FRESENIUS KABI
caring for life

Webinar: June 10, 2020

# Angling for a Better Understanding of Omega-3 Fatty Acids in Parenteral Nutrition

Watch the full webinar at www.freseniuskabinutrition.com/resources.

## Q&A With the Experts

The views and opinions expressed by the Experts during this Q&A are solely those of the individual healthcare professionals based on their experiences in the medical field and are not intended to reflect the views or opinions of Fresenius Kabi or to provide clinical practice recommendations.


**Robert Martindale, MD, PhD (Moderator)**

Professor of Surgery, Division of General Surgery, Oregon University



**Mette Berger, MD, PhD**

Associate Professor of Intensive Care Medicine, Burns and Clinical Nutrition Specialist, Lausanne University Hospital, Switzerland



**Maurizio Muscaritoli, MD**

Full Professor of Internal Medicine, Director Internal Medicine and Clinical Nutrition Unit and Home Artificial Nutrition Unit, Department of Translational and Precision Medicine, Sapienza University Rome, Italy



**Martin Rosenthal, MD**

Assistant Professor of Surgery, University of Florida College of Medicine



**Lorenzo Pradelli, MD**

Medical Director, AdRes Health Economics and Outcome Research, Torino, Italy

## Question:

What evidence is there for omega-3 fatty acid containing lipids in patients with septic shock in ARDS, such as those with COVID-19?

## Answers:

**Dr. Martindale:**

We just wrote the guidelines for the SCCM and ASPEN for this and a paper came out yesterday in JPEN reviewing the data of COVID-19 nutrition. We feel strongly that this lipid should be used in this, if nothing else, to prevent inflammation. This is a highly inflamed population, and, in fact, we've got good data, now, showing you we can lower the inflammatory response and enhance resolution. A paper came out day before yesterday on resolution of inflammation in this setting. So I think for COVID-19 patients, it is still going to be beneficial.

**Dr. Berger:**

Well, having seen what I've seen over 20 years, I would think it was silly to go back to non-lipid first and only omega-6 ILEs. Clearly, we need the anti-inflammatory effects in these patients. So avoiding overfeeding and giving the correct lipid emulsions is basics.

**Dr. Muscaritoli:**

I don't have personal data on this aspect; although, we had many cases of COVID-19. But if true that inflammation is in the clinical picture of these patients there is no reason why we should use lipid emulsions other than these, with omega-3 fatty acids. On one side, to try to reduce inflammation and on the other side, to try to promote a more rapid resolution of inflammation. I do not have clinical data, but I completely support the use of the lipid emulsions in these patients in the ICU if parenteral nutrition is needed.

**Dr. Berger:**

There is one thing people are not often thinking about - is that the sedation of the sickest COVID patient requires high doses of propofol. And this means most of the time, LCT, omega-6s. So, there is an option to have MCT/LCT lipid propofol in Propoven 2%, and if you have it, you should use it. But, for sure, you should not increase the omega-6 load. And when we're talking about maximal doses of lipids, don't forget to integrate the dose of propofol you deliver. That's very important.

## Question:

Please share your experience using fish-oil containing ILEs, especially in ICU surgical patients, touching on timing, frequency, dose, and duration that you're using in your ICU and surgical patients.

## Answers:

**Dr. Rosenthal:**

We've got a lot of surgical patients now using these mixed lipid emulsions. You know, our PharmDs and our dietitians are preferentially using the mixed lipid emulsions, basically for what everything that we've talked about. And my patient population is trauma, surgical, sepsis, and we've got a pretty robust elective practice in fish oil management. And one of the cool things with our fish oil management is, it's more of a little bit of an elective population. And we have a lot of good data with immunomodulatory enteral feeds in the elective surgical setting to enhance wound healing and decrease issues in the postoperative period. And now that we have omega-3 fatty acids as a parenteral formula, if we could, you know, start adding maybe even some arginine, we can start developing robust ERAS protocols with parenteral nutrition, going forward. And I think you know, in the future, for fish oil management, developing these types of protocols is going to be paramount for better delivery of nutrients and better care for our patients.

**Dr. Berger:**

For many years now, we have no more parenteral nutrition without lipid emulsions including omega-3s. And we even go, in some surgical patients, the very inflammatory ones, totally over to pure omega. So we really use it as a drug; although, you respect the doses. But for us, it's a component of the therapy. We need the two right hands of the surgeon and then we need to do good things afterwards to help the patient resolve inflammation.

**Dr. Martindale:**

I don't do trauma surgeries much anymore, but certainly, we use these in our transplant people - use them routinely. So pretty much, this is our only formula. To get a pure soy-based formula you have to have a special situation. So our standard formula for parenteral lipid is this.

**Dr. Berger:**

And, again, you're talking about liver transplant probably. We know that the omega-3s improve the liver function. So even in the most important surgery, these are essential. I've been, just recently, treating patients in liver encephalopathy and treating them with pure omega-3s to get the liver right then, and that works perfectly every time.

**Dr. Martindale:**

For those in U.S., remember, pure omega-3 solutions are only approved by the FDA for pediatrics, so we have to be cautious there. We can use the mixed lipid that's approved for adults.

## Question:

If platelets are lowered or the INR is high when beginning an ILE, would you use omega-3 containing ILEs in your patients?

## Answers:

**Dr. Berger:**

My word was simple. Without hesitation.

**Dr. Muscaritoli:**

As she said, with no hesitation.

**Dr. Martindale:**

I feel the same. In fact, I have an operation this afternoon - a patient with platelets at 34,000, she's getting intravenous lipids right now containing fish oil.

**Dr. Rosenthal:**

Also, it's not only that, but most surgeons, this day and age, are pretty comfortable doing some really big operations on an aspirin. We're giving platelet inhibitors to our patients and still doing hernia operations, gall bladders, appendectomies. You know, some of the bigger ones, a liver transplant – probably should hold the aspirin.

**Dr. Martindale:**

Yeah, I think this fits very well with the paper published in 2009 by Watson. You know, that paper was a very nice paper where they looked at patients on antiplatelet drugs like Clopidogrel, aspirin, and showed no abnormalities in their bleeding in those populations. So I think we've got good data in this area with plenty of patients showing that exposure.

## Question:

Can you provide clarity around the safe use of propofol in COVID-19 patients?

## Answers:

**Dr. Berger:**

We have been surprised at the enormous doses of propofol that are required by our COVID-19 patients on mechanical ventilation. We were lucky because the majority of them were fed enterally and we have a solution, which is high protein and low fat. So by doing that, the propofol was not too much trouble. I'm just exploring the data just now. But in those few patients where we needed parenteral nutrition, we, of course, used those containing omega-3s, so no problem. And that is, of course, then a worry, and you have to monitor your triglycerides. And what you can do then is to shift the propofol solution from a pure LCT solution to an MCT containing solution.

**Dr. Muscaritoli:**

Just to add something about propofol, which is a real issue because of it's content of omega-3 fatty acids. It represents a significant source of calories and in these patients you may risk overfeeding, which is probably something we want to avoid in critically ill patients. We're talking about very low intake of calories and other substrates, particularly in the first phases of a critical illness. And so this should never be overlooked because a lot of calories are administered in the form of propofol in those patients requiring high doses of propofol. So this should be included in the total calorie count in these patients, in order to avoid the risk of overfeeding.

**Dr. Berger:**

It represents four to five hundred calories a day. And this reduces the space for proteins, so one has to really integrate those in the total calorie count.

**Dr. Rosenthal:**

The biggest thing is to add it to your daily calories. But, you know, one of the things that we saw was when Puerto Rico got hit with a hurricane. They're a huge producer of propofol for us, and we actually had a propofol shortage, and exploring other options for sedation using ketamine, Precedex, you know—you don't really want to go with benzos anymore because it's been shown to heighten delirium. But, you know, ketamine and Precedex are really good medications, so if you do find yourself overfeeding somebody and they're on propofol, you can always reduce the propofol concentration and just go offhand with a different sedative. So, there's tricks and trades.

## Question:

With respect to propofol, have you altered your triglyceride levels or thresholds to stop or change your therapy with the COVID-19 patients?

## Answers:

**Dr. Martindale:**

We have not. Mette, have you changed yours?

**Dr. Berger:**

No, for sure, not. I mean, these levels have been set by the American Heart Association and other associations. We should be cautious if they rise, so we really do need to monitor. And, Maurizio, you said we should check for our triglycerides when we start patients on PN, but it's true to propofol, as well. So when we start sedation, we should make a basal level of triglycerides and then follow up at least once a week - I would recommend twice weekly - to see how it works. And the amounts of lipids we have in the parenteral nutrition are not the problem. The problem is the lipids from propofol. And we have published papers showing that it's really proportionate to the propofol dose, so this must be monitored, clearly.

**Dr. Martindale:**

I think it's important. Because, remember, a subset of those COVID-19 ICU patients will have hypertriglyceridemia associated with that rapid onset. It seems to be the ones who come in respiratory distress and rapidly get intubated, rapidly moved to the ICU, and either on prone positioning in ECMO, those seem to be the ones we see hypertriglyceridemia in, and I think we have to be really be careful with that population.

**Dr. Rosenthal:**

Another added clinical picture to worry about is some of these COVID-19 patients come in with biliary pancreatitis, and if you're not checking levels and you end up having really high triglycerides, you're going to be kind of rearing up that flame in the retroperitoneum and worsening their pancreatitis. So it's super important that we take everything into context.

## Question:

Dr. Pradelli, when can we expect to see U.S. data for the omega-3 PN hospitalized patients?

## Answers:

**Dr. Pradelli:**

Well, as I said, the paper was submitted, so it depends on the timelines of the journal. So it does not depend on us anymore. We are expecting it in a couple of months to be published.

**Dr. Martindale:**

I know you don't want to spoil the press release, but was the data pretty good and consistent with the European data and Chinese data?

**Dr. Pradelli:**

They are. Yes, they are.

**Dr. Martindale:**

Good to hear. I know that, for us, we've got a bunch of medical students collecting data, now, and we found it costs just about $4 per day to change over from soy-based, and it really is an insignificant increase in total cost. Remember, an ICU bed in the United States costs about $3,000 a day, and so that's insignificant when you're saving ICU days. There's multiple papers, as you know - and showed us - the multiple papers - they get people out of the ICU faster, less sepsis days, less ICU days, less total hospital days - more than pays for itself in that setting.

**Dr. Pradelli:**

Yes, that's actually the point. The enhanced recovery permits us to avoid other costs that are not PN-related, which largely offset the excess in cost of the omega-3s. This is what we have seen in almost all settings.

## Question:

If your patients are on enteral or PO post-surgical, would you recommend them taking omega-3 supplements?

## Answers:

**Dr. Berger:**

Well, the modern enteral nutrition solutions include blends of the different fatty acids, and they should do. But actually, in which patients would I give additional omega-3s? It would be those coming in with hypertriglyceridemia because omega-3 is the treatment of hypertriglyceridemia. So if a patient was coming in with that, on enteral nutrition - it has happened that I have been delivering additional omega-3s, yes. But it's not the rule, and it's especially in the patients on parenteral.

**Dr. Martindale:**

I found that the enteral products - if they're getting full dose enteral products - the problem I find is that many times these really sick people will give only 20, 30 cc's a day and then we're not giving adequate. So then we have to discuss supplemental parenteral, and, of course, omega-3s, intravenous would be part of that. But, in general they're getting full enteral feeding with the fish-oil containing formula, we don't add anything extra.

**Dr. Muscaritoli:**

In the future, companies should develop a new product for enteral nutrition with a better ratio between omega-6 and omega-3. In most, if not in all the available enteral formulas, the ratio is still quite high, and it should be a little bit reduced either by reducing omega-6 or increasing omega-3 fatty acids. But I think this is the trend that will be followed in the next year.

**Question:**

Do you have any stability data for home patients?

**Answer:**

It will be forthcoming. The current data that is available for soybean-based oils is a visual test. And we're actually looking at some PFAT5 data. So stay tuned and definitely reach out to our medical affairs if you have any questions or need any other information.

**Question:**

Will a recording be shared post webinar?

**Answer:**

The full recorded webinar is currently available at www.freseniuskabinutrition.com.

**Question:**

Will these slides be available for print?

**Answer:**

Not at this time.

**Question:**

Can you point me to the JPEN article you were speaking of related to COVID?

**Answer:**

Early nutrition supplementation https://www.sciencedirect.com/science/article/pii/S0899900720301180 and ASPEN recommendations https://onlinelibrary.wiley.com/doi/full/10.1002/jpen.1930

**Question:**

Do you have any data for using omega-3 lipids in neonatal premature patients?

**Answer:**

Please reach out to our medical science liaisons or medical affairs team at (800) 551-7176 (option 4) or via email at nutrition.medinfo.USA@fresenius-kabi.com.

**Question:**

Any noted issues with implementation of SMOFlipid with interactions with other medications run via the central line?

**Answer:**

Please reach out to our medical science liaisons or medical affairs team at (800) 551-7176 (option 4) or via email at nutrition.medinfo.USA@fresenius-kabi.com.

**Question:**

If the use of omega 3 is beneficial intravenously, do you also supplement your non-PN surgical patients either enterally or orally? If no why not? If yes, what dose do you give?

**Answer:**

**Dr. Martindale:**

Yes, I do suggest EPA/DHA oral intake by using one of several commercial formulae for patients getting tube fed. In the outpatient setting we recommend intake of either eating the fish (optimal method) or supplementing with fish oil (EPA/DHA). I recommend at least 2 g per day for anyone with potential inflammatory risk. We routinely give an oral preop supplement containing fish oils for five days before surgery.

**Question:**

It is important to have data about mortality, why do we not have this data?

**Answer:**

**Dr. Martindale:**

Mortality is very difficult to prove in critical care studies as the mortality is between of 15% and 25% in most ICUs nationally. To show mortality changes with a intervention we need sample sizes in the 1000's. No one has those kind of numbers and the cost to do a study like that would be prohibitive. The changes with fish oils are subtle and should be considered as an optimizing agent.

**Question:**

If cost is an issue to restrict usage, who would clearly benefit from this in an ICU setting?

**Answer:**

**Dr. Martindale:**

First of all, the cost difference is literally a few dollars per day, which is obviously trivial in the ICU setting. Two recent studies actually have shown that the use of a mixed intravenous lipid emulsion containing fish oils in the ICU actually decreases ICU length of stay and decreases infections. These benefits more than outweigh the small increase in cost of the mixed IVLE.

**Question:**

Is a TG threshold of up to 400 too high?

**Answer:**

TG levels should also be checked when the ILE dose changes. For adult patients requiring long-term PN therapy (>1 month), TG levels should be obtained once a month. Hypertriglyceridemia (TG > 400 mg/dL) may be related to the ILE infusion rate when it exceeds the ability of lipoprotein lipase to clear TGs from the blood. Other common causes include high doses of lipid-based medication (eg, propofol) hyperglycemia, overfeeding, and inflammation. Cautious initiation of ILE has been recommended when serum TG exceed 200 mg/dL; however, concentrations up to 400 mg/dL are acceptable during PN with routine monitoring during therapy.

**You may watch the full recorded webinar at www.freseniuskabinutrition.com and for any further questions please email nutrition.us@fresenius-kabi.com.**

**SMOFLIPID (lipid injectable emulsion), for intravenous use**

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

**This brief summary does not include all the information needed to use Smoflipid safely and effectively. Please see full prescribing information, including Boxed Warning for Smoflipid (lipid injectable emulsion), for intravenous use at www.smoflipid.com.**

**WARNING: DEATH IN PRETERM INFANTS**

- **Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the medical literature.**
- **Autopsy findings included intravascular fat accumulation in the lungs.**
- **Preterm infants and low-birth-weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion.**

### INDICATIONS AND USAGE

Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Limitations of Use:
The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.

### DOSAGE AND ADMINISTRATION

The recommended daily dosage in adults is 1 to 2 grams/kg per day and should not exceed 2.5 grams/kg per day. Smoflipid 1000 mL is supplied as a Pharmacy Bulk Package for admixing only and is not for direct infusion. Prior to administration, transfer to a separate PN container.

### CONTRAINDICATIONS

Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or excipients.

Severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides > 1,000 mg/dL..

### WARNINGS AND PRECAUTIONS

- Death in Preterm Infants: (see BLACK BOX WARNING)
- Hypersensitivity Reactions: Smoflipid contains soybean oil, fish oil, and egg phospholipids, which may cause hypersensitivity reactions. Cross reactions have been observed between soybean and peanut oil. Signs or symptoms of a hypersensitivity reaction may include: tachypnea, dyspnea, hypoxia, bronchospasm, tachycardia, hypotension, cyanosis, vomiting, nausea, headache, sweating, dizziness, altered mentation, flushing, rash, urticaria, erythema, pyrexia, or chills. If a hypersensitivity reaction occurs, stop infusion of Smoflipid immediately and undertake appropriate treatment and supportive measures.
- Risk of Catheter-Related Infections: Lipid emulsions, such as Smoflipid, can support microbial growth and is an independent risk factor for the development of catheter-related bloodstream infections. The risk of infection is increased in patients with malnutrition-associated immunosuppression, long-term use and poor maintenance of intravenous catheters, or immunosuppressive effects of other concomitant conditions or drugs.
- Fat Overload Syndrome: This is a rare condition that has been reported with intravenous lipid emulsions. A reduced or limited ability to metabolize lipids accompanied by prolonged plasma clearance may result in a syndrome characterized by a sudden deterioration in the patient's condition including fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, fatty liver infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma).
- Refeeding Syndrome: Reintroducing calories and protein to severely undernourished patients with PN may result in the refeeding syndrome, characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop.
- Aluminum Toxicity: Smoflipid contains no more than 25 mcg/L of aluminum. During prolonged PN administration in patients with renal impairment, the aluminum levels in the patient may reach toxic levels. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Patients with renal impairment, including preterm infants, who receive parenteral intakes of aluminum at greater than 4 to 5 mcg/kg/day can accumulate aluminum to levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of PN products.
- Risk of Parenteral Nutrition-Associated Liver Disease (PNALD): PNALD has been reported in patients who receive PN for extended periods of time, especially preterm infants, and can present as cholestasis or steatohepatitis. The exact etiology is unknown and is likely multifactorial. Intravenously administered phytosterols (plant sterols) contained in plant-derived lipid formulations have been associated with development of PNALD, although a causal relationship has not been established. If Smoflipid-treated patients develop liver test abnormalities, consider discontinuation or dose reduction.
- Hypertriglyceridemia: Impaired lipid metabolism with hypertriglyceridemia may occur in conditions such as inherited lipid disorders, obesity, diabetes mellitus, and metabolic syndrome.
- Monitoring/Laboratory Tests: Routinely monitor serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, blood count including platelets, and coagulation parameters throughout treatment. Monitoring patients for signs and symptoms of essential fatty acid deficiency (EFAD) is recommended.
- Interference with Laboratory Tests: Content of vitamin K may counteract anticoagulant activity. The lipids contained in this emulsion may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase [LDH], bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream.

### ADVERSE REACTIONS

Most common adverse drug reactions >1% of patients who received Smoflipid from clinical trials were nausea, vomiting, hyperglycemia, flatulence, pyrexia, abdominal pain, increased blood triglycerides, hypertension, sepsis, dyspepsia, urinary tract infection, anemia and device-related infection.

Less common adverse reactions in ≤ 1% of patients who received Smoflipid were dyspnea, leukocytosis, diarrhea, pneumonia, cholestasis, dysgeusia, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, increased C-reactive protein, tachycardia, liver function test abnormalities, headache, pruritis, dizziness, rash and thrombophlebitis.

The following adverse reactions have been identified during post-approval use of Smoflipid in countries where it is registered. Infections and Infestations: infection. Respiratory, Thoracic and Mediastinal Disorders: dyspnea.

**To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, at 1-800-551-7176, option 5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### DRUG INTERACTIONS

Coumarin and Coumarin Derivatives, Including Warfarin: Anticoagulant activity may be counteracted; monitor laboratory parameters.

### USE IN SPECIFIC POPULATIONS

- Pregnancy and Lactation: There are no available data on risks associated with SMOFlipid when used in pregnant or lactating women.
- Pediatric Use: The safety and effectiveness of Smoflipid have not been established in pediatric patients.
- Hepatic Impairment: Parenteral nutrition should be used with caution in patients with hepatic impairment. Hepatobiliary disorders are known to develop in some patients without preexisting liver disease who receive PN, including cholestasis, hepatic steatosis, fibrosis and cirrhosis (PN associated liver disease), possibly leading to hepatic failure.

### OVERDOSE

In the event of an overdose, fat overload syndrome may occur. Stop the Smoflipid infusion until triglyceride levels have normalized. The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from serum.

FRESENIUS KABI
caring for life

Fresenius Kabi USA, LLC
Three Corporate Drive,
Lake Zurich, IL 60047
Phone: 1.888.386.1300
www.fresenius-kabi.com/us