Pharmacoeconomics of Parenteral Nutrition with ω-3 Fatty Acids in Hospitalized Adults

Lorenzo Pradelli, MD; Maurizio Muscaritoli, MD, PhD; Stanislaw Klek, MD, PhD; and Robert G. Martindale, MD, PhD

Abstract
The inclusion of ω-3 fatty acids as part of parenteral nutrition is associated with clinical benefits such as a reduced likelihood of infectious complications and shorter hospital and intensive care unit (ICU) stays. As healthcare resources are limited, pharmacoeconomic analyses have been performed, typically modeling studies, using cost and outcomes data to investigate the cost-effectiveness of parenteral nutrition regimens including ω-3 fatty acids from fish oil compared with standard parenteral nutrition without such ω-3 fatty acids. This review covers pharmacoeconomic studies encompassing Italian, French, German, and UK hospitals for ICU and non-ICU hospitalized patients, and for ICU patients in China. The results show that the use of parenteral nutrition including ω-3 fatty acids more than offsets any additional acquisition costs in all national scenarios investigated to date, indicating that parenteral nutrition including ω-3 fatty acids is a clinically and economically beneficial strategy compared with standard parenteral nutrition. (JPEN J Parenter Enteral Nutr. 2020;44(suppl S1):S68–S73)

Keywords
China; cost-effectiveness; Europe; fish oil; infections; intensive care; lipids; omega-3; parenteral nutrition; pharmacoeconomics

Introduction
Pharmacoeconomic evaluations are a way to assess the efficiency of interventions such as a particular pharmaceutical product or treatment strategy, providing information allowing the optimal allocation of limited healthcare system resources. To assess efficiency, pharmacoeconomic studies simultaneously consider both inputs (ie, “costs”) and outcomes (ie, clinical “benefits”) resulting from an intervention. Evaluation methods include cost-benefit, cost-effectiveness, cost-minimization, and cost-utility analyses. Cost and outcomes are used to inform a decision on whether to adopt a particular pharmaceutical product or treatment strategy compared with an alternative (control or comparator). Often, a new intervention

From the 1AdRes–Health Economics and Outcome Research, Turin, Italy; 2Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy; 3Department of General and Oncology Surgery with Intestinal Failure Unit, Stanley Dudrick’s Memorial Hospital, Skawina, Poland; and the 4Department of Surgery, Oregon Health and Science University, Portland, Oregon, USA.

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Corresponding Author:
Lorenzo Pradelli, MD, AdRes–Health Economics and Outcome Research, Via Vittorio Alfieri 17, Turin 10121, Italy.
Email: l.pradelli@adreshe.com
may have a better health effect than the comparator but is more costly, and in these cases there needs to be a judgment by the decision maker on whether or not (and how much) they are willing to pay for this improvement in healthcare.\(^3\) One such intervention that has received much attention within the field of parenteral nutrition is whether to use fish oil (henceforward referred to as \(\omega-3\) fatty acids). Thus, this review will cover pharmacoeconomic evidence regarding the use of parenteral nutrition with \(\omega-3\) fatty acids (intervention) vs standard parenteral nutrition (ie, containing lipids such as soybean oil, olive oil, and medium-chain triglycerides, but without \(\omega-3\) fatty acids), using modeling studies and collecting data from a variety of sources to apply these pharmacoeconomic analyses to a range of scenarios.

This review is based on presentations given at the international summit “Lipids in Parenteral Nutrition” on November 2–4, 2018 (Miami, FL, USA).

**Modeling and Meta-Analyses**

A thorough pharmacoeconomic analysis usually requires the use of modeling. This is because it is rare that a single trial contains all the evidence that should be considered when making evidence-based decisions, so otherwise any other evidence on treatment effects, outcomes, and resources is effectively ignored.\(^6\) In contrast, modeling studies can collect data from a wide range of sources (including meta-analyses, observational studies, etc) and perform syntheses using an economic model.\(^7\) Models are used very widely in a range of scientific disciplines and are a way of representing the complexity of the real world in a simpler and more understandable form.\(^8,9\) Furthermore, modeling is particularly useful within the field of parenteral nutrition, as large-scale clinical trials are uncommon and collection of economic data is not generally performed as part of these studies.

When performing a modeling study, the reliability of any outcomes depends on the quality of data used. As such, the hierarchy of evidence used in modeling is as relevant as in any other field of evidence-based medicine. Thus, meta-analyses have proven to be valuable tools, as they are the highest level of the evidence-based medicine hierarchy,\(^10\) though others still believe that individual randomized controlled trials remain the “gold standard.” Furthermore, many meta-analyses have been conducted showing that parenteral nutrition including \(\omega-3\) fatty acids is associated with clinical benefits.\(^11-19\) Results from these meta-analyses have been discussed in more detail in another review in this supplement.\(^20\)

The 2012 meta-analysis by Pradelli et al\(^13\) has formed the basis for clinical outcomes data for all published \(\omega-3\) parenteral nutrition pharmacoeconomic studies,\(^21-23\) as it formed the largest and most comprehensive dataset until being updated in 2019.\(^19\) Pradelli et al, 2012, included 23 randomized controlled trials and 1502 patients, covering intensive care unit (ICU) populations (13 studies, 762 patients) as well as non-ICU/major abdominal surgery patients (10 studies, 740 patients).\(^13\) This meta-analysis found that the use of \(\omega-3\) fatty acids was associated with \(\approx40\%\) fewer infections (relative risk [RR] 0.61; 95% confidence interval [CI], 0.45–0.84; \(P = .002\)) compared with standard parenteral nutrition for Italian, French, German, and UK hospitals for ICU and non-ICU patients,\(^21\) and for ICU patients in China.\(^22,23\)

**Cost-Effectiveness of Parenteral Nutrition Including \(\omega-3\) Fatty Acids**

**European Perspective**

To find out whether potential clinical benefits were economically justifiable, a pharmacoeconomic evaluation was performed to investigate the cost-effectiveness of parenteral nutrition with lipid emulsions with or without \(\omega-3\) fatty acids in a variety of clinical settings (ie, ICU or surgical/non-ICU) and in 4 national scenarios (Italy, France, Germany, and the UK).\(^21\) The perspective of the analysis was from the point of view of a healthcare provider of these 4 countries, with a time horizon limited to patients’ hospital stay. The method used a model based on a patient-level, probabilistic, discrete-event simulation (DES) technique. In this, the experience of individuals is modeled over time in terms of the events that occur and the consequences of those events. Thus, 2 alternative treatment arms were simulated, representing parenteral nutrition (1) with \(\omega-3\) fatty acids from fish oil, or (2) without \(\omega-3\) fatty acids (standard parenteral nutrition, such as soybean oil, medium-chain triglycerides/long-chain triglycerides, or olive oil/soybean oil emulsions). Two patient populations were considered: (1) medical and surgical patients with an ICU stay, and (2) surgical patients without an ICU stay. The main clinical
Table 1. Results of a Cost-Effectiveness Analysis for Italy.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ICU Patients</th>
<th>Non-ICU Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST + ω-3</td>
<td>ST</td>
<td>Difference</td>
</tr>
<tr>
<td>Total cost, €</td>
<td>19,825</td>
<td>24,504</td>
</tr>
<tr>
<td>ICU cost, €</td>
<td>7475</td>
<td>10,166</td>
</tr>
<tr>
<td>Ward (pre-ICU) cost, €</td>
<td>4318</td>
<td>4318</td>
</tr>
<tr>
<td>Ward cost, €</td>
<td>6336</td>
<td>8531</td>
</tr>
<tr>
<td>Infection cost, €</td>
<td>90</td>
<td>119</td>
</tr>
<tr>
<td>Treatment cost, €</td>
<td>1605</td>
<td>1370</td>
</tr>
<tr>
<td>ICER, €/LOS day</td>
<td>ST</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td>ST + ω-3</td>
<td>ST + ω-3</td>
</tr>
<tr>
<td>Total cost, €</td>
<td>13,595</td>
<td>14,619</td>
</tr>
<tr>
<td>ICU cost, €</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ward (pre-ICU) cost, €</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ward cost, €</td>
<td>12,171</td>
<td>13,399</td>
</tr>
<tr>
<td>Infection cost, €</td>
<td>131</td>
<td>261</td>
</tr>
<tr>
<td>Treatment cost, €</td>
<td>1292</td>
<td>959</td>
</tr>
<tr>
<td>ICER, €/LOS day</td>
<td>Dominant</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

Note: Death rates per 10,000 patients are 2509 (ICU patients) and 511 (non-ICU patients), regardless of treatment in all of the base-case scenarios. Results are mean costs (€) per patient (Pradelli et al, 2014).ICER, incremental cost-effectiveness ratio (ST + omega-3 vs ST); ICU, intensive care unit; LOS, length of stay; N/A, not applicable; ST, standard parenteral nutrition, defined as any parenteral nutrition not containing fish oil; ST + omega-3, any parenteral nutrition containing fish oil; Reproduced with permission from Pradelli 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.

The results showed that parenteral nutrition containing ω-3 fatty acids was more effective than standard parenteral nutrition containing lipids without ω-3 fatty acids, both in ICU and in non-ICU patients, in all 4 countries, reducing infection rates and overall LOS, and resulting in a lower total cost per patient. Thus, the base-case model outcomes were that ω-3 fatty-acid enriched lipid emulsions prevented 23.8% and 49.7% of ICU and non-ICU patient infections, respectively, and reduced overall LOS by 4.6 days (ICU patients) and 1.6 days (non-ICU patients). Thus, the model reflects the results from the meta-analysis very well, providing further confidence in the model results. Results for Italy showed a total mean cost saving of €4679 per ICU patient and €1025 per non-ICU patient when using parenteral nutrition containing ω-3 fatty acids compared with the use of standard lipid emulsions (equating to US $4212 and US $923, respectively, calculated at exchange rates on August 15, 2019). Extension of the model to also include France, Germany, and the UK, revealed overall cost savings of about €4000–€4900 per ICU patient and €600–€1800 per non-ICU patient for this treatment strategy (equating to US $3601–US $4411, and US $540–US $1620, respectively, calculated at exchange rates on August 15, 2019). These findings indicate that the extra acquisition cost of parenteral nutrition containing ω-3 fatty acids is more than offset by savings arising from reductions in the cost of ICU and hospital stay, and to a lesser extent by lower costs resulting from fewer nosocomial infections. Thus, parenteral nutrition containing ω-3 fatty acids is said to “dominate” standard parenteral nutrition for Italy (Table 1) and the other 3 countries (results not shown).

The model results were shown to be robust according to the sensitivity analyses performed for each national scenario. In addition, the deterministic sensitivity analyses also showed that the most influential cost parameters were reduction in length of stay in both ICU and non-ICU patients. Because of the robustness of these results, these findings are likely to be applicable in healthcare settings and systems similar to those in the 4 European countries. Thus, the results of this study strongly suggest that parenteral nutrition containing ω-3 fatty acids is a clinically and economically attractive strategy compared with standard parenteral nutrition in Italian, French, German, and UK healthcare systems. For both patients and healthcare providers.

Chinese Perspective: Omegaven Validation Study

The same cost-effectiveness pharmacoeconomic techniques used in the European study were utilized and validated in a Chinese ICU setting, this time comparing parenteral nutrition including ω-3 fatty acids (specifically Omegaven 10% fish-oil emulsion, Fresenius Kabi, Bad Homberg, Germany) with standard lipid emulsions that did not contain fish oil. The perspective of the analysis was
from the point of view of patients and their families in China, with a time horizon limited to patients’ time in hospital. The method used a model based on a patient-level, probabilistic DES. Importantly, part of this study involved the validation of the model predictions by a formal comparison of predicted data from the model with real-life data not used in the modeling exercise.

Methods used by Wu et al.22 were similar to those in the previous European pharmacoeconomics study.21 In brief, a similar DES model was used, and the events considered were transfers between ICU and ward, new nosocomial infection, discharge from the hospital, and death. However, only ICU patients were considered in this analysis. Two treatment arms were simulated: parenteral nutrition (1) with ω-3 fatty acids from fish oil, or (2) without fish oil (standard parenteral nutrition, control population). No discounting was applied to outcomes and costs owing to the short time frame of the simulation. The DES model used was based on efficacy data from an international meta-analysis,13 and clinical and economic input parameters were derived from a Chinese observational study conducted in a large hospital based in Shanghai.31 Cost inputs were based on regression analyses of cost data from the same Chinese hospital dataset. The reliability of the results was tested by using probabilistic and deterministic sensitivity analyses. The model’s predictive accuracy for clinical outcomes in the Omegaven cohort was also validated externally by comparison with actual data obtained from this subset of patients in the Shanghai hospital database not used in the modeling. One potential drawback of this study was that it only considered direct costs to the patients and their family, which may be of particular importance given the study perspective. Thus, we do not know the effect of any indirect medical or non-medical expenses or benefits. However, it seems likely that the faster recovery and shorter hospital stay for the Omegaven group might result in lower indirect costs (eg, earlier return to work resulting in reduced income losses).

The model predicted (and observed data confirmed) that Omegaven would “dominate” standard lipid emulsions, with better clinical outcomes and lower overall healthcare costs (mean savings ≈10,000 Chinese yuan renminbi [¥], equating to US $1421 or €1274 calculated at exchange rates on August 15, 2019), mainly because of faster recovery and shorter hospital stay (by ≈6.5 days).22 The external validation process also confirmed the reliability of the model’s predictions as all external observations were reasonably close to the mean of model predictions and were well within the 95% CI of the values predicted by the probabilistic sensitivity analysis. If anything, the model results were somewhat conservative, as the model slightly underestimated the stay reduction compared with the stay reduction observed in the ICU patient population admitted. Thus, the results of this study showed that the use of Omegaven for Chinese ICU patients can shorten recovery as well as more than offset any extra acquisition costs, resulting in net savings for the overall hospital stay.22

Chinese Perspective: SMOFlipid

The same cost-effectiveness pharmacoeconomic techniques used in the European study23 were again used in a Chinese ICU setting, but this time comparing parenteral nutrition including standard lipid emulsions (without fish oil) with those containing ω-3 fatty acids (specifically SMOFlipid [Fresenius Kabi, Bad Homburg, Germany], a multi-component intravenous lipid emulsion containing 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil [henceforward referred to as SMOF]).23 In this case, the perspective was that of the hospital, and this study also incorporated an update to the meta-analysis of Pradelli et al,13 leading to the inclusion of data from 5 additional recent clinical trials.23 To perform the pharmacoeconomic analysis, a DES model was again produced based on these updated efficacy data and China-specific clinical and economic input parameters.32,33 Two treatment arms were simulated: parenteral nutrition including (1) an ω-3 fatty-acid enriched lipid emulsion (SMOF), and (2) standard lipid emulsions (ie, that did not contain fish oil, control population). Again, no discounting was applied, and the robustness of the findings was tested by using probabilistic and deterministic sensitivity analyses.23

The model predicted that a strategy of parenteral nutrition with SMOF would “dominate,” as it was more effective and less expensive than parenteral nutrition with standard lipid emulsions for Chinese ICU patients.23 In brief, for parenteral nutrition with SMOF vs standard lipid emulsions, results showed a reduced overall LOS (19.48 vs 21.35 days, respectively), reduced length of ICU stay (5.03 vs 6.18 days, respectively), and prevention of 35.6% of nosocomial infections, leading to a lower total cost per patient (¥47,189 [US $6937] vs ¥54,783 [US $8053], respectively). Any extra costs for parenteral nutrition with SMOF were more than offset by savings in the cost of hospital and ICU stay and antibiotic costs, leading to an average cost saving of ¥7594 (US $1116) per patient. The robustness of these findings was also confirmed by sensitivity analyses. Thus, in the Chinese ICU setting, giving patients parenteral nutrition with SMOF may be an effective way of reducing the length of hospital and ICU stays and infectious complications and also decreasing overall treatment costs. As such, this represents a “win–win” situation for patients, hospital administration, and health insurance companies.23

Summary and Future Perspectives

So far, in all national scenarios investigated, the use of parenteral nutrition including fish oil has more than offset any additional acquisition costs, indicating that this an
economically and financially beneficial strategy. The studies in this review have covered different perspectives, demonstrating cost-effectiveness for different stakeholders (ie, healthcare provider, patient and family, or hospital). However, none of these studies have assessed cost-effectiveness from a third-party payer perspective, which is helpful for insurance providers to decide whether to adopt the intervention for their formulary. Although the third-party payer perspective is generally extremely relevant within pharmacoeconomic studies, it has presumably been omitted in all of the studies reviewed here because it is less relevant than other perspectives, owing to the acquisition dynamics of parenteral nutrition products (ie, these tend to be accounted for out of hospital budgets—or by patients and their families in China—rather than reimbursed by the third-party payer).

Further work is also needed to update and extend the pharmacoeconomic analyses. To this end, the 2019 meta-analysis by Pradelli et al, which is the largest and most comprehensive conducted to date, has been used as the basis for a pharmacoeconomic study published recently as a conference abstract. This cost–consequence analysis using a DES technique showed average cost savings in the UK, Germany, France, Italy, and Spain, ranging from €1766 to €2528 for ω-3 fatty-acid enriched parenteral nutrition vs standard parenteral nutrition (equating to US $1590–US $2276, respectively, calculated at exchange rates on August 15, 2019). Thus, ω-3 fatty-acid enriched parenteral nutrition seems likely to be a cost-effective alternative to standard parenteral nutrition in the majority of patients. However, the studies conducted thus far have only covered adult hospitalized patients in China, Italy, France, Germany, and the UK, and so it would be beneficial to perform further pharmacoeconomic studies encompassing other countries and clinical settings.

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Statement of Authorship
L. Pradelli, M. Muscaritoli, S. Klek, and R. G. Martindale, equally contributed to the conception and design of the research; L. Pradelli, M. Muscaritoli, S. Klek, and R. G. Martindale, contributed to the acquisition, analysis, and interpretation of the data; R. Clark 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.

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