Role of Arginine and Omega-3 Fatty Acids in Wound Healing and Infection

J. Wesley Alexander[1,2,*] and Dorothy M. Supp[1,2]

[1]Research Department, Shriners Hospitals for Children, Cincinnati, Ohio.
[2]Department of Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio.

J. Wesley Alexander, MD, ScD

Submitted for publication May 16, 2013.
*Correspondence: Research Department, Shriners Hospitals for Children–Cincinnati, 3229 Burnet Ave., Cincinnati, OH 45229-3095 (E-mail: jalexander1@shrinenet.org).

Abbreviations and Acronyms

CLP = cecal ligation and puncture
DHA = docosahexaenoic acid
EPA = eicosapentaenoic acid
HOSF = high oleic acid sunflower oil
ICU = intensive care unit
IGF-1 = insulin-like growth factor I
IL = interleukin
iNOS = inducible nitric oxide synthase
IV = intravenous
KO = knockout
LTB = leukotriene B
MDSC = myeloid derived suppressor cells
NO = nitric oxide
NOS = nitric oxide synthase

(*continued*)

Significance: Only a few decades ago, the primary focus of nutritional supplementation was to prevent deficiencies of essential nutrients. It is now recognized that, at higher than essential levels, selected nutrients can have a pharmacologic effect to prevent or treat disease.
Recent Advances: Two of the most important pharmaconutrients, arginine, and the omega-3 polyunsaturated fatty acids in fish oil, have been shown to have profound effects on wound healing and infections.
Critical Issues: Both arginine and fish oils have independent benefits, but the combination appears to be much more effective. This combination has been shown to affect outcomes involving wound healing and infections, as reviewed here, and can also affect incidence and outcomes in cardiovascular disease, diabetes, organ transplant rejection, and other inflammatory conditions. These possibilities have not yet progressed to widespread clinical application.
Future Directions: The optimal combinations of immunonutrients, timing of administration, and the doses needed for best results need to be determined in preclinical and clinical studies. Also, the mechanisms involved in the administration of pharmaconutrients need to be established.

SCOPE AND SIGNIFICANCE

This review examines the effects of arginine and omega-3 fatty acids in fish oil on wound healing and the development of wound infections. The amount of data available in the literature is expansive, but this review will focus on the potential impact on clinical care. In particular, we wish to emphasize the potential benefit of a safe, easily-applied and effective treatment that could potentially save billions of healthcare dollars on a yearly basis.

TRANSLATIONAL RELEVANCE

Animal studies on the use of arginine and fish oil, as well as other amino acids, such as ornithine, glutamine or citrulline, and other lipids, such as oleic acid, are needed to instruct the conditions for clinical studies.

CLINICAL RELEVANCE

Immunonutrients may have clinical relevance in treatment or prevention of wound complications, including poor healing and the development of hypertrophic scars, as well as decreasing wound infections by more than 50%, which could have profound benefits for improving quality of life.

DISCUSSION

Arginine and wound healing

L-Arginine (referred to hereafter simply as arginine) is a conditionally indispensable amino acid that is a component of the urea cycle and is

ADVANCES IN WOUND CARE, VOLUME 3, NUMBER 11

DOI: 10.1089/wound.2013.0469

readily intraconverted to citrulline, ornithine, and agmatine.[1] Arginine is synthesized in healthy humans but additional arginine is needed for young growing animals and after injury, including burns and certain diseases.[1] Each gram of dietary protein supplies about 54 mg of arginine, but this can vary greatly with food type and arginine can be destroyed by cooking. Thus, ~4–5 g of arginine is ingested by adults consuming an average diet in the United States. About 2 g arginine/day is synthesized by the kidney from citrulline.[2] Highly reactive nitric oxide (NO) is generated from arginine by nitric oxide synthase (NOS), which also releases citrulline that can be recycled to arginine.[1] NO has many biological effects related to regulation of vascular tone and blood flow and thus, hypertension and atherosclerotic disease. Administration of arginine improves blood flow to limbs of both healthy and diseased individuals,[1] or to free myocutaneous flaps,[3] and some of the effects persist for weeks after intravenous (IV) infusion. Another important finding is that arginine stimulates the release of growth hormone, as well as insulin-like growth factor I (IGF-1), both of which can improve wound healing. Agmatine, also derived from arginine, can promote vasodilatation and lower blood pressure. When given orally, arginine is absorbed quickly, varying between 21% and 68% with a half-life of 1.5–2 h after an oral dose of 6 g. It is excreted by the kidney but almost totally reabsorbed. Thus, arginine is a normal dietary ingredient that can be given in oral doses of 2–3 times the normal dietary intake without evidence of significant toxicity.

The role of arginine in wound healing has been summarized extensively in reviews by Arnold and Barbul[4] and Stechmiller *et al.*[5] In 1978, Seifter *et al.*[6] showed that animals previously fed an arginine-deficient diet, when supplemented with arginine, had an increased survival rate and increased wound-breaking strength, as well as increased wound collagen accumulation. Other experiments by the same group showed that animals fed a normal diet supplemented with 1% arginine had enhanced wound healing.[6] Stechmiller *et al.*[5] emphasized that there are two pathways for arginine metabolism within wounds that contribute to improved wound healing: NOS isoforms and arginase isoforms. The production of inducible nitric oxide synthase (iNOS) peaks within 24–72 h after wounding, producing NO and citrulline. NO plays a major role in antimicrobial activity and improving blood flow to the healing wound. The iNOS pathway is inhibited by transforming growth factor-β (TGF-β), which is thought to be an autocrine regulator of macrophage NO production. TGF-β can additionally stimulate the arginase pathway and production of collagen. Conditions that inhibit iNOS in the wound, such as corticosteroids and diabetes, are associated with impaired wound healing.

Arginase catalyzes the breakdown of arginine to ornithine and urea, and is the final step in the urea cycle. Two isoforms, arginase 1, and arginase 2, are encoded by distinct genes and differ in their tissue distribution and subcellular localization. Both arginase 1 and arginase 2 appear to play a role in wound healing by generating ornithine, which may be further metabolized to polyamines through the action of ornithine decarboxylase.[7] The polyamines are factors necessary for cellular growth and regulate numerous genes.[8] However, restriction of polyamine synthesis has not yet proven useful for cancer prevention or other complications. In iNOS knockout (KO) mice, arginine does not enhance wound healing, while ornithine continues to be ef-

Abbreviations and Acronyms (*continued*)

RNA = ribonucleic acid
SSI = surgical site infections
TGF = transforming growth factor
TPN = total parenteral nutrition
VEGF = vascular endothelial growth factor

fective. Ornithine can enhance wound breaking strength and collagen deposition in both wild type and iNOS KO mice.[9] Arginine may also be important for stimulation of TGF-β, vascular endothelial growth factor (VEGF) and keratinocyte growth factor.[10]

Arginine supplementation is, perhaps, best known for its beneficial effect on the healing of cutaneous wounds,[11] but it also improves the healing of fractures[12] and impaired wounds under a variety of circumstances, such as diabetes,[13] and after hemorrhage/trauma.[14] In burn wound healing, the effect may be dose-dependent.[15] The effect of arginine supplementation on wound healing is partly dependent upon growth hormone[16] and is partly mediated by NO because dietary supplementation did not enhance wound healing breakage strength and/or collagen deposition in iNOS KO mice.[17] However, Zhang *et al.*[18] reported that arginine supplementation increased protein balance in skin wounds and muscle by a mechanism independent of NO production. Almost all animal studies have been done in acute wounds, rather than chronic wounds, which may be considerably different.

Surprisingly few studies have been done on the role of arginine supplementation for healing of wounds in humans. Leigh *et al.*[19] performed a study in which doses of arginine (4.5 or 9 g) were administered orally twice daily for 3 weeks to patients with pressure ulcers. The healing rate was similar between the two groups, but both groups were estimated to achieve improvements compared to historical control patients. Hurson *et al.*[20] administered 17 g free arginine or a placebo for a period of 14 days to healthy, nonsmoking elderly volunteers and found that arginine caused a significant elevation of IGF-1 and improved nitrogen balance compared to controls. In another study, arginine supplementation (17 g free arginine) was given daily for 2 weeks to 30 healthy elderly subjects and compared to 15 subjects in a placebo group.[21] Volunteers had subcutaneous placement of polytetrafluoro-ethylene catheters and, in addition, small split thickness wounds were created on the upper thigh. Arginine enhanced hydroxyprolene accumulation, indicating increased collagen production, but did not influence the rate of epithelialization of the wounds. Further, the arginine group had increased responses of peripheral lymphocytes to mitogenic and allogeneic stimulation, and serum IGF-I levels were significantly elevated. Perhaps the most convincing positive clinical wound healing study was done by De Luis *et al.*[22] Seventy-two patients with oral or laryngeal cancer were randomly allocated to receive supplement with arginine and fiber; controls received an isocaloric, isonitrogenous enteral formula. Both supplements were started within 24 h after surgery via an enteral tube. Fistula formation was significantly reduced by the arginine-containing formula (5.2% vs. 17.6%, $p = 0.026$) and the length of postoperative stay was shorter (24.3 days vs. 36.1 days, $p = 0.036$). In a subsequent study by De Luis *et al.*,[23] patients with oral or laryngeal cancer received an enteral diet supplemented with 20 g arginine/day or an isocaloric, isonitrogenous enteral formula containing 12.3 g arginine/day. Fistula formation was significantly less frequent in the high dose arginine group compared to the low dose group (3.4% vs. 10.5%, $p = 0.006$). The length of postoperative stay, however, was similar. Also in this study, arginine was started postoperatively. No differences were detected in postoperative infectious complications.

Thus, arginine appears to improve wound healing through a variety of mechanisms involving secretion of growth hormone and IGF-1, the effects of NO and polyamines, and increased synthesis of proline and hydroxyproline. Administration of arginine to improve wound healing demonstrated that supplementation with up to 20 g/day is safe and relatively well tolerated in adults, but to date there is insufficient evidence regarding the most effective doses and timing of administration.

Arginine and infection

Several animal studies have demonstrated that arginine administration may favorably influence outcome during sepsis. In a study by Wang *et al.*,[24] arginine was given to rats for 10 days before sepsis was induced by cecal ligation and puncture (CLP). Rats were then given total parenteral nutrition (TPN) for 3 days, with one group receiving supplementation with arginine. Phagocytic activity of peritoneal macrophages was improved and bacterial counts were diminished in animals receiving IV arginine. In another model, arginine, given by gavage for 3 days before CLP or at the time of surgery, was associated with an improved survival, although not when it was started immediately after CLP.[25] In still another experiment using rats, supplemental arginine was given enterally for 7 days after a 30% burn injury and compared to controls receiving no arginine.[26] Survival was significantly improved in the 8 days after burn injury in arginine-treated animals (100% survival vs. 66.6%). These effects are thought to be due, in part, to a reduction in bacterial translocation from the

intestine.[27,28] The effects of arginine are also associated with production of NO,[29,30] restoration of depressed macrophage functions,[31] improvements in T cell function[32–34] and the production of polyamines.[35]

While excess enteral arginine may be protective in preventing infections, it does not seem to be as effective in combatting established infections.[36] Guinea pigs were implanted with osmotic pumps infusing a mixture of *Escherichia coli* and *Staphylococcus aureus*, and then fed by gastrostomy with isonitrogenous and isocaloric diets containing different concentrations of arginine. Survival was significantly decreased in animals receiving 6% of energy from arginine, and was modestly decreased in animals receiving 2% or 4% of energy from arginine. In another experiment, Peck *et al.*[37] showed high doses of supplemental arginine (50 g arginine/kg) increased mortality in protein malnourished mice after infection with *Salmonella typhimurium*. However, the administration of 2% of energy from arginine 10 days before allogeneic blood transfusion and 5 days before undergoing CLP improved survival (56% in the arginine supplemented group vs. 28% and 20% in the control diet groups). After burn injury and gavage with *E. coli* (to produce translocation), survival was 100% in an arginine-supplemented group versus 35% or 50% in control groups.[28] In another study,[38] prefeeding mice with arginine and/or glutamine was able to reverse the susceptibility to infections caused by prednisone in a burn model with gut-induced sepsis.

Wischmeyer[39] reviewed the use of arginine in critical care and emphasized that there was little benefit and, perhaps, harm when arginine alone was given to septic patients. Heyland *et al.*[40] also suggested harmful effects. Any adverse effects of arginine supplementation during sepsis are most likely related to generation of NO and its effects on cardiovascular function, including reduction in systemic blood pressure. However, other mechanisms could be important, including an increase in microbial growth rate and suppression of phagocyte function. This obviously requires further study. Kalil and Danner[41] reported studies in mice, rats, guinea pigs, rabbits, pigs, sheep, and dogs that showed mixed results, particularly related to mortality. These results, mostly beneficial, may have been partly related to the dose of arginine administered, with 2% of dietary energy provided by arginine being the most effective in reducing mortality. The patients in clinical studies have mostly been reported using combinations of immunonutrients, such as found in Impact® (Nestle, Inc.), a product containing supplemental arginine, omega-3 fatty acids, and ribonucleic acid (RNA). Like the animals studies, a variety of results have been obtained. When adverse effects have been reported, it has been mostly in patients with severe sepsis requiring vasopressors and/or cardiovascular disease. Luiking and Deutz[42] suggest that there is little evidence that additional arginine, by itself, is beneficial in septic patients, especially those in shock, and this could be due to enhanced NO production, which might have detrimental effects on cardiovascular stability.

In brief, arginine can be used safely and effectively to prevent infections in patients, but has possible adverse effects in patients with established sepsis, especially in the presence of hypotension. It appears that a dose of $\sim$2% of energy is optimal and that supplementation is more effective when given before challenge.

OMEGA-3 FATTY ACIDS AND WOUND HEALING

Because the biologic role of omega-3 fatty acids in vascular physiology and immunologic responses has been studied in depth for decades, it is surprising that their potential role in the healing of both acute and chronic wounds has generated so little attention.

Ekci *et al.*[43] performed colon anastomoses in rats and demonstrated that postoperative anastomotic bursting strength was significantly higher in animals receiving preoperative dietary supplementation with a combination of ascorbic acid and fish oil. Bursting strength was also improved in animals supplemented with either ascorbic acid or omega-3 fatty acids, but these improvements were not statistically significant in this study, which had only a small number of animals per group. In contrast, Albina *et al.*,[44] fed animals a diet containing fish oil for 21 days before surgical incision was made and for 10 or 30 days after wounding. They showed that collagen content was similar at both 10 and 30 days, but 30 day wounds were significantly weaker in animals treated with fish oil compared to animals receiving corn oil.

McDaniel *et al.*[45,46] studied the effects of fish oil administration compared to mineral oil in healthy adults. Patients between the ages of 18 and 45 were randomly assigned to receive a total of 1.6 g of eicosapentaenoic acid (EPA) and 1.2 g of docosahexanoic acid (DHA) per day, or 2.4 mL mineral oil per day orally, both along with low-dose aspirin. Eight millimeter blisters were created on the nondominant arm. As expected, plasma fatty acid profiles showed a significant shift to the omega-3 fatty

acids with a significant reduction in the ratio of omega-6/omega-3 fatty acids. On day 5, the group receiving the omega-3 supplement had greater epithelialization of the blisters than did the control group, and they also had a shift in plasma eicosanoids toward the EPA profile, clearly suggesting improved wound healing.

Other fatty acids may also have important effects on wound healing. For example, 20 mm^2 open excisional skin wounds in mice were treated with topical linolenic acid (omega-3), linoleic acid (omega-6), or oleic acid (omega-9) for 20 days. The wounds treated with oleic acid closed much quicker than ones treated with linoleic acid or vehicle control.[47] Oleic acid also downregulated cyclooxygenase 2 (COX-2) and induced collagen type III expression in another study.[48] The same study also showed that omega-3 fatty acids accelerated early (5 days) closure of open wounds, although not as much as oleic acid. Interestingly, levels of tumor necrosis factor-α, interleukin-10 (IL-10), and IL-17 mRNA were significantly up regulated by oleic acid, whereas linoleic acid did not cause significant changes in these cytokines. Unfortunately, no studies have compared EPA and/or DHA with oleic acid.

Our interpretation is that omega-3 fatty acids in fish oil may have a beneficial effect on early wound epithelialization, but may inhibit later collagen deposition, possibly minimizing scar formation.

Omega-3 fatty acids and infection

The omega-3 fatty acids clearly inhibit many inflammatory responses. A prospective randomized double-blind clinical trial compared the gene expression profiles of peripheral blood mononuclear cells from normal subjects who consumed daily either 1.8 g EPA plus DHA, 0.4 g EPA plus DHA, or 4.0 g high oleic acid sunflower oil (HOSF).[49] The high EPA plus DHA intake changed the expression of 1,040 genes, whereas HOSF intake changed the expression of only 298 genes. EPA plus DHA intake resulted in decreased expression of the genes involved in inflammatory and atherogenic-related pathways. The HOSF group also showed downregulation of these same classes of genes but to a lesser degree. Further, Trocki *et al.*[50] showed that burned guinea pigs fed diets containing 5–50% of nonprotein calories as fish oil had better outcomes with the lower levels of fish oil, the best being with 15%.

Wang *et al.*[51] reported clinical outcomes from a prospective randomized clinical trial in which patients were given TPN containing either an omega-3 fatty acid enriched emulsion or medium chain and long chain triglycerols for 5 days after surgery for gastrointestinal disease. There were no differences in changes of VEGF, C-reactive protein, IL-8, IL-1, and IL-10, but administration of fish oil led to an increase in leukotriene B (LTB5/LTB4 ratio) and a decrease in IL-6 and nuclear factor kappa B. Slight but not statistically significant reductions in infections occurred in the patients receiving omega-3 fatty acids. The conclusion was that IV omega-3 fatty acids will favorably influence cytokine profiles to an anti-inflammatory state. In similar studies by Han *et al.*,[52] a nonsignificant reduction in infection rates was observed in patients receiving IV omega-3 lipids.

Evaluations were made by Heller *et al.*[53] on 661 patients from 82 hospitals that received TPN for 3 or more days (mean 8.7 ± 7 days). The amount of fish oil infused as Omegaven® (Fresenius-Kabi), had a significant inverse relationship with mortality, reducing mortality, infection rates and length of stay when administered in doses between 0.1 and 0.2 g/kg/day. The least antibiotic demand was seen in patients receiving 0.15–0.2 g/kg/day of the fish oil. Pradelli *et al.*[54] performed a meta-analysis of controlled trials of surgical and intensive care unit (ICU) patients receiving parenteral nutrition who were randomized to receive omega-3 PUFA-enriched lipid emulsions or not. A total of 23 studies involving 1,502 patients were analyzed. No significant difference in mortality was found (relative risk = 0.89), but omega-3 enriched emulsions had a strong reduction in infection rate (relative risk = 0.61) and length of stay in the ICU (-1.92 days) and in the hospital overall (-3.29 days). Gas exchange, liver function, and antioxidant status were also improved.

The conclusion is that omega-3 fatty acids from fish oil will reduce wound infections.

Studies with both arginine and omega-3 fatty acids

In an animal experiment,[55] different combinations of arginine, glutamine, glycine, fish oil, and medium-chain triglycerides were added to a highly defined AIN-76A oral diet (ICN Biomedicals, Inc.) for 10 days before allogeneic blood transfusion and an additional 5 days before being challenged with burn injury and gavage with *E. coli* to induce translocation. Survival was reproducibly improved in animals that received fish oil or glutamine compared to regular chow, AIN-76A diet, or diets supplemented with medium chain triglycerides plus glutamine, glycine or arginine. These findings show that combinations of arginine and fish oil fed preoperatively are superior to their use individually and that the effect of individual immunonutrients,

such as arginine or fish oil can have a significant influence on outcome.

A number of clinical studies have shown the effectiveness of dietary supplements containing combinations of arginine and fish oil. Daly *et al.*[56] were among the first to show a beneficial effect of Impact on outcome after upper gastrointestinal surgery for malignancies. Impact is a commercial dietary product containing fish oil and arginine, which is based mostly on studies performed at the Shriners Hospitals for Children—Cincinnati for treatment of seriously burned patients. Significantly fewer wound complications occurred in the supplement group compared to the standard group (11% vs. 37%, $p = 0.002$) and mean length of stay was shorter. In another study by Farreras *et al.*,[57] patients having resection for gastric cancer were randomized to receive Impact® or an isocaloric nitrogenous control diet. Wound healing was assessed by placing a subcutaneous catheter. Patients receiving Impact had fewer episodes of wound healing complications (0% vs. 26.7%, $p = 0.005$) and had higher hydroxyprolene content within subcutaneously implanted catheters. Okamoto *et al.*[58] also performed a study in patients undergoing resection for gastric cancer. Impact was given for 7 days preoperatively and compared to a group receiving standard formulas. Significantly fewer infections occurred in the patients receiving Impact (6%) compared to a standard diet (28%) ($p < 0.05$). Importantly, the mean duration of the systemic inflammatory response syndrome in the supplemented group was 0.77 ± 0.9 days compared to 1.34 ± 1.45 days in the conventional group ($p < 0.05$).

Horie *et al.*[59] examined the effects of Impact on patients undergoing resection for colorectal cancer. The Impact group had no surgical site infections (SSI) compared to 14.7% of patients in the control group. Improvement in wound healing using combined immunonutrients was also documented in a meta-analysis by Waitzberg *et al.*[60] In patients having gastrointestinal surgery, anastomotic leaks were decreased by 46% when Impact supplementation was part of the preoperative treatment.

Several meta-analyses have been done which show the benefit of combinations of arginine and fish oil. Zheng *et al.*[61] reviewed 13 randomized controlled trials involving 1,269 patients. Immunonutrition significantly reduced the postoperative infection rate (odds ratio = 0.41) and hospital stay (-3.48 days) without any serious side effects. Similar findings were observed in studies by Marik and Zaloga[62] and Wilhelm and Kale-Pradhan.[63] Braga[64] recently published a meta-analysis of the potential clinical benefits of perioperative immunonutrition in surgical patients, important because he was responsible for performance of many of the baseline studies. The conclusion of that analysis was that studies which included arginine and omega-3 fatty acids (usually with RNA, as Impact) consistently reduced postoperative infections and length of hospital stay in patients undergoing gastrointestinal surgery and many other types of surgery. Economic analysis showed that there was a cost savings related to use of immunonutrition, especially when started preoperatively and continued for a few days postoperatively in both well-nourished and malnourished patients. Braga further concluded that additional studies should be done to test the efficiency of long-term treatment and also the benefit of different combinations of the immunonutrients. In still another meta-analysis, Drover *et al.*[65] also showed that Impact given perioperatively reduced SSI by 51%, but immunonutrients containing arginine without fish oil were not nearly as effective.

CONCLUSIONS

It is clear that both arginine and the omega-3 long chain polyunsaturated fatty acids can have major effects on wound healing and wound infection in both experimental animals and humans. However, it must be emphasized that energy and protein requirements must be met before any supplement, including arginine, can be effective. The administration of arginine by itself can improve wound healing when given during the perioperative period, but it has variable effects on responses to infections. High doses of arginine should be avoided in patients with established sepsis, especially when given intravenously, since it may cause hypotension or other adverse cardiovascular events. Less than 10 g daily given orally to adults is well tolerated and safe. Omega-3 fatty acids (given as fish oil) are also safe when given orally in doses approximating 3.5% of energy ($\sim$1.5–2% of energy as DHA + EPA). These doses of omega-3 fatty acids appear to have a relatively strong effect in reducing wound infections and also recovery from serious generalized infections in both experimental animals and man. However, omega-3 fatty acids may inhibit tensile strength of healing wounds after several days. In doing so, it might reduce the incidence of excessive scar formation, but this has not been studied in humans and there are few good animal models. A combination of omega-3 fatty acids and arginine appears to be much more effective than either given alone. Several

meta-analyses involving thousands of patients have shown that a combination of arginine and omega-3 fatty acids is effective in reducing SSI by ~50% and also significantly reducing hospital and ICU length of stay. This combination appears to be more effective because there is a shift toward the development of anti-inflammatory mediators and cells (Th2 and M2) and much more arginase resulting in a marked increase in myeloid derived suppressor cells (MDSC) that have anti-infective properties. We are currently studying the effects of different nutrients on development of different types of MDSC.

What has not yet been established by appropriate animal or clinical studies are the following: (1) What is the optimal amino acid and fatty acid mixture to improve wound healing and protect against infection? (2) What are the optimal dosages? (3) What is the most effective timing and duration of administration of these combined preparations?

It will be possible, using optimal mixtures and concentrations of immunonutrients, to have a profound improvement in the care of surgical and traumatic wounds.

TAKE-HOME MESSAGES

- Arginine administration can improve wound healing.
- The best dose for arginine supplementation appears to be about 2% of energy.
- The effects of arginine on both wound healing and infection are better when started preoperatively or before challenge.
- Arginine is safe except when given to patients with active sepsis, especially those with hypotension.
- Omega-3 fatty acids from fish oil can prevent wound infections and can improve early wound healing, but after several days may decrease the deposition of collagen, possibly preventing extensive scarring.
- Combinations of omega-3 fatty acids and arginine are much more effective in preventing infection than either one alone.
- When given to surgical patients, immunonutrients containing arginine and fish oil can have anti-inflammatory effects and reduce wound infections by ~50%.
- Combinations of arginine and fish oil can also reduce the incidence of adult respiratory distress syndrome and shortened hospital stay in surgical patients.
- Energy and protein requirements must be met if supplemental arginine is to be effective.

AUTHOR DISCLOSURE AND GHOST WRITING

Dr. Alexander serves as a consultant to 3M Corporation for their surgical infections section. There is no relationship to the current publication. Dr. Supp has nothing to disclose. The content of this article was expressly written by the authors as listed. No ghost writers were used to write this article.

ABOUT THE AUTHORS

Dr. J. Wesley Alexander is currently Director of Research at the Shriners Hospitals for Children–Cincinnati. He is Professor Emeritus at the University of Cincinnati and has served as Director of the Transplantation Division and Center for Surgical Weight Loss at the University of Cincinnati. He has trained 66 fellows and has more than 650 publications in the medical literature. He has also served as President of the American Burn Association, the American Society for Transplant Surgeons and the Surgical Infection Society. **Dr. Dorothy M. Supp** is currently an Associate Investigator at the Shriners Hospitals for Children–Cincinnati and is an Adjunct Research Assistant Professor in the Department of Surgery at the University of Cincinnati College of Medicine. Her research focuses on wound healing, scar formation, and tissue engineering.

REFERENCES

1. Böger RH and Bode-Böger SM: The clinical pharmacology of L-arginine. Annu Rev Pharmacol Toxicol 2001; **41:** 79.
2. Brosnan ME and Brosnan JT: Arginine metabolism: enzymology, nutrition, and clinical significance. Renal arginine metabolism. J Nutr 2004; **134:** 2791S.
3. Booi DI, Debats IB, Deutz NE, and van der Hulst RR: Arginine improves microcirculation in the free transverse rectus abdominis myocutaneous flap after breast reconstruction: a randomized, double-blind clinical trial. Plast Reconstr Surg 2011; **127:** 2216.
4. Arnold M and Barbul A: Nutrition and wound healing. Plast Reconstr Surg 2006; **117 (Suppl):** 42S.
5. Stechmiller JK, Childress B, and Cowan L: Arginine supplementation and wound healing. Nutr Clin Pract 2005; **20:** 52.
6. Seifter E, Rettura G, Barbul A, and Levenson SM: Arginine: an essential amino acid for rats. Surgery 1978; **84:** 224.
7. Witte MB and Barbul A: Arginine physiology and its implication for wound healing. Wound Repair Regen 2003; **11:** 419.
8. Pegg AE: Mammalian polyamine metabolism and function. IUBMB Life 2009; **61:** 880.
9. Shi HP, Fishel RS, Efron DT, Williams JZ, Fishel MH, and Barbul A: Effect of supplemental ornithine on wound healing. J Surg Res 2002; **106:** 299.
10. Alves CC, Torrinhas RS, Giorgi R, Brentani MM, Logullo AF, and Waitzberg DL: TGF-β (1) expres-

sion in wound healing is acutely affected by experimental malnutrition and early enteral feeding. Int Wound J 2012 Nov 30 [Epub ahead of print]; DOI: 10.1111/j.1742-481X.2012.01120.x.

11. Barbul A, Rettura G, Levenson SM, and Seifter E: Arginine: a thymotropic and wound-healing promoting agent. Surg Forum 1977; **XXVIII:** 101.

12. Kdolsky RK, Mohr W, Savidis-Dacho H, Beer R, Puig S, Reihsner R, Tangl S, and Donath K: The influence of oral L-arginine on fracture healing: an animal study. Wien Klin Wochenschr 2005; **20:** 693.

13. Witte MB, Thornton FJ, Tantry U, and Barbul A: L-arginine supplementation enhances diabetic wound healing: involvement of the nitric oxide synthase and arginine pathways. Metabolism 2002; **51:** 1269.

14. Shi HP, Wang SM, Zhang GX, Zhang YJ, and Barbul A: Supplemental L-arginine enhances wound healing following trauma/hemorrhagic shock. Wound Repair Regen 2007; **25:** 66.

15. Chen X, Li Y, Cai X, Xu W, Lu S, and Shi J: Dose-effect of dietary L-arginine supplementation on burn wound healing in rats. Chin Med J (Engl) 1999; **112:** 828.

16. Barbul A, Rettura G, Prior E, Levenson SM, and Seifter E: Supplemental arginine, wound healing, and thymus: arginine–pituitary interaction. Surg Forum 1978; **XXIX:** 93.

17. Shi HP, Efron DT, Most D, Tantry U, and Barbul A: Supplemental dietary arginine enhances wound healing in normal but not inducible nitric oxide synthase knockout mice. Surgery 2000; **128:** 374.

18. Zhang X-J, Chinkes DL, and Wolfe RR: The anabolic effect of arginine on proteins in skin wound and muscle is independent of nitric oxide production. Clin Nutr 2008; **27:** 649.

19. Leigh B, Desneves K, Rafferty J, Pearce L, King S, Woodward MC, and Brown D: The effect of different doses of an arginine-containing supplement on the healing of pressure ulcers. J Wound Care 2012; **21:** 150.

20. Hurson M, Regan MC, Kirk SJ, Wasserkrug HL, and Barbul A: Metabolic effects of arginine in a healthy elderly population. J Parent Ent Nutr 1995; **19:** 227.

21. Kirk SJ, Hurson M, Regan MC, Holt DR, Wasserkrug HL, and Barbul A: Arginine stimulates wound healing and immune function in elderly human beings. Surgery 1993; **114:** 155.

22. De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, and Aller R: High dose of arginine enhanced enteral nutrition in postsurgical head and neck cancer patients. A randomized clinical trial. Eur Rev Med Pharmacol Sci 2009; **13:** 279.

23. De Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, and Venosa M: A randomized double-blind clinical trial with two different doses of arginine enhanced enteral nutrition in postsurgical cancer patients. Eur Rev Med Pharmacol Sci 2010; **14:** 941.

24. Wang Y-Y, Shang H-F, Lai Y-N, and Yeh S-L: Arginine supplementation enhances peritoneal macrophage phagocytic activity in rats with gut-derived sepsis. J Parenter Enteral Nutr 2003; **27:** 235.

25. Madden HP, Breslin RJ, Wasserkrug HL, Efron G, and Barbul A: Stimulation of T cell immunity by arginine enhances survival in peritonitis. J Surg Res 1988; **44:** 658.

26. Cui X-L, Iwasa M, Iwasa Y, and Ogoshi S: Arginine-supplemented diet decreases expression of inflammatory cytokines and improves survival in burned rats. J Parenter Enteral Nutr 2000; **24:** 89.

27. Quirino LEP, Correia MITD, and Cardoso VN: The impact of arginine on bacterial translocation in an intestinal obstruction model in rats. Clin Nutr 2007; **26:** 335.

28. Gianotti L, Alexander JW, Pyles T, and Fukushima R: Arginine-supplemented diets improve survival in gut-derived sepsis and peritonitis by modulating bacterialclearance. The role of nitric oxide. Ann Surg 1993; **217:** 644.

29. Efron D and Barbul A: Role of arginine in immunonutrition. J Gastroenterol 2000; **35 (Suppl XII):** 20.

30. Ward DT, Lawson SA, Gallagher CM, Conner WC, and Shea-Donohue T: Sustained nitric oxide production via L-arginine administration ameliorates effects of intestinal ischemia-reperfusion. J Surg Res 2000; **89:** 13.

31. Angele MK, Small N, Ayala A, Cioffi WG, Bland KI, and Chaudry IH: L-arginine: a unique amino acid for restoring the depressed macrophage functions after trauma-hemorrhage. J Trauma Injury Infect Crit Care 1999; **46:** 34.

32. Barbul A, Wasserkrug HL, Seifter E, Rettura G, Levenson SM, and Efron G: Immuno-stimulatory effects of arginine in normal and injured rats. J Surg Res 1980; **29:** 228.

33. Taylor-Robinson AW, Liew FY, Severn A, Xu D, McSorley SJ, Garside P, Padron J, and Phillips RS: Regulation of the immune response by nitric oxide differentially produced by T helper Type 1 and T helper type 2 cells. Eur J Immunol 1994; **24:** 980.

34. Ochoa JB, Strange J, Kearney P, Gellin G, Endean E, and Fitzpatrick E: Effects of L-arginine on the proliferation of T lymphocyte subpopulations. J Parenter Enteral Nutr 2001; **25:** 23.

35. Grimble RF and Grimble GK: Immunonutrition: role of sulfur amino acids, related amino acids, and polyamines. Nutrition 1998; **14:** 605.

36. Gonce SJ, Peck MD, Alexander JW, and Miskell PW: Arginine supplementation and its effect on established peritonitis in guinea pigs. J Parenter Enteral Nutr 1990; 14**:** 237.

37. Peck MD, Babcock GF, Alexander JW, Billiar T, and Ochoa J: High doses of dietary arginine during repletion impair weight gain and increase infectious mortality in protein-malnourished mice. Br J Nutr 1995; **74:** 787.

38. Gennari R and Alexander JW: Arginine, glutamine, and dehydroepiandrosterone reverse the immunosuppressive effect of prednisone during gut-derived sepsis. Crit Care Med 1997; **25:** 1207.

39. Wischmeyer P: Nutritional pharmacology in surgery and critical care: "you must unlearn what you have learned." Curr Opin Anesthesiol 2011; **24:** 381.

40. Heyland DK, Novak F, Drover JW, Jain M, Su X, and Suchner U: Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 2001; **286:** 944.

41. Kalil AC and Danner RL: L-arginine supplementation in sepsis: beneficial or harmful? Curr Opin Crit Care 2006; **12:** 303.

42. Luiking YC and Deutz NE: Exogenous arginine in sepsis. Crit Care Med 2007; **35 (9 Suppl):** S557.

43. Ekci B, Karabicak I, Atukeren P, Altinli E, Tomaoglu K, and Tasci I: The effect of omega-3 fatty acid and ascorbic acid on healing of ischemic colon anastomoses. Ann Ital Chir 2011; **82:** 475.

44. Albina JE, Gladden P, and Walsh WR: Detrimental effects of an omega-3 fatty acid-enriched diet on wound healing. J Parenter Enteral Nutr 1993; **17:** 519.

45. McDaniel JC, Belury M, Ahijevych K, and Blakely W: Omega-3 fatty acids effect on wound healing. Wound Repair Regen 2008; **16:** 337.

46. McDaniel JC, Massey K, and Nicolaou A: Fish oil supplementation alters levels of lipid mediators of inflammation in microenvironment of acute human wounds. Wound Repair Regen 2011; **19:** 189.

47. Cardoso CRB, Souza MA, Ferro EAV, Favoreto S, Jr, and Pena JDO: Influence of topical administration of n-3 and n-6 essential and n-9 nonessential fatty acids on the healing of cutaneous wounds. Wound Repair Regen 2004; **12:** 235.

48. Cardoso CR, Favoreto S, Jr, Oliveira LL, Vancim JO, Barban GB, Ferraz DB, and Silva JS: Oleic acid modulation of the immune response in wound healing: a new approach for skin repair. Immunobiology 2011; **216:** 409.

49. Bouwens M, van de Rest O, Dellschaft N, Bromhaar MG, de Groot LCPGM, Geleijnse JM, Müller M, and Afman LA: Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. Am J Clin Nutr 2009; **90:** 415.

50. Trocki O, Heyd TJ, Waymack JP, and Alexander JW: Effects of fish oil on postburn metabolism and immunity. J Parenter Enteral Nutr 1987; **11:** 521.

51. Wang J, Yu JC, Kang WM, and Ma ZQ: Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. Nutrition 2012; **28:** 623.

52. Han Y-Y, Lai S-L, Ko W-J, Chou C-H, and Lai H-S: Effects of fish oil on inflammatory modulation in

surgical intensive care unit patients. Nutr Clin Pract 2012; **27:** 91.

53. Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, and Koch T: Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med 2006; **34:** 972.
54. Pradelli L, Mayer K, Muscaritoli M, and Heller AR: N-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit Care 2012; **16(R184):** 1.
55. Gennari R, Alexander JW, and Eaves-Pyles T: Effect of different combinations of dietary additives on bacterial translocation and survival in gut-derived sepsis. J Parenter Enteral Nutr 1995; **19:** 319.
56. Daly JM, Lieberman MD, Goldfine J, Shou J, Weintraub F, Rosato EF, and Lavin P: Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. Surgery 1992; **112:** 56.
57. Farreras N, Artigas V, Cardona D, Rius X, Trias M, and González JA: Effect of early post-operative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. Clin Nutr 2005; **24:** 55.
58. Okamoto Y, Okano K, Izuishi K, Usuki H, Wakabayashi H, and Suzuki Y: Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition. World J Surg 2009; **33:** 1815.
59. Horie H, Okada M, Kojima M, and Nagai H: Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition. Surg Today 2006; **36:** 1063.
60. Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Hwang T-L, Mijares JM, and Bihari D: Postsurgical infections are reduced with specialized nutrition support. World J Surg 2006; **30:** 1592.
61. Zheng Y, Li F, Qi B, Luo B, Sun H, Liu S, and Wu X: Application of perioperative immuno-nutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr 2007; **16(Suppl 1):** 253.
62. Marik PE and Zaloga GP: Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med 2008; **34:** 1980.
63. Wilhelm SM and Kale-Pradhan PB: Combination of arginine and omega-3 fatty acids enteral nutrition in critically ill and surgical patients: a meta-analysis. Expert Rev Clin Pharmacol 2010; **3:** 459.
64. Braga M: Perioperative immunonutrition and gut function. Curr Opin Clin Nutr Metab Care 2012; **15:** 485.
65. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, and Heyland DK: Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg 2011; **212:** 385.