The Gut in Trauma: The Source or The Potential Cure For Multiple Organ Failure?

Infectious etiology concept supported by key papers in 1970's Polk, Fry etc.

Research in the 70's focused on 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 (+/-)
  - Most patients dying with MOF with negative cultures
  - Early enteral feeding showing benefit
    - Primarily pneumonia outcome was decreased

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 infectious 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
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)
- Teixeira et al: Germ free animal showing increased survival following IR (4)
- Clark et al: epithelial apoptosis elevated in sepsis, prevented by overexpression of anti-apoptotic protein Bcl-2 (6)
- Deitch et al: Toxin from gut damages lung via lymphatics (5)
- Alverdy et al: interaction between bacteria and host. Most patients dying of “MOF” have no + cultures (3)


Temporal trends of postinjury multiple-organ failure: Still resource intensive, morbid, and lethal

- Data collection from 20 institutions 2003 to 2010
  - 1643 patients with MOF
  - Strict criteria for sepsis / injury / MOF
- Results
  - MOF incidence decreased over time 17% 2003 to 9.8% in 2010
  - MOF death 33% 2003 to 36% 2010
  - No change in ventilator days length of stay in ICU
  - Most MOF death occurred within 2 days of MOF diagnosis
  - Lung dysfunction decrease 58 to 51%
  - Cardiac dysfunction decrease from 21 to 13 %
  - Renal and hepatic failure rates did not change

Gut Integrity Following Trauma

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

Pathophysiology of Splanchnic Hypo-perfusion

- Sepsis- Trauma- Shock- MOF
- Increased catecholamines
- Increased vasomotor tone
- Reduced mesenteric blood flow
- Cardiac output
- Hypovolemia

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

Does Trauma 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

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>&quot;Altered&quot; 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.
Martindale RG et al NCP 2013

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
  - Changes in luminal bacteria and bacterial products
  - Mucosal barrier disruption
    - Visceral hypoperfusion
    - Absence of biliary and pancreatic secretions

*NO=nitric oxide; †VIP=vasoactive intestinal peptide; ‡iNOS=inducible nitric oxide synthase; §GALT=gut associated lymphoid tissue.

What are the mechanisms? 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 0₂ consumption at rest

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

Villus 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!

Life and death only one cell layer away

**Approaches to Maximizing Gut Function in Critical Illness**

- Correction of acidosis and electrolyte abnormality
- Glycemic control
- Maintain visceral perfusion
- 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
- Selective gut decontamination
- Supporting gut microbiome

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**Gastrointestinal Motility and Glycemic Control**

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

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**Visceral perfusion**

- Hasler et al, Gastroenterology, 1995

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**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
Enteral Feeding During Low Flow States

<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>

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

What happened to TPN?
The disappearance of its use in the Trauma ICU
- Retrospective analysis of all Level 1 TICU admissions over 6 year period
  - Comparative cohorts matched case-control approaches
  - Logistic regression analysis adjusting for significant risk factors
- 2,964 patients admitted
  - 464 received TPN

Results:
- TPN used decreased from 26% in 2000 to 3 % in 2005
- Mortality in the higher TPN group higher (5.4% vs 10.2%)
- Complications higher in the TPN group
- Decrease resource utilization with enteral

Reasons Why TPN Traditionally has Resulted in Poor Outcomes in Trauma
- Propagates the inflammatory response
- 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
  - Fatty acids limited to soybean in USA
  - pro-inflammatory and increase infection risk
  - Amino acid profile is poor and unphysiologic

Does use of PN in critical care need to be re-evaluated?
- Traditionally EN significantly improved outcome over PN
  - Historic and current data to support
    - 39 well done RCT EN v PN with 37 showing EN benefit
    - Caesar EpaNIC Trial 2011
    - Early PN detrimental – “autophagy” etc etc
  - Recent data would suggest PN may not be so bad
    - SPN trial 2013 Lanced (Heiddegger, Berger et al)
    - Doig GS early PN in those unable to take EN improved outcome JAMA 2013
    - Harvey SE et al NEJM 2014

Recent literature will change the way we think about nutritional intervention in Surgery / Trauma and SICU !
- Supplemental PN / Nutrition -Van den Berghe G (NEJM 2011)
- Nutritional intervention shuts off “autophagy”? ?
- Trophic vs full feeds - Rice T (JAMA 2012)
- How much is enough
  - Redox trial - Heyland DK (NEJM 2013)
  - Intervention with high dose GLN is harmful in real sick people ?
- Changing from SIRS and CARS concept to PICS- Moore (JTACS 2013)
- MDSC, Th2 (Persistent immunosuppression catabolism syndrome)
- Resolving inflammation vs inhibiting it Serhan (Nature 2014)
- Resolvins, Protectins, Maresins
- PN = EN ? Harvey S (NEJM 2014)
- No benefit of EN over PN
- New assessment methodology – x sectional imaging
- The science behind the “microbiome”
N= 2388 collected data (1191 PN and 1197 EN)

Pragmatic PCT 33 ICU’s in England
EN v PN started within 36h, >5 days of nutrition
Evenly matched for co-morbidity, demographics etc
Mortality primary outcome with 14 other secondary outcomes
Minimal differences: hypoglycemia and emesis
NO significant differences in Mortality or other 14 parameters (33% PN vs 34% EN)

Other studies supporting the concept:
Heidegger CP Lancet 2013 SPN Study
Doig GS JAMA 2013 – Early PN beneficial

Questions regarding Harvey study
• Why the mortality is so high with APACHE II score of only 15.3 and SOFA 9.3?
• World wide ICU mortality with APACHE II under 20 is 14 to 16%, 20 to 30 rises to 31% (septic shock 60%)
• Interesting that very small percentage were malnourished?

What has changed in PN therapy to potentially support considering changing practice?
• Better understanding of the importance and physiology of glucose control and insulin resistance
• Better understanding of PN makeup
  • Improved AA solutions
    – Gln dipeptide, taurine, carnitine
  • Still not very physiologic
• Wider variety of lipid emulsions available
  – SMOF, Olive oil, fish oil, MCT
  » Olive oil now approved in USA (2014)
• Trace minerals / antioxidants
  » Quantity and timing still controversial
• Increase in the use of trophic feeding with PN

Use of Parenteral Nutrition
2015 CC Guidelines
• Withhold PN in low risk
  If EN not feasible (NRS 2002 ≤ 3 or Nutric Score ≤ 5)
• Initiate exclusive PN ASAP in high risk or severely malnourished pt
  if EN not feasible (NRS 2002 ≥ 5, Nutric Score ≥ 6)
• Add supplemental PN after 7-10 days if EN providing < 60% goal
• Maximize efficacy of PN
  • Use protocols – Do not use parenteral glutamine
  • Hypocaloric dosing (80%) first week
  • Withhold soy-based lipids first week
  • Moderate glucose control (140-180 mg/dL)
  • Transition off PN when EN provides > 60% goal

SCCM / ASPEN Critical Care Guidelines 2015 in review
CCM / JPEN
**Human Studies: Enteral vs PN**

### What Does the Data Show?

**Author**
- Moore
- Kudsk
- Hasse
- Reynolds
- Shirabe
- Kalfarentzos
- Windsor
- Gramlich
- Heyland
- Elke

**Population**
- Trauma
- Trauma
- Hepatic transplant
- GI surgery
- Hepatic resection
- Pancreatitis
- Pancreatitis
- Meta-analysis
- Critical care
- Sepsis

**Year**
- 89
- 92
- 95
- 96
- 97
- 97
- 98
- 04
- 12
- 13

### 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>Shirose</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>
<tr>
<td>Heyland</td>
<td>12</td>
<td>Critical care</td>
<td>↓ Decrease mortality</td>
</tr>
<tr>
<td>Elke</td>
<td>13</td>
<td>Sepsis</td>
<td>↓ LOS, Infections</td>
</tr>
</tbody>
</table>

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**Gut Associated Lymphoid Tissue (G.A.L.T.)**

- BM, spleen, LN
- 2.5 x 10^{10} Ig producing cells

**GALT / MALT**

**Results of EPaNIC Study**

- **PRCT 4640 adult ICU patients multicenter**
- Received 2009 Stouvenbeek Award for study design
- All patients started on EN, tight glucose control

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Early PN (ESPEN) (n=2312)</th>
<th>Late PN (ASPN) (n=2232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>26.2%</td>
<td>22.8% *</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>4.0 d</td>
<td>3.0 d *</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>14.0 d</td>
<td>12.0 d *</td>
</tr>
<tr>
<td>Duration CRRT</td>
<td>10.0 d</td>
<td>7.0 d *</td>
</tr>
<tr>
<td>MV &gt; 2 days</td>
<td>40.2%</td>
<td>36.3% *</td>
</tr>
<tr>
<td>Hosp mortality</td>
<td>10.9%</td>
<td>10.4% (pNS)</td>
</tr>
<tr>
<td>ICU discharge</td>
<td>71.7%</td>
<td>75.2% *</td>
</tr>
<tr>
<td>Healthcare cost</td>
<td>17,973 Euro</td>
<td>16,863 Euro *</td>
</tr>
</tbody>
</table>

* * p<0.05  MP Casear, G Van Den Berghe (NEJM June 2011;365:506)

**Supplemental PN:**

**EPaNIC Trial**

- Early PN (ESPEN)
- Late PN (ASPEN)

- Nutritional strategy: during the first week in ICU, increasing in enteral nutrition with a goal of 20 kcal/kg/day.

**Casaer MP, Van den Berghe G (NEJM June 2011;365:506)**

**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=208 Med-Surg ICU**
  - **Conclusions:**
    - Increased delivery of nutrient
    - Shortened duration of mechanical ventilation
    - Decrease mortality

- **Prospective review of retrospectively collected data**
- **N=6406**
  - 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**

**Bar J et al Chest 2004; 125:1446-1467**

**Artinian V et al Chest 2006;129:960-967**
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>Mark, DCM 2001.</td>
<td>Feeding &lt; or &gt;36 hr</td>
<td>15 studies 763 patients</td>
<td>↓ Infections ↓ LOS*</td>
</tr>
<tr>
<td>Lewis, BMJ 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, JPEN 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 Gf Surg 2008</td>
<td>&lt; 24 hr</td>
<td>13 studies 1173 patients</td>
<td>Decrease mortality</td>
</tr>
<tr>
<td>Dong 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>1240 patients</td>
<td>45% decrease in mortality, no increase anastomotic leak</td>
</tr>
<tr>
<td>Dong 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 (both thrmultiples reviews)</td>
<td>&gt; 45 studies</td>
<td>Preop feeding beneficial, Decl infections</td>
</tr>
</tbody>
</table>

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

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

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


Trophic feeding in the Surgical ICU

- Now multiple studies in MICU
  - Rice JAMA 2011, Choi JPEN 2014
- PRCT in surgical ICU setting
  - SICU setting (n=84)
  - 12.5-15 kcal/kg/d vs 25-30 kcal/kg/d (normal Prot 1.5 gm/kg/d)

Results:
No difference ICU LOS
No difference in Hospital LOS
No difference in total infection incidence
No change in mortality

-Charles E et al AJCM 2014

Caution: Extrapolation can be dangerous!

Trophic may not be for every ICU population

- In sepsis it appears that a higher energy and protein intake is associated with improved outcome by:
  - Improved mortality
  - Fewer ventilator days
  - Fewer ICU days

- Preferred route of delivery
  - EN better than EN+PN
- Macronutrients
  - Increase by 30 gm protein per day improved outcome

Elke G et al Critical Care 2014
Elke G, Heyland DK JPEN 2014
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 pathognomonic
  • Theories
    • Increase oxygen demand with decrease supply
    • Bacterial overgrowth with poor motility
    • Bacterial toxins alter mucosal barrier

Even the sickest patients can be fed safely via the enteral route!

• 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

Enteral Feeding With Open Abdomen
N=78 patients with > 4d of open abdomen
Early vs. late initiation of enteral nutrition

% Closure < 8d (p = 0.03)
% Fistula (p=0.05)

Feeding the open abdomen w/in 36h

Clinical parameter | Odds ratio for development of VAP* (95% CI)
Immediate enteral nutrition | 0.32 (0.12 - 0.79)

Dissanaike, JACS 2008

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>
</tr>
<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>

Collar, S JPEN 2007
The Gut as Regulator of Inflammatory Response

- Gut disuse:
  - inflammation
- Feed the Gut:
  - inflammation

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

Etiology of ICU Induced Changes in Commensal Microflora

- Broad spectrum antibiotics
- PPI / H₂RI
- Vasoactive pressor agents
  - Changes in pH
  - Decrease pO₂
  - Increase pCO₂
- Opioids
  - Decrease motility and bacterial clearance mechanisms
- Decrease in luminal nutrient delivery

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
  - pH predicts mortality
    - Loss of anaerobic bacteria

Probiotics: Exploring the Mutually Beneficial Effects of Bacteria and Their Substrates in the Human Host

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

PN changes in Human Model

Alverdy J NCP 2014

Osuka A, Shimizu K et al. Critical Care 2012
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
- Lactobacillus casei
- Lactobacillus paracasei
- Lactobacillus rhamnosus
- Lactobacillus plantarum
- Lactobacillus reuteri
- Bifidobacterium animalis
- Bifidobacterium bifidum
- Bifidobacterium breve
- Bifidobacterium longum
- Bifidobacterium adolescentis

Multiple clinical mechanisms well described

- Competitive inhibition of pathogens
- Enhance HSP in gut mucosa
- Tight junction protein synthesis
- Enhance mucosal blood flow
- Stimulate gut immunity
- Butyrate (fermentive end product) enhances neutrophil killing
- Increases return of motility
- Helps maintains diversity in colon

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

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
Mechanisms: Enhancing mucosal blood flow


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

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Thangaraju M et al J GI Surg 2008
Ganapathy V 2011

Lactobacillus salivarius (UCC118) prevents disruption of epithelial cell tight junctions

- Human epithelial cell model

Miyachi et al Am J Physiol Gastrointest Liver Physiol 2012

Lactobacillus salivarius (UCC118) prevents disruption of epithelial cell tight junctions

- Human epithelial cell model

Miyachi et al Am J Physiol Gastrointest Liver Physiol 2012

UCC118 alters tight junction protein localization.

- Tight junction proteins

Miyachi et al Am J Physiol Gastrointest Liver Physiol 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
  - Control: 1/12 cleared
    - Allowed to crossover at 4 weeks 8/11 crossed over
    - Bill 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

Rising Incidence of C. difficile

- Incidence of C. difficile by year
- Rising Incidence of C. difficile

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
- Halabi WJ JACS 2013

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

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

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
### 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, 2004</td>
<td>RCT N=20</td>
<td>TBI</td>
<td>Decrease: Nosocomial infections and LOS</td>
</tr>
<tr>
<td>Olguin 2005</td>
<td>RCT N=31 (prebio)</td>
<td>Burns</td>
<td>No benefit</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>Spindler-Vesel 2007</td>
<td>RCT N=113</td>
<td>Multiple trauma</td>
<td>Decrease: infections, VAP,</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. thermophillus*

### 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 !!!

### Fecal Microbiota Transplantation for Sepsis?

- Dysbiosis postulated at etiology on ongoing sepsis following vagotomy
  - 44 yo with 30 days of low grade sepsis tx with antibiotics, probiotics and supportive therapy
- 16S fDNA based molecular techniques
  - Pre and post treatment analysis
  - Nasoduodenal delivery
- Results:
  - Septic symptoms resolving rapidly
  - Stool microbiome changes over 7 days
    - Rapid rise in Firmicutes and decrease in Proteobacteria
  - Inflammatory markers improved

Li Q, Wang C et al Critical Care 2015

### 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 anastomatic disruption
  - Altered by MBP, antibiotic Bowel Prep, ischemia etc

Fink D, et al J Trauma 2011
Stern JR et al J Surg Res 2013

### A Closer Look at GI Function in Trauma:

**Summary**

- Visceral hypoperfusion is common in the ICU and results in 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
- Maintaining normal gut microbiome
  - Probiotics should be considered in enteral feeding plans

### 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
“..., one of the greatest opportunities to improve patient outcomes will probably come not from discovering new treatments but from more effective delivery of existing therapies.”

Pronovost PJ et al., Lancet 2004; 363:1061-7