GASTRO-INTESTINAL FAILURE IN ICU

Jo Ann Vosloo
Department Critical Care
SBAH
Definition of GIT failure

• **Food intolerance**
  - Vomiting (and/or nausea)
  - Increased volume of NG aspirate
  - Abdominal pain
  - Diarrhoea (related to EN, infection, medication)

• **Gastro-intestinal haemorrhage** (visual → hematemesis or hematochezia/malena)

• **Ileus**
  - Abdominal distension
  - Constipation

• **Liver/Gallbladder failure/Pancreatitis**

**Results in decreased provision of enteral feeding**
Incidence
Intolerance of feeding: Up to 60% ICU admissions

Regulation of gut function

GI Motility = complex function
Regulated by : CNS
  : Autonomic nervous system
  : Enteric nervous system
Modulated by : Regulatory GI peptides
  : Neurotransmitters
  : Hormones
  : Food and chyme presence

Disordered gut motility leads to:
Altered gut-mucosa contact time $\rightarrow$ bacterial overgrowth /abnormal food/drug absorption
Can be limited to stomach, small bowel or colon or can affect entire GIT
Enteric nervous system

Figure 26-1. Diagrammatic representation of the layers of the wall of the stomach, small intestine, and colon. The structure of the esophagus and the distal rectum is similar, except that they have no serosa or mesentery. (Reproduced, with permission, from Bell GH, Emslie-Smith D, Paterson CR: Textbook of Physiology and Biochemistry, 9th ed. Churchill Livingstone, 1976.)
Regulation of GI function

- Enteric (Intrinsic) nervous system:
  - 2 Enteric plexus → interconnected
    - innervate smooth muscle of bowel
    - secretory neurons regulate endocrine and exocrine secretion in mucosa
    - sensory neurons that respond to stretch, tonicity, glucose and amino-acids
    - can be seen as a 3rd division of the autonomic nervous system
    - substances secreted: NO, acetylcholine, serotonin, GABA,
      large number of polypeptides (synaptic transmitters, hormones and paracrine function)

NO is a major mediator of smooth muscle relaxation
Regulation of GI function

• **Extrinsic innervation:**
  Dual innervation from the autonomic nervous system
  ➔ Parasympathetic pathway increases activity
  ➔ Sympathetic system = relaxes bowel movement
    = cause sphincters to contract

• **Blood vessels of the bowel**
  ➔ Extrinsic = sympathetic innervation = vasoconstriction
  ➔ Intrinsic from the enteric nervous system = **VIP** and **serotonin** causes vasodilatation during digestion

• **Peristalsis:**
  = Reflex response to stretching (integrated activity of enteric nervous system)
  = Can be increased or decreased by autonomic input
  = **Relaxation** is mediated by **NO** and **VIP**
Table 26–1. Polypeptides secreted by neurons in the enteric nervous system.¹

<table>
<thead>
<tr>
<th>Polypeptide</th>
<th>Principal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor neurons</strong></td>
<td></td>
</tr>
<tr>
<td>VIP</td>
<td>Relaxation in front of peristaltic wave, relaxation of sphincters</td>
</tr>
<tr>
<td>Substance P</td>
<td>Contraction of intestinal smooth muscle</td>
</tr>
<tr>
<td>CCK</td>
<td>Inhibition of gastric emptying</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Inhibition of intestinal motility</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Relaxation of circular smooth muscle</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>Relaxation of intestinal smooth muscle, pyloric contraction</td>
</tr>
<tr>
<td>Galanin</td>
<td>Contraction of intestinal smooth muscle</td>
</tr>
<tr>
<td><strong>Secretory neurons</strong></td>
<td></td>
</tr>
<tr>
<td>GRP</td>
<td>Release of gastrin</td>
</tr>
<tr>
<td>CGRP</td>
<td>Release of somatostatin</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Inhibition of acid and intestinal secretion</td>
</tr>
<tr>
<td>VIP</td>
<td>Stimulation of intestinal secretion</td>
</tr>
<tr>
<td>Substance P</td>
<td>Inhibition of acid secretion, stimulation of pepsin secretion</td>
</tr>
<tr>
<td><strong>Sensory neurons</strong></td>
<td></td>
</tr>
<tr>
<td>CGRP</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
</tbody>
</table>

Table 26-7. Principal functions of the liver.\(^1\)

<table>
<thead>
<tr>
<th>Function</th>
<th>Chapter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation of bile</td>
<td>(26)</td>
</tr>
<tr>
<td>Carbohydrate storage and release</td>
<td>(17)</td>
</tr>
<tr>
<td>Formation of urea</td>
<td>(17)</td>
</tr>
<tr>
<td>Cholesterol metabolism</td>
<td>(17)</td>
</tr>
<tr>
<td>Manufacture of plasma proteins</td>
<td>(27)</td>
</tr>
<tr>
<td>Many functions related to metabolism of fat</td>
<td>(17)</td>
</tr>
<tr>
<td>Metabolism of some polypeptide hormones</td>
<td>(19)</td>
</tr>
<tr>
<td>Reduction and conjugation of adrenocortical and gonadal steroid hormones</td>
<td>(20, 23)</td>
</tr>
<tr>
<td>Synthesis of 25-hydroxycholecalciferol</td>
<td>(21)</td>
</tr>
<tr>
<td>Detoxification of many drugs and toxins</td>
<td>(17, 26)</td>
</tr>
</tbody>
</table>

\(^1\)Numbers in parentheses are chapters in this book in which the functions are considered.
Dysmotility

• Can involve the entire GIT or can be limited to specific areas acting as a focus of obstruction
• Cause of dysmotility in critically ill = multifactorial
  - Stomach → reduced frequency and amplitude of antral contractions
    → Abnormal fundus motor activity leading to abnormal relaxation of the rest of the gut in response to nutrient stimulus → failure to redistribute gastric content to rest of bowel
  - Small bowel → Abnormal duodenal contractility impairs food clearance from the proximal duodenum
  - Reduced colon motoric function

These abnormal functions may be due to the enhanced secretion of CCK and Peptide YY in critically ill → partially due to high lipid feeds.
Diagnosis of gut failure

**Clinical evaluation**
- Bowel sounds: ?Clinical significans → lack of evidence. Doesn’t correlate with effective peristalses
- Abdominal distension/constipation/Diarrhoea/Abdominal pain/Vomiting

**Gastric residual volume**
- Which volume indicates Gut failure → million dollar question!
  - ASPEN and SCCM: GRV < 500ml → EN feeding should not be stopped in the absence of other signs of intolerance or GIT failure. GRV 250ml -500ml should raise concern.
  - Poulard et al, 2010: Challenged assumption: GRV is an accurate assessment of EN tolerance. Monitored GRV vs episodes of vomiting. Pts who did not receive GRV monitoring, received larger volumes EN without an increase in VAP.
  - Each unit own protocol → significant improvement of nutrient delivery.

**Paracetamol absorption test**
- Drug is absorbed from small bowel. Good correlation between stomach emptying time and peak plasma concentrations. Drugs, upper GI operations, aspiration can influence results.
Relevance of GI failure in critically ill

Two schools of thought:
• GIF $\rightarrow$ increased bacterial translocation $\rightarrow$ gut failure is a motor of MOF
• GIF is a symptom of MOF

Problem: GIF is a common problem in ICU patients, yet it is not given the same consideration other organ systems receive when scoring and predicting outcome in ICU. Absence of a consensus definition of GIF is a major limiting factor.

Rientam and colleagues (2006):
=Retrospective study Berlin and Estonia (2588 patients $\rightarrow$ 252 with GIF).
=Analysed 47 variables $\rightarrow$ 23 variables were identified as highly predictive for development of GI failure. Independent predictors for development of GIF were identified: APACHE II, SOFA, Pts’ emergency profile and use of catecholamines.
IAP measurement was not performed.
=GIF to be a relevant independent clinical predictor of mortality in ICU. It significantly prolonged mechanical ventilation and ICU stay.
=GIF is a syndrome with a variable onset during ICU treatment (80% were identified after 1 week stay in ICU and 20% developed GIF later).
# Gut failure score

## Table 1

Lausanne Intestinal Failure Estimation (LIFE) based on the SOFA model including symptoms and continuous signs compared with the variables of Reintam and colleagues

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintam and colleagues [1]</td>
<td>Normal function</td>
<td>EN &lt;50% of needs of no EN at day 3</td>
<td>EN intolerance (residues) or IAH</td>
<td>EN intolerance and IAH</td>
<td>Abdominal compartment syndrome</td>
</tr>
<tr>
<td>IAH (mmHg)</td>
<td>&lt;12</td>
<td>12 to 15</td>
<td>15 to 20</td>
<td>20 to 25</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Lactate with pH &lt;7.25 (mmol/l)</td>
<td>&lt;2</td>
<td>2.0 to 3.0</td>
<td>3.0 to 4.0</td>
<td>4.0 to 5.0</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Gastric residue every 6 hours (ml)</td>
<td>&lt;100</td>
<td>200 to 300</td>
<td>&gt;300</td>
<td>&gt;400 or vomiting regurgitation</td>
<td>–</td>
</tr>
<tr>
<td>Progression of feed by day of EN</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation (stools over time)</td>
<td>One per 1 to 3 days</td>
<td>Zero in 4 days</td>
<td>Zero in 5 days, bloating</td>
<td>Abdominal distension</td>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Diarrhea(^a) (number per day)</td>
<td>–</td>
<td>–</td>
<td>4 to 6</td>
<td>6 to 10</td>
<td>Ogilvie syndrome</td>
</tr>
<tr>
<td>Bowel sounds</td>
<td>Normal</td>
<td>Silence</td>
<td>–</td>
<td>Tympanic</td>
<td></td>
</tr>
</tbody>
</table>

The different items should be considered separately as relevant for the patient's condition, the highest (that is, worst) value being the gut score. EN, enteral nutrition; IAH, intra-abdominal pressure; SOFA = Sequential Organ Failure Assessment. \(^a\)Liquid stool occurring at least four times per day.
• Rientam et al 2008
  GIT failure is associated with a sharp increase of ICU mortality
  GIF = independent risk factor for death
  Use of catecholamines to treat CVS failure = independent risk factor for GIF

• Food intolerance alone is not an independent predictor of outcome

• Cheatham et al, 2007
  IAH and ACS has a strong impact on mortality.
  Prediction of pt outcome : APP > 50mmHg better predictor of survival than arterial pH, lactate, base deficit, hourly urine output.
Contributing Factors: GIF

- Inflammation (SIRS, aseptic pancreatitis)
- Surgery (handling of bowel)
- Medication
  - Opioids
  - Anticholinergic medication (Atropin, Ditropan, Atrovent, Buscopan)
  - Vasopressors
- Electrolyte imbalances
- Acidosis
- Hyperglycaemia
- Sepsis
- Increased intracranial pressure (cranial outflow of vagal nerve/hypothalamus and medulla influences the sympathetic activity)
- Presence of disease itself/Admission diagnosis
- Comorbid conditions
- Mechanical ventilation (respiratory failure)
- Altered hemodynamics
Alterations of GI tract in critically ill

- **Delayed** gastric emptying (increased CCK)/reduction in intestinal transit time
- Absence **biliary and pancreatic** secretions / abnormal **glucose** metabolism
- Mucosal ischemia/bowel oedema/pH and electrolyte abnormality/Excessive sympathetic tone/Pro-inflammatory mediators
- Altered **carrier** and nutrient **transport** proteins
- Villus atrophy/reduction **mucosal surface area**
- Loss of barrier function (**MALT** and **GALT**)
- **Splanchnic blood flow**
  - GI tract uses 30% of total O\(_2\) consumption at rest
  - Ischemia → tips of villi at highest risk
  - Ischemia → low PO\(_2\) → vasodilatation (metabolites) → increase blood flow
    → oedema of bowel wall → dysmotility and altered absorption → bacterial overgrowth and toxin production / translocation of bacteria
- Increased **inhibitory neurotransmitter peptides** (NO/VIP/Substance P)
Feeding Maintains
GALT / MALT

GALT

MALT

antigens

gut lumen

d L

Ma

M

A

basal membrane

Bacteria

Liver

Genitourinary tract

Mesenteric lymph nodes

Peyer patches

Thoracic duct

Lymphocytes

Monocytes

B and T lymphocytes

Mucosa

Lamina propria

Stem cells

Migration from lymph nodes to thoracic duct

Critical Illness 2001
Proposed mechanism of gut dysfunction

- SIRS
- Hypotension
- Anaesthesia
- Manipulation

Up regulation of ICAM receptor and binding to endothelium (smooth muscle)

Leucocyte extravasation into smooth muscle

Increased cytokine response

Decreased contractility and altered electrical activity
Mechanisms to maintain and improve gut function in critical illness

- Maintain **visceral perfusion**
  = Early resuscitation and maintenance of APP > 50mmHg
- **Strict glycaemic control**
  = Maintain macrophage function
  = Preserve LBM (improved protein metabolism)
- Correct **acidosis** and **electrolyte** abnormalities
- **Early nutritional** support → Adherence to EN feeding protocols
  → Placement of feeding tubes
- Minimize **medication** that alter bowel function
- Daily dialysis if indicated (correct **fluid balance**)
  = Better metabolic control improves bowel motility (excess water, acidosis, electrolytes)
- Add **motility agents**: Erythromycin/Metoclopramide
• Antral motility alter and correlates with blood glucose concentration  
  (Rayner et al, 2001)

• Glucose/Insulin control influences protein absorption
  → Insulin stimulates peptide-1( responsible for 60% protein transport in gut mucosa)  
    (Adibi et al, 2003)
  → Maintains the structure and function of hepatocyte mitochondria  
    (Vanhorebeck I, 2005)
Reasons why TPN resulted in poor outcomes

• Mucosal atrophy
• Systemic immune suppression
• Lack of luminal nutrient delivery → GALT atrophy
• Overfeeding
• Hyperglycaemic control
• Imbalance of specific nutrients
• Systemic vs portal delivery of nutrients
Why early enteral feeding

**Early** means initiation of enteral feeding **within 24h** after admission to ICU

- **Safer**, better patient outcome, shorter **ICU stay**
- Prevents **villi atrophy** → food absorption (food supply to mucosal cells itself)
  Helps maintain GALT
- Maintains gut **mucosal barrier**
  Less bacterial translocation due to improved MALT function → reduction of systemic sepsis incidence and severity
- Better **glucose control**
- Delivery of food not into systemic circulation, but into **portal system** to liver.
- Protects against **LBM** loss
- Helps maintain **visceral blood flow**
- Helps maintain **hepatic cell (mitochondria)** function
  Visceral protein synthesis/glutathione production
- Delivers **calories and nitrogen**
Large animal model of mucosal changes during TPN
Proposed mechanism of Glutamine to alternate SIRS response

• Tissue protection
  = HSP production
  = Anti-apoptotic
  = Fuel source for epithelial cells → Primary fuel for rapid dividing cells (enterocyte, lymphocyte)

• Anti-inflammatory - alternate cytokine expression

• Preservation of tissue function in stress states
  Preserve ATP in sepsis and SIRS (nucleotide transport)
  Preserve mitochondrial function (liver)

• Anti-oxidant
  Enhances glutathione production
  Alternate iNOS in sepsis

(Wischmeyer 2006)
Glutamine

- >60% of free amino-acid pool in muscle
- Helps maintain acid-base balance → critical for synthesis of Arginine (NH₃ metabolism)
- Decrease insulin resistance

HSP:
- Refolds misfolded proteins (due to stress response)
- Helps to eliminate irreversibly damaged proteins
- Decrease pro-inflammatory cytokines
Consider Probiotics

- Inhibit growth of pathogenic bacteria in GIT by:
  - decreasing the luminal pH
  - secreting bactericidal proteins
  - stimulate defensin production
- Blocks epithelial attachments or invasion by pathogens
- Eliminate pathogenic toxins
- Improve epithelial and mucosal barrier function
- Alter or improve host immune response
  - Activate T-cells
  - Enhances macrophage function
  - Decrease IL-8 and 1, TNF and NFkB
  - Stimulate IgA production
Enteral nutrition

**Quality** of EN more critical than quantity
- Immune modulation
- Avoid overfeeding
  - Avoid immunosuppressive regimens (hyperglycaemia, excessive Omega 6 lipids)
- Anti-oxidants

Inappropriate enteral feeding can result in disaster
References

6. Lecture Prof Pretorius
7. Prof Martindale lecture, Oregon, USA