Case scenario

Mechanisms Of Malabsorption and Diarrhea

objectives

- Understand that the malabsorption is caused by either abnormal digestion or small intestinal mucosal disease.
- Know that malabsorption can affect many organ systems (alimentary tract, hematopoietic system, musculoskeletal system, endocrine system, epidermis, nervous system).
- Know the pathogenesis, clinical features, pathology (gross and microscopic features) and complications (T-cell lymphoma and GI tract carcinoma) of celiac disease.
- Know the cause and types of Lactose intolerance.
- Define diarrhea.
- Understand the four categories of diarrheal diseases, and list the major causes in each category.
- List the causes of chronic diarrhea.

Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by: Razan AlRabah & Ibrahim AlDakhil

Editing File

Malabsorption Syndrome

Malabsorption syndrome

It is the inability of intestine to absorb nutrients adequately into the bloodstream. Such impairment can be of single or multiple nutrients depending on the abnormality. (Single: Lactose intolerance, Multiple: Celiac disease)

Pathophysiology Of Malabsorption Syndrome:

The malabsorption syndrome is caused either by **inadequate digestion** or **small intestine abnormalities**.

1 Inadequate digestion

- **Stomach**
  - Postgastrectomy[1]: less stomach tissue (surface area) to digest food.
  - Zollinger Ellison syndrome.
- **Pancreas**
  - Deficiency of pancreatic lipase.
  - Chronic pancreatitis.
  - Cystic fibrosis: pancreatic juices become thick and enzymes can't reach the intestine.
  - Pancreatic resection.
- **Bile**
  - Obstructive jaundice: obstruction of the bile duct
  - Terminal ileal resection[2]

2 Small intestine abnormalities

- **Mucosa**
  - **Celiac disease**
  - Tropical Sprue injury to enterocytes and villi by microbial insult. After visiting a tropical area
  - Whipple's disease gram positive infection
  - **Giardiasis** protozoan infection
- **Inadequate small intestine**
  - Intestinal resection
  - Crohn's disease. Autoimmune transmural inflammatory disease
- **Lymphatic obstruction**
  - Intestinal lymphangiectasia
  - Malignant Lymphoma

1- surgical removal of a part or the whole of the stomach.
2- site of reabsorption of bile

Malabsorption Syndrome

Clinical features of malabsorption syndrome:

- **Steatorrhea:** increased fecal excretion of fat; soft, yellowish, greasy stools Which causes systemic effects of deficiency of vitamins (Fat soluble), minerals, protein and carbohydrates.
- Growth retardation, failure to thrive[1] in children.
- Weight loss and anorexia despite increased oral intake of nutrients.
- Abdominal distension and borborygmi (increased bowel sounds)

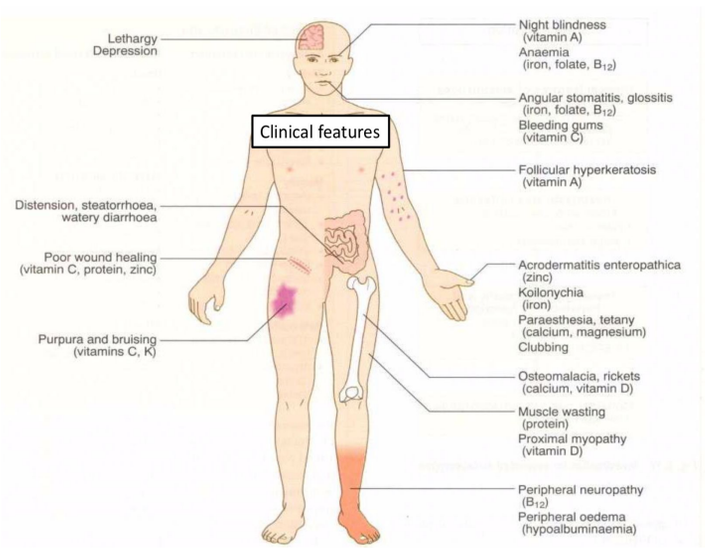
Clinical features that depend on the deficient nutrients:

1. Deficiency of **Protein**
   - Muscle wasting
   - Edema[2] and Swelling
2. Deficiency of **B12, folic acid and iron**
   - Anemia (fatigue & weakness)
3. Deficiency of **Vitamin D, Calcium**
   - Muscle cramp
   - Osteomalacia & Osteoporosis
4. Deficiency of **Vitamin K, Other Coagulation Factors**
   - Bleeding tendencies

Diagnosis of Malabsorption Syndrome

There is no specific test for malabsorption. Investigation is guided by symptoms and signs .

1. **Fecal fat study to diagnose steatorrhoea**
2. **Blood tests**
3. **Stool studies**
4. **Endoscopy** : Biopsy of small bowel



(1)- Grow
(2)-due to hypoalbuminemia

Celiac disease

An immune reaction to gliadin[1] fraction of the wheat protein gluten

- Usually diagnosed in childhood – mid adult.
- Patients have raised antibodies to gluten autoantibodies (Anti-tissue Transglutaminase Antibody)
- Highly specific association with **class II HLA (DQ2 or DQ8)** and, to a lesser extent, DQ8 (haplotype DR-4).

Clinical features

- GI symptoms appear at age 9-24 months.
- Symptoms begin at various times after the introduction of foods that contain gluten**.**

Age of onset and the type of presentation

- **Infants and toddlers** : GI symptoms and failure to thrive.
- **Childhood** : minor GI symptoms, inadequate rate of weight gain.
- **Young adults** : anemia is the most common form of presentation.
- **Adults and elderly** : GI symptoms are more prevalent.

Histological appearance

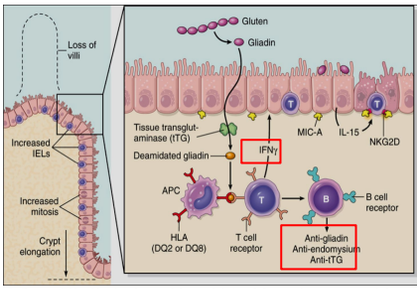
- Mucosa is **flattened** with marked **villous atrophy.**
- Intraepithelial **lymphocytosis.**
- **Crypt elongation(hyperplasia).**
- Mainly in duodenum, Tropical sprue affects most of small intestine

Diagnosis

- Clinical documentations of malabsorption.
- Stool : increased fat
- Small intestine biopsy demonstrate **villous atrophy.**
- Serology is +ve for IgA to tissue transglutaminase or IgG to deamidated gliadin or anti-endomysial antibodies
- Improvement of symptom and mucosal histology on gluten withdrawal from diet (wheat, barley, rye, flour)[2]. (Reversible)

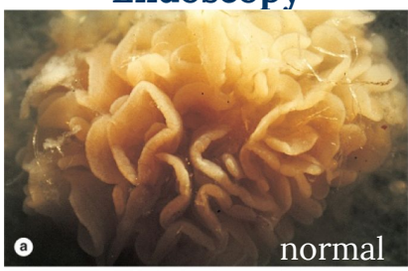
Complications

1. Osteopenia
2. Osteoporosis
3. Infertility in women, short stature, delayed puberty, anemia,
4. Malignancies,(intestinal T-cell lymphoma)
5. 10 to 15% risk of developing GI lymphoma.



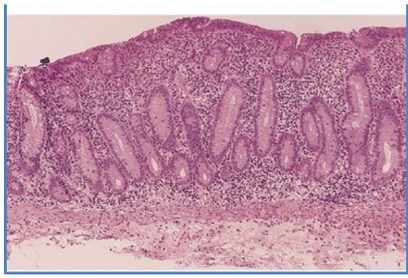
When Gliadin is deamidated it's able to interact with HLA complexes on antigen-presenting cells and then be presented by these cells to CD4+ T cells. These T cells in lamina propria produce cytokines that contribute to the tissue damage and it's a characteristic mucosal histopathology. An antibody response follows.

Endoscopy



Microscopy

Partial villous atrophy



Total villous atrophy

1- A 33-amino acid peptide, resistant to degradation by gastric, pancreatic, and small intestinal proteases.
2- wheat, barley, flour Other grains, such as rice and corn flour, **do not have such an effect.**

Lactose intolerance

Low or absent activity of the enzyme lactase .

Pathophysiology :

Lactose → (**Lactase**, At the brush border of enterocytes) → **glucose** + **galactose**

Causes

Inherited lactase deficiency

Congenital lactase deficiency :
Extremely rare

Childhood-onset and adult-onset lactase deficiency :

- common
- Genetically programmed progressive loss of the activity of the small intestinal enzyme lactase.

Acquired lactase deficiency

Transient

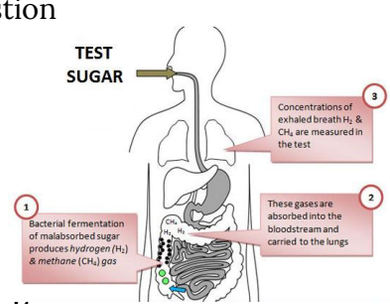
Secondary lactase deficiency
due to intestinal mucosal injury by an infectious, allergic, or inflammatory process

Gastroenteritis: Infectious diarrhea, particularly viral gastroenteritis in younger children, may damage the intestinal mucosa enough to reduce the quantity of the lactase enzyme. (acquired lactase deficiency)

Clinical features of Lactose intolerance: 1 hour to a few after milk ingestion

- **Bloating**
- **Abdominal discomfort**
- **Flatulence** (Accumilation of gas)

- **Specific to Lactose intolerance only, so you will not see anemia and hyperplasia in contrast to Celiac disease which is malabsorption of all nutrients.**



A 3-week trial of a diet that is free of milk and milk products is a satisfactory trial to diagnose lactose intolerance

Diagnosis:

- Empirical treatment with a **lactose-free diet (3 weeks)**, which results in resolution of symptoms
- **Hydrogen breath test**
  - Administer oral dose of lactose.
  - Since H_2 in the GI can only be produced by bacteria fermenting lactose in the colon.
  - Unabsorbed lactose that reached the colon will result in increase H_2 production, which is exhaled.

Diarrhea

Fecal osmolality

- Normal fecal fluid values:
  Osmolality: ~290 mOsm/kg equal to the serum osmolality.
  Na^+: ~30 mmol/L
  K^+: ~75 mmol/L
- Under normal circumstances, the major osmoles are Na^+, K^+ Cl^-, and $HCO3^-$

Stool (fecal) osmotic gap Female's slides

Fecal Osmotic Gap
290 mosm/kg H_2O - 2([Na+] + [K+])

- **Stool osmotic gap = Stool osmolality - 2 x (stool Na + stool K)**
- A calculation to distinguish among different causes of diarrhea.
- A normal gap is between 50 and 100 mosm/kg
- A **low stool osmotic gap** <50 mosm/kg → **secretory diarrhea.**
  - That secreted sodium and potassium ions make up a greater percentage of the stool osmolality in secretory diarrhea
- A **high gap** >125 mosm/kg → **osmotic diarrhea.**
  - Molecules such as unabsorbed carbohydrates are more significant contributors to stool osmolality.

Diarrhea

- 3 or more loose or liquid stools per day.
- Abnormally high fluid content of stool 200-300 gm/day (more than 250g of stool per day)
- The loss of fluids through diarrhea can cause **dehydration** and **electrolyte imbalances.**[1]
- Easy to treat but if untreated, **may lead to death** especially in **children**. More than 70% of almost 11 million child deaths every year are attributable to 6 causes: **Diarrhea,** Malaria, Neonatal infection, Pneumonia, Preterm delivery, Lack of oxygen at birth.

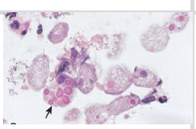
Classification (based on duration)

1. **Acute** 2 weeks
2. **Persistent or subacute** 2-4 weeks
3. **Chronic** 4 weeks

1-Treatment is mainly IV fluid replacement.

Types of Diarrhea

Type	Secretory	Osmotic
Definition	• An increase in the **active secretion of water and electrolytes**. • Enterotoxins stimulate Cl-channels regulated by cAMP and cGMP • loss of isotonic fluid.	• Excess amount of **poorly absorbed substances that exert osmotic effect**, so water is drawn into the bowels causing diarrhea, loss of hypotonic fluid. • Doesn't cause inflammation in bowel mucosa.
Stool output	High output	Output is usually not massive
Fasting effect	Lack of response	Improves the condition
Stool osmotic gap	Stool osmotic gap is normal or **low** < 100 mOsm/kg.	Stool osmotic gap is **high**, > 125 mOsm/kg (loss of hypotonic fluid)
Causes	The most common cause is a **bacterial toxin (E. coli, cholera)** that stimulates the secretion of anions. Other causes: • **Neuroendocrine tumours: Zolinger-elison** tumor carcinoid tumor, gastrinomas. • **Enteropathogenic virus** e.g. rotavirus and norwalk virus. • **Rectal villous adenoma.**The villous surface of this tumor secretes water and ions . • **Chronic laxative use causing Melanosis coli (dark pigment is deposited in the lamina propria of the colon).**	• **Malabsorption** in which the nutrients are left in the lumen to pull in water e.g. **lactose intolerance, chronic pancreatitis, celiac diseases stool is high in fats.** • **Osmotic laxatives** e.g. Lactulose (non-absorbable sugar) • Poorly absorbed hexitols, sorbitol, mannitol, xylitol. (Non absorbable sugars). Additive food e.g.in gum. (sugar-less sweater). • Disaccharidase deficiency. • **Ingestion of poorly absorbed solutes.**
Screening test	Stool osmotic gap <50 mOsm/kg Fecal smear for leukocytes: **negative**	Stool osmotic gap > 125 mOsm/kg Fecal smear for leukocytes: **negative**

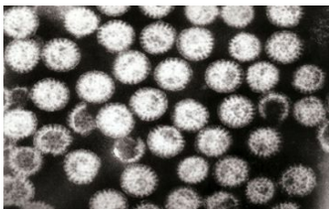
Type	Exudative	Motility related
Definition	Results from the outpouring of blood protein, or mucus from an inflamed or ulcerated mucosa.	Caused by **hypermotility**: the rapid movement of food through the intestines.
Stool output	**Bacterial dysentery:** diarrhea with blood and pus in stool	-
Fasting effect	Persists on fasting not related to food	-
Causes	Female's slides  • **Inflammatory bowel diseases.** • **Invasive infections** e.g. E. coli, Clostridium difficile and Shigella. • Some bacterial infections cause damage by invasion of the mucosa → **bacterial dysentery** • Entamoeba histolytica is a parasite that infect the small intestine causing (amoebiasis), and liver amebic abscess. • Colon cancer **The main organisms of bacterial dysentery are:** ○ *Campylobacter* invades mucosa in the jejunum, ileum and colon, causing ulceration and acute inflammation. ○ *Salmonella typhi*, *S. paratyphi* A, B, and C ○ *Shigella* are mainly seen in young children. ○ **Enteroinvasive and enterohemorrhagic *E. coli*** **Stool culture for O&P (ova and parasites)**	• **Irritable bowel syndrome (IBS)**: a motor disorder that causes abdominal pain and altered bowel habits (diarrhea and constipation) with diarrhea predominating. • Increased serotonin: **carcinoid syndrome** ○ Serotonin increases bowel motility but no inflammation in bowel mucosa. • Diabetic diarrhea • Hyperthyroid diarrhea
Screening test	Fecal smear for leukocytes: **positive**	**Increased 5-HIAA** (5-hydroxyindoleacetic acid)

Acute Diarrhea

Causes

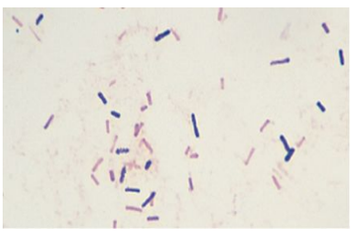
- **Infections:** Approximately 80% of acute diarrheas (viruses, bacteria, helminths, and protozoa).
- **Viral gastroenteritis,** viral infection of the stomach and the small intestine is the most common cause of acute diarrhea worldwide.
  - **Rotavirus** cause of:
    - **Most common cause of Severe childhood diarrhea and diarrhea related deaths worldwide.**
    - 40% of hospitalizations from diarrhea in children under 5.
    - 50% of acute diarrhea in infants.
- **Preformed toxin**, enterotoxin, cytoxin or invasive.
- **Food poisoning.** (Preformed enterotoxin, usually caused by staph.)
- **Drugs**: antibiotic, NSAID, antiacid, bronchodilators, antiarrhythmics.
- **Others**: occlusive colitis, ischemia, toxin (insecticides).

Rotavirus



Clinical manifestation

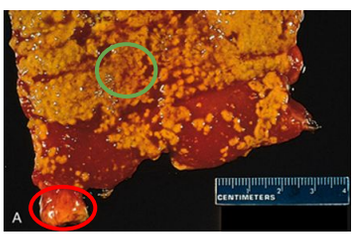
- Person become **dehydrated** with **electrolyte disturbance** and low bicarbonate in blood.
- Mild self limited, need rehydration.



Clostridium species
Gram-positive rods

Antibiotic associated diarrhea

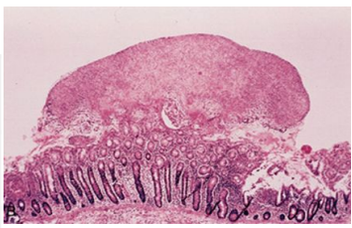
- Diarrhea occurs in 20% of patients receiving **broad-spectrum antibiotics**; about 20% of these diarrheas are due to **Clostridium difficile** (it will replace normal flora after treatment and causes necrosis and ulcerations)
- Leading to **pseudomembranous colitis:** swelling or inflammation of the colon due to an overgrowth of Clostridium difficile.



Pseudomembranous colitis
Necrosis and exudate making a membrane with hemorrhagic area, compare to normal pale tissue.

Evaluatory test

Fecal leukocytes	
Non present	**Present**
Non-Inflammatory diarrhea Suggests a small bowel source or colon but **without** mucosal injury.	**Inflammatory diarrhea** Suggests **colonic mucosa damage caused by invasion:** • Shigellosis, Salmonellosis, Campylobacter or Yersinia infection, amebiasis). • Toxin (C difficile, E coli). • **Inflammatory bowel diseases.**



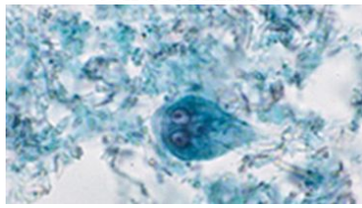
Chronic Diarrhea

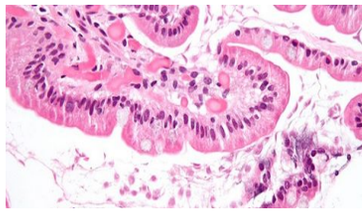
Aetiology most of the causes are noninfectious

- **Infection** e.g. **Giardia lamblia** (Giardiasis) unicellular parasite found in the lumen of duodenum causing mechanical barrier not allowing the food to be absorbed. **AIDS** often have chronic infections of their intestines that cause diarrhea. E.g **Cryptosporidiosis**
- **Post-infectious** Following acute viral, bacterial or parasitic infections
- **Malabsorption**
- **Inflammatory bowel disease (IBD)**
- **Endocrine diseases** e.g. carcinoid, gastrinoma
- **Colon cancer**
- **Irritable bowel syndrome**

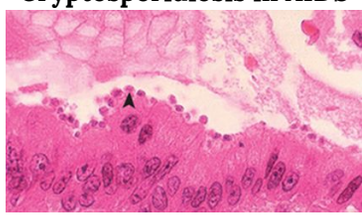
Parasitic and protozoal infections affect over half of the world's population on a chronic or recurrent basis.

Giardia lamblia





Cryptosporidiosis in AIDS



Complications

Fluid loss → **Dehydration** → Electrolytes loss → **Electrolytes imbalance** → Low Sodium bicarbonate in blood→ **Metabolic acidosis** → If persistent will→ **malnutrition**

Evaluatory test

Stool analysis ova, parasites		
+ve	**-ve**	
Infection	Stool fat test (normal <20%)	
	-ve	**+ve**
	Secretory, Non infectious and Inflammatory diarrhea	Malabsorption

Female's slides

If malabsorption is +ve do:

- **Quantitative stool for fat**:
  - Best screening test
  - 72-hour collection of stool
  - Positive test >7g of fat/24 hours.
- **Serum Anti-tissue transglutaminase antibodies.**
- **Anti-endomysial IgA antibodies.**
- **Antigliadin antibodies to check for celiac disease.**
- **Duodenal biopsy.**

Signs of dehydration

Early signs	Mature signs
• Fatigue • Anxiety • Irritability • Depression • Cravings • Cramps • Headaches	• Heartburn • Joint pain • Back pain • Migraines • Fibromyalgia • Constipation • Colitis

Summary

malabsorption	
Definition	• **It is inability of intestine to absorb nutrients adequatly into the bloodstream.** • **Highly specific association with class II HLA DQ2 (haplotypes DR-17 or DR5/7) and to a lesser extent, DQ8 (haplotype DR-4).**
causes	**a) Inadequate digestion:** **1) Stomach:** postgastrectomy **2) pancrase :** Cystic fibrosis, Chronic pancreatitis **3) bile:** Obstructive jaundice , Terminal ileal resection **b) Small intestine abnormalities:** **1) Mucosa** : **Celiac disease**,Giardiasis **2)Inadequate small intestine** : Intestinal resection ,Crohn's disease. **3)Lymphatic obstruction**: Intestinal lymphangiectasia ,Malignant Lymphoma
Diagnosis	**Fecal fat study to diagnose steatorrhoea** **Blood tests** **Stool studies** **Endoscopy** : Biopsy of small bowel
Celiac disease	
Definition	An immune reaction to **gliadin** fraction of the wheat protein **gluten**
Typical presentation	GI symptoms that characteristically appear at age 9-24 months.
Histology	**Mucosa is flattened with marked villous atrophy.**
Diagnosis	Steatorrhoea Histology Improvement of symptom and histology on gluten withdrawal from diet.
Complications	**1) Osteopenia 2) Osteoporosis 3) Infertility in women Short stature 4) delayed puberty 5) anemia 6) Malignancies(intestinal T-cell lymphoma)**
Lactose intolerance	
Definition	**Low or absent activity of the enzyme lactase**
causes	• **Acquired lactase deficiency** : Transient => infectious, allergic, or inflammatory process • **Inherited lactase deficiency**: a) Childhood-onset and adult-onset lactase deficiency b) Congenital lactase deficiency
Clinical features	1) Bloating abdominal 2) discomfort 3) flatulence **After 1 hour of consuming lactose**
Diagnosis	**1)Hydrogen breath test** **2) lactose-free diet** which results in **resolution of symptoms**

Summary

Classifications (Duration):

- Acute → 2 weeks
- Persistant → 2-4 weeks
- Chronic → 4 weeks in duration

	Secretory	Osmotic	Exudative	Motility-related
Osmotic gap	Normal <100 mosm/kg	High >125		
Fasting effect	No response	Fasting helps	Persists on fasting	
Stool	High stool output	Not massive	Blood and pus in stool	
Causes	**Increased secretion** due to: - Bacterial toxin (E. coli, cholera) - Zolinger elison tumors	**Poorly absorbed substance** that exert osmotic effect. 1- Malabsorption 2- laxatives	**Outpouring of blood** or mucus from inflamed or ulcerated mucosa. 1- inflammatory bowel disease 2- invasive infection 3- colon cancer	**Rapid movement** of food through intestine - IBS -Diabetic diarrhea - Hyperthyroid diarrhea

Aetiology

Acute	Chronic
- **Infections**: viral gastroenteritis (rotavirus) - Food poisoning - Drugs - **Antibiotic-Associated Diarrhea:** Clostridium difficile	**- Infection:** Giardia lamblia, AIDS -> cause other infections that cause diarrhea (Aids have low immunity) - Post-infectious why? Malabsorption lactose intolerance - Malabsorption - IBD - Endocrine disease - Colon cancer - IBS

Quiz

Q1: Which one of the following organisms may cause secretory diarrhea ?

A) Cholera
B) gonorrhea
C) s.aureus
D) l.monocytogenes

Q2: Which of the following is NOT a chronic malabsorptive disorder?

A) celiac disease
B) pancreatic insufficiency
C) Crohn disease
D) GERD

Q3: A 1-year-old girl is brought to the emergency room by her parents who report that she had a fever and diarrhea for 3 days. The child's temperature is 38°C (101°F). The CBC shows a normal WBC count and increased hematocrit. Which of the following microorganisms is the most likely cause of diarrhea in this young child?

A) Cytomegalovirus
B) Rotavirus
C) Salmonella typhi
D) Shigella dysenteriae
E) Yersinia jejuni

Q4: A 30-year-old woman presents with 2 days of abdominal cramping and diarrhea. Her temperature is 38°C (101°F), respirations are 32/minute, and blood pressure is 100/65 mm Hg. Stool culture shows a toxigenic E.coli infection. Which of the following best explains the pathogenicity of this organism in this patient?

A) Destruction of Peyer patches.
B) Invasion of the mucosa of the colon.
C) Invasion of the mucosa of the ileum.
D) Stimulation of acute inflammation in the superficial bowel mucosa.
E) Stimulation of fluid transport into the lumen of the intestine.

Q5: All of the following are causes of acute diarrhea except:

A) Viral gastroenteritis
B) Food poisoning
C) Inflammatory bowel disease
D) Antibiotic Associated Diarrhea

1-A,2-D,3-B,4-E,5-C

Quiz

Q1: Malabsorption Diagnosis is difficult due to which of the following?

A) Different presentation from patient to another
B) Difficult and invasive tests.
C) Low sensitivity of the tests.
D) Uncooperative patients.

Q2: Which of the following is diagnostic for celiac disease?

A) Increased fat in stool.
B) Detection of antibodies against gliadin.
C) Small intestine biopsy with villous atrophy.
D) Improvement with gluten free diet.

Q3: lactose intolerance may cause which type of diarrhea ?

A) osmotic
B) secretory
C) inflammatory
D) motility related diarrhea

Q4: malabsorption diarrhea is classified as?

A) Chronic invasive
B) Acute invasive
C) Chronic osmotic
D) Acute osmotic

Q5: Which of the following complications are associated with celiac disease but not other malabsorption diseases?

A) Osteoporosis
B) Short stature
C) Anemia
D) Malignancies

Q6: A 4-year-old girl is brought to the physician because her parents noticed that she has been having pale, fatty, foul-smelling stools. The patient is at the 50th percentile for height and 10th percentile for weight. Her symptoms respond dramatically to a gluten-free diet. Which of the following is the most likely diagnosis?

A) Celiac sprue
B) Cystic fibrosis of the pancreas
C) Ménétrier disease
D) Tropical sprue

Q7: which of the following is not a step of Celiac pathogenesis?

A) Gluten is digested into amino acids and peptides including including "Gliadin" which will get deamidated by "tTG"
B) it will interact with HLA-DQ2/HLA-DQ8 of the antigen presenting cells which will present it to CD4 leading to cytokines release
C) B-Cell activation leading to generation of antibodies against tTG , Gliadin and CD8 will enterocytes who expresses surface MIC-A
D) all of the above are true

1-A 2-D 3-A 4-C 5-D 6-A 7-D

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THANK YOU