Incidence and Development of Cholestasis in Surgical Neonates Receiving a Mixed-Oil Lipid Emulsion

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Alexis Potemkin Hurley, RN, BSN; Duy T. Dao, MD, MPH; Scott C. Fligor, MD; Bennet S. Cho, MD; Savas T. Tsikis, MD; Kathleen M. Gura, PharmD, RPh; and Mark Puder, MD, PhD

Boston Children’s Hospital, Boston, MA

†These authors contributed equally to this work.
Disclosures

• No commercial relationships to disclose

• Co-authors Dr. KM Gura and Dr. M Puder are consultants for *Fresenius Kabi* and receive royalties
Parenteral Nutrition (PN)
Intestinal Failure-Associated Liver Disease (IFALD)
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85%

27%
Intestinal Failure-Associated Liver Disease (IFALD)

Surgical neonates on PN are at high risk for IFALD$^1$

Oley2022 "Alive, Well, and Even Better!"
Other risk factors include infection/sepsis\textsuperscript{2,3}, prematurity\textsuperscript{4-6}/low birth weight\textsuperscript{7}
Intestinal Failure-Associated Liver Disease (IFALD)

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Intestinal Failure-Associated Liver Disease (IFALD)

Other risk factors include infection/sepsis\(^2,3\), prematurity\(^4-6\)/low birth weight\(^7\)
Intravenous Lipid Emulsions (ILE)

Historically, the only FDA-approved initial ILE in children was soy oil-based lipid emulsion (SO-ILE)
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Historically, the only FDA-approved initial ILE in children was soy oil-based lipid emulsion (SO-ILE)

- SO-ILE may contribute to pathogenesis and exacerbation of IFALD\(^8,9\)

Omega-6 FAs

Phytosterols

\(^{8,9}\)
Intravenous Lipid Emulsions (ILE)

Fish oil lipid emulsion (FOLE) is for treatment but not for prevention (not used as initial ILE)\(^8,10-12\)
Intravenous Lipid Emulsions (ILE)

Fish oil lipid emulsion (FOLE) is for treatment but not for prevention (not used as initial ILE)\(^8,10-12\)

Omega-3 FAs

- Linolenic acid
- Eicosapentaenoic acid (EPA)
- Docosahexaenoic acid (DHA)
Intravenous Lipid Emulsions (ILE)

Soy, MCT, olive, fish oil-based ILE is used for potential hepatoprotection
Intravenous Lipid Emulsions (ILE)

Soy, MCT, olive, fish oil-based ILE is used for potential hepatoprotection

- Soybean Oil: 30%
- MCT: 30%
- Olive Oil: 25%
- Fish Oil: 15%
Components of ILE

• Components of ILE contributing to cholestasis includes pro-inflammatory n-6 fatty acids and phytosterols\textsuperscript{8,9}

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>FA composition, %</strong></td>
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<td></td>
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</tr>
<tr>
<td>LA (n-6)</td>
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<td>4</td>
</tr>
<tr>
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<td>0</td>
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Standard Practice Dosing of ILEs

In patients requiring PN for >14 days, the standard practice dosing of SO-ILE is 1g/kg/d and SO, MCT, OO, FO-ILE is 3g/kg/d

- Lower doses of SO, MCT, OO, FO-ILE may increase risk of EFAD\textsuperscript{17}

- Standard dosing of SO, MCT, OO, FO-ILE provides similar amount of soybean oil as SO-ILE (30% soybean oil in SO, MCT, OO, FO-ILE)
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SO, MCT, OO, FO-ILE

Preterm piglet model of IFALD

- May reduce bile acid-sensitive gram-positive bacteria and prevent cholestasis\textsuperscript{13}
- Reduced total bilirubin, CRP, n-6 fatty acid levels (compared to SO-ILE)\textsuperscript{14,15}
SO, MCT, OO, FO-ILE

Premature piglet model of IFALD

- May reduce bile acid-sensitive gram-positive bacteria and prevent cholestasis\(^\text{13}\)
- Reduced total bilirubin, CRP, n-6 fatty acid levels (compared to SO-ILE)\(^\text{14,15}\)

**IFALD may still develop on SO, MCT, OO, FO-ILE** \(^\text{16}\)
To assess the incidence of cholestasis in gastrointestinal surgical neonates administered SO, MCT, OO, FO-ILE in order to determine whether it may serve as a hepatoprotective ILE
Methods: Study Design and Cohorts

- Single-institution (tertiary care center)
- Study group: SO, MCT, OO, FO-Ile ≥ 14 consecutive days, July 2016 to July 2019
- Control group: SO-Ile ≥ 14 consecutive days, January 2013 to January 2019

IRB-approved retrospective review

Exclusion Criteria

- Excluded (n=28)
  - Unknown prior lipid (n=3)
  - Prior other lipid >7 days (n=18)
  - Receiving >1 lipid (n=7)

Entire Cohort (n=152)
- Includes n=39 with:
  - 1-7 days prior lipid (n=2)
  - ≥ 7 days without lipids (n=10)
  - 1-6 days without lipids (n=27)
Exclusion criteria

- ILE other than SO, MCT, OO, FO-ILE or -SO-ILE at outside institution for >7 days
- Dose/content of PN/ILE at outside institution could not be verified
- Confounding comorbidities
  - Congenital/acquired primary liver pathology (biliary atresia, α1-antitrypsin deficiency, Alagille syndrome, hepatitis)
  - Hepatic congestion
  - Heart failure, congenital heart defects (except isolated PDA)
  - MSOF
  - Cystic fibrosis
  - Medical necrotizing enterocolitis (not requiring surgery)
IRB-approved retrospective review

- Single-institution (tertiary care center)
- Study group: SO, MCT, OO, FO-ILE ≥ 14 consecutive days, July 2016 to July 2019
- Control group: SO-ILE ≥ 14 consecutive days, January 2013 to January 2019

Surgical neonates requiring PN support for ≥ 14 days (n=180)

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Methods: Study Design and Cohorts

Analysis Cohort 1 (n=152)
Includes n=39 with:
• 1-7 days prior lipid (n=2)
• ≥ 7 days without lipids (n=10)
• 1-6 days without lipids (n=27)

Analysis Cohort 2 (n=140)
Includes n=27 with:
• 1-6 days without lipids

Analysis Cohort 3 (n=114):
• No prior lipid
• No days without lipid

SO, MCT, OO, FO-ILE
n=16

SO-IILE
n=136

Excluded (n=1)
1-7 days prior lipid (n=1)
≥7 days without lipids (n=0)

Excluded (n=11)
1-7 days prior lipid (n=1)
≥7 days without lipids (n=10)

SO, MCT, OO, FO-ILE
n=15

SO-IILE
n=125

Excluded (n=5)
1-6 days without lipids (n=5)

Excluded (n=22)
1-6 days without lipids

SO, MCT, OO, FO-ILE
n=10

SO-IILE
n=103

Excluded (n=1)
1-7 days prior lipid (n=1)
≥7 days without lipids (n=0)
Methods: Study Design and Cohorts

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SO, MCT, OO, FO-ILE
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Analysis Cohort 3 (n=114):
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SO, MCT, OO, FO-ILE
n=10

SO-ILE
n=136

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SO-ILE
n=125

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1-6 days without lipids

SO-ILE
n=103

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Methods: Study Design and Cohorts

SO, MCT, OO, FO-ILE  
n=9

Analysis Cohort 4 (n=18)  
(PAIR-MATCHED 1:1)

SO-ILE  
n=9

SO, MCT, OO, FO-ILE  
n=9

Analysis Cohort 5 (n=27)  
(PAIR-MATCHED 1:2)

SO-ILE  
n=18
Methods: Study Design and Cohorts

- **Analysis Cohort 4 (n=18) (PAIR-MATCHED 1:1)**
  - SO, MCT, OO, FO-Ile
  - n=9

- **SO-Ile**
  - n=9

- **Analysis Cohort 5 (n=27) (PAIR-MATCHED 1:2)**
  - SO, MCT, OO, FO-Ile
  - n=9

- **SO-Ile**
  - n=18

- **Baseline Bilirubin**
- **# of available DB measurements**
  - Min. differences in total phytosterols
Methods: Study Design and Cohorts

SO, MCT, OO, FO-Ile
n=9

Analysis Cohort 4 (n=18)
(PAIR-MATCHED 1:1)

SO-Ile
n=9

Analysis Cohort 5 (n=27)
(PAIR-MATCHED 1:2)

SO-Ile
n=18

• Post-menstrual age
• Baseline weight
• Total days follow-up
• % calories from PN
• Diagnosis

➢ Baseline Bilirubin
➢ # of available DB measurements
  • Min. differences in total phytosterols

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Daily data collection (when available):

- Anthropometric measures – weight, length, head circumference
- Nutritional intake -- PN/ILE, enteral nutrition (EN)
- Laboratory data – Direct bilirubin, ALT, triglycerides, triene to tetraene (T:T) ratio
- PN administered – kcal/kg/d
  - Percent calories from PN (calculated)
  - Total phytosterol load (calculated)

Primary Outcome: Cholestasis

- Direct bilirubin ≥ 2 mg/dL
- Study endpoint: 9 weeks observation period
  - Earlier if: Cholestasis w/direct bilirubin normalized or Patient weaned off PN

Secondary Outcomes

- Latency to cholestasis
- Growth
- EFAD (T:T ratio >0.2)
- Transaminitis
- Dyslipidemia
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Primary Outcome: Cholestasis

- Latency to cholestasis
- Growth
- Essential Fatty Acid Deficiency (EFAD) (T:T ratio >0.2)
- Liver inflammation (ALT)
- Dyslipidemia (TG)

Secondary Outcomes
## Results – Assessment of Balance (entire cohort)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>SO-ILE (n=136)</th>
<th>SO, MCT, OO, FO-ILE (n=16)</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>68 (50%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>46 (34%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>NEC</td>
<td>39 (29%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Intestinal atresia</td>
<td>28 (21%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>16 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>10 (7%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Post-menstrual age (weeks), median (range)</td>
<td>34 (24 – 40)</td>
<td>34 (25 – 43)</td>
</tr>
<tr>
<td>Weight-for-age Z score, median (range)</td>
<td>-0.34 (-6.52 – 18.05)</td>
<td>-0.28 (-2.19 – 1.37)</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available on Day 1 (N\textsubscript{SOLE}=126; N\textsubscript{MOLE}=15)</td>
<td>57 (45%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Otherwise, day first available, median (range)</td>
<td>2 (2 – 7)</td>
<td>3 (2 – 7)</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL), median (range)*</td>
<td>0.3 (0.1 – 1.6)</td>
<td>0.4 (0.2 – 3.0)</td>
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<tr>
<td>Percent of calories from PN, median (range)</td>
<td>20.5 (0.5 – 100)</td>
<td>43.7 (0.3 – 100)</td>
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## Results – Assessment of Balance

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<td><strong>Post-baseline</strong></td>
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<tr>
<td>Total days followed, median (range)</td>
<td>32 (14 – 63)</td>
<td>43 (14 – 62)</td>
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<tr>
<td>Total days of lipid, median (range)</td>
<td>28 (12 – 63)</td>
<td>43 (10 – 62)</td>
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<tr>
<td>Total phytosterols (mg/kg), median (range)</td>
<td>342 (96 – 952)</td>
<td>470 (76 – 720)</td>
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<td>Total number of direct bilirubin measurements, median (range)</td>
<td>7 (1 – 25)</td>
<td>8 (2 – 14)</td>
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## Results: Incidence of Cholestasis

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<tr>
<th>GROUP</th>
<th>N</th>
<th>SO-ILE</th>
<th>SO, MCT, OO, FO-ILE</th>
<th>OR (95% CI)</th>
<th>Adj. OR (95% CI)</th>
<th>P</th>
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<tr>
<td>Cohort 1</td>
<td>152</td>
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### Results: Incidence of Cholestasis

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Results: Latency to Cholestasis

Cohort 1 (n=152, 136:16)
SO-ILE: SO, MCT, OO, FO-ILE

Cohort 2 (n=140, 125:15)
SO-ILE: SO, MCT, OO, FO-ILE

Cohort 3 (n=113, 103:10)
SO-ILE: SO, MCT, OO, FO-ILE

Matched 1:1 (n=18, 9:9)
SO-ILE: SO, MCT, OO, FO-ILE

Matched 2:1 (n=27, 18:9)
SO-ILE: SO, MCT, OO, FO-ILE

SO, MCT, OO, FO-ILE
SO-ILE
Results: Latency to Cholestasis

- **Cohort 1** (n=152, 136:16)
  - SO-Ile: SO, MCT, OO, FO-Ile
  - Week of lipid vs. Probability of Cholestasis

- **Cohort 2** (n=140, 125:15)
  - SO-Ile: SO, MCT, OO, FO-Ile
  - Week of lipid vs. Probability of Cholestasis

- **Cohort 3** (n=113, 103:10)
  - SO-Ile: SO, MCT, OO, FO-Ile
  - Week of lipid vs. Probability of Cholestasis

**Matched Groups**
- **Matched 1:1** (n=18, 9:9)
  - SO-Ile: SO, MCT, OO, FO-Ile
  - Week of lipid vs. Probability of Cholestasis

- **Matched 2:1** (n=27, 18:9)
  - SO-Ile: SO, MCT, OO, FO-Ile
  - Week of lipid vs. Probability of Cholestasis

**Graph Key**
- Black line: SO, MCT, OO, FO-Ile
- Gray line: SO-Ile
Results – Anthropometric Data (Weight)

SO, MCT, OO, FO-ILE is associated with slightly higher weight-for-age Z-scores compared to SO-ILE (not statistically significant)
Results – Anthropometric Data (Length)

SO, MCT, OO, FO-ILE is associated with slightly higher length-for-age Z-scores compared to SO-ILE (not statistically significant)
Results – Anthropometric Data (Head Circumference)

SO, MCT, OO, FO-IILE is associated with slightly higher head circumference-for-age Z-scores compared to SO-IILE (not statistically significant)
Results – T:T Ratio

T:T ratios were comparable in all cohorts. No subject developed EFAD.
Results -- ALT
SO, MCT, OO, FO-Ile is associated with higher ALT levels

Cohort 1 (n=92)

Cohort 2 (n=89)

Cohort 3 (n=76)

Matched 1:1 (n=10)

Matched 2:1 (n=17)

SO, MCT, OO, FO-Ile
SO-Ile

P=0.03
P=0.04
P=0.002
P=0.002
P=0.005

SO, MCT, OO, FO-Ile
SO-Ile

Oley2022 “Alive, Well, and Even Better!”
Results -- Triglycerides
SO, MCT, OO, FO-IHE is associated with higher triglyceride levels
Results -- Triglycerides

SO, MCT, OO, FO-ILE is associated with higher triglyceride levels

Cohort 1 (n=113)

Cohort 2 (n=107)

Cohort 3 (n=90)

Matched 1:1 (n=17)

Matched 2:1 (n=24)

SO, MCT, OO, FO-ILE

SO-ILE

P=0.22

P=0.20

P=0.002

P=0.01

P=0.007

SO, MCT, OO, FO-ILE

SO-ILE

SO, MCT, OO, FO-ILE

SO-ILE

SO, MCT, OO, FO-ILE

SO-ILE

SO, MCT, OO, FO-ILE

SO-ILE

Oley2022 “Alive, Well, and Even Better!”
Key Findings and Conclusions

SO, MCT, OO, FO-ILE in the neonatal gastrointestinal surgical population does not reduce the incidence of IFALD compared to SO-ILE
Key Findings and Conclusions

SO, MCT, OO, FO-IIE in the neonatal gastrointestinal surgical population does not reduce the incidence of IFALD compared to SO-IIE

Latency to cholestasis is shorter in patients on SO, MCT, OO, FO-IIE
Key Findings and Conclusions

SO, MCT, OO, FO-ILE in the neonatal gastrointestinal surgical population does not reduce the incidence of IFALD compared to SO-ILE

Latency to cholestasis is shorter in patients on SO, MCT, OO, FO-ILE

SO, MCT, OO, FO-ILE is associated with slightly higher weight-, length-, and head circumference-for-age Z-scores compared to SO-ILE
Key Findings and Conclusions

- **SO, MCT, OO, FO-IKE in the neonatal gastrointestinal surgical population does not reduce the incidence of IFALD compared to SO-IKE**

  - Latency to cholestasis is shorter in patients on SO, MCT, OO, FO-IKE

- **SO, MCT, OO, FO-IKE is associated with slightly higher weight-, length-, and head circumference-for-age Z-scores compared to SO-IKE**

  - Analysis did not reach statistical significance
Key Findings and Conclusions

SO, MCT, OO, FO-Ile in the neonatal gastrointestinal surgical population does not reduce the incidence of IFALD compared to SO-Ile

Latency to cholestasis is shorter in patients on SO, MCT, OO, FO-Ile

SO, MCT, OO, FO-Ile is associated with slightly higher weight-, length-, and head circumference-for-age Z-scores compared to SO-Ile

Analysis did not reach statistical significance

After adjusting for number of PN days, total phytosterols administered in SO, MCT, OO, FO-Ile patients were higher than in SO-Ile patients
Limitations

**Retrospective review design**
- Limited information on patients prior to transfer from outside institutions

**Small study population**

**Additional clinical factors not analyzed**
- Reasons for PN disruption
- Co-administration of antibiotics
- Number and timing of line exchanges
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GI surgical neonates are a high risk population for developing IFALD.

SO, MCT, OO, FO-ILO may not be hepatoprotective in this population.
**Significance and Implications for Clinical Care**

- **GI surgical neonates are a high risk population for developing IFALD**

- **SO, MCT, OO, FO-ILE may not be hepatoprotective in this population**

- **Regardless of ILE administration, this population should be closely monitored for development of IFALD**
Significance and Implications for Clinical Care

- GI surgical neonates are a high risk population for developing IFALD
- SO, MCT, OO, FO-ILE may not be hepatoprotective in this population
- Regardless of ILE administration, this population should be closely monitored for development of IFALD
- Further research to develop novel hepatoprotective ILE for use in this population is imperative
Acknowledgements

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The Rappaport Fellowship of the Boston Children’s Hospital Department of Surgery
Boston Children’s Hospital Surgical Foundation
National Institutes of Health grants 5T32HL007734, 2T32DK007754
Howard Hughes Medical Institute
References


Incidence and Development of Cholestasis in Surgical Neonates Receiving a Soy, MCT, Olive, Fish Oil-Based ILE

Lumeng Jenny Yu, MD†; Research Fellow

Lorenzo Anez-Bustillos, MD, MPH†; Paul D. Mitchell, MSc; Victoria H. Ko, MD; Jordan D. Secor, MD, MSc; Alexia Potemkin Hurley, RN, BSN; Duy T. Dao, MD, MPH; Scott C. Fligor, MD; Bennet S. Cho, MD; Savas T. Tsikis, MD; Kathleen M. Gura, PharmD, RPh; and Mark Puder, MD, PhD

Boston Children’s Hospital, Boston, MA

†These authors contributed equally to this work.