Digestive System

◯ Slide ✦ Sheet ◯ Handout ◯ Other

☐ Anatomy   ☐ Embryology

☐ Physiology   ☐ Histology

☐ Pathology   ☐ Pharmacology

✦ Microbiology   ☐ PBL

Sheet #: 1
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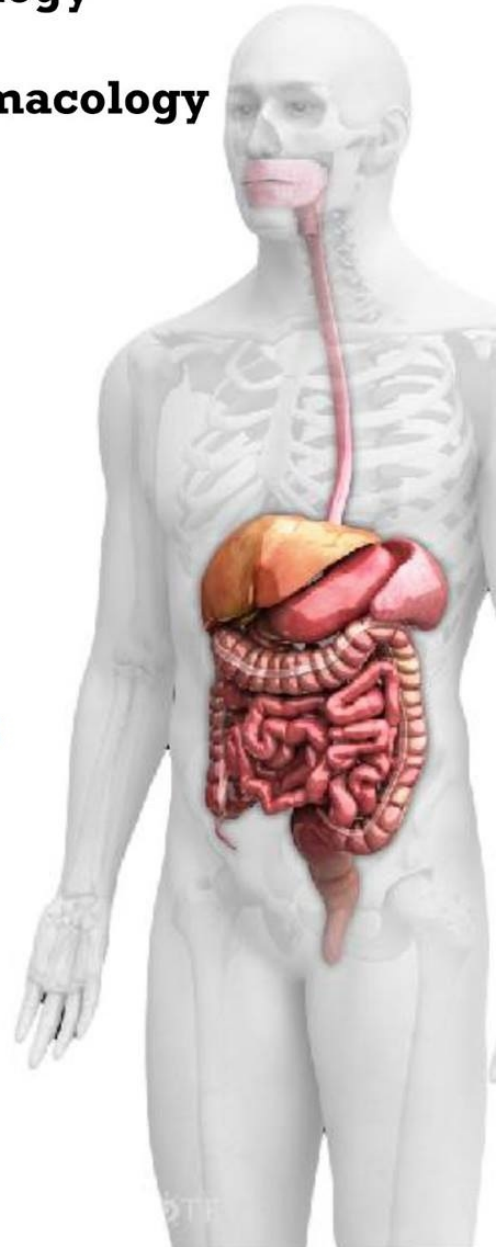
Bacterial Gastrointestinal Infections

- This topic has been planned to be in 3 lectures, but we will take only 2 lectures skipping some of the slides details that we've already taken before.

Let's start ☺

- Gastrointestinal infection -whether it is bacterial or viral- causes **gastroenteritis**. Signs & symptoms of gastroenteritis are associated with **stomach** and **(small and large) intestine;** manifested in the form of vomiting (related to stomach) or diarrhea (related to intestine) or both.
- Gastroenteritis is so important & is associated with a large number of infected people every year. According to the W.H.O statistics, we have at least one billion cases of gastroenteritis each year, mostly in the developing countries due to the low standards of hygiene. It is usually associated with water and food contamination.

Manifestations

Simple features of: diarrhea, vomiting, fever & abdominal pain. It can rarely be associated with blood sepsis or meningitis.

- ❖ **Diarrhea** is divided into:
    1) **Watery diarrhea** → there is excretion of at least 3-5 stool motions within a short period (few hours). Often associated with release of water from small & large intestines. [Mild fever] .
    2) **Bloody diarrhea** →there will be WBC's (mainly neutrophils) , inflammatory cells & pus cells within the stool. Often associated with more damage in the large intestine & manifested with at least 3 motions of bloody diarrhea. [High fever] .
    3) **Enterocolitis** → inflammation of both large and small intestines. Not necessarily associated with a bacterial causative agent, it may be due to release of toxins. [High fever].

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> Incubation period: **24 hours.** It may be short or long, it depends on: number of infectious doses, replication in the intestinal tract & the presence of certain immune response in the intestine.

- Another feature associated with gastroenteritis is **Bacterial food poisoning**. Food poisoning is not necessarily associated with bacterial agents, it may be associated with toxins produced outside the body (in the food) and then ingested , causing some clinical features, starting with <u>vomiting</u> and later might be followed by <u>watery diarrhea</u> and <u>abdominal pain</u>... fever often not recognized in association with intoxication.

Incubation period: <u>2-8 hours</u> (short)

Bacteria that causes gastroenteritis:

- Divided into:
  1) <u>Gram negative</u> {represented by: **Salmonella**... divided into: enteric (typhoidal) & gastrointestinal (non-typhoidal) salmonella, **diarrheagenic E. coli** strains, **Campylobacter spp.**, **V. cholerae**, **Listeria** & **Aeromonas spp.** }

- There are other organisms of less importance and only may cause diarrhea, such as **P.aeruginosa** in patients with underlying disease.

  2) <u>Gram positive</u>: especially in association with production of toxins. {represented by: **Cl. perfingens, Cl.difficile, Staphylococcus aureus, Bacillus cereus** }

  - Clostridium Perfingens may excrete the toxins outside the body (within the food) and may be associated with food intoxication.

Salmonella

- Gram-negative bacilli /Facultative anaerobes.
- The most important positive agent of gastrointestinal diseases especially diarrhea.
- In all countries of the world, at least 500 million cases of gastrointestinal salmonellosis are recorded each year.

- Widely distributed in the nature, especially in association with animals and poultry birds (especially chicken).
- Classification of salmonella depends on the presence of: <u>somatic antigens</u> , <u>H-antigen</u> (May in certain types of salmonella be recognized during systemic infection in the human serum) & <u>Vi (virulence) factor</u> .

> NOTE: Vi factor is associated with only one type of salmonella called salmonella typhi (the causative agent of the enteric fever).
>
> - Enteric fever follows salmonella typhi or paratyphi serotypes.

- **Human Salmonellosis** is divided into:
    1- **Enteric Fever Salmonella /Typhoid fever** (subtypes: Salmonella typhi & paratyphi)

- **Related only to humans (can't infect animals or birds).**

- The new classification in relation to salmonella has been simplified only in one genus and one major serotype called: **serotype enteritis** ... from this serotype, we have subtypes which are associated with systemic infections in form of enteric fever or typhoid fever (caused **by salmonella typhi** & **paratyphi A,B,C**).

  ❖ The most common serotypes in Jordan & other Arab countries → Salmonella typhi & paratyphi B. Whereas, A &C are common in south-east Asia.

- Incubation period :<u>1-3 weeks</u>
    ↘ Depends again on number of cells ingested within food or water.

Process of Tyhoidal Salmonella Infection

- Generally, once this organism -which is considered highly virulent- reaches the intestinal tract, it begins to replicate slowly in **peyer patches** & mesenteric lymphatic tissue ... later, spreads slowly to the blood stream & carried to other body organs (especially liver & spleen... enlargement).In addition, high fever may develop, due to the presence of the bacteria in the blood (sepsis) . Then, returns back after another incubation period of about few days to the intestinal tract & begins to produce more damage to the mucosa of the large intestine. It might be so dangerous in association with perforation of the intestinal tract ; severe damage in the mucosa of the intestinal tract, manifested later with severe bloody diarrhea & other complications associated with the circulatory system (there will be kidney failure or respiratory failure) ...death if not treated with anti-microbial drugs within a short period of time, or if the patient didn't develop immune-response against the invading organism.
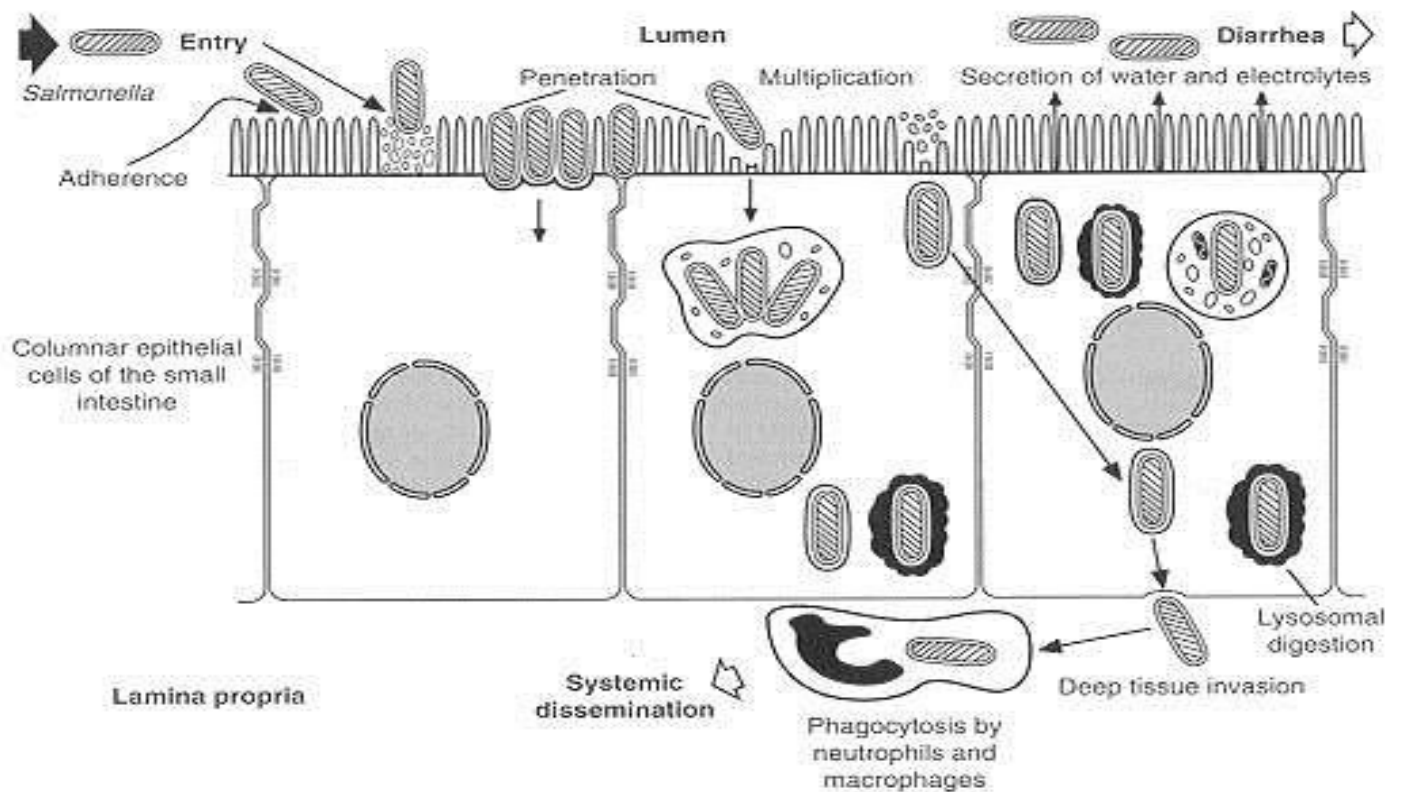
- During infection with typhoid salmonella –if not treated- about **30%** of patients dies due to complications (mainly perforation of the intestinal tract & severe sepsis).

- During infection with salmonella typhi & paratyphi, at least **3%** of recovered patients turn into healthy carriers.

  > NOTE: in a healthy carrier, the organism –which is salmonella typhi & paratyphi- is present mainly in the **gallbladder**. Under normal conditions, the organism may be excreted due to eating a meal rich in fatty acids.

  ↘ Healthy carriers are important for public health; because they are the main source to circulate the organism in the community & produce more single and outbreaks of salmonellosis.

  > Healthy carriers (asymptomatic carriers) →
  >
  > They will excrete the organism with their feces their lifelong normally &
  >
  > this can be a source of infection in the community, especially in association
  >
  > with close contact or contamination of water and food.

- Generally, infection with typhoid salmonella results in **humoral specific antibodies,** which protects against re-infection.

  ❖ During infection, there will be 2 types of anti-bodies: somatic (against O-antigens) & H-antibodies (against flagella) … recognized by <u>widal test</u>.

- During infection with systemic typhoid fever, the organism can be excreted in feces & urine. In addition, it can be found in the blood stream & CSF (in association with meningitis)… in chronic cases, the organism resides in the bone marrow.

  ↘ If the patient was treated partially with antimicrobial drugs, it will be difficult to isolate the causative agent from blood/stool/urine. So, serological test will be used and blood samples will be obtained from the infected person to look for antibodies.

↘ According to our studies in Jordan ,the titer level of antibodies must be over 160
⎡ Titer >160 ⎤ (for H or O) ,this might give indication that the patient is infected
with salmonella typhi or paratyphi, if there's a negative culture. Titer may reach 320
or 640 or more ,depending on the process of infection & the duration of infection.

↘ Serological test –which is known as **widal test**- is very important to recognize the
presence of typhoid fever in certain clinical cases without the presence of positive
culture from blood or stool.

Treatment:

- It is important to start the treatment as rapid as possible, in order to reduce the severity of
infection.
- It depends on the susceptibility of the organism.
   ↘ **Chloramphenicol** was widely used in the past, but not anymore. Nowadays, other
   drugs are used, which may give the same result but slowly. Chloramphenicol within
   2-3 days controls the developing of typhoid fever & prevents complications.
   ↘ **Ciprofloxacin, Augmentin & Ceftriaxone** requires 1-2 weeks to reduce the
   severity of infection.

- **Oral vaccine available √** (can be used in certain conditions, especially in areas with
endemic infections, in the army ...etc)

- It is more important to rely mainly on hygienic measurements (to control water & food)
and to detect a positive case of healthy carrier to prevent the spread of the disease.

2- <u>Salmonella enterica (</u>subtypes **Typhimurium**, **Enteritidis** and **infantis**) = gastrointestinal salmonella = food-poisoning salmonella.

- \>2000 subtypes.
- Widely distributed in animals & birds. (especially chicken and eggs...shells are contaminated) ... contaminate grounded meat & eggs.
- Humans acquire the infection due to contact with those birds or their products.

<u>Pathogenesis</u>

- Mainly related to multiplication of the organism in the intestinal tract & releasing of lipopolysaccharide of the bacterial cells & releasing of cytotoxins, which are associated with inflammatory reactions in the intestine ... diarrhea or (vomiting & diarrhea) {depends on the infectious dose & the immunity status of each infected person}.

- Generally, the process of infection can be recognized in the following steps:
  1) The organism reaches the small & large intestines.
  2) Inflammatory rxn is associated with the large intestine rather than the small intestine. Releasing of cytotoxins...stimulate adynylyl cyclase in the mucosal cells ,which later stimulates the release of cAMP ,which is responsible for outpouring of water , sodium ions & chloride ... later, it inhibits the re-absorption of sodium, which will result in outpouring of watery diarrhea.

- Watery diarrhea may be associated -in infants &young children- with presence of blood cells due to certain damage in intestinal blood vessels or without (depends on the immunity status of the infected person).
- In the first 24 hours, mainly watery diarrhea ... later, bloody pussy (filled with pus) diarrhea.

❖ In general, gastrointestinal salmonellosis is <u>self-limited</u> → there's no need for antimicrobial drugs within the first 48 hours. (rehydration is needed).
   ↘ Giving antibiotics may complicate the situation & increase diarrhea.
   ↘ <u>Exception:</u> infants & immune-compromised patients (treated with antibiotics to prevent the development of sepsis)

❖ Gastrointestinal salmonellosis is considered slightly invasive, it may reach the blood stream (in infants & immune-compromised patients) causing blood sepsis and meningitis, and then it will be very difficult to cure; due to severe inflammatory rxns & release of cytotoxins and endotoxins within a short period.

-Lab diagnosis

-<u>Limited to detect the organism in stool</u> .You might obtain blood culture or CSF culture, if there's feature of blood sepsis or meningitis .But, generally it's enough to detect the organism in stool .

- **S-S agar** & **Heckton-enteric agar** (selective for salmonella (90-95 %) /inhibits other organisms, which means easily detection of the organism).
-S-S agar; salmonella- shigella agar (culture media).

   ❖ You can't rely on using serological tests ,due to the lack of specific anti-O & anti-H antibodies during infection. So, widal test is used only in detection of Tyhoidal Salmonella, and it is not used to detect gastrointestinal salmonella.

- <u>NO VACCINE AVAILABLE.</u>

-<u>NO HEALTHY CARRIERS FOR A LONG PERIOD.</u> (Bacteria can survive for a few weeks, then excreted with stool. Not like the salmonella typhi and paratyphi ,which can stay in healthy carriers for a long time).

Shigella

- Gram-negative/facultative anaerobes.

- Important causative agent, not of food-poisoning or gastroenteritis. There's a misconception; that they consider infection with shigella as gastroenteritis (shigella infection is not gastroenteritis; because gastroenteritis is associated with stomach and intestines, and shigella is limited to the large intestine).

- Shigella is limited to the large intestine, mainly with developing of bloody-watery diarrhea.

- Not associated with vomiting.

- 4 important serotypes: **S. dysenteriae, S. sonnei , S.boydii, S. flexneri.**
  - ↘ They all share the same clinical features, but **S. dysenteriae** is associated with more severe complications and may be associated with more clinical features related to meningitis & sepsis...may be fatal.
  - ↘ All species of shigella (except for **S. dysenteriae**) produce the same type of cytotoxins & are associated with bloody diarrhea...rarely cause blood sepsis.
  - ↘ **S. dysenteriae** produces special toxins known as **shiga neurotoxin**, which can be absorbed from the intestines & carried to the blood stream... meningitis (without the presence of bacterial cells/only toxins)...kidney failure &death due to severe inflammatory rxn in the large intestine & the release of large amount of blood.

  NOTE: **S. dysenteriae** is the most serious and dangerous serotype of shigella.

- In our country, we have a few cases associated with shigella species. Majority related to: **S. sonnei , S.boydii, S. flexneri.**

  - ❖ When you examine the patient's stool, how to tell that it's associated with shigella rather than salmonella?
    By the presence of numerous WBC's .

- Shigella is associated with more severe abdominal pain & fever (easily differentiated).

Treatment

- Requires treatment with antibiotics. Why? Because shigella is more invasive for the intestinal tract & associated with inflammatory rxns in the large intestine.
  - ↘ Treatment with antibiotics is required to shorten the duration of inflammation & release of blood. And to prevent the spread of organism in the community.
- Shigella is highly infectious & communicable (few number of cells may be enough to induce infection).

> - In salmonella gastroenteritis , there must be at least 10^5 cells in order to produce a case of gastroenteritis. {less virulent}.
>
> - In shigella, 100 cells are enough to produce a case of shigellosis.
> - In typhoid salmonella, 10 cells are enough to produce infection.

- The infectious dose increases in relation to the invasive biological characteristic of each organism.
- NO HEALTHY CARRIERS; after treatment the organism will be eliminated from intestine. And the infected person will not be a healthy carrier ,unlike the salmonella typi and paratyphi .
- Prevention depends again on hygiene, especially water control, (shigella and salmonella typhi) can easily survive in clean water. Whereas, salmonella gastroenteritis can't.
- In relation to shigella, it's important to collect stool specimens & to send the specimens within 30 minutes to the laboratory. We prefer to have a rectal swap rather than a stool samples, in order to isolate the organism; due to the fact that the organism is highly susceptible to the environmental factors ... it can be eliminated or killed under room temperature / acidity/dryness ...etc

Diarrheagenic E. coli

- We have some difficulties in relation to this group, since E.coli is part of our commensal intestinal flora.
- Within E.coli, we have certain types of strains associated with production of certain cytotoxins or other types of enterotoxin → development of gastrointestinal disease (mainly diarrhea).
- 6 types... 4 of them are associated with 90% of E.coli diarrhea.

1) Enterotoxigenic E. coli (ETEC).
   ↘ Releases 2 types of toxins at the same time (heat labile & heat stable) .

- Heat labile can be inactivated within few minutes at 100°C .
- Heat stable require at least 30 minutes to be inactivated .
   ↘ Important in food preparing process.(short period of heating is not enough to kill Enterotoxigenic E. coli ,which produce Heat stable toxins)

- Both heat stable & heat labile toxins are carried on a transmissible plasmid, which means that not all E.coli can be associated with these toxins. Only a few percentage is associated, and this few percentage later transfers the plasmid to other E.coli strains or other bacteria & spread the toxin.

- ❖ Mechanism of action of **heat labile** toxin is similar to some extent to cholera toxins, which at the end resulted in increased stimulation of adenylyl cyclase & release of cAMP ... development of watery diarrhea.
- ❖ **Heat stable** toxins activate cGMP, which activates cAMP ...development of watery diarrhea.
   ↘ Both heat labile & heat stable toxins have the same feature at the end –watery diarrhea-

NOTE: heat labile toxins are mainly related to E.coli found in the intestinal tract of humans, whereas heat stable toxins are related to E.coli found in animals' intestines. (but at the end both can be found in humans intestinal tract).

- The importance of all types of E.coli in order to produce Infection, especially in the intestinal tract ,or later , in the extra intestinal tract <u>depends on</u> the presence of specific **pili (fimbriae)** for adhesion ... without the presence of these adherens fimbriae, which are composed of adherens factors 1&2, the E.coli can't produce extra intestinal infection.

Best of luck :)