Abstract
Dietary arginine supplementation has been suggested as a means of improving T lymphocyte function and has found its greatest clinical utility in patients undergoing elective surgery. In other illnesses, arginine supplementation is controversial. Breakthroughs in understanding arginine metabolism have led to the identification of myeloid cells that express arginase 1, causing significant depletion of arginine – an essential amino acid for normal T lymphocyte function. Hence, myeloid cells expressing arginase 1 are also known as myeloid-derived suppressor cells. This chapter discusses the hypothesis that arginine replacement therapy may be necessary in arginine deficiency states.

Introduction
The ultimate goal of our research is the improvement of host defenses to successfully prevent infections after physical injury (PI), be it surgery or trauma. T-lymphocyte dysfunction (called by multiple different terms including immuno-paralysis) is characteristically observed after PI and is a major cause of altered host defenses. T lymphocyte dysfunction is thought to render the host susceptible to infection. Infections after surgery or trauma (SI) significantly increased morbidity and mortality, and because of their high cost, are recognized as a major public healthcare problem. As such, multiple
strategies aimed at prevention of SI focus on eradication of pathogens and/or modification of the environment. To our knowledge, there is no public health policy aimed at improving host defenses as a means of preventing SI [1, 2].

We have used 2 different but related approaches to better understand the mechanisms that lead to immune-paralysis and designed successful translational treatment strategies as follows: First, we have successfully developed and extensively tested an animal model of PI that is realistic, associated with T lymphocyte dysfunction, and that is susceptible to a subsequent infection. In addition, we have identified a novel mechanism of T cell suppression by immature myeloid cells – that of arginine depletion through the expression of arginase 1 (ARG1). ARG1 pharmacological blockade or large quantities of arginine overcome T cell dysfunction and prevent increased susceptibility to infection caused by PI. This work has joined others at identifying now officially called myeloid-derived suppressor cells (MDSC), which also play important roles in T cell suppression in several diseases such as cancer, tuberculosis, parasitic diseases and others. Second, based on the observations gained through the animal model, we have focused a portion of the work on clinical translation. Local and systemic arginine deficiency develops in humans after PI similar to that observed in mice. In addition, we have identified myeloid cells that express large amounts of ARG1 and are capable of depleting arginine and can cause T cell dysfunction in coculture experiments. More importantly, we have proceeded to test different strategies aimed at providing arginine replacement therapy (ART), and in collaboration with experts in the field demonstrate clear evidence that diets containing supraphysiologic quantities of arginine given perioperatively are associated with a 40% decrease in infection rates. These clinical observations all support the hypothesis that arginine deficiency is a clinically relevant syndrome that can be treated successfully through modulation of MDSC activity.

This chapter explains in further detail how a repeated research process starts with clinical observations followed by testing of mechanistic hypothesis in animal models that then leads to the translation of these findings back to the bedside followed by new clinical observations that start the process anew. This never-ending cycle has led to a dramatic increase in our understanding of arginine metabolism after PI and in other disease process. The knowledge generated now permits practical clinical applications of arginine replacement. In the future, this work will continue to contribute to the development of exciting personalized therapeutic possibilities utilizing arginine replacement strategies in a growing number of illnesses.
Public Health and Surgical Infections

Trauma is currently the most expensive illness in the USA. It is thought that there are over 50 million injuries per year, and it is calculated that approximately 10% of all trauma patients develop wound infections. Infection risk jumps up to 30% in traumatized patients that remain in the intensive care unit for over 48 h. Infections are the main cause for the development of late organ failure and may contribute to up to 10% of all trauma-related deaths. Infections dramatically add to morbidity in all trauma patients and significantly increased length of stay, the need for institutional rehabilitation and cost. Strategies aimed at infection prevention after trauma should result in a significant decrease in morbidity, mortality and cost.

Like trauma, infections after elective surgery are a major health care problem and the largest contributor to health care-associated infections (HAIs). HAIs also add significant morbidity and mortality to the patient undergoing elective surgery. Although it is difficult to calculate, trauma and elective surgery-related HAIs add a cost burden that can be measured in the tens of billions of dollars or even more. Awareness of the negative impact of infections in surgery and in trauma has led to the development of national prevention initiatives such as the Surgical Infection Prevention Project and the Surgical Care Improvement Project and other interventions that demand large amounts of resources (http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf).

All infections occur as a result of the interaction between a pathogen and a host in a given environment. Interventions in any of these (pathogen, host or environment) constitute the basis for infection prevention. In nonsurgical illnesses, interventions include eradication of pathogens, initiatives to improve the environment (i.e. clean water) and boosting of host defenses with strategies such as vaccination or dietary improvement. In surgical patients, infection prevention initiatives concentrate on eliminating pathogens (i.e. antibiotics) and modifying the environment (i.e. hand washing, gowns and gloves).

Improving host defenses as a strategy to prevent SI is particularly important. To date, therapies aimed at improving host defenses have failed with one exception, that of the provision of supraphysiologic quantities of arginine as an ART generally in conjunction with the provision of omega 3 fatty acids and nucleotides [3]. For more than two decades, ART strategies in elective surgery and after trauma have been known to improve T lymphocyte function and are associated with decreased infection rates. Yet, the mechanism of how ART works has eluded us. Lack of knowledge of mechanisms of action along with poorly defined concern of harm in patients other than surgical or trauma patients has contributed to a significant amount of controversy and lack of uniformity in the utilization of ART.
It follows that understanding arginine metabolism after PI should help us dictate when and where to prescribe arginine replacement and monitor its physiologic and clinical effects. In addition, mechanistic understanding of arginine metabolism should help clinicians personalize arginine replacement avoiding patients in whom benefit would not be observed and side effects could occur.

In 1978, Adrian Barbul reported that the provision of 2% arginine in the drinking water of rodents undergoing a skin injury to their dorsum prevented thymic involution when compared to controls. The rationale for supplemental arginine stemmed from the observation by Rowe and others that arginine was a ‘conditionally’ or semi-essential amino acid, meaning that its supplementation was needed during times of stress. This label of ‘conditional’ underscored the fact that arginine deficiency developed soon after injury and its supplementation was necessary to sustain important cellular functions [4].

The drop in circulating arginine can be observed within minutes or a few hours after injury. The time that arginine remains decreased in the circulation is proportional to the severity of the PI and occurs across species including humans and rodents. Thus, in severe injury observed in trauma, arginine levels remain persistently low for up to one week or more (fig. 1a) [5]. In contrast, in mice with only a moderate injury, arginine plasma levels recover in less than 24 h (fig. 1b) [6].

However, a drop in arginine levels does not mean that a clinically significant deficiency exists. Indeed, a nutritional deficiency, and arginine is no exception, is only present if biological processes dependent on the nutrient are compromised, and if this compromise leads to abnormal physiologic responses that are causative of poor clinical outcomes. Causality is determined in a nutritional deficiency syndrome when the following criteria are met: (1) a decrease in the availability of the nutrient, (2) identification of the processes that lead to the decrease in nutrient availability, (3) alterations in biochemical and biological processes that lead to a clinically identifiable pathology (i.e. poor wound healing, increased infection), and (4) that replacement or restoration of the nutrient improves biochemical and biological processes and reverses the signs and symptoms of clinical illness. These criteria meet the requirements of determination of causality classically known as the Bradford Hill criteria, best described for cancer. These criteria include the four categories of enumerative induction, eliminative induction, deduction and analogy [7, 8].

Our work has concentrated on determining whether a drop in arginine availability after PI conforms to the Bradford Hill criteria. As a first step, we have studied arginine metabolism in two cell types: (1) myeloid cells and (2) T lymphocyte function.
Myeloid cells constitute a complex cell lineage that includes granulocytes, macrophages, dendritic cells and others. It is difficult to generalize how arginine is metabolized by these cell types as their characteristics and functions may vary significantly between healthy states and different illnesses and among species. As a general rule, however, arginine metabolism plays little if any significant role.

**Fig. 1.** 

**a** Arginine plasma levels drop within hours after trauma and remain decreased for at least one week. Citrulline levels are also decreased. Ornithine levels decrease initially but return towards normal values. **b** Arginine plasma levels decrease within 1 h after injury (exploratory laparotomy) in mice. The nadir is reached at 4 h.

**Myeloid Cells**

Myeloid cells constitute a complex cell lineage that includes granulocytes, macrophages, dendritic cells and others. It is difficult to generalize how arginine is metabolized by these cell types as their characteristics and functions may vary significantly between healthy states and different illnesses and among species. As a general rule, however, arginine metabolism plays little if any significant role.
in myeloid cells in the absence of immune activation. Immune activation during illness can lead to the utilization of arginine through two very different metabolic pathways with dramatically unique metabolic functions and biological consequences.

Classic inflammatory response by myeloid cells has been called by the term M1 responses. M1 responses are observed commonly during acute infections and lead to the induction of nitric oxide synthase (iNOS). Large amounts of nitric oxide are produced through iNOS during septic responses in mice and in humans and can be identified by the accumulation of nitric oxide metabolites (NOx) in blood and urine. Nitric oxide production by myeloid cells is essential as a defense mechanism and is involved in the killing of microorganisms and cancer cells. Nitric oxide is a potent vasodilator and is also produced in small amounts in the vascular endothelium through constitutively expressed NOS [9].

In 1989, soon after the production of nitric oxide was identified, we tested the hypothesis that when produced in excess, nitric oxide could contribute to the hemodynamic instability of sepsis. Our group measured the accumulation of NOx in plasma in septic patients. As expected, NOx accumulated in plasma in patients with sepsis. Increased NOx in these patients correlated with decreased systemic vascular resistance suggesting inappropriate vasodilation. Increased NOx also correlated with elevated levels of endotoxin. This observation, published in 1991 constituted the first observation in humans that excessive nitric oxide production could be a causative factor in the pathophysiology of sepsis [10].

In contrast to the observations in septic patients, trauma patients fail to accumulate NOx, and indeed decreased amounts of nitrates are excreted in urine. Most striking is the fact that little if any NOx accumulate in trauma victims that subsequently become septic. The explanation for these human observations remained unclear until the development of a successful model of moderate injury in rodents with which to study arginine and nitric oxide metabolism. In this model, animals are anesthetized and a laparotomy with gentle bowel manipulation is performed. Subsequently, endotoxin or an infection with live bacteria (such as Listeria monocytogenes) is subsequently given. The similarities between human and rodent accumulation of NOx are striking. NOx accumulate in large quantities after endotoxin injection in mice in the absence of injury. However, accumulation of NOx is significantly blunted after injury even when mice are injected with endotoxin (fig. 2) [11].

The availability of a rodent model opened the possibility of gaining a better understanding of arginine metabolism in myeloid cells after injury. M2 myeloid responses, also known as alternative macrophage activation responses are associated with the induction of ARG1, an enzyme that metabolizes arginine to or-
Arginine Deficiency and Immunity

notinine and urea. Induction of ARG1 in immune tissues in rodents and peripheral blood mononuclear cells in humans was described after PI by us as early as 2001 (fig. 3) [5]. ARG1 expression was subsequently found to be localized to a particular cell type. These cells were characterized by the membrane markers CD11b+ denoting their myeloid cell origin. In addition, these cells expressed GR-1+ on the cell membrane, a marker of biologic immaturity, and a number of these cells were observed actively dividing in the spleen.

**Fig. 2.** NOx accumulation after endotoxin (LPS) injection and after trauma. NOx accumulate in large quantities after endotoxin but not after trauma. Strikingly, mice subjected to injury and a subsequent endotoxin injection fail to accumulate NOx.

**Fig. 3.** Arginase activity is significantly increased in peripheral blood mononuclear cells after trauma. Arginase activity remained elevated for up to 7 days compared to controls.
There appear to be significant differences in ARG1 expression in humans when compared to rodents. In humans, ARG1 is constitutively expressed in neutrophils and is released outside of the cell as neutrophils are activated and degranulate. Immature myeloid cells are not typically observed in humans, though it may well be that we are limited in studying immune tissues such as the spleen. In contrast, in rodents, it is particularly difficult to isolate neutrophils in the peripheral circulation. However, we have recently described that there is a significant increase in circulating arginase in rodents soon after injury demonstrating a source of ARG1 that is constitutively expressed and could be coming from granulocytes, suggesting that indeed the interspecies differences may not be as significant as initially observed.

**The Role of Arginase and Immature Myeloid Cells**

The fact that arginase is highly efficient at metabolizing arginine to ornithine and urea opens the possibility that its expression in myeloid cells could explain the rapid depletion of arginine from the circulation, and we raised this hypothesis with our first descriptions of increased ARG1 expression in humans. To test this, we measured arginase activity in plasma after injury and correlated this with circulating arginine plasma levels. As expected, a significant increase in arginase activity is observed acutely after injury in mice. This closely correlates with the disappearance of arginine from the circulation ($R^2 = 0.92, p < 0.001$; fig. 4) [6].

**Fig. 4.** Arginase activity is significantly increased in plasma in rodents after moderate injury (exploratory laparotomy). Arginase activity is also found to be increased in plasma in humans soon after trauma.
Immature myeloid cells expressing ARG1 distribute in a characteristic fashion in the marginal zones of the spleen in close proximity to T lymphocytes; this opens the possibility that myeloid cells could be acting locally regulating arginine availability for other cells [12]. We thus measured intracellular arginine levels in T cells after trauma finding a significant depletion by 24 h and extending up to 96 h. Preliminary data suggest that blocking ARG1 expression in vivo with nor-hydroxy-L-arginine results in a significant recovery in intracellular arginine after trauma.

**T Lymphocytes and Arginine**

T lymphocyte function is highly dependent on arginine availability. Without arginine, T cell proliferation is significantly blunted and the production of interferon-γ and interleukin-2 is also inhibited. Furthermore, T lymphocyte-mediated cytotoxicity and memory responses are nearly completely abrogated. The provision of arginine to the culture media restores T lymphocyte function [13, 14]. One of the most striking in vitro observations is the fact that the number of T cell receptors on the cell membrane is directly proportional to the amount of arginine in the culture media. In particular, the ζ-chain, a peptide in the T cell receptor complex is exquisitely sensitive to arginine deprivation.

T lymphocyte dysfunction observed after PI is strikingly similar to that observed through arginine deprivation in vitro. Loss of the ζ-chain expression was first reported in 1993 by Mizoguchi in patients and animal models of cancer, and was also associated with profound T cell suppression [15]. Loss of ζ-chain was then described in a number of illnesses including tuberculosis and leprosy; finally, Ichihara reported loss of ζ-chain after PI [16].

The fact that T cell dysfunction of trauma was so similar to certain forms of cancer and other chronic diseases suggested the existence of a common cause in all of these illnesses. The discovery that arginine deprivation in vitro could cause loss of ζ-chain prompted us, in collaboration with other investigators, to look for alterations in arginine metabolism beyond that of trauma or surgery [17, 18]. Parallel to our investigation, increased ARG1 expression was identified in tumor-associated macrophages and in immature myeloid cells. In addition, profound decreases in arginine plasma levels were also identified in patients with renal cell carcinoma, sickle cell anemia, after blood transfusions, and even in atherosclerosis.

A growing amount of evidence demonstrates that myeloid cells are capable of depleting arginine, and through this mechanism regulates biological func-
tions including T lymphocyte function. When placed in culture, immature myeloid cells (CD11b+/Gr1+) will actively metabolize arginine. CD11b+/Gr1+ cells placed in coculture with T lymphocytes impair T lymphocyte function and cause phenotypical changes that are similar to illnesses associated with arginine deficiency states (table 1). These observations have led to the understanding that arginine deficiency caused by myeloid cells expressing arginase is a mechanism of regulation of T lymphocyte function. Acknowledgement of the suppressive role of immature myeloid cells expressing ARG1 has led to the creation of a distinctive name: myeloid-derived suppressor cells – MDSC.

### Personalized Diagnosis of Arginine Deficiency

Evidence that arginine deficiency caused by MDSC is more widespread than previously thought prompts the need to develop practical biomarkers that accurately allow for early diagnosis. A significant number of potential biomarkers have already been identified and include measures of increased arginase expression, isolation of MDSC in peripheral blood, measuring circulating arginine and ornithine levels to name a few.

It is also possible that abnormal T lymphocyte function and phenotypical changes could be used to identify states of arginine deficiency and monitor the effectiveness of treatment. Measuring the membrane expression of the T cell receptor and the ζ-chain are some examples. Gene microarray technology offers an exciting possibility of screening for multiple changes in gene expression, some of which could be used as potential diagnostic tools. One of the most interesting genes identified is argininosuccinate synthase whose expression increases significantly in arginine deficiency states [19].

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**Table 1.** Phenotypical and functional changes in T lymphocytes when arginine is depleted from culture media (in vitro) can be reproduced when T lymphocytes are co-cultured in vitro with myeloid-derived suppressor cells (MDSC). T lymphocyte dysfunction is also observed in illnesses where MDSC expressing arginase 1 are increased

<table>
<thead>
<tr>
<th>Function/phenotype</th>
<th>Arginine deprivation (in vitro)</th>
<th>T cell/myeloid cell coculture (in vitro)</th>
<th>Surgery/trauma/cancer/infection</th>
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<td>Proliferation</td>
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TCR = T cell receptor.
We still have to make significant progress to adequately identify arginine deficiency in a given individual and provide accurate monitoring of its treatment. However, the knowledge gained so far demonstrates that the goal of personalized ART is possible and necessary.

**Treating Arginine Deficiency**

Along with the identification of arginine deficiency states comes the possibility of restoring arginine homeostasis as a means of improving arginine-dependent biological functions and outcome. We are aware of three different strategies to overcome arginine depletion caused by MDSC: (1) blocking the signaling molecules that result in upregulation of MDSC, (2) using pharmacologic blockade of ARG1, and (3) dietary supplementation with supraphysiologic quantities of arginine or citrulline.

**Nitric Oxide Production**

Restoration of nitric oxide production may provide significant benefits including the improvement of microcirculation and the capacity to fight infection and tumor growth. Our laboratory previously identified that MDSC accumulation in the spleen (and thus increased arginase activity) was dependent on the production of interleukin-4 and interleukin-13, both which share a common signaling pathway through STAT6. We thus tested the accumulation of NOx in STAT6 knockout mice after injury in response to endotoxin injection (LPS). As expected, nitric oxide production was restored once MDSC accumulation was prevented (fig. 5) [20].

Arginine replacement as a form of improving nitric oxide production has been tested extensively. Plastic surgeons routinely elevate skin flaps (called pedicled flaps) to transpose skin from one site to another. These flaps depend on capillary blood flow for their survival. Indeed, necrosis of the flap is a feared and unfortunately common complication. In 2001, Lovett et al. [21], in collaboration with our laboratory measured nitric oxide production in local skin flaps as they were being surgically manipulated. Surgical manipulation decreased local nitric oxide production. Systemic arginine infusion significantly increased local nitric oxide production and doubled the size of the flap that remained viable.

In humans, the use of ART has systematically shown to increase nitric oxide production. de Luis et al. [22] demonstrated a dramatic reduction in the
presence of orocutaneous fistulae in patients undergoing head and neck surgery, a result reminiscent of our observations in pigs. In 2001, Tepaske et al. [23] demonstrated that dietary arginine given preoperatively was associated with a significant improvement in lactate level postoperatively. In 2002, Braga et al. [24] demonstrated that arginine replacement significantly improved tissue oxygenation in patients undergoing colon surgery. Not surprisingly, ART has been shown to significantly improve wound healing and decrease the incidence of anastomotic breakdown in gastrointestinal surgery [24].

T Lymphocyte Function

T lymphocyte function is restored upon blocking MDSC in multiple experimental settings including our own models of injury and in cancer. In humans, ART using so-called immune-enhancing diets consistently improves T lymphocyte function including an increase in CD4+ (helper T cell counts), and increased cytokine production.

In our laboratory, Zhu has extensively studied the role of MDSC as a cause of increased susceptibility to infection. Mice subjected to moderate injury exhibited a dramatic increase in susceptibility to bacterial growth associated with a subsequent infection with \textit{L. monocytogenes}. This increased susceptibility to infection can be reproduced in the absence of injury by transferring MDSC into an otherwise normal mouse or by the injection of arginase. Pharmacologic blockade using nor-hydroxy-L-arginine improves T lymphocyte function and restores the capacity of mice to fight infection [Zhu, in print].

**Fig. 5.** Accumulation of NOx in plasma is significantly impaired in wild-type mice receiving an endotoxin injection (LPS) but is maintained in STAT6 knockout (STAT6KO) mice. STAT6KO mice exhibit impaired upregulation of ARG1 activity after trauma.
Clinical Benefits of Arginine Replacement Therapy

Parallel and independent of the basic work being performed in several laboratories including ours, others were doing clinical studies using arginine supplementation. Arginine was incorporated at supraphysiologic concentrations along with other dietary products such as omega 3 fatty acids, vitamin A and nucleotides, and tested in multiple patient populations including patients undergoing surgery. These diets were developed with only modest understanding of the potential function of the specific nutrients within the immune system. Furthermore, little testing of dose-responses or interactions between these nutrients has been done. Despite these significant problems, diets containing supraphysiologic quantities of arginine were called by several names such as ‘immune-enhancing diets – IEDs’. Others call them ‘immune-modulating diets’. To complicate matters further, different proprietary formulas were created, incorporating multiple nutrients and varying dosages; these nutrients included an array of amino acids, antioxidants and different types of oils. In addition, these diets were tested (and continue to be evaluated) in multiple patient populations without the development of a mechanistic hypothesis of action. It is thus no wonder that most of these trials have yielded no significant benefit and that under some unfortunate circumstances have suggested possible harm.

Based on the multiple observations described above, our laboratory suggests that diets containing supraphysiologic quantities of arginine may benefit patients when arginine deficiency develops. This hypothesis is easily testable and explains a possible mechanism of action of IEDs; furthermore, it allows for adequate identification of patient populations who could potentially benefit from arginine replacement. We thus propose that arginine replacement is of therapeutic value; arginine replacement therapy (ART) better reflects how these diets could work and should replace older acronyms such as immune-enhancing/modulating diets.

ART has been tested extensively in critically ill patients and in patients undergoing elective surgery. More than 30 different prospective randomized trials have been performed; most of these using the original diet containing 15 g of arginine/l, omega 3 fatty acids and nucleotides [3]. The majority of these trials have been done in patients undergoing gastrointestinal surgery, though other patient populations including patients undergoing elective heart surgery or surgery for head and neck cancer have also been studied. Level 1 evidence demonstrates that use of IEDs is of significant benefit in prevention of postoperative infections and other surgical complications (fig. 6) [3]. The results are homogeneous and have been endorsed by all major nutrition societies with a grade A
recommendation. In fact, some authors have gone as far as recommending the routine use of these diets in elective surgery, particularly in patients undergoing gastrointestinal surgery [25].

ART has also been shown to be beneficial in victims of severe trauma, where arginine deficiency is prominent. However, the number of patients accrued is significantly less than the number of patients studied for elective surgery. The results of these trials are limited by the amount of arginine that can be delivered in the diets of these patients during the first week. Further research is clearly necessary.
ART appears to be beneficial only in states of true arginine deficiency. Empiric use of arginine in the form of IEDs has been tested in patients with sepsis. Sepsis is a heterogeneous disease with multiple causes and clinical presentations. To date, it is unclear whether arginine deficiency truly develops in sepsis as there is a wide variation in plasma arginine levels. MDSC have been identified in models of sepsis late in the disease process. Interestingly, blocking arginase in these models significantly increases mortality. It will only be possible to determine the role of ART in sepsis when we successfully identify states of arginine deficiency in a given individual patient. This will truly be the time of personalized nutrition care.

Controversy as to whether mortality is increased by arginine during sepsis has unfortunately obscured the clear benefits observed in surgery and trauma. Misinterpreted editorials and presentations have caused a dramatic sense of confusion in clinicians. As a result, multiple patients are being deprived of a highly needed and desirable therapy. Physicians, surgical organizations and governments should make a concerted effort to clarify the indications for the use of ART and create quality practice improvement processes aimed at making ART a standard of care [26].

Conclusions

Arginine deficiency is observed after PI and in other disease processes including cancer and chronic infections. Arginine deficiency negatively affects key biological functions including the production of nitric oxide and T lymphocyte functions. Patients that exhibit arginine deficiency are at increased risk of developing complications due to poor immune function and tissue oxygenation leading to increased risk of infections, tumor growth, and poor wound healing. Arginine deficiency is caused by the activation of MDSC expressing ARG1, actively destroying arginine.

Arginine deficiency conforms to a nutrition deficiency syndrome in that it presents with signs of immune suppression that are common to several disease processes. Immune suppression caused by arginine depletion results in worsening of outcome. To our knowledge, arginine deficiency is the first form of malnutrition of a single amino acid caused by active nutrient destruction by the immune system.

A decrease in arginine availability after surgery or trauma conforms to the Bradford Hill criteria of causality and as a nutrition deficiency syndrome may worsen prognosis. ART significantly improves outcomes and should be considered to be incorporated into quality practice improvement initiatives in patients
undergoing elective surgery. Trauma patients should benefit from ART, though further research would be important. Techniques for detection of arginine deficiency in a given individual will allow us to monitor the success of therapy and provide true personalized care. ART in the future may become important in other illnesses associated with arginine deficiency.

Disclosure Statement

Dr. Ochoa discloses that he is the Medical and Scientific Director for Nestlé HealthCare Nutrition in North America. He is also an Adjunct Professor of Surgery at the University of Pittsburgh.

References


