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M2 GI Sequence

Malabsorption of Nutrients

Rebecca W. Van Dyke, MD
Learning Objectives

- At the end of this lecture on malabsorption, students should be able to:
- 1. Identify the major pathophysiological mechanisms responsible for generalized malabsorption and malabsorption of specific nutrients.
- 2. Construct a differential diagnosis for a patient with suspected malabsorption with items listed in the order of relative likelihood.
- 3. Identify the most appropriate tests to identify malabsorption of specific nutrients.
Gastrointestinal Tract

A series of organs connected in series to the outside world whose function is:

1. Efficient uptake from a mixed intake of sufficient amounts of fuel (hexoses, amino acids, fatty acids) and essential chemicals (i.e., those that cannot be synthesized).

2. Exclusion other, potentially harmful, organic and inorganic compounds and infectious agents.

This process is not normally perfect, however malabsorption is the clinical state in which digestion/absorption are impaired sufficiently to lead to clinical symptoms.
Normal Digestion and Absorption

These phases of digestion are reviewed and defined in the textbook.
Efficiency of Small Bowel Absorption: not perfect

• Nutrients
  – Fat 93-95% of triglyceride
  – Starch 80-95% depending on type
  – Disaccharides 96-98%
  – Protein 95-99%

• Minerals
  – Iron 6-20% depending on body iron status
Intestinal Reserve: excessive capacity is built-in

- Several processes/enzymes are present for some digestive processes
  - Pancreatic and brush-border oligosaccharidases and proteinases
- Pancreas secretes an excess of enzymes
- Surface area for absorption is in excess
- Colon scavenges malabsorbed carbohydrates as short chain fatty acids, products of bacterial fermentation
Colon Salvage of Malabsorbed Carbohydrate

\[ R-\text{COO}^- + \text{CO}_2 \rightarrow R-\text{COOH} \]

Fermentation

\[ \text{CHO} \rightarrow \text{Na}^+ \rightarrow \text{H}_2\text{O} \]
Malabsorption = input – absorption
Relationship between Diarrhea and Malabsorption
Malabsorption: Relationship to Diarrhea

**LOSS OF INGESTED MATERIALS IN STOOL**

- **BOWEL DISEASE**
  - Normal nutrients not absorbed

- **ORAL INTAKE OF SUBSTANCES**
  - The bowel cannot absorb
    - Magnesium
    - Sorbitol
    - Lactulose

Either process may generate diarrhea if:
1. Enough osmotically active molecules reach the colon
2. Malabsorbed molecules stimulate colon/SB ion secretion (long-chain fatty acids, bile acids)
Clinical Clues to Nutrient Malabsorption

Weight loss, fatigue, “out of gas”
Intake of excess calories without weight gain
Diarrhea: bulky, oily stools (fat)
          liquid stools (carbohydrates)
Excess flatus
Evidence of vitamin/mineral deficiencies
  glossitis, cheilosis (iron/B vitamins)
  acrodermatitis (zinc)
  dry skin and hair (essential fatty acids)
  anemia microcytic - iron deficiency
      macrocytic - folate/B-12 deficiency
  osteopenia/osteoporosis Vit D/calcium
  night blindness Vitamin A
  easy bruising Vitamin K
Steatorrhea
Angular Cheilosis

Deficiencies:
- Vitamin B-12
- Iron
- Folate
- B vitamins
Glossitis

Deficiencies of:
- Vitamin B-12
- Iron
- Folate
- Niacin
Red tongue with burning sensation

B-12 deficiency with hypersegmented PMNs
Zinc Deficiency

Acrodermatitis

Chronic zinc deficiency resulting in chronic eczematous eruption.
Acrodermatitis

Loss of hair, skin rash and diarrhea due to zinc deficiency
Normal digestion: a play in 3 acts

- **Luminal digestion** (pancreatic enzymes)

- **Mucosal digestion** (small bowel brush border enzymes)

- **Mucosal absorption** (small bowel mucosa, lymphatics)
Examples of Malabsorption

- **Luminal Maldigestion:** Fat
  - Chronic pancreatitis (Dr. Anderson)

- **Mucosal Maldigestion:** Disaccharide
  - Lactase deficiency

- **Mucosal Maldigestion/Malabsorption:** Generalized malabsorption
  - Celiac sprue
  - Bacterial overgrowth
Luminal Digestion of Fat

• Requires pancreatic lipases

• Requires conjugated bile acids (salts) from the liver

• No small intestinal back-up available
Chronic Pancreatitis: the disease

- Often due to long-standing alcohol use
- Marked destruction of ducts/acini
- Reduced secretion of digestive enzymes, fluid, bicarbonate
- Lipases most affected
- Anatomic damage assessed by ERCP or endoscopic ultrasound (EUS) or pancreatic calcifications on x-rays
Bile duct

Pancreatic duct
ERCP view of Chronic Pancreatitis

Endoscopic Retrograde CholangioPancreatography

Single arrow points to bile duct compressed by fibrotic pancreas

Double arrow points to dilated pancreatic duct with short stubby side branches
Chronic Pancreatitis: Manifestations

- Weight loss
  - Malabsorption of fat due to loss/inactivation of pancreatic enzymes
- Bulky, oily stool
  - Steatorrhea is predominant abnormality
  - Loss of protein/carbohydrate in stool is much less as back-up mechanisms exist for protein/carbohydrate digestion
- Fat soluble vitamin deficiency may occur in long-standing severe cases
- Edema/hypoproteinemia
  - Due to malnutrition with decreased hepatic synthesis of albumin/serum proteins
Relationship between Pancreatic Function and Steatorrhea

Pancreatic Function (%)

Fecal Fat (g/day)
Malabsorption due to Luminal Maldigestion of Fat: Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic insufficiency:</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Bile salt deficiency:</td>
<td>Loss of terminal ileum:</td>
</tr>
<tr>
<td></td>
<td>loss of bile salts in stool</td>
</tr>
<tr>
<td></td>
<td>insufficient bile salts</td>
</tr>
<tr>
<td>Bacterial overgrowth:</td>
<td>Deconjugation and loss of bile acids</td>
</tr>
<tr>
<td>Gastric hypersecretion:</td>
<td>Acid inactivation of pancreatic enzymes</td>
</tr>
</tbody>
</table>
Examples of Malabsorption

• Luminal Maldigestion: Fat
  – Chronic pancreatitis

• Mucosal Maldigestion: Disaccharide
  – Lactase deficiency
  – Any malabsorbed carbohydrate

• Mucosal Maldigestion/Malabsorption: Generalized malabsorption
  – Celiac sprue
  – Bacterial overgrowth
Lactase Deficiency

• Lactase: enterocyte brush-border disaccharidase found in nursing mammals.

• Lactase splits lactose in milk to the monosaccharides glucose and galactose for absorption.

• Normally little of the enzyme is made by villus enterocytes after weaning
  – exceptions are groups of humans who exhibit unusual persistence of lactase throughout adulthood
  – northern Europeans and other "dairying" cultures

• Symptoms occur upon ingestion of lactose by lactase-deficient individuals.
Lactase-Deficient Patient with low activity enzyme other individuals may also downregulate genes, etc.

A
Protein stained
Protein present

B
Lactase activity stained
Poor enzyme activity
To understand flatus, one must understand the bacterial inhabitants of the gut.

Adapted from Mariana Ruiz Villarreal (LadyofHats), Wikimedia Commons
Mechanism of Lactose-Induced Diarrhea and Flatus

Lactase-sufficient people absorb >80% of lactose

Lactase-deficient people absorb <50% of lactose

6-20 grams malabsorbed lactose = flatus
(1 g = 44 ml H₂)

>20 grams malabsorbed lactose = flatus+diarrhea

Small bowel

Colon

Lactose → Glucose, Galactose → Lactose

Lactose → SCFA, CO₂ + H₂, lactose, glucose, galactose

FLATUS → OSMOTIC DIARRHEA
Examples of Malabsorption

- Luminal Maldigestion: Fat
  - Chronic pancreatitis
- Mucosal Maldigestion: Disaccharide
  - Lactase deficiency

- Mucosal Maldigestion/Malabsorption: Generalized malabsorption
  - Celiac sprue
  - Bacterial overgrowth
Celiac Sprue I

• Immune-mediated destruction of enterocytes in response to ingestion of the protein gluten found in wheat and certain other grains. A fraction termed gliadin contains the immunogenic material.

• Small intestinal villi are damaged or destroyed - "flat gut" appearance.

• Mature digesting and transporting enterocytes are virtually absent.
Celiac Sprue - II

- Patchy disease - usually affects proximal intestine more than distal intestine (? why).

- Mucosal digestion and absorption are both severely impaired.

- Characteristic antibodies used in diagnosis: IgA antibodies to tissue transglutaminase or gliadin.

Pathophysiology of Celiac Sprue
Stereomicroscopic view of small bowel biopsies:
Normal (below)
Celiac sprue (right)

87 Normal dissecting microscope appearances of finger-like villi.

94 Flat jejunal biopsy under dissecting microscope showing no villi and only crypts in coeliac disease.
Small Bowel Biopsies

Normal

Celiac Sprue

Villi and mature enterocytes destroyed
Deep crypts (arrows)
Inflammation
Clinical Manifestations of Sprue

- Weight loss, often with increased appetite
- Bulky, oily stools – steatorrhea - fat malabsorption
- Flatus/frothy stools – carbohydrate malabsorption
- Anemia – deficiencies of iron, folate
- Osteopenic bone disease – Vitamin D and calcium malabsorption
- Edema/hypoproteinemia – protein deficiency and malnutrition
- Cheilosis and glossitis – B vitamin deficiencies
Malabsorbed Nutrients in Celiac Sprue

The degree of malabsorption depends on the severity and extent of the disease: how much of the small bowel is affected and how severely?

- Iron (why is this so??)
- Fat
- Fat-soluble vitamins
- Carbohydrate
- Protein
- Water-soluble vitamins
- Other minerals
- (Bile acids - rarely)
# COMPARISON OF MALABSORPTION

Celiac Sprue versus Pancreatic Insufficiency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pancreatic Insufficiency</th>
<th>Celiac Sprue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatorrhea (gm/day)</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>Anemia</td>
<td>0%</td>
<td>21%</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>0%</td>
<td>10-20%</td>
</tr>
<tr>
<td>Tetany (low calcium)</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>Bleeding (low Vit K)</td>
<td>uncommon</td>
<td>25%</td>
</tr>
<tr>
<td>Low serum protein</td>
<td>14%</td>
<td>71%</td>
</tr>
</tbody>
</table>

These are examples only and the actual numbers depend on severity of the respective disease.
## Bacterial Overgrowth: Background

### Distribution of Intestinal Flora

<table>
<thead>
<tr>
<th>Predominant organisms</th>
<th>Concentration (per gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obligate anaerobes Streplococci</td>
<td>$&gt;10^6$</td>
</tr>
<tr>
<td>Staphylococci Neisseria</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>$10^2$</td>
</tr>
<tr>
<td>Lactobacilli Streptococci</td>
<td>$&lt;10^4$</td>
</tr>
<tr>
<td>Anaerobes Bacteroides Coliforms</td>
<td>$10^6$</td>
</tr>
<tr>
<td>E. coli</td>
<td>$10^9$</td>
</tr>
<tr>
<td>Streptococci Candida Protozoa</td>
<td>$10^{11}$</td>
</tr>
</tbody>
</table>
Anatomical Causes of Small Intestinal bacterial Overgrowth

• Stricture
• Blind pouch
• Entero-enteric anastomosis
• Afferent loop syndrome
• Jejunal diverticula
• Small intestinal dysmotility diseases
Bacterial Overgrowth-I

• Definition: overgrowth of bacteria in small bowel due to anatomic or motility factors.

• Clinical consequences:
  – Deconjugation of bile acids by bacterial enzymes
    • Loss of deconjugated bile acids in stool
    • Decreased bile acid pool - not enough for lipid digestion/absorption
  – Damage to enterocytes by bacteria
Bacterial Overgrowth-II

• Clinical consequences:
  – Intraluminal consumption of nutrients by bacteria (competition)
    • Carbohydrates, amino acids
    • Vitamin B-12, iron
  – Damage to small bowel enterocytes causing a sprue-like histologic appearance
  – Mild to severe generalized malabsorption
INVESTIGATION OF MALABSORPTION

1. Consider possibility of malabsorption based on clinical clues

2. Identify nutrient deficiencies

3. Document impaired digestion and/or absorption of nutrients

4. Identify causative process and treat appropriately
Approach to Thinking about Malabsorption

1. How many nutrients?
   - Single nutrient (i.e., Vitamin B-12)
   - Subset of nutrients (i.e., fats)
   - Generalized malabsorption (i.e., several nutrients)

2. What type of nutrient?
   - Fat, carbohydrate, protein, vitamins, minerals or combinations

3. Pathophysiologic process likely to be involved?
   - Luminal maldigestion
   - Mucosal maldigestion
   - Mucosal malabsorption
Tests of Malabsorption: what types are available?

- Screening tests
- Quantitate nutrient malabsorption
- Specific diagnostic tests
Tests of Malabsorption

• Screening tests – simple, cheap, fast
  – Stool smear with fat stain
  – CBC for evidence of anemia
  – Cholesterol/carotene blood levels
  – Stool osmotic gap for carbohydrates
  – Weight loss/clinical clues
Example of a positive (right) and negative (left) Sudan fat stain

Magnification = 400 X

NEGATIVE

POSITIVE
Tests of Malabsorption

• Quantitate nutrient malabsorption: messy, take time, accurate and quantitative
  – 72-hour fecal fat
  – D-xylose excretion (monosaccharide)
  – Schilling’s test for B-12 absorption (no longer available)
  – Breath hydrogen test (carbohydrate)
72-hour Fecal Fat Test

Fat input = 100 g/day

Fat Absorption

Malabsorbed fat: Normal < 7 g/day
100 Gram Fat Diet

- Butter/Margarine
  - 1 pound = 453 grams
  - 1 stick = 113 grams

Average US diet = ~30-40 grams fat/day
Add ~ 1/2 stick butter/margarine per day to make a ~100 gram fat diet

72 hour Fecal Fat Test
- Eat the equivalent of ~1/2 stick of butter/margarine per day for 4-6 days
- Collect stool for the last 3 days in tightly sealed container
- Assay for total stool weight, fat content
D-xylose

Monosaccharide used to measure mucosal absorption of sugars

Administer 25 grams orally
Draw blood sample at 2 hours
Collect urine for 5 hours
Analyze d-xylose in blood and urine
Fate of d-xylose in the body

d-xylose consumed

50% absorbed in gut

50% excreted

25% released into general circulation

25% hepatic metabolism

25% excreted via kidney

measure blood level (>20 mg/dL)

measure fraction of ingested dose excreted (>22%)
This test is no longer available as no one makes the radio-labeled cobalt anymore.

**Basis of the Schilling's Test for Vitamin B-12 Malabsorption**

For test to work:
1. Give IV vit B-12 to load body stores.
2. Renal function must be good.
3. Urine is collected for 24 hours.

Absorbed B-12 is preferentially taken up by body stores (liver)

Excess is excreted in urine and can be quantitated
Hydrogen Breath Test for Carbohydrate Malabsorption

- **Principle:**
  - malabsorbed sugar passes into colon
  - bacteria produce hydrogen gas
  - $H_2$ diffuses into blood and is excreted by lungs

- **Practice:**
  - Administer 25-50 grams of glucose or other sugar orally
  - Measure hydrogen in exhaled breath at 2-4 hours

- **Variants:**
  - Other sugars can be employed to test for specific disaccharidase or transporter defects
    - lactase deficiency
    - glucose-galactose malabsorption
Breath H₂ excretion increases after lactose load in lactase deficiency.
**Examples: INTERPRETATION OF TESTS OF MALABSORPTION**

| Fat malabsorption only: | Luminal maldigestion  
pancreatic insufficiency  
bile salt deficiency |
|------------------------|-----------------------|
| Fat and B-12 malabsorption: | Luminal maldigestion due to  
ileal loss of bile salts and bile salt deficiency  
Bacterial overgrowth:  
decomjugation of bile acids  
and bacterial uptake of B-12 |
| (have to involve terminal ileum) | |
| Specific disaccharide  
malabsorption: | Mucosal maldigestion  
disaccharidase deficiency |
| Fat and d-xylose malabsorption: | Mucosal malabsorption  
Celiac sprue  
Tropical sprue  
Bacterial overgrowth  
Severe Crohn’s disease  
Whipple’s disease |
| (+/- B-12 malabsorption  
depending on involvement of TI) | |
Tools for Evaluation of Malabsorption: diagnosis of underlying disease once you have identified a small group of possible diseases.

- Radiographs of the small bowel to delineate anatomy
- Endoscopic retrograde cholangiopancreatography (ERCP) to define the anatomy of biliary and pancreatic ducts
- Pancreatic secretory function tests
- Small bowel biopsy and/or antibody tests for celiac sprue
- Quantitative small bowel bacterial culture, bile acid or glucose breath tests for bacterial overgrowth
Approach to Diagnosis
Algorithm is included in syllabus

Suspicion of Malabsorption
- Diarrhea
- Nutritional deficiencies
- Weight loss
- Excessive food intake

Screening Tests
- Blood Tests (clues to nutritional deficiencies)
  - Albumin
  - Fe/TIBC
  - PT
  - Calcium
  - Carotene
  - Folic acid
  - Vitamin B-12

- Stool Tests (presence of malabsorbed materials)
  - Sudan stain for fat
  - Volume and consistency of stool
  - Reducing substances
  - Fecal leukocytes (rule out inflammatory process)

Specific Tests for Malabsorption
- 72 hour fecal fat
- d-xylose absorption
- H2 breath test
- Pancreatic function tests
- 14C (13C) bile acid breath tests
- Schilling’s test

Diagnostic Tests
- Small bowel biopsy
- Small bowel culture
- Small bowel/pancreatic x-rays
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