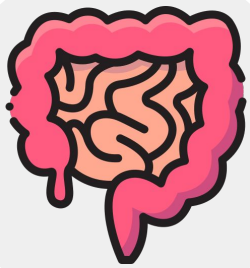
MED439

Medicine Team 439

REVISED BY MISHAL ALTHUNAYN & MUNEERAH ALSADHAN

Editing file

Chronic diarrhea



Online MedEds High-Yield Brilliant Summary!

Objectives :

★ **To have an overview regarding chronic diarrhea:**
- **Definition.**
- **Pathophysiology.**
- **Classification.**
- **Approach.**

I don't ask about the first part of the lecture, it's beneficial in understanding diarrhea

★ **To discuss common causes of chronic diarrhea:**
- **Celiac Disease.**
- **Whipple Disease.**
- **Tropical Sprue.**
- **Small Bowel Bacterial Overgrowth.**
- **Exocrine Pancreatic Insufficiency.**
- **Bile Salt-Induced Diarrhea.**

This list of diseases are what you need to know and read about, unless the department write different questions, that's what I will ask you about

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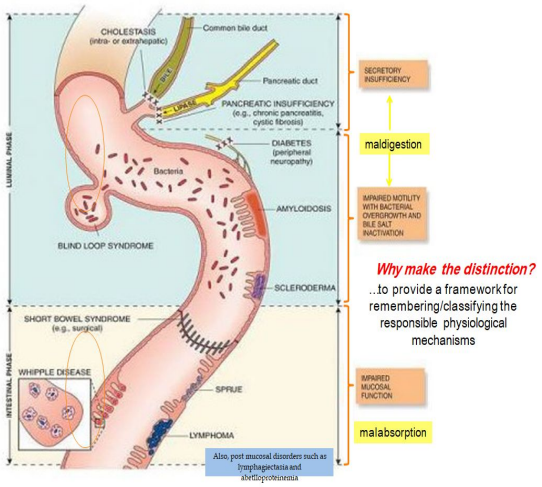
Diarrhea

◀ Definitions

- ➔ **Diarrhea[1]:** A change in consistency (subjectively become loose) or volume of liquid in the stool or increased frequency.
- ➔ **Acute Diarrhea:** <2 wks (Usually due to infectious causes)
- ➔ **Subacute Diarrhea:** 2-4wks
- ➔ **Chronic Diarrhea[2]:** >4-6 wks (Usually autoimmune diseases)
- ➔ **Maldigestion:** Inadequate **breakdown** of large molecules.
- ➔ **Malabsorption:** Inadequate mucosal **transport** of digested products to the blood stream



◀ Pathophysiology

Each day, **9–10L** of fluid enter the jejunum. **Small intestine absorbs 90%** of this **fluid** load.

The **colon** absorbs 90% of the **remaining** load (about 900 ml/24 hours); leaving approximately **80–100 ml excreted each day in feces**. (normal)

A normal colon can **compensate** (if there is diarrhea) by absorbing up to **3000–4000** ml/24 hours. the colon can't adapt for more than 4L

So, Which one will cause LARGE VOLUME diarrhea; Small or large bowel disease?
Small bowel, because normally it absorb most of the fluid (9L)

◀ Classification of Diarrhea

- **Diarrhea**
  - **Non-inflammatory**
    - **Fatty**
    - **Watery**
      - Secretory
      - Osmotic
  - **Inflammatory**

OVERVIEW:
- Sudden onset of bowel frequency associated with crampy abdominal pains, and a fever, will point to an infective cause.
- bowel frequency with loose, blood-stained stools to an inflammatory basis
- The passage of pale, offensive stools that float, often accompanied by loss of appetite and weight loss, to steatorrhoea.

1. Let's assume that someone is used to have a bowel movement once every three days (which is within normal) and now he is having two bowel movements per day (which is still within normal) then this can also be considered diarrhea according to what's he's used to.
2. Chronic diarrhea can also be caused by infections sometimes (more likely atypical organisms, parasitic infection and fungi in immunocompromised pts).

Common medications and toxins associated with diarrhea

- **Acid-reducing agents (H2 blockers, PPIs).**
- Magnesium-containing antacids.
- **Antiarrhythmics** (eg, digitalis, quinidine).
- **Antibiotics.**
- Antineoplastic agents.
- Antiretrovirals.
- **Beta blockers.**
- Colchicine.
- **Levothyroxine.**
- **SSRIs**.
- **Furosemide.**
- Metformin.
- **NSAIDs**, ASA.
- Prostaglandin analogs (ie, misoprostol).
- Theophylline.
- Amphetamines.
- **Caffeine[1].**
- Alcohol.
- **Narcotic/opioid withdrawal.**
  - Narcotic it self can cause constipation, after withdrawal Diarrhea.

1) Watery Diarrhea

a. Osmotic Diarrhea

- Poorly absorbed substances that **remain** in the lumen of the intestine and obligate **retention of water** within the lumen by virtue of their **osmotic effects**
- Osmotic diarrhea is **RELIEVED** by fasting (or NPO)
- Fecal osmotic Gap = 290 - 2(stool Na + stool k)
  - **>50 mOsm/Kg** is Suggestive of an osmotic diarrhea
  - **>100 mOsm/Kg** is more specific (Definitive!)

Ingestion of poorly absorbed agent

- **Carbohydrate malabsorption:** diet high in Fructose or sugar alcohols
- **Diuretics:** Mannitol
- **Osmotic laxatives:** Magnesium, phosphate, sulfate, sorbitol, lactulose

Loss of nutrient transporter

- **Lactose intolerance (due to lactase deficiency)**
- **Disaccharidase deficiency**
- **Glucose-galactose malabsorption**

1. We ask people with IBS to limit their caffeine consumptions because it increases motility resulting diarrhea.

1) Watery Diarrhea

b. Secretory Diarrhea[1]

- There is both active intestinal secretion of fluid and electrolytes, and decreased absorption.

How to differentiate between Osmotic and Secretory ?

1) **Diagnostic fast test:** Osmotic diarrhea is **RELIEVED** by fasting, while secretory diarrhea **does NOT** respond to fasting !
2) **Fecal osmotic gap (not used in clinical practice):**
   a) >100 mOsm/kg → Osmotic diarrhea
   b) <50 mOsm/kg → Secretory diarrhea

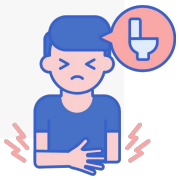
Causes include:

1. **Infections:** The most common cause is a bacterial toxin.
2. **Pancreatic insufficiency**
3. Inflammation & Dysregulation: Diverticulitis, Vasculitis, **microscopic colitis**, Gastroenteritis
4. Absence of an ion-transport mechanism.
5. Reduction of mucosal surface area by surgery or disease.
6. Congenital chloridorrhea
7. **Bile Acid induced diarrhea:** Ileal bile acid malabsorption.
8. **Idiopathic:** Epidemic (Brainerd), Sporadic.
9. Medications (NSAIDs, Colchicine), stimulant laxative abuse, toxins.
10. **Malignancy:** Colon CA, lymphoma, rectal villous adenoma
11. **Abnormal motility:** DM-related dysfunction, IBS, Post-vagotomy diarrhea.
12. **Circulting secretagogues (endocrinopathies)**: as in Addison's disease, Hyperthyroidism, **Carcinoid syndrome**, Pheochromocytoma, **Gastrinoma** (a.k.a ZE syndrome) VIPoma, Somatostatinoma.

1. Some diseases can cause **both** osmotic and secretory diarrhea. e.g. if someone has viral gastroenteritis; there will be inflammation of the bowels which will cause secretory diarrhea. There will also be **destruction** of villi and brush border of enterocytes (which job is to increase surface area for absorption + which has digestive enzymes such as lactase) → decreased absorption → osmotic diarrhea.

2) Fatty Diarrhea (Steatorrhea)

- Present with **Bloating**, flatulence, **greasy** malodorous stools that is **foul smelling** and **difficult to flush**
- **Weight loss**, s/s of **vitamin deficiencies**[1] (peripheral neuropathy, easy bruising)
- Iron deficiency **anemia**, **coagulopathy**, hypoalbuminemia, osteopenia.

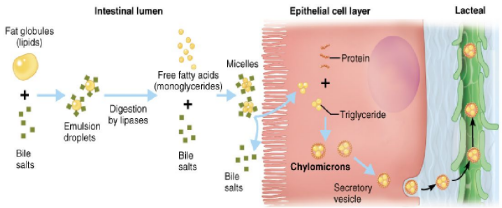


Malabsorption
inadequate mucosal transport of digestion products

- **Mucosal diseases** (eg, Celiac sprue, Whipple's disease).
- **Mesenteric ischemia**.
- **Structural disease:** Short bowel syndrome, Post-resection diarrhea.
- **Small bowel bacterial overgrowth** (bile salt deconjugation).
- **Lymphatic obstruction**[2] (Due to radiation, infection, Lymphoma)

Maldigestion
inadequate breakdown of triglycerides

- **Pancreatic exocrine insufficiency** (eg, chronic pancreatitis, CF).
- **Inadequate luminal bile acid concentration** (eg, advanced primary biliary cirrhosis).



3) Inflammatory Diarrhea

- Presents as **small volume** diarrhea with **Blood, mucus**, and **pus**, with **abdominal pain** and **fever**.
- Positive fecal **leukocytes**, gross or occult **blood**, **ESR/CRP, leukocytosis** , **Persists on fasting**.

Causes/DDx

Inflammatory bowel disease:

Ulcerative colitis, **Crohn's disease**, Diverticulitis, Ulcerative jejunoileitis.

Infectious diseases:[4]

- ➔ Pseudomembranous colitis (Clostridium difficile infection)[3]
- ➔ Invasive bacterial infections (e.g., some types of E. Coli, Shigella, **TB**, MAC, yersiniosis)
- ➔ Ulcerating viral infections (e.g., **cytomegalovirus**, Herpes simplex)
- ➔ Invasive parasitic infections (e.g., amebiasis, strongyloides).

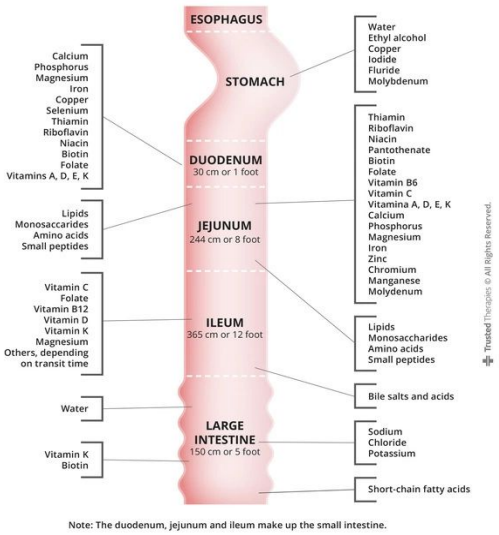
- **Ischemic colitis.**
- **Radiation colitis.**
- **Neoplasia**:
  - Colon cancer
  - Lymphoma

1. Fat soluble vitamins (AKED)
2. Most fat gets absorbed as chylomicrons by entering lymphatic system (except medium chain fatty acids which go directly into the portal vein). If a patient came with lymphatic obstruction presenting with fatty diarrhea. To replenish that, we give them medium chain fatty acids.
3. Diarrhoea occurs in the first few days after taking the antibiotic or even up to 6 weeks after stopping the drug. The causative agent is C. difficile. First-line antimicrobial therapy involves metronidazole (500 mg orally 3 times daily for 10 days) or vancomycin (125 mg orally 4 times daily for 7–10 days). Although vancomycin is more effective than metronidazole against hypervirulent C. difficile strains (e.g. ribotype 027), it is more expensive and may drive the emergence of vancomycin resistance in other organisms (e.g. enterococci, Staph. aureus). For these reasons, some authorities reserve its use for relapse (15–30% of patients), failure of initial response or severe infection.
4. **SEECSY: S**almonella, **E**.coli, **E**ntamoeba, **C**ampylobacter, **S**higella, **Y**ersinia enterocolitica

Malabsorption

◀ Nutrient / vitamin absorption[1]

Duodenum/Jejunum	Ileum
• Carbohydrates / simple sugars. • **Fats**. • Amino Acids. • Iron (needs acidic medium) • Fat Soluble Vitamins (A, D, E, K). • Calcium. • Magnesium. • Minerals.	• **Vitamin B12.** • **Bile salts.** • Magnesium.
Colon	
• **Short-chain fatty acids.** • **Vitamin K** * • Vitamin B7 (Biotin) * * Produced by bacterial gut flora.	



Note: The duodenum, jejunum and ileum make up the small intestine.

Signs / Symptoms of Malabsorption

Dr: I don't think I'll ask you about this

Malabsorption of	Clinical features	Lab findings
Calories	Weight loss w/ normal appetite	-
Fat	Pale voluminous stool, steatorrhea	Stool fat >6 g daily
Protein	Edema, muscle atrophy, amenorrhea	Low albumin, low protein
Carbohydrates	**Watery diarrhea**, flatulence, milk intolerance	Stool pH < 6[2]; stool osmotic gap >100; increased breath hydrogen
Vitamin B12	**Anemia**, subacute combined **degeneration of spinal cord** (paresthesias, ataxia, loss of position/ vibratory sense), hypersegmented neutrophils, **neuropathy**	**Macrocytic anemia**; low B12 level; increased MMA and homocysteine levels; abnormal Schilling test
Folic acid	Anemia	**Macrocytic anemia;** decreased serum/RBC folate; increased homocysteine level
Iron	Anemia, glossitis, pagophagia	**Microcytic anemia;** decreased serum iron and ferritin levels; increased TIBC
Calcium and Vitamin D	Paresthesia, tetany, pathologic fractures, positive Chvostek and Trusseau signs, osteoporosis	Low serum calcium; abnormal DEXA; elevated Alk Phos
Vitamin A	Follicular hyperkeratosis, night blindness	Decreased serum carotene
Vitamin K	**Easy bruising**, **bleeding** disorders	Elevated INR; decreased Vitamin K-dependent coagulation factors (2, 7, 9, 10)
Vitamin B (general)	Cheilosis, painless glossitis, angular stmatitis, acrodermatitis	-

1. Why this is important? You expect abnormalities when resecting a certain part of the GI. For eg, disease of the terminal ileum → Vit. B12 deficiency. Disease of the colon → Vit. K deficiency (coagulopathy and megaloblastic anemia).
2. due to colonic bacterial fermentation to CO2, H2, and short chain FA

How to approach a patient with diarrhea?

History

Onset	Stool characteristics	Abdominal pain	Aggravating factors	Iatrogenic diarrhea	Systemic diseases
Congenital, abrupt or gradual	Watery, bloody, fatty	IBD, IBS or ischemia	Diet, stress	Drugs, radiation, surgery	Hyperthyroidism, DM, Collagen vascular disease, tumor syndromes, AIDS, Ig deficiencies
Pattern	**Fecal incontinence**	**Weight loss**	**Mitigating factors**	**Factitious diarrhea**	
Continuous, intermittent		Malabsorption, Neoplasm	Diet, OTC or Rx drugs	Laxatives	
Duration			**Previous evaluation**		
Acute, Subacute, Chronic					
Epidemiology					
Travel, Food, water					

Physical examination

General	Skin	Thyroid	Chest	Heart	Abdomen	Anorectal	Extremities
Fluid balance, nutrition	Flushing, rashers, dermatog raphism	Masses	Wheezing	Murmur	Hepatomegaly, mass, ascites, tenderness	Sphincter competence, Fecal occult, blood test	Edema

Routine laboratory tests

CBC	Chemistry screen
Anemia*, leukoctosis** *As a consequence of nutrients deficiency or GI bleeding **Seen in inflammatory etiologies	Fluid electrolyte, nutritional status and serum protein/ globulin

Stool analysis

Weight	Electrolytes	pH[1]	Fecal occult blood testing	Stool WBCs	Fat output	Laxative screen
	Osmotic gap	carbohydrates malabsorption	Bleeding	inflammation	Sudan stain Quantitative[2]	

1. Because if the CHO didn't get absorbed, the normal flora will fermit them generating acidic radicals
2. it binds to acids found it fat, more fat = more stain

Special laboratory tests

- **Stool culture** (more useful only for acute), An ova and parasite (O&P) exam, Giardia Ag, **C diff**, Coccidia, Microsporidia, Cryptosporidiosis.
- **Fecal leukocytes** (or marker for neutrophils: lactoferrin or calprotectin).
- **Fecal occult blood**.
- Stool electrolytes for **osmolar gap = 290 – 2[Na + K].**
- **Fat content** (48h or 72h **quantitative** or Sudan stain).
- **Laxative screen** (if positive, repeat before approaching pt).
- **Imaging:**
  - Small bowel series.
  - CT/MRI or CT/MR enterography.
- **Endoscopy** with small bowel biopsy and aspirate for quantitative culture. (Esp. for celiac disease)
- **Colonoscopy**, including random biopsies. (Esp. for IBD)

Now after all of this you should be able to classify the type/cause of diarrhea in this patient.

◀ Summary (Extra)

Type	Secretory	Osmotic	Inflammatory
Osmolar Gap	Normal <50 mOsm/kg	Elevated >100 mOsm/kg	-
Mucus	-	-	+
Pus	-	-	+
WBCs	-	-	+
RBCs	-	-	+
Change with NPO	No response	Relieved	No response
Causes	Infections Pancreatic insufficiency	Osmotic laxatives lactase deficiency	Ulcerative colitis Crohn's disease

Celiac Disease[1]

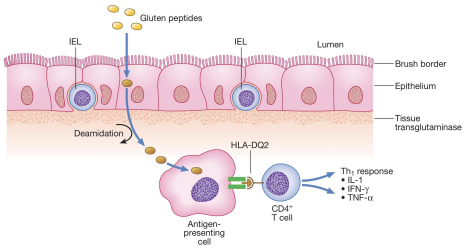
حساسية القمح \ الجلوتين

Introduction

- **Small intestinal**[2] malabsorption of nutrients following the ingestion of **wheat** gluten or related proteins from **rye**, **barley** **and oats**.
- A characteristic, though not specific, **villous atrophy** of the small intestinal mucosa.
- **Prompt** clinical and histologic **improvement following** strict adherence to a **gluten free diet**.
- Clinical and histologic relapse when gluten is reintroduced.
- Associated with **HLA-DQ2** and **HLA-DQ8**

◀ Pathophysiology

1. The disease affect the mucosa with marked variation ⟹Loss of normal villous structure (**flattening**) ⟹ Intestinal crypts are elongated and open onto a flat absorptive surface.
2. Leaky mucosa with **increased permeability** due to structural changes of the tight junctions between damaged absorptive cells.
3. Marked **increase in cellularity** of the lamina propria – plasma cells and **lymphocytes**.



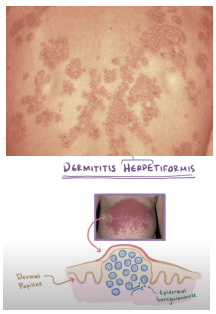
◀ Presentations

It could be totally asymptomatic (in the guidelines, first degree relatives should be screened for celiac disease). Sometimes we find that they have celiac disease but showing no symptoms at all.

Non-specific GI symptoms	Nutritional deficiency	Fat soluble vit. deficiencies	Malignancy[7]	Other
Most common: Diarrhea. Bloating. Dyspepsia.	Anemia[6] (Iron & folate). Osteoporosis.	**Vit A**: poor night vision, follicular hyperkeratosis. **Vit D**: hypocalcemia, osteoporosis. **Vit K**: easy bruising & bleeding, elevated INR.	**T-cell lymphoma**[8]**.** **Small bowel adenoCa**[9]**.**	**Dermatitis herpetiformis.**[5] Elevated ALT & AST. Asymptomatic[4]

◀ At Risk[3]

- IgA deficiency (2-3%).
- Autoimmune thyroid disease (6-8%).
- Type 1 DM (3-6%).
- Connective tissue disease.
- Down's syndrome.



1. Autoimmune disease that is positive in serology, complicated when uncontrolled, differ from gluten intolerance that has no microscopic abnormalities or antibodies.
2. **Endoscopic biopsy (GOLD standard)** taken from the duodenum because it is the first contact with gluten
3. If these patients present with non-specific GI symptoms, you should think of celiac. + patients with autoimmune diseases are at higher risk of developing another autoimmune disease due to dysregulation of immune system (e.g. type 1 DM) .
4. If you diagnosed someone with CD, you have to screen 1st degree relatives. You may find structural abnormalities with no symptoms. There is a strong genetic component, with around 10% of first-degree relatives of an index case affected, and there is strong (approximately 75%) concordance in monozygotic twins.
5. If they start **gluten-free strict diet**, it will disappear but some patients require additional treatment with dapsone
6. That's why anemia workup includes celiac disease serology testing and upper GI endoscopy.
7. Generally celiac increase the risk of malignancies throughout the GI tract, but the worst two are small bowel lymphoma & adenocarcinoma
8. T cell Lymphoma can also be seen in stomach. however; small bowel T cell lymphoma has much worse prognosis than the gastric one.
9. Adenocarcinoma of bowel has much worse prognosis than adenocarcinoma of the colon (worst malignancy throughout GI tract).

Celiac Disease Cont'

◀ Serology

Dr: اذا جاكم بالاختبار خيارات فيها هذي الAntibodies اختارو منها Anti-TTG IgA

★ **Anti-tissue transglutaminase antibody (IgA):**[1]

- Sensitivity 95%; specificity 97.5%.
- **BEST INITIAL**

Endomysial antibody (IgA):

- Sensitivity 85-98% (~93)
- Specificity 97-100% (~99).

IgA anti-gliadin antibodies:

- Sensitivity 75-90% (~80)
- Specificity 82-95% (~85).

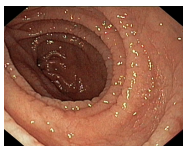
IgG anti-gliadin antibodies:

- Sensitivity 69-85% (~75) Spec 73-90% (~80).
- Can be used in IgA deficient patients.

◀ Diagnosis

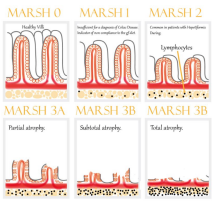
Endoscopy: might be Normal.[2]

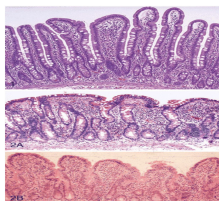
- Loss of mucosal folds, Crypt hyperplasia
- Flattening of mucosa. (**Villous atrophy**)
- **Scalloping of mucosa** تقوقع**.**
- In severe disease: Ulcerations and masses
- **HLA- DQ2** is present in 90–95% of coeliac disease patients and **HLA- DQ8** in about 8%




Not important

Biopsy histology: MARSH classification





As the disease progress, there is more villous atrophy and leukocytosis

◀ Management

Education[4]**:** to prevent accidental or unrecognised gluten ingestion. most common reason for failure to improve with dietary treatment is accidental or unrecognised gluten ingestion. They shouldn't use the same spoons & forks their family use (may cross-contaminate with gluten food)

Gluten-free diet: avoid wheat, barley, rye & oat.

Correct nutritional deficiencies (Iron, Ca, Vit D, folate).

Anticipate complications (like osteoporosis → you have to do bone densitometry) .

Whipple Disease

Chronic systemic infection by **Tropheryma whipplei.** (an intracellular gram-positive bacteria)

Has GI, CNS, CVS, MSK & skin manifestations.

Think about whipple disease if the patient is presenting with systemic manifestations along with diarrhea

◀ Pathophysiology

- Malabsorption – **weight loss**, **diarrhea** (watery or fatty[3]) and abdominal pain:
  - Caused by bacterial and **macrophage-predominant** inflammatory cell infiltration of the small intestinal mucosa and **obstruction of mesenteric lymph nodes.**

1) If the antibody screen is positive, **adult** patients should remain on a gluten-containing diet until **duodenal biopsies are taken.** High-titre serology in **children** can be diagnostic **without the need for endoscopy and biopsy**. Antibody titres usually become negative with successful treatment.
2) It could be normal in early celiac disease or celiac disease that is under-control. Endoscopic appearances should not preclude biopsy, as the mucosa usually looks normal. As the histological changes can be patchy, an adequate number of biopsies – currently, more than four biopsies from the second part of the duodenum plus one from the duodenal bulb – should be retrieved.
3) Fatty diarrhea because of lymphatic obstruction
4) If the celiac disease was well controlled, the risk of malignancy becomes equal to non-celiac disease individuals. Telling this to patients helps in motivating them to adhere to gluten-free diet.

Whipple Disease Cont'

PAS the foamy Whipped cream in a CAN

Effect of The Disease on Other Organs or Systems[1]

Neurologic:

- Progressive dementia.
- Supranuclear ophthalmoplegia.
- Altered LOC.
- Oculo-masticatory & oculo-facial skeletal dysfunction.

CVS:

- Endocarditis – MV most common.
- Myocarditis.
- Pericarditis.

MSK:

- Seronegative oligo or polyArthralgias.

Skin (common):

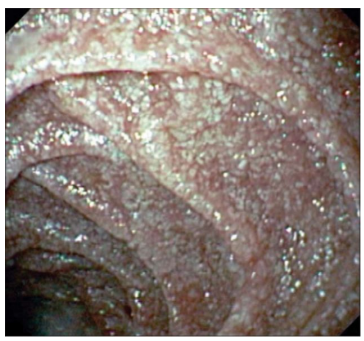
- Hyperpigmentation.

Histopathology

- **Foamy macrophages** on routine H&E.
- Numerous **PAS-positive granular particles**[2] (pink/purple appearing):
  - Lysosomes filled with T. whipplei.

Diagnosis

- Diagnosis is made by the characteristic features on **small bowel biopsy**, with characterisation of the bacillus by polymerase chain reaction (PCR).
- **Whitish to yellow plaque-like patches** in 75% of patients (representing lipid droplets and/or **lymphangiectasia (Congested lymphatic vessels)**



Management

- **2 weeks with Abx to cross BBB:**
  - **Ceftriaxone** 2g IV daily monotherapy **THEN Septra (TMP/SMX)** DS tab BID x **1 year.**[3]
  - **OR Penicillin G** (2 MU IV q4h) PLUS **streptomycin THEN Septra (TMP/SMX)** DS tab BID x **1 year**

1. Low-grade fever is common and most patients have joint symptoms to some degree, often as the first manifestation. Occasionally, neurological manifestations may predominate and CNS involvement is the most serious consequence.
2. **periodic acid–Schiff (PAS) very specific for whipple disease**
3. Long-term follow-up is essential, as clinical relapse occurs in up to one-third of patients, often within the CNS; in this case, the same therapy is repeated or else treatment with doxycycline and hydroxychloroquine is necessary.

Small Bowel Bacterial Overgrowth (SBBO)

◀ Normal Microbiome

1. **Stomach 0-10^3 CFU/ml.**
2. **Jejunum 0-10^4:**
   - Gram +ve aerobes (oral streptococci, lactobacillus); no gram –ve aerobes.
3. **ileum 10^5-10^9.**
4. **Colon 10^{10}-10^{12}:**
   - **Anaerobes:** bacteroides, peptostreptococcus, lactobacillus, bifidobacterium, clostridium.
   - **Facultative aerobes:** e. coli, enterococcus, staphylococcus.

Notice the increasing concentration throughout the tract

What prevents gut bacteria from being the same in each part? pH, competitive flora, ileocecal valve

◀ Normal barriers that prevent SBBO (a.k.a blind loop syndrome)

- **Gastric acid** & **pancreatic enzymes**
  - **What disrupts this barrier?** chronic pancreatitis, low HCl from surgery, pernicious anemia, partial gastrectomy or Long Term PPI.
- **Intact bowel structure**
  - **What disrupts this barrier?** Surgery, diverticulum. because of bowel stasis
- **Cleansing effect of bowel motility – interdigestive migrating motor complex**
  - **What disrupts this barrier?** dysmotility (Systemic sclerosis, Diabetic autonomic neuropathy, Chronic intestinal pseudo-obstruction)
- **Gut immunity – intraluminal secretory IgA**
  - **What disrupts this barrier?** immunodeficiency (Eg, hypogammaglobulinemia)
- **Competent ileocecal valve**
  - **What disrupts this barrier?** scarring from inflammation (crohn's disease), surgery
- **Competition by other bacteria**
  - **What disrupts this barrier?** antibiotics.

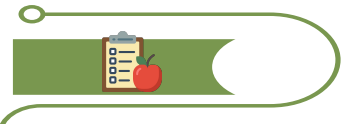
Small Bowel Bacterial Overgrowth (SBBO)

Effect of SBBO

1. **Bile acids** metabolism → **deconjugated** bile acids. (Bile is important for fat absorption)
2. **Bilirubin** metabolism → **Deconjugated** bilirubin.
3. **CHO** metabolism → C02, H2, D-lactic acid, organic acids (short chain fatty acids).
4. **Lipid** metabolism → short chain fatty acids.
   Protein metabolism → amines, ammonia

Presentation

- Bloating, **watery diarrhea**, **abdominal pain**, weight loss, **neuropathy**.
- **Vitamin A,D,E,K deficiency:** therefore bruising, night blindness, bone diseases.



- Iron deficiency.
- Hypoproteinemia, hypoalbuminemia.
- Fat and CHO malabsorption.

- **B12 deficiency**[1] – utilized by the bacteria for nutrition.
- **Elevated/Normal folic acid**[2] level - produced by bacteria.

Investigations

Jejunal culture[3] **– Gold standard.**
(If >10^4 it's abnormal)

Schilling's test:
determine whether you're absorbing vitamin B-12 properly
(Explained Next slide)

C14-labeled bile acid breath test.
C14-xylose breath test.
H breath test.

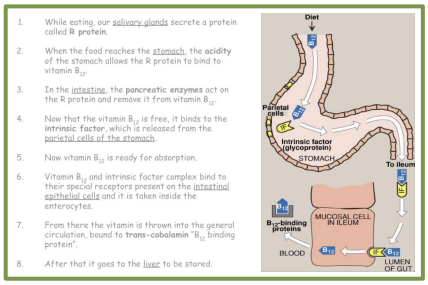
Management

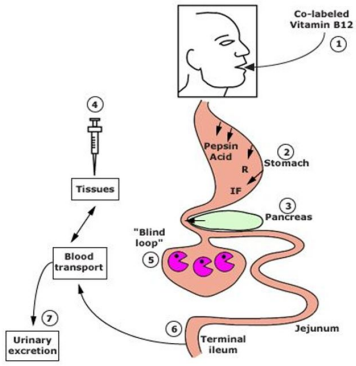
1. **Treat underlying cause: Most important thing.**
   e.g. discontinue acid suppressive meds, treat inflammatory Crohn's disease, remove strictures, etc.
2. **Nutrition – replace fat soluble vitamins, B12:**
   - Low CHO diet to limit bacteria substrate.
3. **7 – 10 days of antibiotics:**
   - **Metronidazole**, Amox/Clav, **Tetracycline**, Doxycycline, Amoxicillin.
   - May need to cycle Abx to avoid resistance.
   - If breath testing reveals high methane production, addition of neomycin may be beneficial.
4. - Bowel cleanse with PEG, Prokinetic.
   - Octreotide – at low dose, has a promotility effect: Causes hypomotility at higher doses.
   - Probiotics – minimal evidence.

1. leading to anemia
2. There is **NORMAL to ELEVATED** folate; in contrast to extensive celiac disease or bowel resection
3. Not practical and not used clinically. what we do is giving the patient antibiotics for 7 days, if he improved then what we did is **diagnostic** and **therapeutic** at the same time

Small Bowel Bacterial Overgrowth (SBBO) Con.

◀ Schilling's Test





- Malabsorption of vitamin B12 may occur as a consequence of:
  - Deficiency of intrinsic factor (eg, pernicious anemia (improved with intrinsic factor), gastric resection).
  - Pancreatic insufficiency (improved with pancreatic enzyme).
  - Bacterial overgrowth (improved with antibiotic).
  - Ileal resection or disease.

★ To distinguish between these causes of fat malabsorption, the **Schilling test** is performed on 4 stages. **Radiolabeled B_{12} is given orally (given in every stage)**, in each stage you'll **add one** of the following and then measure B_{12} from urine sample:

- **Stage I: + IM unlabeled vitamin B_{12}.** if B_{12} levels are normal then the cause of its deficiency was **decreased intake**. If not do Stage II
- **Stage II: + intrinsic factor (IF)** if B_{12} is normal after supplement of IF then the cause was **lack of intrinsic factor (Eg, pernicious anemia)**. If not do Stage III
- **Stage III: + oral antibiotics.** if B_{12} is normal after antibiotics then the cause was **bacterial overgrowth**. If not do Stage IV
- **Stage IV: + supplement of pancreatic enzymes.** if B_{12} is normal after supplement of **pancreatic enzyme** (trypsin) then the cause was pancreatic insufficiency.

- If B_{12} is not normal after all of these stages the cause of deficiency might be **ileal disease**.

Differential Results of The Schilling Tests in Several Diseases Associated With Cobalamin Malabsorption

Cause of Fat Malabsorption	^{58}Co-Labeld Cobalamin	With Intrinsic Factor	With Pancreatic Enzymes	After 5 Days of Antibiotics
Pernicious Anemia	Reduced	**Normal**	Reduced	Reduced
Chronic Pancreatitis	Reduced	Reduced	**Normal**	Reduced
Bacterial Overgrowth	Reduced	Reduced	Reduced	**Normal**
Ileal Disease	Reduced	Reduced	Reduced	Reduced

Tropical Sprue

◀ Introduction

- Is characterized by villous atrophy and crypt hyperplasia.
- Most **tropical regions** of Asia, Africa, the Middle East, the Caribbean and Central and South America:
  - It is an acquired defect – not present in newborns. Travelers from the industrialized world may develop it. (only if they stay there for a long period)

The cause is unknown, but seems to be due to continuous bacterial contamination of the upper small bowel and nutritional deficiency.

Present with:

- **Chronic diarrhea** often with **steatorrhea**, anorexia, abdominal cramps, bloating
- **B12 and folate deficiency. (both here unlike SBBO)**
  - features of megaloblastic anaemia

Investigation:

- If suspicion is high ⟹ **jejunal aspirate and biopsy**. **GOLD STANDARD**

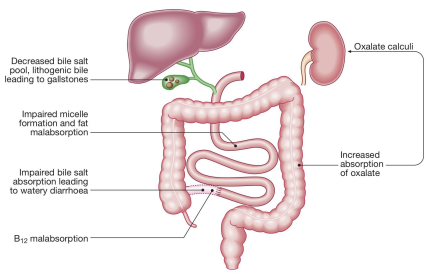
Management:

- **Tetracycline** for 3-6 months is the treatment of choice
- **Folate** & B12 Supplement .
- Severely ill patients require resuscitation with fluids and electrolytes for dehydration, and nutritional deficiencies should be corrected. Vitamin B12 (1000 µg) is also given to all acute cases.

Bile Acid-Induced Diarrhea

Obj.

- **Definition:**
  - Bile acids get synthesized in the liver and secreted into the bowel (95% get absorbed in the terminal ileum and only 5% go to the colon). If the small intestine is resected and bile is not absorbed, free bile acid is very irritant to the colon. Bile salts which overflow into the colon causes secretion of water and electrolytes → Diarrhea
  - increased oxalate absorption → renal oxalate stones.
- **Etiology:**
  - Bile acid diarrhoea can occur idiopathically (type 1) or as a complication of small bowel resection, **post cholecystectomy** (type 2)
- **SxS:**
  - Urgent **watery diarrhea** or mild steatorrhea
- **Diagnosis:**
  - Contrast studies and tests of B12 and bile acid absorption, such as the 75Se-homocholic acid taurine (SeHCAT) test
  - An elevated serum 7α-hydroxycholestenone is a useful non-invasive marker of bile acid diarrhoea.
- **Treatment:**
  - **Bile acid sequestrants e.g. cholestyramine** (it binds to bile acids thus reducing its irritant effects).



Most common scenario is in patients with Crohn's disease who have undergone ileal resection.

Exocrine Pancreatic Insufficiency

◀ Introduction

- Mainly in patients with **chronic pancreatitis (most common cause is alcohol)**, Steatorrhea
- Improves with pancreatic enzymes replacement therapy (Protease and lipase supplements)
- Hx of abdominal pain, high alcohol intake for long time, diarrhea = pancreatic insufficiency.
- Best way to diagnose it is to give the patient pancreatic enzymes, if they improve then that is the diagnostic and therapeutic at the same time.

Enzyme Secretion of Pancreas and Role in Digestion

Secretion	Site of Action	Active Enzyme	Substrate and Products
Pancreatic Juice	Duodenum	Pancreatic Amylase	Starch → Maltose
		Trypsin	Protein → Peptide
		Chymotrypsin	Protein → Peptide
		Pancreatic Lipase	Fats → Fatty Acids + Glycerol

Diseases & Mechanisms Associated With Exocrine Pancreatic Insufficiency

Disease or Condition	Pathological Mechanism
Chronic Pancreatitis, CF, Diabetes, Sequelae of Acute Necrotizing Pancreatitis, Hereditary Pancreatitis.	Loss of Pancreatic Parenchyma (Responsible for Most Cases of EPI).
Periampullary Tumors, IPMN, Pancreatic Head Carcinoma, Benign Pancreatic Tumors.	Obstruction of Main Pancreatic Duct.
Celiac Disease, Crohn's Disease, Schwachman-Diamond Syndrome.	Decreased Pancreatic Stimulation.
Zollinger-Ellison Syndrome.	Acid-mediated Inactivation of Pancreatic Enzymes.
Gastrectomy, Gastric Bypass, Extensive Small Bowel Surgery.	Gastrointestinal/Pancreatic Surgery.

Summary

Diarrhea

Diarrhea is present if one of the following criteria is fulfilled:

Frequent defecation: ≥ 3 times per day | Altered stool consistency: increased water content |Increase in stool quantity: more than 200–250g per day

Type	Acute	Chronic	
Duration	Less than 2 weeks	More than 4 weeks	
Causes	Viral Infections **(most common)**	Organic Causes	Functional Causes
		- Celiac Disease - IBD - Infections (Bacterial / Parasitic) - Pancreatic Insufficiency - Intestinal Neoplasms	- IBS - Lactose Intolerance - Abuse of drugs / Alcohol

———-	———-	**How to distinguish organic from functional diarrhea?**	
		Duration	
		Weeks/Years	Over 6 months
		Volume of diarrhea	
		Larger	Smaller
		Blood?	
		Often / Possible	NEVER
		Timing	
		No pattern / wake patient up	Morning often / doesn't wake patient up
		Extra symptoms	
		Fever / Arthritis / Skin lesion/ Weight loss	Weight loss only with anorexia

Classifications of diarrhea

Inflammatory	**Non inflammatory**		
Exudative	Osmotic	Secretory	Motor
Damage to the intestinal mucosa may cause cytokine-induced water hypersecretion, impair absorption of osmotically active substances or fat, and/or disrupt water and electrolyte absorption. Mucus, blood, and leukocytes present in stool	Poor absorption or excessive ingestion of hydrophilic substances (e.g., salts and sugars, laxatives) causes water to be drawn into the intestinal lumen.	Active secretion of water into the intestinal lumen more than absorption via inhibition/activation of enzymes (e.g., ↑ cAMP activity)	Rapid intestinal passage due to increased bowel movements. This reduces the extent of water absorption in the colon and leads to diarrhea
1- Blood and/or mucus in stool 2- Usually with abdominal pain 3- Systemic symptoms (common)	1- Watery or Greasy stool 2- May or may not associated with abdominal pain 3- Bloating 4- Systemic symptoms (uncommon)		

Summary

- Chronic diarrhea (>4 weeks) can be osmotic, secretory, inflammatory or fatty diarrhea.
- Fecal osmotic gap is helpful to point toward osmotic diarrhea
- Iron, Ca & folate are absorbed in proximal bowel;
  - while B12 is absorbed in ileum.

Celiac disease	• Should always be suspected in patients with iron-def anemia, diarrhea or dyspepsia. • Anti-TTG is most helpful. • Biopsy shows villus atrophy. • Gluten-free diet. • Watch for complications: nutritional & malignancy
Whipple Disease	• Chronic systemic infection by Tropheryma whipplei. • Has GI, CNS, CVS, MSK & skin manifestations • Biopsy: Foamy macrophages & PAS-positive granular particles • Tx Ceftriaxone 2g IV daily monotherapy THEN Septra (TMP/SMX) DS tab BID x 1 year. OR Pen G (2 MU IV q4h) PLUS streptomycin THEN Septra (TMP/SMX) DS tab BID x 1 year
SBBO	• Look for & treat underlying causes • B12 def • Schilling's test
Tropical Sprue	• Hx of travel to tropical area for long period
Bile acid-induced diarrhea	• Watery diarrhea • Improves with cholestyramine
Exocrine pancreatic insufficiency	• Mainly in patients with chronic pancreatitis • Steatorrhea • Improves with pancreatic enzymes replacement therapy

Lecture Quiz

Q1: You see a 25-year-old woman who presents with a 24-hour history of watery diarrhoea. She states that she has opened her bowels 11 times since her onset of symptoms. Associated symptoms include nausea and vomiting with abdominal cramps and pain which started in the evening following a barbeque meal in the afternoon that day. The patient is alert and orientated and her observations include a pulse rate of 69, blood pressure of 124/75 and temperature of 37.1°C. On examination, her abdomen is soft, there is marked tenderness in the epigastric region and bowel sounds are hyperactive. The patient is normally fit and well with no past medical history. The most likely diagnosis is

A. Irritable bowel syndrome
B. Gastroenteritis
C. Ulcerative colitis
D. Laxative abuse

Q2: A 35-year-old woman presents with a 24-hour history of watery diarrhoea. She has opened her bowels nine times since the onset of her symptoms. You diagnose gastroenteritis after learning that the patient and her family all ate at a new restaurant and the rest of her family have had similar problems. The most appropriate management is:

A. Oral rehydration advice, anti-emetics and discharge home
B. Oral antibiotic therapy and discharge home
C. Admission for intravenous fluid rehydration
D. Admission for intravenous antibiotic therapy
E. No treatment required

Q3: A 56-year-old man presents with a 2-week history of diarrhoea which has not settled following an episode of 'food poisoning'. Which of the following would be the most appropriate investigation?

A. Full blood count
B. Urea and electrolytes
C. Stool sample for microscopy, culture and sensitivities
D. Abdominal x-ray
E. Liver function tests

Q4: A 2-year-old boy presents with a history of smelly, bulky diarrhea and poor weight gain. A small bowel biopsy shows villous atrophy. What is the most likely etiology?

A. Bacillus cereus
B. Campylobacter jejuni
C. Carcinoid
D. Celiac disease
E. Clostridium difficile
F. Crohn's disease

Q5: A 62-year-old farmer presents for a second opinion after unrevealing extensive workup of migrating joint pain for the past 2 years and chronic diarrhea, postprandial abdominal cramping, and weight loss for the past 6 months. Your suspicion for Whipple disease is high. Which of the following statements regarding this disease is true?

A. Chronic diarrhea is common, but extraintestinal symptoms are rare.
B. Prolonged antibiotic treatment is required to eradicate the causative organism.
C. The causative organism, Tropheryma whipplei, is easily cultured.
D. The disease is more common in women than in men.
E. Colonoscopy with biopsy is the diagnostic test of choice.

Q6: A 47-year-old woman has been experiencing a four-month history of diarrhoea and bloating. Associated symptoms include lethargy and weight loss. Full blood count reveals haemoglobin of 9.3d/gL and MCV 70fL. Which of the following investigations would be helpful in the patient's diagnosis?

A. Anti-mitochondrialantibodies
B. Anti-smooth muscle antibodies
C. Anti-tissue transglutaminase antibodies
D. Anti-nuclearantibodies
E. Anti-neutrophil cytoplasmic antibodies

Answers: Q1:B | Q2:A | Q3:C | Q4:D | Q5:B | Q6:C

Answers Explanation File!

GOOD LUCK !

This work was originally done by ***438 Medicine team:***

Team Leaders

- *Raghad AlKhashan*
- *Amirah Aldakhilallah*
- *Mashal AbaAlkhail*
- *Ibrahim AlAsous*

Members : Jehad Alorainy
Noura Alturki
Abdulrahman Bedaiwi

Edited by ***439 Medicine team:***

Team Leaders

- *Shaden Alobaid*
- *Ghada Alabdi*
- *Hamad Almousa*
- *Naif Alsulais*

Member : Duaa Alhumoudi

Note taker : Abdurahman Addweesh

CONTACT US THROUGH OUR EMAIL :

MEDICINE439@GMAIL.COM