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Diarrhoea and malabsorption

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Learning Objectives

By the end of this interactive session students should be able to
• describe the physiological principles underlying healthy gastrointestinal function including fluid flux, normal flora, and the absorption of major nutrients, vitamins and minerals
• define the terms diarrhoea, steatorrhoea and malabsorption
• understand the common causes diarrhoea and malabsorption in our community
• describe the different pathophysiological mechanisms of diarrhoea and malabsorption
• describe the differences and similarities in the medical history, physical examination and investigations of the common or more severe causes of diarrhoea and malabsorption
• outline the appropriate clinical investigation and management of patients with diarrhoea or malabsorption.
Let’s revise how the healthy gut functions

• Roughly how much fluid enters the gastrointestinal tract each day, and how much exits the body?

• Where is most fluid from the gastrointestinal tract absorbed?

• What are the mechanisms of protein, carbohydrate and fat digestion?

• Where is iron absorbed. What about vitamin B12?

• What is the distribution of intestinal bacteria?
Normal gastrointestinal function

• 9 litres of fluid enter the GI tract
• 7 litres absorbed in small bowel, 1800 ml in colon
• Absorption of water dependent on absorption of solutes, especially Na
• Wide margin of reserve for water absorption in the colon (up to 4.5L)
• CHO – Salivary, pancreatic amylases, brush border enzymes
• Protein – HCL, gastric pepsin, pancreatic proteases (peptidases)
• Fat – Bile, pancreatic lipase
• Nutrients absorbed via passive & active transport mechanisms
What is diarrhoea?

• Diarrhoea is abnormal frequency and liquidity of stool which can cause excess fluid & electrolyte loss

• It is important to clarify what your patient means when they report they have “diarrhoea”
  → are they referring to frequency &/or consistency?

• Stool > 200 g/day and number of movements > 3/day

• Considered chronic if persists > 4 weeks
What are the mechanisms that cause diarrhoea?

- Variety of mechanisms: osmotic, secretory, inflammatory & altered intestinal motility (can occur in combination).

- Appearance can be helpful in distinguishing underlying cause: watery, bloody or fatty (steatorrhoea).

- Volume can indicate location and pathological mechanism e.g. large volume (> 750 mL/d) imply small bowel disease and secretory diarrhoea; small volume stools are typical for colonic diseases and IBS.
What tests on faeces could help establish the mechanism or diagnosis for diarrhoea?

- **Microscopy and culture**
  - Gram stain for bacteria, examination for ova, cysts, parasites & culture for pathogens
  - White blood cells (suggestive of colitis) and/or red blood cells
- **Faecal electrolytes and osmolarity.**
- **Faecal fat** (presence of fatty acids or neutral fat) on a single sample.
- **Faecal elastase** (marker of exocrine pancreatic sufficiency)
- **Clostridium difficile toxin**
- **Faecal laxative screen** (anthroquinones, bisacodyl, phenolphthalein)
- **Faecal alpha1-antitrypsin** (marker of protein losing enteropathy)
Let’s revise the key mechanisms

**Osmotic diarrhoea**

<table>
<thead>
<tr>
<th>Caused by:</th>
<th>Presence of excess unabsorbed substrates in gut lumen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common causes:</td>
<td>Fermentable carbohydrate malabsorption (FODMAPs)</td>
</tr>
<tr>
<td>Stool volume:</td>
<td>Stool volume typically &lt; 1 litre</td>
</tr>
<tr>
<td>Stool osmotic gap:</td>
<td>Increased (&gt; 100)</td>
</tr>
<tr>
<td>Effect of fasting:</td>
<td>Stops with fasting</td>
</tr>
<tr>
<td>Stool leukocytes (WBC):</td>
<td>No stool leukocytes</td>
</tr>
<tr>
<td>H2/methane breath test:</td>
<td>Increased breath hydrogen with malabsorption</td>
</tr>
</tbody>
</table>
# Secretory diarrhoea

**Caused by:** Due to active anion secretion from enterocytes

**Common causes:** Bacterial toxins (cholera, toxigenic *E. coli*), hormone secreting tumours (e.g. carcinoid, gastrinomas), laxative abuse, hyperthyroidism

<table>
<thead>
<tr>
<th><strong>Stool volume:</strong></th>
<th>Stool volume &gt; 1 litre/d, watery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stool osmotic gap:</strong></td>
<td>Normal osmolality (osmolar gap &lt; 100)</td>
</tr>
<tr>
<td><strong>Effect of fasting:</strong></td>
<td>Diarrhoea <em>persists</em> during fasting</td>
</tr>
<tr>
<td><strong>Stool leukocytes (WBC):</strong></td>
<td>No stool leukocytes</td>
</tr>
</tbody>
</table>
## Inflammatory diarrhoea

### Caused by:
- Altered membrane permeability
  - Exudation of protein, blood, mucus

### Common causes:
- Invasive bacteria (*Shigella, Salmonella, Campylobacter, Clostridium difficile*), *Entamoeba histolytica*, cytomegalovirus colitis, inflammatory bowel disease (IBD)

### Stool volume:
- Volume of faeces usually small

### Stool leukocytes (WBC) and red blood cells (RBC):
- Increased red blood cells and leukocytes.
  - Stools may contain frank blood and be associated with urgency, tenesmus and constitutional upset e.g. fever
Deranged intestinal motility

**Rapid transit**

**Mechanism:** Inadequate time for absorption of fluid (& nutrients)

**Causes:** Irritable bowel syndrome (IBS), thyrotoxicosis, diabetic neuropathy

**Slow transit (may be associated with malabsorption)**

**Mechanism:** Bacterial overgrowth → nutrient consumption → bile salt inactivation (unable to solubilise)

**Causes:** Intestinal stasis due to anatomical defects (strictures, blind loops, surgical procedures)
Malabsorption

• More appropriately thought of as “malassimilation”
  1. Intraluminal disorders (maldigestion)
  2. Intramural disorders & transport (malabsorption)

• What symptoms & signs might be present?

• What are some examples of:
  – intraluminal disorders that cause maldigestion?
  – intraluminal disorders that cause malabsorption?
Luminal phase (maldigestion)

Mechanical - Mixing disorders

Post-gastrectomy

Reduced nutrient availability

Co-factor deficiency e.g. pernicious anaemia
Bacterial overgrowth (nutrient consumption)

Defective nutrient hydrolysis (digestion)

Pancreatic insufficiency e.g. chronic pancreatitis

Reduced fat solubilisation (reduced bile salt concentration)

Cholestasis, bacterial overgrowth
Mucosal phase (malabsorption) and defective transport

Inadequate absorptive surface
  Intestinal resection or bypass due to disease

Diffuse mucosal disease
  Coeliac disease, Crohn’s disease, *Giardia* infection
  Brush border enzyme deficiency e.g. lactase

Mucosal absorptive defects
  lymphoma, lymphatic obstruction, radiation damage
  vascular problems
Now let’s look at some clinical cases...
Brian, 42 yo

HPc:
Three months of feeling unwell
Loose-stools, 6-8 times a day (normally once every 1-2 days)
Often bloody with mucous mixed in
Crampy abdominal pain prior to defecation
Urgency and tenesmus
Occasional nocturnal diarrhoea

O/E:
Abdominal examination: unremarkable
What other history might be helpful in making a diagnosis?

Constitutional symptoms: Feeling lethargic & sleeping poorly, occasionally “feverish”; weight loss 2-3 kg in past 3 months

Recent travel: 6 months ago holiday in Thailand. Was not unwell there.

Social History: Lawyer, lives with partner Paul

Past medical history: No significant past medical history. Non-smoker.

Medications: Nil, and none OTC

Family history: Nil significant
What are the most likely diagnostic possibilities?

The clinical presentation is of bloody, mucousy diarrhoea with tenesmus

This is usually due to an inflammatory mechanism

Common causes are:
1. Infection (“dysentery”) e.g. Salmonella, Shigella, Yersinia, Entamoeba histolytica (amebiasis) and cytomegaloviral colitis
2. Inflammatory bowel disease
3. Ischaemic colitis
4. Radiation colitis

Other causes of bleeding per rectum include:
Haemorrhoids (“piles”)
Colorectal cancer

Which of these causes are likely? Why?
What investigations would you like to order?

Specimen Type: Faeces

Description: Unformed, mucoid and bloody

Microscopy direct examination:

- Leucocytes: +++
- Erythrocytes: +++
- *Giardia cysts*: Not identified

*Clostridium difficile* toxin A/B: Not detected

Rotavirus antigen: Not detected

Adenovirus antigen: Not detected

Norovirus by RTPCR: Not detected

Culture: No *Salmonella, Shigella* or *Campylobacter* isolated
Full blood examination (FBE)

Haemoglobin: 115 g/L (ref range 130-170)
White cell count: Normal
Platelets: Normal

Inflammatory markers:
ESR 25 mm/hr (ref range 3-12)
CRP 80 mg/L (ref range < 5)

Nutritional:
Iron studies, B₁₂, folate, Vit D Normal
What’s the most likely diagnosis & how will you confirm it?

Inflammatory bowel disease (IBD) - ulcerative colitis

Confirm the condition by performing colonoscopy and colonic biopsies to assess the histological appearance.
Colonoscopy and biopsies

- superficial ulceration with distortion of crypts
- acute and chronic diffuse inflammatory infiltrate
- goblet cell depletion
- crypt abscesses
- lymphoid aggregates but no granulomas
Inflammatory bowel disease

• What is it?

• How is it classified?
Inflammatory bowel disease

• Comprises the conditions Crohn’s disease and ulcerative colitis
• Incidence range 5-20/100,000 (peak at 15-24 years) and is increasing
• Prevalence 200-400/100,000 (~1 in 300 population has IBD)
• 10% in children, diagnosis peaks again age 50+
• Chronic inflammatory disorders of uncertain aetiology (genetics, environment, immune response)
• Two conditions differ in clinical aspects
• In some patients it is difficult to decide between the two diagnoses - “indeterminate colitis”
Inflammatory bowel disease

Can you describe the key differences in the two main types?

• typical symptoms
• typical histology
• goals of treatment and treatment options
Ulcerative colitis

• Features:
  – Affects the large bowel starting at the rectum and proceeding proximally (i.e. no skip lesions)
  – Increased risk of colonic malignancy in longstanding ulcerative colitis

• Symptoms:
  – Characterised by frequent episodes of rectal bleeding
  – Urgency and tenesmus are often a feature of distal disease
  – Other symptoms include abdominal cramps, weight loss and fever in severe cases

• Treatment:
  – 5-ASA compounds (sulphasalazine) and steroids.
  – Topical therapy (suppositories/enemas) used for distal disease.
  – Immunosuppressants used in severe or recurrent disease
  – Surgery for severe or refractory cases (this is curative)
Crohn’s Disease

• Features:
  – Focal transmural inflammation with fissures, ulcers and granulomas and with healthy intestine between the lesions (skip lesions)
  – Can affect any part of the gut from mouth (aphthous ulcers) to anus (most commonly terminal ileum and colon).
  – Anal and perianal fistulae.
  – Extra-intestinal features include arthritis, uveitis and rashes

• Symptoms:
  – Abdominal pain, diarrhoea, weight loss, fever, failure to thrive.
  – The disease progresses with relapses and remissions

• Treatment:
  – Steroids, 5-ASA compounds, immunosuppressants (e.g. azathioprine, methotrexate), biologicals (monoclonal Ab), surgery
Mandy, 26 yo

HPc:
~ 10 year history of intermittent diarrhoea with bloating & flatulence
Up to 2-5 bowel motions per day (erratic), no blood
No weight loss
Stress, dairy products and some fruits make her symptoms worse
She tried a gluten free diet on advice of a friend and felt better.

SHx: Office manager, lives with partner
FHx: Sister is “gluten intolerant”
PHx: Depression

What are possible diagnoses in Mandy and why?

1. Irritable bowel syndrome

2. Coeliac disease

3. Infection such as *Giardia*

4. Inflammatory bowel disease
How is irritable bowel syndrome diagnosed?

1. Typical clinical history
   “Rome III” criteria
   • Symptoms for at least 3 months
   • Recurrent abdominal discomfort or pain associated with (2 or more of):
     – Improvement of symptoms with defecation
     – Change in stool appearance (form)
     – Change in stool frequency

2. Exclude other diagnoses
   • Presence of “red-flag” symptoms or signs such as weight loss, rectal (PR) bleeding, nocturnal symptoms, and age >45 should prompt further investigation before a diagnosis of IBS is made
How is coeliac disease diagnosed?

• Screen for coeliac disease
  – blood test measuring antibodies to transglutaminase (tTG-IgA) and gliadin (“deamidated gliadin peptides”, DGP-IgA and DGP-IgG).
  – The DGP assay replaces the older and less accurate anti-gliadin antibodies (AGA-IgA, AGA-IgG) test.

• If antibodies are abnormally elevated (positive), a small bowel biopsy showing villous atrophy is required to confirm the diagnosis

• Current diagnostic criteria for coeliac disease require:
  i. demonstration of small bowel damage (villous atrophy, crypt hyperplasia and raised intra-epithelial lymphocytosis) whilst a person is consuming gluten, and
  ii. improvement in histology, serology and clinical picture following a gluten free diet
How accurate is coeliac serology?

- Both transglutaminase and DGP Ab assays have a sensitivity of 80-90% (i.e. 10-20% of real coeliac diagnoses will be missed using serology alone)

- False positive results can occur – so a diagnosis of coeliac disease is never made on the blood test result alone (biopsy is needed).

- The accuracy of a diagnostic test is affected by the pre-test probability of the condition. Contrast an average-risk vs. high-risk population

What might cause false negative serology results?

- Gluten free diet
- IgA deficiency (seen in 3% of coeliac disease – that is why the total IgA level is measured or the IgG isotype of DGP assessed
- Immunosuppression e.g. prednisolone
How can you test for coeliac disease if a person is already following a gluten free diet?

A gluten free diet will normalise serology and histology and therefore could cause false negative investigations

Options are:

- HLA DQ2/8 gene test. This is seen in most (99.6%) patients with coeliac disease. If negative, it can be used to exclude coeliac disease.

- 6 week gluten challenge (4 serves gluten/day) followed by small bowel biopsy
How can you exclude infection and inflammatory bowel disease?

- Faecal assessment
- Inflammatory markers
- Gastroscopy and colonoscopy with biopsies may be required in some instances
Investigations

Full blood examination (FBE)
Haemoglobin/White cell count/Platelets: Normal

Iron studies:
Ferritin: 31 μg/L (ref range 30-300)
ESR: 4 mm/hr (ref range 3-12)
CRP: < 1 mg/L (ref range < 5)

Thyroid function (TSH): Normal

HLA DQ2/8 gene test: Negative for coeliac disease
Specimen Type: Faeces

Description: Unformed

Microscopy direct examination:
- Leucocytes: Not detected
- Erythrocytes: Not detected
- *Giardia* cysts: Not detected

*Clostridium difficile* toxin A/B: Not detected
*C. difficile* culture: No growth
Rotavirus antigen: Not detected
Adenovirus antigen: Not detected
Norovirus by RTPCR: Not detected

Culture: No *Salmonella*, *Shigella* or *Campylobacter* isolated
What is your diagnosis?

Irritable bowel syndrome

- **Common**: affects 15-20% of general population of Western countries, more common in females
- Important to exclude conditions such as: coeliac disease and inflammatory bowel disease and colorectal cancer (in 45 year old+)
- Clinically can be constipation-predominant, diarrhoea-predominant, pain-predominant or mixed pattern
Irritable bowel syndrome: Pathogenesis

Serotonin (5-HT) a key mediator in IBS

1. disordered intestinal motility
2. altered perception of nociceptive stimuli (visceral hypersensitivity)
3. psychogenic factors
4. post-infectious component in some people

“Stress” and small bowel bacterial overgrowth can be a trigger

Role of genetics is unclear
Why might foods like dairy, wheat and fruit trigger Mandy’s symptoms?

- FODMAP malabsorption is a common trigger for IBS
- FODMAPs are poorly absorbed fermentable carbohydrates
- Malabsorption of these sugars leads to fermentation by bacteria in the colon
  - \( \rightarrow \) hydrogen/methane gas leading to distention
  - \( \rightarrow \) osmotic diarrhoea
  - \( \rightarrow \) triggering of IBS symptoms
- A low FODMAP diet is now the 1\textsuperscript{st} line treatment for IBS
- Hydrogen/methane breath testing is available to test for lactose and fructose malabsorption
Poorly absorbed fermentable carbohydrates (FODMAPs)

<table>
<thead>
<tr>
<th>Fermentable...</th>
<th>Examples</th>
<th>Significant food sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligosaccharides</td>
<td>Fructans, Galactans, e.g. raffinose</td>
<td>Onions, wheat, legumes, lentils, cabbage, brussel sprouts</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Lactose</td>
<td>Milk, yoghurt, ice-cream, custard, soft cheeses</td>
</tr>
<tr>
<td>Monosaccharides And Fructose (when consumed in excess of glucose)</td>
<td>Honey, apples, pears, mangoes, peaches, watermelon</td>
<td></td>
</tr>
<tr>
<td>Polyols</td>
<td>Sorbitol, mannitol, xylitol</td>
<td>Stone fruits; also used as artificial sweeteners</td>
</tr>
</tbody>
</table>
How is IBS treated?

Primarily aimed at alleviating symptoms

• Dietary modification
  - Avoiding common food triggers – FODMAPs
  - Avoiding caffeine, alcohol, smoking

• Pharmacological therapies
  - Probiotics
  - Antispasmodics, antidiarrhoeals, laxatives
  - Antibiotics (Rifaximin) to treat bacterial overgrowth
  - ? Increase fibre ? Decrease fibre

• Psychological therapies
  - Relaxation, cognitive behaviour therapy, hypnotherapy

In the future, targeted treatments will become available that address the underlying enteric nervous system dysfunction e.g. 5-HT antagonists
Peter, 62 yo retiree

HPc:
6 month history of pale, smelly, greasy stools, difficult to flush
Frequently feels bloated and nauseated after meals.
More lethargic and has lost 15 kg weight in past 6 months.
Denies drinking alcohol for the past 2 years

PHx:
1. Hypertension
2. Ex-smoker.
3. Heavy drinker in the past
4. Alcoholic pancreatitis 10 years ago, subsequent two recurrent episodes

O/E: Bruises on arm. Evidence of subcutaneous fat loss. Several spider naevi on chest.
Abdominal exam normal. No hepatic flap or fetor.
What features suggest malabsorption might be present and how can we confirm it?

• History of steatorrhoea, lethargy, weight loss

• Examination findings of bruising, muscle wasting, weight loss

*Confirm it by:*

• Nutrient levels (Iron studies, $B_{12}$, folate, vitamins)

• Faecal assessment
  Increased faecal fat
What are potential causes for Peter’s malabsorption and how might they cause it?

1. **Defective nutrient hydrolysis (digestion)**
   Pancreatic insufficiency due to chronic pancreatitis or pancreatic cancer

2. **Reduced nutrient availability**
   Poor oral intake (especially if still an alcoholic); bacterial overgrowth

3. **Reduced fat solubilisation (reduced bile salt concentration)**
   Cholestasis (failure of bile flow) due to underlying liver disease; bacterial overgrowth will inactivate bile salts

4. **Diffuse mucosal disease**
   e.g. coeliac disease, *Giardia* infection, brush border enzyme deficiency

5. **Mucosal absorptive defects**
   e.g. lymphoma, lymphatic obstruction
How can we investigate the following?

Pancreatic insufficiency
- Imaging with CT scan (¿ chronic pancreatitis ¿ cancer)
- Faecal elastase level as marker of exocrine sufficiency
- Empiric trial of pancreatic enzyme supplementation
- Secretin stimulation test (rarely done)

Bacterial overgrowth
- Hydrogen/methane breath test (assess for “early rise” in breath hydrogen due to fermentation in the small bowel)
- Empiric trial of broad-spectrum antibiotics

Cholestasis/liver disease
- Assess for underlying liver disease and alcoholic cirrhosis
- LFTs, liver imaging (ultrasound), possibly biopsy
- History of jaundice, dark urine and pale stools suggest extrahepatic cholestasis
- Corroborate history of alcohol intake with family
Summary

• Diarrhoea is frequently encountered in clinical practice and is associated with impaired quality of life, significant morbidity, and can be life-threatening

• The most common causes of chronic diarrhoea in our community are irritable bowel syndrome, FODMAP malabsorption, coeliac disease, infection and inflammatory bowel disease

• An understanding of the pathophysiological mechanisms causing diarrhoea and malabsorption provides the basis for optimal clinical work-up, diagnosis and management
Clinical approach to diarrhoea

Fulfil Rome III Criteria
Other causes excluded
No red-flags* = IBS

“Diarrhoea”

- Take a comprehensive history & build up the clinical picture
- Clarify description of diarrhoea
- Exclude issues like faecal incontinence or constipation with overflow which could mimic diarrhoea

Stool appearance

Bloody diarrhoea
- Exclude haemorrhoids
  - Pathogen screen
  - Colonoscopy + biopsy

Watery diarrhoea
- FBE, coeliac serology, nutritional screen, inflammatory markers, thyroid function
- Faecal testing (microscopy/culture, wbc/rbc, fat)

Osmotic
- Response to fasting
  - High osmotic gap
    - Hydrogen/methane breath testing

Secretory
- Typically large volume
  - Unresponsive to fasting
    - Low osmotic gap

Steatorrhoea

Malabsorption work-up
- Coeliac serology
- Gastroscopy

- Pancreatic assessment:
  - CT scan
  - Faecal elastase
  - Endoscopic retrograde pancreatography (ERCP)
  - Other

* Weight loss, rectal (PR) bleeding, nocturnal symptoms, age >45

Doctor of Medicine