n-3 Fatty Acids, Inflammation, and Immunity—Relevance to Postsurgical and Critically Ill Patients

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ABSTRACT: Excessive or inappropriate inflammation and immunosuppression are components of the response to surgery, trauma, injury, and infection in some individuals and these can lead, progressively, to sepsis and septic shock. The hyperinflammation is characterized by the production of inflammatory cytokines, arachidonic acid-derived eicosanoids, and other inflammatory mediators, while the immunosuppression is characterized by impairment of antigen presentation and of T helper cell type-1 responses. Long-chain n-3 FA from fish oil decrease the production of inflammatory cytokines and eicosanoids. They act both directly (by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain n-3 FA are potentially useful anti-inflammatory agents and may be of benefit in patients at risk of developing sepsis. As such, an emerging application of n-3 FA is in surgical or critically ill patients where they may be added to parenteral or enteral formulas. Parenteral or enteral nutrition including n-3 FA appears to preserve immune function better than standard formulas and appears to partly prevent some aspects of the inflammatory response. Studies to date are suggestive of clinical benefits from these approaches, especially in postsurgical patients.

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SEPTIC SYNDROMES

The systemic inflammatory response syndrome is the name given to the uncontrolled inflammatory response to insult or injury involving excessive production of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 (1,2). Sepsis has been defined as "the systemic inflammatory response syndrome that occurs during infection" (1). Sepsis is the leading cause of death in critically ill patients in Western countries. Using records from 1995 for state hospitals in the United States it was estimated that there were more than 750,000 cases of sepsis with a 28.6% mortality rate (215,000 deaths) and a total cost of almost US$17 billion (3). Death from septic shock is the result of multiple organ failures and represents the extreme end of a continuum of events of increasing severity and decreasing likelihood of survival (4,5; Fig. 1). The systemic inflammatory response syndrome, sepsis, and septic shock may together be termed as "septic syndromes."

The involvement of inflammatory cytokines in septic syndromes has been long recognized and Vervloet *et al.* (6) wrote "these mediators [i.e., inflammatory cytokines] are largely, if not completely, responsible for the clinical signs and symptoms of the septic response to bacterial infection." In support of this idea, patients with sepsis were found to have markedly elevated circulating concentrations of TNF-α, TNF receptor 1, IL-1β, IL-1 receptor antagonist (IL-1ra), and IL-6, and those patients with the highest concentrations were more likely to die (6–9). In addition, circulating white cells from septic patients exhibited high levels of activated nuclear factor kappa B (NFκB), a transcription factor that promotes the expression of numerous genes associated with inflammation, and again levels of activated NFκB were higher in those patients who went on to die (9). Animal studies also support a role for inflammatory cytokines in the septic response. These studies have often used bacterial endotoxin (also called lipopolysaccharide) as a surrogate for infection, although endotoxin is a fragment of the gram-negative bacterial cell wall

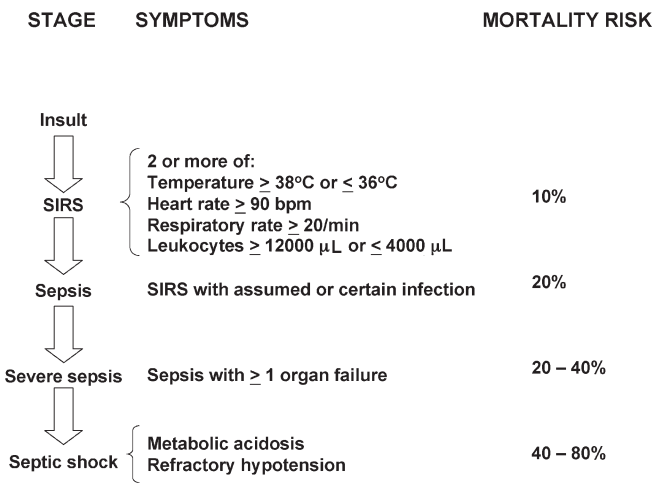

FIG. 1. The progression to septic shock and the risk of mortality at the different stages. bpm, beats per minute; SIRS, systemic inflammatory response syndrome.

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Abbreviations: COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HLA, human leukocyte antigen; IFN, interferon; IκB, inhibitory subunit of nuclear factor kappa B; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; LOX, lipoxygenase; LT, leukotriene; NFκB, nuclear factor kappa B; PG, prostaglandin; SNPs, single nucleotide polymorphisms; Th, T helper; TNF, tumor necrosis factor; TX, thromboxane.

and not a viable organism. Mice injected with endotoxin exhibit high circulating concentrations of TNF-α, IL-1β, IL-6, and IL-8, and survival of these animals can be improved by administering anti-cytokine antibodies (10,11), cytokine receptor antagonists (12), or anti-inflammatory cytokines such as IL-10 (13), or by knocking out the TNF-α receptor (14). Despite this evidence, it is important to note that some studies report that many septic patients do not show detectable or elevated circulating concentrations of TNF-α or IL-1β (15–18). Furthermore, it appears that inflammatory cytokines do play a beneficial role in sepsis. For example, in some animal models, blocking TNF-α increases mortality (19–21), while a TNF-α antagonist increased mortality in a clinical trial (22). Thus, the situation regarding the pathological role of inflammatory cytokines in sepsis is unclear; it may be that a little is beneficial but that excess is harmful and that complete blocking negates the beneficial effects. Another consideration is that there may be large between-individual differences in the generation of inflammatory cytokines, in the sensitivity to the harmful effects of these cytokines, and in the effects of blocking these cytokines. Thus, there may be significant variation in the susceptibility of individuals to exhibit the systemic inflammatory response syndrome and to progress toward septic shock. This may partly relate to the extent and site of the initial injury, partly to the nature and site of the infection, if any, and partly to aspects of the patient's well-being prior to receiving the injury (e.g., nutritional state). It is now recognized that genetics may also play a role. In fact there are likely to be genetic variations in many aspects of the septic response to infection and injury. These most likely relate to adaptations of various population groups to withstand infection and injury in different ecological settings. In the context of this article, genetic variations in the propensity to produce inflammatory cytokines are of relevance. It is now recognized that there are single base variations in genes or in their promoter regions called single nucleotide polymorphisms or SNPs (pronounced "snips").

SNPs have been described for TNF-α, TNF-β, IL-1β, IL-6, IL-10, TNF receptors, IL-1 receptors, IL-1ra, and for many other genes involved in the septic response (23). These SNPs are of functional significance since they partly determine the extent of expression of the gene once it is activated (23). Thus TNF-α production by monocytes in response to endotoxin is higher in individuals who have a G rather than an A at –308 in the TNF-α gene promoter region (24). Intriguingly, TNF-α production is also affected by a polymorphism in the TNF-β gene: TNF-α production by monocytes in response to endotoxin was higher if there was an A at +252 in the TNF-β gene than if there was a G (25). Genotypes affecting TNF-α production appear to be of relevance with respect to sepsis mortality. For example, possession of a G at –308 in the TNF-α gene was found in 39% of patients with septic shock compared with 18% of controls, and among patients with septic shock this polymorphism was significantly more common among patients who died (52% vs. 24% among survivors) (26). In controlling for age, it was identified that, for the same clinical score, patients with a G at –308 of the TNF-α gene had a 3.7-fold higher risk of death than those without a G (26). In another study, patients with sepsis who were homozygous for A at +252 in the TNF-β gene displayed significantly higher plasma TNF-α concentrations than heterozygotes or homozygotes for G, and they showed 88% mortality compared with 37% for heterozygotes and 25% for G homozygotes (27). In a more recent study, postoperative patients who were homozygous for A at +252 in the TNF-β gene had a 1.5-fold higher risk of developing severe complications than heterozygotes (28). Furthermore, among the patients who developed sepsis, those who were homozygous for A at +252 in the TNF-β gene were more likely to die (71 vs. 20% for heterozygotes and 0% for homozygotes for G) (28). These findings raise the possibility of being able to identify patients at high risk of complications and mortality on the basis of genetic polymorphisms.

Although there has been much focus on the potential detrimental role of inflammatory cytokines in sepsis, other mediators including arachidonic acid-derived eicosanoids, reactive oxygen species, nitric oxide, and adhesion molecules are involved in the pathological processes that accompany critical illness. Prostaglandin (PG) E_2 is implicated in sepsis, burns, and critical illness (29,30), while leukotriene (LT) B_4 and oxidants released by neutrophils are involved in acute respiratory distress syndrome [see Kollef and Schuster (31)].

In addition to hyperinflammation, patients with sepsis also display immunosuppression (32–34). There are reports that septic patients have high circulating concentrations of the anti-inflammatory cytokine IL-10 and that these are strongly correlated with mortality (35,36). Note that this is contrary to the predicted effect of IL-10 since this cytokine down-regulates TNF-α production and its early administration is protective in murine endotoxemia (37–39). However, the apparently harmful effect of IL-10 may relate to the timing of its production. Lymphocytes from patients with burns or trauma produce low levels of the T helper (Th) 1-type cytokines [e.g., interferon (IFN)-γ] associated with host defense against bacteria and viruses but high levels of the Th2- and Treg-type cytokines (IL-4, IL-10) associated with inhibition of host defense against bacteria and viruses (33,35). There also appears to be decreased monocyte expression of human leukocyte antigens (HLA) (40–43), the proteins involved in antigen presentation to T cells, and this is associated with impaired ability of monocytes to stimulate T cells (43). Interestingly, IL-10 downregulates both Th1-type cytokine production and HLA expression (44,45), and this might be the origin of the harmful effect of this cytokine in septic patients. Recent studies have revealed impaired proliferative or secretory functions of T cells from patients with sepsis, trauma, or burns (46,47).

The traditional view is that the immunosuppressed phase of septic syndromes lags behind the hyperinflammatory phase (Fig. 2); that is, initially sepsis is characterized by increased generation of inflammatory mediators (the systemic inflammatory response syndrome), but as it persists there is a shift toward an anti-inflammatory, immunosuppressed state sometimes called the compensatory anti-inflammatory response syndrome. However, some recent studies challenge this and

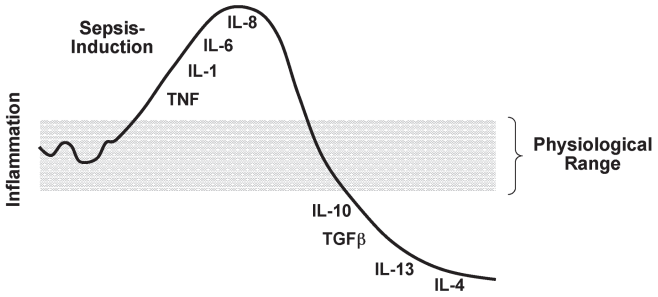

FIG. 2. Hypothetical biphasic immunoinflammatory response to a traumatic insult. IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

suggest that the hyperinflammatory and immunosuppressed states coexist. Some authors report that immunosuppression is present at the onset of sepsis (46,48,49), rather than being a later compensatory response. For example, Tschaikowsky *et al.* (49) identified that significantly decreased monocyte expression of HLA-DR was evident at the onset of severe sepsis in postsurgical patients; in survivors there was some recovery of expression but in nonsurvivors there was a further decrease or even a permanent suppression of HLA-DR expression. These authors identified that the timing of the peak of the systemic inflammatory reaction (identified as the time of maximum C-reactive protein concentration) coincided with the timing of the lowest monocyte expression of HLA-DR. From this they concluded that decreases in monocyte HLA-DR expression occur simultaneously with "signs of hyperinflammation" and as early as the onset of severe sepsis (49).

Thus, it appears that immune cells and cytokines have both detrimental and protective roles in patients as they move through the stages of sepsis. However, the traditional view that hyperinflammation precedes immunosuppression, as shown in Figure 2, may be a simplification of the real situation, and this increases the challenge to finding interventions that might benefit high-risk patients.

POTENTIAL RELEVANCE OF n-6 AND n-3 FA TO IMMUNOINFLAMMATORY RESPONSES

Human immune and inflammatory cells are rich in polyunsaturated FA (PUFA), especially arachidonic acid (20:4n-6) [see Calder (50)]. Classically the influence of PUFA on immunity and inflammation has been viewed as relating to their influence on eicosanoid generation (51–54). Arachidonic acid is the principal substrate for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes giving rise to 2-series PG and thromboxanes (TX) or 5-hydroxyeicosatetraenoic acids (HETE) and 4-series LT, respectively. These mediators have cell- and stimulus-specific sources and frequently have opposing effects (Table 1). For example, PGE_2 is produced mainly by monocytes, macrophages, and, to a lesser extent, neutrophils and inhibits the production of TNF-α and IL-1β [see Miles *et al.* (55) and references therein; 56,57] and IL-12 (57,58), while LTB_4 is produced mainly by neutrophils, other granulocytes, and, to a lesser extent, monocytes and macrophages and increases the production of TNF-α and IL-1β [see Rola-Pleszczynski *et al.* (59) and references therein]. Thus, the overall physiological (or pathophysiological) outcome will depend upon the cells present, the nature of the stimulus, the timing of eicosanoid generation, the concentrations of different eicosanoids generated, and the sensitivity of target cells and tissues to the eicosanoids generated. Recent studies have demonstrated that PGE_2 induces COX-2 in fibroblasts cells and so upregulates its own production (60), induces production of IL-6 by macrophages (60), inhibits 5-LOX and so decreases production of 4-series LT (61), and induces 15-LOX so promoting the formation of lipoxins (61,62) that have been found to have anti-inflammatory effects (63,64). Thus, PGE_2 possesses both pro- and anti-inflammatory actions. PGE_2 also inhibits T-cell proliferation [see Calder *et al.* (65) and references therein] and the production of Th1-type cytokines especially IFN-γ [see Miles *et al.* (66) and references therein; 56].

It is frequently considered that the effects of arachidonic acid are solely related to its role as an eicosanoid precursor. Cell culture studies have shown that arachidonic acid acti-

TABLE 1
Some Immunoinflammatory Effects of PGE_2 and LTB_4[a]

PGE_2	LTB_4
Proinflammation	Proinflammation
Induces fever	Increases vascular permeability
Increases vascular permeability	Enhances local blood flow
Increases vasodilatation	Chemotactic agent for leukocytes
Causes pain	Induces release of lysosomal enzymes
Enhances pain caused by other agents	Induces release of reactive oxygen species by granulocytes
	Increases production of TNF, IL-1, and IL-6
Anti-inflammation	
Inhibits production of TNF and IL-1	
Inhibits 5-LOX	
Induces lipoxin production	
Immunosuppression	
Inhibits production of IL-2 and IFN-γ	
Inhibits lymphocyte proliferation	

[a]PG, prostaglandin; LT, leukotriene; TNF, tumor necrosis factor; IL, interleukin; LOX, lipoxygenase.

vates NFκB in a monocytic cell line (67), and induces TNF-α, IL-1α and IL-1β in osteoblasts (68), IL-6 in macrophages (60) and osteoblasts (69), and COX-2 in fibroblasts (60), and it appears that these effects are exerted directly by arachidonic acid rather than by an eicosanoid metabolite. What is evident from these studies is that arachidonic acid may be able to regulate inflammatory mediator production in its own right and, if so, that it has effects that are sometimes the opposite of those of PGE_2, for example, with respect to TNF-α production.

A series of cell culture-based studies with human endothelial cells has suggested that another n-6 FA, linoleic acid (18:2n-6), may also play a role in inflammation through activation of NFκB and increased production of TNF-α, IL-6, and other inflammatory mediators (70–76).

Increased consumption of long-chain n-3 PUFA, usually as components of fish oil, by humans results in increased amounts of EPA (20:5n-3) and DHA (22:6n-3) in cells involved in immunity and inflammation [see Calder (50)]. The incorporation of these FA from the diet into immune/inflammatory cells of humans is near-maximal within a few weeks (77,78) and occurs in a dose-dependent manner (79). Incorporation of EPA and DHA into human cells is partly at the expense of arachidonic acid [see Calder (50)], and the functional significance of this is that it decreases the amount of arachidonic acid available as a substrate for eicosanoid synthesis. Thus, fish oil supplementation of the human diet has been shown to result in decreased production of PGE_2 (80–83), TXB_2 (82), LTB_4 and 5-HETE (84,85), and LTE_4 (86) by inflammatory cells. However, the mechanism of the effect of long-chain n-3 FA on eicosanoid generation extends beyond simply decreasing the amount of arachidonic acid substrate. For example, EPA competitively inhibits metabolism of arachidonic acid by COX (87–89) and 5-LOX (87,90). *In vitro* studies also report that DHA can inhibit COX activity (91,92) but not that of 5-LOX (90,92). Interestingly, however, both EPA and DHA suppressed cytokine-induction of COX-2 and 5-LOX gene expression in cultured bovine chondrocytes and in human osteoarthritic cartilage explants (93,94). By inhibiting COX and LOX activities and by suppressing the up-regulation of the genes for these enzymes in response to inflammatory stimuli, long-chain n-3 FA act to oppose generation of eicosanoids from arachidonic acid. The final element of the effects of long-chain n-3 FA on eicosanoid production is the ability of EPA to act as a substrate for COX and LOX enzymes, so giving rise to a different family of eicosanoids: the 3-series PG and TX, the 5-series LT, and the hydroxyeicosapentaenoic acids (HEPE). EPA, which appears to be a good substrate for 5-LOX (86,90), is also a substrate for COX enzymes (95,96). Thus, fish oil supplementation of the human diet has been shown to result in increased production of LTB_5, LTE_5, and 5-HEPE by inflammatory cells (84–86), although generation of PGE_3 has been more difficult to demonstrate (97). The functional significance of this is that the mediators formed from EPA are believed to be less potent than those formed from arachidonic acid. For example, LTB_5 is 10- to 100-fold less potent as a neutrophil chemotactic agent than LTB_4 (98,99). Recent studies have compared the effects of PGE_2 and PGE_3 on production of cytokines by cell lines and by human cells. Bagga *et al.* (60) reported that PGE3 was a less potent inducer of COX-2 gene expression in fibroblasts and of IL-6 production by macrophages. PGE_2 and PGE_3 had equivalent inhibitory effects upon production of TNF-α (55,56) and IL-1β (55) by human mononuclear cells stimulated with endotoxin and upon production of IFN-γ production by mononuclear cells stimulated with mitogen (56,66). However, IL-2 production appeared to be less sensitive to PGE_3 than PGE_2 (66).

Studies using the isolated, perfused rabbit lung have identified contrasting effects of arachidonic acid- and EPA-derived eicosanoids. Infusion of *Escherichia coli* hemolysin caused hypertension mediated by TXB_2 and increased vascular leakage mediated by 4-series LT (100). Inclusion of arachidonic acid in the perfusate increased TXB_2 and 4-series LT generation, arterial pressure, and vascular leakage (100,101). In contrast, inclusion of EPA in the perfusate decreased TXB_2 and 4-series LT generation, decreased arterial pressure and vascular leakage, and increased generation of TXB_3 and 5-series LT (100). Perfusion with fish oil attenuated the hypertension induced by calcium ionophore (102). Compared with soybean oil infusion, fish oil decreased the concentration of LTC_4 by 50% and increased the concentration of LTC_5 from barely detectable to very similar to that of LTC_4 (102).

In addition to long-chain n-3 FA modulating the generation of eicosanoids from arachidonic acid and to EPA acting as substrate for the generation of alternative eicosanoids, recent studies have identified a novel group of mediators, termed E-series resolvins, formed from EPA by COX-2 that appear to exert anti-inflammatory actions (103–105). In addition, DHA-derived mediators termed D-series resolvins, docosatrienes, and neuroprotectins also produced by COX-2 have been identified, and these too appear to be anti-inflammatory (106–108). This is an exciting new area of n-3 FA and inflammatory mediators, and the implications for a variety of conditions may be of great importance.

Cell culture studies investigating the direct effects of arachidonic acid on inflammatory mediator production have also investigated effects of long-chain n-3 FA. EPA did not activate NFκB in a monocytic cell line (67), while EPA and DHA inhibited endotoxin-stimulated production of IL-6 and IL-8 by cultured human endothelial cells (109,110). More recent studies showed that EPA did not induce TNF-α, IL-1β, or IL-1α (68) or IL-6 (69) in osteoblasts, and even countered the upregulating effect of arachidonic acid (68); that EPA and DHA could totally abolish cytokine-induced up-regulation of TNF-α, IL-1α, and IL-1β in cultured bovine chondrocytes and in human osteoarthritic cartilage explants (93,94); and that EPA or fish oil inhibited endotoxin-induced TNF-α production by monocytes (111–114). EPA was also less potent than arachidonic acid in inducing COX-2 expression by fibroblasts and IL-6 expression by macrophages (60). EPA prevented NFκB activation by TNF-α in cultured pancreatic cells, an effect that involved decreased degradation of the in-

hibitory subunit of NFκB (IκB), perhaps through decreased phosphorylation (115). Similarly, EPA or fish oil decreased endotoxin-induced activation of NFκB in human monocytes (111,113,114), and this was associated with decreased IκB phosphorylation (113,114), perhaps due to decreased activation of mitogen-activated protein kinases (116). These observations suggest direct effects of long-chain n-3 FA on inflammatory gene expression *via* inhibition of activation of the transcription factor NFκB.

Animal feeding studies with fish oil support the observations made in cell culture with respect to the effects of long-chain n-3 FA on NFκB activation and inflammatory cytokine production. Compared with feeding corn oil, fish oil lowered NFκB activation in endotoxin-activated murine spleen lymphocytes (117). Feeding fish oil to mice decreased *ex vivo* production of TNF-α, IL-1β, and IL-6 by endotoxin-stimulated macrophages and decreased circulating TNF-α, IL-1β, and IL-6 concentrations in mice injected with endotoxin [Sadeghi *et al.* (118) and references therein].

Several studies in humans involving supplementation of the diet with fish oil have demonstrated decreased production of TNF-α, IL-1β, and IL-6 by endotoxin-stimulated monocytes or mononuclear cells (a mixture of lymphocytes and monocytes) (80–82,119). The study of Caughey *et al.* (82) reported a significant inverse correlation between the EPA content of mononuclear cells and the ability of those cells to produce TNF-α and IL-1β in response to endotoxin. Recent studies have confirmed the ability of dietary fish oil to decrease production of TNF-α (120) and IL-6 (120,121) by human mononuclear cells. Furthermore, these studies provide for the first time information on the dose-response relationship between dietary intake of long-chain n-3 FA and production of these cytokines. It should be noted that there are also several studies that fail to show effects of dietary long-chain n-3 FA on production of inflammatory cytokines in humans [see Calder (50) for references]. It is not clear what the reason for this is, but the dose of n-3 FA used and other technical factors are likely to be contributing factors. One other factor that has recently been identified is polymorphisms in genes affecting cytokine production (122). It was found that the effect of dietary fish oil on cytokine production by human mononuclear cells was dependent on the nature of the –308 TNF-α and the +252 TNF-β polymorphisms. This study raises the possibility of being able to identify those who are more likely and those who are less likely to experience specific anti-inflammatory effects of fish oil.

Thus, examination of FA composition and of eicosanoid profiles, cell and tissue culture work, and animal and human feeding studies have revealed a range of anti-inflammatory actions of long-chain n-3 FA (Table 2). These may be of benefit in sepsis, particularly during the "early" hyperinflammatory phase. The benefits of fish oil in animal models of experimental endotoxemia have been clearly demonstrated. For example, dietary fish oil or fish oil infused intravenously significantly enhanced survival of guinea pigs to intraperitoneal endotoxin compared with safflower oil (123,124). Dietary fish oil resulted in a decreased concentration of circulating postendotoxin eicosanoids (PGE_2, TXB_2, 6-keto-$PGF_{1\alpha}$) in rats and in decreased eicosanoid generation by alveolar macrophages (125,126). Furthermore, compared with dietary safflower oil, fish oil resulted in lower circulating TNF-α, IL-1β, and IL-6 concentrations following endotoxin administration to mice (118). Dietary fish oil also appears to decrease sensitivity to inflammatory cytokines (127,128). Fish oil decreased endotoxin-induced metabolic perturbations in guinea pigs and rats (129,130) and improved heart and lung function and decreased lung edema in endotoxic rats (126,131–133) and pigs (134–136).

In addition to effects on production of inflammatory eicosanoids and inflammatory cytokines, long-chain n-3 FA

TABLE 2
Summary of the Anti-inflammatory Effects of Long-Chain n-3 FA

Anti-inflammatory effect	Mechanism(s)[b]
Decreased generation of arachidonic acid-derived eicosanoids (many with inflammatory actions)	Partial replacement of arachidonic acid in cell membrane phospholipids Inhibition of arachidonic acid metabolism by phospholipase A_2, COX, and 5-LOX Decreased induction of COX-2, 5-LOX, and 5-LOX-activating protein
Increased generation of EPA-derived eicosanoids (many with less inflammatory and some with anti-inflammatory actions)	Increased cell membrane phospholipid content of EPA
Increased generation of DHA-derived docosanoids (some with anti-inflammatory actions)	Increased cell membrane phospholipid content of DHA
Decreased generation of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8)	Decreased activation of NFκB (via decreased phosphorylation of IκB) ? Activation of peroxisome proliferation-activated receptor γ* ? Differential effects arachidonic acid vs. EPA ? Differential effects of arachidonic acid- vs. EPA-derived eicosanoids
Decreased expression of adhesion molecules[a]	Decreased activation of NFκB (*via* decreased phosphorylation of IκB) ? Other transcription factors

[a]Not discussed here [see Calder (54)].
[b]COX, cyclooxygenase; NFκB, nuclear factor kappa B; IκB, inhibitory subunit of NFκB.

also exert effects on cell-mediated immunity [see Kinsella *et al.* (51), Calder (52), and Calder *et al.* (137) for reviews]. Large amounts of fish oil in the diet of laboratory animals have been reported to exert immunosuppressive effects [see Kinsella *et al.* (51), Calder (52), and Calder *et al.* (137)]. However, it is the effects of lower amounts of long-chain n-3 FA that are of relevance to the patient setting. Several studies in humans, typically providing long-chain n-3 FA as fish oil, and investigating aspects of cell-mediated immunity have been performed. Phagocytic uptake of *Escherichia coli* appears unaffected by dietary long-chain n-3 FA in humans (138–141). One study reported that fish oil decreased expression of HLA-DP, -DQ, and -DR on human monocytes (142), suggesting impaired ability to present antigen, but there have been no studies attempting to confirm this finding. Meydani *et al.* (81) reported that fish oil providing 2.4 g EPA plus DHA per day decreased T-lymphocyte proliferation in older but not younger women. However, that study also reported increased oxidative stress in the older subjects (143), and it may be that the effect of n-3 FA was due to excessive lipid peroxidation. Several other studies report no effect of various doses of long-chain n-3 FA on lymphocyte proliferation (78,121,140), although there are studies reporting a decrease (144,145). One recent study reported that long-chain n-3 FA caused a dose-dependent increase in proliferation of T cells (83). It is noteworthy that the fish oil used was given in combination with an antioxidant mix. This might be important in terms of preventing excessive lipid peroxidation and so in determining the overall effect of n-3 FA. The study by Meydani *et al.* (81) also reported decreased production of IL-2 in the older women, but this effect has not been confirmed by others in either older (145), young (121,141), or mixed-age (78,140) subjects. A recent study reported a dose-dependent increase in IFN-γ production following n-3 FA supplementation as fish oil (83). That antioxidants were given in combination with fish oil may have been important in generating this finding.

Thus, the effects of long-chain n-3 FA on aspects of cell-mediated immunity are rather unclear, although recent human studies suggest that adverse immune effects are not exerted at modest doses (see previous discussion for references) and that enhanced T-cell responses (proliferation and IFN-γ production) may occur at modest doses so long as antioxidants are also given (83). In terms of sepsis, the true test of immunocompetence occurs when live pathogens are administered. This is a different situation from using endotoxin that is not living and that therefore does not require a robust cell-mediated immune response to eliminate it. As indicated previously, it is clear that long-chain n-3 FA protect against the deleterious effects of endotoxin. However, the situation regarding live pathogens is much less clear. This is because animal studies, frequently using high intakes of n-3 FA, report opposing findings. Infusion of fish oil into rats also receiving low-dose endotoxin decreased the number of viable bacteria in mesenteric lymph nodes and liver (146). Fish oil did not decrease bacterial translocation across the gut, and so the authors concluded that fish oil must have improved bacterial killing. Compared with linoleic acid-rich vegetable oils, fish oil fed to rats before exposure to live bacteria (147,148) resulted in increased survival, which was associated with decreased production of PGE_2. More recently, infusion of fish oil after induction of sepsis by cecal ligation and puncture decreased mortality (and PGE_2 production) compared with vegetable oil (149). Intragastric administration of fish oil into chow-fed rats before cecal ligation and puncture improved survival compared with saline or vegetable oil infusion (150). Compared with vegetable oil feeding to mice, fish oil feeding increased survival to an intramuscular injection of *Klebsiella pneumoniae* (151). The findings from these studies (146–151) contrast with those reporting that fish oil feeding decreases the survival of mice to oral *Salmonella typhimurium* (152) and to intraperitoneal *Listeria monocytogenes* (153), of guinea pigs to *Mycobacterium tuberculosis* (154), and of neonatal rabbits to *Staphylococcus aureus* (155). Thus, animal studies do not provide a clear picture of the effect of high-dose fish oil on ability to survive an infectious challenge. There are few human studies that address exposure to long-chain n-3 FA and infection; most intervention studies performed to date have been too small and of too short duration to monitor infection as an outcome. However, it is worth noting that an epidemic of measles in Greenland triggered by its introduction to a naive population by an infected Danish sailor showed the same characteristics as previous epidemics in other naive populations (156). This suggests that the very n-3 FA-rich diet of the Greenland Inuits did not worsen their response to the virus and this could indicate that these FA do not increase infectious susceptibility in humans.

STUDIES OF LONG-CHAIN n-3 FA IN SURGICAL PATIENTS

Surgery is typically accompanied by an inflammatory response that may be exaggerated in some patients, especially if the surgery is major. If the patient is exposed to pathogenic organisms and is unable to cope with these, then sepsis may develop. Artificial nutrition is frequently used post-surgery and this may involve parenteral (i.e., intravenous) infusions, especially where the gastrointestinal tract is not fully functional (e.g., post-abdominal surgery). Lipids are included in parenteral nutrition to provide an alternative source of calories to glucose and the lipid source used most frequently has been soybean oil, which is rich in the n-6 FA linoleic acid, although it also contains a proportion of α-linolenic acid (18:3n-3). A meta-analysis of total parenteral nutrition suggested that inclusion of lipids might be detrimental ($P = 0.09$ for lipids vs. no lipids) (157), at least in very ill patients. It is not clear why this is, although a number of *in vitro* experiments have shown that soybean oil-based lipid emulsions can exert immunosuppressive effects [see Calder *et al.* (158) for references], which would clearly be detrimental in patients at risk of infection and sepsis. Clinical trials provide conflicting evidence, some showing some immunosuppressive effects (159,160) and others not (161–163), at least in some patient

groups. The concern about potential harm, the view of sepsis as a hyperinflammatory state followed by an immunosuppressed state (Fig. 2), and the idea that n-6 FA might be "proinflammatory and immunosuppressive" has led to the development of alternative lipid emulsions for parenteral applications. Emulsions using a mix of medium-chain triglycerides and soybean oil or based upon olive oil instead of soybean oil have been developed, but these will not be discussed here. However, of relevance to the present discussion is the development of emulsions that include fish oil as a partial replacement for soybean oil. Several such emulsions have been tested in surgical patients.

Intravenous infusion of a lipid emulsion containing fish oil for 5 d into patients who had undergone major abdominal surgery resulted in much higher LTC_5 production by blood leukocytes stimulated *ex vivo* at 6 d postoperation (164). In another study, patients who had undergone abdominal surgery received soybean oil or a mix of medium-chain triglycerides, soybean oil, and fish oil (50:40:10, by vol) for 5 d post surgery (165). Leukocytes from these patients produced more LTB_5 and LTB_5 isomers at postoperative days 6 and 8. Patients who had undergone major gastrointestinal surgery received a medium-chain triglyceride/soybean oil mix (50:50, vol/vol) or a mix of medium-chain triglycerides, soybean oil, and fish oil (50:30:20, by vol) for 5 d postsurgery (166). Patients receiving fish oil got 3 (days 1 and 2) and 6 g (days 3, 4, and 5) of long-chain n-3 FA per day. Neutrophils from these patients produced less LTB_4 and more LTB_5 at postoperative days 6 and 10. Plasma TNF-α concentrations were lower in the fish oil group at day 6, while plasma IL-6 concentrations were lower at day 10. The study did not report clinical outcomes. A more recent study infused a fish oil-rich formula on the day before abdominal surgery and on days 1 to 5 following abdominal surgery (167). On days 4 and 5 the patients also received standard total parenteral nutrition that included 50 g of fat/d (n = 12; n = 11 in the control group). TNF-α production by endotoxin-stimulated whole blood tended to be lower at postoperative day 5 in the fish oil group, but this was not significant. Serum IL-6 concentrations were significantly lower at days 0, 1, and 3 in the fish oil group. Monocyte expression of HLA-DR was preserved in the fish oil group but declined at postsurgery days 3 and 5 in the control group. No differences in infection rates or mortality were observed. However, postoperative stay in intensive care tended to be shorter in the fish oil group (4.1 vs. 9.1 d) as did total hospital stay (17.8 vs. 23.5 days), although neither of these was a significant effect. Postoperative stay on medical wards was significantly shorter in the fish oil group. Another recent study compared the effects of lipid-free total parenteral nutrition or parenteral nutrition including 10% soybean oil or 8.3% soybean oil plus 1.7% fish oil for 5 d after large bowel surgery (168). There were no differences between the groups with respect to the numbers of circulating lymphocytes, B cells, $CD4^+$ cells, $CD8^+$ cells, or natural killer cells before surgery or at days 3 and 6 postsurgery, although these were affected by surgery itself. There were no differences between groups with respect to T-lymphocyte proliferation, but IL-2 production was increased in the fish oil group and the postsurgery decline in IFN-γ production was prevented by fish oil. These studies indicate that inclusion of fish oil in parenteral nutrition regimens for gastrointestinal surgical patients modulates generation of inflammatory eicosanoids (164–166) and cytokines (166,167) and may help to counter the surgery-induced declines in antigen-presenting cell activity (167) and T cell cytokine production (168). Importantly, these studies do not reveal deleterious immunologic effects of fish oil infusion in these patients. Furthermore, the only one of these fairly small studies to have examined hard end points like length of hospital stay suggests some clinical benefit from fish oil infusion in these patients (167). However, larger studies are required to evaluate the effects of this approach on complication rates, hospital stay, and mortality rate. A very recent report from a larger cohort of patients receiving parenteral nutrition postsurgery does indicate benefit of inclusion of fish oil in the regimen (169). Patients received fish oil postoperatively (n = 86) or controls received a 50:50 medium-chain triglyceride-soybean oil mix (n = 110). There were no differences between the two groups with respect to the proportions of patients who died or developed wound infections or with respect to length of hospital stay. However, the proportion of patients who were readmitted to intensive care (5%) was significantly lower in the fish oil than in the control group (17%). A group of patients also received the fish oil-containing emulsion for 2 d preoperatively (n = 53). Here there were a number of very significant benefits. This group showed a significantly decreased need for mechanical ventilation (17 vs. 31% in the control group), a significantly shorter length of hospital stay (22 vs. 29 d), significantly less need for readmission to intensive care (5 vs. 17%), and a significantly lower mortality rate (3 vs. 15%) (169). This study demonstrates a benefit from the inclusion of long-chain-3 FA in parenteral nutrition regimens used in abdominal surgery patients. However, it also demonstrates a much greater benefit if the FA are additionally provided before surgery, which, of course, is only possible in elective surgery. The greater benefit of preoperative infusion of long-chain n-3 FA may relate to better incorporation of the FA into leukocytes and other tissues.

Enteral nutrition is an alternative form of artificial nutrition. It describes provision of nutrients directly into the gastrointestinal tract *via* a tube and is sometimes referred to as "tube feeding." Enteral nutrition is used in patients with a functional gastrointestinal tract and is considered preferable to parenteral nutrition. The influence of enteral feeds including long-chain n-3 FA in their composition has been examined in surgical patients, generally in those who have undergone surgery to remove cancerous regions of the intestine. These studies have frequently used an enteral formula named Impact® (Novartis, Basel, Switzerland), which contains arginine, long-chain n-3 FA, and nucleotides, each of which is lacking from control formulas. Thus, any effects observed cannot be ascribed to a particular component of Impact. The effect of Impact on immunoinflammatory outcomes in surgical

patients has been widely examined. Daly *et al.* (170) reported that Impact results in time-dependent incorporation of EPA into mononuclear cells and that this is associated with a time-dependent decrease in PGE_2 production. Studies have reported that Impact increases phagocytosis by monocytes but not by neutrophils (171,172), increases T-cell proliferation (173) and cell-mediated immunity (172,174), and decreases circulating concentrations of IL-6 (172,175). Several of these studies report significantly improved clinical outcomes related to lower infection rate (170,172,173,175) and decreased length of hospital stay (170,172,175). Studies of Impact and similar enteral formulas investigating clinical outcomes in postsurgical patients have been subject to meta-analyses (176–178), which conclude that this approach to enteral nutrition significantly decreases infectious complications and length of hospital stay in elective surgery patients. It is possible that the modulation of inflammation and the improvements in immune function reported in these patients receiving Impact contribute to the improved clinical outcomes. However, it is not possible to ascribe these benefits to long-chain n-3 FA.

STUDIES OF LONG-CHAIN n-3 FA IN CRITICALLY ILL PATIENTS

Critically ill patients frequently require artificial support, depending upon the extent of organ damage or failure, and this will include nutritional support. The influence of enteral feeds including long-chain n-3 FA has been examined in critically ill patients; again, many of these studies have involved Impact. A study in intensive care unit patients (a mix of trauma, sepsis, and major surgery patients) reported that Impact resulted in higher T-cell proliferation at days 3 and 7 (179), while a study of severe trauma patients reported greater HLA-DR expression at day 7 (180). These studies did not report improvements in clinical outcomes. Studies of Impact and similar enteral formulas investigating clinical outcomes in trauma and critically ill patients have been subject to meta-analysis (176–178). The most recent of these concluded that this approach to enteral nutrition decreases length of hospital stay but has no effect on infectious complications or mortality in critically ill patients (178).

Another trial performed in patients with moderate and severe acute respiratory distress syndrome used an enteral preparation that differed mainly in lipid source from the control (181). The control group of patients (n = 72) received a formula in which the lipid source was 97% corn oil plus 3% soy lecithin. The experimental group (n = 70) received a lipid source that was 32% canola oil, 25% medium-chain triglycerides, 20% borage oil, 20% fish oil, and 3% soy lecithin. The experimental formula also contained more vitamin C and vitamin E than the control and it contained β-carotene, taurine, and carnitine, which the control formula did not. Patients receiving the experimental formula got about 7 g of EPA, 3 g of DHA, 6 g of γ-linolenic acid, 1.1 g of vitamin C, 400 IU of vitamin E, and 6.6 mg of β-carotene per day for 6 d. By 4 d the numbers of total leukocytes and of neutrophils in the alveolar fluid declined significantly in the experimental group and were lower than in the control group. Arterial oxygenation and gas exchange were improved in the experimental group. These patients had a significantly decreased requirement for supplemental oxygen, decreased time on ventilation support (11.0 vs. 16.3 d), and a shorter length of stay in intensive care (12.8 vs. 17.5 d). Total length of hospital stay tended to be shorter in the experimental group (29.6 vs. 34.6 d). Significantly fewer patients in the experimental group developed new organ failure (8 vs. 28%). The mortality rate was 12% in the experimental group and 19% in the control group, but this difference was not statistically significant. More recently, new data from this study have become available (182). Patients receiving the experimental formula had significantly lower concentrations of IL-8 in their alveolar fluid and tended to have lower concentrations of LTB_4 and TNF-α. It is possible that the lower concentrations of LTB_4 and IL-8, both of which are potent leukocyte chemoattractants, may have been responsible for the lower neutrophil infiltration reported in the experimental group, and indeed neutrophil counts were significantly associated with these concentrations (182). This study establishes that the experimental treatment decreases production of inflammatory mediators and infiltration of inflammatory leukocytes and that this can result in significant clinical improvement in extremely ill patients. Because of the many differences in composition between the experimental and control formulas used it is not possible to ascribe the effects and benefits to any particular nutrient. However, the effects on LTB_4, IL-8 and TNF-α concentrations are consistent with effects of long-chain n-3 FA reported elsewhere.

Recently, data from studies using parenteral nutrition with fish oil in sepsis patients have become available (183,184). Patients received a standard soybean oil-based emulsion or an emulsion containing fish oil for 5 (178) or 10 (177) d. Blood leukocyte counts and serum C-reactive protein concentration tended to be lower, and production of LTB_5 by stimulated neutrophils was significantly higher in patients receiving long-chain n-3 FA (177). Production of TNF-α, IL-1β, IL-6, IL-8, and IL-10 by endotoxin-stimulated mononuclear cells did not increase during infusion of the fish oil-containing emulsion whereas production of the four proinflammatory cytokines was markedly elevated during the first 2 d of soybean oil infusion (178). These studies establish that infusion of long-chain n-3 FA into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes. However, the impact of this on hard clinical outcomes in these patients is not yet clear.

In summary, long-chain n-3 PUFA from fish oil decrease the production of inflammatory cytokines and eicosanoids. They act both directly, by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism, and indirectly, by altering the expression of inflammatory genes through effects on transcription factor activation. Thus, long-chain n-3 PUFA are potentially useful anti-inflammatory agents and may be of benefit in patients at risk of developing sepsis. An emerging application of n-3 PUFA is in surgical or

critically ill patients where they may be added to parenteral or enteral formulas. Parenteral or enteral nutrition including n-3 PUFA appears to preserve immune function better than standard formulas and appears to partly prevent some aspects of the inflammatory response. Studies to date are suggestive of clinical benefits from these approaches, especially in post-surgical patients.

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