MEDICINE

432 Team

25

Chronic Diarrhea and Malabsorption

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

1. To know the definition and different classification of chronic diarrhea.
2. To understand the mechanism of chronic diarrhea
3. To learn a systematic approach of patient with chronic diarrhea.
4. To understand the different mechanisms and causes of malabsorption.
5. To be able to recognize the clinical manifestations of malabsorption and approach to patient with malabsorption.

1) Chronic Diarrhea:

Diarrhea is a common and usually transient symptom

Chronic diarrhea, decrease in fecal consistency lasting for 4 or more weeks

(Weight of stool and frequency are not reliable)

May occur in up to 5% of the population in any given year

Diarrhea is a symptom not a disease and may occur in many different conditions

Note(s):

Diarrhea is a manifestation of a disease not a diagnosis. Just like anemia, it is secondary to something else.

Mechanism of Diarrhea:

Normal:

The gut absorbs most of the fluid that it secretes, and its motility provides a favorable milieu (media) for water, electrolyte and nutrient absorption

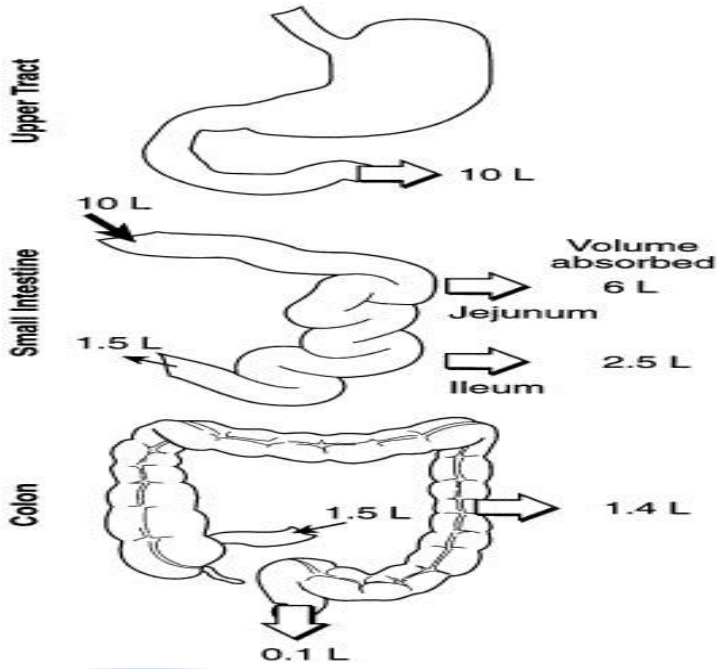
Abnormal:

When infectious agents, toxins or other noxious substances are present within the gut → fluid secretion and motility are stimulated to expel the unwanted material, thereby producing diarrhea

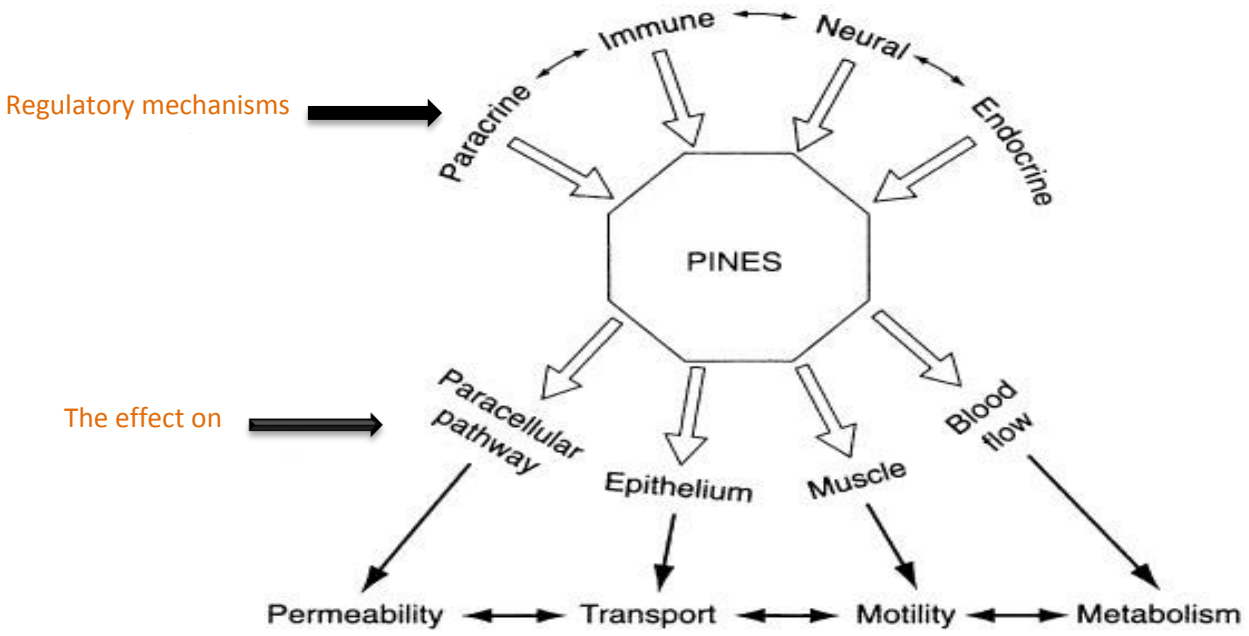
Note(s):

- *Fluid from the gut is around 10 L but what comes out in the stool is around 0.1L so most of the fluid is normally absorbed in the small intestine and part of it is absorbed in the large intestine*

Fluid loads along the gastrointestinal tract:



"PINES" regulatory system in the intestine



Classification:

- Time course (acute vs. chronic)
- Volume (large vs. small)
- Pathophysiology (secretory vs. osmotic)
- Stool characteristics (watery vs. fatty vs. inflammatory)
- Epidemiology (epidemic vs. travel related vs. immunosuppression related)

Secretory Diarrhea:

✓ Clues: Large volume (>1L/D), little change with fasting, normal or low stool osmotic gap

- Bacterial toxins (bacterial infection causing bacterial toxin leading to diarrhea)
- Inflammatory bowel disease:
  - Chron's disease
  - Ulcerative colitis
- Microscopic colitis
  - Collagenous colitis
  - Lymphocytic colitis

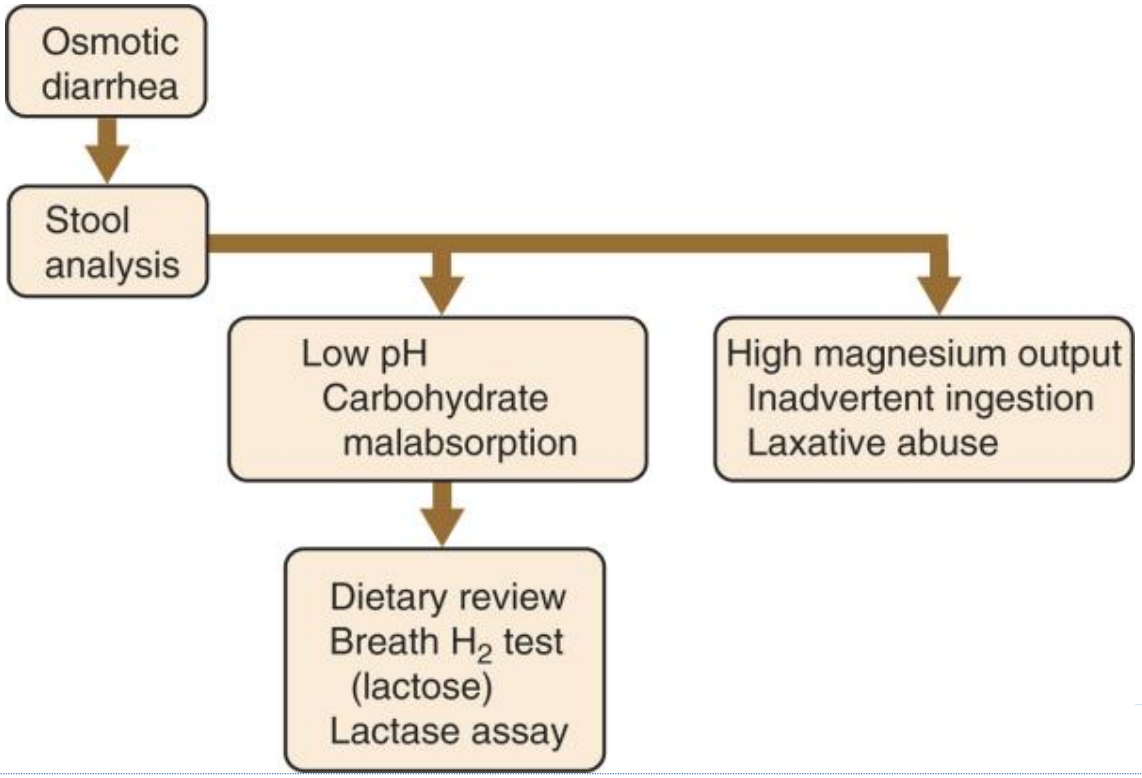
- Vasculitis
- Endocrinoapthies (in general they are not common causes)
  - Addison's disease
  - Carcinoid Syndrome
  - Hyperthyroidisim (diarrhea or hyperdefecation)
  - Medullary carcinoma of the thyroid
  - Pheochromocytoma
  - Gastrinoma, somatostatinoma, VIPoma
- Disordered motility
  - Diabetic autonomic nephropathy
  - Irritable bowel syndrome
  - Post sympathectomy diarrhea
  - Post vagotomy diarrhea
- Ileal bile acid malabsorption (surgery, chron's, lymphoma)
- Laxatives abuse (stimulant laxatives)
- Medications and toxins
- Neoplasia
  - Colon carcinoma
  - Lymphoma
  - Villous adenoma in rectum
- Congenital syndrome (congenital chloridorrhea)
- Idiopathic

Note(s):

Any disease affecting the bowel can lead to diarrhea
Magnesium and phosphorus types of laxative can give you osmotic diarrhea rather than secretory

Osmotic Diarrhea:

Reduced by fasting and increased osmotic gap



Inflammatory Diarrhea:

- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease
- Infectious diseases
  - Invasive bacterial infections (e.g. tuberculosis, yersinosis)
  - Invasive parasitic infections (e.g. amebiasis, strongyloidiasis)
  - Ulcerating viral infections (e.g. cytomegalovirus, hepres simples virus)
  - Pseudomembranous colitis (e.g. clostridum difficile infection)
- Ischemic colitis
- Radiation colitis
- Neoplasia
  - Colon cancer
  - Lymphoma

Fatty diarrhea: (Steatorrhea)

- Malabsorption syndromes:
  - Mucosal diseases
  - Short bowel syndrome post resection diarrhea
  - Small bowel bacterial over growth
  - Mesenteric ischemia
- Maldigestion:
  - Pancreatic exocrine insufficiency
  - Inadequate luminal bile acid

Note(s): important

Steatorrhea is the presence of fat or lipids in the stool and is hard to flush and floats and is malodorous also greasy.

Common causes of diarrhea:

Developing countries: (usually the infection is high)

- Chronic bacterial, Mycobacterial, Parasitic infections

Then

- Functional disorders
- Malabsorption
- Inflammatory bowel disease

Developed countries

- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)
- Malabsorption syndromes (such as lactose intolerance and celiac disease)
- Chronic infections (particularly in patients who are immunocompromised)

Acute vs. Chronic

- Most of acute diarrhea is due to infectious cause while chronic is due to noninfectious cause (as a general rule)

Approach to patient with diarrhea

- History (always the first thing to do!)
- Physical examination
- Investigations
  - Laboratory tests
  - Radiology
  - Endoscopy
- Management

History: (this is important to always keep in mind when pt. has diarrhea)

- ✓ What led the patient to complain of diarrhea? (e.g. consistency or frequency of stools, the presence of urgency or fecal soiling)
- ✓ Stool characteristics: (e.g. greasy stools that float and are malodorous may suggest fat malabsorption while the presence of visible blood may suggest inflammatory bowel disease)
- ✓ Duration of symptoms, nature of onset (sudden or gradual)
- ✓ Volume of the diarrhea: (e.g. voluminous watery diarrhea is more likely to be due to a disorder in the small bowel while small-volume frequent diarrhea is more likely to be due to disorders of the colon)
- ✓ Occurrence of diarrhea during fasting or at night (suggesting a secretary diarrhea.
- ✓ Weight loss, appetite.
- ✓ Association of symptoms with specific food ingestion. (such as dairy products or potential food allergens)
- ✓ Epidemiological factors, such as travel before the onset of illness, symptoms of nutritional deficiency.
- ✓ A history of recurrent bacterial infections (eg, sinusitis, pneumonia), which may indicate a primary immunoglobulin deficiency.
- ✓ Systems review: The presence of systemic symptoms: (such as fevers, joint pains, mouth ulcers, eye redness)→ IBD, CTD, thyroid.
- ✓ Family history: IBD.
- ✓ Drug Hx: including over the counter mediation.

Note(s):

1) Clarify the patient's definition of diarrhea it might not be actual diarrhea. (Differentiate diarrhea from fecal soiling)
Timing in diarrhea is important because if it is a functional disease not an organic disease it does not present while the patient is sleeping (like, IBS).

Likely cause of diarrhea in certain epidemiologic classifications

- Travelers: bacterial, protozoal, tropical sprue (very rare)
- Diabetics patients
- AIDS patients: infections, drugs
- Hospitalized patients: drugs, infections, ischemia, C.D toxin

Note(s):

In hospitalized patients, Clostridium difficile associated diarrhea is possible, which is called pseudomembranous colitis

Physical Examination:

- Rarely provides a specific diagnosis.
- Findings suggestive of IBD (e.g. mouth ulcers, a skin rash, episcleritis, an anal fissure or fistula, the presence of visible or occult blood on digital rectal examination, abdominal masses or abdominal pain)
- Evidence of malabsorption (wasting, physical signs of anemia, scars indicating prior abdominal surgery)
- Lymphadenopathy (possibly suggesting HIV infection
- Palpation of the thyroid and examination for exophthalmos and lid retraction may provide support for a diagnosis of hyperthyroidism

Investigations:

- CBC
- ESR
- Electrolytes
- Total protein and albumin
- TFT
- Stool: occult blood, C/S (stool culture and sensitivity), ova and parasites C-D toxins (if history is suggestive)

Specific Investigations

The history and physical examination may point toward a specific diagnosis for which testing may be indicated

2) Malabsorption:

Definition: abnormality in absorption of food nutrients across the gastrointestinal tract.

Causes of malabsorption:

- ***Congenital defects (rare):*** in the membrane transport systems of the small intestinal epithelium.
- ***Acquired defects:*** in the epithelial absorptive surface.

Phases of absorption:

- ***Luminal phase:*** dietary fats, proteins, and carbohydrates are hydrolyzed and solubilized by secreted digestive enzymes and bile.
- ***Mucosal phase:*** relies on the integrity of the brush-border membrane of intestinal epithelial cells to transport digested products from the lumen into the cells.
- ***Post-absorptive phase:*** nutrients are transported via lymphatics and portal circulation from epithelial cells to other parts of the body.

Defects in any of the previous phases can result in malabsorption (most commonly the first two phases).

Note(s):

- ***Defects in the luminal phase*** → *intraluminal maldigestion.*
- ***Defects in the mucosal phase*** → *mucosal malabsorption.*
- ***Defects in the post-absorptive phase*** → *post-mucosal lymphatic absorption.*

LUMINAL PHASE

Phase and nature of malabsorptive defect	Example
A. Substrate hydrolysis	
1. Digestive enzyme deficiency	Chronic pancreatitis
2. Digestive enzyme inactivation	Zollinger-Ellison syndrome
3. Dyssynchrony of enzyme release, inadequate mixing	Post Billroth II procedure
B. Fat solubilization	
1. Diminished bile salt synthesis	Cirrhosis
2. Impaired bile secretion	Chronic cholestasis
3. Bile salt de-conjugation	Bacterial overgrowth
4. Increased bile salt loss	Ileal disease or resection
C. Luminal availability of specific nutrients	
1. Diminished gastric acid	Atrophic gastritis - vitamin B12
2. Diminished intrinsic factor	Pernicious anemia - vitamin B12
3. Bacterial consumption of nutrients	Bacterial overgrowth - vitamin B12

Note(s):

- ***Digestive enzyme inactivation:*** *Zollinger-Ellison syndrome (ZES) is caused by a non–beta islet cell, gastrin-secreting tumor of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity, with consequent gastrointestinal mucosal ulceration.*

Hypersecretion ***of acid → deactivation of the small intestinal enzymes (require alkaline media to work) → malabsorption.***

- ***Dyssynchrony of enzyme release, inadequate mixing:*** *in bariatric surgeries (weight loss surgeries) including gastric bypass where malabsorption is induced by connecting the stomach to the jejunum and bypassing the duodenum.*

MUCOSAL (ABSORPTIVE) PHASE

Phase and nature of malabsorptive defect	Example
A. Brush border hydrolysis*	
1. Congenital disaccharidase defect	Sucrase-isomaltase deficiency
2. Acquired disaccharidase defect	Lactase deficiency
B. Epithelial transport	
1. Nutrient-specific defects in transport	Hartnup's disease
2. Global defects in transport	Celiac sprue
(a) decreased absorptive surface area	intestinal resection
(b) damaged absorbing surface	celiac sprue, tropical sprue, giardiasis, Crohn disease, AIDS enteropathy, chemotherapy, or radiation therapy;
(c) infiltrating disease of the intestinal wall	lymphoma and amyloidosis

*This process is sometimes considered as part of the luminal phase.

Note(s):

Hartnup disease *is an autosomal recessive disorder caused by impaired neutral (ie, monoaminomonocarboxylic) amino acid transport in the apical brush border membrane of the small intestine and the proximal tubule of the kidney. Patients present with pellagralike skin eruptions, cerebellar ataxia, and gross aminoaciduria.*

POSTABSORPTIVE, PROCESSING PHASE

Phase and nature of malabsorptive defect	Example
A. Enterocyte processing	Abetalipoproteinemia
B. Obstruction of Lymphatic	Both congenital (e.g. intestinal lymphangiectasia)
	Acquired (e.g. Whipple diseases , lymphoma, tuberculosis),

Clinical features of malabsorption:

- Depends on the cause and severity of the disease.
- Malabsorption may either be global or partial (isolated):
  - ***Global malabsorption:*** results from diseases associated with either diffuse mucosal involvement or a reduced absorptive surface. Example: ***Celiac disease*** in which diffuse mucosal disease "sloughed villi and villous atrophy" can lead to impaired absorption of almost all nutrients.
  - ***Partial or isolated malabsorption:*** results from diseases that interfere with the absorption of specific nutrients. Example: defective cobalamin absorption can be seen in patients with ***pernicious anemia*** or those with disease or resection of the terminal ileum such as patients with ***Crohn's disease.***

SIGNS AND SYMPTOMS OF MALABSORPTION

Malabsorption of	Clinical features	Laboratory findings
Calories	Weight loss with normal appetite	
Fat	Pale and voluminous stool, diarrhea without flatulence, steatorrhea	Stool fat >6 g/day
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, acidic stool pH, milk intolerance, stool osmotic gap	Increased breath hydrogen
Vitamin B12	Anemia, subacute combined degeneration of the spinal cord (early symptoms are paresthesias and ataxia associated with loss of vibration and position sense)	Macrocytic anemia, vitamin B12 decreased, abnormal Schilling test, serum methylmalonic acid and homocysteine increased

SIGNS AND SYMPTOMS OF MALABSORPTION....

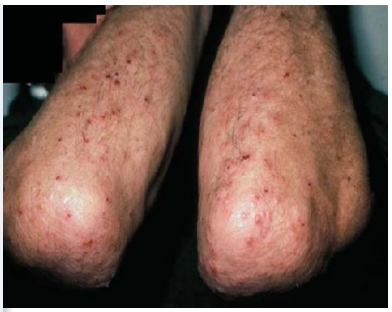
Malabsorption of	Clinical features	Laboratory findings
Folic acid	Anemia	Macrocytic anemia, serum and RBC folate decreased, serum homocysteine increased
Vitamin B, general	Cheilosis, painless glossitis, acrodermatitis, angular stomatitis	
Iron	Microcytic anemia, glossitis, pagophagia	Serum iron and ferritin decreased, total iron binding capacity increased
Calcium and vitamin D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek and Trousseau signs	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum retinol decreased
Vitamin K	Hematoma, bleeding disorders	Prolonged prothrombin time, vitamin K-dependent coagulation factors decreased

Examples of manifestations associated with Celiac disease:

- ***Dermatological manifestations:***
  - *Pale skin*
  - *Dermatitis Herpetiformis:*

Note(s):

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy (GSE). Dermatitis herpetiformis is characterized by grouped excoriations; erythematous, urticarial plaques; and papules with vesicles. The classic location for dermatitis herpetiformis lesions is on the extensor surfaces of the elbows, knees, buttocks, and back.



- ***Neurological manifestations:***
  - *Motor weakness*
  - *Peripheral neuropathy*
  - *Ataxia (may be present)*
  - *The Chvostek sign or the Trousseau sign may be positive due to hypocalcemia:*

Note(s):

1) ***The Chvostek's sign:***
- ***Elicitation:*** *Tapping on the face at a point just anterior to the ear and just below the zygomatic bone.*
- ***Positive response:*** *Twitching of the ipsilateral facial muscles, suggestive of neuromuscular excitability caused by hypocalcemia.*

2) ***The Trousseau's sign:***
- ***Elicitation:*** *Inflating a sphygmomanometer cuff above systolic blood pressure for several minutes.*
- ***Positive response:*** *Muscular contraction including flexion of the wrist and metacarpophalangeal joints, hyperextension of the fingers, and flexion of the thumb on the palm, suggestive of neuromuscular excitability caused by hypocalcemia.*

Investigations of malabsorption:

1) Lab studies:

- ***Hematological tests:***
  - CBC "to detect anemia"
  - Serum iron, vitamin B12 and Folate
  - Prothrombin time
- ***Electrolytes and chemistries:***
  - Hypokalemia, hypocalcemia, hypomagnesemia, and metabolic acidosis.
  - Protein malabsorption may cause hypoproteinemia and hypoalbuminemia.
  - Fat malabsorption can lead to low serum levels of triglycerides, cholesterol.

Note(s):

Q) How can you link the type of anemia to the malabsorption disease?

- Microcytic anemia (Low MCV) → iron deficiency → caused by Celiac or chronic GI blood loss.

- Macrocytic anemia (High MCV) → Vitamin B12/Folate deficiency → caused by Celiac, bacterial overgrowth and parasitic infections.

- ESR which is elevated in Crohn's disease and Whipple disease.

❖ ***Stool analysis:***

- Stool pH may be assessed. Values of <5.6 are consistent with carbohydrate malabsorption.
- Stool Culture and Sensitivity → "detect clostridium difficile in pseudomembranous colitis"
- Pus cells in the stool "invasion of the epithelium" → IBD, infection.
- Fat in the stool → pancreatic insufficiency, celiac.

❖ ***Tests of fat malabsorption:***

- For a quantitative measurement of fat absorption, a 72-hour fecal fat *collection*
- Qualitative test Sudan III stain of stool (less reliable)

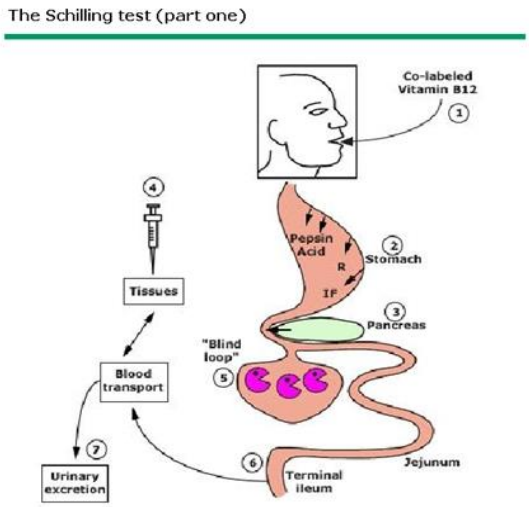
❖ ***The Schilling test:***

Malabsorption of vitamin B-12 may occur as a consequence of:

- Deficiency of intrinsic factor (eg, pernicious anemia, gastric resection)
- Pancreatic insufficiency, bacterial overgrowth.
- Ileal resection or disease.

Schilling test stages:

- Stage I: Oral vitamin B12
- Stage II: Oral vitamin B12 + intrinsic factor (IF)
- Stage III: Oral vitamin B12 + IF + oral antibiotics



Note(s):

The Schilling test: *used to determine whether the body absorbs vitamin B12 normally.*

How the test is performed:
This test may be done in four different stages to find the cause of a low vitamin B12 level.

Stage I: *Patient is given two doses of vitamin B12 (cobalamin). A small, first dose (a radioactive form of B12) by mouth. A second, larger dose by a shot 1-hour later. Then, collect the patient's urine over the next 24 hours. The urine is checked to see if there is normal absorption of Vitamin B12. If Stage I is abnormal, Stage II may be done 3 to 7 days later.*

Stage II: *radioactive B12 along with intrinsic factor. Intrinsic factor is a protein produced by cells in the stomach lining. The body needs it so the intestines can absorb vitamin B12.*

Stage II of the test can tell whether a low vitamin B12 level is caused by problems in the stomach, preventing it from producing intrinsic factor. If Stage II is abnormal, a Stage III test is done.

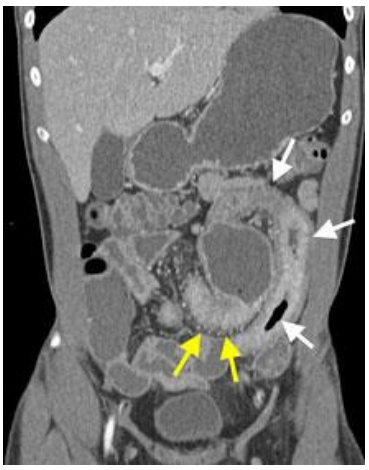
Stage III: *This test is done after the patient has taken antibiotics for 2 weeks. It can tell whether abnormal bacterial growth has caused the low vitamin B12 levels.*

Stage IV: *This test determines whether low vitamin B12 levels are caused by problems with the pancreas. With this test, the patient takes pancreatic enzymes for 3 days. Then, a radioactive dose of vitamin B12.*

- ***Bacterial overgrowth:***
  - *Bacterial overgrowth cause an early rise in breath hydrogen*
  - *Diagnosed by jejunal culture.*
  - *14c D–xylose breath test, high sensitivity and specificity*
- ***Serology:***
  - *No serologic tests are specific for malabsorption*
  - *Serum Anti-TTG and antiendomysial antibodies can be used to help diagnose celiac sprue*
  - *Serum IgA to rule out IgA deficiency*
  - *Determination of fecal elastase and chymotrypsin (2 proteases produced by the pancreas) can be used to try to distinguish between pancreatic causes and intestinal causes of malabsorption*

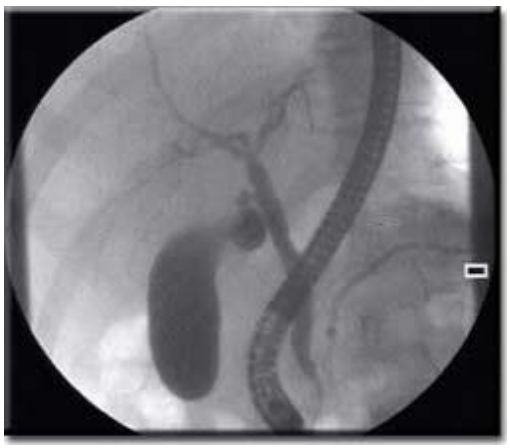
Note(s):

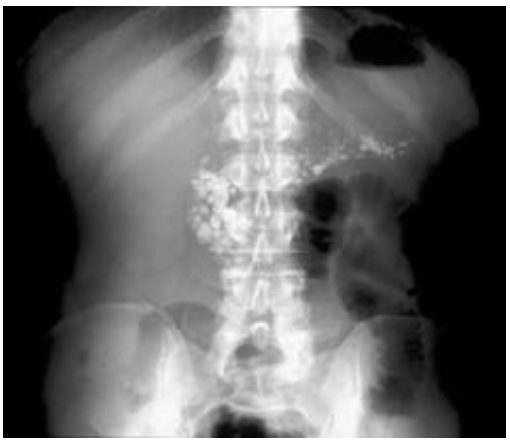
- *Anti-TTG and antiendomysial antibodies are IgA antibodies.*
- *It's important to rule out IgA deficiency by measuring the patient's serum IgA levels because this condition could give false negative results.*
- *Anti-TTG, antiendomysial antibodies and antigliadin (IgG) play an important role in diagnosing celiac diseases.*



2) Imaging studies:

- ***Small bowel barium studies:***
  - Strictures
  - Mucosal changes
  - Diverticula "where bacterial overgrowth can occur"
- ***CT scan of the abdomen:***
  - Strictures
  - Mucosal changes
  - Diverticula
  - Masses, lymph nodes.
- ***Endoscopic Retrograde CholangioPancreatography (ERCP):***
  - Biliary diseases
  - Calcification of pancreas in chronic pancreatitis
- ***Plain abdominal x-ray:***
  - Pancreatic calcification in chronic pancreatitis



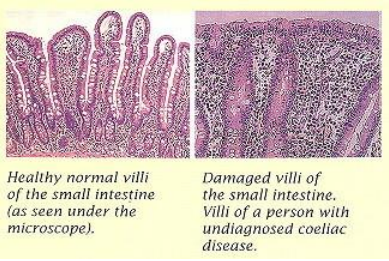


3) Endoscopy:

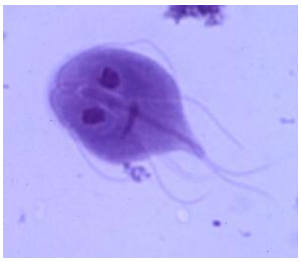
- ***Upper endoscopy with small bowel mucosal biopsy:***

Examples:

- *Celiac sprue*
- *Giardiasis*
- *Crohn's disease*
- *Whipple's disease*
- *Amyloidosis*
- *Lymphoma*



Healthy normal villi of the small intestine (as seen under the microscope). *Damaged villi of the small intestine. Villi of a person with undiagnosed coeliac disease.*



- ***Lower GI endoscopy for colonic and terminal ileal pathologies:*** *Crohn's disease*

Treatment:

- ***Treatment of causative disease:*** *"depends on the etiology"*
  - *A gluten-free diet helps treat celiac disease.*
  - *Similarly, a lactose-free diet*
  - *Protease and lipase supplements are the therapy for pancreatic insufficiency.*
  - *Antibiotics are the therapy for bacterial overgrowth*
  - *Corticosteroids, anti-inflammatory agents, such as mesalamine, and other therapies are used to treat CD.*
- ***Nutritional support:***
  - *Supplementing various minerals calcium, magnesium, iron, and vitamins*
  - *Caloric and protein replacement also is essential.*
  - *Medium-chain triglycerides can be used for lymphatic obstruction.*
  - *In severe intestinal disease, such as massive resection and extensive regional enteritis, parenteral nutrition may become necessary*

Cases:

- ***Case #1: A 30 year old man presented with right iliac fossa pain associated with diarrhea for 5 months and weight loss. What is your differential diagnosis?***
  - *Most likely: Crohn's disease and lymphoma.*
- ***Case #2: A 26 year old female with bloody diarrhea for 8 weeks.***
  - *Key questions that need to be asked:*
    1) *Weight loss → suggests malignancy*
    2) *Fever → suggests infection*
- ***Case #3: A 22 year old female with anemia only.***
  - *Ask about:*
    Nutrition, diarrhea, blood loss… etc.
  - *Check for the type of anemia:*
    1) *Macrocytic → diseases in terminal ileum*
    2) *Microcytic → diseases in the upper GIT*
  - *If her anemia happens to be microcytic hypochromic anemia → iron deficiency anemia*
  - *Most likely: Celiac disease "sometimes the only manifestation is anemia".*

SUMMARY

1. Chronic diarrhea: decrease in fecal consistency lasting for 4 or more weeks, it is mostly due to noninfectious causes.
2. Secretory diarrhea: large volume of diarrhea that shows little change with fasting, and has a normal or low osmotic gap. Osmotic diarrhea: reduced by fasting and has an increased osmotic gap.
3. Causes of malabsorption could be a result of congenital defects (rare) or acquired defects.
4. There are three phases of absorption:
   A) Luminal phase
   B) Mucosal phase
   C) Post-absorptive phase
5. Defects in any of these phases can result in malabsorption (the first 2 phases are the most commonly affected)
6. An example of luminal phase defects is Zollinger-Ellison syndrome which causes hypersecretion of acid → deactivation of small intestinal enzymes → malabsorption
7. Clinical features of malabsorption depend on the cause and severity of the disease.
8. Types of malabsorption:
   A) Global
   B) Partial
9. Serological tests of Celiac include: Anti-TTG, antiendomysial antibody and antigliadin.

Questions

1) Which of the following causes osmotic diarrhea?

a. Cholera
b. Crohn's disease
c. Lactase deficiency
d. Pancreatic exocrine insufficiency

2) A gluten-free diet is the treatment of:

a. Crohn's disease
b. Celiac disease
c. Whipple disease
d. Tropical sprue

3) The most common cause of acute diarrhea is:

a. Infections
b. IBS
c. Addison's disease
d. Ulcerative colitis

432 Medicine Team Leaders

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Answers:

1st Questions: C

2nd Questions: B

3rd Questions: A