Coeliac Disease

History of Presenting Illness

TABLE 15. Symptoms of coeliac disease

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Probable causes or deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Iron, folate, B₁₂, pyridoxine</td>
</tr>
<tr>
<td>Glossitis</td>
<td>Iron, folate</td>
</tr>
<tr>
<td>Weight loss/Weakness</td>
<td>Malnutrition - Negative nitrogen balance</td>
</tr>
<tr>
<td>Diarrhoea/Flatulence</td>
<td>Fat and carbohydrate malabsorption</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Increased intestinal gas production secondary to carbohydrate malabsorption</td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
</tr>
<tr>
<td>Folicular hyperkeratosis and dermatitis</td>
<td>Vitamin A, folate</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>Associated adrenal insufficiency</td>
</tr>
<tr>
<td>Edema</td>
<td>Hypoproteinaemia</td>
</tr>
<tr>
<td>Tetany</td>
<td>Vitamin D, calcium, magnesium</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Vitamin D, calcium</td>
</tr>
<tr>
<td>Purpura</td>
<td>Hypoalbuminemia (vitamin K)</td>
</tr>
<tr>
<td>Rino</td>
<td></td>
</tr>
<tr>
<td>Spinal cord degeneration</td>
<td>B₁₂</td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td>Vitamin E, thiamine, pyridoxine</td>
</tr>
<tr>
<td>Psychosis</td>
<td>B₁₂</td>
</tr>
<tr>
<td>Malignancy (usually small bowel lymphoma)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

In adults it usually occurs between 20 and 60 years.

Sole presentation nowadays may be a microcytic hypochromic anaemia which cannot be otherwise explained.

Diarrhoea is usually mild: fewer than three bowel movements per day in most.

Malabsorption diarrhoea: WORST SMELL EVER

Fatigue is the most frequent symptom at presentation.

Weight loss is usually only ~10kg

A clue to the diagnosis of celiac disease is the development of lactose intolerance in person whose heritage is northern European.

It only takes ONE GLASS OF MILK to induce diarrhoea and flatulence in a lactose-intolerant person.

Differential Diagnoses

- Bacterial Overgrowth Syndrome
- Collagenous and Lymphocytic Colitis
- Crohn Disease
- Cytomegalovirus Colitis
- Eosinophilic Gastroenteritis
- Gastroenteritis, Bacterial
- Gastroenteritis, Viral
- Giardiasis
- Hypoalbuminemia
- Hypocalcemia
- Hypokalemia
- Hypomagnesemia
- Hypothyroidism
- Immunoglobulin A Deficiency
- Inflammatory Bowel Disease
- Iron Deficiency Anemia
- Irritable Bowel Syndrome
- Malabsorption
- Protein-Losing Enteropathy
- Jejunoileitis
- Intestinal lymphoma

Findings on Examination

- Abdominal examination = protuberant and tympanic abdomen due to distension with fluids and gas.
- Ascites occasionally
- Evidence of weight loss, including muscle wasting or loose skin folds
- Orthostatic hypotension
- Peripheral edema
- Ecchymoses
- Hyperkeratosis or dermatitis herpetiformis (itchy vesicles on elbows)
- Cheilosis and glossitis
- Evidence of peripheral neuropathy
- Chvostek sign: tapping on facial nerve over mastoid process causes a tic of facial muscles
- Trousseau sign: when the cuff is inflated to just over the systolic pressure, the hand will spasm
Tests and Investigations

For it to be called COELIAC DISEASE, you have to demonstrate SMALL BOWEL MUCOSAL VILLOUS ATROPHY that IMPROVES UPON GLUTEN WITHDRAWAL

Full Blood Count
Anemia is present in less than 50% of adult patients.
Also want to make sure that the coagulopathy is due to malnutrition and vitamin K depletion, not thrombocytopenia.

Serum Ferritin.
Iron deficiency is the most common laboratory abnormality.

Serum Biochemistry
Depletion of minerals (zinc, magnesium) and ions (potassium) (occurs only with severe disease)
Malnutrition = decreased serum albumin.

RBC Folate
Folate deficiency is uncommon, but happens.

Hydrogen Breath test
The absorptive cell lesion also results in secondary lactase deficiency; thus, the H₂-lactose breath test may be abnormal in celiac disease.

Stool Examination
Steatorrhea can be confirmed by a 72-hour fecal fat study.
It is usually mild (10-20 g/24 hours) and may be absent in some patients.
Severity of steatorrhea correlates with the extent of the intestinal lesion.
PLUS you look for ova, cysts, parasites, Leucocytes and BLOOD

Barium Swallow radiography (IGNORE AS IT IS USELESS)
Barium studies of the small bowel may show dilation of the bowel and slight thickening of the mucosal folds. Intraluminal signs of malabsorption with flocculation, segmentation and clumping of the barium (features due to excess amount of fluid present within the lumen) are variable and not common. (The new barium suspensions now used have made this a rare finding.) Radiographic findings in celiac disease are not specific for this syndrome of malabsorption.

Serum Anti-Endomyseal Antibodies
Anti-endomysial IgA antibody: antibodies against reticulin in monkey oesophageal smooth muscle.
The most sensitive and specific test (>98%)

SMALL BOWEL BIOPSY is the gold standard: so get in there = can be obtained endoscopically from the distal duodenum (at least four forceps biopsies).
You don't need to do another biopsy to prove that a gluten-free diet made it better

Looking for:
- SUBTOTAL VILLOUS ATROPHY
- flat surface
- hyperplastic lengthened crypts
- increased cellularity
- more plasma cells and lymphocytes
- proximal small bowel most severely involved
Management: **STOP EATING GLUTEN!**

which requires avoiding wheat, rye, barley and oats

PLUS: may want to think about replacing + supplementing haematinics and other micronutrients

**THIS DIET IS LIFE-LONG:** Mention to the patient – persistent non-compliance may be associated with small bowel malignancy

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Nutritional approaches to GI disease

Gluten is found in
- wheat (wheat flour is ~8% gluten)
- rye and barley
- wheaten cornflour,
- malt
- some thickeners
- oats (contaminated with traces)

<table>
<thead>
<tr>
<th>Gluten-free flours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>rice,</td>
</tr>
<tr>
<td>soy,</td>
</tr>
<tr>
<td>maize,</td>
</tr>
<tr>
<td>besan (chickpea)</td>
</tr>
<tr>
<td>potato</td>
</tr>
<tr>
<td>Arrowroot,</td>
</tr>
<tr>
<td>buckwheat,</td>
</tr>
<tr>
<td>lupin,</td>
</tr>
<tr>
<td>maize cornflour,</td>
</tr>
<tr>
<td>millet,</td>
</tr>
<tr>
<td>modified maize starch,</td>
</tr>
<tr>
<td>polenta,</td>
</tr>
<tr>
<td>psyllium,</td>
</tr>
<tr>
<td>rice,</td>
</tr>
<tr>
<td>sago,</td>
</tr>
<tr>
<td>seeds,</td>
</tr>
<tr>
<td>sorghum</td>
</tr>
<tr>
<td>tapioca</td>
</tr>
</tbody>
</table>

elastic properties of the wheat gluten protein permit the baking of leavened bread.

many foods on the market that are gluten-free are not labelled as such

A person on a normal diet consumes about 10-14g of gluten per day.

---

**Prognosis: EXCELLENT provided gluten is withdrawn**

Vast improvement within weeks if not days

**Epidemiology**

Commonest cause of malabsorption in the western world! 1:250 to 1:75

**Frequency:**
- **Internationally:** Celiac sprue is prevalent in some European countries with temperate climates. For example, the frequency of the disease is between 1 in 250 persons and 1 in 300 persons in Italian and Irish populations. In comparison, the disease is rare in Africans or Asians.

**Mortality/Morbidity:**
- increased risk for lymphomas and adenocarcinomas of the intestinal tract.
- Untreated pregnant women are at risk of miscarriage
- There is risk of congenital malformation of the baby.
- celiac sprue @ childhood = FAILURE TO THRIVE and short stature
  (1%30% have clubbing and 20% can have constipation. How very weird)

**Race:** Celiac sprue is most prevalent in Europeans and is rare in Africans and Asians.

**Sex:** Incidence of celiac sprue is slightly higher in females.

**Age:** The age distribution of patients with celiac disease is bimodal,

- first peak is at 8-12 months
- second peak in the third to fourth decades.
**Nutrient Absorption and Transport**

**Trace nutrients: Water soluble vitamins**
- **Riboflavin**: Released from proteins by stomach acid → Absorbed by SATURABLE TRANSPORT SYSTEM @ proximal **Jejunum**
- **Niacin**: De-phosphorylated → FACILITATED or PASSIVE transport @ **Jejunum**
- **B6**: Released from proteins by stomach acid: binds to R-proteins in saliva → Liberated from R-proteins by pancreatic proteases @ **duodenum**
- **B12**: Released from proteins by stomach acid: binds to R-proteins in saliva → Liberated from R-proteins by pancreatic proteases @ **duodenum** → Absorbed via a specific receptor in **terminal ileum** then bound to transcobalamine for transport in plasma
- **Vitamin C**: Converted to dihydro-derivatives → Energy-dependant facilitated transport
- **Folate**: Cleaved from polyglutamates by upper jejunal brush border conjugases (!! conjugase action impaired by alcohol) → Energy-dependant facilitated transport

**Fat soluble vitamins**
- Incorporated in bile salt micelles prior to absorption by the enterocytes usually in the **upper jejunum**.
- Vitamin A is not as reliant on bile and pancreatic enzymes.
- Vitamin D is absorbed in the upper jejunum presumably by diffusion.
- Vitamin E absorption is very dependent on adequate micelle formation.
- Vitamin K requires both bile and pancreatic enzymes for absorption.

**Trace metals**
- Most trace metals are absorbed by passive diffusion.
  - Iron bonds to a membrane receptor protein, and absorption may be facilitated by a cytosolic apotransferrin. Iron absorption is impaired by certain foods, eg milk protein, tea and coffee, phytates, and enhanced or impaired according to iron storage status.

**Cholesterol** has its own transporter: then, esterified in enterocyte; secreted into portal blood.

**Glucose**
- Poly saccharides → delivery amylase → mouth → brush border Es → maltase, lactase → sucrose SML intestine

**Lipids**
- 3-GLys (Fat globules) → bile salts emulsification → 3-Glycyl FA's (micelles)

**Amino acids** are transported by 7 different specific transporters. Some are Na+ coupled, some are not.
Most pancreatic enzymes are activated in the lumen—**EXCEPT** amylase and the lipases.

<table>
<thead>
<tr>
<th>Enzyme Type</th>
<th>Activating Enzyme</th>
<th>Activated Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsinogen</td>
<td>Enteropeptidase</td>
<td>Trypsin + peptide</td>
</tr>
<tr>
<td>Chemotrypsinogen</td>
<td>trypsin</td>
<td>Chemotrypsin + peptide</td>
</tr>
<tr>
<td>Proelastase</td>
<td>trypsin</td>
<td>Elastase + peptide</td>
</tr>
<tr>
<td>Procarboxypeptidase</td>
<td>trypsin</td>
<td>Carboxypeptidase + peptide</td>
</tr>
<tr>
<td>Phospholipase A</td>
<td>trypsin</td>
<td>Phospholipase A + peptide</td>
</tr>
</tbody>
</table>

Amylase and lipases are secreted as active enzymes.
Protein and lipid breakdown products stimulate a vagovagal reflex that stimulates primarily the acinar cells.

Protein and lipid breakdown products stimulate I cells in duodenum to secrete secretin, which acts on receptors on duct cells, stimulating HCO₃⁻ secretion.

Dietary carbohydrate

Intestinal lumen

Starch, glycogen

Amylase

Lactose

Maltose

Maltotriose

α-Dextrin

Sucrose

Luminal digestion

Membrane digestion

Galactose

Glucose

Glucose

Glucose

Fructose
Carbohydrate absorption

Protein absorption

At least three distinct Na⁺-independent amino acid transporters move amino acids out of the cell across the basolateral membrane.
Emulsification of lipid

Pancreatic lipases

- Triglyceride: lipase + colipase → monoglyceride + 2 fatty acids
- Cholesterol ester: cholesterol ester hydrolase → cholesterol + fatty acids
- Phospholipid: phospholipase A₂ → lysolecithin + fatty acids
Breakdown of emulsion droplets

1) A multilamellar liquid crystalline layer buildup on the surface.

2) Budding of digested lipids and formation of multilamellar vesicle.

3) Bile salt micelles transform the multilamellar vesicle into unilamellar vesicle and mixed micelle.

Micellar transport of lipolytic products
Absorption of lipids

96% of the total weight of the pancreas is exocrine

Function of Exocrine Pancreas
96% of the total weight of the pancreas is exocrine

2 litres of pancreatic juice per day.

ACINAR Secretory stimulus: from Cholecystokinin and Acetylcholine (increase Ca++, which is the 2ndary transmitter)

FAILURES OF PANCREATIC FUNCTION:
For example cystic fibrosis: pancreatic lipase requires a steady alkaline pH, but if the CFTR protein cant channel HCO3-, the duodenum stays acidic and the lipase doesn’t work, hence → FAT MALABSORPTION
Patients with pancreatic insufficiency present with diarrhoea and often describe their stools as containing "bacon fat", "melted butter" or "olive oil". NOTHING LIKE COELIAC DISEASE!! → where malabsorption is of the fatty acids, not whole triglycerides
Mucosal Immunity: Mucosa-associated lymphoid tissue (MALT)

The tonsils contain a considerable amount of lymphoid tissue, often with many large germinal centres.
- The bronchi contain diffuse lymphoid aggregates and respiratory epithelium contains dendritic cells for uptake, transport and processing of antigens.
- Peyer’s patches of the lower ileum are particularly prominent diffuse accumulations of lymphoid tissue are seen in the lamina propria of the intestinal wall. They form follicles with segregation of lymphocytes into T and B cell areas.

HOW EVERYTHING WORKS:
- Peyers patch is COVERED BY A DOME OF EPITHELIUM.
- This dome is composed of “M” CELLS (microfold cells)
- These cells TOTALLY ENVELOP the B and T lymphocytes!
- Their job is to allow the antigens to penetrate through into the lymph

IgA IMMUNITY
- Secreted by B cells in the mucosa
- Actively transported through the epithelium:
  - Internal surface of epithelium has special receptor
  - The receptor + IgA complex is endocytosed
  - Gets transported in vesicles
  - @ the LUMEN MEMBRANE, enzymes cleave the receptor
  - the IgA is released, bound to the secretory component
  - Protected from destruction by the secretory component

Mucosal T cells:
- MAIN FUNCTION seems to be virus surveillance: they are mainly CD8 cytotoxic T-cells

Recirculation and homing
- Cells activated in the mucosa migrate to regional lymph nodes and then "home" back to mucosal surfaces via the thoracic duct and blood stream.

This tissue-specific recirculation is dependent on recognition of adhesion molecules (of the selectin and integrin family) expressed on MALT-derived lymphocytes and on endothelial cells of the mucosal postcapillary venules.
- Thus, antigen stimulation at one mucosal site can elicit an antibody response at other surfaces as well.
Overview of Spectrum of non-infectious diarrhoea: worth ignoring

Inflammatory bowel disease is the term used to describe ulcerative colitis and Crohn's disease. These are chronic, relapsing conditions of unknown aetiology affecting the gastrointestinal tract. Onset can be at any age, but with a peak from late teens to mid-30s.

Aetiology
The cause of either condition is unknown. Factors implicated in Crohn's disease include smoking, genetic factors and intraluminal bacteria. Mucosal inflammation with activation of the immune system is a feature of both diseases.

Ulcerative colitis
Pathology: affects only the large intestine. Always involves the rectum and usually a variable length of colon proximal to this in continuity. The inflammation is confined to the mucosa. Neutrophils prominent in the inflammatory infiltrate.

Clinical features: typically presents with diarrhoea containing blood and mucus. Patients with proctitis may have bleeding only. Pain is a feature of severe disease. Toxic megacolon and perforation may result. Extraintestinal manifestation can develop, affecting joints, skin, eyes and liver. The risk of colorectal cancer is increased in patients with extensive disease after 7-10 years.

Diagnosis: sigmoidoscopy or colonoscopy, with biopsy. Barium enema occasionally used as the alternative. Infectious causes of colitis must be excluded by stool microscopy and culture.

Treatment: in active disease depends upon the extent of involvement and degree of inflammation. Corticosteroids are used rectally for left-sided disease, orally if more extensive, more active or unresponsive, and intravenously in severe cases. 5-aminosalicylic acid (5-ASA) compounds, sulphasalazine, mesalazine and olsalazine, of benefit in mild-moderate disease, but their main role is in maintenance therapy. Immunosuppressants (azathioprine, 6-mercaptopurine) are used for resistant disease or for their steroid-sparing effect. Cyclosporine may have a limited role in severe colitis where surgery is not possible.

Maintenance therapy with 5-ASA compounds reduces the relapse rate by 50% or more. Treatment should be continued indefinitely. Azathioprine/6-MP can also be used for maintenance. Surgery, usually ileal pouch-anal anastomosis, is required in approximately 20% of patients. Indications include severe active disease, chronic unresponsive disease, cancer risk or overt cancer.

Crohn's disease
Pathology: can involve any part of the gastrointestinal tract, most commonly the ileum, colon or both. Discontinuous involvement, with characteristic "skip" lesions. The inflammation is transmural, leading to wall thickening. Fistulae may develop and are specific for Crohn's disease. Histologically there is a mononuclear infiltrate with the characteristic granulomas present in 70%.

Clinical features: In small bowel disease the main symptom is pain. Patients with colitis develop diarrhoea, but with bleeding in only 50%. Fistulae may develop between loops of intestine or between intestine and skin or other organs. Systemic symptoms such as fatigue, fever and weight loss are also common in Crohn's disease. Perianal complications occur in 25%. Extraintestinal manifestations may develop as in ulcerative colitis.

Diagnosis: a high index of suspicion is required. Colonoscopy with biopsy and small bowel radiology are generally used. Other investigations depend on the site of involvement.

Treatment: active disease is treated with corticosteroids. Azathioprine or 6-MP are also used as in ulcerative colitis. Oral mesalazine in high dose may be of benefit in ileal inflammation. In resistant disease methotrexate has been tried. Cessation of smoking is essential because of its adverse effect on the course of the disease. New treatments include broad-spectrum antibiotics and anti-tumour necrosis factor (infliximab).

Maintenance therapy with oral mesalazine is used in ileal disease. Immunosuppressants can also be used in selected patients.

Surgery is needed in up to 80% of patients, especially those with small bowel involvement. This is mostly segmental resection of the most inflamed areas, with a conservative approach. Strictureplasty is performed on small bowel strictures. Surgery is not curative, with approximately 50% of patients requiring a subsequent operation.

Prognosis: although these are chronic diseases, most patients can lead productive lives. Only a small proportion are disabled by the condition. Death from inflammatory bowel disease is rare.
INNERVATION OF THE GUT

CHRONIC DIARRHOEA: a synopsis of pathophysiology:

OSMOTIC
Poorly absorbed nutrient drags water into the lumen
DIAGNOSIS:
it will stop with fasting,
…or with removal of the offending solute
CAUSES:
Lactase deficiency
Ingestion of excess mannitol, sorbitol, etc
Even fibre can do it
Magnesium, laxatives, antacids

EXUDATIVE
associated with mucosal damage that leads to
an outpouring of mucus, blood, & plasma proteins
(eg. - chronic ulcerative colitis, radiation enteritis)
WILL NOT STOP WITH FASTING

WHERE IS IT COMING FROM? SMALL BOWEL, LARGE BOWEL, OR STEATORRHOEA?

SMALL BOWEL:
Large volume
Liquid
No blood or mucus
May have undigested food
Audible gurgling
Periumbilical PAIN
LARGE BOWEL:
Small volume but frequent
Blood AND mucus
Straining, tenesmus
(constant urge)
pain @ lower abdomen
STEATORRHOEA:
Bulky, pale, oily, STINKY
Floating!!
Either liver or pancreas:
are they YELLOW?
Is there PRURITIS (bile duct obstruction)

MOTILITY
Too fast
Thyrotoxicosis
Post-abdominal surgery
Too slow
Bacterial overgrowth
Primary intestinal hypomotility
Scleroderma (constrictions)
Diabetic autonomic neuropathy

SECRETORY
results from
active secretion of electrolytes & water from
the intestinal epithelium
eg. – CHOLERA TOXIN
Fasting does not relieve this type.
Secretory is not a common type.
→ secretory gastric carcinoma, VIPoma, laxative abuse, loss of 100cm of terminal ileum
PATHOGENESIS of Coeliac Disease and Lactose Intolerance

most common cause of lactose intolerance in children is viral gastroenteritis.

Ingested LACTOSE

Ingested GLUTEN

rye

wheat

barley

Gut Lumen

Dendritic APC

Mucosa-Associated Lymphoid Tissue

Villus Surface Enterocyte

\[ \text{Ingested} \quad \text{LACTOSE} \]

\[ \text{Ingested} \quad \text{GLUTEN} = 35\% \text{ gliadin}, \quad \text{the rest} = \text{glutemins} \]

Flatus

Bloating

Borborygmi

Osmotic effects

(lactose drags water out of bowel)

@ small intestine

@ colon

Bacterial Metabolism

Absent brush border lactase
(normally lactose \( \rightarrow \) galactose)

Proteinases, peptidases

H+

Peptides transported

Tissue transglutaminase

and negatively charged glutamic acid \((\text{TG} + \text{G})\)

= the EPITOPE

DQ2 subtype of MHC II

Th1, Th2 lymphocytes: Pick up the antigen and kick-start a specific immune response, with production of detectable antibodies, and the subsequent recruitment of leucocytes and complement.

Tissue transglutaminase

and negatively charged glutamic acid \((\text{TG} + \text{G})\)

= the EPITOPE

MALIGNANCY will result if gluten is persistently being consumed

(? Because of continuous cell turnover in the gut?)

!SPECULATION! May be inaccurate

\[ \text{Bacterial Metabolism} \]

\[ \text{H}^+ \]

\[ \text{Ingested} \quad \text{GLUTEN} \]

\[ \text{rye} \]

\[ \text{wheat} \]

\[ \text{barley} \]

Absence brush border lactase
(normally lactose \( \rightarrow \) galactose)

\[ \text{Flatus} \]

\[ \text{Bloating} \]

\[ \text{Borborygmi} \]

\[ \text{Osmotic effects (lactose drags water out of bowel)} \]

\[ \text{Peptides transported} \]

\[ \text{Tissue transglutaminase} \]

\[ \text{and negatively charged glutamic acid (TG + G)} \]

= the EPITOPE

\[ \text{MALIGNANCY will result if gluten is persistently being consumed (Because of continuous cell turnover in the gut?)} \]

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