DIARRHOEA

Nigel Sykes
Diarrhoea

- The size of the problem
- What is diarrhoea?
- Assessment
- Mechanisms
- Causes
- Management
  - Rehydration
  - Specific drugs
  - High output stomas
  - Existing antidiarrhoeal therapies
  - Newer antidiarrhoeal therapies
The Size of the Problem

- 7% to 10% of hospice cancer patients complain of diarrhoea. Three causes account for half the cases (Twycross, 1986):
  - Too much laxative
  - Faecal impaction with overflow
  - Partial intestinal obstruction
  - (Intestinal infection accounted for about 4% of diarrhoeas)

- Up to 80% of cancer patients undergoing chemotherapy report diarrhoea

- Around 50% of patients receiving pelvic or abdominal radiotherapy have diarrhoea (Benson et al., 2004)

- 28% to 63% of people living with HIV experience diarrhoea

Now mainly a secondary effect of anti-retroviral therapy rather due to infection (Clay and Crutchley, 2014)
What is diarrhoea?

- The passage of frequent loose stools with urgency
- How frequent?
  - More than 3 per 24 hours
- How loose?
  - Bristol stool scale forms 5 to 7

But for patients a single loose stool, frequent stools (even hard ones) or an episode of faecal incontinence may count as diarrhoea, so a complaint of diarrhoea needs to be clarified.
Assessment of Diarrhoea

- **How often?**
  - ‘Diarrhoea’ only once or twice a day may be faecal incontinence

- **Pattern?**
  - Sudden onset after constipation suggests impaction

- **Type of stool?**
  - Profuse, watery stools suggest colonic diarrhoea
  - Pale, fatty stools indicate fat malabsorption from pancreatic or small bowel cause

- **Involvement of medication?**
  - Check laxatives, antacids, elixirs, recent chemotherapy

- **Investigations:**
  - Abdominal and rectal examinations
  - Stool culture if systemically unwell
  - Check electrolytes if persistent
  - Anion gap (difference between the stool osmolality and double the sum of the cation concentrations) distinguishes between secretory (<50mmol/L) and osmotic (>50mmol/L) types of diarrhoea
# National Cancer Institute Common Toxicity Criteria for Diarrhoea (version 4.02)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of $&lt;$4 stools per day over baseline</td>
<td>Increase of 4-6 stools per day over baseline</td>
<td>Increase of $&gt;$7 stools per day over baseline. Incontinence. Hospitalisation indicated</td>
<td>Life-threatening consequences requiring urgent intervention,</td>
<td>Death</td>
</tr>
</tbody>
</table>

(NCI, 2009)
### Victoria Bowel Performance Scale (revised) (rBPS)

<table>
<thead>
<tr>
<th>Constipation</th>
<th>GOAL</th>
<th>BPS Score</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impacted or Obstructed ± small leakage</td>
<td>Characteristic</td>
<td>-4 -3 -2 -1 +1 +2 +3 +4</td>
<td>Unformed or paste-like</td>
</tr>
<tr>
<td>Formed Hard with pellets</td>
<td>Formed Solid</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Formed Hard</td>
<td>Formed Semi-solid</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Formed Solid</td>
<td>Formed Soft</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>No Stool produced after Goal plus 3 days</td>
<td>Pattern</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Goal plus 3 or more days delay</td>
<td>Pt's Goal for frequency</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Goal plus 1-2 days delay</td>
<td>Pt's Goal frequency occurs</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Unable to defecate despite maximal effort or straining</td>
<td>Minimal or no effort required to defecate</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Moderate effort or straining required to defecate</td>
<td>Minimal or no effort required to control urgency</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
<tr>
<td>Minimal or no effort to defecate</td>
<td>Minimal or no effort required to control urgency</td>
<td></td>
<td>Unformed Liquid ± mucus</td>
</tr>
</tbody>
</table>

Downing, Hawley, Barwich, Black. BPS revised scale. © 2009, Victoria Hospice Society

Hawley, Barwich and Kirk,
The origins of diarrhoea

- The gut handles 8 to 10 litres of fluid per day
  - 99% is reabsorbed (95% in the small intestine and 4% in the colon)
    - Colon can absorb up to 4 litres/day if infused slowly
    - Initial ileostomy volumes are 1.5 to 2 litres/day until adaptation
  - The difference between constipation and diarrhoea is about 100ml per day

- Diarrhoea happens if there is either excessive secretion or impaired absorption of fluid across the gut wall
  - Stimulation or inhibition of transport mechanisms
  - Damage to intestinal epithelium
  - Excess osmotic load in the gut lumen
  - Acceleration of transit, reducing the time taken for absorption
Fluid movement across the intestinal wall:

- Water passively accompanies actively transported:
  - $\text{Na}^+$, $\text{K}^+$, $\text{Cl}^-$ and $\text{HCO}_3^-$ ions
  - Solutes, mainly glucose and short chain fatty acids

- Requires coordinated activity of epithelial membrane transporters

- Is modulated by:
  - the autonomic nervous system
    - Parasympathetic is pro-secretory
    - Sympathetic is pro-absorptive
  - via the enteric nervous system
    - Acetylcholine ($M_3$ muscarinic) and VIP are pro-secretory
    - Noradrenaline and somatostatin are pro-absorptive
  - intracellular messengers
  - cell surface receptors, e.g. CaSR (Calcium-sensing receptor)
Mechanisms of intestinal fluid absorption and secretion

Thiagarajah, Donowitz and Verkman, 2015
**Mechanisms of intestinal fluid absorption**

*Absorption* is driven by active $\text{Na}^+$ transport with accompanying $\text{Cl}^-$ or $\text{HCO}_3^-$

- Powered by $\text{Na}^+/ \text{K}^+$ ATPase
- A principal sodium transporter is NHE3 (Na/Hydrogen transporter 3), found in ileum, jejunum and colon
- A principal chloride/bicarbonate transporter is DRA, found mostly in duodenum and colon
- NHE3 and DRA are both inhibited by intracellular messengers, notably calcium and cAMP
Mechanisms of intestinal fluid secretion

Secretion is driven by active Cl⁻ transport

- Key transporter into the cell from the circulation is NKCC (Na/K/Cl symporter)
- Key transporters out of the cell into the lumen are CFTR (cystic fibrosis transmembrane conductance regulator) and CaCCs (Calcium-activated Chloride Channels)
  - Both CFTR and CaCC are, in effect, activated by cAMP and calcium
Mechanisms of intestinal fluid absorption and secretion

Thiagarajah, Donowitz and Verkman, 2015
Causes of diarrhoea in palliative medicine - 1

- **Motility disorders**
  - Malignant obstruction
  - Faecal impaction
  - Narcotic bowel syndrome
  - Diabetes mellitus
  - Hyperthyroidism
  - Irritable bowel syndrome

- **Disturbance of intrinsic gut function**
  - VIPoma
  - Serotonin (Carcinoid) tumours
  - Inflammatory bowel disease
  - Gastrointestinal infection
    - viral
    - bacterial

- **Malabsorption**
  - Pancreatic carcinoma
  - Ileal resection
  - Colectomy
  - Internal fistulae

- **Diet**
  - Bran
  - Fruit
  - Spices
  - Alcohol
Drug causes of diarrhoea in palliative medicine

- Laxatives
- Magnesium antacids
- Antibiotics
  - Impaired Short Chain Fatty Acid production by antibiotics through alteration of gut flora, leading to osmotic diarrhoea from the unabsorbed carbohydrates
  - All antibacterials are associated with *C. difficile* infection, but penicillins, cephalosporins, clindamycin, and the fluoroquinolones (-floxacins) are associated with the highest risk
    - Occurrence has more than doubled since 2000
    - *C. difficile* represents no more than 20 % of all antibiotic-associated diarrhoea
- Chemotherapy agents
- Anti-retroviral agents
- Iron preparations
  - Idiosyncratic
- Disaccharide-containing elixirs
  - Easy to miss the presence of sorbitol in a liquid medication
  - Acquired lactose intolerance has the same effect
  - Check the anion gap if in doubt
- Radiation
Mechanisms of diarrhoea

- Stimulation of CFTR and CaCC, with inhibition of NHE3 and DRA, as a result of increased cAMP and calcium levels
  - e.g. Bile acid excess (ileal resection) via specific colonic bile acid receptor
- Damage to epithelium leading to increased porosity
- Excess osmotic load in the gut lumen
  - Failure to metabolise carbohydrates, e.g. lactose intolerance
- Acceleration of transit
  - Via enteric nervous system as a result of specific receptor interaction, e.g. bile acids
  - Mimicry of intrinsic gut hormones
  - Damage to parasympathetic or enteric nervous systems, e.g. diabetes mellitus
Chemotherapy diarrhoea - *can be life-threatening*

- 5FU causes diarrhoea on its own but worse if combined with irinotecan (up to 80%) or leucovorin (up to 50%)
  - 5FU appears to cause direct gut epithelial damage
  - More diarrhoea in women and Caucasians
    - Genetic differences in drug clearance
  - Irinotecan diarrhoea may be delayed (over 24 hours post chemotherapy)
    - Not dose-related, but linked with poor performance status and impaired renal function
- Up to 60% have diarrhoea with tyrosine kinase inhibitors, e.g. erlotinib, gefitinib
  - But rarely serious
Irinotecan

- Pro-drug converted in the liver to an active metabolite (SN-38)
- High SN-38 levels cause severe diarrhoea in 20 to 25% of patients and myelosuppression in 15 to 20%
- SN-38 is removed via glucuronidation by the UGT1A1 enzyme, whose coding gene is highly polymorphic
  - UGT1A1*28 polymorphism reduces UGT1A1 by 30-80%
- In the gut SN-38 Glucuronide is *changed back* into SN-38 bacterial glucuronidase enzymes (Ma and Liu, 2011)
- A structurally-modified *E. coli* glucuronidase can selectively inhibit bacterial glucuronidase without impairing cell viability
  - Mice given irinotecan with the inhibitor showed no gut mucosal damage and 75% less diarrhoea than mice given irinotecan alone (Wallace et al., 2010)
Diarrhoea in solid organ transplantation

- Mostly due to infection
  - *C. difficile*, *Cryptosporidium*, Cytomegalovirus
- But 25% to 50% cases are caused by immuno-suppressant drugs (Angarone and Ison, 2015)
- Mycofenolic acid has the highest incidence (36%)
  - Directly damages enterocytes
- Tacrolimus and cyclosporin cause diarrhoea by stimulating motility through a macrolide-like effect (Helderman and Goral, 2002)
- Graft-versus host disease diarrhoea is rare but has a mortality rate of up to 75%
  - 6% to 9% of small bowel transplants
  - <1% of other transplants
  - Epithelial damage thought to be caused by induction of antibodies in the graft by host alloantigens
HIV disease and its treatment

- HIV causes intestinal mucosal atrophy, leading to malabsorption
- Protease inhibitors (nelfinavir and indinavir) also increase gut mucosal cell apoptosis and necrosis
- Protease inhibitors increase net sodium, chloride and water secretion (Braga Neto et al., 2010)
  - Nelfinavir is known to stimulate basolateral calcium transport which in turn stimulates apical chloride and water secretion via CFTR and CaCC
  - The mechanism by which other protease inhibitors affect secretion remains to be clarified
Mechanisms by cause - 4

- **Radiation**
  - Na/K ATPase inhibition
  - Lactose intolerance (Harb, Fadel and Sharara, 2014)
  - Intestinal dysmotility leading to bacterial overgrowth
    - Patients who do not develop post-radiotherapy diarrhoea have a different gut bacterial profile *at baseline* from those who do (Manichanh et al., 2008)

- **Ileal resection**
  - Loss of water absorptive capacity (but some colonic adaptation occurs)
  - Reduced bile acid resorption leads to excessive colonic bile acid levels, activating a specific colon receptor GPBAR1 (aka TGR5) and thereby:
    - Stimulating 5HT release in enteric nervous system, which hastens transit
    - Increasing cAMP levels and hence stimulating chloride and water...
Treatment
Hydration is key and is best achieved by mouth

**Oral Rehydration Solution:**

- Should contain water, sodium and a source of glucose – why?
  - Glucose stimulates Na absorption via a cAMP-independent transport process
  - Even an increase in cAMP caused by bacterial toxins does not inhibit glucose-stimulated Na and fluid absorption
  - Glucose reverses cAMP’s inhibition of NHE3
- Short Chain Fatty Acids are synthesized by colonic bacteria from non-absorbed carbohydrates (as in dry biscuits)
  - Short Chain Fatty Acids are rapidly absorbed in the colon and stimulate fluid and Na absorption
- Maize starch (or a dry biscuit?) significantly improves the effectiveness of oral rehydration solution (Binder et al., 2014)
Mechanisms of intestinal fluid absorption and secretion

Thiagarajah, Donowitz and Verkman, 2015
Specific treatments for diarrhoea in palliative medicine

**Fat malabsorption:**
- Pancreatin
  - may be more effective if H$_2$ antagonist or PPI given before meals

**Cholegenic diarrhoea (post-ileal resection or cholecystectomy):**
- Bile acid-binding agent: colestyramine 4–12 g tds

**Gastrinoma (Zollinger–Ellison syndrome):**
- H$_2$ -antagonist or PPI

**Carcinoid syndrome:**
- Serotonin antagonist: Cyproheptadine, initially 12mg daily

**Pseudomembranous colitis (C. difficile):**
- Oral metronidazole 200mg tds for 10 to 14 days for first episode if mild to moderate severity
  - Subsequent or severe episodes: oral vancomycin 125 mg qds for 10 to 14 days (£132) or oral fidoxamicin 200 mg bd for 10 days (£1,350)
  - Unresponsive or life-threatening infection: oral vancomycin + iv metronidazole
Non-specific treatments for diarrhoea
Opioid Antimotility Drugs

- Mu receptor activity slows gut transit
- Weak delta activity may contribute some reduction in fluid secretion
- Relative specificity for antidiarrhoeal as opposed to analgesic effects:
  - Codeine 5.24
  - (Morphine 6.45)
  - Diphenoxylate, 23.7
  - Loperamide >552
- Diphenoxylate usually combined with atropine (Co-phenotrope), which discourages abuse and adds a reinforcing anticholinergic effect
- Loperamide does not cross the blood-brain barrier in adults
  - Because it is expelled by the P-glycoprotein efflux pump
  - This appears to continue even when given in HIV disease alongside protease inhibitors, which inhibit the pump (Mukwaya et al., 2005)
Non-specific treatments for diarrhoea
Somatostatin analogues

- Somatostatin is a gut hormone acting to inhibit secretion and peristalsis
- Available preparations: octreotide, lanreotide, pasireotide
- Octreotide has shown effectiveness in a variety of diarrhoea aetiologies:
  - Carcinoid syndrome, VIPoma, gastrinoma
  - Ileostomy, enterocolic fistula
  - HIV
- Administration is parenteral
  - Octreotide combines with opioids, midazolam, haloperidol for subcutaneous infusion (individual injections can be painful)
- Long-acting preparations: lanreotide, Sandostatin Lar
High output stomas

- Definition: stoma output >1500 ml/day
- Liable to occur with jejunostomies or ileostomies
- Small bowel effluent resembles cellular physiology
  - High sodium, low potassium, high magnesium
    - cf. faecal effluent, which has low sodium and high potassium
  - Small bowel stomas cause hyponatraemia, hypomagnesaemia, hyperkalaemia (looks like Addison’s) and fat malabsorption
    - Diarrhoea causes hypokalaemia
- Oral saline/glucose solution (Na⁺ 90mmol/L) may be sufficient
  - Specialist dietary advice essential
- If output remains > 1200 ml despite omeprazole, loperamide and octreotide may need long term i.v. fluids with magnesium supplementation
- If output remains > 1500 ml likely to need TPN as well as i.v. fluids

(BSG Guidelines - Nightingale and Woodward, 2006)
Non-specific treatments for diarrhoea

Assorted...

- **Adsorbent drugs**
  - Crystalline minerals that take up dissolved or suspended substances onto their surfaces
  - Kaolin is the only adsorbent marketed in the UK – no evidence for effectiveness

- **Absorbent drugs**
  - Take up water to form a gelatinous mass that thickens (or loosens) stools
  - Ispaghula, methylcellulose
  - Useful in colostomy management but can exacerbate electrolyte loss from ileostomies

- **Probiotics**
  - Bacterial cultures (usually *Lactobacillus* spp.) intended to normalise disordered gut flora
  - Evidence for antidiarrhoeal efficacy mixed, but may help adult infective diarrhoea and acquired lactose intolerance
Rececadotril is an enkephalinase inhibitor
- Potentiates the delta-receptor activity of endogenous enkephalins in the gut to reduce secretion
- Does not cross the blood-brain barrier
- No effect on gut motility

Enkephalin effect is to reduce cAMP levels through adenylyl cyclase inhibition and so inhibit secretion and stimulate absorption

Effective in non-specific acute diarrhoea in adults, (Hamza et al. 1999) but not in proven cholera (Alam et al, 2003)

Prescribable in UK but not endorsed by either NICE or SMC
- Dose regime: 100mg stat, then 100mg tds for up to 7 days
- This course costs £8.42 (loperamide would be £1.74)
Newer treatments for diarrhoea
Chloride channel inhibitor - 1

**Crofelemer**
- Obtained from the latex of the South American tree *Croton lecheri*
- Inhibits both the CFTR and the CaCC channels
- Minimally absorbed
- Effective in HIV diarrhoea and licensed for this indication in USA *(Fulyzaq™)* (Clay and Crutchley, 2014)
- Pack costs $600

(loperamide $70)
Newer treatments for diarrhoea
Chloride channel inhibitor - 2

- **Krisanaklan**
  - Herbal extract used in Thailand for treatment of diarrhoea
  - Inhibits cAMP and calcium-induced chloride conductance
  - Agarwood and clove extracts are primarily responsible for chloride channel inhibition
    - Low cost
    - Broad antidiarrheal efficacy
    - Defined cellular mechanisms
    - Potentially useful for treating cholera and other enterotoxin-mediated secretory diarrhoeas (Tradtrantip, Ko and Verkman, 2014)
Newer treatments for diarrhoea

- **Anti-secretory factor**
  - Produced naturally in the pituitary but has been cloned
  - Active against diarrhoea regardless of cause
  - Effect is abolished by vagotomy
  - Salovumil is an egg-based nutritional product fortified with anti-secretory factor
    - Halved the recovery time of children with mixed aetiology diarrhoea (Zaman et al., 2014)

- **Obeticholic acid (Ocaliva™)**
  - Semi-synthetic bile acid analogue
  - Triggers feedback loop to reduce hepatic bile acid synthesis
  - Primarily intended for diarrhoea in primary biliary cirrhosis, but may have a wider role e.g. ileal resection? some cases of irritable bowel disease?
  - FDA gave accelerated approval in March 2016

- **Bovine Serum-Derived Immunoglobulin**
  - Reduces inflammation of the intestine, restoring mucosal immunity, and normalising gastrointestinal function
  - Licensed as a medical food in USA for diarrhoea-predominant irritable bowel syndrome (*EnteraGam™*)
  - Reported to reduce diarrhoea in HIV enteropathy (Asmuth et al. 2013)
Potential treatment for diarrhoea

Another Chloride channel inhibitor

- Red wine (Cabernet Sauvignon) can inhibit CaCC chloride channels
- A small molecule wine extract both inhibited CaCC chloride channels and prevented rotavirus diarrhoea in mice
- It did not affect the virus or CFTR channel activity

(Ko et al., 2014)
Potential treatment for diarrhoea
Other ways of blocking secretion

- **Potassium channel inhibition**
  - Clotrimazole blocks both cAMP and calcium-sensitive K\(^+\) channels in vitro, reducing cholera toxin-induced secretion in mice

- **Lysophosphatidic acid**
  - Naturally occurring phospholipid present in many foods (especially cabbage and radish)
  - Acts via an intestinal receptor to modulate CFTR and NHE3 activity
  - Prevents enterotoxin-mediated fluid secretion in rodents
    (Xu et al., 2014)
Conclusion

- A complaint of diarrhoea needs careful assessment
- Identify causes that have specific treatments, including bacterial infections (particularly \textit{C. difficile})
- Most cases of diarrhoea in palliative care are mild and are either self-limiting or will respond to adjustments of treatment
- The same is not true in oncology and HIV medicine
- Hydration is key and best maintained orally if possible
- Better understanding of intestinal ion channels and transporters is providing targets for new anti-diarrhoeal therapies