

## **Arginine Immunonutrition in Critically Ill Patients: A Clinical Dilemma**

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Am J Crit Care 2004;13:17-23  
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# ARGININE IMMUNONUTRITION IN CRITICALLY ILL PATIENTS: A CLINICAL DILEMMA

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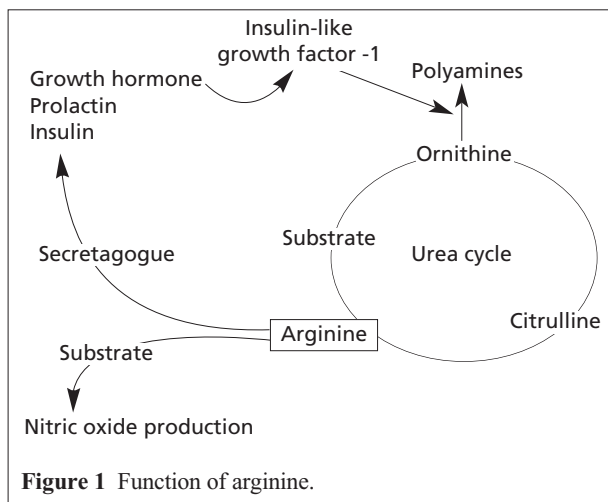
*Commercial enteral nutritional formulas for enhancement of the immune system are widely used in critical care. Immunonutrition with arginine can enhance inflammatory and immunologic responses in animal models and in humans. Although clinical improvements in surgical patients have been reported, benefits in critically ill patients with systemic inflammatory response syndrome, sepsis, or organ failure are less clear. Recent meta-analyses on the use of immunonutrition with arginine in critically ill and surgical patients revealed methodological weaknesses in most published studies. Specifically, a meta-analysis indicated that critically ill patients with preexisting severe sepsis may have an increased mortality rate when fed an immunonutritional enteral formula that contains arginine. These findings brought about confusion and controversy over the use of immunonutritional formulas in subsets of critically ill patients. A review of the literature on the function of arginine, its effect on the immune system, its roles in immunonutrition and in the clinical outcomes of critically ill patients, and the implications for nursing practice indicated that the benefits of immunonutrition with arginine in critically ill patients are unproven and warrant further study. Until more information is available, nutritional support should focus primarily on preventing nutritional deficiencies rather than on immunomodulation. (American Journal of Critical Care. 2004;13:17-23)*

Infectious complications in critically ill patients can cause increased morbidity and mortality. Recent advances in nutritional support involved enhancing immune function through the beneficial effects and therapeutic actions of amino acids. In the past decade, many investigators<sup>1-13</sup> compared nutritional formulas supplemented with arginine, n-3 fatty acids, structured lipids, and nucleotides with standard enteral formulas to determine the efficacy of the supplemented formulas in critically ill patients. The results revealed reduced occurrence of infections, reduced length of stay in the hospital or intensive care unit (ICU), reduced duration of mechanical ventilation, and decreased hospital costs for patients given

the supplemented formulas. Unfortunately, the safety and efficacy of immunonutrition in critically ill patients have not been clearly established, because flaws in the methods in previous studies limit generalizations of the findings to clinical practice.<sup>1,4</sup> Interpreting the results of clinical trials in critical care patients is difficult because the severity of illness varies, resulting in a heterogeneous population of patients.<sup>1,4</sup> Moreover, except for a few randomized prospective clinical studies, the investigations have not included the most severely ill patients.<sup>1,4</sup> Therefore, accurate inferences cannot be drawn, and the use of enteral immunonutritional formulas in critically ill patients remains controversial.

The amino acid arginine, which is classified as a semiessential amino acid and conditionally as an essential nutrient for adults in injured or stressed states, is important in a number of biological and physiologi-

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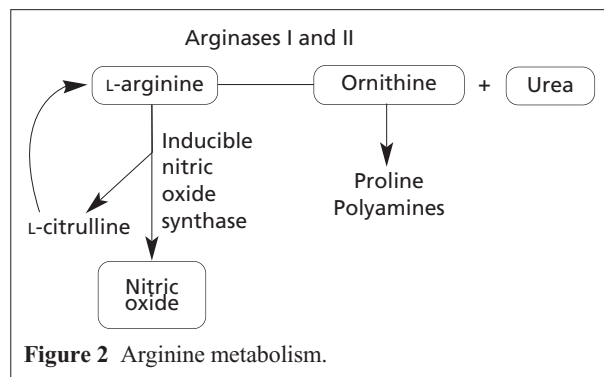
cal processes. In trauma and sepsis states, its bioavailability is reduced.<sup>14,15</sup> In clinical studies,<sup>16,17</sup> arginine supplementation enhanced nitrogen retention and protein synthesis in animals and in healthy human subjects. Nutritional formulas with arginine can enhance immune parameters after stress and surgery.<sup>10-13</sup> However, immunonutrition with arginine has also been implicated in an intensification of the systemic inflammatory response system in critically ill patients, resulting in increased morbidity.<sup>1-4</sup> In patients with shock, sepsis or organ failure, immunonutrition with arginine may not be beneficial and may actually have harmful effects.<sup>1,4</sup>

*Arginine, an essential amino acid for adults in injured or stressed states, is less available in the body under these conditions.*

In this article, we review the function of arginine, its effect on the immune system, and its role in the immunonutrition of critically ill patients. We discuss key studies on the efficacy of arginine immunonutrition and on the clinical outcomes of critically ill patients given enteral formulas containing arginine. Finally, we discuss the implications for nursing practice and review how to assess patients for indications of adverse reactions to immunonutrition with arginine.

### Function of Arginine

Arginine plays a role in protein synthesis, as a substrate for the urea cycle and the production of nitric



oxide, and as a secretagogue for growth hormone, prolactin, and insulin (Figure 1). Whereas most amino acids are 16% nitrogen, arginine is 32% nitrogen.<sup>18-21</sup> Arginine is synthesized primarily in the kidney from gut-derived citrulline via the urea cycle, which also detoxifies ammonia and facilitates excretion of nitrogen.<sup>22</sup> Ornithine is a metabolite of arginine and is involved in the synthesis of polyamines, which are important for cellular division.

Arginine is metabolized via 2 pathways<sup>23</sup> (Figure 2). In the first pathway arginine is broken down by either arginase I or arginase II. Arginase I, an enzyme found primarily in the liver, breaks down arginine into ornithine and urea, a step required in hepatic and intestinal synthesis of urea from ammonia.<sup>24-27</sup> Arginase II, a mitochondrial enzyme found throughout the cells of the body, is primarily involved in intracellular metabolism of arginine. Although arginase I may be more directly responsible for the production of polyamines, arginase II may direct the synthesis of arginine into ornithine and proline. Proline is converted into hydroxyproline and then to collagen,<sup>18-21</sup> a substance necessary for wound healing.

The second pathway of arginine metabolism is responsible for producing nitric oxide,<sup>23</sup> which is associated with alterations in the structure and function of the intestinal mucosa,<sup>28</sup> the liver,<sup>29</sup> and the kidney<sup>30</sup> and with dysfunction in gastrointestinal motility. Three isoenzymes, known as nitric oxide synthases (NOSs), produce nitric oxide: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). Of the 3 enzymes, nNOS and eNOS are calcium dependent; iNOS is calcium independent and is produced in response to cytokines and endotoxin signals.<sup>23</sup> Once induced, iNOS produces high levels of nitric oxide.<sup>31</sup>

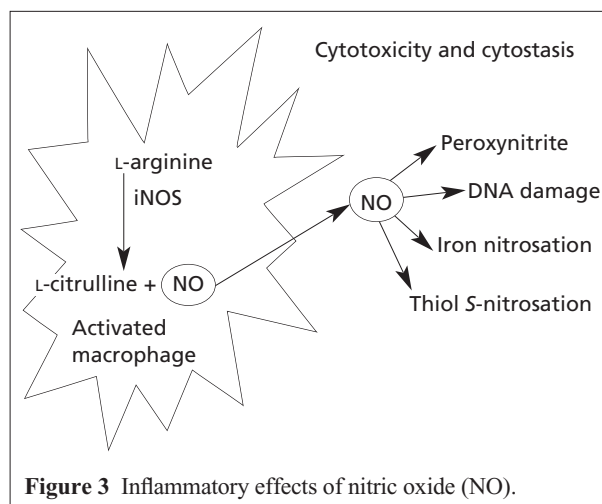
Nitric oxide has several properties that aid local response to acute injury and reduce the risk of wound infection.<sup>22</sup> Synthesized by the vascular endothelium via eNOS, nitric oxide causes vascular relaxation, which regulates blood pressure.<sup>32</sup> Nitric oxide also

regulates cardiac contractility via nNOS and acts as a neurotransmitter that facilitates numerous functions, including memory formation.<sup>32</sup> In addition, a nitric oxide-dependent mechanism is responsible for mediating neurogenic vasodilatation and for regulating functions of the respiratory, genitourinary, and gastrointestinal tracts.<sup>32</sup> Platelet aggregation is also controlled by nitric oxide.<sup>32</sup> During stress and immunologic reactions, nitric oxide is released in large quantities<sup>32</sup> and is involved in nonspecific immunity and the pathophysiology of septic shock, inflammation, and other hyperdynamic states. The oxide also has cytotoxic properties and is thought to mediate the cytotoxic effects of macrophages on microbes, parasites, and tumors (Figure 3).

### Arginine and the Immune System

Strong evidence<sup>33,34</sup> suggests that dietary supplementation with arginine enhances immunocompetence in adults in humans and in animal models. Dietary L-arginine modulates the activities of immune cells in several ways.<sup>35,36</sup> For example, dietary arginine can increase the weight of the thymus in healthy animals, an effect that is directly correlated with an increase in the number of thymic T lymphocytes.<sup>22</sup> Intravenous infusion of arginine is also associated with an increase in the release of T cells from the thymus.<sup>37</sup> In addition, arginine has a direct effect on T-cell activity in vivo and in vitro.<sup>38,39</sup> In one study,<sup>40</sup> maximal proliferation of peripheral mononuclear blood cells occurred when the cells were cultured in medium containing 0.04 mM arginine. In another study,<sup>41</sup> athymic nude mice fed a diet supplemented with arginine had greater numbers of splenic T cells and a stronger delayed-type hypersensitivity reaction, a measure of T-cell function, than did control mice not fed arginine. In a study in humans,<sup>38</sup> subjects had an increase in mitogenic responses in T cells after a few days of arginine supplementation at 30 g/d. This increase persisted for 2 to 3 weeks.

Arginine-derived nitric oxide also plays a major role in inflammation and immunity,<sup>42</sup> affecting most immune cells, including T cells. At low doses, nitric oxide enhances T-cell mitogenesis; at higher doses, the effect is inhibitory.<sup>40</sup> Macrophages use L-arginine as a major substrate for many of their functions. In inflammation, macrophages are primarily responsible for the expression of iNOS.<sup>43-45</sup> Although the production of nitric oxide varies according to the nature of the stimulus, early release of the oxide is due to iNOS activity. Arginase expression occurs several hours later.<sup>23</sup> Although interleukin (IL)-4, IL-10, and prostaglandin E<sub>2</sub> inhibit iNOS expression, they induce



**Figure 3** Inflammatory effects of nitric oxide (NO).

arginase expression. During a septic inflammatory response, competition between the functions of iNOS and arginase may occur, and as a result macrophages help organize cells and prioritize cellular responses. Macrophages also defend against growth, activity, and killing of bacteria and parasites by releasing nitric oxide.

Arginine also enhances phagocytosis by neutrophils and adhesion of polymorphonuclear cells, activities that help produce nitric oxide for immunomodulation. This enhancement is protective and is different from the cytotoxic response generated by macrophages that results in the production of superoxide.<sup>46</sup>

### Immune Response in Critical Illness

Mediators of shock and inflammation known as cytokines are important in the pathogenesis of critical illness.<sup>47</sup> Two cytokines, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-1, are produced by macrophages and are considered the main mediators of shock, sepsis, and multiple organ failure syndrome.<sup>47</sup> Macrophages are triggered to produce TNF- $\alpha$  by a variety of inflammatory stimuli, including bacteria and other cytokines. TNF- $\alpha$  has many functions: It stimulates white blood cells to release IL-1, IL-6, IL-8, platelet activating factor, leukotrienes, thromboxanes, and prostaglandins. It also stimulates the production and activity of polymorphonuclear leukocytes and promotes adhesion of immune cells to the endothelium. It activates the coagulation and complement systems. It depresses myocardial contractility, and it stimulates fever production by the hypothalamus.<sup>47</sup> As these observations suggest, any interventions that stimulate the synthesis or activity of mediators such as TNF- $\alpha$  and IL-1 can exacerbate the pathogenesis of shock and sepsis and thus should be avoided.<sup>47</sup>

Commercial enteral formulas with arginine for enhancement of the immune system								Energy content, kJ/mL (kcal.mL)
Product	Manufacturer	Protein source	Carbohydrate source	Fat source	Protein, g/L	Carbohydrate, g/L	Fat, g/L	
Immun-Aid	B Braun	Lactalbumin, amino acids	Maltodextrin, cornstarch	MCT, canola oils	80	120	22	4.184 (1.0)
IntensiCal	Mead Johnson Nutritionals	Casein hydrolysate, arginine	Maltodextrin, modified corn starch	MCT, canola, high oleic sunflower, corn, menhaden oils	81	150	42	5.439 (1.3)
Crucial	Nestle Clinical Nutrition	Hydrolyzed casein, arginine	Maltodextrin, corn starch	MCT, marine, soy oils	94	135	68	6.276 (1.5)
Impact	Novartis	Sodium and calcium caseinates, arginine	Hydrolyzed cornstarch	Palm kernel, sunflower, menhaden oils	56	130	28	4.184 (1.0)
Impact with fiber	Novartis	Sodium and calcium caseinates, arginine	Hydrolyzed cornstarch, soy fiber, partially hydrolyzed guar gum	Palm kernel, menhaden, sunflower oils	56	140	28	4.184 (1.0)
Impact 1.5	Novartis	Sodium and calcium caseinates, arginine	Hydrolyzed cornstarch	MCT, palm kernel, menhaden, sunflower oils	84	140	69	6.276 (1.5)
Impact glutamine	Novartis	Wheat protein hydrolysate, free amino acids, sodium caseinate	Maltodextrin, partially hydrolyzed guar gum, soy fiber	Palm, menhaden, sunflower oils	78	150	43	5.439 (1.3)

Abbreviations: MCT, medium-chain triglycerides; RDI, recommended daily intake.

Adapted from Russell and Charney,<sup>5(pp160-161)</sup> with permission from the American Society for Parenteral and Enteral Nutrition. The society does not endorse the use of this material in any form other than its entirety.

Systemic inflammatory response syndrome (SIRS) is an abnormal host response characterized by generalized inflammation caused by infectious or noninfectious entities. SIRS is defined by the presence of 2 or more of the following: (1) body temperature greater than 38°C or less than 36°C, (2) heart rate greater than 90/min; (3) respirations greater than 20/min or PaCO<sub>2</sub> less than 32 mm Hg, and (4) white blood cell count greater than 12 x 10<sup>9</sup>/L, less than 4 x 10<sup>9</sup>/L, or more than 0.10 band cells.<sup>48</sup> These signs provide a framework for assessing the cellular and immunologic mechanisms that cause sepsis and organ dysfunction.<sup>47</sup>

Multiple organ failure syndrome is defined as the progressive failure of 2 or more organ systems associated with a hypermetabolic systemic inflammatory state. The syndrome is preceded by a variety of events, includ-

ing shock, sepsis, hemorrhage, burns, trauma, ischemia, pancreatitis, and major surgery. The systemic response to shock follows a sequential course once initiated. A relative state of stability lasting 48 to 72 hours is followed by a state of hypermetabolism that typically peaks in 3 to 4 days and resolves in 2 weeks. However, often the initial response may lead to a progressive series of complications resulting in a persistent state of hypermetabolism and the development of multiple organ system failure, which is now the leading cause of death in patients with sepsis, trauma, and burns.<sup>47</sup>

### Role of Arginine Immunonutrition in Critically Ill Patients

Immunonutrition with arginine is a popular approach to augment the immune response of patients with criti-

Volume to meet 100% RDI, mL	Fiber, g/L	Other, per liter
2000	0	14 g arginine, 1 g nucleotides, N-6 to N-3 ratio 2.18:1, 9 g glutamine, 2665 IU vitamin A, 60 mg vitamin C, 25 mg zinc
1000	0	2% of energy content as arginine, N-6 to N-3 ratio 3.4:1, 5.5 g glutamine, no dietary nucleotides, 7500 IU vitamin A (60% $\beta$ -carotene), 750 mg vitamin C, 21 mg zinc
1000	0	15 g arginine, N-6 to N-3 ratio 2.14:1, no glutamine or dietary nucleotides, 6000 IU vitamin A, 5.4 mg $\beta$ -carotene
1500	0	1000 mg vitamin C, 36 mg zinc
1500	10	12.5 g arginine, N-6 to N-3 ratio 1.4:1, no glutamine, 1.2 g dietary nucleotides, 6700 IU vitamin A (50% from $\beta$ -carotene), 80 mg vitamin C, 15 mg zinc
1250	0	18.7 g arginine, N-6 to N-3 ratio 1.4:1, no glutamine, 1.8 g dietary nucleotides, 8000 IU vitamin A (50% from $\beta$ -carotene), 96 mg vitamin C, 18 mg zinc
1000	10	16.3 g arginine, 15 g glutamine, 1.6 g dietary nucleotides, 8700 IU vitamin A (20% from $\beta$ -carotene), 260 mg vitamin C, 20 mg zinc

cal illnesses. In early studies,<sup>27-30</sup> immunonutrition with arginine led to improvements in cellular immunity in patients with postoperative or posttraumatic stress. Zaloga<sup>49</sup> reviewed 13 prospective randomized clinical studies in which an enteral immunonutritional formula with arginine was compared with a standard one in surgical and critically ill patients. He reported that in 12 of the 13 studies, the experimental groups had improved outcomes. Specifically, hospital and ICU lengths of stay, number of days of mechanical ventilation required, and number of infections decreased after immunonutrition with arginine. Subsequently, the conclusions of 2 other meta-analyses, by Beale et al<sup>2</sup> and Heys et al,<sup>3</sup> were similar.

Heyland et al<sup>1</sup> did a more comprehensive meta-analysis of immunonutrition in which they examined

the results of 22 individual studies in which an immunonutritional enteral formula was compared with a standard enteral formula in a total of 2419 surgical and critically ill patients. Using a scoring system to document the methodological limitations of the studies, Heyland et al found that although some of the investigators used an evidence-based approach, the study methods had many shortcomings, resulting in invalid conclusions and inferences. Thus, the findings of Heyland et al conflict with those of previous meta-analyses and suggest that immunonutrition in surgical and critically ill patients may decrease the rate of infectious complications but is not related to an overall decrease in mortality. Specifically, Heyland et al concluded that the treatment effect of immunonutrition with arginine varies according to the type of enteral formula, the subset of patients, and the quality of the study method.

Heyland et al examined studies of patients undergoing elective surgery, critically ill patients with severe trauma, critically ill patients with severe burns, and critically ill patients in an ICU. Analysis of the aggregated trials revealed that immunonutrition was associated with no mortality advantage. The aggregated results also indicated that patients given immunonutritional formulas had fewer infectious complications and shorter lengths of stay in the hospital than did patients given standard enteral formulas.

*Arginine immunonutrition in surgical patients results in fewer infectious complications, but when used in patients with shock, sepsis, or organ failure, results in higher mortality.*

Studies were further examined by Heyland et al<sup>1</sup> to determine the effects of immunonutrition on mortality, infectious complications, and duration of ICU stay and mechanical ventilation in subgroups of critically ill patients. Treatment with formulas containing arginine had no effect on mortality or rate of infectious complications; it did result in a reduction in length of hospital stay. Mortality was higher in the studies in which formulas other than those high in arginine content were used. In addition, the number of infectious complications tended to be lower in studies in which formulas with high arginine content were used.

In critically ill patients with shock, sepsis, or organ failure, treatment effects differed significantly from those of surgical patients.<sup>1</sup> Although immunonu-

trition with arginine was associated with a significant reduction in the rate of infectious complications in surgical patients, it had no effect on mortality or rate of infectious complications in critically ill patients, indicating possibly a trend toward harm.<sup>1</sup> A possible explanation for this finding is that the use of immunonutrition with arginine can increase the release of proinflammatory cytokines and the production of nitric oxide, changes that may be detrimental in critically ill patients who are already experiencing a heightened inflammatory response. In patients with severe SIRS and sepsis, administration of enteral formulas containing arginine can cause transient hypotension, increases in cardiac index, and decreases in systemic and pulmonary vascular resistance.<sup>50,51</sup> Further research is needed to determine underlying deleterious mechanisms of immunonutrition with arginine in this vulnerable population of patients.

Findings from other studies also support the assumption that immunonutrition may be harmful in critically ill patients. Bower et al<sup>9</sup> compared the effect of Impact, an immunonutritional supplement with arginine, and Osmolite HN in 326 critically ill patients. Data on 47 patients were dropped from the primary analysis because of inconsistency in feedings. The results indicated that more deaths occurred in patients who received the arginine-supplemented formula (15.7%) than in the control group (8.4%;  $P=.055$ ). Among the patients with sepsis who received the arginine supplement, the death rate was 3 times that of patients with sepsis who received the control feedings (25% vs 8.9%,  $P=.051$ ).

The results from the studies<sup>1,4</sup> described do not support the use of currently available immunonutritional formulas with arginine in the most critically ill patients who have sepsis. The studies indicate that early immunonutrition in selected surgical patients may improve clinical outcomes, but the issue needs further study.

### **Implications for Nursing Practice and Research**

Immunonutritional formulas supplemented with arginine (Table) are widely used in acute and critical care units to enhance immune function in metabolically stressed patients. These formulas are expensive, and on the basis of the clinical evidence, significant improvements are restricted to surgical patients.

We think that immunonutrition with arginine can be safely used in surgical patients. Patients with critical illness, however, have a heightened immune response and systemic inflammation. Patients with SIRS, sepsis, and organ failure have had adverse

effects when given immunonutritional formulas containing high concentrations of arginine, a substance that may increase systemic inflammation and compromise clinical outcomes. Because arginine is potentially toxic, critically ill patients should be given immunonutritional formulas containing arginine only in situations in which extreme caution is taken and under controlled study conditions. Indications of the toxic effects of arginine may include immunosuppression, hemodynamic instability, organ dysfunction, and cytotoxicity. Because arginine intensifies the inflammatory response, the likelihood of toxic effects is highest in patients who have sepsis, SIRS, organ failure, or severe infections. Furthermore, differentiating sepsis from the toxic effects of arginine may be difficult, because the signs and symptoms are similar. Toxic effects due to arginine can also occur in patients with renal or hepatic dysfunction. The effects of immunonutrition with arginine in other subgroups of critically ill patients are less clear, and further research is necessary to determine the safety and efficacy of such immunonutrition.

*Differentiating toxic effects of arginine from sepsis is difficult because the signs and symptoms are similar.*

Further studies are needed that incorporate prospective, randomized, controlled clinical trials designed to carefully investigate the effect of treatment with immunonutrition and arginine in subsets of patients (eg, patients with trauma, sepsis, or SIRS). In addition, clinical trials should include study groups stratified according to severity of illness, and control groups should receive isoenergetic and/or isonitrogenous treatments. Statistical analyses should include intent to treat subjects, and interactions between compliance or tolerance to the study interventions should be dealt with because of the threat of bias. Furthermore, studies should include comparable groups of patients to increase the generalizability of the results.<sup>1</sup>

### **Summary**

The benefits of enteral immunonutrition with arginine are most significant in surgical patients. Unfortunately, questions still exist about the effect of treatment with immunonutritional formulas containing arginine in critically ill patients, and further research is necessary to determine underlying mechanisms by

which arginine may be deleterious. Sound nursing practice is guided by scientific rationale for therapy. Current research does not support the use of currently available immunonutritional formulas with arginine in most critically ill patients experiencing SIRS, sepsis, or organ failure.

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