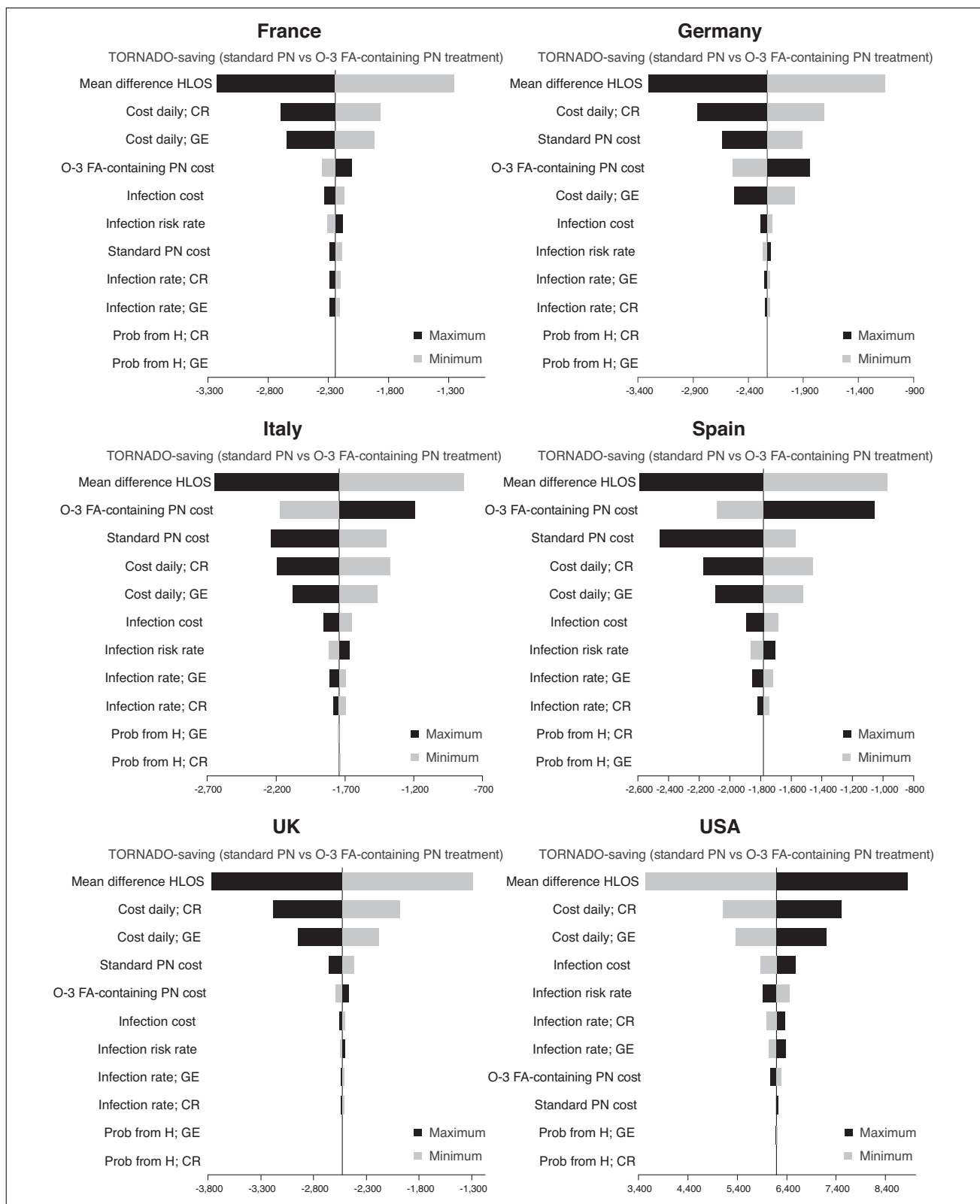


Figure 3. Country-specific tornado plots representing the sensitivity of savings with ω -3 FA-containing PN to a variation in key parameters (parameters ranked by degree of influence). CR, critically ill cohort; FA, fatty acid; GE, acute general ward cohort; HLOS, hospital length of stay; O-3, ω -3; PN, parenteral nutrition; Prob from H, probability to be discharged alive from the general and/or critical care pathways.

This model, in conjunction with a recently published meta-analysis,⁴ has shown that ω -3 FA-containing PN is beneficial for patients in terms of improved clinical outcomes as well as for healthcare systems because of lower overall costs. The higher acquisition cost for ω -3 FA-containing PN compared with standard PN is offset by cost reductions due to shorter HLOS and fewer infections, demonstrating that not only acquisition costs but overall treatment costs should influence the choice of treatment option. We would like to place particular emphasis on the fact that clinical interventions that improve patient outcomes while providing saving costs are very rare and support the use of ω -3 FA-containing PN in appropriate settings.

The accumulating evidence regarding the improvement of clinical outcomes with ω -3 FA-containing PN in comparison with standard PN in adult hospitalized patients^{4,9,13,14,50} may contribute to evidence-based treatment decisions and future guideline development. Concurrent cost savings with PN containing ω -3 FA, as shown in this cost-effectiveness analysis, may provide an additional benefit in this regard.

In summary, we demonstrate that ω -3 FA-containing PN is likely a dominant alternative to standard PN from a hospital point of view, with a decrease in mean costs for all 6 countries evaluated (France, Germany, Italy, Spain, UK, US). With regard to the positive clinical and economic outcomes demonstrated in the present analysis and in the recent meta-analysis⁴ on which this pharmacoeconomic evaluation is built, we suggest that ω -3 FA-containing PN be considered as standard of care and suggest using the present publication and that by Pradelli et al⁴ as a reference for guideline recommendations.

Acknowledgments

The technical reports of the cost-effectiveness analyses were generated by AdRes Health Economics & Outcomes Research, Torino, Italy. Medical writing assistance was provided by Physicians World Europe GmbH, Mannheim, Germany.

Statement of Authorship

L. Pradelli, S. Klek, K. Meyer, A. J. Omar Alsaleh, M. D. Rosenthal, A. R. Heller, and M. Muscaritoli equally contributed to the conception and design of the research, acquisition and analysis of the data, and interpretation of the data; L. Pradelli and A. J. Omar Alsaleh drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Calder PC, Adolph M, Deutz NE, et al Lipids in the intensive care unit: recommendations from the ESPEN expert group. *Clin Nutr*. 2018;37(1):1-18.
2. Calder PC. Rationale and use of n-3 fatty acids in artificial nutrition. *Proc Nutr Soc*. 2010;69(4):565-573.
3. Klek S. Omega-3 fatty acids in modern parenteral nutrition: a review of the current evidence. *J Clin Med*. 2016;5(3):34.
4. Pradelli L, Mayer K, Klek S, et al Omega-3 fatty-acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. *J Parenter Enteral Nutr*. 2019;44(1):44-57.
5. Xie H, Chang YN. Omega-3 polyunsaturated fatty acids in the prevention of postoperative complications in colorectal cancer: a meta-analysis. *Oncol Targets Ther*. 2016;9:7435-7443.
6. Bae HJ, Lee GY, Seong JM, Gwak HS. Outcomes with perioperative fat emulsions containing omega-3 fatty acid: a meta-analysis of randomized controlled trials. *Am J Health Syst Pharm*. 2017;74(12):904-918.
7. Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med*. 2007;35(3):700-706.
8. Li NN, Zhou Y, Qin XP, et al Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. *Clin Nutr*. 2014;33(2):226-239.
9. Wei C, Hua J, Bin C, Klassen K. Impact of lipid emulsion containing fish oil on outcomes of surgical patients: systematic review of randomized controlled trials from Europe and Asia. *Nutrition*. 2010;26(5):474-481.
10. Grau-Carmona T, Bonet-Saris A, Garcia-de-Lorenzo A, et al Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU lipids study. *Crit Care Med*. 2015;43(1):31-39.
11. Hassan MP, Tuckman HH, Patrick R, Kountz D, Kohn J. Hospital length of stay and probability of acquiring infection. *Int J Pharm Healthc Mark*. 2010;4:4, 324-338.
12. Koukourikos K, Tsaloglidou A, Kourkouta L. Muscle atrophy in intensive care unit patients. *Acta Inform Med*. 2014;22(6):406-410.
13. Chen H, Wang W, Hong C, et al Omega-3 fish oil reduces mortality due to severe sepsis with acute gastrointestinal injury grade III. *Pharmacognosy Magazine*. 2017;13(51):407-412.
14. Berger MM, Tappy L, Revelly JP, et al Fish oil after abdominal aorta aneurysm surgery. *Eur J Clin Nutr*. 2008;62(9):1116-1122.
15. Edmunds CE, Brody RA, Parrott JS, Stankorb SM, Heyland DK. The effects of different IV fat emulsions on clinical outcomes in critically ill patients. *Crit Care Med*. 2014;42(5):1168-1177.
16. Pradelli L, Eandi M, Povero M, et al Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: a discrete event simulation model. *Clin Nutr*. 2014;33(5):785-792.
17. Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care*. 2012;16(5):R184.
18. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. *Intensive Care Med*. 2000;26(7):893-900.
19. Perinel J, Mariette C, Dousset B, et al Early enteral versus total parenteral nutrition in patients undergoing pancreaticoduodenectomy: a randomized multicenter controlled trial (Nutri-DPC). *Ann Surg*. 2016;264(5):731-737.
20. Parienti JJ, Lucet JC, Lefort A, et al Empirical therapies among adults hospitalized for community-acquired upper urinary tract infections: a decision-tree analysis of mortality, costs, and resistance. *Am J Infect Control*. 2015;43(9):e53-59.
21. Defez C, Fabbro-Peray P, Cazaban M, Boudemaghe T, Sotto A, Daures JP. Additional direct medical costs of nosocomial infections: an estimation from a cohort of patients in a French university hospital. *J Hosp Infect*. 2008;68(2):130-136.

22. Heller AR, Rossler S, Litz RJ, et al Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med*. 2006;34(4):972-979.
23. Turpin RS, Solem C, Pontes-Arruda A, et al The impact of parenteral nutrition preparation on bloodstream infection risk and costs. *Eur J Clin Nutr*. 2014;68(8):953-958.
24. Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen. Deutsche nationale punkt-prävalenzstudie zu nosokomialen infektionen und antibiotika-anwendung. Published 2011. Accessed February 4, 2020. <https://www.nrz-hygiene.de/fileadmin/nrz/download/PPS-Abschlussbericht-Stand05-08-2013final.pdf>
25. Arefian H, Hagel S, Heublein S, et al Extra length of stay and costs because of health care-associated infections at a German university hospital. *Am J Infect Control*. 2016;44(2):160-166.
26. Leistner R, Gurntke S, Sakellariou C, et al Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive *K. pneumoniae* and *E. coli*: an analysis of the disease burden in a large cohort. *Infection*. 2014;42(6):991-997.
27. Radrizzani D, Bertolini G, Facchini R, et al Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: a randomized clinical trial. *Intensive Care Med*. 2006;32(8):1191-1198.
28. Ponta ML, Rabbione L, Borgio C, et al Assessing the appropriateness of parenteral nutrition use in hospitalized patients. A comparison on parenteral nutrition bag prescription in different wards and nutritional outcomes. *Clin Nutr ESPEN*. 2018;25:87-94.
29. Luzzati R, Antozzi L, Bellocco R, et al Prevalence of nosocomial infections in intensive care units in triveneto area, Italy. *Minerva Anestesiol*. 2001;67(9):647-652.
30. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med*. 2001;29(2):242-248.
31. Progetto Margherita. ICU report. Published 2010. Accessed September 2, 2019. <http://www.giviti.marionegri.it/MargheritaDue.asp>.
32. Tan SS, Bakker J, Hoogendoorn ME, et al Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Health*. 2012;15(1):81-86.
33. Portinari M, Ascanelli S, Targa S, et al Impact of a colorectal enhanced recovery program implementation on clinical outcomes and institutional costs: a prospective cohort study with retrospective control. *Int J Surg*. 2018;53:206-213.
34. Tarricone R, Torbica A, Franzetti F, Rosenthal VD. Hospital costs of central line-associated bloodstream infections and cost-effectiveness of closed vs. open infusion containers. The case of intensive care units in Italy. *Cost Eff Resour Alloc*. 2010;8:8.
35. Mateu-de Antonio J, Grau S, Luque S, Marin-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr*. 2008;99(4):846-854.
36. Tapia MJ, Ocon J, Cabrejas-Gomez C, et al Nutrition-related risk indexes and long-term mortality in noncritically ill inpatients who receive total parenteral nutrition (prospective multicenter study). *Clin Nutr*. 2015;34(5):962-967.
37. Rello J, Nieto M, Sole-Violan J, et al Nosocomial pneumonia caused by methicillin-resistant staphylococcus aureus treated with linezolid or vancomycin: a secondary economic analysis of resource use from a Spanish perspective. *Med Intensiva*. 2016;40(8):474-482.
38. Cots F, Riu M, Pi-Sunyer T, Terradas R, Grau S, Castells X. Incremental cost due to nosocomial infections. Published April 2017. Accessed February 2019. <http://www.postermedic.com/parcdesalutmar/npimas072809/pdfbaja/npimas072809.pdf>.
39. Harvey SE, Parrott F, Harrison DA, 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(28):1-144.
40. Hearnshaw SA, Thompson NP, Northern Nutrition Network. Use of parenteral nutrition in hospitals in the North of England. *J Hum Nutr Diet*. 2007;20(1):14-23.
41. Marti J, Hall P, Hamilton P, et al One-year resource utilisation, costs and quality of life in patients with acute respiratory distress syndrome (ARDS): secondary analysis of a randomised controlled trial. *J Intensive Care*. 2016;4:1,56.
42. Plowman R, Graves N, Griffin MA, et al The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *J Hosp Infect*. 2001;47(3):198-209.
43. Magee G, Zaloga GP, Turpin RS, Sanon M. A retrospective, observational study of patient outcomes for critically ill patients receiving parenteral nutrition. *Value Health*. 2014;17(4):328-333.
44. Chheng ML, Heidebreder C, Btaiche IF, Blackmer AB. Infectious complications with nondaily versus daily infusion of intravenous fat emulsions in non-critically ill adults. *Nutr Clin Pract*. 2013;28(6):737-744.
45. Modi RM, Mikhail S, Ciombor K, et al Outcomes of nutritional interventions to treat dysphagia in esophageal cancer: a population-based study. *Dis Esophagus*. 2017;30(11):1-8.
46. Butler AM, Olsen MA, Merz LR, et al Attributable costs of enterococcal bloodstream infections in a nonsurgical hospital cohort. *Infect Control Hosp Epidemiol*. 2010;31(1):28-35.
47. Higgins JPT, Deeks JJ. Selecting studies and collecting data - Extracting study results and converting to the desired format - Data extraction for continuous outcomes - Combining groups - Table 7.7.a: Formulae for combining groups. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0 [updated March 2011]. Version 5.1. 2011;177.
48. Cumulative percent distributions of population. *U.S. Census Bureau, Statistical Abstract of the United States*. 2011. <https://www2.census.gov/library/publications/2010/compendia/statab/130ed/tables/11s0205.pdf>
49. McClave SA, Taylor BE, Martindale RG, et al 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.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
50. Honeywell S, Zelig R, Rigassio Radler D. Impact of intravenous lipid emulsions containing fish oil on clinical outcomes in critically ill surgical patients: a literature review. *Nutr Clin Pract*. 2019;34(1):112-122.