The Gut in Trauma: 
The Source or The Potential Cure for Multiple Organ Failure?
The origins of the SIRS CARS concepts

Surg Gyn Obstet 1977

B. Eiseman, m.d., f.a.c.s., R. Beart, m.d., and L. Norton, m.d., f.a.c.s., Denver, Colorado

A New Syndrome

ICU Technology Allows Patients To Survive Single Organ Failure

Ben Eiseman
Infectious etiology concept supported by key papers in 1970’s Polk, Fry etc.

Research in the 70’s focused on infectious etiology
1970’s > 50% of cases of MOF from intraabdominal infections

- By 1980’s IAI showing better outcomes but MOF still occurring at the same rate as in the 70’s?
  - Better initial management of trauma and post op patients
  - More potent and appropriately dosed antibiotics
  - Earlier recognition of IAI with the use of CT
  - Interventional radiologic techniques allowing drainage of abscess without open surgery

- Series of papers from EU reporting MOF without infection source
  - Faist- 1983 MOF in polytrauma
  - Nuytinck – 1987 “whole body inflammation in trauma…”
  - Waydhas – 1992 Inflammatory mediators infection, trauma, MOF
  - All supporting a convincing story that MOF in trauma often occurs without infectious etiology
Question 1980’s: if not infection what was driving MOF?

• Shock (septic, hemorrhagic, cardiogenic etc) seemed to be consistent with patients getting MOF

• Concept that low flow states and tissue ischemia / reperfusion is etiology becomes popular;
  • Giving rise to gut origin of sepsis (multiple authors)
    » Gut as “Motor for Multiple Organ Failure”
  • “unrecognized flow-dependent oxygen consumption”
    » Supranormal oxygen delivery (Shoemaker)

• Supporting evidence at the time
  – Animal models of bacterial translocation following trauma
  – Selective gut decontamination in humans (+/-)
  – Early enteral feeding showing benefit
    » Primarily pneumonia was improved
Pathophysiology of Splanchnic Hypoperfusion

Sepsis - Trauma - Shock

- Increased catecholamines
- Increased vasoconstriction

\[ \downarrow \text{Cardiac output} \]

Hypovolemia

Proinflammatory cytokine release

Splanchnic hypoperfusion

- Reduced mucosal blood flow
- Barrier disruption
- Altered GI motility
- Changes in bacterial flora and virulence

Barrier Dysfunction, MOF, worsening sepsis

Major research discoveries supporting hypothesis of gut as the “motor” for MOD

• **Moore et al**: shock and hypoperfusion allows gut release of proinflammatory cytokines increasing ARDS/Sepsis (1)

• **Fink et al**: epithelial tight junctions are compromised leading to increased permeability….inflammation (2)

• **Alverdy et al**: interaction between bacteria and host (3)

• **Teixeira et al**: Germ free animal showing increased survival following I/R (4)

• **Deitch et al**: Toxin from gut damages lung via lymphatics (5)

• **Clark et al**: epithelial apoptosis elevated in sepsis, prevented by overexpression of anti-apoptotic protein Bcl-2 (5)

Gut Integrity

- Increased gut permeability linked to MOF and disease severity
- Bacterial translocation to MLNs, peritoneum, blood in sepsis
- Sepsis dose Pseudomonas, Staph, E Coli: gut << IV

Protective mechanisms

Mechanical
- Epithelial barrier
- Mucous layer
- Tight Junctions

Non-Mechanical
- Normal gut flora
- Secretory IgG
- GALT
- Dendritic cells
- Macrophages
- Antigen receptors

Mechanical
- Epithelial barrier
- Mucous layer
- Tight Junctions

Modified from Clark J Shock 2007
Leaphart CL Surgery 2007
GI Alterations commonly noted in severe trauma

- Delayed gastric emptying
- Alterations in intestinal transit
- Altered carrier and nutrient transporter proteins
- Mucosal ischemia
- Villus atrophy
- Reduction in mucosal surface area
- Loss of barrier function/altered permeability
- Significant changes in the microbial / host interrelationship

Pathophysiology of Splanchnic Hypoperfusion

sepsis- trauma- shock

- Increased catecholamines
- Increased vasoconstriction
- Hypovolemia
- Proinflammatory cytokine release

Splanchnic hypoperfusion

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Barrier Dysfunction, MOF, worsening sepsis

Splanchnic Hemodynamics

GI tract receives 25% of cardiac output (varies widely)

- 1.25 L/min at rest, 3.0 L/min with meal, 0.5 L/min with exercise
- Dilates to nutrient bolus in segmental fashion

Uses 20 to 30% of total body O$_2$ consumption at rest

Small intestine receives nearly 50% of arterial blood flow to splanchnic bed (uneven distribution)

Villous tips are at highest risk

### Blood flow (ml/min*100g)

- Splanchnic: 50
- Kidneys: 400
- Brain: 55
- Skeletal Muscle: 3
- Heart: 80
Cells at the villus tip are exposed to greater hypoxic stress during hemodynamic instability.
Compromised Bowel

- Relative ischemia can result in loss of villous tips
- SB at high risk due to countercurrent mechanism
- Villous tips affected first – Absorption
  - Peptide transporter is first to return after injury
The Critical Balance!

- Barrier function
- Selective absorption
GI Dysfunction in the Trauma: When does it become a “problem”

Heterogeneous group dependent upon
- Admitting diagnosis
- Premorbid conditions

Mechanical ventilation
- Ventilation mode

Metabolic factors
- Acidosis
- Electrolyte abnormalities

Medications
- Narcotics
- Anticholinergic agents
- Vasopressors
- Antibiotics

## ICU Conditions Commonly Associated With GI Dysfunction

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>50%–60%</td>
</tr>
<tr>
<td>↑ ICP*</td>
<td>70%–80%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>60%–80%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>50%–70%</td>
</tr>
<tr>
<td>“Altered” hemodynamics</td>
<td>40%–60%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>80%–90%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10%–40%</td>
</tr>
<tr>
<td>Open Abdomen</td>
<td>20%–30%</td>
</tr>
</tbody>
</table>

*ICP=intracranial pressure.*
Proposed Mechanisms of ICU Gut Dysfunction

- Altered motility
  - Bowel edema
  - pH/electrolyte abnormalities/hyperglycemia
  - Excessive opiates
  - Inhibitory neurotransmitters/peptides (NO*, VIP†, substance P)
  - Excess sympathetic tone
  - ↑ Inflammatory mediators into muscularis (iNOS‡, COX-2)

- Mucosal and GALT§ atrophy
  - No luminal delivery of nutrient

- Mucosal barrier disruption
  - Visceral hypoperfusion
  - Absence of biliary and pancreatic secretions

- Changes in luminal bacteria and bacterial products

*NO=nitric oxide; †VIP=vasoactive intestinal peptide; ‡iNOS=inducible nitric oxide synthase; §GALT=gut associated lymphoid tissue.
Proposed “Sequence of Events” in the Development of Dysfunction

I/R, hypotension, anesthesia, manipulation → Up-regulation of ICAM-1 on endothelium of muscularis vasculature → Leukocyte extravasation into muscularis

Up-regulation of iNOS, COX-2, IL-6, STAT-3 → Decrease in contractile response and altered electrical activity

Approaches to Maximizing Gut Function in Critical Illness

• Maintain visceral perfusion
• Correction of acidosis and electrolyte abnormality
• Strict glycemic control
• Early nutritional support
  • Enteral preferred
  • < 48 hours (<24 hours may be even better)
  • Specific nutrients to attenuate metabolic response
• Minimize medications that alter GI function
  • Anticholinergics
  • Narcotics
  • Pressors
• Supporting gut microbiome
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US Army Blast Over Pressure Studies.1982
Jejunal Feeding Associated Small Bowel Necrosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>Am J Surg</td>
<td>1988</td>
<td>(R) 5 / 148 (3%)</td>
</tr>
<tr>
<td>Schunn</td>
<td>JACS</td>
<td>1995</td>
<td>(R) 4 / 1359 (.02%)</td>
</tr>
<tr>
<td>Myers</td>
<td>Am J Surg</td>
<td>1995</td>
<td>(R) 3 / 2022 (.01%)</td>
</tr>
<tr>
<td>Rai</td>
<td>Am Surg</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Lawler</td>
<td>Can J Surg</td>
<td>1998</td>
<td>(R) 3 / 386 (0.7%)</td>
</tr>
<tr>
<td>Holmes</td>
<td>J Trauma</td>
<td>1999</td>
<td>(R) 3 / 222 (1.3%)</td>
</tr>
<tr>
<td>Degottardi</td>
<td>E J Surg</td>
<td>1999</td>
<td>(P) 0/100 (0%)</td>
</tr>
<tr>
<td>Munshi</td>
<td>J Trauma</td>
<td>2000</td>
<td></td>
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</tbody>
</table>
Why is the Gut So Vulnerable?

• Disproportionate vasoconstriction to stress
• Metabolically very active tissue
• Feeding increases $O_2$ requirement
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Model</th>
<th>VBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goshe</td>
<td>90</td>
<td>E. coli sepsis</td>
<td>↑</td>
</tr>
<tr>
<td>Flynn</td>
<td>92</td>
<td>Hemorrhage</td>
<td>↑</td>
</tr>
<tr>
<td>Purcell</td>
<td>92</td>
<td>ARDS</td>
<td>↑</td>
</tr>
<tr>
<td>Smith</td>
<td>94</td>
<td>Sepsis</td>
<td>↑</td>
</tr>
<tr>
<td>Kazamias</td>
<td>98</td>
<td>Sepsis</td>
<td>↑</td>
</tr>
<tr>
<td>Revelly</td>
<td>01</td>
<td>Human / cardiac</td>
<td>↑</td>
</tr>
</tbody>
</table>
SCCM Guideline A5. In setting of hemodynamic compromise, EN should be withheld until the patient is fully resuscitated and/or stable (Grade E).

- Early Enteral Feeding Associated Nonocclusive Bowel Necrosis
- Rare but highly lethal
- Onset usually 10 to 14 days following period of enteral tolerance
- Clinical findings (similar to early sepsis)
  - Tachycardia
  - Fever
  - Leukocytosis
- NO specific clinical patterns are pathonomonomic
- Theories
  - Increase oxygen demand with decrease supply
  - Bacterial overgrowth with poor motility
  - Bacterial toxins alter mucosal barrier
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  - Narcotics
  - Pressors
**Gastrointestinal Motility and Glycemic Control**

* Antral Motility correlates with blood glucose concentration
* Rayner et al, Diabetes Care, 2001

![Graph showing relationship between antral motility index and blood glucose levels.](image)

Hasler et al, Gastroenterology, 1995
Meticulous Glycemic Control (Insulin) May Influence Protein Absorption

- **Insulin stimulates Pept-1**
  - Stimulation of transport is rapid
  - Increases membrane Pept-1 population
    - $V_{max}$ increase without change in $K_m$

- **Peptide transporters in critical illness**
  - First transporter to return following mucosal injury
  - Pept-1 increases with fasting / starvation
  - Transports 60 to 70 percent of total protein in normal gut
  - Very non-selective transporter

“Protection of hepatocyte mitochondrial ultrastructure and function by strict glucose control with insulin in critically ill patients”

- **Study design:**
  - 36 critically ill patients +/- glycemic control
  - Enzyme activities respiratory-chain and oxidative-stress sensitive GAPDH muscle and liver
  - Subset had mitochondrial EM

- **Findings:**
  - Hypertrophic mitochondria with abn cristae with decreased matrix electron density in control
  - No difference in muscle between groups

- **Conclusion:**
  - Strict glycemic control prevented or reduced structural and functional abnormalities of hepatocyte mitochondria

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  - Anticholinergics
  - Narcotics
  - Pressors
Reasons Why TPN Traditionally has Resulted in Poor Outcomes

- Mucosal atrophy
- Systemic immune suppression
- Lack of luminal delivery (GALT atrophy)
- Overfeeding
- Hyperglycemia common
- Systemic venous nutrient delivery vs portal
- Imbalance or lack of specific nutrients
Large animal model of mucosal changes during TPN

Day 0

Day 14

Day 28
"Parenteral nutrition is associated with intestinal morphologic and functional changes in humans"

- 8 normal subjects / 14 days TPN
- Morph / biochem / permeability
- Conc:
  Morphologic changes
  Permeability changes
  Enteral rapidly returns

Buchman, JPEN 19:453-460, 1995
Potential Reasons Why TPN Traditionally has Resulted in Poor Outcomes

- Mucosal Atrophy
- Systemic immune suppression
- Lack of luminal delivery (GALT atrophy)
- Overfeeding
- Hyperglycemia common
- Systemic venous nutrient delivery
- Imbalance or lack of specific nutrients
## Human Studies: Enteral vs TPN

### What Does the Data Show?

48 studies in adult populations (46 in english literature)
20 surgical, 9 critical care, 7 pancreatitis, 5 IBD, 3 Hepatic disease, 3 mixed populations

General conclusions: fewer infections, shorter hospital stay

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore</td>
<td>89</td>
<td>Trauma</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Kudsk</td>
<td>92</td>
<td>Trauma</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Hasse</td>
<td>95</td>
<td>Hepatic transplant</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Reynolds</td>
<td>96</td>
<td>GI surgery</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Shirabe</td>
<td>97</td>
<td>Hepatic resection</td>
<td>↓ Infections</td>
</tr>
<tr>
<td>Kalfarentzos</td>
<td>97</td>
<td>Pancreatitis</td>
<td>↓ Sepsis/Comp</td>
</tr>
<tr>
<td>Windsor</td>
<td>98</td>
<td>Pancreatitis</td>
<td>↓ MOF/SIRS</td>
</tr>
<tr>
<td>Gramlich</td>
<td>04</td>
<td>Meta-analysis</td>
<td>↓ infections</td>
</tr>
</tbody>
</table>
Gut Associated Lymphoid Tissue
G.A.L.T.

- BM, spleen, LN
  $2.5 \times 10^{10}$ Ig producing cells

- Gut
  $8.5 \times 10^{10}$ Ig producing cells
Feeding Maintains GALT / MALT
# Early Enteral Feeding Meta-analysis

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Study Parameters</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik. <em>CCM.</em> 2001.</td>
<td>Feeding &lt; or &gt;36 hr</td>
<td>15 studies 753 patients</td>
<td>↓ Infections ↓ LOS*</td>
</tr>
<tr>
<td>Lewis. <em>BMJ.</em> 2001. (surgery patients)</td>
<td>NPO vs &lt;24 hr</td>
<td>11 studies 837 patients</td>
<td>↓ Infections ↓ LOS ↑ Vomiting risk</td>
</tr>
<tr>
<td>Heyland. <em>JPEN.</em> 2003 (medical ICU)</td>
<td>&lt;24 to 48 hr</td>
<td>8 studies</td>
<td>Trend to ↓ infections and mortality</td>
</tr>
<tr>
<td>Lewis SJ J GI Surg 2008</td>
<td>&lt; 24 hr</td>
<td>13 studies 1173 patients</td>
<td>Decrease mortality</td>
</tr>
<tr>
<td>Doig GS Int Care Med 2009 (Critically ill patients)</td>
<td>&lt; 24 hr</td>
<td>5 studies</td>
<td>Decrease infection and mortality</td>
</tr>
<tr>
<td>Osland E JPEN 2011 (GI Surg with resection)</td>
<td>&lt;24 hr</td>
<td>15 studies 1240 patients</td>
<td>45% decrease in morbidity, no increase anastomotic leak</td>
</tr>
<tr>
<td>Doig GS Injury 2011 (Trauma Pts)</td>
<td>&lt; 24 hr</td>
<td>3 studies</td>
<td>Decrease mortality</td>
</tr>
<tr>
<td>Burden S Cochrane Rev 2012</td>
<td>Preop and early postop (multiple reviews)</td>
<td>&gt; 45 studies</td>
<td>Preop feeding beneficial, Dec infections</td>
</tr>
</tbody>
</table>
Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials

Gordon S. Doig, Philippa T. Heighes, Fiona Simpson, Elizabeth A. Sweetman

Mortality improved

Injury 2011
With virtually 100% agreement that early EN is a benefit, why is it such a problem getting EN started?

- Lack of understanding of the potential benefits
  - Not a priority in many most surgical teams?
- Information overload: > 400 RCT peri-op Nutrition
- Lack of skills for tube placement
- Misperception / misunderstanding post-op ileus
  - Waiting for “bowel sounds”
- Concern for complication
  - “aspiration”
  - Ischemic bowel
  - “leak” of bowel anastomosis
- Unable to feed while on “pressors”
- How much is enough to show benefit?
- Lack of communication between team members
Barriers to feeding the critically ill: A multicenter survey of Critical Care Nurses

- (1) other aspects of patient care taking priority over nutrition
- (2) not enough feeding pumps available
- (3) enteral formula not available on the unit
- (4) difficulties in obtaining small bowel access in patients not tolerating gastric enteral nutrition
- (5) Inadequate or no dietitian coverage during weekends and holidays.

• Cahill N et al J Critical Care 2012
Trophic vs Full Feeds

ARDSNet Multi-Center PRCT

ALI/ARDS patients on mechanical Ventilation

Trophic 20cc/hr x 6days (n=508)
vs Full feeds (n=492)
400 kcal vs 1300kcal

No difference in outcome: early or late outcome similar

Mortality, vent-free days, MOF, or infection

80% Goal calories

25% Goal calories

Rice T et al JAMA (Feb 9, 2012)
Needham DM et al BMJ 2013
Figure 3

- Deceased
- Alive, Ventilated
- Discharged, Off Vent

Rice T JAMA 2012
Optimal Initial Amount of Enteral Feeding in Critically Ill Patients: Systematic Review and Meta-Analysis

• Meta-analysis of adult Med/Surg ICU patients

• Initial trophic vs full feeding

• 4 RCTs (N=1540 participants total)

• Primary analyses: Mortality

• Conclusions:
  – No diff in Mortality (OR 0.95; 0.74-1.20; P=0.65)
  – No difference in Hospital or ICU LOS
  – Serious GI Intolerance: 23% trophic vs 31% full

What Direction Are “We” Going?

- PRCT presented at Annual Surgical Infection Society Sept 2013
  Eric Charles, Univ of Virginia SICU setting (n=84)
  12.5-15 kcal/kg/d vs 25-30 kcal/kg/d (normal Prot 1.5 gm/kg/d)
  No difference ICU or Hosp LOS, infection, mortality

"These risks are lessened if the amount of calories needed were less than the traditional amounts. Thus, this study shows that feeding less in the ICU may be better, as overall morbidity was the same," Dr. Cheadle said.

- WG Cheadle

- E Charles (J Gastroent Hepatol 2013;28:687)
Altering Outcomes with Early Enteral Feeding

“Outcomes in Critically Ill Patients Before and After the Implementation of an Evidence-Based Nutritional Management Protocol”
- Prospective evaluation before and after evidence based protocol introduction
- N=200 Med-Surg ICU
- Conclusions:
  - Increased delivery of nutrient
  - Shortened duration of mechanical ventilation
  - Decrease mortality

“Effects of Early Enteral Feeding on the Outcome of Critically Ill Ventilated Medical Patients”
- ICU patients
- Retrospective review of prospectively collected data
- N=4049
  - 2537 patients fed < 48 hours
  - 1512 patients fed > 48 hours
- Propensity scoring system to control for confounding variables
- Conclusions:
  - 20% decrease in ICU mortality (18.1 vs 21.4%)
  - 25% decrease in hospital mortality (28.7 vs 33.5%)
  - Influence greatest in sickest patients
    - Beneficial effect noted despite increase in VAP

Artinian V et al Chest 2006;129:960-967
Early enteral feeding in patients with open abdomen

- Multicenter Prospective cohort study patient with Damage Control Laparotomy
- Evaluating safety and effect of immediate EF
- 1000 patient study (Glue Grant) 100 patients met criteria
  - 32 immediate EF / 68 delayed EF (> 36 hours)
  - Similar severity of injury
- Results:
  - Time to closure: 6.47 vs 8.55 days (NS)
  - No difference in MOF, ICU days, Ventilator days, mortality
  - Rate of pneumonia 43.8 vs 72.1 % (p=0.008)
- Conclusion:
  - Immediate enteral feeding is safe in open abdomen cases
  - No delay in closure, trend toward faster closure
  - Significant reduction in pneumonia

Feeding the open abdomen w/in 36h

Dissanaike, JACS 2008

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Odds ratio for development of VAP* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate enteral nutrition</td>
<td>0.32 (0.13–0.79)</td>
</tr>
</tbody>
</table>
Fistula (p=0.05)
% Closure < 8d (p = 0.03)

Collier, B  JPEN 2007
Enteral Feeding While on Pressors for Hemodynamic Support: Helpful or Harmful?

- Prospectively collected data 1174 ICU patients ventilator > 48 requiring pressors to maintain BP
- 2 groups
  - Those receiving EN with 48h (N=707)
  - Those not receiving EN within 48h (N=467)
- Endpoints ICU stay, mortality
  - Propensity scoring to eliminate confounding variables
    - i.e. severity of injury / illness
- Conclusion:
  - Mortality lower in the early EN (22.5% vs 28.3%) p<0.001
  - greatest benefit noted in the sickest people

Khalid I Am J Crit Care 2010
**Early Feeding in Post-Op and Trauma Setting Can Be Done Safely!**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Population</th>
<th>Timing</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald</td>
<td>1991</td>
<td>106</td>
<td>Burn</td>
<td>6h</td>
<td>85%</td>
</tr>
<tr>
<td>McCarter</td>
<td>1997</td>
<td>167</td>
<td>UGI</td>
<td>24h</td>
<td>78%</td>
</tr>
<tr>
<td>Heslin</td>
<td>1997</td>
<td>195</td>
<td>UGI CA</td>
<td>24h</td>
<td>80%</td>
</tr>
<tr>
<td>Velez</td>
<td>1997</td>
<td>46</td>
<td>GI</td>
<td>6h</td>
<td>81%</td>
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<tr>
<td>Hedberg</td>
<td>1999</td>
<td>225</td>
<td>Post-op</td>
<td>12h</td>
<td>85%</td>
</tr>
<tr>
<td>Braga</td>
<td>2002</td>
<td>650</td>
<td>Post-op</td>
<td>12h</td>
<td>91%</td>
</tr>
<tr>
<td>DiFronzo</td>
<td>2003</td>
<td>86</td>
<td>Colon (PO)</td>
<td>48h</td>
<td>97%</td>
</tr>
<tr>
<td>James</td>
<td>2004</td>
<td>170</td>
<td>Whipple</td>
<td>24h</td>
<td>85%</td>
</tr>
<tr>
<td>Mosier</td>
<td>2011</td>
<td>153</td>
<td>Major burn</td>
<td>24 v 48</td>
<td>88%</td>
</tr>
</tbody>
</table>
Metabolic Benefits of Early Enteral Feeding are Numerous

- Attenuates inflammatory response to stress / critical illness
- Prevents mucosal atrophy, loss of gut barrier
- Luminal delivery maintains GALT and MALT
- Systemic immune support
- Helps maintain normal gut bacteria growth
- Less insulin resistance Hyperglycemia more common
- Maintains vagal mediated anti-inflammatory reflex
- Portal nutrient delivery allows for first pass effect
- More balanced nutrient delivery possible
**Cholinergic anti-inflammatory pathway**

- Activation of vagal efferents results in regulation of cytokine production of macrophages in the gut wall
- Shown to improve survival in septic animal models (rat model)
- Dietary fat can activate the cholinergic anti-inflammatory pathway
  - Gut permeability, ileal lipid binding protein, intestinal myeloperoxidase, mast cell protease
  - CCK antagonists blocks benefit

**Conclusion:**

- Luminal delivery of nutrient required to show benefit
- Lumen macronutrient content critical in supporting barrier function

Eisner F JACS 2011, de Haan JJ Crit Care Med 2010
Enteral Feeding Attenuates Hyperdynamic Response to Endotoxemia

- **Study Design:** PDBCT trial N=18 healthy volunteers
  - Study done to evaluate influence of EN on endotoxin induced metabolic response
    - 3 groups (nutrient infusion via FT 1 hr before and 6 hr after
      - Placebo – fasted (n=6)
      - Fed control – received standard 1 kcal/cc formula (n=6)
      - Experimental - High protein/high fat 1 kcal/cc formula (n=6)
    - All given hydration then E.coli endotoxin bolus (2ng/kg)
    - Multiple metabolic parameters monitored
      - Cytokines, vitals, CCK levels, etc
- **Results:** enteral fed group with experimental formula
  - Decrease in IL-6, TNF α, IL-1RA \((p <0.05)\)
  - Increase IL-10 \((p<0.0001)\)
  - Decrease iFABP (marker of mucosal damage) \((p<0.05)\)

Lubbers T et al CCM 2013
So many mechanisms, so little time: early enteral feeding in surgery!

- Attenuating systemic inflammation
  - Alters metabolic response to stress
  - Limits protein catabolism

- Central vagal mediated cholinergic anti-inflammatory pathways in gut wall

- GALT / MALT

- Maintaining mucosal and brush border integrity
  - Gap junctions
  - Mucosal synthesis, mucous secretion
    - Decreases bacteria products across BB

- Improved glycemic control

- “optimal” hepatic nutrient metabolism (first pass metabolism)
  - Lipid, CHO, protein metabolism
  - Decrease cholestasis
The Gut as Regulator of Inflammatory Response

Gut disuse: inflammation

Feed the Gut: inflammation
Approaches to Maximizing Gut Function in Critical Illness

- Maintain visceral perfusion
- Strict glycemic control
- Correction of acidosis and electrolyte abnormality
- Early nutritional support
  - Enteral preferred
  - < 48 hours
  - Specific nutrients to attenuate metabolic response
- Minimize medications that alter GI function
  - Anticholinergics
  - Narcotics
  - Pressors
The GI Mucosal Barrier: Is It the Motor for MOF?
From Intestinal Crosstalk; Clark Shock JA 2007
Luminal Bacteria: Friend or Foe?

- Data showing protection from disease
  - IBD
  - Diarrhea Diseases
  - Sepsis
  - Pancreatitis
  - Systemic infection
    - VAP
    - Sepsis
    - Wound infection

- Data supporting causing disease
  - Epithelial barrier disruption
  - Disruption of tight junction
  - Proinflammatory cytokine release
  - Cell apoptosis
  - Activation of neutrophiles
Probiotics Background

- Biblical references to “sour milk” longevity of Abraham
- Metchnikoff (1874-1961)
  - Increase longevity
  - Macrophage
- Widely used in animal products
  - Decrease infections
  - Increase growth rates
- Radical changes in western diet
  - Wide variation in “normal” fecal flora
- Human GI tract
  - 400 to 600 species, 1 to 2 Kg
  - > 2 million genes (35K in human)
  - Primarily anerobic
- Body covered with thin layer of bacteria
  - Lung, vagina, oral pharynx approximately 20 gm each
- Germ free animal studies and mucosal development
  - Decrease vascular development
  - Altered transporters
  - Altered systemic growth and development
  - Significantly suppressed immune function
- “Cross talk” between bacteria and host
  - Large surface area
  - Toll receptors
  - One bacterial species turns on > 100 genes
Where “man meets microbe”
a dynamic interplay

- 400 sq meter surface area
  - Surface area of a tennis court
- > 2 million genes in the bacterial genome vs 35,000 in the human
  - 100 trillion living bacteria in the human intestine
  - Over 500 species in human colon
- Significant “cross-talk” between bacteria and host
  - One bacteria species can turn on > 100 genes
  - Toll receptors on dendritic cells / macrophages
  - Gut contains complex neuroendocrine system
- Quorum sensing
  - Molecules secreted by bacteria: they partially explain bacterial community behavior and activation of virulence genes etc
Does Surgery or Peri-op Therapy Alter the Microbiome?

- Inflammatory changes
- Bacterial interrelationships
- Bacterial changes with host stress situations
  - Bacterial use environmental clues
    - pH, temperature, redox potential, osmolality
  - When energy supply is limited genes “switch on” virulence factors
  - Ex: E.coli and Pseudomonas can rapidly become virulent with host stress (epinephrine, cortisol, morphine etc)

Alverdy J, CCM 31:598-607, 2003
Alverdy J Molecular Biol 2008
Changes in fecal bacterial products in trauma ICU are predictive of outcome!

- Gut represents most diverse and fragile microenvironment and ecosystem in the body
  - Dramatic alteration by critical illness and broad spectrum antibiotics

- Population in ICU > 48h (N= 491 samples, 138 pts)
  - Acids measured
    - Acetate, lactate, succinate, formate
    - Cytoprotective SFA; propionate, butyrate

- ↑ in pH predicts mortality
  - Loss of anaerobic bacteria

Osuka A, Shimizu K et al. Critical Care 2012
“Persistent decrease of total obligate anaerobes in gut is related to high mortality in patients with severe SIRS”

- Gut flora significantly altered in ICU settings
- Anaerobic bacteria known to enhance immune regulatory function and inflammatory responses
- Methods:
  - 81 patients with SIRS (CRP >10 mg/dl)
  - ICU stay > 2 days descriptive study
  - 3 groups based on # of obligate anaerobes
    - NI anaerobes >10⁹/gm stool
    - Decreased then recovered
    - Persistently low
- Conclusions
  - Mortality
    - NI anaerobes 16%
    - Low then recovered 25%
    - Persistently low 81%
  - Bacteremia
    - NI anaerobes 6%
    - Decreased then recover 50%
    - Persistently low 75%

Kentaro S et al SCCM 2007
Probiotics: Exploring the Mutually Beneficial Effects of Bacteria and Their Substrates in the Human Host

- Prevent infections (systemic and GI)
- Regulate local and systemic immune function
- Metabolic pathway nutrients: glycemic control, cholesterol, amino acids
- Support mucosal barrier
- Regulate bowel motility
- Prevent neoplastic changes
- Regulate appetite (leptin, ghrelin)
- Enhance nutrient utilization

Probiotics
Criteria for Probiotic Designation

- Human origin
- Viable and hardy in human GI tract
- Acid and bile stable
- Adhesion to mucosa
- Clinically demonstrated benefit
- Safe

WHO, FAO (Food and Agriculture Organization) of the UN definition:

- “live microorganisms in which when administer in adequate amounts confer a health benefit on the host”

Most Common Probiotics Commercially Used

- Lactobacillus acidophilus/johnsonii/gasseri
- Lactobacillus casei
- Lactobacillus paracasei
- Lactobacillus rhamnosus
- Lactobacillus plantarum
- Lactobacillus reuteri
- Bifidobacterium animalis/lactis
- Bifidobacterium bifidum
- Bifidobacterium breve
- Bifidobacterium longum
- Bifidobacterium adolescentis

Lactobacillus
Bifidobacteria
Mechanisms:

1. Enhancement of the epithelial barrier
   - Mucins and defensins

2. Increased adhesion to intestinal mucosa

3. Inhibition of pathogen adhesion

4. Competitive exclusion of pathogenic microorganisms

5. Production of anti-microorganism substances
   - Example: bacteriocins

6. Modulation of the immune system
   - IL-10, TGFβ
   - Immature DC
   - Macrophage
   - Th1, Th2, Th17
   - Treg
Mechanisms:
Colonization Resistance
Antimicrobial Factors

Mechanisms:
• Competitive inhibition
• Physical barrier (mucous)
• ↓ Adherence, attachment
• Produce bacteriocins
  Defensins, Trefoil
  Bind pathogens
• ↓ pH reduces growth
• Interferes quorum sensing
  ↓ Virulence expression
• Breaks up biofilms

Bacteria
• Escherichia coli (pathogenic)
• Salmonella typhimurium
• Shigella spp.
• Campylobacter jejuni
• Streptococcus mutans
• Bacillus subtilis
• Clostridium perfringens
• Helicobacter pylori
• Staphylococcus aureus
• Listeria monocytogenes
• Pseudomonas fluorescens

Fungi
Candida albicans
Aspergillus flavus

L. reuteri inhibits
H. pylori
PM Sherman (NCP2009)
Morowitz M J (SCNA 2011)

L. reuteri inhibits
Staph aureus
Protecting the mucosal lining:
“Soluble factors for *Lactobacillus rhamnosus GG* activate MAPKs and induce cytoprotective heat shock proteins in intestinal epithelial cells”

- 70% of energy for colonocyte derived from luminal butyrate
- Cell culture model
- DNA microarray methods, real-time PCR and electrophoretic mobility shifts studied
- Studies confirm:
  - *L. GG* modulates signaling pathways
  - Activates via MAP kinase
  - *L.GG* protects mucosa from oxidant stress via expressing HSP

Tao K, Drabik K, Waypa T
Am J Physiol Cell Physiol 290;1018-1030, 2006
Mechanisms: Enhancing mucosal blood flow

- Stappenbeck TS, Hooper LV, Gordon JI.
SCFAs, Fiber Fermentation and Butyrate Receptors

- Trophic effect, colonocyte fuel
- Anti-inflammatory
- Enhance WBCs, macrophage
- ↓Adhesion molecules
- (↓microvascular thrombosis)

Thangaraju M et al J GI Surg 2008
Ganapathy V 2011
Clinical Use of Probiotics

Where does the rubber meet the road?
“Probiotic treatment of VRE: Randomized Controlled Trial.”

- PRPCBT 27 VRE positive patients
- Yogurt (containing live Lactobacillus GG vs Pasteurized yogurt)
- 100 gm daily x 4 weeks
- Primary outcome measure: clearance of VRE
- Results:
  - L.GG group: 11/11 cleared VRE at 4 weeks, 3/11 reconverted + at 4 weeks
  - Control: 1/12 cleared
    » Allowed to crossover at 4 weeks 8/11 crossed over
    » 8/8 of the crossover group cleared in 4 weeks

PRPCBT = Prospective Randomized Placebo Control Blinded Trial
Antibiotic Associated Diarrhea: Preventable or Inevitable?

- Hempel S et al JAMA 2012
- Meta-analysis 82 RCT met criteria for inclusion
- Probiotics strains were poorly documented
- N=11,811 participants (pooled data)
- Conclusion:
  - Probiotics confer significant decrease in AAD (p<.001)
  - # needed to treat N=13

Hempel S et al JAMA 2012
Rising Incidence of C. difficile

- Incidence of C. difficile by year

Pathogenesis of CDAD

Antibiotic therapy

Alteration in colonic microflora

*C. difficile* exposure and colonization

Release of toxin A and Toxin B

Colonic mucosal injury and inflammation

- Badger, VO et al JPEN 2012
Emergence of B1/NAP1 Strain

- Produces 16-23 times C. diff. toxins A and B in vitro,
- represented 50% of isolated strains between 2001-2003
  - Produces a 3rd binary toxin
- Increased risk of relapse
- Less responsive to standard therapies

Major Genes in the Pathogenicity Locus (PaLoc) of Clostridium difficile and Relation to the Genes for Binary Toxin

- McDonald NEJM 2005
Use of probiotic preparations to prevent C. difficile Associated Diarrhea

• RDBPCT N=135
• Age 64 all taking antibiotics
• 100 gm BID L. casei as drink

Results:
• AAD: 7/57 (12%) vs 19/56 (34%)
• 21% relative risk reduction, NNT 5
• C.diff 0/57 vs 9/53 (17%)

• Meta-analysis 28 studies
• N=3818 patients

“Moderate quality” of evidence probiotics as prophylaxis
• decreases incidence of CDAD by 66%
• No adverse influence by receiving probiotics

Johnston BC Ann Internal Medicine 2012
The ultimate probiotic: Is stool from a “good friend” or family member the answer for refractory C. difficile diarrhea

- RTC 39 patients with proven refractory C. difficile
- 16 got Donor feces / 13 received QID vancomycin

Results:
- Feces group
  - 13/16 resolved with single infusion
  - 2/3 resolved with second infusion
- Vancomycin group
  - 4/13 resolved

Nood EV NEJM 2013

Hamilton MJ et al
Frozen “fecal” prep for C.diff
43 consecutive, recurrent CDI
95% success
Am J Gastroenterology 2012
"Probiotic treatment of VRE: Randomized Controlled Trial."

- PRPCBT 27 VRE positive patients
- Yogurt (containing live Lactobacillus GG vs Pasteurized yogurt)
- 100 gm daily x 4 weeks
- Primary outcome measure: clearance of VRE
- Results:
  - L.GG group: 11/11 cleared VRE at 4 weeks, 3/11 reconverted + at 4 weeks
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    - 8/8 of the crossover group cleared in 4 weeks

PRPCBT = Prospective Randomized Placebo Control Blinded Trial
## Probiotics in Trauma

<table>
<thead>
<tr>
<th>Author year</th>
<th># patients</th>
<th>Patient characteristics</th>
<th>Outcome parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falcao de Arruda</td>
<td>RCT N=20</td>
<td>TBI</td>
<td>Decrease: Nosocomial infections and LOS</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olguin 2005</td>
<td>RCT N=31</td>
<td>Burns</td>
<td>No benefit</td>
</tr>
<tr>
<td></td>
<td>(prebio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kotzampassi 2006</td>
<td>RCT N=65</td>
<td>Multiple trauma</td>
<td>Decrease: VAP, LOS, Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spindler-Vesel</td>
<td>RCT N=113</td>
<td>Multiple trauma</td>
<td>Decrease: infections, VAP,</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tan 2011</td>
<td>N=52</td>
<td>TBI</td>
<td>Decrease: nosocomial infections, VAP</td>
</tr>
</tbody>
</table>

- Variety of bacterial strains used: L johnsonii, L paracasei, L plantarum, L bulgaricus, L thermophilus
Meta-analysis: Probiotics in Trauma

- Gu, WJ  JPEN 2013
- 5 RCT  N=281 patients:
  - Use of probiotics reduction;
    - of nosocomial infections
    - VAP
    - Length of stay in ICU
    - No mortality advantage

- Caution: large heterogeneity between groups
- Use of meta-analysis for hypothesis generation not hypothesis confirmation !!!
Prevention of GI Anastomosis Failure

• Animal models (Alverdy’s group)
  – IR increases mortality with Pseudomonas after inoculation
    • Expression of barrier disrupting adhesin PA-IL

• Bacteria at sight of anastomosis change phenotype and become more aggressive and produce adhesins and enzymes with increase risk of anastomotic disruption
  • Altered by MBP, antibiotic Bowel Prep, ischemia etc

Fink D, et al J Trauma 2011
Stern JR et al J Surg Res 2013
Etiology of ICU Induced Changes in Commensal Microflora

- Broad spectrum antibiotics
- PPI / H$_2$RI
- Vasoactive pressor agents
  - Changes in pH,
  - Decrease pO$_2$
  - Increase pCO$_2$
- Opioids
  - Decrease motility and bacterial clearance mechanisms
- Decrease in luminal nutrient delivery
Does the Mucosal Surface Environment Alter Function and or Clinical Outcome?

- Inflammatory changes
- Bacterial interrelationships
- Bacterial changes with host stress situations
  - Bacteria use environmental cues
    - pH, temp, redox potential, osmolality
  - When energy supply is limited, virulence genes “switch on”
    - This on/off can be rapid, depending on host
  - Example: *E. coli* with host stress (norepinephrine) rapidly changes to become much more virulent
    - Exposure of *E. coli* to norepinephrine induces fimbration

Bacterial-host interactions can be: symbiotic or parasitic. The parasitic can be without damage to host, or highly aggressive with disruption of the host cellular architecture and physiology. Depending on:
1) Physiologic state of host
2) Availability of nutrients
3) Adversity of the local environment
The Missing Link?

Toll Like Receptors (TLR’s)

- Pathogen recognition receptors
  - Flagellin, LPS, viral proteins etc
- Mammalian TLR genes
  - 10 human and 9 murine
  - 7 on membrane and 3 w/in cell
- Within 30 minutes of E.coli exposure 685 genes turned on
- Well conserved homologs in animals and plants
- Primary signal apparatus for innate immune system
  - NFkB, etc etc
- Modulate phagocytosis and Ag presentation, and inflammatory response
- Now felt to activated by stress response, tissue damage, in addition to bacteria etc

Murphy TJ et al Journal of Leukocyte Biology 75:400-407, 2004
“Altered gut flora and environment in patients with severe SIRS”

- Quantitatively evaluated changes in gut microflora and environment in patients with SIRS
- N=25 with SIRS
  - CRP >10
  - ICU stay > 2 days
- Followed:
  - Fecal flora
  - Organic acids
  - pH
- Conclusions
  - Significantly fewer “beneficial” flora, and increase in “pathogenic” flora
  - Decrease concentration in butyrate and propionate
  - Increase in pH

Shimizu K et al. J. Trauma 2006;60:126-133
“Persistent decrease of total obligate anaerobes in gut is related to high mortality in patients with severe SIRS”

- Gut flora significantly altered in ICU settings
- Anaerobic bacteria known to enhance immune regulatory function and inflammatory responses

Methods:
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- 3 groups based on # of obligate anaerobes
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Conclusions
- Mortality
  - NI anaerobes 16%
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- Bacteremia
  - NI anaerobes 6%
  - Decreased then recover 50%
  - Persistently low 75%

Kentaro S et al SCCM 2007;34:abstract #3
General Considerations: The Gut in Critical Illness

• Nutrition Support:
  • Enteral is superior to parenteral
  • Early is better than later
  • Quality of nutrition appears more critical than quantity
    » immune modulation in select populations
    » Avoid overfeeding
    » Avoid immune suppressive regimens (hyperglycemia, excessive omega 6 lipids etc)
    » Antioxidants in select at risk populations
  • Inappropriate enteral feeding can result in disaster

• Protocols or guidelines increase nutrient delivery, improve outcome
A Closer Look at GI Function in Trauma:
Summary

• Visceral hypoperfusion is common in the ICU and results in SRMD and barrier disruption from stomach to colon

• Hypomotility is common; etiology is multifactorial, involving multiple mechanisms
  – Often associated with
    • Decreased nutrient delivery
    • Limited enteral drug delivery
    • Increased aspiration risk

• Data continues to support the concept that the “Gut is responsible in many cases of MOF”

• Early enteral feeding with appropriate nutrients can be preventative and therapeutic
  • Probiotics should be considered in enteral feeding plans
Thank You