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# Change to Mixed-Lipid Emulsion From Soybean Oil–Based Lipid Emulsion in Pediatric Patients

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## Abstract

**IMPORTANCE** Critically ill pediatric patients often require parenteral nutrition (PN) in the intensive care unit (ICU). Literature suggests mixed lipid emulsions (LE) with soybean oil reduction strategies may improve outcomes.

**OBJECTIVE** To examine the association of a hospital-wide switch to a mixed-lipid formula (4-OLE) with pediatric outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study at a large US academic referral center. Pediatric patients aged 1 month to 17 years requiring parenteral nutrition from May 2016 to September 2019 were included. Data were analyzed from October 2020 to February 2023.

**EXPOSURE** In 2017, Duke University Health System fully converted to a soybean oil/MCT/olive/fish oil lipid (4-OLE) from pure soybean oil–based LE in pediatric patients. Pediatric patients before the change (Intralipid [IL] group) were compared with patients after (4-OLE group).

**MAIN OUTCOMES AND MEASURES** Clinical outcomes were compared between treatment periods via multivariable regression models. The primary outcome was hospital length of stay (LOS). Fourteen secondary outcomes included hospital mortality of any cause, 30-day or 90-day readmission, pneumonia, urinary tract infections (UTIs), total caloric delivery, and liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and total bilirubin).

**RESULTS** A total of 684 children dependent on PN were identified (342 were critically ill), with 30% (206 children) in the preswitch (IL) period and 70% (478 children) in the postswitch (4-OLE) period; 123 were male (59.7%). In comparing IL vs 4-OLE, there was a significant difference in median (IQR) age (4.0 [1.2-13.0] vs 3.0 [0.8-9.0] years, respectively; $P = .04$), without difference in body mass index or baseline comorbidities except for significant differences in cancer diagnosis (26 patients in the IL group [12.6%] vs 29 patients in the 4-OLE group [6.1%]; $P = .004$) and chronic obstructive pulmonary disease (24 patients in the IL group [11.7%] vs 30 patients in the 4-OLE group [6.3%]; $P = .02$). In the all children cohort, 4-OLE was associated with shorter hospital LOS (IRR, 0.81; 95% CI, 0.05-0.78), and reduced UTI risk (OR, 0.33; 95% CI, 0.18-0.64). In the ICU cohort, 4-OLE was associated with shorter hospital LOS (IRR, 0.81; 95% CI, 0.78-0.83), and reduced UTI risk (OR, 0.23; 95% CI, 0.11-0.51). Other secondary outcomes were not significant.

**CONCLUSIONS AND RELEVANCE** In this observational study of clinical outcomes among children dependent on PN, a switch to 4-OLE in a large academic hospital was associated with a significant decrease in hospital LOS in ICU and non-ICU patients. These findings suggest switching to a soy–LE

*(continued)*

## Key Points

**Question** Does switching from soybean oil–based lipid emulsion (Intralipid) to a mixed-lipid formula (4-OLE) improve outcomes in pediatric patients who were parenteral nutrition (PN)–dependent?

**Findings** In this cohort study of 684 children who were PN-dependent, 4-OLE was associated with a statistically significant shorter hospital length of stay in the all children and ICU cohorts.

**Meaning** These findings suggest that switching to 4-OLE parenteral nutrition formula over soybean oil–based lipid emulsion may lead to improved outcomes in pediatric patients.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

*Abstract (continued)*

sparing strategy using 4-OLE is feasible, safe, and associated with improved clinical outcomes in pediatric PN patients.

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## Introduction

In the hospitalized and critically ill pediatric population, many clinical conditions such as burns, trauma, necrotizing enterocolitis, and malabsorption require parenteral nutrition (PN) as a primary or supplemental source of nutrition care.[1] This is often essential to prevent malnutrition, which increases the risk of mortality, infections, and hospital length of stay (LOS).[2-4] The most commonly used intravenous lipid emulsion (LE) in PN is Intralipid (IL) (Baxter Inc), which is composed of 100% soybean oil. In adult patients, soybean oil LEs have been associated with significant adverse effects, including worsening inflammation and immunosuppression, mainly due to omega-6 fatty acids.[5-8] The use of soybean oil–based LE has been implicated in several PN complications including increased oxidative stress, cholestasis, hepatic steatosis, liver dysfunction, risk of infection, and sepsis.[5-12] Furthermore, in premature and low birth weight infants, the risk of these complications is particularly prevalent and challenging, as these patients often need prolonged PN support to avoid complications related to neurodevelopment and postnatal growth.[9,10]

Given the adverse effects associated with traditional soybean oil–based LE, consensus guidelines in adult and pediatric populations now advocate for soybean oil–sparing strategies to reduce the risk of omega-6 lipid–related complications.[11-13] Active metabolites such as resolvins in the omega-3 fatty acids of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce inflammatory cytokine production as well as other beneficial immunomodulatory effects.[5,14,15] Soybean oil reduction strategies, including using lipid preparations with increased EPA or DHA lipid content, may decrease hospital LOS, intensive care unit (ICU) LOS, and time on the ventilator.[16] However, there is a lack of conclusive evidence in other recent publications to support their benefit on mortality.[17-19]

Using soybean oil–sparing strategies reduces the amount of omega-6 fatty acids and increases omega-3 fatty acids content in lipids, providing potential anti-inflammatory benefit.[5,14] SMOFLipid (4-OLE) (Fresenius Kabi) is a new generation of LE commonly used worldwide to provide a more optimal lipid profile. It is composed of a mixture of 6 g soybean oil–based, 6 g MCT, 5 g olive oil, 3 g fish oil, 1.2 g egg phospholipids, 2.5 g glycerin, and 16.3 to 22.5 mg all-rac-α-tocopherol.[20] The use of omega-3 containing LE formulations, such as 4-OLE, has led to associated clinical benefit in adult ICU and surgical patients, including reduced length of stay, reduced time on mechanical ventilation, and lower rates of infectious complications.[12,21] Overall, in the adult population, there is a growing body of evidence for improved outcomes with soybean oil–sparing strategies.

However, in the pediatric population, much of the previous literature is focused on newborn and infant patients, who are more sensitive to the negative effects of malnutrition.[22] Many conditions requiring PN commonly occur in premature infants, such as necrotizing enterocolitis.[1,22] Many of these patients concomitantly experience cholestasis or hyperbilirubinemia, which is thought to be exacerbated when using soybean oil–based PN formulas. In infants, fish oil–based LE was found to help reduce sepsis risk, reverse parenteral nutrition associated cholestasis (PNAC), and reduce retinopathy of prematurity with mixed results regarding effects on overall growth and mortality[23-26].

Routine use of 4-OLE for PN has been limited in the noninfant pediatric population due to a lack of existing trials examining clinical outcomes in the older pediatric and pediatric ICU populations.[27] In Europe, however, the use of 4-OLE in pediatrics has increased and has exhibited a favorable safety profile.[28,29] A recent 2022 meta-analysis in adult ICU patients demonstrated significant benefits when fish oil–based LEs were used, with a reduction in LOS and infectious complications, as well as a potential mortality benefit.[16] Given the current lack of available evidence on the effect of 4-OLE on

clinical outcomes in pediatric patients, there is an urgent need for data on this key clinical question. An opportunity to address this occurred in 2017 when the Duke University Health System underwent a switch on a single day from IL (omega-6 lipid) to 4-OLE. This is a clinical observational study of a switch from IL to 4-OLE and its association with clinical outcomes in critically ill and noncritically ill pediatric patients requiring PN.

## Methods

### Study Design and Patient Selection

This retrospective study used electronic health record data from 2016 to 2019, comparing participants receiving IL 1 year before conversion to 4-OLE and 2 years following implementation within the Duke University Health System. This study was reviewed by the Duke institutional and ethics review board and was granted approval as exempt from consent requirement because it was retrospective in nature. IL was switched entirely to 4-OLE in all PN patients on May 16, 2017. Inclusion criteria were pediatric patients aged from 1 month to 17 years requiring PN for adequate nutrition from May 2016 through September 2019. We followed appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational cohort studies.

We collected the following for each patient: age, sex, race, ethnicity, body mass index (BMI), ICU admission, emergency department (ED) admission, malnutrition at admission, and comorbidities using the binary Elixhauser comorbidity indicators.[30] A total of 35 comorbidities, pneumonia, and urinary tract infections (UTIs) were identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis codes. Race and ethnicity were collected via patient self-report and were assessed in this study because health disparities and inequities have been shown to influence the severity of comorbidities and pediatric clinical outcomes.

Characteristics of PN formulations, type of LE, cumulative calories, dosage of lipids, protein dose, as well as the PN duration were evaluated. Additionally, hospital outcomes, including ICU LOS, hospital LOS, in-hospital mortality, 30-day readmission, 90-day readmission, pneumonia, UTIs, insulin use, antibiotic use, as well as influence on lab values (alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin), were assessed.

Pediatric patients from May 2016 to May 2017, before the change (IL group), were compared with patients from May 2017 to September 2019, after the clinical change (4-OLE group). The primary outcome of the study was hospital LOS. Fourteen secondary outcomes included hospital mortality of any cause, 30-day or 90-day readmission, pneumonia, UTIs, total caloric delivery, and liver function tests (AST, ALT, ALP, and total bilirubin). Changes in values were calculated by subtracting initial admission values from the maximum values during the hospital stay. Our analysis included the following covariates: age, sex, race, ethnicity, insurance status, cancer, diabetes, pulmonary disease, heart disease, liver disease, kidney failure, obesity, malnutrition, ED admission, ICU admission, and BMI.

### Statistical Analysis

Descriptive statistics were calculated and presented as number and percentage for categorical variables and median (IQR) or mean (SD) for continuous variables. Continuous variables were compared using a *t* test or a Wilcoxon test. When indicated, categorical data was analyzed via Pearson $\chi^2$ test or Fisher exact test. A Poisson regression model to estimate the incident rate ratio (IRR) was performed to identify any association between the type of LE and LOS. Multivariable logistic models were performed to assess the association between the type of LE and hospital mortality and 30-day and 90-day readmissions. Multivariable linear regression models were performed to assess the association between the type of LE, nutrition delivery variables, and liver function tests. In the sensitivity analysis, we restricted the cohort to patients admitted to the ICU. We

performed the same analysis previously described except for covariates where ICU admission was removed. The type I error rate was set at a 2-sided .05 as the threshold for statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute) from October 2020 to February 2023.

## Results

### Clinical Characteristics in the All Hospitalized Pediatric Patients Cohort

We identified 684 patients in the pediatric cohort meeting inclusion criteria. Of these, 206 were in the IL group (30.1%) and 478 in the 4-OLE group (69.9%) with similar male distribution in both groups (123 male patients [59.7%] vs 253 male patients [52.9%], respectively; OR, 0.76; 95% CI, 0.54 to 1.06; *P* = .10). In comparing IL vs 4-OLE, there was a significant difference in median (SD) age (4.0 [1.2-13.0] vs 3.0 [0.8-9.0] years, respectively; mean difference, −1.2 years; 95% CI, −2.1 to −0.2; *P* = .04). There was no significant difference in median (IQR) BMI (17.5 [15.3-20.2] for patients in the IL group vs 17.0 [15.5-19.2] for patients in the 4-OLE group; mean difference, 0.1; 95% CI, −0.8 to 0.6; *P* = .57). We observed no significant difference in diabetes, obesity, kidney failure, liver disease, congestive heart failure, or malnutrition between the IL and 4-OLE groups in reviewing baseline comorbidities. However, when comparing the IL group with the 4-OLE group, we found significant differences in cancer diagnosis (26 patients [12.6%] vs 29 patients [6.1%], respectively; OR, 0.45; 95% CI, 0.26 to 0.78; *P* = .004) and chronic obstructive pulmonary disease (COPD) (24 patients [11.7%] vs 30 patients [6.3%], respectively; OR, 0.51; 95% CI, 0.29 to 0.89; *P* = .02). Additionally, there was no difference in insulin use or antibiotic use between the cohorts. Full details of the pediatric baseline characteristics can be found in **Table 1**.

### Association of Switch to 4-OLE With Clinical Outcomes in Hospitalized Pediatric Patients

Crude outcomes are summarized in **Table 2**. In the multivariable regression models, there was no difference in the number of days receiving lipids, daily lipid dosage, and daily protein-based calories. We also observed no significant difference in changes in levels of liver function tests among the 2 groups and no significant difference in readmission rates and mortality. We observed a statistically significant lower LOS in the 4-OLE cohort (IRR, 0.81; 95% CI, 0.78-0.83; *P* < .001) as well as a lower risk of UTIs (OR, 0.33; 95% CI, 0.17-0.64; *P* < .001). These results did not change when analysis was performed excluding patients who had cancer or COPD, as well as on analysis without diabetes and insulin use, to account for the higher demographics of these patients among the IL groups.

### Clinical Characteristics of Pediatric ICU Patient Cohort

The pediatric ICU cohort consisted of 342 patients who met inclusion criteria, with 27% in the IL group (91 patients) and 73% in the 4-OLE group (251 patients). The median (IQR) age was 1.7 (0.3-8.0) years (mean difference, −0.3; 95% CI, −1.6 to 0.9; *P* = .89), median (IQR) BMI was 17.4 (15.3-19.3; mean difference 0.2; 95% CI, −0.8 to 1.2; *P* = .94), and male distribution for the entire cohort was similar between both groups (46 patients in the IL group [50.5%] vs 140 patients in the 4-OLE group [55.8%]; OR, 1.23; 95% CI, 0.76 to 2.00; *P* = .39). Regarding comorbidities, we found no difference in the diagnosis of kidney failure, congestive heart failure, COPD, diabetes, malnutrition, cancer, or obesity. **Table 3** provides further insight into the baseline characteristics of the ICU cohort.

### Association of Switch to 4-OLE With Clinical Outcomes in Pediatric ICU Cohort

Crude outcomes for the pediatric ICU cohort are summarized in **Table 4**. In the multivariable regression models, 4-OLE was associated with lower LOS (IRR, 0.77; 95% CI, 0.74-0.80; *P* < .001). However, no differences in mortality, readmission rates, or changes in liver function tests were observed. Additionally, 4-OLE use was associated with a lower risk of UTIs (OR, 0.23; 95% CI, 0.11-0.51; *P* < .001) but demonstrated no significant difference in pneumonia or any cause of infection. In

the pediatric ICU patient subgroup, the crude data showed the use of 4-OLE was associated with a significant 13.1-day reduction (95% CI, −25.3 to −1.3 days) in hospital LOS vs IL ($P$ = .02). Further detail regarding our analysis of the ICU pediatric cohort can be found in Table 4. These results did not change when analysis was performed excluding patients who had cancer or COPD, as well as on analysis without diabetes and insulin use, to account for the higher demographics of these patients among the IL groups. We performed additional analyses to investigate a potential difference in outcomes for older pediatric patients (7-17 years) vs younger pediatric patients (less than 7 years).

## All Hospitalized Children Cohort

The association between 4-OLE and LOS was modified by age (older vs younger; $P$ for interaction < .001). The use of 4-OLE was associated with lower LOS (IRR, 0.78; 95% CI, 0.75-0.81; $P$ < .001) for older pediatric patients and for younger pediatric patients (IRR, 0.73; 95% CI, 0.71-0.75; $P$ < .001). On the other hand, the outcome of 4-OLE on UTIs was not modified in older pediatric patients ($P$ for interaction = .38).

## Children in ICU Cohort

The association between 4-OLE and LOS was modified by age (older vs younger; $P$ for interaction < .001). The use of 4-OLE was associated with lower LOS (IRR, 0.61; 95% CI, 0.58-0.65; $P$ < .001) for older pediatric patients and for younger pediatric patients (IRR, 0.74; 95% CI, 0.72-0.78;

Table 1. Baseline Characteristics Among All Hospitalized Children

| Characteristic | Patients, No. (%) | | | $P$ value |
|---|---|---|---|---|
| | Total (N = 684) | Intralipid (n = 206)[a] | 4-OLE (n = 478) | |
| Age, median (IQR), y | 3.0 (0.9-11.0) | 4.0 (1.2-13.0) | 3.0 (0.8-9.0) | .04 |
| Sex | | | | |
| Male | 376 (55.0) | 123 (59.7) | 253 (52.9) | .10 |
| Female | 308 (45.0) | 83 (40.3) | 225 (47.1) | |
| Race | | | | |
| Black or African American | 206 (30.1) | 46 (22.3) | 160 (33.5) | .10 |
| White | 350 (51.2) | 115 (55.8) | 235 (49.2) | |
| Other[b] | 128 (18.7) | 45 (21.8) | 83 (17.4) | |
| Hispanic ethnicity | 75 (11.0) | 23 (11.2) | 52 (10.9) | .91 |
| Payer | | | | |
| Managed care organization | 297 (43.4) | 85 (41.3) | 212 (44.4) | .005 |
| Medicaid | 269 (39.3) | 70 (34.0) | 199 (41.6) | |
| Medicare | 7 (1.0) | 4 (1.9) | 3 (0.6) | |
| Other | 111 (16.2) | 47 (22.8) | 64 (13.4) | |
| Comorbidity | | | | |
| Malnutrition | 128 (18.7) | 39 (18.9) | 89 (18.6) | .92 |
| Congestive heart failure | 49 (7.2) | 17 (8.3) | 32 (6.7) | .47 |
| Cancer | 55 (8.0) | 26 (12.6) | 29 (6.1) | .004 |
| Chronic obstructive pulmonary disease | 54 (7.9) | 24 (11.7) | 30 (6.3) | .02 |
| Liver disease | 39 (5.7) | 14 (6.8) | 25 (5.2) | .42 |
| Kidney failure | 20 (2.9) | 8 (3.9) | 12 (2.5) | .33 |
| Diabetes | 7 (1.0) | 4 (1.9) | 3 (0.6) | .21 |
| Obesity | 7 (1.0) | 2 (1.0) | 5 (1.0) | .99 |
| Body mass index, median (IQR)[c] | 17.2 (15.4-19.6) | 17.5 (15.3-20.2) | 17.0 (15.5-19.2) | .57 |
| Emergency department | 218 (31.9) | 54 (26.2) | 164 (34.3) | .04 |
| Intensive care unit admission | 342 (50.0) | 91 (44.2) | 251 (52.5) | .045 |
| Mechanical ventilation | 157 (23.0) | 38 (18.4) | 119 (24.9) | .07 |
| Antibiotic use | 614 (89.8) | 185 (89.8) | 429 (89.7) | .98 |
| Use of insulin | 105 (15.4) | 39 (18.9) | 66 (13.8) | .09 |

Abbreviation: 4-OLE, soy/MCT/olive/fish oil lipid.

[a] Intralipid (Baxter Inc).

[b] Two or more races, American Indian or Alaskan, Asian, Native Hawaiian or other Pacific Islander, not reported or declined, and other.

[c] Body mass index is calculated as weight in kilograms divided by height in meters squared.

*P* < .001). On the other hand, the outcome of 4-OLE on UTIs was not modified in older pediatric patients (*P* for interaction = .76).

## Discussion

To our knowledge, this is the first study demonstrating improved clinical outcomes associated with the use of 4-OLE vs pure soybean oil lipid (or IL) in a pediatric population. After a hospital-wide switch to 4-OLE at Duke University Hospital, there was a significant decrease in LOS as well as lower rates of UTIs for hospitalized and critically ill pediatric patients.

These data are timely for the care of pediatric PN patients as the 4-OLE studied here (SMOFLipid) was just recently FDA-approved for pediatric patients in the US. To our knowledge, this is the first data supporting potential clinical outcome benefits associated with 4-OLE use in a pediatric PN population. Our data are consistent with European studies[28,29] demonstrating the safety of 4-OLE in pediatric patients, whereas these data also demonstrated a reduction of cholestasis and markers of liver injury. We observed no significant change in baseline liver function tests in critically ill and hospitalized pediatric patients receiving 4-OLE, but a potential signal of benefit on changes in liver function tests was observed in our unadjusted pediatric ICU data that we believe deserves further investigation in the nonneonatal pediatric ICU population. There are possible differences between neonatal, infant, and older pediatric patients that require further explanation. Premature infants are at higher risk of cholestasis and PNAC, which may not have been captured fully in our patient population.[22] As most of the previous literature focuses on the neonatal and infant population, this was the first to include older pediatric patients. More direct comparisons of these populations can help determine the ideal PN composition for each age group and which benefits directly relate to complications of prematurity. We also observed no reduction in cumulative protein-based intake and cumulative calorie intake with a switch to 4-OLE use. These results further build upon the limited evidence pertaining to 4-OLE use in the nonneonatal pediatric population,

Table 2. Outcomes Among All Hospitalized Children

| | Patients, median (IQR) | | *P* value for unadjusted analysis | Adjusted multivariable analysis[a] | |
|---|---|---|---|---|---|
| Nutrition profiles | Intralipid (n = 206)[b] | 4-OLE (n = 478) | | Regression (95% CI) | *P* value |
| Total time receiving lipids, d | 9.0 (4.0 to 25.0) | 9.0 (4.0 to 19.0) | .87 | −4.16 (−8.97 to 0.66) | .09 |
| Daily lipid dosage, g/kg/d | 3.4 (1.8 to 7.2) | 3.4 (1.8 to 7.2) | .19 | 0.13 (−1.8 to 2.06) | .90 |
| Daily calories, calories/kg/d | 39.7 (26.0 to 53.8) | 38.6 (28.7 to 51.0) | .65 | −4.71 (−10.29 to 0.87) | .10 |
| Daily protein-based calories, calories/kg/d | 1.0 (0.8 to 1.2) | 1.0 (0.8 to 1.2) | .02 | −0.12 (−0.27 to 0.03) | .13 |
| Liver function tests | | | | | |
| Change in aspartate aminotransferase | 25.5 (0.0 to 80.0) | 18.0 (0.0 to 89.0) | .38 | 65.84 (−191.19 to 322.88) | .62 |
| Change in alanine transaminase | 24.0 (0.0 to 84.0) | 17.0 (0.0 to 80.0) | .34 | −19.71 (−111.98 to 72.57) | .68 |
| Change in alkaline phosphatase | 34.5 (0.0 to 104.0) | 34.5 (0.0 to 87.0) | .74 | −14.07 (−49.47 to 21.32) | .44 |
| Change in total bilirubin | 0.4 (0.0 to 1.0) | 0.3 (0.0 to 0.8) | .19 | 0.03 (−0.81 to 0.86) | .95 |
| Clinical outcomes | | | | | |
| LOS | 27.2 (9.7 to 53.1) | 23.4 (11.2 to 46.0) | .60 | 0.81 (0.78 to 0.83)[c] | <.001 |
| Hospital mortality, No. (%) | 18 (8.7) | 35 (7.3) | .53 | 0.65 (0.32 to 1.3)[d] | .22 |
| 30-d Readmission, No. (%) | 82 (39.8) | 177 (37.0) | .49 | 0.86 (0.58 to 1.29)[d] | .48 |
| 90-d Readmission, No. (%) | 175 (85.0) | 377 (78.9) | .06 | 0.78 (0.46 to 1.34)[d] | .37 |
| Pneumonia, No. (%) | 13 (6.3) | 33 (6.9) | .78 | 0.87 (0.41 to 1.83)[d] | .71 |
| Urinary tract infection, No. (%) | 26 (12.6) | 29 (6.1) | .004 | 0.33 (0.18 to 0.64)[d] | <.001 |

Abbreviations: 4-OLE, soy/MCT/olive/fish oil lipid; LOS, length of stay.

[a] We adjusted for age, sex, race, ethnicity, insurance status, cancer, malnutrition, emergency department admission, intensive care unit admission, and body mass index. The reference was the 4-OLE group.

[b] Intralipid (Baxter Inc).

[c] Presented as incident rate ratio (95% CI).

[d] Presented as odds ratio (95% CI).

demonstrating its safety and its role as an equivalent source of nutritional support with no associated mortality or complication risk.

In addition, 4-OLE was associated with reduced LOS in both critically ill and hospitalized pediatric patients with no significant differences in readmission rates at 30 and 90 days or in mortality. In the pediatric ICU patient subgroup, the crude data showed the use of 4-OLE was associated with a significant 13.1-day reduction in hospital LOS vs IL ($P = .02$). A greater signal of reduced hospital LOS with 4-OLE use was observed in the adjusted multivariable analysis ($P < .001$). These findings coincide with previous literature demonstrating reduced LOS with 4-OLE use in adult ICU and surgical patients.[12,21] A recent meta-analysis corroborates this therapeutic benefit, demonstrating improved outcomes when soybean oil–based sparing strategies were used in conjunction with PN in adult patients.[16] Of note, the reduction in LOS in this adult meta-analysis was only significantly associated with fish oil containing LEs, similar to the composition of the 4-OLE examined in our data.

Using soybean oil–based sparing strategies has also been previously associated with a reduction in infectious complications in adult and neonatal patients.[16,26] The observed results in our data coincide with previous literature as both all pediatric patients and the ICU patient cohorts had a lower risk of UTIs when compared with IL.[12,16] The reduced infectious complications seen with 4-OLE use are believed to be related to its lower amount of omega-6 fatty acids, which are known to impair lymphocyte and natural killer cell activity and are implicated in impaired immune function as well as increased infection risk.[5-7,31,32] This characteristic of traditional omega-6 only LEs (such as IL) has

Table 3. Baseline Characteristics Among Children in Intensive Care Unit

| Characteristic | Patients, No. (%) | | | P value |
|---|---|---|---|---|
| | Total (N = 342) | Intralipid (n = 91)[a] | 4-OLE (n = 251) | |
| Age, median (IQR), y | 1.7 (0.3-8.0) | 1.7 (0.3-8.0) | 1.7 (0.4-8.0) | .89 |
| Sex | | | | |
| Male | 186 (54.4) | 46 (50.5) | 140 (55.8) | .39 |
| Female | 156 (45.6) | 45 (49.5) | 111 (44.2) | |
| Race | | | | |
| Black or African American | 117 (34.2) | 26 (28.6) | 91 (36.3) | .40 |
| White | 155 (45.3) | 44 (48.4) | 111 (44.2) | |
| Other[b] | 70 (20.5) | 21 (23.1) | 49 (19.5) | |
| Hispanic ethnicity | 37 (10.8) | 10 (11.0) | 27 (10.8) | .95 |
| Payer | | | | |
| Managed care organization | 140 (40.9) | 31 (34.1) | 109 (43.4) | .004 |
| Medicaid | 161 (47.1) | 40 (44.0) | 121 (48.2) | |
| Medicare | 1 (0.3) | 0 (0) | 1 (0.4) | |
| Other | 40 (11.7) | 20 (22.0) | 20 (8.0) | |
| Comorbidity | | | | |
| Malnutrition | 58 (17.0) | 18 (19.8) | 40 (15.9) | .40 |
| Congestive heart failure | 47 (13.7) | 16 (17.6) | 31 (12.4) | .21 |
| Cancer | 14 (4.1) | 7 (7.7) | 7 (2.8) | .06 |
| Chronic pulmonary disease | 24 (7.0) | 7 (7.7) | 17 (6.8) | .77 |
| Liver disease | 23 (6.7) | 7 (7.7) | 16 (6.4) | .67 |
| Kidney failure | 11 (3.2) | 4 (4.4) | 7 (2.8) | .49 |
| Diabetes | 5 (1.5) | 3 (3.3) | 2 (0.8) | .12 |
| Obesity | 3 (0.9) | 0 (0) | 3 (1.2) | .57 |
| Body mass index, median (IQR)[c] | 17.4 (15.3-19.3) | 17.6 (15.2-20.0) | 17.4 (15.5-19.3) | .94 |
| Emergency department | 96 (28.1) | 21 (23.1) | 75 (29.9) | .22 |
| Mechanical ventilation | 157 (45.9) | 38 (41.8) | 119 (47.4) | .35 |
| Antibiotic use | 335 (98.0) | 89 (97.8) | 246 (98.0) | .99 |
| Use of insulin | 93 (27.2) | 33 (36.3) | 60 (23.9) | .02 |

Abbreviation: 4-OLE, soy/MCT/olive/fish oil lipid.

[a] Intralipid (Baxter Inc).

[b] Two or more races, American Indian or Alaskan, Asian, Native Hawaiian or other Pacific Islander, not reported/declined, and other.

[c] Body mass index is calculated as weight in kilograms divided by height in meters squared.

been associated with adverse clinical outcomes in adult patients, including increased infectious complications, increased LOS, time on mechanical ventilation, and septic shock, especially in the most vulnerable of ICU patients.[8,31-33] Specific to these risks, Pradelli et al[21] demonstrated a significant reduction in septic complications when soybean oil–based sparing strategies were used in adult patients, further supporting the use of omega-3 containing LEs, such as 4-OLE in PN therapy.

This study is the first we know of to assess the clinical utility of 4-OLE in a pediatric (nonneonatal) population after widespread implementation within a hospital system. The observed results were a reduced LOS, lower risk of infectious complications (UTI), and similar cumulative nutritional intake with no associated risk of hepatic dysfunction or mortality. Overall, the findings in this study suggest that 4-OLE is associated with clinical outcome benefits and has a favorable safety profile when used in the pediatric population of critically and hospitalized patients. We believe the complications associated with traditional omega-6 based LE and the improved outcomes observed with 4-OLE use in this study support a continued transition to 4-OLE use in pediatric PN patients within the US and worldwide.

## Limitations

The presented study has limitations that need to be considered when interpreting its results. This study is retrospective, so it is limited regarding the lack of prospective data collection. This study did not include data on total cumulative lipid calories or changes in lipid panel values from baseline, limiting our ability to assess the association between different LE doses and parameters such as triglyceride levels. Additionally, some specific baseline characteristics are unknown, including premature birth, necrotizing enterocolitis, and specific diagnosis or cause of intestinal failure, which could further shed light on the application of 4-OLE use in these subsets of pediatric patients. UTIs and other complications were identified using *ICD* codes without being present on admission. However, there is still a possibility that UTI (outcome) occurred before patients were exposed to treatments (SMOF or IL). Furthermore, details on interruptions of PN or concomitant enteral support are not available and can potentially confound the calorie delivery data in this study. Additionally, the

Table 4. Outcomes Among Children in Intensive Care Unit

| Nutrition profiles | Patients, median (IQR) | | *P* value for unadjusted analysis | Adjusted multivariable analysis[a] | |
|---|---|---|---|---|---|
| | Intralipid (n = 91)[b] | 4-OLE (n = 251) | | Regression (95% CI) | *P* value |
| Total time receiving lipids, d | 10.0 (4.0 to 29.0) | 9.0 (4.0 to 18.0) | .28 | −7.63 (−15.55 to 0.29) | .06 |
| Daily lipid dosage, g/kg/d | 6.6 (3.3 to 21.0) | 6.9 (3.4 to 20.1) | .41 | 0.23 (−3.41 to 3.87) | .90 |
| Daily calories, cal/kg/d | 44.9 (31.6 to 57.4) | 39.0 (29.9 to 52.9) | .12 | −7.07 (−15.4 to 1.25) | .10 |
| Daily protein-based calories, cal/kg/d | 1.0 (0.8 to 1.2) | 1.1 (0.8 to 1.3) | .07 | −0.16 (−0.40 to 0.08) | .19 |
| Liver function tests | | | | | |
| Change in aspartate aminotransferase | 56.0 (11.0 to 175.0) | 28.0 (0.0 to 185.0) | .16 | 67.37 (−433.22 to 567.95) | .79 |
| Change in alanine transaminase | 41.0 (10.0 to 155.0) | 17.5 (0.0 to 119.0) | .02 | −82.57 (261.59 to 96.45) | .37 |
| Change in alkaline phosphatase | 65.0 (4.0 to 192.0) | 38.5 (0.0 to 119.0) | .047 | −31.87 (−99.28 to 35.54) | .35 |
| Change in total bilirubin | 0.7 (0.3 to 1.5) | 0.5 (0.0 to 1.3) | .04 | 0.12 (−1.49 to 1.73) | .88 |
| Clinical outcomes | | | | | |
| LOS | 44.5 (21.2 to 70.8) | 31.4 (15.8 to 56.2) | .02 | 0.77 (0.74 to 0.80)[c] | <.001 |
| Hospital mortality, No. (%) | 16 (17.6) | 35 (13.9) | .40 | 0.76 (0.37 to 1.56)[d] | .45 |
| 30-d Readmission, No. (%) | 33 (36.3) | 74 (29.5) | .23 | 0.65 (0.36 to 1.17)[d] | .15 |
| 90-d Readmission, No. (%) | 71 (78.0) | 173 (68.9) | .10 | 0.62 (0.33 to 1.19)[d] | .15 |
| Pneumonia, No. (%) | 10 (11.0) | 32 (12.7) | .66 | 1.03 (0.46 to 2.28)[d] | .95 |
| UTI, No. (%) | 19 (20.9) | 15 (6.0) | <.001 | 0.23 (0.11 to 0.51)[d] | <.001 |

Abbreviations: LOS, length of stay; UTI, urinary tract infection.

[a] We adjusted for age, sex, race, ethnicity, insurance status, cancer, malnutrition, ED admission, ICU admission, and body mass index. The reference was the 4-OLE group.

[b] Intralipid (Baxter Inc).

[c] Presented as incident rate ratio (95% CI).

[d] Presented as odds ratio (95% CI).

analysis was performed at a single academic institution, potentially limiting widespread generalizability to other populations. Although we adjusted for all factors we had available in the data set, it is also possible that there were other unmeasured clinical or process changes made at this institution during the same time frame that could have confounding effects, an inherent limitation to the cohort study design. However, given the paucity of literature regarding 4-OLE use in the pediatric population, the results of this study provide urgently needed evidence of its utility and association with clinical benefit in the pediatric population.

## Conclusions

In this observational cohort study of pediatric patients receiving PN, we found that use of soybean-sparing LE was associated with decreased LOS in ICU and non-ICU patients. The use of soybean oil–sparing strategies for LE support in pediatric and adult patients receiving PN has been advocated, with essentially no available clinical evidence to support this change in nonneonatal pediatric patients. The results of our study are the first we know of to demonstrate the successful implementation of 4-OLE use in a pediatric population within a large institution. Our data are also the first we know of to show switching to a 4-OLE was associated with reduced hospital LOS and lower rates of UTIs in a pediatric population. The findings in this study suggest that 4-OLE use is associated with higher efficacy, is safe, and may improve clinical outcomes among pediatric patients requiring PN.

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**SUPPLEMENT.**
**Data Sharing Statement**