14

Microbiology

Doctor 2017 | Medicine | JU

Sheet Slides

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Doctor

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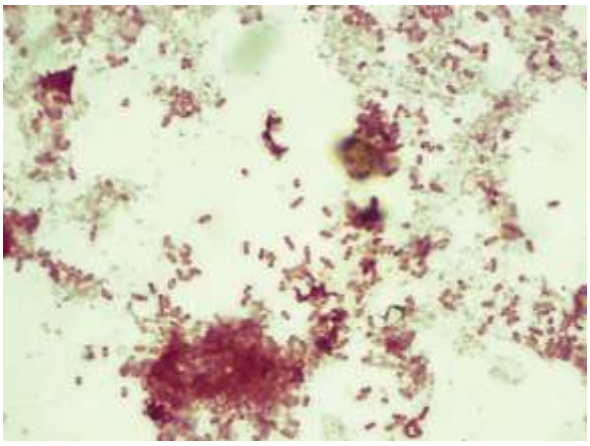
Enterobacteriaceae:

**General properties:*

1. Enterobacteriaceae are moderate-sized (0.3 to 1.0 × 1.0 to 6.0 µm).

2. non–spore-forming. *3. gram-negative rods.* *4. facultative anaerobes.*

5.They share a common antigen (enterobacterial common antigen).



Enterobacteriaceae are *ubiquitous organisms* (found worldwide) in soil, water, and vegetation (plant life) and are part of the normal intestinal flora of most animals, including humans.

Even though they are found normally in humans, they sometimes can be pathogenic, for example in case if they are not at their normal environment. (e.g., ***E. coli*** can spread from the *intestine* to the *peritoneal cavity* following perforation of the intestine).

These bacteria cause a variety of human diseases, such as many ***gastrointestinal infections***. They can cause extensive fluid loss through ***vomiting*** and ***diarrhea***, leading to **dehydration**. Sometimes, they cause (**Tenesmus)**, which is the feeling that you need to have a bowel movement even if you already had one!

Usually, diarrhea can be self-limited, so you don't have to treat it with antibiotics, but in certain cases if it is prolonged you may need them.

Generally, they can be classified according to their pathogenicity into four major groups:

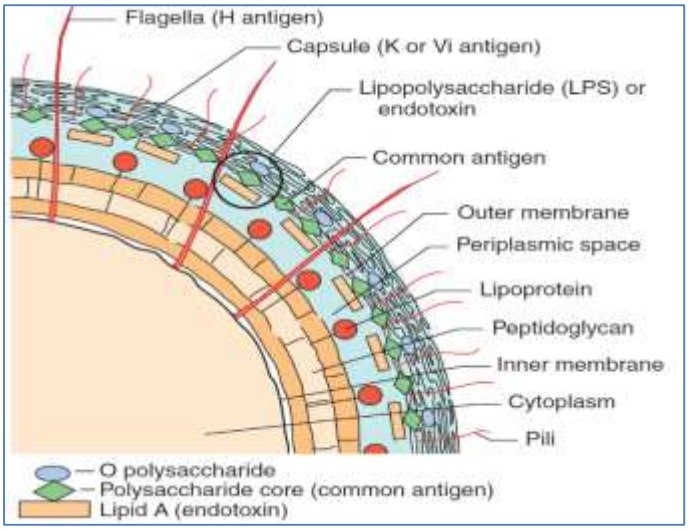
1. The first group can be ***part of the normal intestinal flora***. (causes no infections)

2. The second group is ***always associated with human disease*** when present in clinical specimens.

3. The third one consists of ***members of the normal flora.*** But, ***can cause opportunistic infections.*** e.g., ***E. coli.*** *Revise sheet 11, page 1 for more info. about opportunistic infections.*

4. The fourth group of Enterobacteriaceae exists—***those normally commensal organisms that become pathogenic when they acquire virulence genes present for example on plasmids***, e.g., ***E. coli.***

Lipopolysaccharide (LPS) is the major cell wall antigen in gram-negative bacteria and consists of three components:



1. ***O polysaccharide***.

2.***A core polysaccharide***, (*enterobacterial common antigen mentioned earlier*).

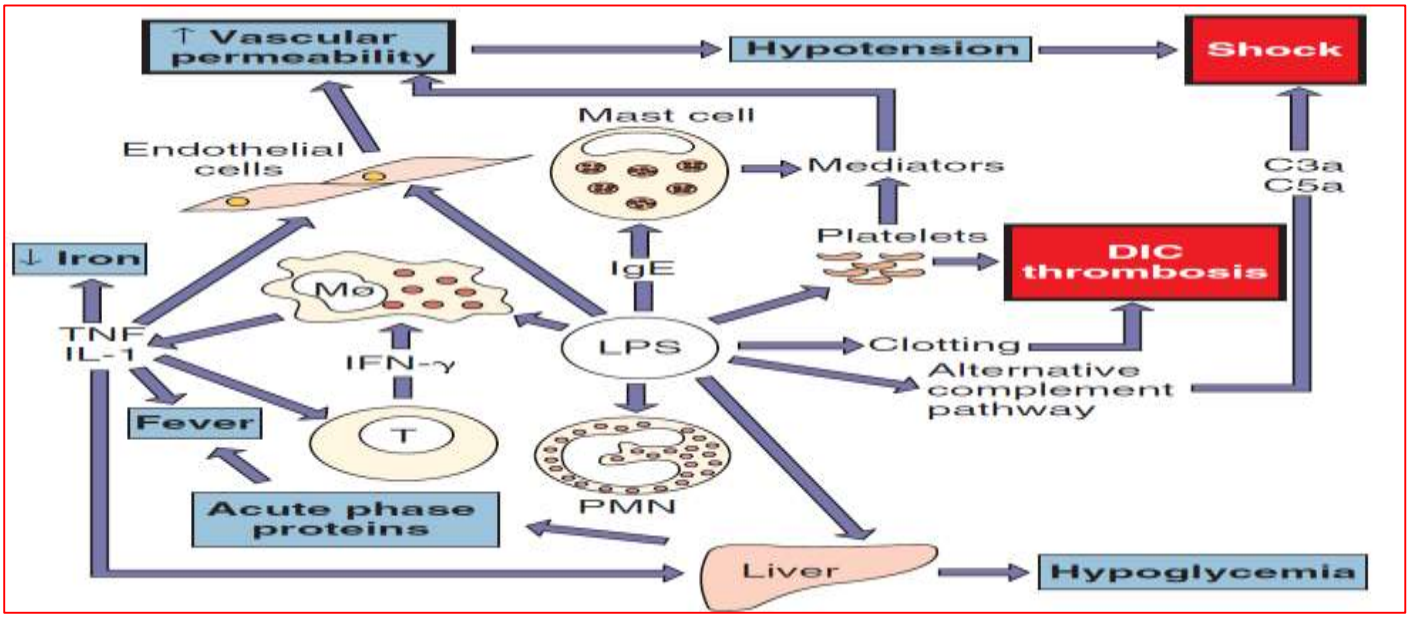
3. ***Lipid A***: It is a component of **LPS** and responsible for endotoxin activity, it's *an important virulence factor.*

The serologic classification of the ***Enterobacteriaceae*** is based on three major groups of antigens: O polysaccharides, K antigens in the capsule (type-specific polysaccharides), and H proteins that is found on the bacterial flagella or capsules.

Pathogenesis and Immunity:

Numerous virulence factors have been identified in the members of Enterobacteriaceae.

1. Endotoxin: it is a virulence factor shared among aerobic and some anaerobic gram-negative bacteria. The activity of this toxin depends on the **lipid A** component of **LPS**, which is released at cell lysis. Many of the systemic manifestations of gram-negative bacterial infections are initiated by endotoxin: **activation of complement**, **release of cytokines**, **leukocytosis**, **thrombocytopenia**, **disseminated intravascular coagulation**, **fever**, **decreased peripheral circulation**, **shock**, and **death**.



2. Capsules: Encapsulated Enterobacteriaceae are protected from ***phagocytosis*** by the ***hydrophilic capsular antigens***, which repel the ***hydrophobic phagocytic cell surface.***

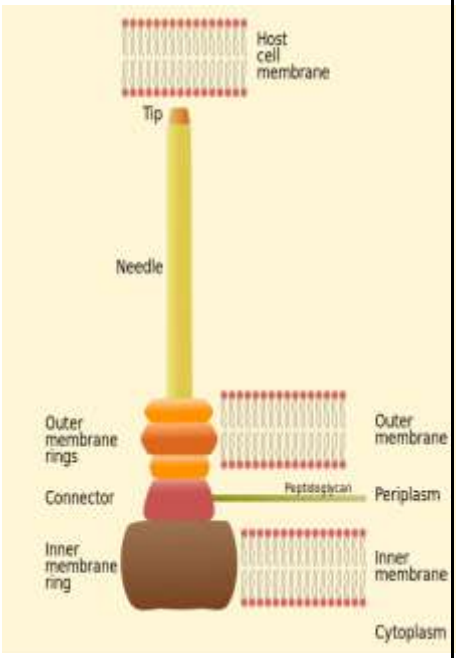
Note: *The protective role of the capsule is diminished, if the patient develops specific anticapsular antibodies.*

3. Antigenic Phase Variation: *Sometimes during phases of bacterial growth, Bactria express different antigens* from bacterial flagella or capsules which makes it harder for the immune system to *target these bacteria, this mechanism is called* ***Antigenic Phase Variation.***

It is the expression of the ***somatic O antigens***, ***capsular K antigens***, and ***flagellar H antigens***. Each of these antigens can be alternately expressed or not expressed (phase variation).

This feature protects the bacteria from ***antibody-mediated cell death.***

4.Type III Secretion Systems: the bacteria counteract iron sequestration by producing their own competitive siderophores or iron-chelating compounds (e.g., enterobactin, aerobactin), or from Iron released from lysed cells.



Type III Secretion Systems proteins (which are found on the bacterial membrane or cell wall), can be grouped into three categories:

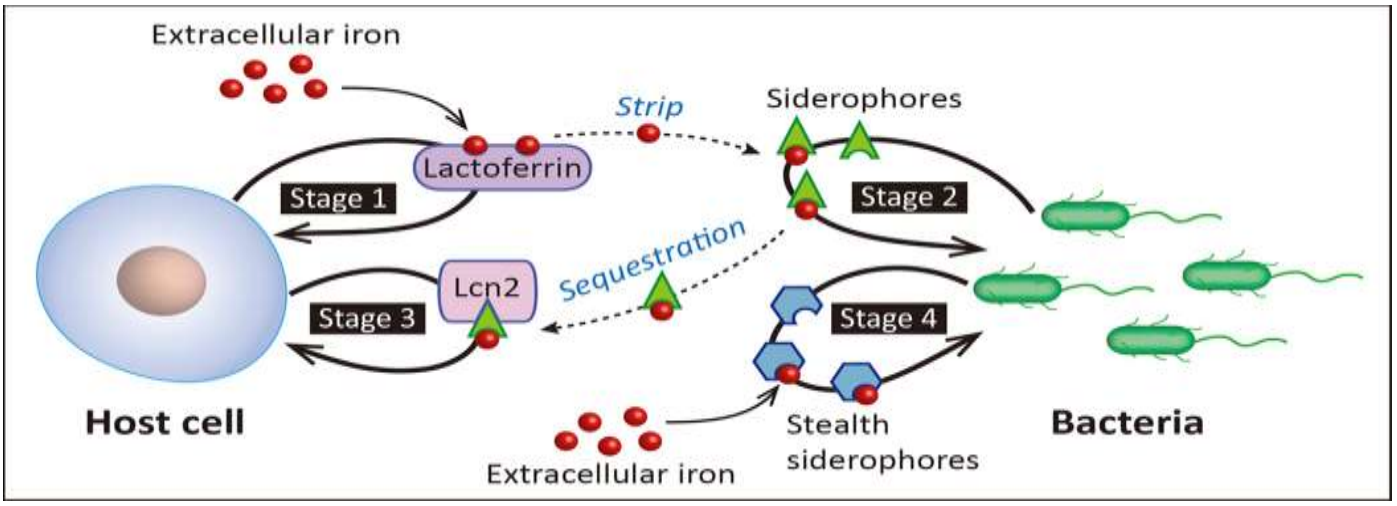
- **Structural proteins**: build the base, the inner rod and the needle.
- **Effector proteins**: get secreted into the host cell and promote infection / suppress host cell defences.
- **Chaperones**: bind effectors in the bacterial cytoplasm, protect them from aggregation and degradation and direct them towards the needle complex.

Exotoxins can go through the secretion system by the help of chaperons then they move from the bacterial cytoplasm to the host cell's cytoplasm.

Iron sequestration: iron is so important for bacterial enzymatic activity, so iron must be sequestered from the host cell to the bacteria for bacterial growth.

But, how will the bacteria get iron from the host cell?

Iron sequestration



*stage 1: Host cells secrete iron-binding proteins, such as **lactoferrin**, to prevent pathogens from acquiring iron.*

stage 2: Pathogens respond by "stealing" iron from host proteins using high affinity siderophores.

stage 3: Host cells secrete the siderophore-binding protein lipocalin 2 (Lcn2) to neutralize the siderophore and prevent pathogen reuptake.

stage 4: Pathogens can also produce "stealth siderophores" that cannot be detected or sequestered by Lcn2.

5.Resistance to Serum Killing: Serum killing event occurs by complement components. Since theses bacteria can produce proteins that inhibit complement components, they are resistance to serum killing.

6. Antimicrobial Resistance: same mechanism above.

Important Enterobacteriaceae that we will study in this lecture:

1) Escherichia coli (E. coli) 2) Salmonella 3) Shigella

1) Escherichia coli (E. coli):

it is the most common and important member of the genus Escherichia.

It is both a common **commensal inhabitant of the gastrointestinal tract** and one of the **most important pathogens** in humans, as well as the most frequent cause of **bloodstream infection** and **urinary tract infections** (UTIs) among **Gram-negative bacteria.**

They are divided into 3 groups:

1) ***Commensal strains innocuously colonize the colon of healthy hosts***, causing extraintestinal disease only in the presence of a large inoculum (e.g., with penetrating abdominal trauma) and/or significant host compromise.

2) ***Diarrhoeagenic strains cause diarrhoea syndromes*** that vary in clinical presentation and pathogenesis according to the strain's distinctive virulence traits

3) ***Extraintestinal pathogenic E. coli*** (ExPEC) often innocuously colonize the human gut. However, they have a unique ability to enter and **survive within normally sterile extraintestinal body** sites, and to **cause disease** when they do so.

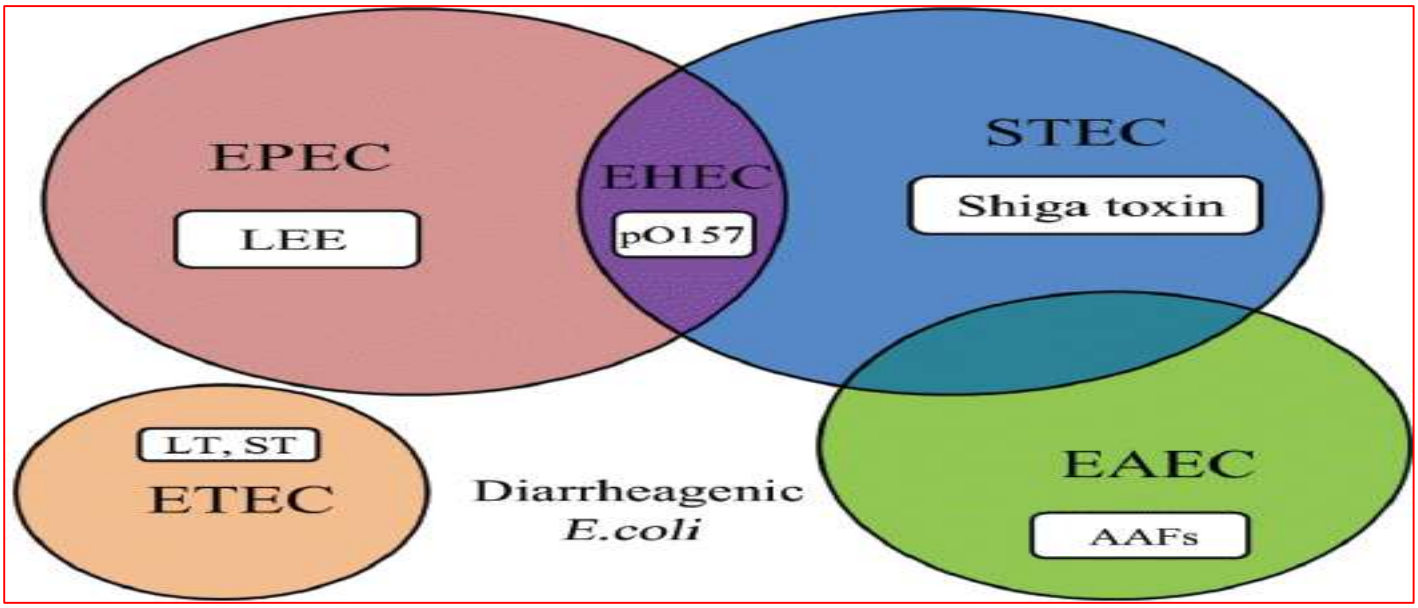
The strains of E. coli that cause gastroenteritis are subdivided into a number of groups. Five of these groups will be the focus of this course:

Classification of diarrheagenic E. coli:

1) ETEC, Enterotoxigenic E. coli. *2)STEC, Shiga toxin-producing E. coli.*

3)EPEC, Enteropathogenic E. coli. *4) EAEC, Enteroaggregative E. coli.*

5) EHEC, Enterohemorrhagic E. coli



1) Enterotoxigenic E. coli (ETEC) *properties:*

A) One of the most common causes of bacterial diarrheal disease in developing countries and 30% of **traveler's diarrhea.**

**** traveler's diarrhea:*** *When you visit a place where the climate or sanitary practices are different from yours at home, you have an increased risk of developing traveler's diarrhea. Usually recovery happens within days with no need for treatment.*

B) Because the inoculum for disease is high, infections are primarily acquired through consumption of fecally contaminated food or water. *Person-to-person spread does not occur.*

C) Secretory diarrhea caused by ETEC ***develops after a 1- to 2-day incubation period*** and ***persists for an average of 3 to 5 days.***

D) The symptoms are (**watery**, ***non-bloody diarrhea*** and ***abdominal cramps***; *less commonly* ***nausea*** *and* ***vomiting***. (Can be fatal in undernourished individuals)

E) ***ETEC produce two classes of enterotoxins:***

1) Heat-stable toxins (ST): *leads to* ***increase in cyclic guanosine monophosphate (cGMP)*** *and subsequent hypersecretion of fluids well as inhibition of fluid absorption.*

2) Heat-labile toxins (LT): *leads to* ***increase in cyclic adenosine monophosphate (cAMP)*** *levels, resulting in enhanced secretion of chloride and decreased absorption of sodium and chloride.*

Both of them will affect the secretion of intestinal epithelia leading to increase the excretion of water, as well as decrease the absorption of some ions and this will lead to ***watery type of diarrhea.***

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2) Enteropathogenic E. coli (EPEC) *properties:*

A) possess a cluster of virulence genes located on a chromosomal pathogenicity island called the **locus of enterocyte effacement (LEE).**

> Note: Two groups of E. coli responsible for enteric disease: EPEC and STEC, which means that both have ***locus of enterocyte effacement (LEE).***

B*) Disease is transmitted by fecal-oral exposure to contaminated surfaces or food products, Disease occurs* ***primarily in children*** *younger than 2 years and is characterized by* ***watery diarrhea.***

C) Infection is initiated by bacterial attachment to epithelial cells of the small intestine, with subsequent effacement (destruction) of the microvillus. Diarrhea *and symptoms are caused by invasion of host cells ("attachment and effacement") rather than by production of toxins.*

D) *Active secretion of bacterial proteins into the host epithelial cell* occurs by the bacterial type III secretion system:

1) One protein, ***translocated intimin receptor (Tir),*** is inserted into the epithelial cell membrane and functions as a receptor for an outer membrane bacterial adhesin, which is called ***(intimin).***

2) Binding of intimin to Tir results in **polymerization of actin**, **accumulation of cytoskeletal elements beneath the attached bacteria**, **loss of cell surface integrity**, **and eventual cell death.**

E) The onset of disease may be as rapid as a few hours after ingestion of EPEC, and although most infections resolve after a few days, persistent diarrhea requiring hospitalization can occur.

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3) Enteroaggregative E. coli (EAEC) *properties:*

A) characterized by their autoagglutination in a "stacked-brick" arrangement over the epithelium of the small intestine and, in some cases.

B) Outbreaks in both developed and developing countries have demonstrated these bacteria are common.

C) One of the few bacteria associated with **chronic diarrhea** and **growth retardation** in children.

Note: Usually diarrhea that is caused by microorganisms is an *acute diarrhea*. But this is an exception.

D) Characteristically, following adherence to the epithelium, cytokine release is stimulated, which results in neutrophil recruitment and progression to an inflammatory diarrhea.

E) Disease is characterized by a watery secretory diarrhea, often with inflammatory cells and accompanied by fever, nausea, vomiting, and abdominal pain. Might progress to chronic in children or HIV patients.

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4) Shiga toxin–producing E. coli (STEC) *properties:*

Additional information: Nomenclature for this group of E. coli is confusing, referring to them as Shiga toxin–producing E. coli (STEC), verocytotoxin-producing E. coli (VTEC), and enterohemorrhagic E. coli (EHEC). To provide some clarity, consider VTEC an outdated name and EHEC a subset of STEC.

A) Enterohemorrhagic E. coli (EHEC) can be thought of as a subset of STEC.

B) Can cause severe **foodborne disease**.

C) Some but not all EHEC strains are LEE positive and form ***Attachment/ effacement*** cytopathology, resembling EPEC strains.

D) Most infections are attributed to the consumption of undercooked meat products, water, unpasteurized milk or fruit juices uncooked vegetables, and fruits. ***Ingestion of fewer than 100 bacteria*** can produce disease, and person-to-person spread occurs.

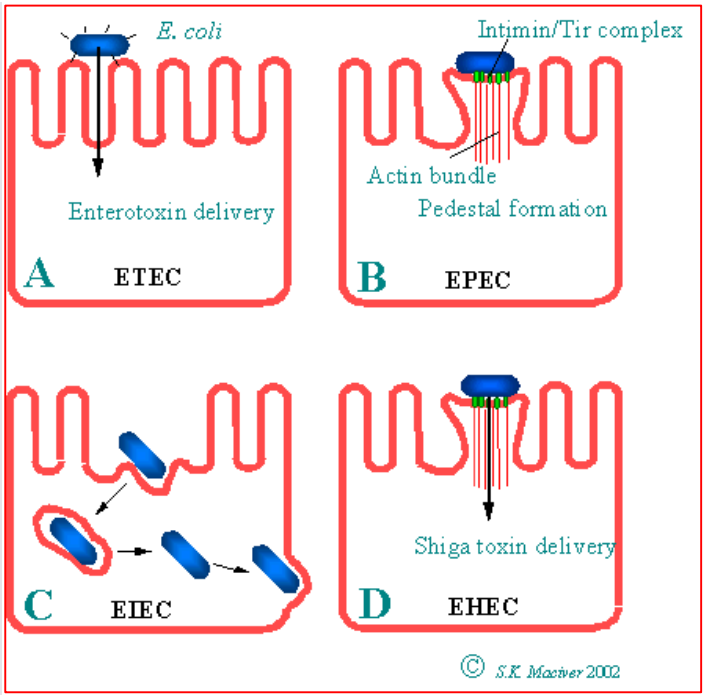
E) Initially, diarrhea with abdominal pain develops in patients after 3 to 4 days of incubation. Within 2 days of onset, disease in 30% to 65% of patients progresses from watery to a bloody diarrhea with severe abdominal pain. Complete resolution of symptoms typically occurs after 4 to 10 days in most untreated patients. It is usually treated by antibiotics.

F) ***Hemolytic uremic syndrome (HUS)***, a disorder characterized by acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia, is a complication in 5% to 10% of infected children younger than 10 years.

G) Disease caused by STEC ranges from mild uncomplicated diarrhea to hemorrhagic colitis with severe abdominal pain and bloody diarrhea. Severe disease is more commonly associated with STEC O157:H7.

Clinical Case 25-1 Multistate Outbreak of Shiga Toxin–Producing *Escherichia coli* (STEC) Infections

In 2006, *E. coli* O157 was responsible for a large multistate outbreak of gastroenteritis. The outbreak was linked to contamination of spinach, with a total of 173 cases reported in 25 states, primarily over an 18-day period. The outbreak resulted in hospitalization of more than 50% of the patients with documented disease, a 16% rate of hemolytic uremic syndrome, and one death. Despite the wide distribution of the contaminated spinach, publication of the outbreak and the rapid determination that spinach was responsible resulted in prompt removal of spinach from grocery stores and termination of the outbreak. This outbreak illustrates how contamination of a food product, even with small numbers of organisms, can lead to a widespread outbreak with a particularly virulent organism, such as strains of STEC.



Note: There is a lot of information that must be memorized, but the doctor said that you should know the major differences between each type, for example:

If we talk about traveler's diarrhea you should consider ***Enterotoxigenic E. coli (ETEC).***

If we talk type chronic diarrhea you should consider ***Enteroaggregative E. coli (EAEC).***

If we talk about a bloody diarrhea and Hemolytic uremic syndrome (HUS), you should consider ***Shiga toxin–producing E. coli (STEC),*** *and so on…*

All E.coli types that have mentioned before, cause mainly ***gastroenteritis (diseases within the intestinal epithelia)*** not ***Extraintestinal Infections!!***

So, now let's talk about ***Extraintestinal Infections*** *(*Urinary Tract Infections) properties:

A) Most gram-negative rods that produce UTIs originate in the colon, contaminate the urethra, ascend into the bladder, and may migrate to the kidney or prostate.

*B) Almost every second woman suffers from a bladder infection at some point in her life (**E. coli involve in 80% of UTI cases**). Also men are affected by cystitis, though less frequently, probably due to **anatomical differences** (e.g. shorter urethra in women makes it easier for bacteria to reach the bladder).*

*Note: Although **most strains of E. coli can produce UTIs**, disease is more common with **certain specific serogroups**. These bacteria are particularly virulent because of their ability to produce **adhesins** that bind to cells, lining the bladder and upper urinary tract.*

C) *E. coli* and ***group B streptococci*** (revise sheet 13), cause the majority of CNS infections in infants younger than 1 month.

Additional information: ***Neonatal meningitis*****:** is a rare type of meningitis, this often life-threatening condition affects newborns and is caused by various bacteria, including group B strep, E. coli.

D) Septicemia: caused by gram-negative rods, such as E. coli, most commonly originates from infections in the urinary or GI tract (e.g., intestinal leakage leading to an intraabdominal infection). with high mortality in immunocompromised patients.

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2) *Salmonella:*

A) Salmonella can colonize virtually all animals (especially poultry). Serotypes such as Salmonella Typhi and Salmonella Paratyphi are **highly adapted to humans** and do not cause disease in nonhuman hosts.

B) After ingestion and passage through the stomach, salmonellae attach to the mucosa of the **small intestine** and invade into the **M (microfold) cells** located in Peyer patches, as well as into enterocytes. **The bacteria remain in endocytic vacuoles**, where they replicate. The bacteria can also be transported across the cytoplasm and released into the blood or lymphatic circulation.

C) Virulence dependent on **pathogenicity island I and II** on the bacterial chromosome. Encoding for toxins, attachment proteins and immune evasion mechanisms.

D) The inflammatory response confines the infection to the GI tract, mediates the release of prostaglandins, and **stimulates cAMP and active fluid secretion.**

E) Asymptomatic Colonization: The strains of Salmonella responsible for causing typhoid and paratyphoid fevers are maintained by human colonization. So even if they do not cause diseases they can colonize and transmit from person to another, that's usually takes place through fecal–oral route.

F) The infectious dose for **Salmonella Typhi (found only in humans)** infections is low, so person-to-person spread is common. Occur also when food or water contaminated by infected food handlers is ingested.

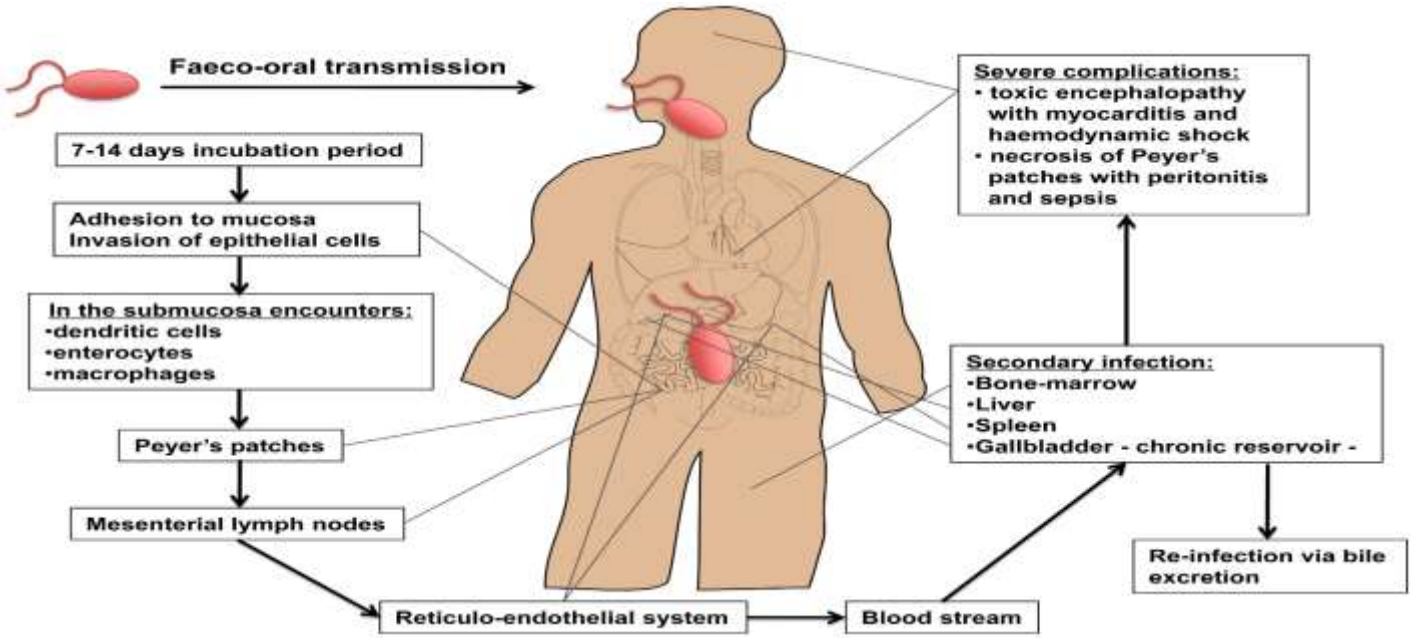
G) In contrast, in the most common sources of human infections which are **poultry, eggs, dairy products,** and foods prepared on contaminated work surfaces, **a large inoculum** (e.g., 106 to 108 bacteria) is required for symptomatic disease to develop with most other Salmonella serotypes.

H) **Gastroenteritis** is a common form of **salmonellosis**, **nausea**, **vomiting**, and **non-bloody diarrhea**. Can persist for 2 to 7 days before spontaneous resolution.

I) A more serious complication can happen like a **Septicemia,** all Salmonella species can cause bacteremia, although infections with Salmonella Typhi and Salmonella Paratyphi lead to a bacteremic phase.

J) Salmonella Typhi produces a febrile illness called **typhoid fever**. A milder form of this disease, referred to as **paratyphoid fever**, is produced by paratyphi Salmonella (The bacteria responsible for enteric fever pass through the cells lining the intestines and are

engulfed by macrophages. They replicate after being transported to the liver, spleen, and bone marrow. Ten to 14 days after ingestion of the bacteria, patients experience gradually increasing fever, with nonspecific complaints of headache, myalgias, malaise, and anorexia).



3) Shigella:

A) There are many types of shigella like **S. dysenteriae**, **Shigella flexneri**, **Shigella boydii**, and **Shigella sonnei**. However, analysis of DNA has determined that these four species are actually biogroups within the species **E. coli!!**

Note: Because it would be confusing to refer to these bacteria as E. coli, their historical names have been retained.

B) Shigella cause disease by invading and replicating in cells lining the **colon**. Structural gene proteins mediate the adherence of the organisms to the cells, as well as their invasion, intracellular replication, and cell-to-cell spread.

C) S. dysenteriae strains produce an exotoxin, **Shiga toxin**. Similar to Shiga toxin produced by STEC.

D) The A subunit in the toxin cleaves the 28S rRNA in the 60S ribosomal subunit, thereby preventing the binding of aminoacyl-transfer RNA and **disrupting protein synthesis**. The primary manifestation of toxin activity is **damage to the intestinal epithelium**; however, in a small subset of patients, the Shiga toxin can mediate **damage to the glomerular endothelial cells**, **resulting in renal failure (HUS).**

E) **Humans are the only reservoir** for Shigella.

F) **S. sonnei** is responsible for almost 85% of U.S. infections, whereas **S. flexneri** predominates in developing countries. Epidemics of **S. dysenteriae** infections occur periodically, most recently in West Africa and Central America.

G) **Shigellosis** (Shigella infection) (is primarily a pediatric disease, with 60% of all infections in children younger than 10 years.

H) Shigellosis is **transmitted person to person by the fecal-oral route**. Because as few as 100 to 200 bacteria can establish disease, shigellosis spreads rapidly in communities where sanitary standards and the level of personal hygiene are low.

I) **Shigellosis** is characterized by abdominal cramps, **diarrhea**, **fever**, and **bloody stools**. The clinical signs and symptoms of the disease appear 1 to 3 days after the bacteria are ingested.

J) Infection is **generally self-limited**, although antibiotic treatment is recommended **to reduce the risk of secondary spread** to family members and other contacts.

Clinical Case 25-3 *Shigella* Infections in Day-Care Centers

In 2005, three states reported outbreaks of multidrug-resistant *Shigella* infections in day-care centers. A total of 532 infections were reported in the Kansas City area, with the median age of patients 6 years old (Centers for Disease Control and Prevention: *MMWR Morb Mortal Wkly Rep* 55:1068–1071, 2006). The predominant pathogen was a multidrug-resistant strain of *Shigella sonnei,* with 89% of the isolates resistant to ampicillin and trimethoprim-sulfamethoxazole. Shigellosis spreads easily in day-care centers because of the increased risk of fecal contamination and the low infectious dose responsible for disease. Parents and teachers, as well as classmates, are at significant risk for disease.