Chronic diarrhea and malabsorption

Objectives:

To have an overview regarding chronic diarrhea:

- Definition - Pathophysiology - Classification - Approach

To discuss common causes of chronic diarrhea:

- Celiac Disease - Whipple Disease - Tropical Sprue - Small Bowel Bacterial Overgrowth
- Exocrine Pancreatic Insufficiency - Bile Salt-Induced Diarrhea

[Color index : Important | Notes | Extra]

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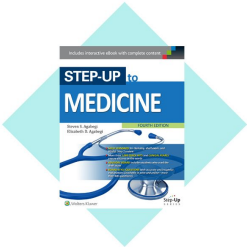
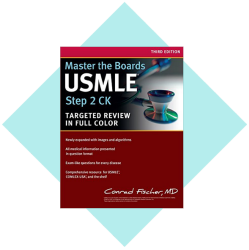
Resources:

- 435 slides and notes. For **Further reading: here**





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Objective 1- To have an overview regarding chronic diarrhea:

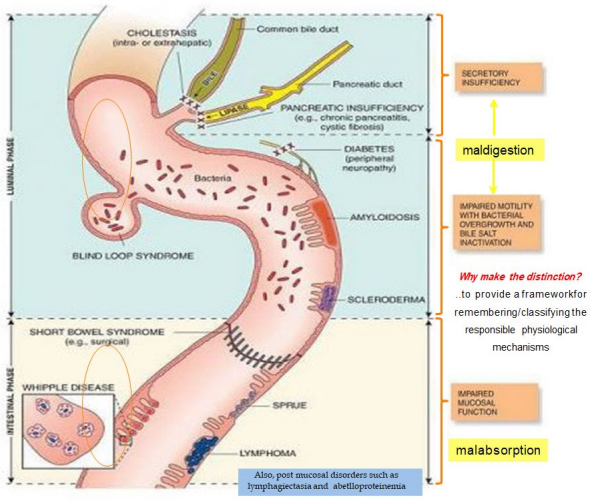
★ If you don't have time to study this lecture, click here

Definitions:

- Diarrhea: Stool output that exceeds **200-300 ml/day** is considered diarrhea

  organic causes of diarrhea have to be distinguished from **functional causes** (Frequent passage of small volume of stools with stool weights < 250g) Exception distal colon cancer and procitis are organic causes that present with stool frequency and normal stool volume

  First of all any patient presents with diarrhea you have to **exclude Infection**! By stool cultures and flexible sigmoidoscopy with colonic biopsy if symptoms persist and no diagnosis has been made.



- **Acute**: common and usually transient, self-limited, Infection related. (less than 2 weeks) : the most common cause is infections.
- Subacute (between 2-4 weeks).
- **Chronic**: A decrease in fecal consistency lasting for 4 weeks or more, usually requires work up, (More than 4 weeks) : infectious organism is a cause but you should rule out other causes (you should not expect IBD or IBS to cause acute diarrhea, because they are associated with chronic diarrhea).
- Maldigestion: inadequate breakdown of triglycerides
- digestion is converting large particles into small particles in the lumen
- Either secretory insufficiency, impaired motility or abnormal enzymes
- Malabsorption: inadequate mucosal transport of digestion products
- absorption is the transition of nutrients from the lumen to portal vein or lymphatics
- Either mucosal disease, lymphatics or vascular disease
- **Fecal Osmotic Gap (FOG)=** 290 (plasma osmolality) – 2 X (stool **Na** + stool **K**) :
  - ➔ FOG of >50 mosm/kg is suggestive of an **osmotic diarrhea** and a gap of >100 mosm/kg is more specific.

  (> 100 = osmotic "MCQs!!!!!!")

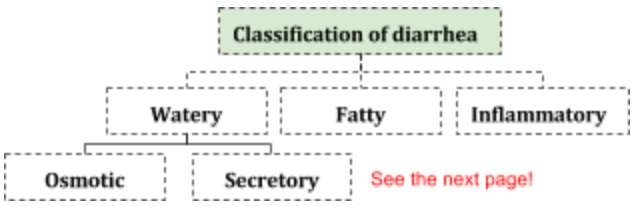
- Tip to differentiate between osmotic and secretory diarrhea is whither it is affected by fasting or not, osmotic diarrhea will improve (relieved) with fasting (you will not retain fluids if you didn't take osmotic argents) but if you have an infection you will have diarrhea that is not related to fasting. Another way to differentiate between them : fecal osmotic gap. 290 is the osmolality of the serum which should be equal to the osmolality of the stool.

Pathophysiology:

Each day, 9–10 L of fluid enter the jejunum.

- Small intestine absorbs 90% of this fluid load.
- The colon absorbs <u>90% of the remaining load</u> (about 900 ml/24 hours); leaving approximately **80–100 ml** excreted each day in feces. around 900 ml get absorbed in the colon (1L) = small amount diarrhea.
- A normal colon can <u>compensate</u> by absorbing up to 3000–4000 ml/24 hours if there is diarrhea due to small intestinal disease

  ★ *Most of absorption occurs in small bowel, therefore; **small** bowel disease > **large** volume diarrhea, and **large** bowel disease > **small** volume diarrhea.*

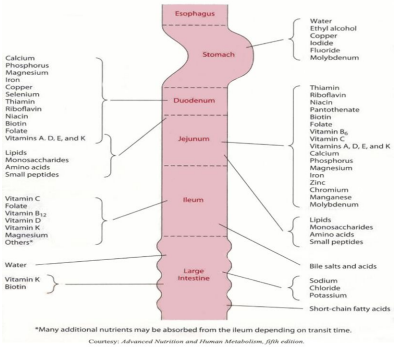


Classification of Diarrhea: *(According to Mechanism):*

Diarrhea	Description, causes and examples	
1.Watery:	**A- Osmotic**	**B- Secretory**
Overview	➢ Excess amount of poorly absorbed substances that is osmotically active remain in the intestine and exert osmotic effect > obligate retention of water within the lumen > diarrhea.	➢ Malabsorption or secretion of electrolytes and water ➢ High stool output : Large volume (>1 L/d). ➢ Mainly in intestinal diseases
Effect of fasting (by history)	➢ **Fasting improve the condition** (Diarrhea is relieved by fasting and gets worse with eating).	➢ **Lack of response to fasting**.
FOG	➢ **Fecal osmotic gap (**FOG) of > 50 mosm/kg is suggestive of an osmotic diarrhea and a gap of >100 mosm/kg is more specific "more definitive for diagnosis" (there is loss of hypotonic fluid)	➢ Low fecal osmotic gap: < 50 mOsm/kg is suggestive of diagnosis with secretory diarrhea, < 25 mOsm/kg is definitive (loss of isotonic fluid).
Causes	➢ **Malabsorption due to** loss of nutrient transporter e.g. lactase deficiency, celiac disease. Lactose is osmotically active so patient with lactase deficiency (AKA Lactose intolerance) will have osmotic diarrhea. ➢ **Ingestion of poorly absorbed agent** (called **Osmotic laxatives):** ○ **Sugar:** Fructose (as in watermelon)[1], Mannitol, Sorbitol and Lactulose (lactulose is used in the treatment of constipation and hepatic encephalopathy) ○ **Antacids** which contain Magnesium ○ **Laxatives** that contain Phosphate and Sulfate	**It has a broad DDX, including: ..** ● **Infections:** The most common cause of this type of diarrhea is a **bacterial toxin** e.g. (some types of E. coli , cholera) that stimulates the secretion of anions. If acute, may be caused by enteropathogenic virus e.g. (rotavirus and norwalk virus) ● **Reduction of mucosal surface area by surgery or disease** bile salts and fatty acids in the colon will draw the water > Diarrhea ● Absence of an ion-transport mechanism ● Inflammation: Diverticulitis, Microscopic colitis ● Dysregulation ● **Circulating secretagogues (endocrinopathies)**, as in Addison's disease, Hyperthyroidism, Carcinoid syndrome, Pheochromocytoma, Gastrinoma, VIPoma, Somatostatinoma ● Pancreatic Insufficiency ● **Bile Acid-Induced Diarrhea:** Ileal bile acid malabsorption ● **Abnormal motility:** DM-related dysfunction, IBS, Post-vagotomy diarrhea ● Malignancy: Colon CA, Lymphoma, Rectal villous adenoma ● Vasculitis ● Congenital chloridorrhea ● Idiopathic: Epidemic (Brainerd), Sporadic ● **Medications**, stimulant laxative abuse, toxins ● Connective tissue diseases (SLE)
2.Inflammatory (Exudative/Mucosal destruction)	➢ 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 increased inflammatory markers (blood and/or stool) ➢ Persists on fasting.	

[1] IBS patients : هال إس يجينا كبيرة بكميات جح أكلنا لو أو عصير شربنا لك يقولون : Large amount of mannitol and fructose retained within the lumen > reabsorb fluids > diarrhea

	■ **Causes/DDx: Infection, Inflammation, Ischemia, and Malignancy** ○ **Inflammatory bowel disease:** ■ Ulcerative colitis, Crohn's disease, Diverticulitis, Ulcerative jejunoileitis ○ **Infectious diseases:** ■ Pseudomembranous colitis[2] (Clostridium difficile infection) ■ Invasive bacterial infections (e.g., some types of E. Coli, Shigella[3], TB, yersiniosis), some other bacteria cause secretory diarrhea e.g. Cholera and other type of E. coli.Bacterial diarrhea is either invasive or non- invasive, pts with cholera will have watery diarrhea because it is non-invasive organism while pts with shigella and salmonella will have bloody diarrhea because they're invasive organisms. E.coli could cause both ■ Ulcerating viral infections (e.g., cytomegalovirus, Herpes simplex), other viruses cause secretory diarrhea ■ Invasive parasitic infections (e.g., amebiasis, strongyloides) ○ **Ischemic colitis** ○ **Radiation colitis** ○ **Neoplasia:** Colon cancer, Lymphoma
3. Fatty Diarrhea: (Steatorrhea)	➢ Present with Bloating, flatulence, greasy malodorous stools "steatorrhea" that can be difficult to flush, weight loss, s/s[4] of vitamin deficiencies (peripheral neuropathy, easy bruising), Anemia, coagulopathy, hypoalbuminemia, osteopenia. Patients with fatty diarrhea can present with coagulopathies (Vit K Deficiency) and fat soluble vitamins deficiency (KADE) ➢ *Most of fats go to **lymphatics**, so any condition that lead to **lymphatic obstruction** such as **lymphoma, infections or HF** will lead to **fatty diarrhea**.* 1. **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) **2. Maldigestion (inadequate breakdown of triglycerides):** ○ Pancreatic exocrine insufficiency (chronic pancreatitis, Cystic fibrosis) ○ Inadequate luminal bile acid concentration (eg, advanced primary biliary cirrhosis)



Nutrients deficient when specific parts of the intestine is affected by lymphoma or resection:

- Duodenum/jejunum: absorption of most nutrients e.g. iron, Ca, folate
- Ileum: vitamin B12. **Terminal ileum: bile salts**
- Colon: short chain fatty acids, **Vitamin K and Biotin** (which are partially produced by gut flora)

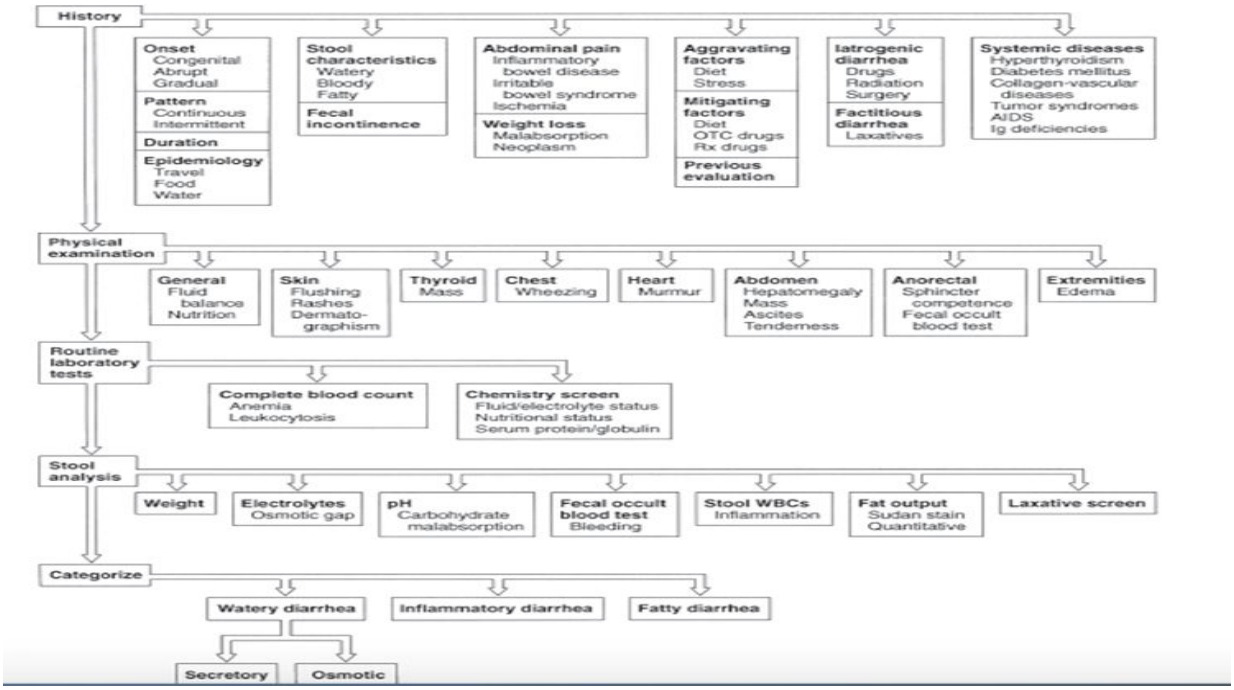
Duodenum and jejunum	Ileum	Colon
Carbohydrates / simple sugars, Fats, Amino acids, Iron, Fat-soluble vitamins (A, D, E, K), Calcium, Magnesium, Minerals and other vitamins	Vitamin B12, Bile salts and Magnesium	Short-chain fatty acids, Vitamin K and Biotin* * In part produced by bacterial gut flora that's why pts on antibiotics could develop vitamin K deficiency

[2] An antibiotic-induced colitis
[3] Shigella infections are mainly seen in young children.
[4] Signs and symptoms

Common Medications and Toxins Associated with Diarrhea :

- Acid-reducing agents (H2 blockers, PPIs)
- Magnesium-containing antacids (osmotic watery diarrhea).
- Anti-arrhythmics (eg, digitalis, quinidine)
- Antibiotics
- Anti-neoplastic agents
- Antiretrovirals
- Beta blockers
- Colchicine
- Levothyroxine
- SSRIs
- Furosemide
- Metformin
- NSAIDs, ASA
- Prostaglandin analogs (ie, misoprostol)
- Theophylline
- Amphetamines
- Caffeine Caffeine is a stimulant for bowel movement
- Alcohol
- Narcotic/opioid withdrawal

Clinical approach to chronic diarrhea :



- Hx : onset, aggravating (medications) and relieving factors, history of travel, stool characteristics (is it watery? fatty? bloody?), fecal incontinence (not every fecal incontinence comes with diarrhea and not every diarrhea comes with fecal incontinence "anal sphincter abnormality (normal stool) > fecal incontinence". Abdominal pain (IBS, IBD), weight loss, Iatrogenic due to medications or laxative abuse. Systemic diseases can present with diarrhea. Metformin (DM) causes diarrhea. SLE and systemic sclerosis (collagen vascular diseases) could causes diarrhea.
- PE : What is the difference between carcinoid tumor and carcinoid syndrome?

carcinoid tumors in the small bowel & bronchial tree releasing histamine and serotonin. If it metastasize to the liver, the liver won't be able to get rid of these substances resulting in carcinoid syndrome. carcinoid tumor produces serotonin which goes to liver and get metabolized to 5-HIAA which has no effects (in this stage there is no evident signs and symptoms). carcinoid syndrome is when carcinoid tumor metastasize to liver so serotonin bypasses the metabolism and is able to produce its effects such as flushing and diarrhea, and less frequently, heart failure, emesis and bronchoconstriction (wheezing).

- CBC :

- anemia (could be due to folic acid, B12, or iron deficiency. It could be due to chronic diseases or blood loss).
-Leukocytosis : infections or inflammatory causes.

- Stool analysis : (>200 cc)

- Electrolytes : osmotic gap (less than 25 = secretory, more than 100 = osmotic).
- pH : bacterial fermentation after eating carbs produce lactic acid which drops pH of the stool. Children with lactase deficiency (lactose intolerance) will have perianal rash and itching.

Investigations:

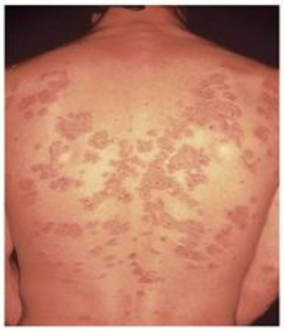
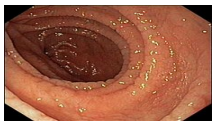
- **Culture** (more useful only for acute), O&P (ova and parasites), Giardia Ag, C diff toxin, Coccidia, Microsporidia, Cryptosporidiosis Opportunistic infections especially pts with HIV
- **Fecal leukocytes** (or marker for neutrophils: lactoferrin or calprotectin, which get secreted from WBC into the stool, important in IBD.)
- **Fecal occult blood**
- **Stool electrolytes for osmolar gap** = 290 – 2[Na + K]
- **Stool pH** (<6 suggests CHO malabsorption due to colonic bacterial fermentation to CO2, H2, and short chain FA)
- **Fat content:** Quantitative: 48h or 72h collection of stool (> 6g fat is abnormal)
  Qualitative: Sudan stain just confirming presence of fat
- **Laxative screen** (if positive, repeat before approaching pt) magnesium > pts with body dysmorphic disorder مهووسين بشكل أجسامهم فياخذونها عشان ينحفون
- **Imaging:** Small bowel series, CT/MRI or CT/MR enterography malignancy?
- **Endoscopy** with small bowel biopsy and aspirate for quantitative culture
- **Colonoscopy**, including random biopsies

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, low serum levels of triglycerides, cholesterol.
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, milk intolerance.	Increased breath hydrogen, High stool osmotic gap, acidic stool (pH <6)
Vitamin B12	Macrocytic Anemia, Subacute combined degeneration of the spinal cord (early symptoms include paresthesias and ataxia associated with loss of vibration and position sense) neuropathy	Vitamin B12 decreased, abnormal schilling test, serum methylmalonic acid and homocysteine increased. Macrocytic Anemia and hypersegmented neutrophils
Folic Acid	Anemia	Macrocytic Anemia and hypersegmented neutrophils, Serum and RBC folate decreased, serum homocysteine increased.
Vitamin B (general) B1,B2,B3, and B7	Cheilosis [5], painless glossitis, acrodermatitis, angular stomatitis Beriberi: nutritional disorder caused by a deficiency of thiamin (vitamin B1)	-
Iron	Anemia, glossitis, pagophagia[6]	Microcytic anemia, Serum iron and ferritin decreased, total iron binding capacity increased
Calcium and vit D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek and Trousseau signs, osteomalacia and osteoporosis	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum retinol decreased
Vitamin K	Hematoma, bleeding disorders Coagulopathy	Prolonged prothrombin time (PT) and elevated INR, decreased vitamin K-dependent coagulation factors (2,7,9,10)

[5] Cheilosis is a painful inflammation and cracking of the corners of the mouth. It also is called cheilitis.
[6] Pagophagia is the compulsive consumption of ice or iced drinks.

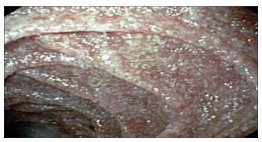
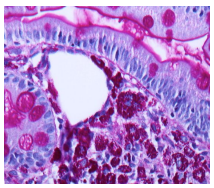
Objective 2- To discuss common causes of chronic diarrhea:

1. Celiac disease

Introduction	- Celiac disease is: Small intestinal malabsorption of nutrients following the ingestion of wheat gluten or related proteins from rye and barley. Celiac disease is an autoimmune disease vs. gluten intolerance (No microscopic abnormalities or antibodies are found) and the prognosis of the two disease is not the same - Villous atrophy of the small intestinal mucosa is a characteristic but not specific can be seen on other diseases (Tropical sprue and whipple's disease) - Strict adherence to a gluten free diet > Prompt clinical and histologic improvement - Reintroducing gluten > Clinical and histologic relapse.
Pathophysiology (duodenum is the first area to be attacked)	Gluten contains gliadin protein which gets deaminated and presented by APC to T-cells > immunoglobulins production which attack Enterocytes > very leaky Enterocytes. 1. The disease affects 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 & lymphocytes)
Who is at risk? **Autoimmune diseases**	Type 1 DM (3-6%), Autoimmune thyroid disease (6-8%), Down's syndrome, Connective tissue disease and **IgA deficiency** (2-3%). If patient have IgA deficiency and present with diarrhea think of celiac disease
Presentations	- Asymptomatic. first degree relatives with celiac disease? > screening - Nonspecific GI symptoms: ➔ 3D (**D**iarrhea, **D**istension (Bloating) and **D**yspepsia) dyspepsia is aggravated by food intake (multiple symptoms) - Nutritional deficiency: Anemia (Iron & folate) and Osteoporosis. ★ **young pt with iron deficiency anemia you have to rule out celiac disease!!!!! (MCQS)** while in elderly you should exclude GI tumor - Fat soluble vitamin deficiencies: ● Vit A: poor night vision, follicular hyperkeratosis ● Vit D: hypocalcemia, osteoporosis. ● Vit K: easy bruising & bleeding, elevated INR.  - Dermatitis herpetiformis: Maculopapules and vesicles in extensor surfaces and above the elbows Biopsy > IgA deposition inside the vesicles (thus won't be present in patients who also have IgA deficiency) .They get cured with gluten free diet. - Elevated ALT & AST. celiac disease is one of the causes of fatty liver (Steatosis) ! - Malignancy (a complication) : The most common types are small bowel T-cell lymphoma & Small bowel adenocarcinoma (may increase the risk of esophageal squamous cell carcinoma), could be the first presentation **(MCQs !!!!!!!!)** Usually there is no screening for Malignancy (patient on gluten free diet but develops anemia, weight loss, night sweats and diarrhea > Malignancy
Endoscopy MCQs!!!!!!	➔ Normal ➔ **Loss of mucosal folds (Flattening of mucosa)** ➔ **Scalloping of mucosa** ➔ Ulcerations 

Histology	villous atrophy and crypts hyperplasia + lamina propria infiltration by lymphocytes. villous atrophy and crypts hyperplasia are suggestive of celiac disease but not every villous atrophy is celiac disease and not every celiac disease will cause villous atrophy.
Serology	- **Anti-tTG: Anti-tissue transglutaminase antibody (IgA) is the best marker/ MCQS!!!** Sensitivity 95%; specificity 97.5% IgG-specific antibody tests for endomysium, gliadin, and tissue transglutaminase are useful for the identification of IgA-deficient patients with CD (celiac disease) so order IgG not IgA! - **IgG anti-gliadin antibodies** (Can be used in IgA deficient patients): Sensitivity 69-85% (~75) Spec 73-90% (~80) not sensitive and not specific - IgA anti-gliadin antibodies, Sensitivity 75-90% (~80) Specificity 82-95% (~85) - Endomysial antibody (IgA), Sensitivity 85-98% (~93) Specificity 97-100% (~99)
Management	- Education - Gluten-free diet: avoid wheat, barley, rye & oat - Correct nutritional deficiencies (**Iron**, Ca, Vit D) - Anticipate complications: ulcerative jejunitis, malnutrition and malignancy
Notes; **MCQs!!!!!!**	➢ Young patient + iron deficiency anemia + villous atrophy >> think of celiac disease ➢ Scalloping mucosa duodenum >> think of celiac disease ➢ IgA deficiency + diarrhea >> think of celiac disease. ➢ Celiac disease has risk of cancers: Small bowel lymphoma and Small bowel adenocarcinoma.

2. Whipple disease

Introduction	- Chronic systemic infection by Tropheryma whipplei. - **Has GI, CNS, CVS, MSK & skin manifestations.** ★ MCQs : patient with joints pain, diarrhea and CNS manifestations? Whipple disease!!!!!
Pathophysiology	Caused by bacterial and macrophage-predominant inflammatory cell infiltration of the small intestinal mucosa and obstruction of mesenteric lymph nodes.
Presentations	- **Malabsorption** – weight loss, diarrhea (watery or fatty) and abdominal pain. - **CNS:** Progressive dementia, Supranuclear ophthalmoplegia, Altered LOC (level of consciousness), Oculo-masticatory & oculo-facial skeletal dysfunction. - **CVS:** Endocarditis – MV most common, Myocarditis, Pericarditis. - **MSK:** Oligo or polyarthralgias - **Skin (Common):** Hyperpigmentation
Endoscopy	Whitish to yellow plaque-like patches in 75% of patients (representing lipid droplets and/or **lymphangiectasia**). Any cause of lymphatic obstruction (TB, Lymphoma and malignancy will cause malabsorption and steatorrhea 
Histology	- **Foamy macrophages (macrophages try to engulf the organism but can't digest it) on routine H&E** - **Numerous PAS-positive granular particles (pink/purple appearing)** ➔ Lysosomes filled with T. whipplei ★ **MCQs : Foamy macrophages and PAS +ve = whipple** 
Management	- 2 weeks with Antibiotics to cross BBB: **Ceftriaxone** 2g IV daily monotherapy, or Penicillin G 2 MU IV q4h PLUS streptomycin… - THEN **Septra** DS tab BID x 1 year (Trimethoprim/sulfamethoxazole)

Notes; MCQs!!!!!!	➢ Fatty **Diarrhea** + **joint pain** + **CNS** symptoms >> think of **whipple** disease. ➢ **Foamy macrophages** with **PAS positive** >> think of **whipple** disease.

3. Small Bowel Bacterial Overgrowth (SBBO)

Normal Microbiome:

1. Stomach 0-10^3 CFU/ml
2. Jejunum 0-10^4 CFU/ml

➔ Gram + aerobes (oral streptococci, lactobacillus); no gram –ve aerobes

3. Ileum 10^5-10^9 CFU/ml
4. **Colon 10^{10}-10^{12} CFU/ml**

➔ Anaerobes: bacteroides, peptostreptococcus, lactobacillus, bifidobacterium, clostridium

➔ Facultative aerobes: e. coli, enterococcus, staphylococcus

Normal barriers that prevent SBBO and their abnormalities

Mechanism to prevent SBBO	Possible causes of SBBO
Gastric acid & pancreatic enzymes (they have bactericidal effect)	chronic pancreatitis, low HCl due to surgery or PPI (proton pump inhibitors)
Intact bowel structure	Surgery, diverticulum stagnation of bacteria
Cleansing effect of bowel motility – interdigestive migrating motor complex	dysmotility
Gut immunity – intraluminal secretory IgA	Immunodeficiency (any type)
Competent ileocecal valve	scarring from inflammation, removal/injury by surgery leading to reflux of stool
Competition by other bacteria	Antibiotics (broad spectrum antibiotics)

Effect of SBBO:

➔ **Bile acids metabolism** – deconjugated bile acids (leading to steatorrhea)

➔ Bilirubin metabolism – deconjugated bilirubin

➔ CHO metabolism – C02, H2, D-lactic acid, organic acids (short chain fatty acids)

➔ Lipid metabolism – short chain fatty acids

➔ Protein metabolism – amines, ammonia

Presentations

- Bloating, diarrhea, abdominal pain, weight loss, neuropathy
- **B12 deficiency – utilized by bacteria for nutrition**
- **Elevated folate level** (normal to high levels) **- produced by bacteria**

Low vit. B12 and high folate (bacteria consumed B12 and produce folic acid) >> think of SBBO **MCQs!!!**

- Vitamin A,D,E,K deficiency (due to steatorrhea)
- Iron deficiency (bacteria consume iron)
- Hypoproteinemia, hypoalbuminemia
- Fat and CHO malabsorption

Investigations

- Jejunal aspirate and culture – **gold standard!**
- C^{14}-labeled bile acid breath test.
- C^{14}-xylose breath test

Normal people when take one of the above substances the bacteria are unable to cleavage the bond so if you breath it you will not find any radio-labeled carbon coming out from the lung

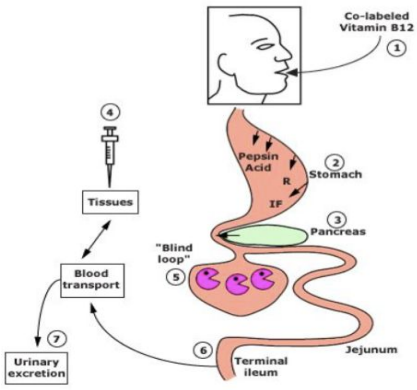
But in people with bacterial overgrowth > Cleavage > systemic circulation > Lungs

- H breath test producing early or double peak of hydrogen
- Schilling's test **(Malabsorption of vitamin B12)** See the next slide

Management	- **Treat underlying cause** e.g. discontinue acid suppressive meds, treat inflammatory Crohn's disease, remove strictures, etc… - Nutrition: replace fat soluble vitamins and B12, follow Low CHO diet to limit bacteria substrate - 7 – 10 days of antibiotics: ➔ Metronidazole, Amox/Clav, Tetracycline, Doxycycline, Amoxicillin (**May need to cycle Abx to avoid resistance)** - Bowel cleanse with PEG (Polyethylene glycol) نغسلها - Prokinetic to stimulate motility > bacterial cleansing - Octreotide – at low dose, has a promotility effect; (causes hypomotility at higher doses) - Probiotics – minimal evidence

The Schilling test:

- B12 deficiency is caused by multiple things, so the idea here is to exclude one by one.
- B12 metabolism: saliva (R factor binds B12) > stomach "IF" > duodenum (get exposed to pancreatic enzymes "trypsin" > trypsin releases R factor from B12 > then IF will bind B12 > terminal ileum > absorption.



Malabsorption of **vitamin B12** may occur as a consequence of:

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

To distinguish between these causes of fat malabsorption, the Schilling test is performed on 4 stages, Radiolabeled B12 is given orally, in each stage you'll add one of the following and then measure B12 absorption using a urine sample:

Stage I: + IM vitamin B12[7] if B12 levels are normal then the cause of its deficiency was decreased intake

Stage II: + intrinsic factor (IF) if B12 is normal after supplement of IF then the cause was pernicious anemia

Stage III: + oral antibiotics if B12 is normal after Antibiotics then the cause was bacterial overgrowth

Stage IV: + supplement of pancreatic enzymes if B12 is normal after supplement of pancreatic enzyme (trypsin) then the cause was pancreatic insufficiency

- if B12 is not normal after all of these stages the cause of deficiency might be ileal disease

TABLE 350e-1 DIFFERENTIAL RESULTS OF THE SCHILLING TEST IN SEVERAL DISEASES ASSOCIATED WITH COBALAMIN MALABSORPTION

	^{58}Co-Labeled 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

Schilling Test - Stages 1 to 4 (mnemonic) 0:36 minutes - **read more**

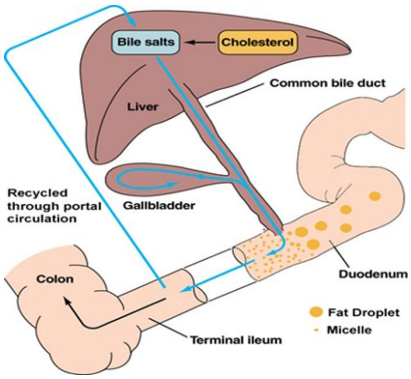
4. Tropical Sprue

Introduction	- Is characterized by villous atrophy and crypt hyperplasia **BUT DUE TO INFECTIOUS CAUSE (celiac : autoimmune)** - It is an acquired defect – not present in newborns. Travelers from the industrialized world to most tropical regions of Asia, Africa, the Middle East, the Caribbean and Central and South America may develop it. - **Hx of travel to tropical area for long period (MCQs!!!!!!)**
Cause	Not known, but seems to be due to continuous bacterial contamination of the upper small bowel and nutritional deficiency. Infection and malnutrition
Presentations	Chronic diarrhea often with steatorrhea, anorexia, abdominal cramps, bloating **Both B12 and folate deficiency** (unlike SBBO, where there is Low vit. B12 and high folate)

[7] This is not enough to replete or saturate body stores of B12. The purpose of the single injection is to temporarily saturate B12 receptors in the liver with enough normal vitamin B12 to prevent radioactive vitamin B12 binding in body tissues (especially in the liver), so that if absorbed from the G.I. tract, it will pass into the urine.

Investigations	If suspicion is high – jejunal aspirate and biopsy
Management	1) Folate & B12 Supplement 2) **Tetracycline** for 3-6 months.
Notes	1. History of **travel** to tropical areas. 2. **Both** vit. B12 and folate are **low**. 3. Fatty diarrhea.

5. Bile Acid-Induced Diarrhea :



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

- ★ Limited resection > **watery diarrhea** (Secretory not osmotic)
- ★ extensive resection > fatty diarrhea.

Tx : **Cholestyramine** (it binds to bile acids thus reducing its irritant effects)

6. Exocrine Pancreatic Insufficiency :

1. Mainly in patients with **chronic pancreatitis,** where the pancreatic enzyme lipase is deficient, which plays a role in fat breakdown and absorption"Maldigestion" resulting in **Steatorrhea**
2. Improves with **pancreatic enzymes replacement therapy** (Protease and lipase supplements)

★ MCQs : Hx of abdominal pain, high alcohol intake for long time, diarrhea = pancreatic insufficiency

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 → peptides
		chymotrypsin	protein → peptides
		pancreatic lipase	fats → fatty acid + glycerol

Diseases and Mechanisms Associated With Exocrine Pancreatic Insufficiency

Disease or Condition	Pathologic 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 disease, Schwachman-Diamond syndrome	Decreased pancreatic stimulation
Zollinger-Ellison syndrome	Acid-mediated inactivation of pancreas enzymes
Gastrectomy, gastric bypass, extensive small bowel surgery	Gastrointestinal/pancreatic surgery

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 villous 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

- **SBBO:**
- Look for & treat underlying causes üB12 def
- Schilling's test
- **Tropical Sprue:**
- Hx of travel to tropical area for long period
- Exocrine pancreatic insufficiency: alcohol
- Mainly in patients with chronic pancreatitis
- Steatorrhea
- Improves with pancreatic enzymes replacement therapy
- **Bile acid-induced diarrhea:**
- Watery diarrhea
- Improves with cholestyramine

Cases

1. 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
E. Crohn's disease

2. 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, antiemetics 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

3. 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

4. A 34-year-old white woman is treated for a UTI with amoxicillin. Initially she improves, but 5 days after beginning treatment she develops recurrent fever, abdominal bloating, and diarrhea with six to eight loose stools per day. What is the best diagnostic test to confirm your diagnosis?

A. a. Identification of Clostridium difficile toxin in the stool
B. b. Isolation of C difficile in stool culture
C. c. Stool for white blood cells (fecal leukocytes)
D. d. Detection of IgG antibodies against C difficile in the serum
E. e. Visualization of gram-positive rods on microscopic examination of stool

Answers

1. **B.** The history of the acute onset of diarrhoea coupled with nausea and vomiting a few hours after a meal is highly suggestive of a clinical diagnosis of gastroenteritis (B). Irritable bowel syndrome (A) sufferers usually experience chronic diarrhoea alternating with constipation. There is no history of blood-stained or mucus-based diarrhoea, which is usually seen in inflammatory bowel disease (C and E) (ulcerative/Crohn's colitis). With regard to the clinical scenario, the patient has no past medical history which therefore makes laxative abuse (D) very unlikely.

2. **A.** Gastroenteritis is usually a self-limiting disease that often does not require pharmacological therapy. The mainstay of treatment is to advise patients to increase oral fluid intake (A) to compensate for the water lost from diarrhoea and vomiting. However, in some circumstances, where severe dehydration secondary to profuse diarrhoea exists (leading to confusion and hypotension) patients may warrant admission for intravenous fluid rehydration (C). Antibiotic therapy (B) and (D) is usually not indicated for gastroenteritis unless a bacterial organism has been isolated. The fact that the patient's observations are within the normal range and she is not systemically unwell, the most appropriate answer here would be to advise the patient on oral fluid rehydration and prescribe antiemetics (e.g. metocloperamide), followed by discharge.

3. **C.** The most appropriate investigation for this patient would be to obtain a stool sample (C), especially if there is a history of travel. Performing tests such as full blood count (A), urea and electrolytes (B), abdominal x-ray (D)

4. **A.** Clostridium difficile is an important cause of diarrhea in patients who receive antibiotic therapy. Clostridium difficile proliferates in the gastrointestinal tract when the normal enteric bacteria are altered by antibiotics. Commonly implicated antibiotics include ampicillin, clindamycin, cephalosporins, and trimethoprim-sulfamethoxazole. The diarrhea is usually mild to moderate, but can be profuse. Other clinical findings include fever, abdominal pain, abdominal tenderness, leukocytosis, and serum electrolyte abnormalities. The diagnosis is made by demonstration at sigmoidoscopy of yellowish plaques (pseudomembranes) that cover the colonic mucosa or by detection of C difficile toxin in the stool. The pseudomembranes consist of a tenacious fibrinopurulent mucosal exudate that contains extruded leukocytes, mucin, and sloughed mucosa. Isolation of C difficile from stool cultures is nonspecific because of asymptomatic carriage, particularly in infants. Testing for fecal leukocytes is also nonspecific and may be negative in C difficile colitis. Serological tests are not clinically useful for diagnosing this infection. Although Clostridia are indeed gram-positive bacilli, they cannot be distinguished microscopically from numerous other anaerobic organisms in stool. Pseudomembranous colitis demands discontinuation of the offending antibiotic. Antibiotic therapy for moderate or severe disease includes oral metronidazole or vancomycin. Cholestyramine can be used therapeutically to bind the diarrheogenic toxin.