Objectives

• Review clinical evidence of benefit with perioperative immunonutrition.
• Describe mechanisms of how immunonutrition benefits organ physiology.
• Evaluate quality improvement processes aimed at incorporating immunonutrition into daily clinical practice.
64 year old with Appendicitis

- Female, healthy
- Local hospital – peri-appendiceal abscess
  - Pigtail drain. Sxs. Do not resolve
- University
  - Colon Cancer eroding into bladder abdominal wall
- Surgery
  - Risk of complications > 35%
  - LOS 7-11 days
  - High Morbidity
Challenge

Optimize Perioperative care to decrease risk and improve outcomes
Heyland Meta-analysis: Immune Enhancing Diets and Infectious Complications

Heyland D. JAMA 2001;(286)8:944-953

Figure 2

Elective Surgical Patients

Daly et al, 1992
Daly et al, 1995
Braga et al, 1996
Schilling et al, 1996
Gianotti et al, 1997
Senkal et al, 1997
Braga et al, 1999
Senkal et al, 1999
Snyderman et al, 1999

Favors Immunonutrition

Favors Standard Diet
Controversy on the use of Arginine (particularly in sepsis)
How does Immunonutrition work?

Is the clinical benefit real?
Mechanistic Hypothesis

Surgery induces an Arginine (Nutrition) deficiency state that is corrected through dietary replacement
Koch’s Postulates

Nutrient Deficiency Syndrome

Decrease in availability

Mechanism of disappearance

Metabolic Consequences

Abnormal organ/tissue Physiology

Negative Clinical Outcome

Successful Treatment
Mouse Model To Study Arginine Metabolism

Laparotomy

Infection/Sepsis:
- Endotoxin
- Listeria Monocytogenes

Response to Infection
- Clearance
  - T lymphocyte Function
  - Nitric Oxide Production
Arginine levels decrease after Physical Injury

**Plasma**

Pribis – Accepted JPEN 2011

**Intracellular**

Zhu – Submitted

Arginine levels decrease after Physical Injury.
Arginine Plasma Levels and Disease Process

Control  Trauma  Sepsis

microMolar

Control

Trauma

Sepsis

Arginine Plasma Levels in Sepsis and Trauma

C. Chiarla, I. Giovannini, and J. H. Siegel
Arginine in the Immune System

Lymphocytes

Myeloid cells
Arginine in Myeloid Cells

• Upon activation:
  – Induces one of two enzymes:
    • inducible nitric oxide synthase (iNos)
    • Arginase
  
  • iNOS is induced by: (TH1 – Inflammatory)
    – IL-1, IL-2, TNF, IFN

  • Arginase is induced by: (TH2 – Anti-inflammatory) – STAT6
    – IL-10, TGF-b, VGEF, IL-4, IL-13
Plasma Nitric Oxide Metabolites in Mice

Nitric Oxide Metab. uM

Control  LPS  Trauma  Trauma+LPS

Human

p=0.02  p<0.01

Ochoa lab archive, Ann Surg 1991
Arginase is also found in the Circulation

Pribis, J.  Ochoa Lab. VARS award in print 2011
Arginase 1 is induced in myeloid cells after Trauma

ARG 1

Makarenkova et. Al. J. Imm 2006
Human Leukocyte Arginase I
Protein Expression after Surgery

+ Internal Control

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Postop</th>
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<tbody>
<tr>
<td>Pt 1</td>
<td></td>
<td></td>
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<tr>
<td>Pt 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tsuei, et. al. J. Trauma 2001
In Humans Arginase is Observed in Peripheral Blood
Also In Myeloid Cells

Log Arginase Activity (nmol ornithine/min/mg)

Post-Injury Day

Control 0 1 2 3 4 5 6 7

Arginase 1 in Myeloid cells Metabolize arginine

Control 5.2%

Injury 19.2%

Arginase 1

Zhu, Ochoa – Under Submission
Arginase 1 in Myeloid cells Metabolize arginine - MDSC

MDSC = Myeloid DerivedSuppressor Cells
T lymphocytes and Arginine in vitro

• Upon activation:
• Is necessary for normal function
• Changes in the absence of arginine are characteristic
  • Loss of the membrane receptor Zeta chain
  • ↓↓↓↓ Cytoxicity
  • ↓↓↓↓ proliferation
  • ↓↓↓↓ Interferon gamma
  • ↓↓↓↓ memory

Ochoa JPEN 2001, Taheri 2001
Effect of arginine on mouse T lymphocyte proliferation
IN VITRO

Stimulation Index

L-arginine concentration in media (uM)

Ochoa JPEN 2001
T cell Receptor Expression and Arginine IN VITRO

CD3 Receptor mean gated channel fluorescence

L-arginine concentration in media (uM)

P<0.05

Ochoa et. al. JPEN 2001

Fig 2
Injury Impairs Adaptive Immune Function

Figure 1

A CD3-ζ

B in vivo CTL

C in vivo proliferation

D Cytokine production

Zhu, Ochoa – Under Submission
T-lymphocyte Dysfunction Observed After Surgery/Trauma is Very Similar to In-vitro Arginine Deficiency States

<table>
<thead>
<tr>
<th>Function</th>
<th>Surgery</th>
<th>Arginine deprivation</th>
<th>T cell/myeloid cell co-culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓</td>
<td>↓↓↓↓</td>
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<tr>
<td>IL-2/IFN g.</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓</td>
<td>↓↓↓↓</td>
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<tr>
<td>TCR zeta Chain</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>
Susceptibility Infection
Surgery/trauma increases susceptibility to Infection

A Spleen

P<0.0001

1,000 fold

Zhu, Ochoa – Under Submission
Physical Injury and Susceptibility Infection

Reproduced by injecting MDSC

Or By Injecting Arginase

Zhu, Ochoa – Under Submission
Nitric oxide production is RESTORED by blocking TH2 (anti-inflammatory) Signals

Concept # 3 – Nitric oxide production predominates in sepsis but not in surgery/trauma

Figure 4

Munera et. Al. – Ann Surg 2010
Nitric Oxide is a Potent Vasodilator

L-arginine

Nitric oxide Synthase (NOS)

Endotoxin induces NOS

Nitrates (end product)

PHYSIOLOGIC

Biological Effect

HYPOTHESIS: Nitric oxide is responsible for hypotension in sepsis
Effect of Arginine Infusion on flap Nitric Oxide Production

Effect of Arginine on % Pedicle Flap Survival

Effect of ARGOM3 on Microcirculation after Open Heart Surgery
Tepaske - Lancet 2001

Circulating NOx were Increased
Treatment Partially corrects T lymphocyte Dysfunction

B in vivo proliferation with Nor-NOHA

C in vivo CTL activity with Nor-NOHA

P < 0.001

P > 0.05

P < 0.01
Treatment corrects susceptibility to Infection induced by Injury

Arginase blockade (Nor- Noha)

Zhu, Ochoa – Under Submission
Arginase blockade (Nor- Noha) restores Arginine deficiency

Zhu, Ochoa Lab Preliminary data
Subgroups: Infections and Immunonutrition

Drover et al. – JACS – with permission 212(3):385-399. 2011

Figure 4. Results of Subgroup Analyses examining the Effect of Arginine Supplemented Diets on Infection

- GI studies (21)
- Non GI studies (7)
- Lower GI studies (1)
- Upper GI studies (16)
- Lower & Upper GI studies (4)
- Pre Op studies (6)
- Peri Op studies (9)
- Post Op studies (15)
- Infections Overall

Arg/ω-3 FA/Ncltds

Numbers in parentheses indicate number of studies.
Subgroups: Hospital Length of Stay

Drover et. al. JACS – 2011

Figure 5. Results of Subgroup Analyses examining the Effect of Arginine Supplemented Diets on Length of Stay

- GI studies (21)
- Non GI studies (8)
- Lower GI studies (2)
- Upper GI studies (14)
- Lower & Upper GI studies (5)
- Pre Op studies (6)
- Peri Op studies (11)
- Post Op studies (14)
- Length of Stay Overall

- WMD Weighted Mean Difference (in days)
- p=0.0007
- p=0.004
- p<0.00001
- p<0.00001

Arg/ω-3 FA/Ncltds
Effect of a SNF on line infections in severely malnourished patients undergoing surgery for Colo-rectal Cancer

![Bar graph showing the effect of a SNF on line infections in severely malnourished patients undergoing surgery for Colo-rectal Cancer. The graph compares the infection rate between different groups: WN, MN, and MN + SNF.

- WN: Lower infection rate
- MN: Higher infection rate, p=0.013
- MN + SNF: Lower infection rate compared to MN

The bar graph indicates a significant reduction in infection rates when a SNF is administered, especially when compared to the MN group.
Specialized Surgical Nutrition in Severely Malnourished Patients with Pancreatic Cancer

Complications

Infection

• Mortality also reduced
  • 1.3% vs 5.9% (p=0.035)

Effect of Arginine, Omega 3 Fatty Acids, Nucleotides on Surgical Infection

Waitzberg et al. World Journal of Surgery

Overall 17 different studies.
Pre-op, Peri-op and Post-operative therapy
Waitzberg et. Al
WJS -30:1592-1604. 2006
Effect of Immunonutrition on Infection

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMD Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Arginine</td>
<td>10</td>
<td>23</td>
<td>12</td>
<td>3.0%</td>
<td>2005</td>
</tr>
<tr>
<td>Casas-Rodera 2008</td>
<td>1</td>
<td>15</td>
<td>3</td>
<td>1.5%</td>
<td>2008</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>38</td>
<td>39</td>
<td>4.2%</td>
<td>0.63 [0.23, 1.73]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.90 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 3.1.2 FO                | 7          | 18             | 6            | 1.7%                          | 1996 |
| Subtotal (95% CI)       | 18         | 17             | 1.7%         | 1.17 [0.30, 4.61]             |      |
| Total events            | 7          | 6              |              |                               |      |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 0.22 (P = 0.83) | | | | |

| 3.1.3 A-F preoperative  | 2          | 30             | 8            | 3.4%                          | 2006 |
| Subtotal (95% CI)       | 30         | 30             | 3.4%         | 0.20 [0.04, 1.02]             |      |
| Total events            | 2          | 8              |              |                               |      |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 1.94 (P = 0.05) | | | | |

| 3.1.4 A-F postoperative | 5          | 41             | 13           | 4.9%                          | 1992 |
| Daly 1995               | 1          | 30             | 9            | 3.9%                          | 1995 |
| Schilling 1996          | 3          | 14             | 6            | 2.1%                          | 1996 |
| Braga 1996              | 2          | 20             | 3            | 1.2%                          | 1996 |
| Senkal 1997             | 17         | 77             | 24           | 8.4%                          | 1997 |
| Gianotti 1997           | 13         | 87             | 20           | 7.6%                          | 1997 |
| Braga 1998              | 9          | 55             | 13           | 4.9%                          | 1998 |
| Di Carlo 1999           | 3          | 33             | 6            | 2.4%                          | 1999 |
| Snyderman 1999          | 19         | 82             | 19           | 8.3%                          | 1999 |
| Jiang 2004              | 9          | 60             | 15           | 5.7%                          | 2004 |
| Farreras 2005           | 2          | 30             | 9            | 3.6%                          | 2005 |
| Lobo 2006               | 24         | 54             | 24           | 6.0%                          | 2006 |
| Subtotal (95% CI)       | 583        | 553            | 59.2%        | 0.52 [0.39, 0.69]             |      |
| Total events            | 107        | 161            |              |                               |      |
| Heterogeneity: Chi² = 9.14, df = 11 (P = 0.61); I² = 0% | | | | |
| Test for overall effect: Z = 4.48 (P < 0.00001) | | | | |

| 3.1.5 A-F perioperative | 14         | 102            | 31           | 11.9%                         | 1999 |
| Braga 1999              | 10         | 78             | 18           | 7.1%                          | 1999 |
| Senkal 1999             | 4          | 25             | 12           | 4.5%                          | 2001 |
| Tepaskie 2001           | 5          | 50             | 12           | 4.8%                          | 2002 |
| Braga 2002              | 7          | 50             | 8            | 3.1%                          | 2007 |
| Subtotal (95% CI)       | 305        | 305            | 31.5%        | 0.42 [0.27, 0.63]             |      |
| Total events            | 403        | 81             |              |                               |      |
| Heterogeneity: Chi² = 2.98, df = 4 (P = 0.68); I² = 0% | | | | |
| Test for overall effect: Z = 4.40 (P < 0.00001) | | | | |

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Nutrition Protocol

Nutrition Optimization Ordered

Date For Surgery Established

Albumin, Prealbumin and CRP Ordered

Order SNF 3X/Day for 5 days
Prior to Surgery

NPO Day of Surgery
(Consider High Protein/Carb/No fat liquid diet)

Start Specialized Nutrition Formula 1-3X/Day on POD # 1

Start a Regular Diet. Continue SNF 1-3X/Day for 5 -10 Days

CONSIDER (ERAS)
- Enhanced Recovery after Surgery
- Minimize use of NG Tube
- Multimodality pain control (NSAIDS)
- Careful with IVF
- Maintain adequate electrolyte balance
- Do NOT try to Meet Caloric Goals
Peri-operative Care

• Prepared for Right hemicolecctomy, partial bladder resection
• Pre-op. Oral supplementation of
  – arginine, ω-3 FA, vitamin A
    • 5 days 3 X a day
  – SCIP abx – 1 hr prior to surgery
• Post-op Early oral Nutrition
  – arginine, ω-3 FA, vitamin A
    • 5 days 3 X a day
• Adjunct therapy – NSAIDS
• Home in 3 days.
  – Standard
    • 7- 11 days
    • 38% complication rate HCUP
    • 10-18% infection rate
Nutrient Deficiency Syndrome

Decrease in availability

Mechanism of disappearance

Metabolic Consequences

Abnormal organ/tissue Physiology

Negative Clinical Outcome

Successful Treatment

Koch’s Postulates
Conclusion

Strong evidence that Arginine deficiency is a nutrition deficiency syndrome that requires treatment after surgery or trauma.
Thank YOU
Are immune enhancing diets really...

Immune- **RESTORING** diets?