Distinct Nutrition Requirements for single amino acids (Arginine)

Arginine Deficiency Syndrome - ADS

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Relevant Financial Information

- Ex - Employee of Nestle Health Care Nutrition North America
  - Ex-Member of the Board of Directors
- I currently have NO commercial links with any for profit company
- I will NOT discuss any proprietary or commercial information
- All the information presented comes from peer-reviewed publications
  - I am an author on a number of these publications
    - Funding comes from
      - NIH - NIGMS. I held KO8 and RO1 grants in the past
      - Nestle Health Science funded some of the studies and the funding will be disclosed in the slide presented
What I will talk about

− Arginine deficiency as a cause of:
  • Clinical manifestations of disease (Arginine deficiency syndrome - ADS) *
    ▪ Poor blood flow due to decreased nitric oxide production
    ▪ Impaired immune function (adaptive immunity – T lymphocyte function)
    ▪ Decreased wound healing - Decreased collagen deposition

− ADS constitutes a distinct nutrition requirement (DNR)
  • Is not necessarily associated with protein-calorie malnutrition – Arginine replacement can benefit well nourished and malnourished patients
  • Cannot be resolved by increasing food intake (e.g. protein intake)
  • Benefit of arginine replacement for ADS does not obey to a “pharmacologic” effect

Arginine deficiency

Diet
- Cafeteria
- Iatrogenic

Requirements
- Large Wounds
- Muscle accretion

Production
- Muscle
- Gut Mucosa
- Kidney

Competitive Inhibitors
- ADMA

↓ Production

↓ Production

Arginine Deficiency

Destruction

Arginine Deficiency

ARGINASE 1

Immune-mediated

Hemolysis

Transfusions

Liver necrosis

Myeloid-Derived Suppressor Cells
MDSC
Diseases with **High arginase** and low Arginine

**LIVER**
- Injury
- Inflammation
- Necrosis
- Ischemia

**Surgery or Trauma**

**Infections**
- HIV
- Tuberculosis
- Staphylococcus
- Many others

**Cancer** (Growing List)
- Renal Cell carcinoma
- Head and Neck Cancer
- Squamous cell (Lung)
- Breast Cancer
- Pancreatic
- Colorectal
- Glioblastoma
- Melanoma

**Red Blood Cell damage**
- Hemolytic diseases
- Transfusions
- Mechanical injury
- Cardiac Pumps
- Damaged Valves
- Cardiac support (LVAD, tandem, others)

Tumors destroy arginine to weaken the immune system
Percent CD16 cells in Mononuclear cell layer by Ficoll Hypaque – in Trauma Patients


Bryk, Ochoa
Cancer’s Bulwark Against Immune Attack: MDS Cells

First noticed in the 1970s, myeloid-derived suppressor cells appear to play a key role in sustaining tumors; new methods of overcoming them are being tested.

—Jean Marx

Further work showed that it was none other than MDSCs. These cells are loaded with the enzyme arginase, which degrades the amino acid. About 2 years ago, Juan Ochoa and his colleagues showed that mice subjected to surgical stress produce large numbers of the cells, which proved to be potent inhibitors of T-cell activation. The researchers have also found high arginase production in cells from human trauma patients but haven’t yet pinned down the exact nature of those cells.
Clinical Manifestations of low arginine associated with illness

- **Immune dysfunction (T lymphocyte dysfunction)**
  - Increased risk of infection
    - Surgical risk, Risk after trauma
  - Worsening of Cancer outcomes
    - Presence of MDSC is pathologic
      - Poor prognostic signs
    - Resistance to immunotherapy

- **Impaired blood flow (due to low nitric oxide production)**
  - Ischemia
  - Breakdown of surgical anastomosis
  - Necrosis of skin and muscular flaps
    - Breast reconstruction
    - Oro-cutaneous fistula (H&N cancer surgery)
Can and should we treat arginine deficiency states?
How do we treat arginine deficiency (ADS)?

- **Pharmacologic**
  - Arginase inhibitors
    - Animal models (nor-hydoxy-L-arginine = NOR-NOHA)
    - Phase II and III clinical trials (Caliterra®)
- **Attack Myeloid-derived suppressor cells (MDSC)**
  - Antibodies against MDSC
  - Retinoic acid (maturation)
  - Chemotherapeutic agents
- **Replace Arginine**
  - Has reached widespread clinical application (called immunonutrition)
  - Use glutamine
    - Approved for the treatment of Sickle cell disease
Arginase I Production in the Tumor Microenvironment by Mature Myeloid Cells Inhibits T-Cell Receptor Expression and Antigen-Specific T-Cell Responses

mice injected s.c. with 1 10^6 3LL cells were injected daily in the opposite flank with PBS, Nor-NOHA (20, 40 or 80 mg/kg), L-Arg (500 mg/kg), or Nor-NOHA plus L-Arg (80 mg/kg and 500 mg/kg, respectively). Tumor volume was determined after 15 days of tumor injection by using the formula: smaller diameter^2  larger diameter  0.5. Data include groups of 6 mice.

(CANCER RESEARCH 64, 5839–5849, August 15, 2004)

Paulo C. Rodriguez et. Al.

Fig 10

Courtesy of Dr. Paulo Rodriguez – LSU 2014
Loading Arginine into T cells Prior to Activation is Important

Roger Geiger, Jan C. Rieckmann,
Tobias Wolf, ..., Nicola Zamboni,
Federica Sallusto, Antonio Lanzavecchia
Cell 167, 829–842, October 20, 2016

- Shows preloading is possible
- Gets T-cells ready to respond to activation from surgery
- Improvements in T cell survival were sustained for 7-10 days
Arginine based immunonutrition protocol

- 5 Days Preoperatively
  - 500 mL – 1000 mL IM formula/day

- At least 5 Days Postoperatively if feasible
  - At least 1000 kcal IM formula/day (meet at least 50-65% of needs)

Effects of Peri-op Immunonutrition for Cystectomy on Infection Rate - A Pilot RCT


<table>
<thead>
<tr>
<th>Antibiotic Use</th>
<th>IM</th>
<th>ONS</th>
</tr>
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<tbody>
<tr>
<td>90 days</td>
<td>14%</td>
<td>53%</td>
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</table>

*p = 0.027
Adapted from Table 1

Arginine concentration plasma

THE JOURNAL OF UROLOGY® 2018 by AMERICAN UROLOGICAL ASSOCIATION Vol. 200, 292-301, August 2018
Perioperative Immunonutrition: Malnourished Patients – Results

Reduced post operative complication rates

Effect of Preoperative Immunonutrition Intervention – Well-nourished Colorectal Surgery Patients (n=200)

Meta-analysis - Arginine based immunonutrition in Surgery

- Same benefit shown for GI surgery vs. non-GI surgery
- Same benefit shown for Upper and Lower GI surgeries
- Note: Formula tested also has fish oil
- Only Arg-n3-nucleotide formula showed statistically significant benefit when compared with other arginine supplemented (IM) formulas (p<0.0001)
- Peri-operative use showed greatest benefit (p=0.03)

Readmissions decreased by 50-58% in S4S-IM group over various time periods. After adjusting for demographics and health conditions, readmissions were significantly lower at 30, 90 and 180 days (p<0.05).

During the index visit S4S-IM patients had lower rates of surgical site infection (0% vs 2.65%, p=0.04), and lower incidence of venous thromboembolism (1.3% vs 5%, p=0.05) compared to S4S-Control.

Total hospital days trended lower in the S4S-IM group at all time points. A 20% decrease (1.4 days) over 180-day follow-up was noted, although not statistically significant.
Impact of a Novel Preoperative Patient-Centered Surgical Wellness Program  
Kristen E. Kelley, MPH, RN, CIC

**TABLE 3. Comparison of HAI Between Intervention and Comparison Groups**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Preintervention (n = 9202)</th>
<th>Intervention Group (n = 6538)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site infection (SSI)</td>
<td>52 (0.57)</td>
<td>22 (0.34)</td>
<td>0.044</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> infection (CDI)</td>
<td>78 (0.85)</td>
<td>34 (0.52)</td>
<td>0.016</td>
</tr>
<tr>
<td>Catheter associated urinary tract infection (CAUTI)</td>
<td>27 (0.29)</td>
<td>6 (0.09)</td>
<td>0.007</td>
</tr>
<tr>
<td>Ventilator associated event (VAE)</td>
<td>14 (0.15)</td>
<td>6 (0.09)</td>
<td>0.367</td>
</tr>
<tr>
<td>Central line associated bloodstream infection (CLABSI)</td>
<td>7 (0.08)</td>
<td>3 (0.05)</td>
<td>0.538</td>
</tr>
<tr>
<td><em>Methicillin resistant staph aureus</em> (MRSA)</td>
<td>3 (0.03)</td>
<td>2 (0.03)</td>
<td>1.000</td>
</tr>
<tr>
<td>Patient safety indicators (PSI)</td>
<td>55 (0.60)</td>
<td>0 (0.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

REAL WORLD demonstration of effectiveness
A prospective phase II study evaluating the efficacy of oral immune modulating formulae on acute oral mucositis during radiochemotherapy in head and neck neoplasms

E. Assenat\textsuperscript{a}, M. Latournerie\textsuperscript{a}, S. Thézenas\textsuperscript{b}, S. Gaillet\textsuperscript{c}, C. Janiszewski\textsuperscript{a}, N. Flori\textsuperscript{a}, A.M. Dupuy\textsuperscript{c}, D. Azria\textsuperscript{e}, E. Crapez\textsuperscript{d}, R. Garrel\textsuperscript{f}, P. Senesse\textsuperscript{a,*}

Fig. 1. Design of the phase II trial.
Fig. 2. Disease-free survival by sub-group.
Conclusions

ARGinine

Nitric Oxide

NITRIC OXIDE

 vasodilation

Oxygenation

↑ Tissue Perfusion

↓ Shock

↓ Ischemia

↓ Necrosis

Microbicidal

OH-Proline

Protein Translation

T, B lymphocyte Function

Protein

Transportation

MUSCLE

NITROGEN BAL.

Infection

Weaning off Vent Ambulation Independence

Postoperative

↓ Readmission

↓ Cost of Care

↑ Long Term Outcome

Public Health
THANK YOU