Malabsorption syndromes
Dr. Abonyi Margit
Small bowel

- Complex organ involved in many different functions:
  - process of digestion
  - absorption of nutrients, electrolytes, water, bile salts and drugs

- Length: ~ 7-8 m, internal surface: ~ 3 m² (200m²)

Malabsorption syndrome ≠ Enteropathy
Definitions

- **Maldigestion**: defective hydrolysis of nutrients

- **Malabsorption**: defective crossing through the intestinal wall by products of normal digestion
  - **Selective malabsorption**: involve only specific substrates
  - **Global malabsorption**: generalized

- **Malabsorption syndrome**: complex of symptoms secondary to maldigestion and/or malabsorption, realizing when the extension of the disease exceeds the ability of intestine compensation.
Malabsorption syndromes

Classification– etiopathogenetic mechanisms

- Alteration of digestive processes
- Alteration of uptake and transport caused by damage or reduction of absorption surface
- Miscellaneous

Montalto M. Dig Dis. 2008

Signs and symptoms

- Modification of the luminal content with persistence of nutrients in the lumen (diarrhea, steatorrhea, meteorism, abdominal discomfort)

- Decreased tissue utilization of nutrients, with deficiency manifestations (paleness, asthenia, loss of weight, delay or stop of growth, edemas, mucosal, skin and adnexal dystrophy, amenorrhea, tetany, bone pain, hemorrhagic and neurological manifestations, hemeralopia, recurrent infections)
## Alteration of digestive processes (intraluminal phase)

<table>
<thead>
<tr>
<th>Type of alteration</th>
<th>Causing condition</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficit of enzymes</td>
<td></td>
<td></td>
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<tr>
<td>● <strong>Brush border</strong></td>
<td></td>
<td></td>
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<tr>
<td>α-Glucosidase</td>
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<tr>
<td>β-Galactosidase (lactase)</td>
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<tr>
<td>Enterokinase</td>
<td></td>
<td></td>
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<tr>
<td>● <strong>Pancreatic exocrin secretion</strong></td>
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<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Primary or secondary deficit</td>
<td>Impaired carbohydrate digestion</td>
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<tr>
<td>Protease</td>
<td>Primary or secondary deficit</td>
<td>Impaired lactose digestion</td>
</tr>
<tr>
<td>Lipase</td>
<td>Congenital</td>
<td>Impaired protein digestion</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatitis, pancreatic cancer, cystic fibrosis, pancreatic surgery, congenital pancreas diseases</td>
<td>Impaired global digestion</td>
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<tr>
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<td>Pancreatic residual function &lt; 10%</td>
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<tr>
<td>Deficit of bile salts</td>
<td>Cholestatic liver diseases, bacterial overgrowth, alterations of enterohepatic circle</td>
<td>Impaired lipid digestion</td>
</tr>
</tbody>
</table>
Enzymatic deficits – Impaired lactose digestion

Lactose
- disaccharide
- principal carbohydrate of mammalian milk
  (7% of human milk, 4.8% of bovine milk and ~ 30% of the caloric content)
- the most important source of energy during the 1st yr of human life
- promote absorption of Ca, P, Mg, Mn
- wide use in food and pharmaceutical industry
  (limited sweetness, browning and tablet forming properties)
- presence in non-dairy products and numerous drugs

Lomer MCE. Aliment Pharmacol Ther. 2007
Human lactase deficiencies

- **Lactase non-persistence (LNP)** (adult-type hypolactasia or primary lactase deficiency) („wild-type” pattern):
  - normal, developmental phenomenon (~ 70%) characterized by the down regulation of lactase enzyme activity after weaning
  - **mutations in lactase gene** (2q21-22) result in retaining high lactase activity throughout life (lactase persistence), advantage for survival
- **Secondary or acquired lactase deficiency**
  - loss of lactase activity in people with lactase persistence
- **Congenital form of lactase deficiency (CLD)**
  - severe GI disorder of new-borns (Finland)

**Key message:**
- both with low lactase enzyme activity
- molecularly distinct conditions
- represent strikingly different phenotypes
Lactose intolerance – Signs and symptoms

Lactase non-persistence ≠ lactose intolerance (symptoms from milk)

- Diarrhoea
- Bloating, excessive flatus, abdominal cramping (nausea, vomiting)

Natural aversion to milk already during childhood

Phenotype of CLD is strikingly different
- Watery diarrhea → dehydration, acidosis, failure to thrive
- First days or weeks of life

Differentiation from cow milk protein allergy

Colonic metabolism of lactose plays an important role

Braden Best Pract Res Clin Gastroenterol. 2009
Lactose intolerance – Diagnosis: Hydrogen breath test

Other options:

- Lactase activity in the mucosal biopsy
- Genetic testing
- Lactose absorption test: monitoring of blood glucose 0, 60, 120 min after ingestion of 50 gr lactose
  \(< 1.1\text{mmol/L increase in blood glucose}\)

50 g lactose is equivalent to 1 L of milk
Saad RJ. Gastroenterology. 2007
### Alteration of uptake and transport caused by damage or reduction of absorptive surface (epithelial and parietal phase)

<table>
<thead>
<tr>
<th>Type of alteration</th>
<th>Causing condition</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alterations of intestinal wall (a reduction or a damage)</td>
<td>Celiac disease, Crohn’s disease, eosinophil gastroenteritis, mastocytosis, autoimmune enteropathy, radiation enteritis, primitive intestinal lymphangiectasia, enteropathic acrodermatitis, abetalipoproteinemia, lymphoma, bowel resection, intestinal bypass</td>
<td>Impaired global absorption</td>
</tr>
<tr>
<td></td>
<td>Primary/secondary deficit of specific carriers</td>
<td>Altered absorption of fructose/glucose amino acids</td>
</tr>
<tr>
<td></td>
<td>Monosaccharides (fructose/glucose)</td>
<td></td>
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<tr>
<td></td>
<td>Amino acids</td>
<td></td>
</tr>
<tr>
<td>Alterations of circulation (blood &amp; lymphatic)</td>
<td>Mesenteric ischemia, heart failure, constrictive pericarditis, portal hypertension, secondary lymphatic obstruction</td>
<td>Impaired global absorption</td>
</tr>
<tr>
<td>Alterations caused by microbes</td>
<td>Bacterial overgrowth, Whipple’s disease, tropical sprue, parasitosis, intestinal tuberculosis, HIV, other infective enteritis</td>
<td>Impaired global absorption</td>
</tr>
</tbody>
</table>
Celiac disease

- One of the commonest chronic disorders in Europe (1%) associated with severe morbidity.

- Autoimmune disorder which is precipitated by ingestion of gluten (storage protein of wheat, barley, rye) in a genetically predisposed person.

- 90% of the cases are unrecognized in childhood, however autoimmune processes are ongoing.

- Gluten-free diet is an effective treatment of the disease and prevent complications.

- Autoantibodies against transglutaminase develop and appear in the circulation during the course of the disease. These antibodies are detectable by laboratory methods.
Celiac disease – pathogenesis

Does not develop unless a person has alleles that encode for HLA-DQ2 or DQ8
Celiac disease – detection of antibodies

- **Patients**
  - **coeliac control I control II**
  - **0.1 1 10 100 1000 10000**
  - **n=78 n=46 n=27**
  - 649 U/ml 1.2 U/ml 1.1 U/ml

- **TG**
  - **fibronectin collagen**

- **Endomysium**

- **Anti-IgA**

- **Recombinant or purified TG**
Celiac disease – damage of the small intestinal wall

Normal structure of villi

Subtotal atrophy of villi

Gluten

Gluten-free diet
Celiac disease – signs and symptoms

- Iron-deficiency anemia
- Lactose intolerance
- Failure to thrive, short stature, delay of puberty
- Hair loss, dry skin
- Eye and tongue redness
- Problem with menstruation
- Headache (iron)
- Neurosis, depression
- Chronic fatigue
Celiac disease – clinical forms

- Malabsorption: 34%
- GI symptoms: 16%
- Hypoalbuminemia: 7%
- Vashiános anaemia: 7%
- RAP és GOR: 4%
- Autoimmune disease: 4%
- Extraintestinal symptoms: 2%
- Family member: 15%
- Population screening: 4%
Celiac disease – clinical forms

- Latent celiac disease
- Silent celiac disease
- Clinical celiac disease
- Refracter sprue

Normal mucosa

Gluten-free diet
Celiac disease – irreversible complications

- Short stature, face deformity
- Osteoporosis (compression of vertebra)
- Ataxia cerebellaris, dementia
- Endocrin deficiency (diabetes mellitus, hypothyreosis)
- Liver failure
- Ulceratv jejunitis
- Mesenterial cavitation syndrome
- Refracter sprue
- Enteropathy-associated T-cell lymphoma
Crohn’s disease

- Chronic inflammatory bowel disease with multifactorial etiology
- Any part of the digestive tract could be involved (segmentary manner)
- Typical endoscopic and histologic findings
- Frequent complications: development of stenosis and fistulae (! bacterial overgrowth)
- Clinical presentation is variable according to different localizations
  - **Ileum**: selective malabsorption of B12 vitamin and bile salts (diarrhea not always be present)
  - **Extensive jejuno-ileal**: malabsorption and steatorrhea are more severe
  - **Colon**: diarrhea with presence of blood, abdominal pain
„Short-bowel syndrome”

- In patients who have undergone a large surgical resection of the small bowel

- Clinical manifestations are various and depend on localization and extension of resection

- Causes of malabsorption:
  - loss of absorption surface
  - impaired synthesis of gastrointestinal hormones
  - accelerated intestinal transit
  - possible loss of the ileocecal valve (retrograd bacterial migration – small intestinal bacterial overgrowth)
Circulatory alterations – hematic and lymphatic I.

- Mucosal ischemic injury → atrophy of the enterocytes
- Global malabsorption with diarrhea, steatorrhea, loss of proteins, weight loss and other signs of malnutrition

- Main alterations:
  - chronic mesenteric ischemia
    (arteriosclerosis, vasculitis, infective arteritis, connective tissue diseases, extrinsic compressions, anatomic abnormalities)
  - venous mesenteric insufficiency
    (phlebitis, thrombosis, thromboembolism, portal stasis, compressions, infiltrations, trauma)
  - secondary lymphatic obstructions
    (lymphatic infiltrations, lymphomas, solid tumors, traumas, thoracic duct damages)
Circulatory alterations – hematic and lymphatic II.

- **Chronic heart failure** (‘cardiac cahexia’):
  Hematic stasis in splanchnic district → edema or congestion → hypoxia of mucosa

- **End-stage liver disease:**
  Inadequate absorption of mico- and macronutrients and impaired digestion
  - malnutrition is a bad prognostic factor
- **common ~ 80% (even in Child A ~ 25%):**
  - associated to severity of liver disease and presence of portal hypertension
  - ‘portal hypertensive enteropathy’: mucosal congestion, villous atrophy, compromised gut barrier function
  - small intestinal bacterial overgrowth
  - cholestasis → ↓ intraluminal bile salt concentration → ↓ absorption of fat-soluble vitamins
  - pancreatic insufficiency is also common
Alterations caused by microbial agents – Small intestinal bacterial overgrowth (SIBO)

- deconjugation of bile acids
  - fat and fat soluble vitamin [A,D,E,K] malabsorption (steatorrhea)

- production of toxic metabolites and injury to the enterocytes

- competition with the host for nutrients
  - B12 vitamin deficit

- carbohydrate malabsorption
  - lactose intolerance

- protein malabsorption

Abnormal bacterial proliferation in small intestinal lumen

<table>
<thead>
<tr>
<th>Table 1. Conditions that predispose to small bowel bacterial overgrowth</th>
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</thead>
<tbody>
<tr>
<td>Old age (particularly with physical disability)</td>
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<tr>
<td>Hypochlorhydria (endogenous or induced by proton pump inhibitors or ( H_2 ) blockers)</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
</tr>
<tr>
<td>Resection of the ileal-cecal valve</td>
</tr>
<tr>
<td>Surgical blind loops (e.g., end-to-side anastomosis)</td>
</tr>
<tr>
<td>Anatomic disruptions leading to intestinal dysmotility and stasis (following massive bowel resection; bowel strictures; adhesions)</td>
</tr>
<tr>
<td>Partial or total gastrectomy</td>
</tr>
<tr>
<td>Crohn’s disease → Bacterial translocation</td>
</tr>
<tr>
<td>Celiac sprue → Bacterial translocation</td>
</tr>
<tr>
<td>Intestinal diverticular disease</td>
</tr>
<tr>
<td>Enterocutaneous fistula</td>
</tr>
<tr>
<td>Impaired peristalsis caused by above gastrointestinal conditions or chronic intestinal pseudo-obstruction; diabetes mellitus; Parkinson’s disease; or neuropathic, myopathic, infectious, autoimmune, or metabolic disease</td>
</tr>
<tr>
<td>Hepatic cirrhosis → Bacterial translocation</td>
</tr>
<tr>
<td>Malnutrition- or illness-associated immunodeficiency</td>
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</tbody>
</table>

SIBO – Diagnosis: Hydrogen breath test

„Gold standard”: culture of jejunum aspirate for bacterial count
- $> 10^4$ or $10^6$ CFU/ml
- colonic type bacteria (GNB aerob, anaerob)

invasive, time-consuming, technical difficulties, contamination, missing distal SIBO

<table>
<thead>
<tr>
<th>Indication</th>
<th>Substrate</th>
<th>Recommended Challenge Dose</th>
<th>Positive Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected small intestinal bacterial overgrowth</td>
<td>Lactulose</td>
<td>10 grams</td>
<td>Baseline $H_2$ or $CH_4 &gt; 20$ ppm Or A double peak in $H_2$ or $CH_4$ levels Or Early rise in $H_2$ or $CH_4 &gt; 20$ ppm Or Incremental increase in $H_2$ or $CH_4 &gt; 10$ ppm in consecutive samples</td>
</tr>
<tr>
<td>glucose</td>
<td>50-75 grams</td>
<td></td>
<td>Baseline $H_2$ or $CH_4 &gt; 20$ ppm Or Rise in $H_2$ or $CH_4$ by 12-15 ppm</td>
</tr>
</tbody>
</table>
## SIBO – Treatment

- Treatment of predisposing condition(s)
- Correct nutritional state and vitamin deficiency
- Suppression of abnormal colonization
  (broad-spectrum antibiotics are effective against Gram-negative and anaerob bacteria)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Period</th>
<th>Outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin (800 mg/day), amoxicillin-clavulanic acid (1500 mg/day)</td>
<td>N=10</td>
<td>7-day (five times)</td>
<td>Breath-expired H(2) volume decreased&lt;br&gt;Significant reduction in stool frequency</td>
<td>Gastroent (1999)</td>
</tr>
<tr>
<td>rifaximin, 1200 mg/day (a non-absorbable rifamycin derivative)</td>
<td>N=21</td>
<td>7-day</td>
<td>Normalization of H2 breath test (70%)</td>
<td>Aliment Pharmacol Ther. (2000)</td>
</tr>
<tr>
<td>metronidazole 1000 mg ciprofloxacin 1000 mg</td>
<td>N=29</td>
<td>10-day</td>
<td>Improvement of intestinal symptoms: bloating (85% -83%), stool softness (44% - 50%), abdominal pain (50% -43%).</td>
<td>Aliment Pharmacol Ther. (2003)</td>
</tr>
</tbody>
</table>
Amyloidosis:
- autonomic neuropathy of enteric nervous system and myopathy → alterations of intestinal transit, SIBO
- amyloid deposits → barrier disruption, ischemia

Systemic sclerosis:
- common (50-90%) and affects many site of GI tract
- typically results from the fibrosis (collagen deposition)
- impaired intestinal motility, digestion, absorption and excretion
- reduce hematic flow, lymphatic obstruction

Autonomic neuropathy: typical of diabetes mellitus (! poor blood glucose control)
- gastroparesis (postprandial gastric stasis) (5-12%) (female> male)
- intestinal enteropathy (small bowel stasis) (4-22%)
  (diarrhea, constipation, fecal incontinency)
! exclude: drug related causes; check: thyroid hormonal function
Miscellaneous II.

- **Zollinger-Ellison syndrome (gastrinoma):**
  hypergastrinaemia $\rightarrow$ acid hypersecretion $\rightarrow$ reduction in gastric pH $\rightarrow$ enzyme inactivation (pancreatic lipase)

- **Atrophic gastritis (H. pylori or autoimmune):**
  - achlorhydria:
    - iron-deficiency anemia (conversion from ferric iron into ferrous form $\rightarrow$ reducing iron absorption)
    - SIBO
  - decreased availability of intrinsic factor:
    - megaloblastic anemia & possible neurological dysfunction (B12 vitamin deficiency)

- **Medicines:**
  - acarbose (selective inhibition of $\alpha$-glucosidase)
  - colchicine – damage of intestinal mucosa (villous atrophy, reversible deficit of lactase)
  - orlistat (selective inhibition of pancreatic lipase)
Miscellaneous III.

- **Hyperthyreoidism:**
  Accelerated intestinal transit → inadequate mixing among nutrients and digestive juices, reduces time of contact with the intestinal mucosa (diarrhea, steatorrhea)

- **Aging:**
  Reduced absorption (carbohydrates and amino acids) without typical histological small bowel alteration
  - Decreased number of sugar and amino acid transporters
  - Reduced enzyme activity (lactase, sucrase)
  - Increased risk of SIBO (atrophic gastritis, PPI use, GI motility disorders)
  - Vascular alterations (chronic mesenteric ischemia, chronic heart failure)

- **Neurofibromatosis**
  Periampullary, duodenal, pancreatic cancer (pancreatic insufficiency, biliary obstruction)
  Mesentery infiltration – vascular and lymphatic obstructions