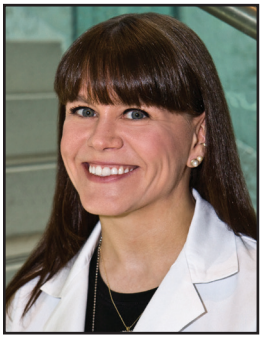
Carol Rees Parrish, M.S., R.D., Series Editor

Essential Fatty Acid Deficiency



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Essential fatty acid deficiency (EFAD) may occur in both the inpatient and outpatient setting. Patients with malabsorptive disorders as a result of pancreatic insufficiency or massive bowel resection are at risk, and it is important to recognize that other patient populations may develop EFAD. A relatively new risk factor for EFAD is the shortage of intravenous fat emulsions in those requiring parenteral nutrition. This article provides a brief review of the role of essential fats, identifies those at risk, the clinical signs and symptoms associated with EFAD, as well as prevention and treatment recommendations.

INTRODUCTION

Essential fatty acid deficiency (EFAD) is rare in healthy adults and children who consume a varied diet with adequate intake of essential fatty acids, linoleic acid (LA) and alpha-linolenic acid (ALA). Clinicians should be aware of the risk of EFAD in specific populations that may suffer from malabsorption syndromes, or have other reasons that severely limit fat intake, absorption, or metabolism. A recent concerning trend in the United States (US) is the increasing incidence of parenteral nutrition (PN) product shortages, including vitamins and minerals, but also lipid injectable emulsion (ILE, formerly known as intravenous fat emulsion or IVFE).[1] This has led to new populations at risk for EFAD, and clinicians must be aware of these shortages and the risks posed to patients dependent on PN.

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Role of Fats

Fat is an essential component in the diet, whether it part of an oral diet, an enteral nutrition formula, or part of a PN admixture. The human body needs fat stores to cushion organs and provide insulation for temperature regulation. The fat depot can be used for energy during times of starvation, although it is important to recognize that some tissues in the body (brain and red blood cells) rely solely on glucose for energy as fat cannot be metabolized to create glucose. Dietary fat is not only an energy source through oxidation, it is also required to facilitate absorption of fat-soluble vitamins in the small bowel.[2]

Fat has important roles at the cellular level as it is an essential part of cell membranes. The cell membrane is composed of phospholipids, which are sensitive to chemical signaling. Consuming diverse types of fat (e.g., omega-3 fatty acids vs. omega-6 fatty acids) will allow incorporation of different types of fat into the cell membrane, modifying the response to a number of metabolic processes including inflammation,

Table 1. Risk Factors Associated with Essential Fatty Acid Deficiency

- Inflammatory bowel disease
- Massive bowel resection, particularly of the distal jejunum and ileum
- Enterocutaneous fistulas involving the small bowel
- Cystic fibrosis
- Pancreatic insufficiency
- Bariatric surgery (particularly malabsorptive procedures)
- Long-term parenteral nutrition with limited or no intravenous fat emulsion provision
- Intravenous fat emulsion shortage
- Carnitine deficiency
- Extreme oral diet or enteral fat restriction
- Chyle leaks requiring long-term fat-restricted diets
  > 3 weeks if normally nourished
  < if poorly nourished

controlling gene expression in the cell, and cellular protein production. A recent review by Calder provides a more detailed discussion of these processes.[3]

Fats are composed of triglycerides, containing a glycerol backbone with three fatty acids that vary in length and number of double bonds. Fatty acids can be classified based on their length, with short chain fatty acids having 2-4 carbon atoms, medium chain fatty acids having 6-12 carbon atoms, and long-chain fatty acids having 12-24 carbon atoms. Fatty acids are further classified by the number of double bonds: saturated fats - 0, monounsaturated fats - 1, and polyunsaturated fats ≥ 2. Humans generally consume enough fat in the diet to meet all fatty acid requirements; the EFAs are those that cannot be synthesized as humans lack the enzymes required.[2-5]

Fat Digestion, Absorption, and Metabolism

Digestion and absorption is a complex process. Understanding normal digestion and absorption of fat helps to identify risk factors for EFAD in patients with gastrointestinal (GI) diseases. Digestion of fat starts in the mouth with salivary lipase; when food enters the stomach there is exposure to gastric lipase, although this primarily digests medium- and short-chain fatty acids. As chyme is released from the stomach into the duodenum, fat is emulsified by bile, while pancreatic lipase and colipase digests fat into free fatty acids and monoglycerides that are packaged into micelles (~ 200 times smaller than emulsion droplets). The micelles transport the free fatty acids and monogylcerides to the brush border of the distal jejunum and ileum for absorption. Once inside the enterocyte, monoglycerides and fatty acids are resynthesized into triglycerides with cholesterol, fat-soluble vitamins, and phospholipids into chylomicrons. Chylomicrons are transported via the lymphatic system to the liver, adipose, and muscle for additional metabolism and/or storage.[2,4]

Within the cell, fatty acids are metabolized through desaturation and elongation. When considering the essential fatty acids, ALA (an omega-3 fatty acid) is metabolized preferentially over LA (an omega-6 fat); when either fat is not available or limited, oleic acid (an omega-9 fat) is metabolized.[5] Interestingly, most reports of EFAD are of LA deficiency, with little comment of ALA deficiency.

Risk factors for EFAD

When fat intake, digestion, absorption, and/or metabolism are impaired, there is risk of EFAD.

Patients with GI disorders are at high risk for EFAD because of potential impairment of pancreatic enzyme secretion or diseased small bowel preventing normal absorption of fat (see Table 1). Siguel and Lerman evaluated 47 patients with chronic intestinal disease (25 Crohn's disease, 11 with ulcerative colitis, 7 with short bowel syndrome, and 4 with celiac disease) and compared them to 57 healthy controls. Using biochemical measures of EFAD, the authors found that the patients with GI diseases had significantly lower levels of fatty acids and biochemical evidence of EFAD.[6] Jeppesen and colleagues evaluated 112 patients with GI disorders (including Crohn's disease, ulcerative colitis, bowel resection, celiac disease, radiation enteritis, and cholestatic liver disease) by conducting fecal fat analysis and serum levels of LA. The authors found that those with higher degrees of malabsorption had lower LA levels.[7]

Cystic fibrosis (CF) is a risk factor for EFAD. There are approximately 30,000 patients in the U.S. with CF and 70,000 worldwide.[8] Although this is a small number of patients, they may be seen by nutrition support clinicians given the intensive nutritional needs of this population. Pancreatic insufficiency is present in

varying degrees in most patients with CF.[8] Strandvik et al evaluated 110 CF patients taking a normal diet; only 15 had no evidence of pancreatic insufficiency. Presence of EFAD was evaluated using biochemical measures. The authors found that serum concentrations of LA and docosahexaenoic acid were significantly lower in patients who had severe CF transmembrane conductance regulator mutations, suggesting that the deficiency was associated with abnormal EFA metabolism.[9] Patients with other causes of pancreatic insufficiency or impairment are also at risk for EFAD. There is very little reported in the literature on prevalence of EFAD in patients with acute or chronic pancreatitis, but one must consider pancreatitis to be a risk factor if pancreatic insufficiency is present.

There are clinical conditions where fat delivery is restricted. For example, patients dependent on PN who have an allergy to ILE and cannot receive it will be at risk for EFAD. PN-dependent patients with significant hypertriglyceridemia (e.g., triglyceride levels > 400 mg/dL) also have ILE restricted to decrease the risk of pancreatitis. Patients who follow extremely low-fat diets may also be at risk for EFAD, including patients with chyle leaks, who must be maintained on very low fat diets for ≥ 3 weeks.[10-12] A small study of patients undergoing Roux-en-Y gastric bypass versus patients who have undergone adjustable gastric banding showed transient signs of EFAD.[13] Carnitine is important in fat metabolism; deficiency may contribute to development of EFAD.[14] Ahmad and colleagues found that maintenance hemodialysis patients with signs of EFAD showed partial correction with L-carnitine supplementation alone.[15] Shortages of ILE are a relatively new risk for EFAD. The American Society for Parenteral and Enteral Nutrition (ASPEN) has published patient care guidelines in the event of ILE shortage on the ASPEN Website on the Product Shortage page (http://www.nutritioncare.org/public-policy/product-shortages/).[16]

Table 2. Biochemical and Physical Signs and Symptoms of Essential Fatty Acid Deficiency

Biochemical	Physical
• Elevated triene:tetraene ratio • Elevated liver function tests • Hyperlipidemia • Thrombocytopenia • Altered platelet aggregation	• Dry, scaly rash • Hair loss • Hair depigmentation • Poor wound healing • Growth restriction in children • Increased susceptibility to infection

Table 3. Soybean Oil Based IVFE vs. New IVFE Products

Lipid Component	Soybean-Oil Based	Smoflipid®	ClinOleic 20%
Soybean oil, %	100	30	20
MCT, %	0	30	0
Olive oil, %	0	25	80
Fish oil, %	0	15	0
Glycerol g/L	22.5	25	22.5
Egg phospholipid, g/L	12	12	1.2
LA, %	50	21.4	18.5
ALA, %	9	2.5	2
EPA, %	0	3	0
DHA, %	0	2	0
AA, %	0	0.15-0.6	0

Abbreviations: MCT, medium chain triglycerides; LA, linoleic acid; ALA, alpha-linoleic acid; EPA, eicosapentaenoic acid; DHA, docosahexaneoic acid; AA, arachidonic acid. Adapted from reference #25

Table 4. Prevention and Treatment of Essential Fatty Acid Deficiency

Prevention	Treatment
• Provide at least 10% of total calories from fat • Provide at least 2%-4% of calories from linoleic acid • Assure adequate provision of carnitine in at-risk patients • Cycle parenteral nutrition • Counsel patients taking an oral diet to increase intake of foods rich in essential fats	• For PN-dependent patients, increase LA delivery from lipid injectable emulsion • Evaluate for carnitine deficiency and treat if deficient • For patients taking an oral diet, encourage vegetable oils, condiments, nuts, and nut butters rich in EFA • Consider lipid injectable emulsion infusion periodically either while inpatient or at an outpatient infusion clinic ➢ Insurance coverage may be difficult to obtain

Clinical Manifestations of EFAD

Patients with EFAD may exhibit both physical and biochemical evidence of deficiency (see Table 2). For patients with known risk factors, clinicians need to monitor for evidence of EFAD.

As stated above, in the absence of adequate ALA and LA, oleic acid is metabolized to mead acid (also known as eicosatrieonic acid [triene]). There is also reduced production of arachidonic acid (also known as eicosatetraenoic acid [tetraene]). An elevated triene:tetraene ratio demonstrates that more mead acid than arachidonic acid is being produced, suggestive of EFAD. A ratio > 0.2 (some suggest > 0.4) is diagnostic of EFAD.[5] An elevated triene:tetraene ratio will manifest before any other signs or symptoms of EFAD.

There are non-specific biochemical changes that should raise suspicion of EFAD in at-risk patients. Richardson and Sgoutas monitored four patients receiving PN and found elevations in serum aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase that paralleled a rise in triene:tetraene ratio with duration of fat-free PN. The authors noted the same pattern with serum triglyceride levels. All improved with the addition of ILE.[17] Alterations in liver function tests have been attributed to mitochondrial dysfunction that occurs with EFAD.[18] Press and colleagues noted that patients with EFAD had altered platelet aggregation.[19]

Physical manifestations of EFAD are often present in the skin. Close examination of the skin may reveal many nutritional deficiencies, including B vitamins, vitamin C, and zinc, as well as EFAD. Much of what is known about the physical manifestations of EFAD come from early case reports in the 1970s and 1980s.[10,17,19-24] Patients who complain of a dry, scaly rash, who also have an underlying disease associated with fat malabsorption, should raise clinical concerns of EFAD and prompt further investigation. It is important to recognize that zinc deficiency can also present as a dry, scaly rash and patients with malabsorption and chronic diarrhea may present with both EFAD and zinc deficiency.

Table 5. Linoleic Acid Content of Selected Vegetable Oils[27]

Oil	Linoleic Acid/Tablespoon
Corn	7.3 g
Sesame	5.6 g
Safflower	10.1 g
Soybean	6.9 g
Sunflower	8.9 g

Prevention of EFAD

Adequate fat provision is the starting point to prevent EFAD. At least 10% of total energy delivery should come from polyunsaturated fat, and 2%-4% of calories from LA. Once high-risk patients are identified, an appropriate nutrition plan can be developed. Patients dependent on PN can develop EFAD in 10 days without

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appropriate fat provision, but most reports are after 4 weeks of fat-free PN.[5] For patients receiving PN with a standard, soybean oil based ILE, the minimum amount of fat to prevent EFAD is 100g (500mL of 20% ILE) per week.[24] ILE products comprised of only soybean oil contain 50% LA.[18] Smoflipid® (Fresenius Kabi, Lake Zurich, IL) is an ILE that contains a blend of soybean oil, medium chain triglycerides, olive oil, and fish oil that was introduced to the US market in 2016. ClinOleic 20% (Baxter Corporation, Mississauga, ON; not available in the U.S.) is a blend of olive oil and soybean oil (see Table 3). With either of the new ILEs, clinicians need to calculate the amount of LA infused to ensure adequate provision of LA.[25] Table 4 summarizes EFAD prevention strategies.

Cycling of PN may also be beneficial to meet fatty acid requirements. Since human adipose tissue is 10% LA, the fat depot may be a significant source of EFAs. When PN is cycled, insulin secretion and lipogenesis are reduced during the time when PN is off or when hypocalorically feeding, allowing for some mobilization of LA from the fat depot;[18,26] adequate fat stores are needed for this to be effective.

With the advent of new ILE products, clinicians may have questions about the ability to use these products to meet EFA requirements. Gramlich and colleagues reported on three obese patients requiring prolonged PN because of complications of GI surgery.[18] All three patients started with standard, soybean oil based ILE, then transitioned to ClinOleic 20% and/or Smoflipid® throughout their prolonged course of PN. All had PN cycled for at least part of their time on PN. Although two of the three patients had mildly elevated mead acid (triene) levels by the end of their PN courses, all had normal triene-tetraene ratios. Patients likely met EFA needs with their ILE, but cycling of PN and their own adipose tissue may have provided some EFAs as well. It will be important for clinicians to report outcomes with these new ILE products in underweight patients with little fat stores.

Treatment of EFAD

If EFAD is identified, the clinician must first consider the cause. For patients taking an oral diet, take a careful diet history and determine adequacy of EFA intake. Counsel patients with known fat malabsorption to consume foods rich in EFAs, including condiments made with oils that have high EFA content (Table 5), such as mayonnaise and margarine made with soybean oil, and spreads such as sunflower seed butter (see Table 5). For those with pancreatic insufficiency, evaluate adequacy of pancreatic enzyme replacement.

For PN-dependent patients, recalculate the fat content of the PN prescription and determine how much LA is being provided. Although 100g soybean oil based ILE per week should be adequate to prevent EFAD, patients may need more to treat pre-existing EFAD. Unfortunately, there are no dosing guidelines to help determine how much more ILE to administer. If the patient is receiving only 4% of calories from LA, the clinician could consider increasing to 6% of calories from LA for a defined period of time (e.g., 2-4 weeks) and then recheck the triene:tetraene ratio. PN-dependent patients may also be at risk for carnitine deficiency and should be evaluated and treated if deficient.

For PN-dependent patients who cannot reliably receive ILE (e.g., patients with severe hypertriglyceridemia), topical oils may be a source of essential fats (Table 6). Use of topical oils to treat EFAD may be worth trying, but clinicians must recognize that this method may not be effective. In some cases, provision of ILE (particularly for those patients who must follow an extremely low fat diet, for example, those with a chyle leak) is the best way to treat EFAD.

Monitoring

There are little data to guide monitoring of EFA status. Standard monitoring practices for long-term PN patients suggest checking a fatty acid panel at least once or twice per year. Clinicians may want to monitor at-risk patients more closely, for example every 3-4 months. Clinicians must maintain a high level of suspicion of EFAD for patients who are at risk and should monitor for physical signs of deficiency that may prompt biochemical evaluation. For patients who require prolonged fat restriction, first conduct a careful physical examination to evaluate for signs or symptoms of EFAD. Check a triene:tetraene ratio if there is concern for EFAD or if the patient is malnourished. If there is no concern for EFAD at the baseline clinical evaluation, check a triene:tetraene ratio after four weeks of extreme fat restriction.

CONCLUSIONS

Although EFAD is rare in the US, there are patient populations at risk for developing this deficiency including malabsorption disorders, those following

Table 6. Topical Oils for Treatment of Essential Fatty Acid Deficiency

POSITIVE REPORTS		
Author, year	**Patient Population**	**Results**
Prottey, et al., 1975[28]	3 patients with SBS and EFAD vs 7 control	Topical sunflower oil applied to the right arm and topical olive oil applied to the left arm (250 mg each) for 15 days; EFAD patients had higher levels of LA in the sunflower seed arm and resolution of scaly lesions; control group had no changes.
Friedman, et al., 1976[29]	2 infants on fat-free PN	Biochemical markers of EFAD corrected with application of topical sunflower seed oil (1400 mg/kg/day).
Skolnik, et al., 1977[23]	19 year old with SBS and IBD (case report)	Resolution of signs and symptoms of EFAD after applying 150 mg LA for 3 weeks, then transitioned to topical safflower oil (dose not provided).
Miller, et al., 1987[30]	5 home PN patients	Phase 1 of trial was four weeks of fat-free PN to induce EFAD; in phase 2, patients were treated with topical safflower oil (3 mg/kg/day) for 4-6 weeks with normalization of triene:tetraene ratio in 4 of 5 patients.
Solanki, et al., 2005[31]	120 neonates randomized to topical safflower oil, coconut oil, or no oil (40 in each group)	Patients received 5 mL of oil massaged into the skin every 6 hours for five days; patients receiving safflower oil had a significant rise in serum LA and AA; coconut oil group had significant rise in total saturated fat.
NEGATIVE REPORTS		
Author, year	**Patient Population**	**Results**
Hunt, et al., 1978[32]	6 study patients, 9 controls	Patients received fat free PN, study patients received 100 mg/kg/day linoleic acid in the form of sunflower seed oil; 5 of 6 had progressive EFAD.
McCarthy, et al., 1983[33]	10 critically ill patients	Patients received fat-free PN; after ~ 7 days, 10 mL corn oil (for a total of 4800 mg linoleic acid) was massaged into the skin daily; all patients experienced a progressive rise in triene:tetraene ratio.
Bougle, et al., 1986[34]	16 infants	Infants were receiving fat-free PN; 10 treated with topical oenethera oil 3 times/day for a total of 1900 mg/kg/day of EFA; 6 infants were untreated. EFAD worsened in both groups over the 20-day study.
Lee, et al., 1993[35]	3 infant pairs receiving fat free PN	3 infants received topical linoleic acid dosed at 1 g/kg/day and 3 did not. All infants developed EFAD rapidly, regardless of use of topical oil, and EFAD resolved with provision of ILE.
Sacks, et al., 1994[36]	40 year old trauma patient (case report)	ILE was contraindicated because of hypertriglyceridemia; topical safflower was applied (3 mg/kg/day) after 3 weeks of fat-free PN, but there was no resolution of EFAD until hypertriglyceridemia resolved and ILE provided.

Abbreviations: SBS, short bowel syndrome; EFAD, essential fatty acid deficiency; LA, linoleic acid; PN, parenteral nutrition; IBD, inflammatory bowel disease; AA, arachidonic acid; ILE, lipid injectable emulsion; table adapted from reference #11

highly fat restrictive diets, PN-dependent patients with restricted fat delivery due to inability to tolerate ILE (e.g., allergy or hypertriglyceridemia), or ILE product shortage. New ILE products coming to the market may reduce the risk of product shortage, and may be tolerated by those patients with adverse reactions to standard ILE products. At risk patients should be monitored closely for signs and symptoms of EFAD as biochemical changes indicative of EFAD will occur before clinical signs and symptoms appear. ■

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