Digestive System

University of Jordan

Faculty of Medicine

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Medical Committee
The University of Jordan

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☐ Anatomy ☐ Embryology

☐ Physiology ☐ Histology

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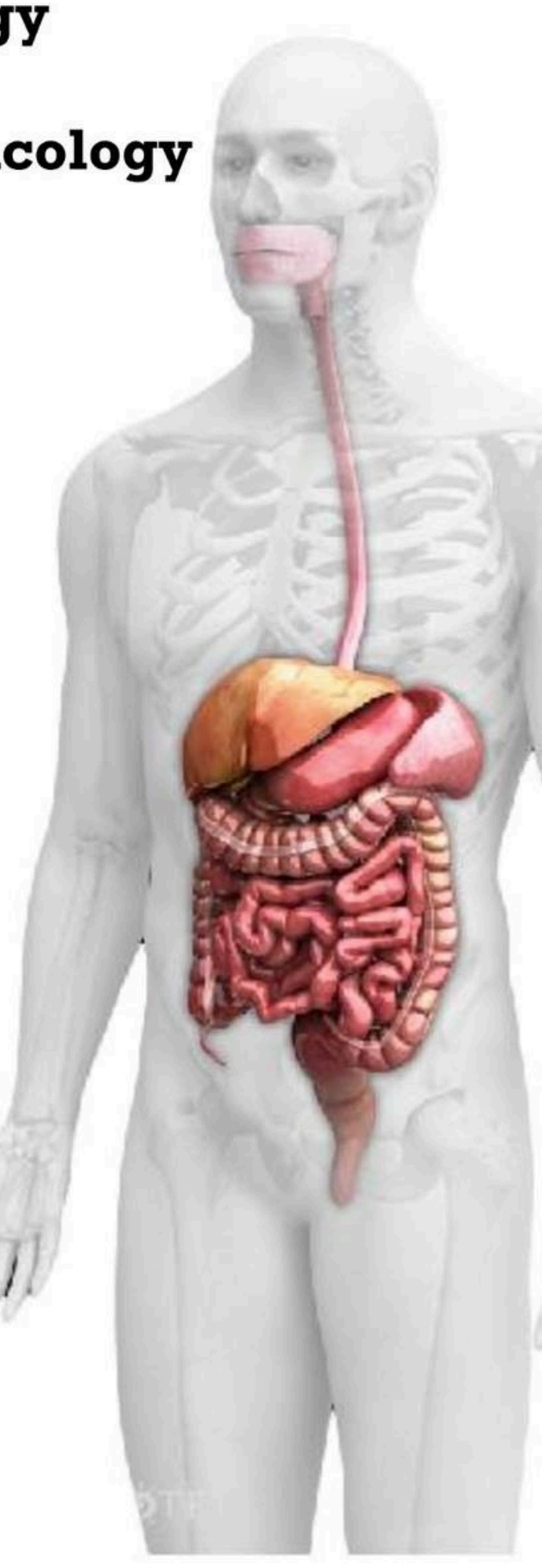

Sheet #: 4

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Small and large intestines

First of all you need to look at the figures in the slides; I couldn't include them as we don't have them yet.

Intestinal obstruction:

Can occur anywhere in the large and small intestines, it is more common in the small intestines because they are smaller in size.

80% of all intestinal obstructions are caused by:

1. **Adhesions** between the loops of intestines. You will find these in patients that went through surgery previously or in patients that had a previous infection (peritonitis for example), causing the deposition of fibrous tissue and this can also cause obstruction. They can also be found in patients that had an infection (observe photo in slide).
2. **Herniation** of a segment in the umbilical or inguinal regions. Herniation is when a part of the bowel through an anatomical location like in inguinal hernias, abdominal hernias, etc. The problem with herniation is if the opening is small enough to obstruct the bowel from coming back in, it could potentially increase edema of the bowel caused by venous stasis, or it could increase the pressure inside that hernia blocking venous supply and eventually arterial blood supply as well, thereby causing an infarct & obstruction.
3. **Volvulus**; when the intestine twists around itself blocking the venous supply and could even block its arterial supply causing ischemia and an infarct (which is dead tissue caused by ischemia).
4. **Intussusceptions**.(which you are all having a problem with)
   A photo of intussusceptions is described now: the upper part of the bowel herniates into the lumen of the lower part; either because there is an enlarged lymph node and dragging, or because there is loss of mechanical support in that particular area.

   All of these are emergencies that need surgical attention.

The remaining 20% for the most parts are caused by:

1) Tumors, this however is a very late presentation of tumors, meaning that the prognosis won't be that good.
2) Infarction, which occurs in two phases: ischemia followed by reperfusion injury. These patients present with pain, distention, vomiting and constipation. You are more likely to distend if the conditions are lower down (more volume) while vomiting is more likely to occur if the obstruction is higher in position.

Hirschspung Disease:

Causes intestinal obstruction and it is a congenital defect occurring in colonic innervations.

Neurons migrate down the GI tract normally; this disease is caused when the migration of neural cells from cecum to rectum is disrupted. This defect can be present with other defects or could be isolated. It is more common in males however it is more severe in females. The presentation of this obstruction because it is congenital is failure to pass meconium (the earliest stool of the baby.)

Unlike later feces, meconium is composed of materials ingested during the time the infant spends in the uterus: intestinal epithelial cells, mucus, amniotic fluid, and water. Meconium, unlike later feces, is viscous and sticky like tar, its color usually being a very dark olive green.

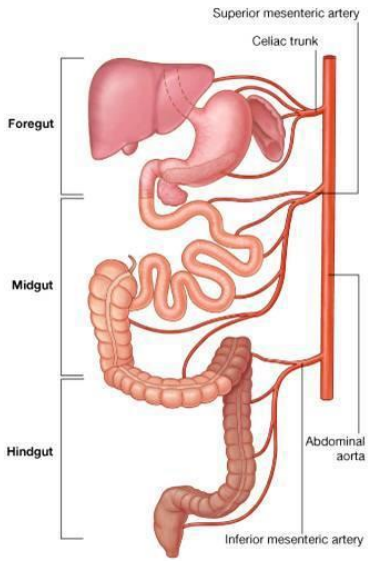
So Hirschspung disease presents with obstructive constipation and failure to pass meconium. This disease can be life threatening, causing: fluid and electrolyte disturbances, enterocolitis (inflammation caused by infections), perforation (from pressure) and peritonitis. All of these are medical emergencies so you need to recognize this properly.

This disease causes a distal intestinal segment lacking both the **meissner submucosal plexus** and the **Auerbach myenteric plexus** which always occurs in the rectum but could happen higher up depending on the movement of

neurons (direction) and where the movement of neurons stopped. The region without the neurons lacks peristalsis (no contraction). It could be a normal size or it could be contracted, the problem is that the region proximal to this will be pushing against an uncooperative region and will dilate. Treatment involves resection of the aganglionic region. Diagnosis depends on histological proof that the neurons are absent; this is also known as **congenital aganglionic megacolon**. In severe cases the whole colon may be distended.

Ischemic bowel disease:

Anatomy: the 3 major vessels are the **celiac trunk, the inferior and superior mesenteric**. As these main vessels approach the intestines they fan-out which means there is going to be multiple interconnections, anastomosis, and even connections between for example the celiac trunk the superior mesenteric, typically seen at the splenic flexure (watershed area). Because of these interconnections, your bowel is fairly resistant to ischemia. However, at some point there is going to be a misbalance between demand and supply and you can get ischemia of the bowel, and no matter how many interconnections you have its not going to help, which means there is going to be a big compromise already before any pathology occurs. Certain areas like the splenic flexure are more compromised than other because they share between 2 different areas, and ischemia that presents particularly there is problematic; as they already have sort of a compromised blood supply (they are sharing the very ends of one area with another area.)



For example you have an abdominal aortic aneurysm, which **compromises the main trunks** and could present with massive bowel ischemia because of the way the anatomy of vasculature to the bowel occurs, so if you take out the superior mesenteric you've destroyed most of the small intestines and a large part of your large intestines because the way these blood vessels fan out.

Infarction could be **transmural** (all the layers are involved) and that typically occurs with acute arterial obstruction (complete obstruction), or **mural** (mucosa and submucosal) or just **mucosal** not exceeding the muscularis mucosa.

The mural and the mucosal types typically occur with chronic ischemia, so there's been a long going reduction in blood flow, and at some point the patient has decompensated. And for whatever reason **locally** thrombosis or atherosclerosis could occur. **Systemic** effects typically occur in patients that are older, so patients that hay have had a cardiovascular disease (maybe a myocardial infarction and now their cardiac output has decreased or went into heart failure.) So don't lose sight of the whole patient and just focus on a small artery in the intestines, remember that when we are talking about ischemia you might be dealing with the system as a whole and not just one artery.

That was the whole point of hypoperfusion vs. acute obstruction, acute obstruction is more likely to present with transmural infarct while chronic hypoperfusion occurs when there is a misbalance between demand and supply and will most likely present with mucosal or mural infarction rather than transmural unless it is a severe misbalance.

In addition to the general vascular anatomy you need to recognize the histological anatomy of the bowel. The stem cells of the bowel are located in base of the crypt which is the closest to the blood supply, while the tips of the villi have the least blood supply; so the first to be affected are the tips whereas the base (stem cells) will be protected.

The doctor describes a photo normally nice villi, goblet cells, no inflammatory infiltrate, collagen disposition and a nice single layer of cells at the crypts (no hyper proliferation)

When injury occurs, stem cells respond by proliferation, so when you see hyper proliferation in crypts there is a problem.

We mentioned there are two steps ischemia (no blood supply, no oxygen, no nutrients no cells) and reperfusion (go over the steps of reperfusion from last semester again).

The outcome depends on the severity of the compromise and the duration as you already know. The vessel determines which part of the intestine is affected and how close it is to the aorta will determine the extent of the ischemia.

So you need to know your anatomy well.

Photo: how it shouldn't look like: epithelium has sloughed off the submucosa (which is a sign of ischemia), if you look at the bottom in chronic ischemia you can see a highly proliferative crypt (lots of cells bunch together) trying to compensate for the loss of the tip cells; additionally this excessively pink material is collagen deposition. You can get fibroses with chronic ischemia and rarely can it present with obstruction because of stricture formation.

Clinical features:

These people may be typically older with coexisting cardiac or cardiovascular disease as we mentioned (decrease in cardiac output) or they are chronic heart failure patients that have decompensated and they will present with severe pain.

Abdominal Guarding: is the tensing of the abdominal wall muscles to guard inflamed organs within the abdomen from the pain of pressure upon them, not allowing anything to poke them, they could present with nausea, vomiting, bloody diarrhea if there has been damage to blood vessels, reduction in peristalsis in areas with ischemia (you need oxygen and ATP to contract muscles). If there is bleeding, the patient can go into shock. (Remember we are talking about the patient as a whole.) Because the mucosa is compromised, any pathogenic bacteria that could get into the blood stream

could lead to sepsis (really bad as 50% of patients that have sepsis due to ischemia die).

The deferential diagnoses unfortunately are confusing, because acute appendicitis, acute cholecystitis and peptic ulcer disease are not as severe (problematic) as bowel ischemia, and they present in very much the same way, so the diagnosis of ischemic bowel disease may be delayed or missed which is disastrous. So always when you have a patient with these signs and symptoms the common thing that comes to mind is acute appendicitis , cholecystitis and peptic ulcer disease, but Don't Forget Ischemic Bowel Disease.

Hemorrhoids:

Hemorrhoids are common in the general population. They are dilated anal and perianal collateral vessels (this is an area of anastomosis between the caval and portal venous systems.)

If we are talking about the anastomosis above the anal line we are talking about internal hemorrhoids, while if below then its external hemorrhoids. This is a dilatation of these vessels due to increase of intra-abdominal pressure, increased straining, pregnancy, and also portal hypertension.

Constipation, pregnancy, and straining hemorrhoids are mostly benign, but if we are talking about hemorrhoids that result in portal hypertension the local problems aren't a big deal but the underlying problems (portal hypertension) should take your attention.

If an internal hemorrhoid goes beyond the lines now it cannot be pushed back in it could be strangulated, it could thrombose , it could ulcerate, it could bleed (externals can bleed but less severly than internal that have prolapsed outlet). These people present with pain, occasionally bright red bleeding (indicating a very close bleeding location), and when examined you will typically find a hemorrhoid.

Treatment: scleratherapy i.e. you obliterate the venous plexuses that are diseased, banding (as it sounds a rubber band that really cuts off that

particular location and eventually that will drop away), infrared coagulation and occasionally (if it's a severe enough case) surgery by hemorrhoidectomy, but we always try to avoid surgery.

Malabsorption

Malabsorbative diarrhea:

You have other types of diarrhea in your book that are not required they are part of your microbiology lectures only what is given now is required.

To understand Malabsorption you need to understand digestion.

Digestion: Has **four stages**, it starts with **intraluminal digestion** you've got enzymes (like peptidases) that result in the breakdown of sugars and fats inside the lumen, but will not be break them down into single building blocks.

We typically have peptidases, disaccharidases in the brush border of the intestines (that is **terminal digestion** that breaks down disaccharides into monosaccharides). People who have lactose intolerance don't have lactase so they can't break lactose into its monosugers.

Then we need to transport these building blocks across the epithelium and there are various transporter proteins on both sides of the epithelial cells **(trans-epithelial transport)**, and finally **lymphatic transport** which is important specifically for fats.

If you have a defect in any of these (could be a combination) you potentially have Malabsorption so if you look at the various diseases in your book you will notice that in chronic pancreatitis you'll have a problem with digestion. why? Because the pancreas produces enzymes that digest inside the lumen, if you have disaccharidase deficiency (lactose intolerance for example) , you have a problem with terminal digestion.

You can also notice diseases that have more than one problem with these steps like celiac disease which has a problem with terminal digestion and the transepithelial transport, so on and so fourth.

The malabsorptive syndromes look like each other more than they differ, most syndromes will present with:

- diarrhea(could cause dehydration which is fluid loss)
- flatus(gas, as you're not breaking down nutrients, so instead bacteria in the GI tract is, thus the gas or CO2)
- abdominal pain and weight loss (not absorbing fats, carbohydrates , proteins)

But more importantly are the consequences of these like:

- anemia (due to pyridoxine, b6 (or type of b6) folate, or vitamin b12 deficiency)
- bleeding due to vitamin k deficiency
- osteopenia(low bone density)
- tetany due to calcium, magnesium, vitamin D deficiency
- neuropathy due to vitamin A or B12 deficiency
- a variety of endocrine & skin disturbances(pigmentation not known why) might occur
- ecchymosis which is the formation of small bruises caused by small breakage of blood vessels and not properly clotting because of vitamin K deficiency
- steatorrhea(a hallmark of Malabsorption)
- fatty stools that float to the top
- edema in severe cases. When Malabsorption has gone for so long ending up with hypoproteinemia (from not absorbing proteins) it leads to changes in osmotic pressure causing excess fluid diffusion to tissue causing the edema.

Celiac disease:

It is also known as gluten-sensitive enteropathy, these patients can't eat wheat, rye or barley a lot of things you take for granted, your daily bread (literary).

It is caused by an immune reaction to the major storage component of these foods: Gluten.

There are two subsets of presentation:

1) Older patients (60 and above) may or may not be related to adenovirus infections we talked about before.

2) Younger patients 6-24 months. At 6 months of age children start eating food containing wheat (cerelac), this leads to villus atrophy which means loss of surface area thus causing problems with absorption.

Intraepithelial lymphocytes are characteristic because this is an immune-mediated disease, epithelial proliferation and crypt elongation. The cells at the base (stem cells) are trying to compensate for the loss of mature enterocytes. Because you have a reduced area, you have reduced absorption and these patients may also present with anemia either from iron or B12 or folate deficiency.

Treatment:

Unfortunately for these patients, treatment is a gluten free diet so no bread made of wheat, barley, rye, etc.

Most patients respond well to a gluten free diet although that is a lot to ask from a person, and recurrences if they do occur are typically dietary related (not sticking to the diet). However these patients have a risk of increased T-cell Neoplasias and adenocarcinoma, if the patients swears up and down that they have been good (no cheating the diet for real) and still have symptoms, these conditions (cancers) should be in your mind. As the patients try to compensate they have developed T-cell Neoplasia or adenocarcinoma or in

rare cases refractory celiac disease which does not respond even to a gluten free diet, because the immune reaction has become self sustained.

The molecular biology of the disease:

You have gliadin that is the breakdown molecule of gluten, this is transported across the epithelial membrane where tissue transglutaminase de-aminates it, and then it is presented by antigen presenting cell CD4+ cells. Now almost invariably, patients who have the HLA-DQ2 or HLA-DQ8 are the patients that get the celiac disease, that means if you are suspecting celiac disease and the patient does not have HLA-DQ2 or HLA-DQ8 most likely the patient doesn't have celiac disease. Absence of these HLA types has a high negative predictive value i.e. if its not there most likely this is not the disease you are looking for.

Activated CD4 cells produce cytokines. Interferons can directly damage the epithelial cells. Cytokines also induce a typical B-cell response where the B-cells produce antibodies against tissue transglutaminase, gliadin, and as a result of cross-reactive epitopes: anti-endomysial antibodies are also formed (the endomysium is a wispy layer of areolar connective tissue that ensheaths each individual myocyte (muscle fiber, or muscle cell).

It also contains capillaries and nerves. There is a tissue glutaminase that is much like the tissue glutaminase in the intestines, and these antibodies while not as sensitive as the first 2 antibodies (affecting gliadin and transglutaminase) are highly specific. The first 2 antibodies are highly sensitive, the third is specific so it can be used in diagnosis. Now whether these antibodies contribute to celiac disease pathogenesis or are just diagnostic we don't know. So far we use them for diagnosis.

In addition to the cytokines and the B-cell responses there is also a CD8+ response that is not gliadin specific, but these epithelial cells are for some reason producing interleukin 15 that recruits and activates these CD8+ cells that have a specific receptor on their surface. This receptor indentifies a help signal from stressed cells (enterocytes), so the CD8+ lymphocytes kill the epithelial cells that have been induced by various stress factors. The problem

with this is that it causes disturbances to the epithelial lining (damage), which means more gliadin will move in which means more CD4 more cytokines, more IL-15 , more CD8 activation so its forming a vicious cycle causing more damage to enterocytes. So in a nutshell more epithelial damage more gliadin more damage.

So far the only treatment we have is a gluten free diet.

Morphologically you will find villous atrophy and crypt hyperplasia, no villi, looks more like the colon than the small intestines. A photo of a very severe celiac disease caused villous atrophy, you can see inflammatory infiltrate , intraepithelial T-lymphocytes we talked about. However these are non-specific changes so you have to use serology to diagnose these patients, you can also take a biopsy but serology is much less invasive.

Some patients may have silent celiac disease i.e. they have positive serology and villous atrophy but no symptoms or no symptoms yet, you have caught it early, and there are a small percentage of patients whom are latent where you find positive serology but no histological changes and no symptoms we don't know why.

Environmental (tropical) enteropathy:

Previously known as tropical sprue, it depends on where you grow in the world, but look up where this is common.

There are 150 million children worldwide that have environmental enteropathy.

Although malabsorption is one of the central problems with these children (which is why they have stunted growth) , replenishing vitamins, fats and carbohydrates to these children does not seem to reverse the process, so is there an infection causing damage to the intestine? We don't know, what we do know is that these patients have repeated bouts of diarrhea between the ages 2-3, we couldn't isolate the microorganism that might be causing this.

Morphology is similar to celiac disease so if you have a patient that old with stunted growth and the symptoms of celiac disease, and grew up in (was born) in an area known to be endemic for environmental enteropathy that should

be part of your deferential diagnosis , unfortunately there isn't much you can do to these patients.

Lactose (disaccharidase) deficiency

It's a biochemical defect and it is autosomal recessive thus rare. Talking about congenital, it could also be acquired after a viral/bacterial infection that has caused damage to the villi and it takes a while for lactase to be expressed by the new cells, or in certain populations because diary products haven't been consumed historically (native Americans , Japan, china) in their diet for generations and generations, down regulation of lactase in their intestines occurred and are known for lactose intolerance.

Because they can't break these disaccharides the bacteria will do it for them by fermentation producing co2 and you will be gassy if you ingest dairy products containing lactose.

Abetalipoproteinemia

It is autosomal recessive and is a transepithelial transport defect. These enterocytes cannot export their triglyceride rich lipoproteins out to the lymphatic vessels. So lipids will accumulate especially after large fatty meals in the intestines, this will manifest in infancy with failure to thrive as you can't absorb fat-soluble vitamins , also you need fat for making membranes , growing up, etc. Patients will have lots of steatorrhea(fatty stool) as the fat won't be absorbed and thus excreted.

THE END
Good luck to all and happy Easter.

المسيح قام
حقا قام ☺