The GI System

Microbiology

☑ Sheet ☐ Slide ☐ Handout

Number: 1

Subject: GI infections

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Date: 4/4/2016

Price: .....

(Note: this sheet was not written according to the exact order of the record).

GI infections

The topic for this lecture is bacterial gastrointestinal infections, one of the most important topics in clinical medicine due to the fact that there are about one billion cases of diarrhea or food poisoning each year worldwide. GI tract infections are more common in developing countries and also more common in children than in adults. Any person can get exposed at least once a year to GI infections, the infection might be mild or severe, might require hospitalization and treatment, it depends on the severity of infection and on clinical manifestations.

The major clinical features of GI infections might begin with vomiting and later abdominal pain and diarrhea, or all three symptoms together at the same time; it depends on the type of the causative agent.

In addition to bacteria, there could be viruses or parasites which might complicate cases of bacterial diarrhea or GI infections. So the causative agent of diarrhea might not necessarily be a single organism, it might be at the same time a bacterium and a virus, causing severe infection, specially certain viruses such as: noroviruses, enteroviruses and many other viruses.

Generally **watery diarrhea** involves <u>both small and large intestines</u>, whereas **bloody diarrhea** (**dysentery**) involves <u>large intestines mainly</u>, another clinical feature is high fever, which is a feature of enterocolitis (inflammation in both small and large intestines). Here the infection might be triggered by elaboration of some toxins from bacteria. But in most cases of food intoxication there is no fever.

Included within GI infections is food poisoning. Bacterial food poisoning is very common and comprises approximately 50% of all types of GI infections.

In order to differentiate between GI infections and food poisoning, we have to look for the following: in **food poisoning** (intoxication), which means the presence of a toxin in food, first we recognize **vomiting**, then **diarrhea** (often it is watery, not associated with blood) and the third thing is that there is **no fever**. These three signs can be easily recognized in clinical cases in order to differentiate between GI infections (Bacterial infections) and food poisoning (Associated to toxins).

Now we'll consider certain types of bacteria associated with both GI infections and food poisoning, including→ Gram -ve bacteria such as: Salmonella, various types of diarrheagenic E-coli (6 types might be involved in GI infections), Campylobacter species

(Campylobacter infantis, Campylobacter fetus, Campylobacter jejuni), Vibrio cholera, Listeria and Aeromonas.

While in Gram +ve bacteria, it's often related to excretion of toxins in food and the feature is intoxication rather than bacterial intestinal infection, examples are: S. aureus (which produces enterotoxins), B. cereus and C. perfringens.

Now we start with Salmonella. According to the recent classification of Salmonella we have only one major species (which is Salmonella enterica) and it can be divided into serotypes (2000 serotypes), three of them are the most important:

1- Typhoidal Salmonella → 2 subtypes Typhi and Paratyphi.

2- S. enterica var Typhimurium→ associated with animals, but keep in mind that it can infect humans and cause the same infection it produces in animals.

3- S. enterica var Enteritidis → related to humans.

2 and 3 are subtypes for the same class called "GI Salmonella, food poisoning Salmonella or non-typhoidal Salmonella".

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1) Typhoidal Salmonella

And it has two subtypes, S. Typhi and S. Paratyphi. It's transmitted by ingestion of contaminated water or contaminated food or by direct contact.

It multiplies slowly in the intestinal tract and after an incubation period of 1 to 3 weeks (depending on the number of ingested cells), you might recognize clinical features of Typhoidal fever as systemic infection due to the fact the S. Typhi and Paratyphi normally reproduce in the mesenteric lymph nodes of the intestinal tract, then they are carried by macrophages to reticuloendothelial system in liver, spleen and bone morrow, and slowly multiply within the incubation period in order to have an increase in the number of cells, then they return back to the intestinal tract for another round of multiplication in the mesenteric lymph nodes (specially in Payer's Patches), they enter the blood again to cause a severe form of sepsis.

Sepsis associated with Typhoidal Salmonella can involve any body tissue (bone morrow, liver, spleen, gallbladder and any part of the body including the urinary system). This can be easily recognized by the presence of continuous high fever (might reach up to 40 C), in addition to severe weakness and malaise in the infected person.

Other clinical features are enlargement of the liver and spleen (hepatosplenomegaly) and skin rash (in the form of rose spots); which might be misdiagnosed as a viral infection, but if the other characteristics are present (High continuous fever, hepatosplenomegaly and severe weakness of all organs) then the only diagnosis is typhoidal Salmonella.

During the 1st stage of the disease, there might be watery diarrhea or constipation, it differs among individuals, but in later stages diarrhea will be absent and more constipation will be recognized, so more damage in infected cells. (**Note**: you will notice that the slides say exactly the opposite, I asked Dr. Asem about it and he said that both cases are possible, but what happens more commonly in later stages is more diarrhea and less constipation, since in systemic infection the intestines become really weak, so just stick to what's in the slides).

Salmonella is associated with two important antigenic structures, somatic antigen (O-antigen, presence of cell wall polysaccharides) and H-antigen (presence of flagella). Both are responsible for the clinical features of the disease. Also Salmonella Typhi -in particular- is associated with special layers like a capsule surrounding the cell, known as Vi (Virulence), a type of proteinous capsule, contributing to the pathogenicity, the virulence of the organism and more severe complications with the infection.

Under normal conditions, without the use of anti-microbial drugs, enteric fever might end up with a severe damage to the large intestine, producing intestinal perforations, obstruction and death of the infected person. Therefore mortality associated with Salmonella Typhi under such conditions, without supportive therapy (use of antimicrobials), might reach 30-40%, especially in a certain category of patients (children, elderly, etc…).

The cell wall polysaccharide is an important virulence factor associated with Salmonella Typhi and Paratyphi. The amount of lipopolysaccharides in the cell wall of typhoidal Salmonella is larger than in any other Gram –ve bacteria. Also the composition of the lipopolysaccharide is related to a stronger immunological reaction, which can be later recognized by the presence of cell-mediated immunity and humoral antibodies.

Generally, healthy people might manage to produce sufficient amount of humoral antibodies, and these are more important than cell-mediated immunity during the acute stage of infection.

Typhoidal fever can be recognized in two major clinical entities:

1- Acute infection: easier to recognize.
2- Chronic infection: more difficult to be recognized.
   ➔ Subacute infection is rare and less.

In children and immunocompromised patients, typhoidal Salmonella might be associated with meningitis and it could be severe, and might involve internal organs (for ex: the kidneys), so during the acute stage we expect the organism to be excreted with feces, urine, as well as blood, and can be also isolated from the bone morrow and CSF (so many options from where we can get the sample and recognize the organism).

Other complications include intestinal tract obstruction, perforation and later might result in pneumonia, osteomyelitis, septic arthritis, abscesses in many other organs specially in urinary tract, and localized abscesses in liver and spleen. So the variation of the infection is so wide and might not be easily recognized specially in chronic cases (as mentioned before).

The figure in the slides demonstrates the process of infecting the intestinal tract, beginning from attachment of the organism to the brush border of small and large intestines, then penetration of the bacterial cells into the subcutaneous mucosa reaching the mesenteric lymph nodes and multiplication within macrophages in order to get carried by the lymph system to other parts of the body specially reticuloendothelial system in liver and spleen, and later to other parts.

During infection with typhoidal fever, we have to consider that 2-5% of infected people become what we call "**healthy carriers**" (either with using antimicrobials or without), they carry the organism in their gallbladder (specially when it contains stones). Carriers are more commonly females rather than males, and they distribute the infection in the community, so they become a source of infection for others; due to the fact that during their lives they will always have a certain number of organisms in their intestines, so they will be excreted with feces and might contaminate food, water or spread by direct contact, and this might cause infection to family members and close contacts. In the community and in relation to public health, the presence of a carrier is part of the endemic disease. We should always be concerned if there is a typhoidal Salmonella outbreak in the community (more than 20 cases), then we have to do a research in order to detect for the presence of healthy carriers, specially people who work in restaurants (as food handlers), or in food factories.

During infection, the human body responds by production of two important antibodies, anti-O-antibodies (somatic) and anti-H-antibodies (flagella), and these can be recognized

after 1-2 weeks. In certain cases, if a person is having a partial treatment with antibiotics, you might not be able to isolate the organism from his feces/urine and the only way is to look for antibodies in his blood. Their presence can help to diagnose a case of what's called "unknown enteric fever" which might be due to any organism, but mainly it is due typhoidal Salmonella or Brucella infection.

There's a serological test called "**Widal test**", a very specific test if done according to the guidelines of doing it. It is done by obtaining a blood sample from a suspected person and look for antibodies against O-antigens and H-antigens.

Generally, if you want to distinguish between acute and chronic infection by using Widal test, you have to take two samples. If the first one indicates a 160 titer of antibodies and the second indicates a higher titer (320, 640 or more) then this means that the person has an acute infection, and the increasing titer indicates that his body is producing more and more antibodies. While in the case of chronic infection, the titer doesn't change and remains the same within 320.

Therapy: In the 50's, 60's and 70's of the last century, especially in our country, typhoidal fever was very common, and in clinical practice they had recognized people with Salmonella Typhi and Paratyphi B (Paratyphi A and C are not found in our country). Treatment back in that time was based on using chloramphenicol, it was an excellent drug in treating typhoidal fever, but it might produce aplastic anemia in some patients.

- ➔ Yet, the doctor mentioned that professor Qandeel Shaker has investigated 3000 cases of typhoidal fever using chloramphenicol during the period between 1950-1985, zero cases of aplastic anemia were noticed!

Anyhow, chloramphenicol is no longer used, instead other drugs are used depending on the stage of the disease (acute or chronic), including:

1- Ciprofloxacin.
2- The third generation of cephalosporins, Ceftriaxone more specifically, given to pregnant women and children.
3- Ampicillin and Amoxicillin (no more used since the majority of strains are resistant to them).

The public measurements in order to control typhoidal fever in any community is to control tap water, to deliver chlorinated tap water. In Jordan, and under such control on tap water, we have had very few cases of typhoidal fever since 1985, so Jordan now is considered to some extinct free of typhoidal fever, although it hosts a huge number of people from other Arab countries and refugees who live in crowded areas and have

limited water sources, but still chlorinated water is considered the most important item in controlling the spread of the infection.

Controlling the hygiene of food is less important, compared to controlling tap water, and it's associated with close outbreaks of the disease if there's a healthy carrier who causes food contamination, and this can be easily recognized.

There's a vaccine against typhoidal fever, but it's not recommended if you have good sanitation, and good control on water in any community. Oral live-attenuated vaccines are better than the injectable form, and should only be given to prevent outbreaks or occurrence of single cases of typhoidal fever in certain countries where the disease is endemic.

As example: there is a huge number of typhoidal fever cases in Iraq. So such cases can come from Iraq and infect people in our community. But there's no need to have the vaccine in countries having good sanitation and procedure preventing the infection.

Now we move to the second part of salmonellosis:

2) GI or food poisoning Salmonella (non-typhoidal Salmonella)

This form of infection is related to GI infection and the organism can rarely reach the blood stream or the meninges and cause blood sepsis or meningitis, respectively.

Non-typhoidal Salmonella might under certain conditions, especially in infants and immunocompromised patients, end up causing blood sepsis and meningitis, but the percentages are very low.

The problem with GI Salmonella is that this group is widely distributed in farm animals, especially farm chickens, about 50% of farm chickens are already infected with GI Salmonella which means their meat and eggs are sources of infection in the community. According to experience, a lot of infections especially GI infections in Jordan are related to Salmonella originating from chickens and eggs, more specifically eggs used in the production of mayonnaise, which is a very nutritional medium to increase the number of Salmonella and produce infection.

Generally, GI Salmonella is associated with mild-medium diarrhea. It can be watery or watery-bloody, it depends on the age of the patient and their health condition, in healthy people it's not considered a serious disease, and is mainly associated with vomiting, diarrhea, fever and abdominal pain for a short period of time, doesn't exceed 48 hours, and the patient will recover without necessarily using any antimicrobial drugs.

In certain patients specially infants, elderly and underlying diseased people, GI Salmonella is associated with severe dehydration in the form of watery-bloody diarrhea, and they require hospitalization and treatment to prevent dissemination of the organism to the blood stream and production of complications (meningitis and septicemia, mentioned earlier). And these complications are only seen with these categories of patients.

The process of infection: Salmonella attaches to the mucosa of small and large intestines, produces damage to the brush border and causes inflammatory reaction, which results in development of watery diarrhea.

The presence of filaments in the bacterial cell wall helps in the attachment, and following the attachment is the invasion of the brush border and the subcutaneous intestinal mucosa, and this results in the release of a cytotoxin, which enhances the activity of adenylate cyclase, and this leads to an increase in cAMP, and this means outpouring of fluid and release of water from the tissue of intestines, inhibiting the absorption of sodium ions, and this results in diarrhea which can be severe in a number of patients. This whole process takes about 24-48 hours, then the intestinal tract manages to produce a certain immunological response, inhibiting the multiplication of the organism, and recovery begins without the need for using antimicrobials.

No healthy carriers for a long time in relation to GI Salmonella. In certain conditions, the organism might reside in Payer's Patches for few weeks, but there are **no life-long healthy carriers** like S. Typhi.

For detection of infection, the only way is to have a stool sample in case of acute infection, or after one week to see the type of organism and to know exactly the susceptibility to antibiotics in case there is any complication and there has to be treatment.

Most infections related to GI Salmonella are related to contamination of eggs and meat products from chickens (mainly) or from cows.
There's no significant importance for doing a serological test to detect the presence of specific antibodies in GI salmonellosis. Widal test can't be applied, because there's no invasion to the blood stream, and if there's production of antibodies it will be very minimal and won't be detected.
There's no vaccine available for human, but there's a vaccine available for chickens and can be used to reduce the incidence of salmonellosis in animals.

Sorry for any mistake.
Shout out to Dana Rida :D