Arginine in the Critical Care Setting[1–3]

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Abstract

Arginine is a nonessential amino acid in the normal physiological state that becomes conditionally essential during periods of hypermetabolic stress. Recent literature supports the hypothesis that arginine plays an important role in the intermediary metabolism of the critically ill patient. Current critical care literature is conflicting on arginine use in the clinical setting, with some proposing it as a panacea, whereas others report it as poison. Multiple individual reports and at least 5 major meta-analyses using combinations of immune-modulating nutrients have reported mostly beneficial results, but few have evaluated the effects of arginine when given as a single supplemental nutrient. This review attempts to objectively analyze the literature and evaluate the potential role of arginine in the critical care setting. J. Nutr. 137: 1687S–1692S, 2007.

Care of the critically ill patient has changed dramatically in the past 5 y. These changes have been driven by evidence-based reports of decreased morbidity and mortality (1). These well-designed prospective randomized trials have focused on meticulous glycemic control, limiting ventilator tidal volumes in acute lung injury/adult respiratory distress syndrome, timing of sepsis resuscitation, use of steroids, activated protein C, and intensivist lead critical care teams. These interventions and others have been summarized in the Society of Critical Care Medicine Surviving Sepsis Campaign (1). Nutritional support has always been an integral part of critical care but was conspicuously absent from the Surviving Sepsis Guidelines. Nutrition was probably omitted, because consistent studies reporting benefits in lowering mortality are lacking. Recently, however, 2 well-designed clinical studies reported lower morbidity and mortality with early (<48 h) feeding (2,3).

The use of immune-modulating specific nutrients and formulas has become routine in the critical care setting in many well recognized major institutions (4). At least 6 so-called immune-modulating formulas are currently commercially available in the US. Some combination of the nutrients arginine, n-3 fatty acids, glutamine, antioxidants, and nucleic acids are those most commonly found in these formulas. Arginine, one of the key components of these formulas, has gained specific attention and has been reported by some to be a panacea, whereas others consider it a poison in the intensive care unit (ICU)[4] setting. This brief review will attempt to objectively evaluate the current concepts supported by clinical or experimental data regarding the use of arginine in the critical care setting.

Arginine metabolism in critical care

Arginine is considered a nonessential amino acid under normal physiologic conditions. It becomes conditionally essential in the stressed mammalian host and plays an important role in the intermediary metabolism of the critically ill patient (5,6). L-Arginine is available to the host from endogenous synthesis (via citrulline conversion in kidney), endogenous protein breakdown, and dietary protein sources (diet only contributing ~20–25% of total arginine supply). Arginine is a prominent intermediate in polyamine synthesis (cell growth and proliferation) and proline synthesis (wound healing and collagen synthesis) and is the only biosynthetic substrate for nitric oxide (NO) production [via endothelial NO synthase, inducible NOS (iNOS), and neuronal NOS]. NO is a potent intracellular signaling molecule that influences virtually every mammalian cell type. Arginine also serves as a potent modulator of immune function via its effects on lymphocyte proliferation and differentiation (5) as well as its benefits in improved bactericidal action via the arginine NO pathway (7–9). Clearly, arginine metabolism and availability will affect outcomes in the critically ill patient.

As mentioned above, the de novo synthesis and dietary intake is reduced in critical illness. Whereas supply is decreased, the cellular demand for arginine is increased. This increased demand in trauma, surgery, sepsis, and critical care settings is driven mainly by the upregulation of arginase yielding urea and ornithine, and iNOS yielding NO and citrulline (10). The upregulation of arginase has recently been the focus of attention for its importance in potentially reducing NO levels, presumably by

[1] Published in a supplement to *The Journal of Nutrition.* Presented at the conference ''The Sixth Workshop on the Assessment of Adequate and Safe Intake of Dietary Amino Acids'' held November 6–7, 2006 in Budapest. The conference was sponsored by the International Council on Amino Acid Science (ICAAS). The organizing committee for the workshop was: David H. Baker, Dennis M. Bier, Luc A. Cynober, Yuzo Hayashi, Motoni Kadowaki, Sidney M. Morris, Jr., and Andrew G. Renwick. The Guest Editors for the supplement were: David H. Baker, Dennis M. Bier, Luc A. Cynober, Motoni Kadowaki, Sidney M. Morris, Jr., and Andrew G. Renwick. Disclosures: all Editors and members of the organizing committee received travel support from ICAAS to attend the workshop and an honorarium for organizing the meeting.

[2] Supported by: no sources of financial support.

[3] Author disclosures: M. Zhou, no conflicts of interest; R. G. Martindale, travel expenses to the meeting were paid by the ICAAS.

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[4] Abbreviations used: GI, gastrointestinal; HTN, hypertension; ICU, intensive care unit; iNOS, inducible nitric oxide synthase; LOS, length of stay; NO, nitric oxide; OKG, ornithine α-ketoglutarate; QSR, quality score rate.

reducing the available arginine (5). Elevated levels of arginase, as reported in acute trauma and surgery, resulted in inhibition of NO synthesis and alterations of gene expression. The increased arginase levels within the activated macrophage results in limiting T-cell proliferation by decreasing the expression of the ζ-chain portion of the receptor. These changes in arginase activity resulted in impaired immune function at multiple levels of the immune response (11,12).

The "critically ill" is a heterogeneous group

The problem with making general statements about critical care metabolism is that the "critically ill" population is not a homogeneous group. Making any generalized statements about the toxicity or benefits of any dietary supplement, let alone an amino acid with the metabolic complexity of arginine, is naive. Both animal and human data are available to support the argument that arginine is potentially beneficial in some models, whereas others have argued that arginine is toxic and could potentially have an adverse influence on clinical outcomes (10,13).

The speculation that arginine may pose a threat to the critically ill patient is mainly based on the concept that critically ill patients are often hemodynamically unstable and that this population is in a state in which iNOS is commonly upregulated. Consequently, delivering supplemental arginine as the substrate for upregulated iNOS will result in increased NO. This increased NO could result in vasodilation and hypotension, leading to greater hemodynamic instability (14). An alternate, equally valid argument would be that controlled vasodilation would be beneficial in critical illness and sepsis. Shock by definition is "inadequate delivery of oxygen and nutrients to maintain normal tissue and cellular function" (10). It is logical that the vasodilation resulting from supplemental arginine is a cellular adaptive mechanism attempting to increase delivery of oxygen to the cell.

Unfortunately, few human studies have evaluated arginine as a single agent in the critically ill population. **Table 1** summarizes the arginine content in currently available immune-modulating formulas in the US. These formulas deliver between 0 and 18.7 g supplemental arginine/L formula. It is estimated that on average, an ICU patient receiving enteral feeding at goal rates would receive between 15 and 30 g arginine/d.

Clinical studies with arginine-containing formulas

Five major meta-analyses (15–19), including various combinations of at least 31 different individual studies, have been conducted using immune-modulating formulas containing arginine in a variety of diagnoses and reached roughly the same conclusions. These arginine-containing formulas can reduce infectious morbidity and decrease length of stay (LOS) in most ICU populations (**Table 2**). Mortality benefit has not been reported (17,20). A consensus conference regarding the use of immune-modulating formulas was published in 2001 (21) (**Table 3**).

Several factors must be considered when deciding if arginine fits into the therapeutic plan of the critically ill patient. One must evaluate organ systems involved, timing of nutrient delivery, and location and route of delivery.

Arginine is available to the host from numerous sources, as mentioned above. Normal arginine intake for a western diet is between 5 and 7 g/d and endogenous production of arginine is estimated at 15–20 g. Numerous studies using differing doses of arginine from 5 to 30 g/d in the normal host have shown varying results. It appears orally delivered arginine supplementation up to 30 g/d is safe with few gastrointestinal (GI) side effects (22,23). **Table 4** shows several studies in which arginine was given i.v. for various disease conditions. In normal healthy controls, 1-time doses >30 g usually result in mild diarrhea (23). So it is fairly clear that levels up to 30 g/d are safe in the healthy individual. The appropriate and safe level in the critically ill or

TABLE 1 Arginine content in various immune-modulating formulas available in the US

Product	Manufacturer	Protein	Arginine
		g/L	
Alitraq	Abbott/Ross	52.5	4.5
Optimental	Abbott/Ross	51.3	5.5
Oxepa	Abbott/Ross	62.5	0
Perative	Abbott/Ross	66.6	6.5
Crucial	Nestle	94	15
Peptamen AF	Nestle	75.6	0
Impact	Novartis	56	12.5
Impact (with fiber)	Novartis	56	12.5
Impact 1.5	Novartis	84	18.7
Impact Glutamine	Novartis	78	16.3
Immunex-Plus	Victus	37	14

TABLE 2 Meta-analyses of immune-modulating formulas containing arginine

Author	*n*	Studies	Outcome
Heys et al. (17)	1009	11	↓ Infection
Beale et al. (15)	1482	12	↓ Infection ↓ Ventilator
Heyland et al. (16)	2419	22	↓ Infection ↓ LOS
Montejo et al. (18)	Not specified	26	↓ Infection ↓ Ventilator ↓ LOS
Waitzberg et al. (19)	2305	17	↓ Infection ↓ LOS

TABLE 3 Consensus recommendations from the U.S. summit on immune-enhancing enteral therapy (21)

Clearly established benefit
Elective GI surgery
Esophageal
Pancreatic
Gastric
Major hepatobiliary
Blunt or penetrating torso trauma
Injury severity score >18
Abdominal trauma index >20
Probable benefit
Elective major surgery
Aortic reconstruction with chronic obstructive pulmonary disease
Expected post op ventilator
Major head and neck surgery
Severe head injury
Burns >30%
Ventilator dependent nonseptic ICU patients
No benefit
Able to resume oral intake within 5 d
In ICU only for monitoring

TABLE 4 Studies in which arginine was given i.v. for various disease conditions

Author	Disease condition	I.v. dose	Outcome
Barbul et al. (50)	Surgical wound	28 g/d	↑ Collagen deposition
Facchinetti et al. (51)	Preterm labor	30 g/30 min	↓ Uterine contractions
Campisi et al. (52)	Cardiac	30 g/45 min	Normalized vasomotor tone in smokers
Mehta et al. (53)	Pulmonary HTN	0.5 g/kg	↓ Pulmonary HTN
Luiking et al. (32)	Sepsis	1.2 μmol·kg^{-1}·min^{-1} for 72 h	No adverse hemodynamics
Komorowska-Timek et al. (54)	Free flap blood flow	30 g/d	↑ Blood flow, ↓ flap loss
Berard et al. (55)	Surgical ICU	Total parenteral nutrition enriched with arginine (129.2 mmol/L vs. 86.1 mmol/L)	↑ Nitrogen balance, ↓ protein myofibrillar catabolism

hypermetabolic patient in which a proinflammatory state exists is much more difficult to determine.

Arginine in sepsis

In an attempt to determine the influence of individual nutrients, several animal studies have been performed that evaluated only arginine. Animal models of supplemental arginine in sepsis have yielded a variety of results. It is difficult to compare results between species secondary to the differences in dosing, models, route of delivery, and variability of amino acid metabolism between the species (24). Reviewing the rodent, rabbit, guinea pig, dog, sheep, and pig data, the results are very mixed, again depending on the model of infection or sepsis, dose, method of delivery, and species. The results are an almost equal mix of benefit, no change, or adverse effect (25–31). The studies that report adverse effects for arginine appear to be at the higher administered levels. At these levels, the imbalance of amino acids may be great enough to affect cellular protein synthesis and alter immune response (25).

Using a canine model of *Escherichia coli* sepsis, intravenous L-arginine was studied as monotherapy at doses of 10 mg·kg^{-1}·h^{-1} and 100 mg·kg^{-1}·h^{-1}. In this model, the arginine supplementation resulted in higher mortality (24). The problem with extrapolation of this study to a human model is that the study used supraphysiologic or pharmacologic levels given i.v. These levels of arginine are 10–20 times greater than the highest levels given in any of the human studies that involved critically ill patients. This study also used i.v. arginine. Arginine delivered via the GI tract undergoes metabolism of ~40% before ever reaching the portal circulation (13). The liver further metabolizes the arginine delivered to it from the portal circulation. Consequently, it is difficult to make any clinically relevant conclusion regarding humans at currently delivered doses enterally. Arginine infusion in septic humans has been recently reported by Luiking et al. (32). This prospective randomized double-blind placebo control study evaluated 18 severely septic patients who required pressor agents to support their hemodynamics. Hemodynamics and protein nitrotyrosine were monitored during infusion of arginine at 1.2 μg·kg^{-1}·min^{-1} or placebo (alanine). This study showed no adverse effects on nitrotyrosine levels or hemodynamics (32).

To answer the issue of arginine safety in critical care, reviewing the currently published studies in which the immune-modulating formulas were delivered to a portion or all of the patients in the study is useful. One study has primarily evaluated the septic population. Galban et al. (33) in 2000 reported that addition of an immune-modulating formula that contained arginine was beneficial in improving outcome. This benefit was observed in only the sub-group with relatively low acute physiology and chronic health evaluation scores (<15). Other major studies in which at least a portion of the patients carried the diagnosis of sepsis while receiving a formula containing arginine have reported that the immune-modulating formulas are either beneficial, no benefit over control, and/or are potentially harmful (34–38). Most of these studies contained heterogeneous populations, suffered from design flaws, or delivered inadequate or subtherapeutic levels of active nutrient.

The arginine controversy essentially revolves around interpretation of 3 studies. Galban (33) showed benefit in the moderately septic patient using a high arginine-containing formula (supplemental arginine 12.5 g/L). Dent et al. (37) reported in abstract form only a placebo-controlled study showing a higher mortality in the experimental group that received a low arginine formula (supplemental arginine 5.5 g/L). This study suffers dramatically from what appears to be a randomization error. A total of 171 patients were randomized with mortality in the control group at 9.6%, whereas the experimental group receiving a low arginine formula had 23% mortality. The randomization ended with the experimental group having a much higher percentage of patients with pneumonia on entry into the study. The mortality in the subgroup with pneumonia was 50% and those without pneumonia 0% (37). The other study that reported adverse effects of supplemental arginine was Bertolini et al. (34). This group compared a low arginine-containing enteral formula to total parenteral nutrition (34). Observers in this study had knowledge of the test groups. The study was discontinued prior to completion and was poorly stratified, with most patients having pneumonia on entry into the study. The only conclusions, if any, that can be made from reviewing these 2 studies is that low arginine-containing enteral solutions should not be given to septic ICU patients with preexisting pneumonia.

The concept that arginine could be potentially detrimental was further elaborated on by Heyland et al. (16) in their meta-analysis. They concluded that arginine was potentially toxic in the medical ICU population. This conclusion was based mainly on a quality score rate (QSR) given to each study in the meta-analysis. The Dent et al. study (37) that has not been published in peer reviewed literature was given a very high QSR, whereas the Galban (33) study was given a low QSR, because it was not an intention to treat. This in effect downplayed considerably the beneficial study while enhancing the importance of the Ross study, showing a low arginine formula having adverse influence on outcome. These effects were discussed in detail by Cynober (39).

Certainly the arginine/NO controversy will continue until more studies have consistently confirmed either benefit or detriment of arginine supplementation. **Table 5** summarizes the cytotoxic vs. protective effects of arginine and NO. This table clearly illustrates that the potential interactions and effects are numerous and extremely complex. Because arginine is so

TABLE 5 Cytotoxic vs. protective effects of arginine and NO

Cytotoxic effects of NO and arginine	Protective effects of NO and arginine
Metabolic pathway inactivation	Hepatic damage following septic insult
Damage to cell structure	GI injury and splanchnic permeability
Lipid peroxidation	Pulmonary HTN
Nitration of tyrosine	Lung neutrophil infiltration
Oxidation of sulfhydryl groups	Myocardial ischemia
DNA mutations	Secondary sinus infections
DNA strand breaks	Inhibits apoptosis
Activates poly(ADP-ribose) polymerases	Antiinflammatory mediator
Alterations in gene expression	Downregulator of intercellular adhesion molecule
Possible detrimental hypotension in sepsis	Decreases neutrophil adhesion
	Inhibits activation of nuclear factor κ B
	Prevents endothelial damage
	Platelet aggregation
	Leukocyte adherence
	Free radical scavenger
	Enhances anastomotic healing
	iNOS inhibitor in sepsis is harmful

critical to the intermediary metabolism of cell survival, this results in a litany of regulatory points for arginine within the cell, including: control of transporters into the cell, enzyme substrate regulation, production of endogenous inhibitors such as dimethylarginine, colocalization of enzyme systems, and competition of arginine for various metabolic pathways.

The potential interactions between arginine and other delivered nutrients must also be considered. In very different models, Bansal et al. (40) and Alexander et al. (41) have both shown that delivery of an n-3 fatty acid with arginine will significantly alter the arginine metabolism via arginase and iNOS and possibly yield more available arginine.

Ornithine α-ketoglutarate (OKG) and citrulline are other nutrients that reportedly have potential interaction with arginine. Citrulline is not metabolized by the liver and thus has higher bioavailability. It can then be converted to arginine in the kidney, making citrulline important in arginine homeostasis (42). OKG also increases serum arginine levels when administered orally as a bolus dose (43). A complete discussion of all the interactions of citrulline and OKG are beyond the scope of this brief review and can be found in the references listed above.

Which patients are candidates for supplemental arginine?

From review of the available animal and human data, arginine appears to be safe and potentially beneficial at doses delivered in immune modulation formulas for most all hemodynamically stable ICU populations able to tolerate enteral feeding. This would include medical and surgical ICU patients, trauma patients, major surgical patients, postmyocardial infarction, and those with pulmonary hypertension (HTN). In elective major surgical patients expected to be admitted to the ICU postoperatively, arginine given before the surgical insult has been shown to be beneficial (**Table 6**) (44,45).

TABLE 6 Pre- or perioperative immune-modulating formula

Author	Population	*n*	Outcome
Braga et al. (56)	GI surgery	206	↓ Infection
Senkal et al. (57)	Surgery	154	↓ Infection
Synderman et al. (58)	Head and neck cancer	134	↓ Infection
Riso et al. (59)	Surgery	44	↓ Infection
Tapaske et al. (60)	Cardiac	50	↓ Infection
Gianotti et al. (45)	GI surgery (nourished)	354	↓ Infection
Braga et al. (44)	GI surgery (malnourished)	196	↓ Infection

Who is not a candidate for supplemental arginine?

Hemodynamically unstable ICU patients with poor gut perfusion are not candidates for supplemental arginine. Generally speaking, patients who are hemodynamically unstable should not be fed enterally with any formula (46). If enteral feeding is pursued in patients during hemodynamically unstable periods, it should be done with extreme caution, so as not to result in mesenteric ischemic injury. Animal data by Sato et al. (47) showed in an in vivo ischemic model of superior mesenteric artery occlusion that free arginine delivered to the lumen was toxic to the mucosal surface.

How much arginine is enough in critical illness?

The optimal level is yet to be determined. It is know that arginine plasma levels rapidly decline in critical illness, trauma, and sepsis (48). This decrease in plasma levels is thought to result from decreased intake, increased tissue uptake, and increased metabolism, mainly from arginase and iNOS. Arginine transport in catabolic states is accelerated in several tissue beds including liver, intestine, and endothelium (49). It can be extrapolated from several studies that the 15–30 g of enteral supplemental arginine, which is the amount commonly given when a critically ill patient is being fed enterally at goal rates with immune-modulating formula, is safe and appears to meet the needs of the patient.

In conclusion, as with any metabolically active nutrient, before any firm conclusion or consensus is made on arginine use in the critical care setting, one must first define the patient's injury or illness, establish the level of nutrients to be delivered, and understand what other active nutrient metabolites are being delivered. The numerous potential beneficial effects of arginine in the critically ill patient include: *1*) stimulation of immune function via its influence on lymphocyte, macrophage, and dendritic cells; *2*) improved wound healing; *3*) increased net nitrogen balance; *4*) increased blood flow to key vascular beds; and *5*) decreased clinical infections and length of hospital stay. These reported benefits cannot be ignored without at least consideration and critical evaluation of the data. The potential that arginine may have detrimental effects in patients at the doses delivered in clinical conditions must also be considered, although this appears to be supported more by theoretical concepts rather than clinical data.

The principle of using nutrients as a therapeutic strategy rather than just as nutritional support requires a shift in the current dogma. As with arginine, if nutrients are used for therapy, one must consider the therapeutic level, the dosing, the timing of delivery, and the metabolic state of the patient just as one would evaluate for any other therapeutic pharmaceutical.

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