Fifty-two Rats
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University of Wisconsin- Madison

![Comparison of different nutritional treatment group mortality after L Cell Ige challenge](image1)

![Enteral Feeding Publications](image2)

**ENTERAL – PARENTERAL STUDY**

**98 Patients Enrolled**

- Inclusion Criteria
  - > 18 Years Old
  - Celiotomy for Trauma
  - Abdominal Trauma Index ≥ 15
- Jejunostomy Placed at Surgery
- Randomized by Nutrition Support Service

**Formulas**

<table>
<thead>
<tr>
<th></th>
<th>Enteral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (%)</td>
<td>16.7%</td>
<td>17%</td>
</tr>
<tr>
<td>BCAA (%)</td>
<td>18.2%</td>
<td>15.6%</td>
</tr>
<tr>
<td>CHO (%)</td>
<td>73.9%</td>
<td>74%</td>
</tr>
<tr>
<td>FAT (%)</td>
<td>9.4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Goal Rate: Protein 1.5-2.0 gm/kg/day
NPC 30-35 kcal/kg/day
Enteral and Parenteral Products on Hospital Formulary
**ENTERAL - PARENTERAL STUDY**

### Septic Morbidity

<table>
<thead>
<tr>
<th></th>
<th>ENT (51)</th>
<th>TPN (45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>6 (12%)</td>
<td>14 (31%)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>IAA</td>
<td>1 (2%)</td>
<td>6 (13%)</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>EMP</td>
<td>1 (2%)</td>
<td>4 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Line Sepsis</td>
<td>1 (2%)</td>
<td>6 (13%)</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Infections/Patient</td>
<td>.25±0.6</td>
<td>.71±0.14</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Infections/Infected Patient</td>
<td>1.06±.08</td>
<td>1.6±.8</td>
<td>&lt;.04</td>
</tr>
</tbody>
</table>

### Injury Severity Score (ISS)

**Regions**
- Head/Neck
- Face
- Thorax
- Abdomen and Pelvic Contents
- Extremities
- External

### ISS

**Three Most Severely Injured Regions**

$$\text{ISS} = (\text{Score}_1)^2 + (\text{Score}_2)^2 + (\text{Score}_3)^2$$

- > 20 Considered Severe
- Correlates With Mortality
- Ignores Multiple Injuries/Regions
- Best for Blunt Injuries

### Abdominal Trauma Index

**High Risk Organs**
- Pancreas: 5
- Vascular: 5
- Duodenum: 4
- Liver: 4
- Colon: 4
- Stomach: 3

### Risk of Intra-abdominal Sepsis

<table>
<thead>
<tr>
<th>ATI</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15</td>
<td>16%</td>
</tr>
<tr>
<td>≥ 25</td>
<td>25%</td>
</tr>
<tr>
<td>≥ 35</td>
<td>43%</td>
</tr>
<tr>
<td>≥ 45</td>
<td>60%</td>
</tr>
</tbody>
</table>
IMMUNE-ENHANCING DIETS (IED) IN TRAUMA & GENERAL SURGERY

GLUTAMINE *
ARGININE
NUCLEOTIDES
OMEGA-3 FATTY ACIDS
BETA CAROTENE

IED vs. ISO Study Protocol

<table>
<thead>
<tr>
<th>Condition</th>
<th>IED: n=17</th>
<th>ISO: n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Blinded Prospective</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Enteral Access</td>
<td>No</td>
<td>Prospective</td>
</tr>
<tr>
<td>18 - 65 y/o</td>
<td></td>
<td>Unfed Controls (n=19)</td>
</tr>
<tr>
<td>ISS ≥ 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATI ≥ 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiotomy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Septic Complications

- Total: p = 0.06
- Major: p = 0.02
- Pneumonia: p = 0.05
- Abscess: p = 0.05

Therapeutic Antibiotic Use

- Days: p = 0.02

Length of Stay

- Ventilator
- ICU
- Hospital

Common Mucosal Immune Hypothesis

- Naïve T & B Cells
- GALT
- IgA
- MAdCAM-1
- Respiratory
- GU
- Mammary
- Blood Stream
- Thoracic Duct
**Feeding Models**

Chow ➔ CED ➔ IG-TPN ➔ IV-TPN

Complexity, Intermittency ➔ Complexity ➔ Route

Degree of Enteral Stimulation
Chow > CED > IG-TPN > IV-TPN

**EFFECTS OF REDUCED ENTERAL STIMULATION**

- Decreased:
  - T & B cells in PP, LP & IE
  - Peyers patch LTPR + MAdCAM-1
  - IgA: from reduced cells and altered CYTOKINES
  - polymeric immunoglobulin receptor (plgR)

**Lymphocyte Mass**

<table>
<thead>
<tr>
<th>% of Chow</th>
<th>TPN Day</th>
<th>Chow Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow 1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>TPN 2</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>TPN 3</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>TPN 4</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Chow 5</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

**GALT T Cells in Small Intestine of Adults:**

Enteral Fed (21) vs. Without (6)

- PF group
- EN group

*Okamoto, et al JPNEN 2005; 29:56*

**GALT T Cells in Small Intestine of Adults:**

Enteral Fed (21) vs. Without (6)

IE space

- IE group
- EN group

LP

- IE group
- EN group

*Okamoto, et al JPNEN 2005; 29:56*

**IgA Levels**

Intestinal

Respiratory

*P < 0.05 vs Day 0*
EFFECTS OF REDUCED ENTERAL STIMULATION

- Decreased:
  T & B cells in PP, LP & IE
  Peyer’s patch MAdCAM-1 + LTβR
  IgA: from reduced cells and altered CYTOKINES
  polymeric immunoglobulin receptor (plgR)

Common Mucosal Immune Hypothesis

MAdCAM-1: Kinetics

MAdCAM-1 Expression in PP

MAdCAM-1 Blocking
Peyer’s Patch Lymphocyte Yield

Common Mucosal Immune Hypothesis
EFFECTS OF REDUCED ENTERAL STIMULATION

• Decreased:
  - T & B cells in PP, LP & ILE
  - Peyer’s patch LTβR + MadCAM-1
  - IgA: from reduced cells and altered CYTOKINES
  - polymeric immunoglobulin receptor (plgR)

LP CD4+/CD8+ RATIO

- LP CD4+/CD8+ ratio at different days (d0, d1, d2, d3, d4, d5)
- TPN DAYS
- p < 0.05 compared to d0
IgA: CYTOKINE CONTROL

<table>
<thead>
<tr>
<th>Th1</th>
<th>Th2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNγ</td>
<td>IL-4</td>
</tr>
<tr>
<td>TNFβ</td>
<td>IL-5</td>
</tr>
<tr>
<td>IgA</td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
</tr>
</tbody>
</table>

Small Intestinal IL-4 Levels

![Graph comparing IL-4 levels in different conditions](image)

- *p<0.05 vs. Chow
- †p<0.05 vs. CED

Small Intestinal IgA Levels

![Graph comparing IgA levels in different conditions](image)

- *p<0.05 vs. Chow
- †p<0.05 vs. CED

EFFECTS OF REDUCED ENTERAL STIMULATION

- Decreased:
  - T & B cells in PP, LP & IE
  - Peyer’s patch LTβR + MAdCAM-1
  - IgA: from reduced cells and altered CYTOKINES
    - polymeric immunoglobulin receptor (plgR)

IgA Transport through the Epithelial Cell

![Diagram of IgA transport](image)
**Intestinal plgR Expression**

![Graph showing Intestinal plgR Expression](image)

* p<0.05 vs. Chow
† p<0.05 vs. CED

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**Route of Diet and Established Respiratory Immunity**

![Route of Diet and Established Respiratory Immunity](image)

% Viral Shedding

- Chow
- CED
- IV-TPN

% Mortality at Ps. Pneumonia

- Chow
- CED
- IV-TPN
- Non-immune

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**Respiratory Immunity-Rodents**

- Naive T & B Cells
- IgA
- Nose
- Nasal Passages
- CLN
- NALT

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**ELISPOT Methods**

1. Add chromagen
2. Add enzyme-conjugated anti-Ig
3. Antigen Coated Plate
4. Separate Lymphocytes

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**Total Ab Producing Cells in NP**

<table>
<thead>
<tr>
<th>Day After Viral Inoculation</th>
<th>CHOW</th>
<th>CED</th>
<th>IV-TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

* p<0.02 vs Chow at Day 13
† p<0.05 vs CED at Day 13

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**Key Event: Neutrophil Activation**

- **Steps**
  - Rolling—selectin
  - Priming—chemoattractants
  - Activation—ICAM-1 and LFA-1/Mac-1 interaction

- **Gut**—An important site of neutrophil priming
Gut PMN Priming

Lung PMN Localization

Insult

Pulmonary injury


Cytokines and GALT Function

\[
\begin{align*}
\text{IgA} & \quad \text{Mucosa} \\
\text{IFN-\gamma} & \quad \text{Endothelium} \\
\text{IL-4} & \quad \text{IL-10} \\
\text{ICAM-1} & \quad \text{ICAM-1} \\
\text{ICAM-1} & \quad \text{IL-4 \& IL-10} \\
\end{align*}
\]

ICAM-1 expression in small Intestine

\[
\begin{align*}
\text{MPO levels in small Intestine} \\
\end{align*}
\]

**β2-Integrin Expression After 15 min Gut I/R**

Lung Vascular Permeability 15 Min I/R
**Patient Characteristics**

<table>
<thead>
<tr>
<th>Trauma (n=12)</th>
<th>Control (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 ± 20 y</td>
<td>41 ± 16 y</td>
<td>0.93</td>
</tr>
<tr>
<td>83% Male</td>
<td>75% Male</td>
<td>1.0</td>
</tr>
<tr>
<td>100% Blunt Injury</td>
<td>n/a</td>
<td>---</td>
</tr>
<tr>
<td>41 ± 14 ISS</td>
<td>n/a</td>
<td>---</td>
</tr>
<tr>
<td>50% smokers</td>
<td>13% smokers</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Methods**

- BAL with 60 mL sterile saline (L, R, Tr)
- Simultaneous venous blood sample
- Urea in BAL samples and blood
  - Epithelial Lining Fluid (ELF) volume
    - Volume ELF = (mg urea in BAL)/(mg/mL plasma urea)
  - S IgA* in BAL samples
- [S IgA] (per mL ELF) in BAL samples
**Experiment 1 Results**

![Graph showing experiment 1 results.]

**Experiment 2 Results**

![Graph showing experiment 2 results.]

**ENTERIC NERVOUS SYSTEM (ENS)**

- # NEURONS IN ENS ≠ # IN SPINAL CORD
- 2 M of NERVE/ MM³ of TISSUE
- 50% of MUCOSA WITHIN 9 μm
- 99% of MUCOSA WITHIN 13 μm
**Effect of Bombesin on GALT**

**Total Cell Yield**

![](chart1.png)

* p<0.05 vs CHOW and BBS

**Effect of Bombesin on GALT**

**LPL CD4/CD8 Ratio**

![](chart2.png)

* p<0.05 vs CHOW and BBS

**BOMBESIN RECOVERY: TOTAL SMALL INTESTINAL IgA**

![](chart3.png)

**MORTALITY RATES AT 48 HOURS**

![](chart4.png)

* p < 0.001 vs CHOW / TPN-BBS