Use of Prokinetic Agents in Intensive Care Medicine - What is Evidence Based?

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Prokinetics and EBM

- What is the evidence?
- Quality of the evidence?
- Recommendations?

Nutritional Support in ICU

- Essential part of management of the critically ill patients
- Close association between malnutrition and adverse outcomes
- Old Clinical Wisdom: “If patient doesn’t eat, patient doesn’t s..t, if patient doesn’t s..t, patient dies!”
- EBM?

Prokinetics in ICU & EBM

- Physiology and pathophysiology
- Epidemiology of GI dysmotility in ICU
- Assessment of GI dysmotility
- Clinical aspects of GI dysmotility
- Treatment options:

  Prokinetics

  Alternative strategies

Prokinetics in ICU & EBM

- Limited evidence from high quality RCT
- Direct feeding into small bowel does not improve nutrient delivery in ICU patients
- Upper GI dysmotility: metoclopramide, erythromycin (best in combination)
- Lower GI dysmotility: neostigmine, laxatives
- Opiate induced GIT dysmotility: enteral naloxone, s.c. naltrexone

Physiology

- Complex interaction of stimulation and feedback
- Enteric nervous system – 100 million neurons
- Myenteric plexus - intrinsic system
- Autonomic - extrinsic innervations (Sympathetic & Parasympathetic): fluid and energy homeostasis, pain and discomfort mediation, immune function

Physiology

- Cajal's interstitial cells – pacemaker of the GI muscle cells
- Motor Migrating Complex (MMC) – movement of nutrients from small bowel to the colon stimulated by motilin, inhibited by dopamine
- GI Reflexes

GI Reflexes

- Entero-gastric reflex

  - distention of small bowel supressing secretion and motor activity of the stomach

- Gastro-colic reflex

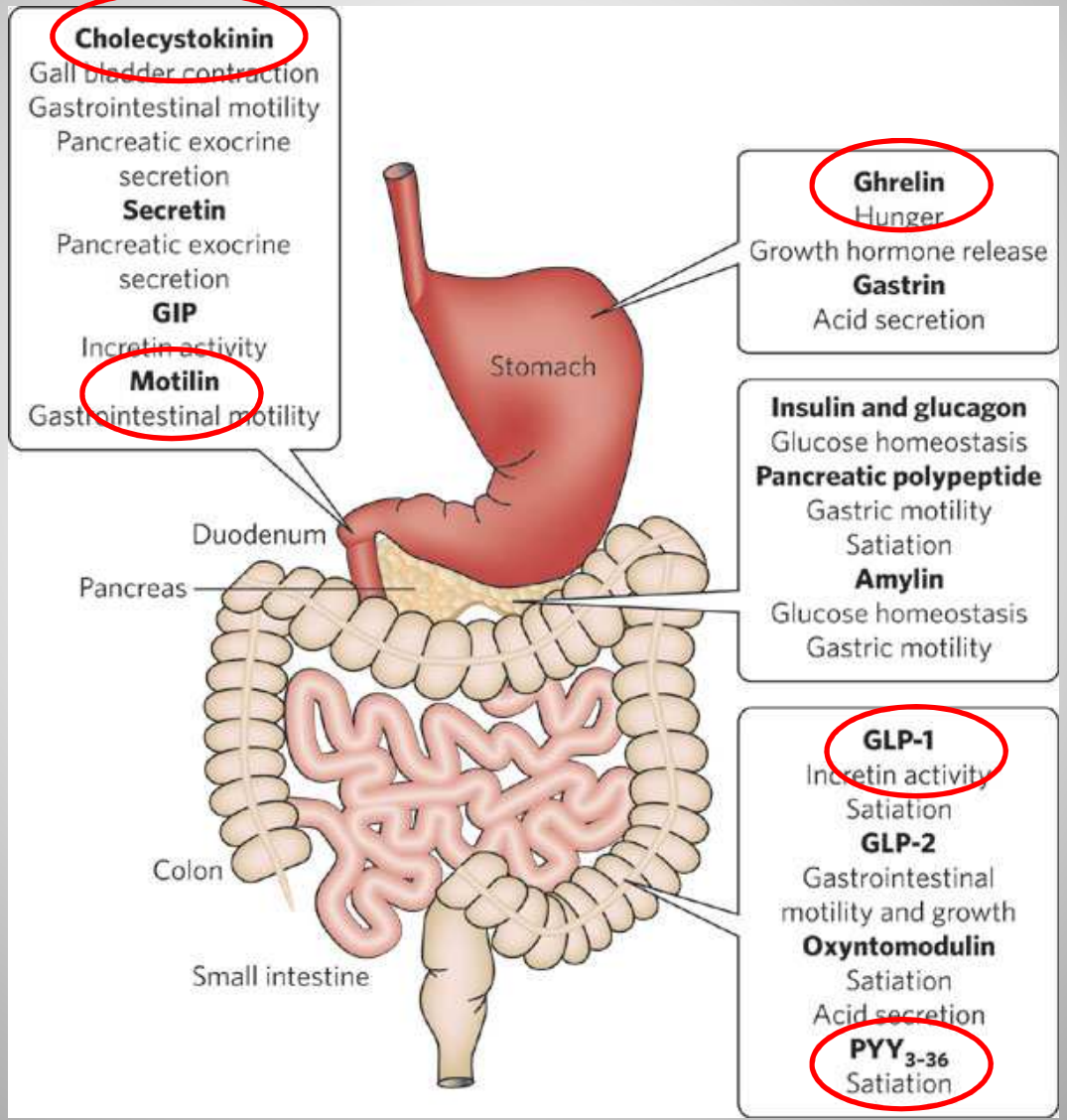
  - gastric distention/ stimulation increasing colonic activity

- Intestino-intestinal

  - distention of one bowel segment inhibiting contractions in other parts of the bowel

- Peristalsis

Physiology – Hormones



Physiology of GE

- Stimulated by 2 principal mechanisms:

  1) neural activity in response to gastric distention

  2) gastrin secretion

- Either or both lead to contraction of distal oesophageal sphincter, gastric contractions and relaxation of the pyloric sphincter
- Stomach empties within 2-6 hrs

Physiology of GE - hormones

Name	Site of Secretion	Action
ghrelin	stomach	↑ GE
motilin	duodenum / stomach	↑ GE
CKK	duodenum	↓ GE
GLP1	small bowel	↓ GE
PYY	colon	↓ GE

Pathophysiology of GI dysmotility

- During critical illness
  - ghrelin and motilin secretion decreases
  - CKK, GLP1,2 & PYY secretion increases
- High blood glucose levels reduce GE even in non-diabetics
- Excessive fluid resuscitation
- Surgical manipulation – paralyzing effect

Pathophysiology – influence of medication

- Side effects of commonly used drugs include delayed gastric emptying (GE) and reduced nutrient absorption:
- Opioids
- Catecholamines
- PPI
- Ca channel blockers
- Tricyclic antidepressants

Epidemiology of GI Dysmotility

- Common occurrence in ICU patients
- 50% of ventilated patients - delayed gastric emptying (GE)
- 60% - gastro-oesophageal reflux
- 80% - neuro-compromised (TBI) patients have delayed GE and colonic dysfunction
- High risk – trauma, burns and septic patients (42%)

- Chapman – Gastric emptying of liquid nutrient meal in the critically ill; GUT 2011; 60: 1336 - 1343

Assessment of GI dysmotility

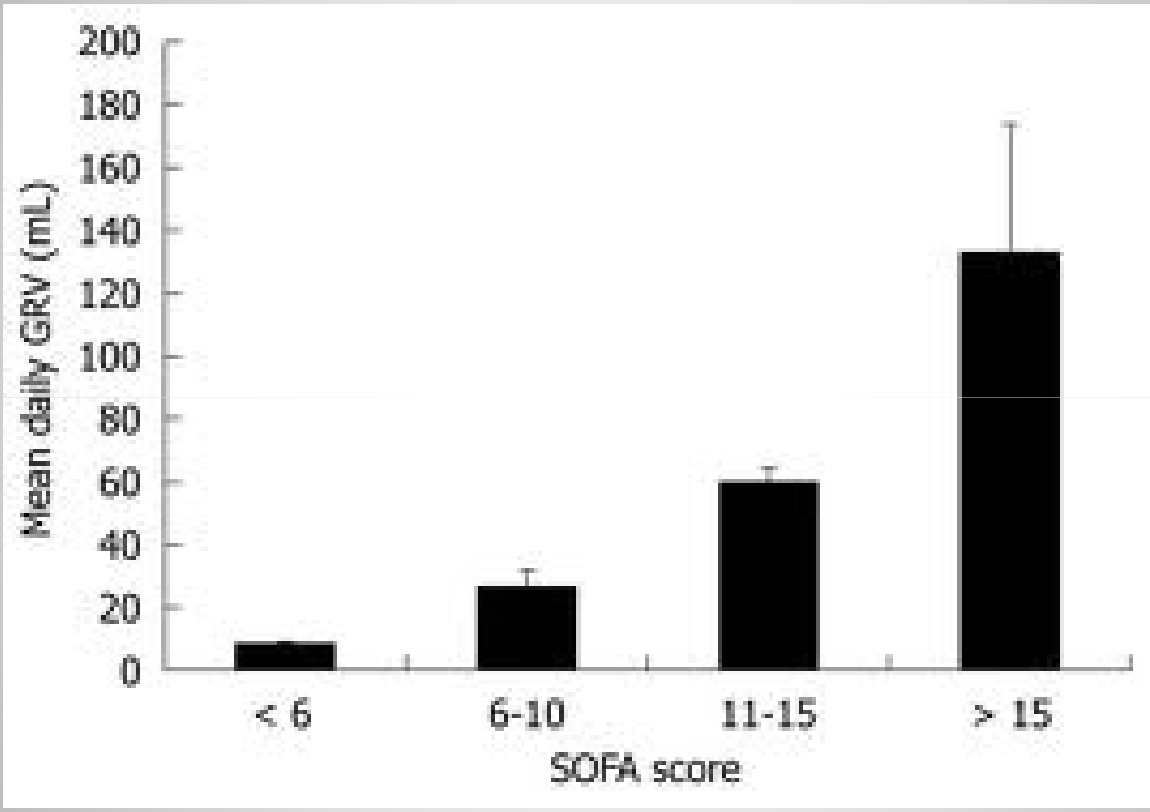
- Clinical evaluation & imaging
- GE - scintigraphy (direct, most accurate)
  - isotope breath test (C isotope labelled nutrition)
  - plasma paracetamol absorption
  - GRV
- Bowel function - endoscopic capsules
  - passage of stool

Assessment of GI dysmotility

- Gastric Residual Volume (GRV) – surrogate parameter
- Different cut-offs (150 vs 300 vs 500 ml)
- Optimal frequency? (2-3-4-6 hrly)
- Defecation/Constipation - reliable parameter of propulsive function of sigmoid & rectum (optimal volume?)

  (No relation to small intestinal function)

Severity of illness and GRV



- Hsu et al. Impact of disease severity on gastric residual volume in critical patients. World J Gastroenterol 2011: 17:2007-12

Clinical presentations of GI dysmotility

Anatomical site	Pathophysiology	Clinical presentation
Oesophagus	Reduced tone of the distal sphincter Reduced propulsive contractions	Regurgitation/Aspiration Reflux Oesophagitis
Stomach	Delayed fundal relaxation Antral hypomotility Increased pyloric activity	Vomiting Gastroparesis Increased GRV Delayed GE
Small bowel	Increased retrograde activity	Paralysis (ileus)
Colon	MMC dysfunction	Acute colonic pseudo-obstruction (Ogilvie's Syndrome)

Non-GI consequences of GI dysmotility

- Sepsis (? bacterial translocation)
- Abdominal distention leading to:
- Reduced venous return and decreased cardiac output
- Acute kidney injury (increased IAP)
- Reduced lung compliance – impaired ventilation and oxygenation

Prokinetics

- Heterogeneous group of drugs promoting gastrointestinal motility
- EBM supported prokinetics:
- Metoclopramide
- Erythromycin
- Neostigmine
- Opiate antagonists
- Laxatives

Metoclopramide

- Histamine receptor antagonist
- Sensitizes GIT to acetylcholine and increases distal oesophageal tone
- Not a strong scientific evidence
- Reduces GRV compared to placebo (Jooste: ICM 1999, Calcroft: ICM 1999)
- Improves tolerance to enteral feeding (Booth: CCM 2002)
- Does not reduce mortality or incidence of pneumonia (Yavagal: CCM 2000)

Metoclopramide

- No effect in treatment of acute colonic pseudo-obstruction (Seta: Pharmacotherapy 2001)
- Inferior to erythromycin in direct comparison in the critically ill (Nguyen, Chapman: CCM 2007)
- Best effect achieved when combined with erythromycin – superior to either agent alone with reduced tachyphylaxis to erythromycin (Nguyen, Chapman: CCM 2007)

Erythromycin

- Macrolide antibiotic and motilin receptor agonist
- Stimulates neurons in gastric antrum and proximal small bowel
- Accelerates gastric emptying (Dive: CCM 1995, Berne: J Trauma 2002)
- Tachyphylaxis occurs after 3-4 days of treatment (Reignier: CCM 2002)

Erythromycin

- Tachyphylaxis – inverse relationship between plasma erythromycin levels (dose) and duration of prokinetic effect
  (Nguyen: CCM 2011)
- Optimal dose? – the lowest with proven prokinetic effect
- 70mg iv BD is as effective as 200mg iv BD
  (Ritz, Chapman: ICM 2005)
- Low dose prolongs the effect up to 7 days
  (Nguyen: CCM 2011)

Side effects - gastric prokinetics

- Metoclopramide: tachyphylaxis, somnolence and lethargy, parkinsonism
- Erythromycin: tachyphylaxis, potential bacterial resistance induction as doses used for the prokinetic effect are much bellow MIC for susceptible bacteria

Neostigmine

- Reversible acetylcholine esterase inhibitor increasing concentration of acetylcholine on NM junctions of the myenteric plexus
- Parasympathetic and enteric stimulation (colon predominantly)
- Bolus dose 1-2 mg reverses colonic pseudo-obstruction in colorectal surgical (Ponec: NEJM 1999, Kreis: Surgery 2001), orthopedic (Althausen: J Spinal Disord 2001) and toxicology patients (Isbister: Ann Emerg Med 2001)

Neostigmine

- 24 hr infusion (0.4 -0.8 mg/hr) resolves colonic pseudo-obstruction in ventilated ICU patients (Van Der Spoel: ICM 2001)
- 48 hr infusion 0.4mg/hr (vs 0.2 mg/hr vs placebo) promotes safe stool passage in the critically ill (Thomas: ICM 2007)
- Epidural neostigmine (Caliskan: Anesth Analg 2008)
- Side effects: bradycardia, abdominal cramps, increased bronchial secretions

Opioid antagonists

- Opioid induced bowel dysfunction (μ receptor activation)
- i.v administration: loss of analgesia and triggers acute withdrawal
- Naloxone NG/PO: 3-12mg/day improves enteral feeding tolerance without attenuating analgesia (Meissner: CCM 2003)
- Methyl-naltrexone – does not cross blood brain barrier; 0.15mg/kg sc improved bowel function – small pilot study only

Laxatives

- Osmotic effect (lactulose, PEG)
- Stool softeners (senna)
- Can cause electrolyte disturbances and substantial fluid shifts
- Shorter time to defecation and ICU LOS (van der Spoel: CCM 2007)
- Can be used as prevention to lower GI dysmotility in the critically ill (Masri: Crit Care 2010)

Experimental treatment

- Non-antibiotic motilin receptor agonists (mitemcinal) – encouraging preliminary results but not yet supported by EBM
- Ghrelin – possibly increases mortality in ICU patients (Takala: NEJM 1999)
- 5-HT_4 agonists, ghrelin agonists, CKK antagonists (dexloxiglumide) – not tested in ICU settings yet
- Local anaesthetics – i.v. (Heroeder: Ann Surg 2007)

Non-pharmacological strategies

- Fluid and electrolyte optimization
- Abdominal massage (Phab: Curr Opin Clin Nutr Metab Care 2012)
- Acupuncture (Phab: Anesth Analg 2012)
- Post-pyloric feeding – does not improve nutrient absorption or clinical outcomes - (Davies: CCM 2012; Ho: ICM 2006; White: Crit Care 2009)

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Thank You