

Perioperative Risks

- Speculation that EPO may increase risk of temporal lobe epilepsy or reduce the seizure threshold in schizophrenic pts taking epileptogenic drugs (e.g., phenothiazines).
- EPO may cause a decrease in blood clotting.

Worry About

- Obstetrics: Oral EPO administration during pregnancy may have an association with a protracted phase of labor, prolonged rupture of membranes, oxytocin augmentation, vacuum extraction, and arrest of descent. One case report exists of transient petechiae and ecchymosis in a newborn after 6.5 g of oral EPO intake by the mother the week before birth.

Overview/Pharmacology

- EPO is a rich source of the essential fatty acids LA and GLA. These essential fatty acids are involved in prostaglandin biosynthetic pathways.

- DGLA, a metabolite of GLA, is a precursor of both the inflammatory prostaglandin series via arachidonic acid (AA), and the less inflammatory series (PGE₁).
- Actions of PGE₁ include anti-inflammatory, immunoregulatory, and vasodilatory properties; inhibition of plt aggregation and cholesterol biosynthesis; hypotension, and elevation of cyclic AMP.
- GLA has been shown to have a favorable effect on the DGLA:AA ratio. The increase in AA is smaller and less consistent when compared with the increase in DGLA. This is beneficial because DGLA leads to the less inflammatory prostaglandin series PGE₁.
- GLA is not normally obtained from the diet. The body relies on the metabolic conversion of LA to GLA. This conversion is rate limiting in the production of GLA. It has been shown that there is a reduced rate of conversion of LA to GLA in several clinical situations, including aging, diabetes, CV disorders and high LDL cholesterol concentrations, high alcohol intake, viral

infections, cancer, nutritional deficits, atopic eczema, and premenstrual syndrome. Dietary supplementation of GLA, via EPO, bypasses the rate-limiting conversion step and has a beneficial effect on the ratio of inflammatory to less inflammatory prostaglandin synthesis.

Drug Class/Mechanism of Action/Usual Dose

- Dose of EPO is specific for each condition being treated; for example, the EPO dose for atopic eczema is 6–8 g for adults or 2–4 g for children. These doses of EPO are based on standardized products containing 8% GLA. EPO may be swallowed directly, mixed with milk or another liquid, or taken with food. The clinical response is usually seen after 3–4 mo of continuous use.

Drug Effects

System	Effect*
CV	Inhibits increase of serum total cholesterol + VLDL + IDL + LDL cholesterol concentrations in the presence of excess cholesterol in the diet. Serves as an antioxidant in hyperlipemic states. Reduces oxidative stress by inhibiting lipid peroxidation and reinforcing the glutathione-dependent antioxidant defense system.
GI	Has antiulcer and cytoprotective effects on experimentally induced gastric lesions.
HEME	Reduces plt aggregation when subject fed an atherogenic diet.
DERM	May be used for Rx of atopic eczema. Treatment of atopic eczema with EPO is controversial. Clinical studies have been equivocal on whether symptoms of atopic eczema benefit from EPO. May be used for the treatment of limited scleroderma, or CREST syndrome. Clinical studies have been equivocal in relation to fatty acid placebos but have shown qualitative improvement in symptoms of Raynaud phenomenon.
GU	Has been used for PMS and to help reduce frequency of nighttime hot flashes during menopause. Treatment is controversial because clinical studies have not shown a clear benefit of EPO for PMS and menopause. Has been shown to be no better than fatty acid placebo or topical NSAIDs for treatment of mastalgia. Has been used by many midwives to hasten cervical ripening in an effort to shorten labor and ↓ incidence of postdate pregnancies. One retrospective study showed that EPO does not shorten gestation or ↓ length of labor. Moreover, it was found that EPO may be associated with above-mentioned adverse effects on labor.
CNS	Significantly reduced headache in women with PMS. Pts given both EPO and fish oil had fewer symptoms associated with headache, such as depression and fatigue. Animal studies suggest EPO may be useful in the treatment of diabetic neuropathy, although the exact physiologic mechanism remains to be demonstrated.
IMMUNE	In pts with mild RA, EPO has been shown to improve morning stiffness, and there was also improvement in the Ritchie articular index for each pt. Pts with severe RA did not exhibit improvement. Although not scientifically proved, EPO has been taken by asthmatics to gain the anti-inflammatory effects of PGE ₁ .

*EPO studies are in a preliminary phase; its effects have been proved only in animal models. The effects mentioned here have yet to be proved in humans.

Key References: Stonemetz D: A review of the clinical efficacy of evening primrose, *Holist Nurs Pract* 22(3):171–174, 2008; Evening primrose. *Natural medicines: pharmacist's letter/prescriber's letter natural medicines comprehensive database*, ed 13, Stockton, CA, 2012, Therapeutic Research Faculty, pp 608–611.

Perioperative Implications

Preoperative Concerns

- EPO may cause increased risk of developing temporal lobe epilepsy, specifically in pts taking known epileptogenic drugs such as phenothiazines. Seizures have not been seen in pts not taking phenothiazines.

- Insufficient evidence regarding its use with other drugs, such as antihypertensive agents or pressors, anticoagulants or antiplatelet agents, nonsteroidal anti-inflammatory drugs, as well as herbs and supplements that might affect plt aggregation.

Preinduction/Induction

- No known interactions

Maintenance

- No known interactions

Postoperative Period

- No known interactions

Fish Oil

Alan David Kaye | Rachel J. Kaye | Orlando J. Salinas

Uses

- Active ingredient for brain and retinal health (more than 40% of brain and retina is structural fat and more than 50% of fat in brain and retina is DHA).
- Decreases arrhythmias and deaths related to coronary artery disease.
- Important component for cell signaling.
- Data from the MIDAS trial indicate that 900 mg of DHA (about 3 g of fish oil) per d in pts with minimal

- cognitive dysfunction restored memory to that of a person 3.5 y younger.
- Data from a trial in non-breastfed infants indicate better IQ by about 16 points in babies who were formula fed with 20 mg of DHA per d compared with those fed formula without DHA.
- While reducing plasma concentrations of triglycerides, also reduces elevated VLDL and chylomicrons and causes slight elevation in HDL; tends to

- reduce risk of death from CAD as well as the risk of stroke.
- Lowers BP (minimal effect).
- Decreases the risk of arrhythmias and MI.
- Beneficial antithrombogenic from EPA (DHA has no ant clotting effect) and anti-inflammatory effects from DHA or EPA

- Management of collagen vascular diseases (lupus, psoriasis, Raynaud phenomenon) and promotion of symptomatic improvement in rheumatic disease.
- May prevent immunologic injury in pts with IgA nephropathy by retarding loss of renal function. May benefit renal transplant recipients treated with cyclosporine. Significant beneficial effects on diabetic nephropathy and macroangiopathy.
- Beneficial in chronic and severe mental disorders (bipolar disorder, depression, ADHD, dementia).
- Reduces inflammatory symptoms associated with inflammatory bowel diseases.
- Other uses: Dysmenorrhea, kidney stones, diabetic neuropathy, gout, migraine headaches, male infertility, osteoporosis, multiple sclerosis, cancer-related cachexia, modest reduction in cataract risks, may improve risk of depression.

Perioperative Risks

- Risks of long-term use not known. Variable increase in bleeding time with EPA (but not with DHA).

Worry About

- Coagulation disorders; >3 g/d can inhibit blood coagulation and potentially reduce platelet aggregation, thus increasing risk of bleeding.

- Large doses of fish oil have been linked to a theoretical increased incidence of cancer via an increase in free radicals and elevated oxidative stress (e.g., prostate cancer). However, it should be noted that another study has demonstrated that omega-3 fatty acids protect against death from prostate cancer.

Overview/Pharmacology

- Omega-3 fatty acids: EPA and DHA.
- Also known as cod liver oil, marine oil, menhaden oil, N-3 fatty acids, N3-polyunsaturated fatty acids, omega 3, omega-3 fatty acids, polyunsaturated fatty acids, salmon oil, W-3 fatty acids, algal DHA.
- Dietary supplements available in capsules or oil by brand names: Coromega, Solgar Omega 3 700, Nature Made, Spring Valley, Bounty, Barleans, LifeFitness DHA, Nature Made DHA, and others.
- Recent research has focused on omega-3 fatty acids and omega-6 fatty acids and their respective ratios, with 1:1 and 4:1 ratios having more omega-6 fats that appear to be beneficial (greater omega-3 fatty acids levels are associated with inflammation-mediated chronic disease).
- Fish oils and DHA supplements are not regarded as drugs and, except for Lovaza, are not regulated by the FDA.

- Have biologic effects on prostaglandins, thromboxanes, and leukotrienes; they increase levels of TXA₂ and decrease levels of TXA₃, thus stimulating formation of prostaglandin I₃, moderately reducing the formation of TXB₂ in platelet, and inhibiting aggregation and adhesion.
- Use results in reduced platelet aggregation (EPA) and vasoconstriction (DHA).
- Recent studies show a small increase in levels of LDL with large doses.
- Improves large artery endothelium-dependent dilation of hypercholesterolemics (both EPA and DHA) without affecting endothelium-independent dilation.
- Reduces blood viscosity by increasing deformability of RBCs.
- Substantial reduction of triglyceride levels; variable effects on cholesterol levels.

Drug Class/Usual Dose

- Not clear: Usual dosage is 2–9 g/d of fish oil or 20 mg per year of life up to age 45 (900 mg), where dose stays constant (DHA).

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GI	Abdominal distention, belching, halitosis, heartburn, flatulence, diarrhea			
HEME	Prolongs bleeding time, inhibits platelet aggregation (EPA only)	Anticoagulant Rx, fatigue, weakness, bleeding problems	Vital signs	Bleeding time, Hct
ENDO	Mild glucose intolerance in pts with NIDDM	FBS		

Key References: Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association Nutrition Committee: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease, *Circulation* 106(21):2747–2757, 2002; Yurko-Mauro K, McCarthy D, Rom D, et al.: Beneficial effects of docosahexaenoic acid on cognitive function in age-related cognitive decline, *Alzheimers Dement* 6(6):456–464, 2010.

Perioperative Implications

Preoperative Concerns

- May reduce blood clotting and increase risk of bleeding (not an effect of DHA alone); pts on 3 g of fish oil per d can be switched to 900 mg of DHA a d with perhaps same antiarrhythmic and brain-function-preserving effects; half-life is variable depending on preparation. Ideally a pt having surgery or a pain procedure should be off fish oil for 7 d, allowing enough time for fish oil–induced blood thinning effects to be gone, but patient should also be switched to DHA at same time.

Induction/Maintenance

- No interactions known.

Adjuvants/Possible Drug Interactions

- Caution if pt is receiving heparin, warfarin, dipyridamole, ticlopidine, sulfapyrazone, or aspirin.
- Can reduce vitamin E levels. Caution with herbals that have antiplatelet and/or anticoagulant constituents (angelica, clove, danshen, garlic, ginger, ginkgo, *Panax* ginseng, red clover, turmeric, willow, and others) with EPA, not DHA.

Anticipated Problems/Concerns

- Assess for possible adverse effects on the coagulation system.
- Rare side effects include abdominal pain with cramps, blurred vision, diarrhea, dizziness, fatigue, headache disorder, nausea.
- Medical-grade fish oil is now available (Lovaza), which reduces indirect risk of mercury polychlorinated biphenyls, dioxin, and dioxin-related compounds, as does DHA from algae (algal DHA).

Garlic (*Allium sativum*)

Amit Prabhakar | Alan David Kaye

Uses

- Administered orally and topically as a powder, oil, tablet, and raw clove. Allicin is the pharmacologically active component.
- Potentially beneficial to the CV system as an anti-hyperlipidemic (conflicting results in recent clinical trials); also useful as an antimicrobial (*Microsporium canis*, sporotrichosis, tinea pedis), antiplatelet (via increased thromboxane levels), fibrinolytic, antioxidant (increased catalase and glutathione peroxidase), antidiabetic, and vasoprotective agent (i.e., antihypertensive and protective of elastic properties of the aorta).
- Note: These indications are not approved by FDA, but garlic is generally recognized as safe. Interpretation of data must take into account publication bias (preferential publication of positive findings).

Perioperative Risks

- Increased bleeding diathesis via inhibition of platelets mediated by COX inhibition.

Worry About

- Major drug interactions: Anticoagulants, antidiabetic agents, ASA, NSAIDs, plt inhibitors, herbs (danshen, dong quai, feverfew, ginger, ginkgo biloba, ginseng, horse chestnut), thrombolytic agents.
- Garlic has dose-dependent side effects, including breath and body odor, possible stimulation of the uterus, GI irritation and heartburn, nausea, vomiting, diarrhea, allergic reactions, dermatitis, and other skin-related pathogenesis.

Overview/Pharmacology

- Intact cells of garlic bulbs contain alliin, an odorless, sulfur-containing amino acid. Crushed garlic causes

the enzyme allinase to convert alliin to alliin—a potent antibacterial agent that is odoriferous and unstable. Ajoene, a self-condensation product of alliin, has antithrombotic activity. Fresh garlic releases alliin in the mouth during the chewing process. Dried garlic preparations lack alliin but contain alliin and allinase; they should be enteric-coated so that they will pass through the stomach into the small intestine, where alliin can be enzymatically converted to alliin. Alliin is unstable in oil. Allinase is inactivated by heat (cooking) and acid.

- Potency can vary substantially among manufacturers.
- Dosage: No clear consensus, but dosage varies with reason for use. Hypercholesterolemia/arteriosclerosis: German Commission E recommends 4 g/d (1.5–2 average-sized garlic cloves) of fresh garlic, or at least 5000 µg of alliin, or chewing one garlic clove daily. Extract standardized to 1.3% alliin is