UNIT 9

Intestinal bacteria that cause secretory diarrhea

Causes of invasive gastrointestinal infections

Causes of non-invasive gastrointestinal and intra-abdominal infections

Intestinal bacteria that cause secretory (watery) diarrhea

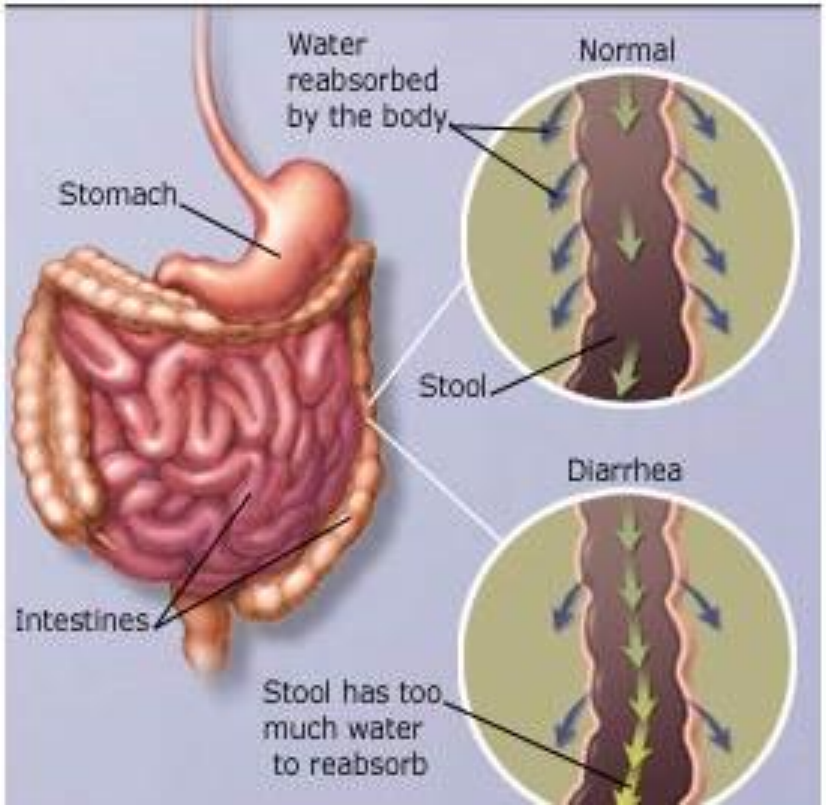
Vibrio cholerae

Enterotoxigenic *Escherichia coli(ETEC)*

Enteropathogenic *Escherichia coli(EPECs)*

Secretory or watery diarrhea - occurs due to **loss of water and electrolytes in the small intestine**

Diarrhea - the leading cause of infant and child mortality in underdeveloped and developing countries



Among the bacteria, the most common cause of watery diarrhea are:

E. coli, Shigella sonnei u **nonthypoid** ***Salmonella***, among the viruses *Rotavirus* and among protosoas *Giardia, Cryptosporidium andCyclospora*

General characteristics of the cause of watery diarrhea

The largest number of intestinal bacteria that cause watery diarrhea belong to the facultative anaerobic Gram-negative bacilli from the family

Enterobacteriaceae and *Vibrionaceae*

- Bacteria of the family Enterobacteriaceae are mainly conditionally pathogenic bacteria, many of which inhabit the intestinal microflora. Among them there are strictly pathogenic bacteria
- The causes of diarrhea, urinary tract infections, sepsis and meningitis

- **Cholera** is an example of watery diarrhea. It is caused by the bacterium **Vibrio cholerae**, a member of the Vibrionaceae family
- **subtype Vibrio cholerae O1: world cholera epidemics**
- **two types: classic and "El Tor"**
- Among the bacteria of the family Vibrionaceae there are conditionally pathogenic bacteria that can cause epidemic cholera, sporadic diarrhea and bacterial skin infections

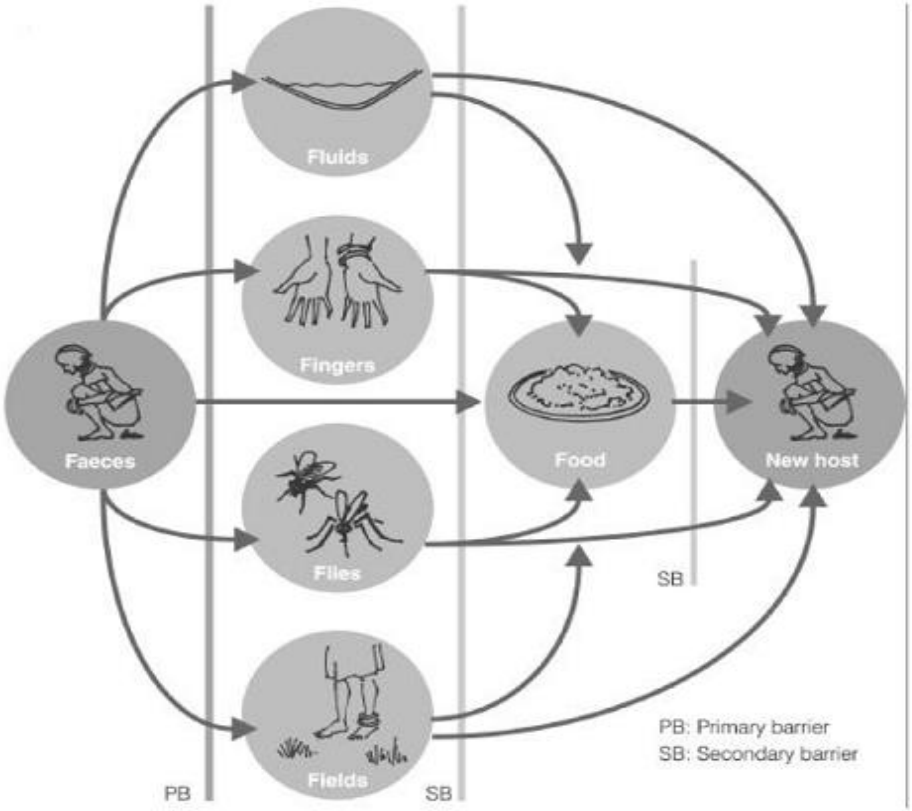
Gram-negative bacteria that cause watery diarrhea, hemorrhagic diarrhea or dysentery

type	watery diarrhea	hemorrhagic diarrhea	Inflammatory diarrhea or dysentery	
			Ileitis	*Colitis*
Enterobacteriaceae				
ETEC	+			
EPEC	+		±	
EAggEC	+			
EIEC		+		+
EHEC		+		+
Shigella		+	±	+
Nontyphoid *Salmonella*	+	±	+	±
Salmonella typhi			+	
Yersinia enterocolitica	+	+	+	
Vibrionaceae				
Vibrio cholerae	+			
Vibrio parahaemolyticus	+	+	±	±
Campylobacter jejuni	+	+	±	+

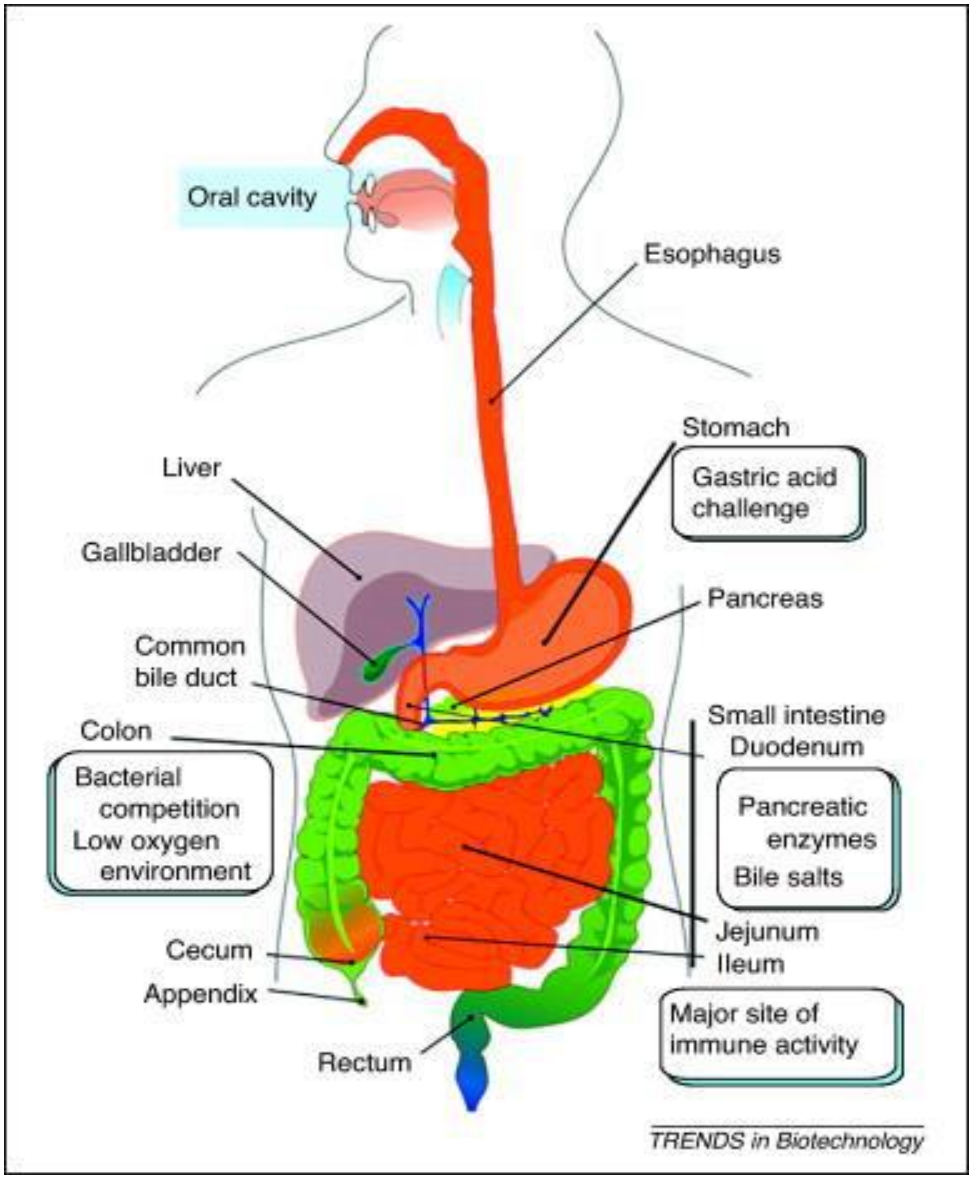
Intestinal pathogens are ingested by the feco-oral route

7 factors important for infection spreading:

"**7 F":** *"Feces, Food, Fluids, Fingers, Flies, Fomites, Fornication"*



The entry of bacteria into the body



"Traveling" through the digestive tract is dangerous for the microorganism, because they face the defense mechanisms of the host

Acidity of gastric juice
Pancreatic juice
Mucus
Peristaltic bowel movements
Enzymes: lysozyme, protease and lipase
Secreted IgA and bile salts
Phagocytes
Physiological microflora of the colon – bactericidins

Inoculum size

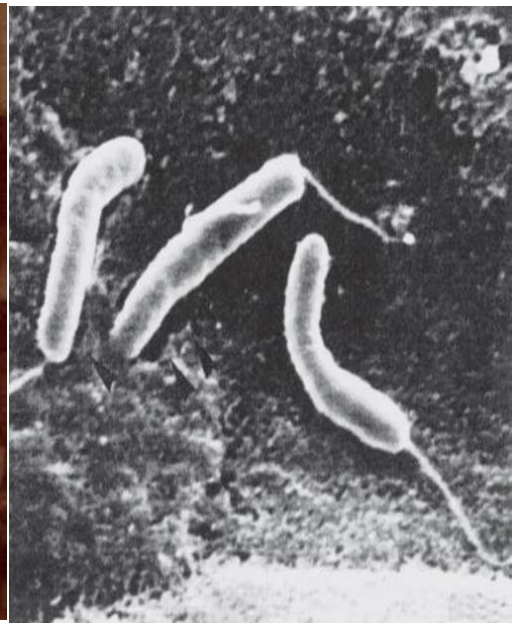
Vibrio cholerae...

... the cause of cholera.

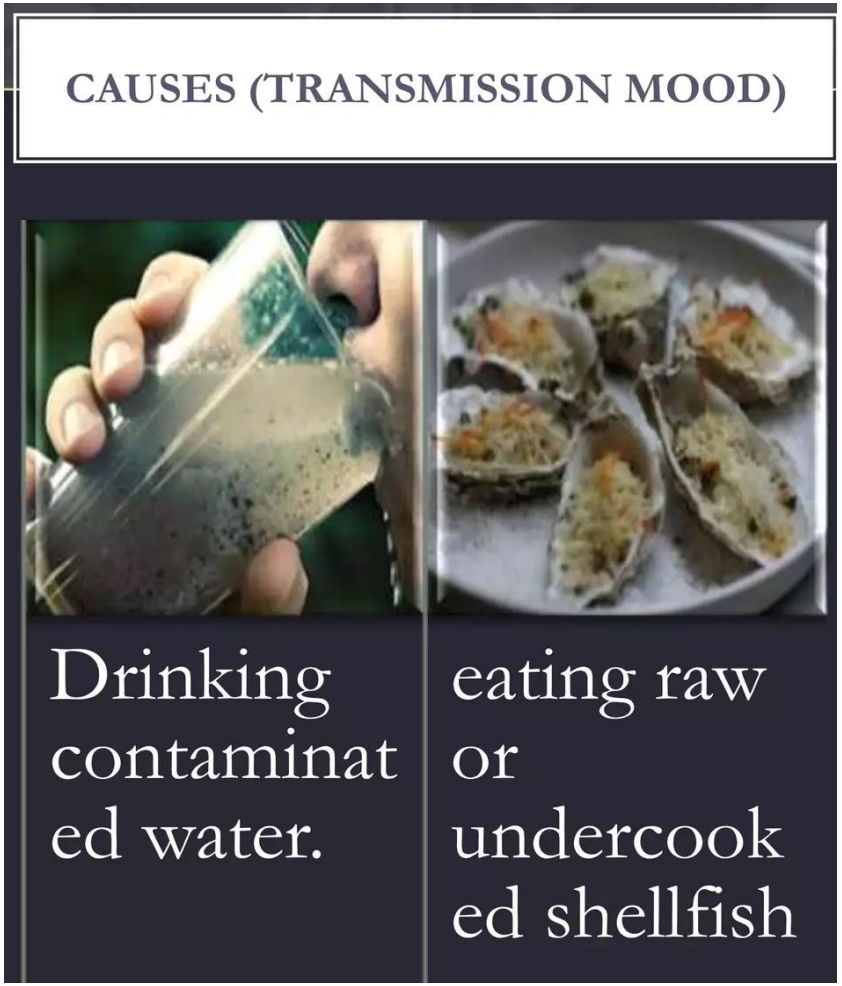
Cholera is an acute diarrheal illness caused by infection of the intestine

Natural habitat and way of transmission

- ***Vibrio cholerae*** **-** a normal inhabitant of coastal waters, where it lives in cohabitation with phytoplankton. People accidentally become infected when they enter this ecosystem or when bacteria contaminate drinking water or food
- Shellfish

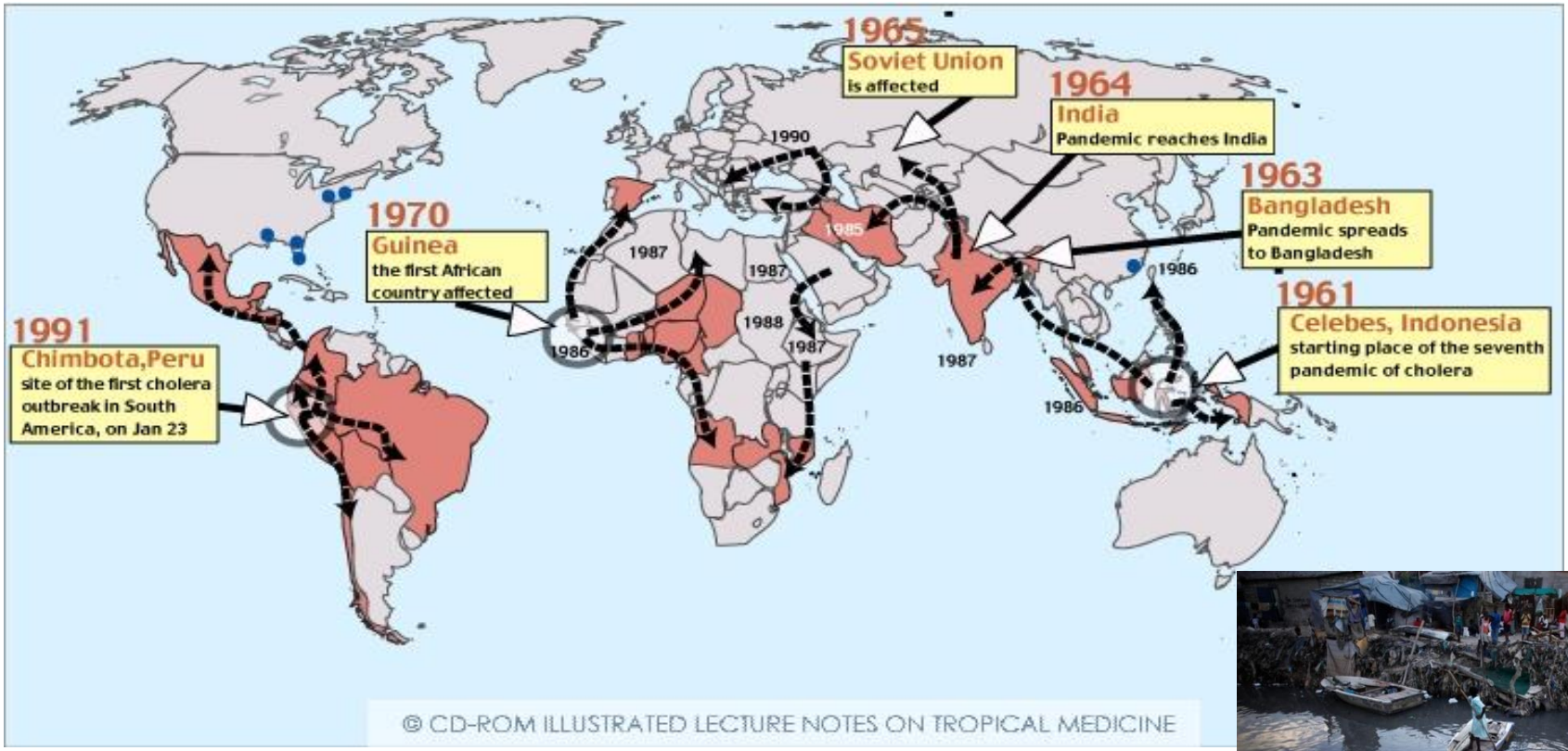


Identified by Robert Koch in 1883. during the cholera epidemic in Egypt



Vibrio cholerae is transmitted by the feco-oral route

- Cholera can be an endemic, epidemic, or pandemic disease
- Epidemic cholera primarily spreads in poor sanitary conditions through contaminated water

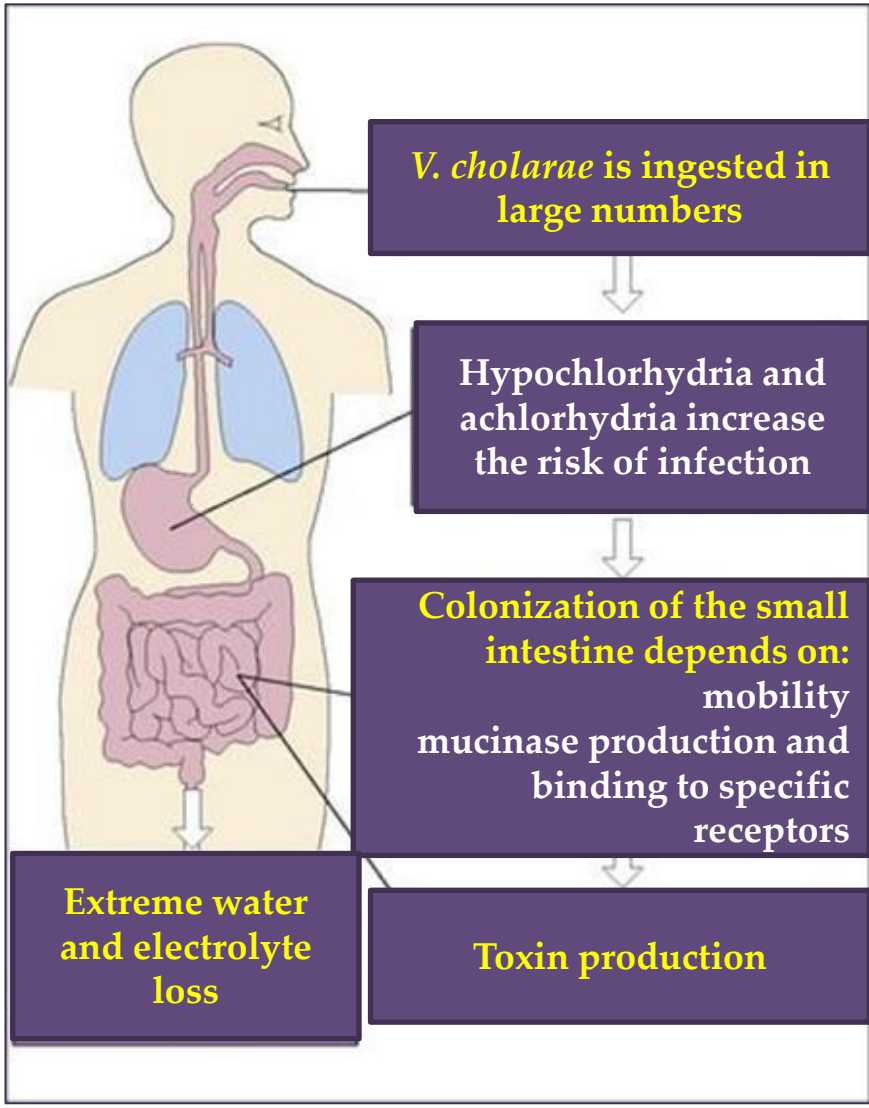


- **Cholera is an endemic disease in India and Africa**

Spread and multiplication

In healthy people, it is necessary to ingest a large number of bacteria in order to overcome the gastric barrier.

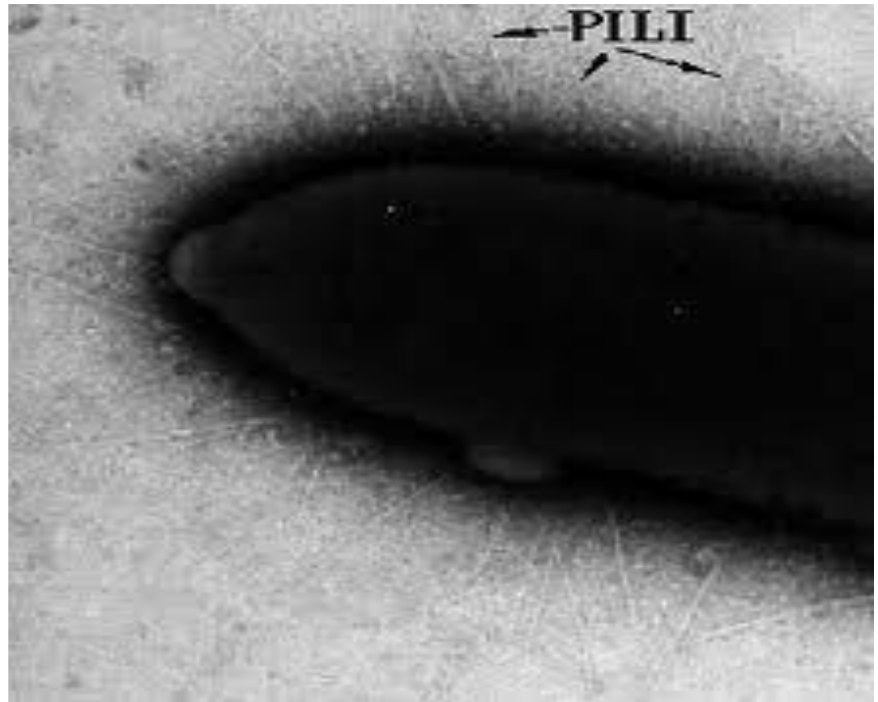
For the development of cholera, it is necessary for vibrios of cholera to colonize the small intestine, to multiply and to produce virulence factors.



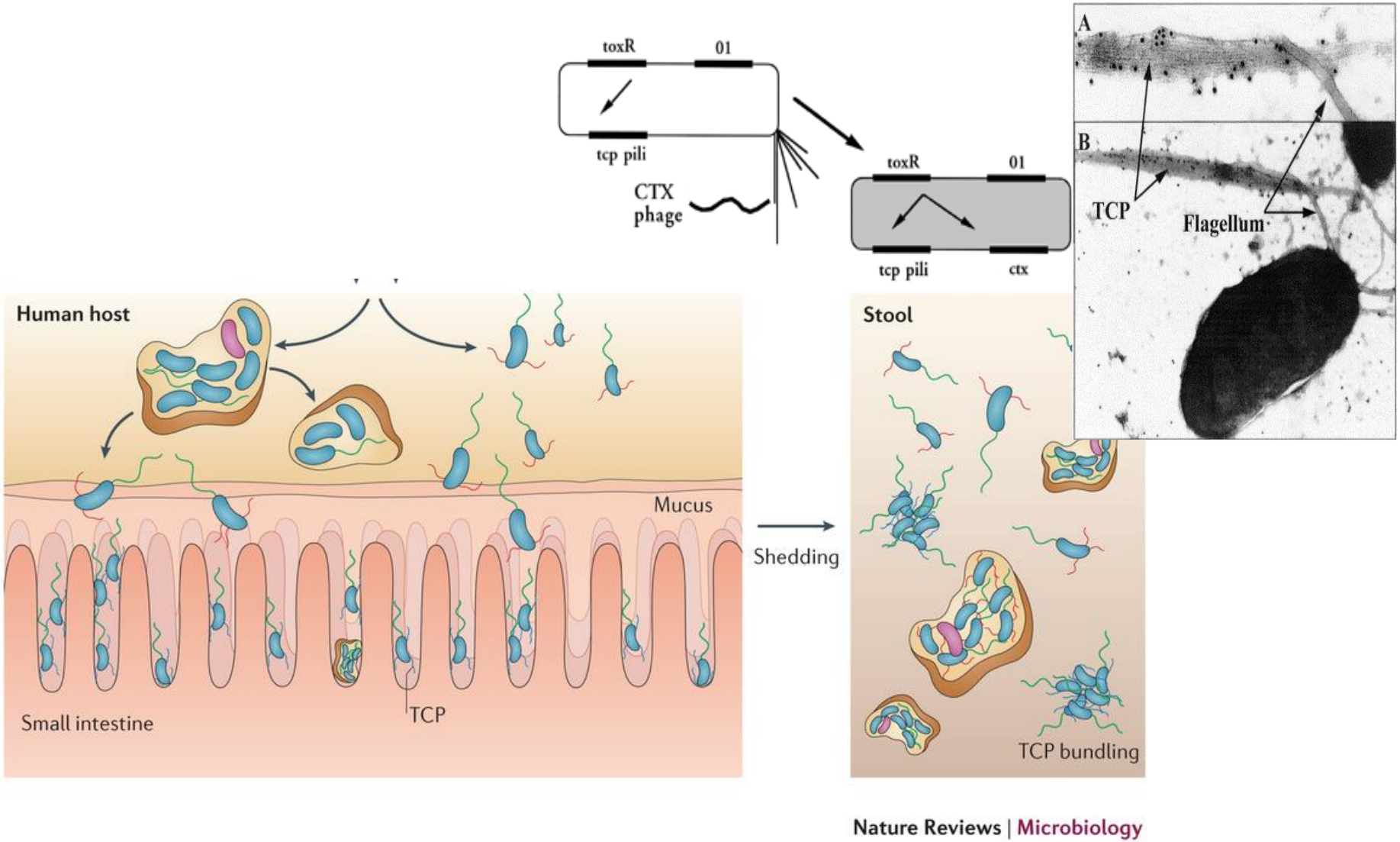
...

Vibrio cholerae, as well as other intestinal pathogens, have specific **pili or fimbria**e that increase the distance between the surface of the host cell and the bacteria and thus reduce electrostatic repulsion.

Practically all Gram-negative bacteria have **type 1 or so-called. common pili**, proteins that have a special affinity for proteins and lipids that contain mannose and help in the adhesion of bacteria to the mucous membrane of the digestive system ...



.... Vibrio cholerae are held together and grouped by specific pili: **TCP *(toxin-coregulated pili)***

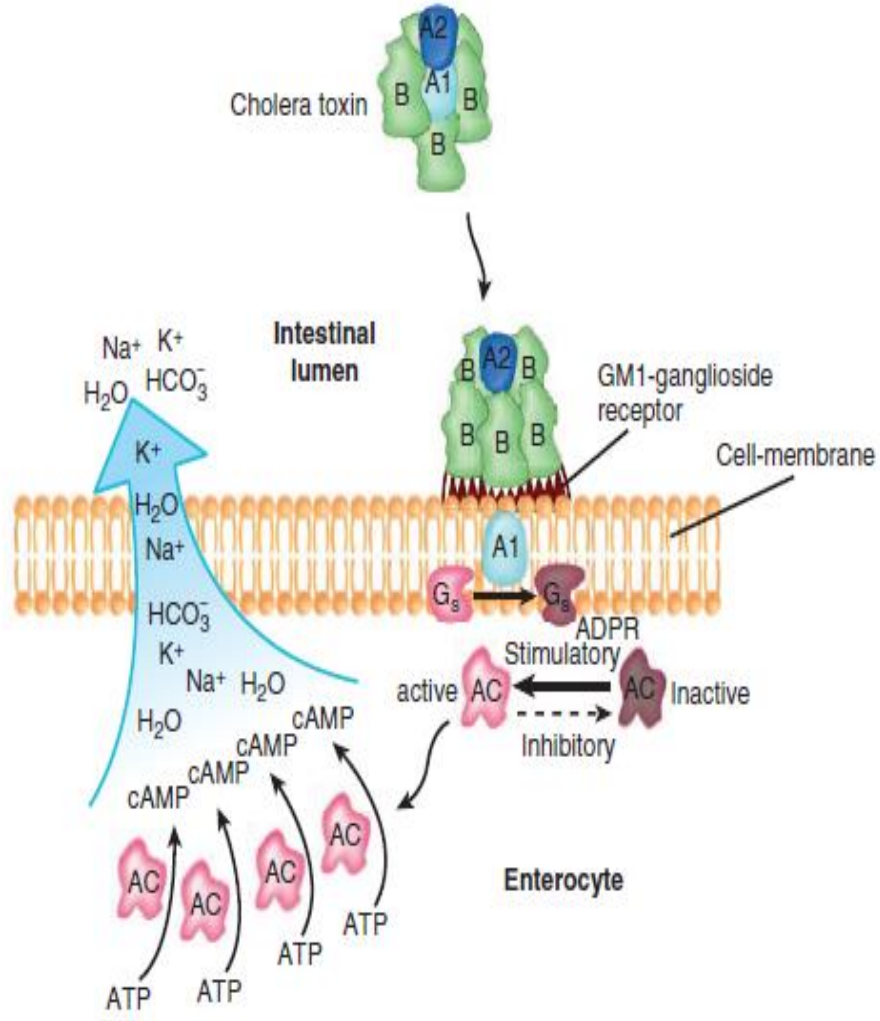


Mechanism of action of cholera toxin

After colonization, **cholera toxin** binds to its receptor, entering the vesicles. The **active subunit** of the toxin is transported to the basolateral membrane of the adenylate cyclase complex

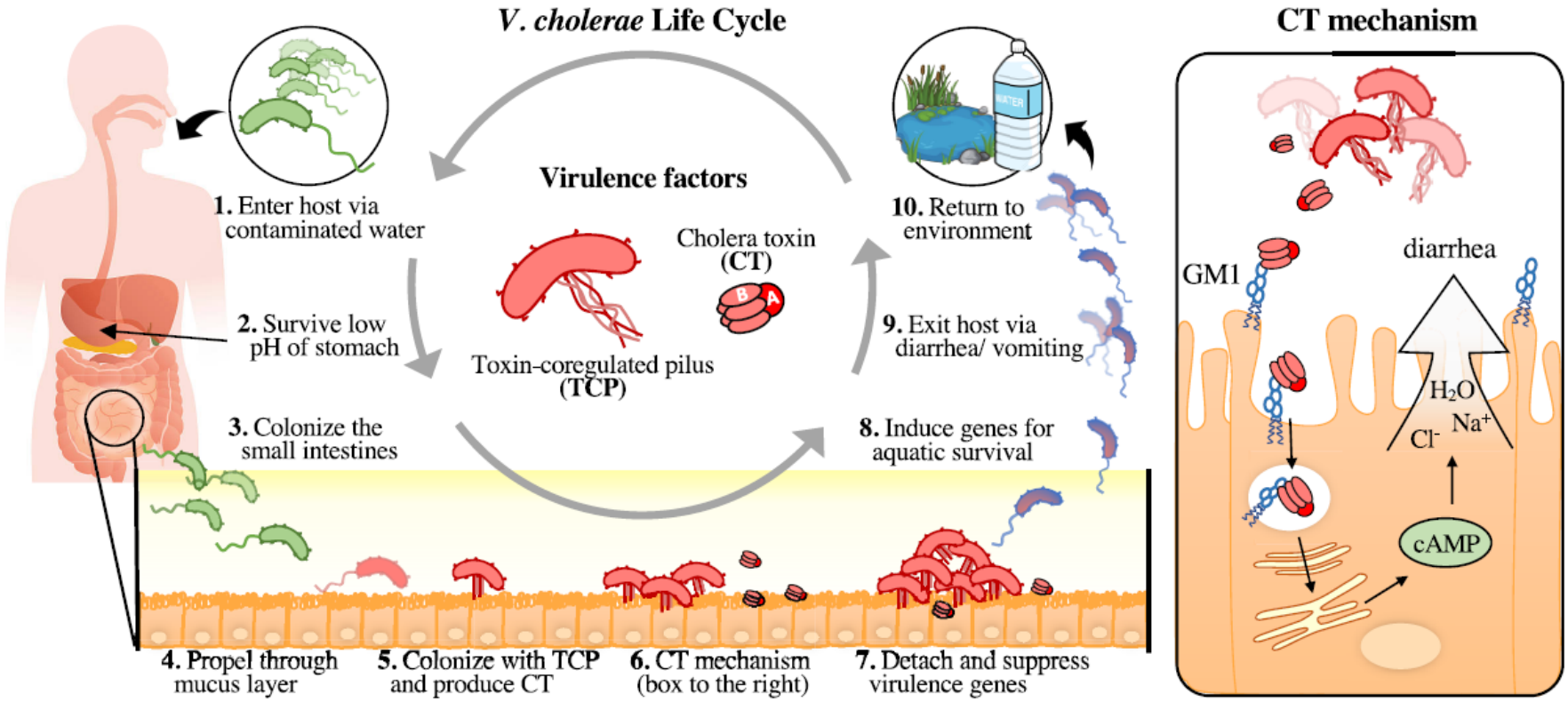
The toxin transmits ADP ribose to guanosine 5 triphosphate binding protein AC, **thus increasing the concentration of cAMP**

Increased cAMP concentration results in reduced sodium absorption in ciliated cells and increased chlorine secretion in goblet cells causing **watery diarrhea**



V. cholerae life cycle and pathogenesis.

LET'S REPEAT

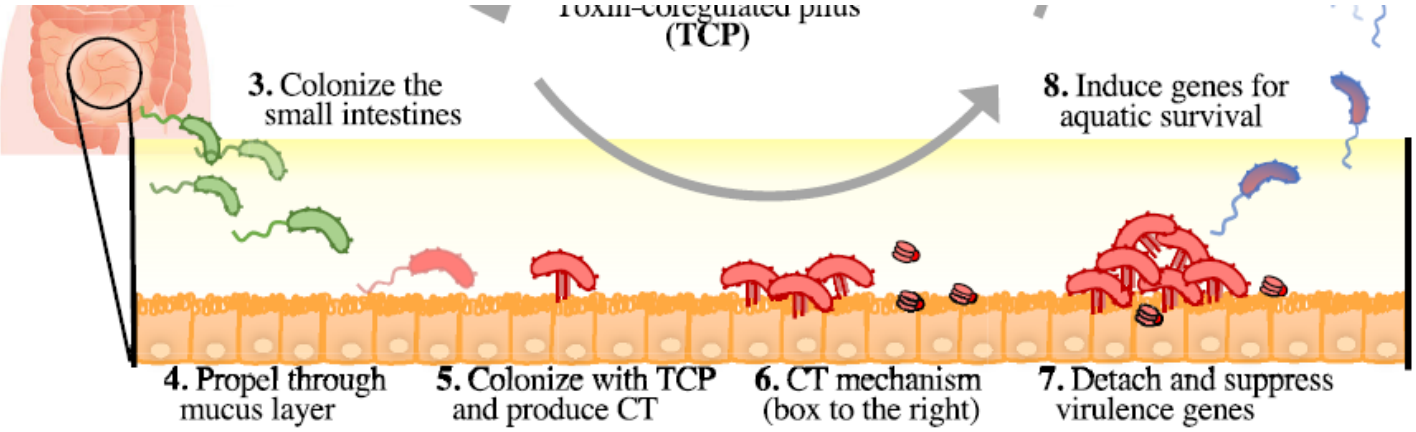


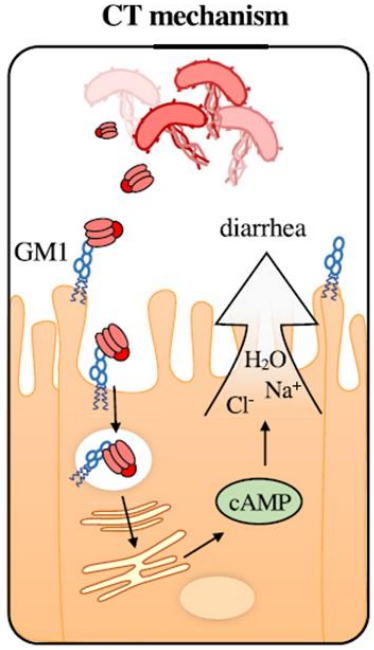
(1) V. cholerae is introduced to the human host through contaminated water.

(2) In the stomach, V. cholerae encounters a low pH environment.

(3) To induce disease, V. cholerae colonizes the small intestine.

V. cholerae life cycle and pathogenesis.



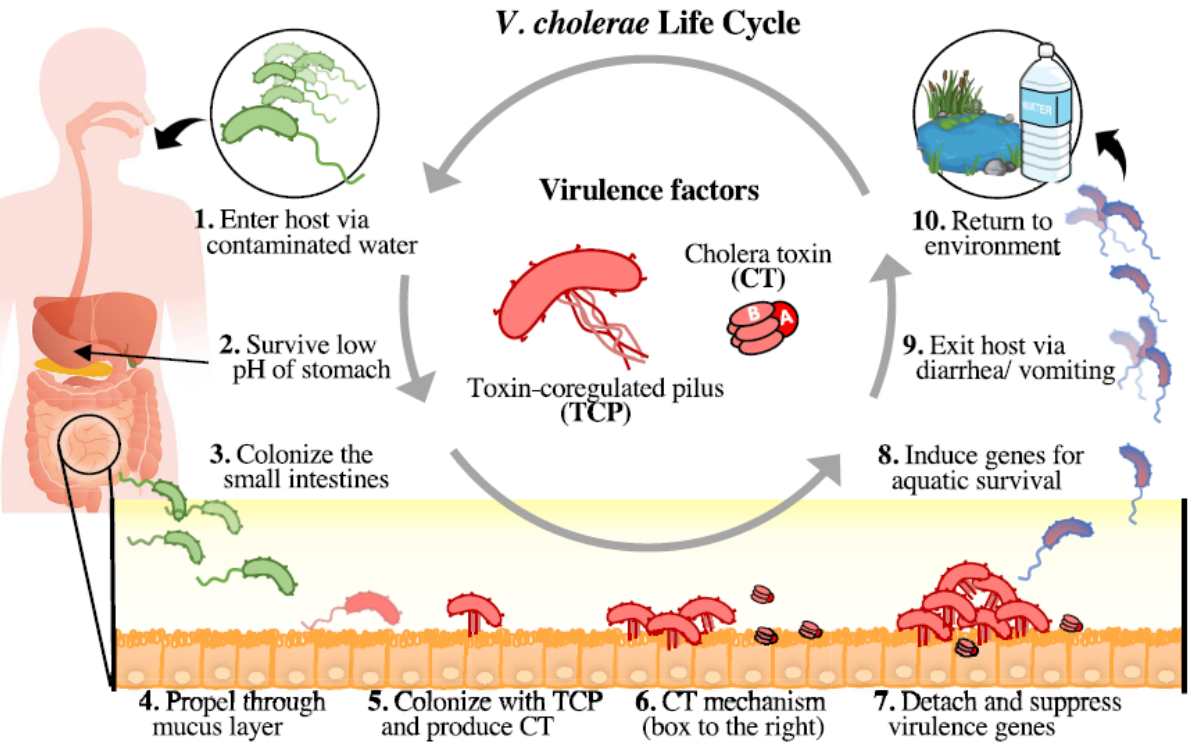


(4) V. cholerae uses a single flagellum to propel through the mucus and reaches the epithelial surface. V. cholerae responds to host signals to induce virulence factors such as toxin coregulated pilus (TCP) and cholera toxin (CT).

(5) TCP facilitates the colonization of the epithelial surface, and CT is produced, binding GM1 on the host cells.

(6) CT is then endocytosed and induces cyclic AMP (cAMP). High cAMP levels cause the efflux of electrolytes and water, resulting in the characteristic watery diarrhea of cholera.

V. cholerae life cycle and pathogenesis.



(7) Microcolonies form, and *V. cholerae* represses virulence genes

(8) At this high density, *V. cholerae* detaches from the epithelial surface and migrates to the lumen. Genes required for transitioning are upregulated.

(9) *V. cholerae* is excreted from the host in diarrheal stool and in vomitus.

(10) *V. cholerae* returns to the environment, where contamination of drinking water may infect another host.

Clinical manifestations of cholera

Quick start

Abdominal pain

A large number of liquid stools

(appearance of rice water)

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Loss of water and electrolytes in the small intestine

(several liters per day)

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Loss of water and electrolytes in the small intestine
(several liters per day)

Extreme dehydration
(loss of isotonic fluid)
hypokalaemia
(potassium loss)
metabolic acidosis
(loss of bicarbonate)

Clinical manifestations of cholera

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Loss of water and electrolytes in the small intestine
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hypokalaemia
(potassium loss)
metabolic acidosis
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The intestinal mucosa is not visibly damaged.

Watery stools do not contain leukocytes or erythrocytes, and there is no inflammation in the intestinal wall

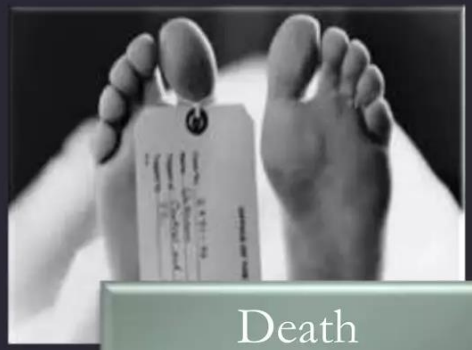
The horror of cholera in Bangladesh in the 1970s. However, the disease need not be a killer if simple prevention and treatment measures are taken.

Complications

severe dehydration

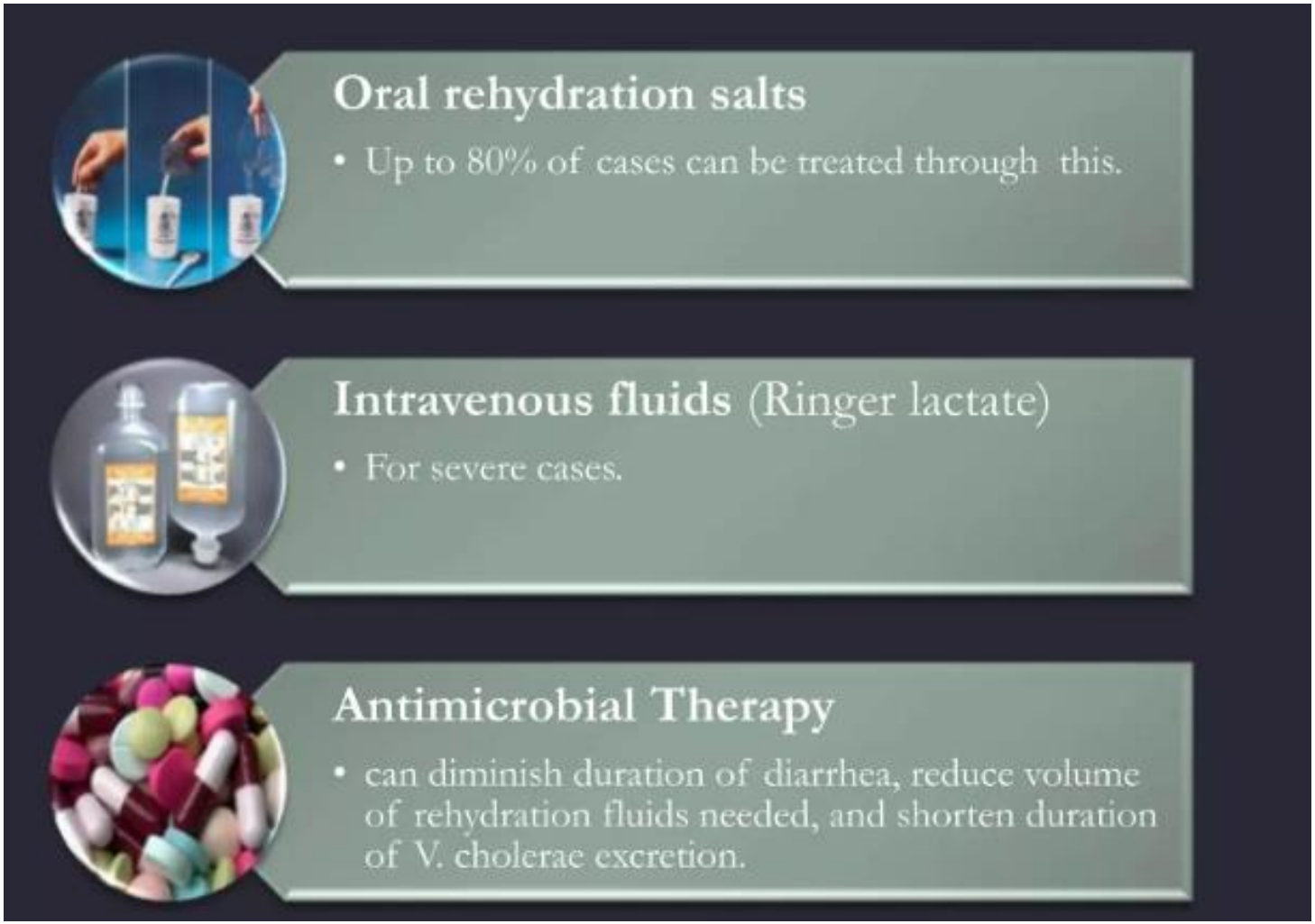
Shock

Renal failure



Death

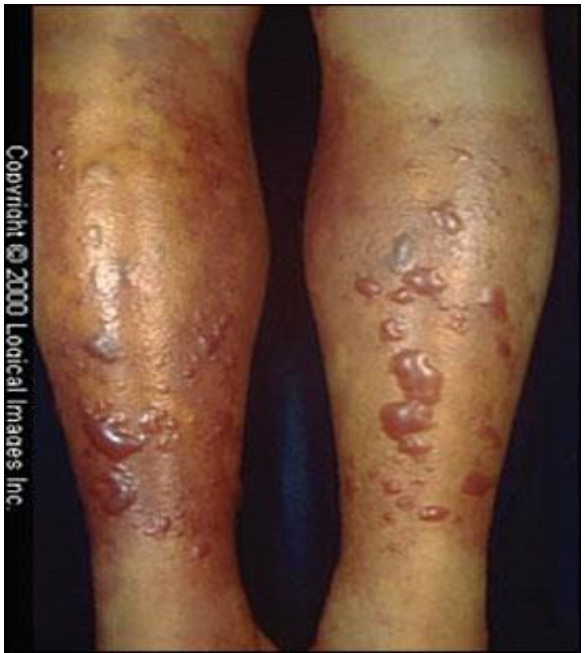
Treatment


Oral rehydration salts
• Up to 80% of cases can be treated through this.
Intravenous fluids (Ringer lactate)
• For severe cases.
Antimicrobial Therapy
• can diminish duration of diarrhea, reduce volume of rehydration fluids needed, and shorten duration of V. cholerae excretion.

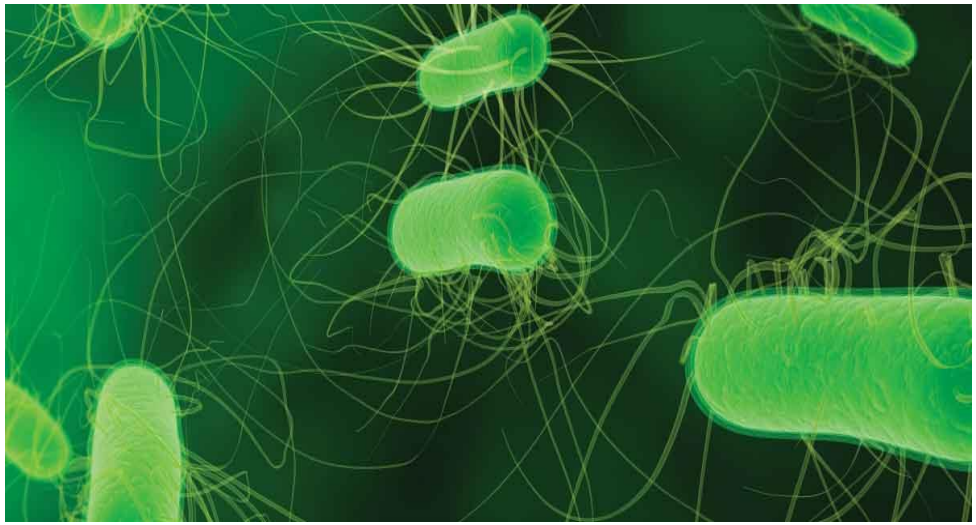
Infections caused by other species of the genus Vibrio

- ***V. parahaemolyticus*** causes hemorrhagic diarrhea, occurs after consuming sushi or raw oysters, especially in Japan

- After a skin injury, ***V. vulnificus*** and ***V. alginolyticus*** can cause serious invasive or subcutaneous infections



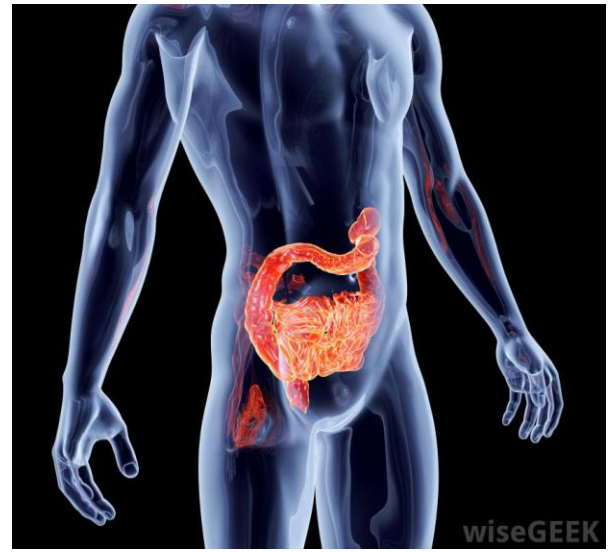
Escherichia coli...



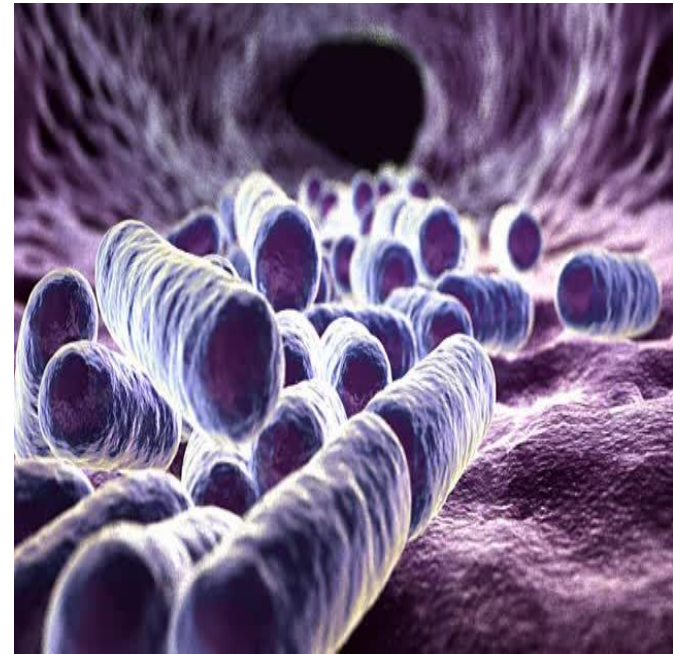
... the cause of opportunistic and intestinal infections

General characteristics

The most numerous facultative anaerobic bacterium **that colonizes the lower parts of the digestive system of humans and animals**



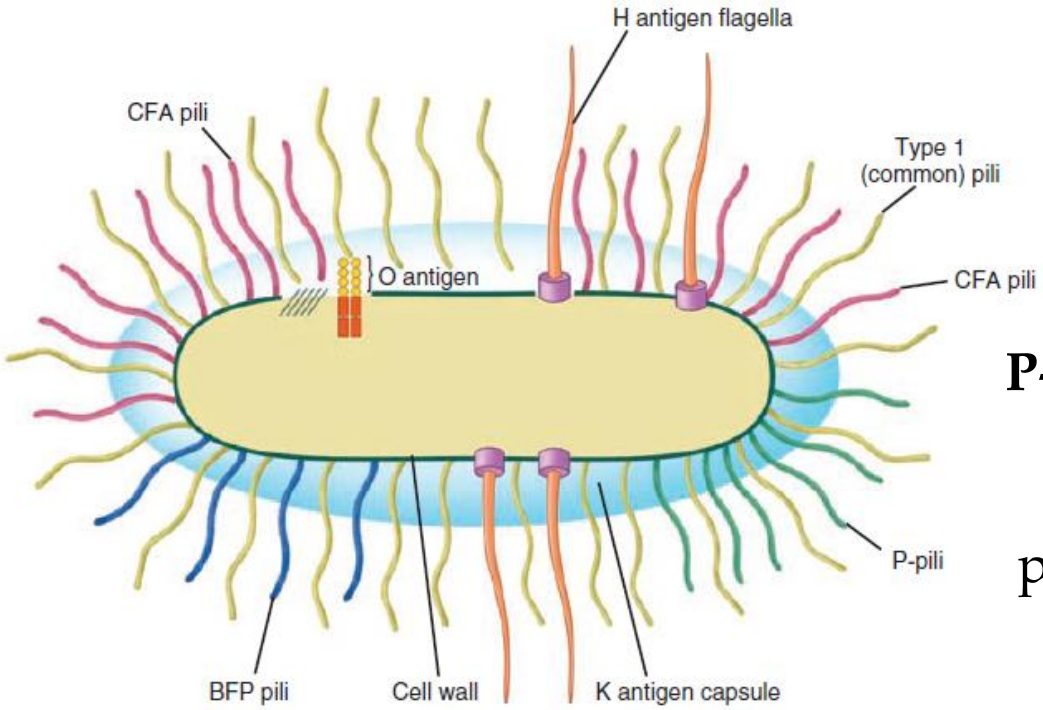
The most common species of the family *Enterobacteriaceae*, which is a **member of the permanent intestinal microflora**



This genus includes a large number of pathogenic and apathogenic strains.

The most commonly analyzed are **O lipopolysaccharide antigen, H antigen, and capsular K antigen**

Pili are an important virulence factor and show tropism for different types of host epithelial cells



Most E. coli exhibit **type 1 of pili (common pili)** that binds to a wide range of cell types

Some strains have **specialized pili**: **P-pili** bind to digalactoside residues on kidney cells

Pathogenic *E. coli* that cause diarea poses specific pili that bind glycolipids and glycoproteins in the surface of enterocytes

Classification of pathogenic strains *E. coli*

Type	Symptoms	Epidemiology
ETEC **Enterotoxic *E. coli***	Watery diarrhea (passenger diarrhea)	Worldwide, children and adults
EPEC **Enteropathogen *E. coli***	Watery diarrhea	Children under 1 year
EaggEC **Enteroaggregative *E. coli***	Watery diarrhea, persistant diarrhea	Infants younger than 6 months and AIDS patients
EIEC **Enteroinvasive *E. coli***	Haemoragic diarrhea	There are no rules, after consuming contaminated food
EHEC **Enterohaemoragic *E. coli***	Hemorrhagic diarrhea, haemorrhagic colitis, haemorrhagic-uremic syndrome and thrombotic thrombocytopenic purpura	Western countries

E. coli inoculum - about 100,000,000 bacteria;
mode of transmission: intake of contaminated food and water

Enterotoxic *E. coli* *(ETEC)*
-epidemiology-

- The most important cause of **traveler diarrhea**

Enterotoxic *E. coli* *(ETEC)*
-epidemiology-

- The most important cause of **traveler diarrhea**
- It also causes **diarrhea in babies** in developing countries where they are the leading cause of morbidity and mortality during the first 2 years of life.

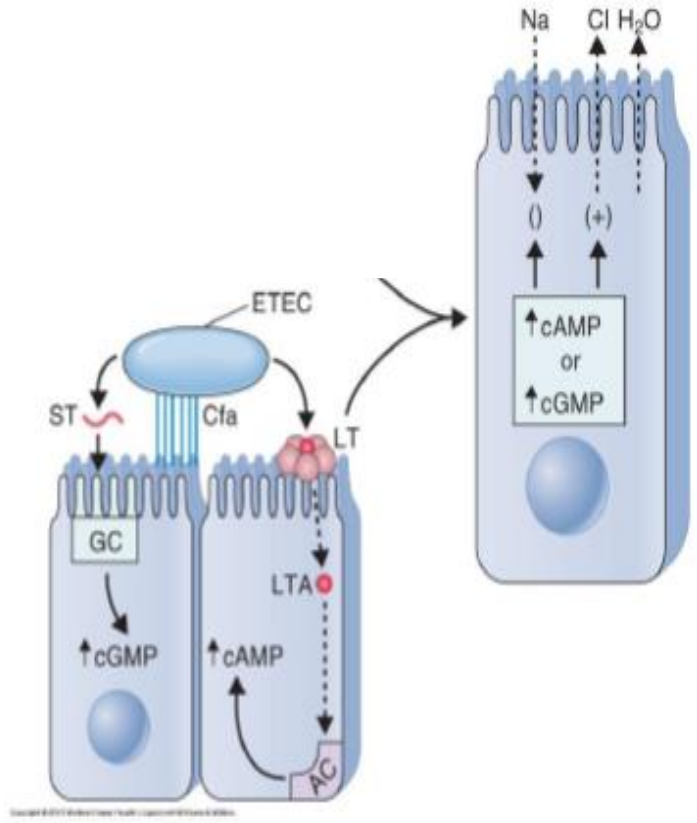
Enterotoxic *E. coli* *(ETEC)*
-epidemiology-

- The most important cause of **traveler diarrhea**
- It also causes **diarrhea in babies** in developing countries where they are the leading cause of morbidity and mortality during the first 2 years of life.
- Transmission route: consumption of contaminated water and food, as well as interhuman contact transmission. Marinated meats, salads and vegetables are associated with an increased risk of disease

Mechanism of diarrhea

Diarrhea is the result of the action of **LT and / or ST toxins**

Microvillus surface adhesion mediated by numerous variants of **CF (colonizing factor) pili** is essential for efficient delivery of toxins to target enterocytes



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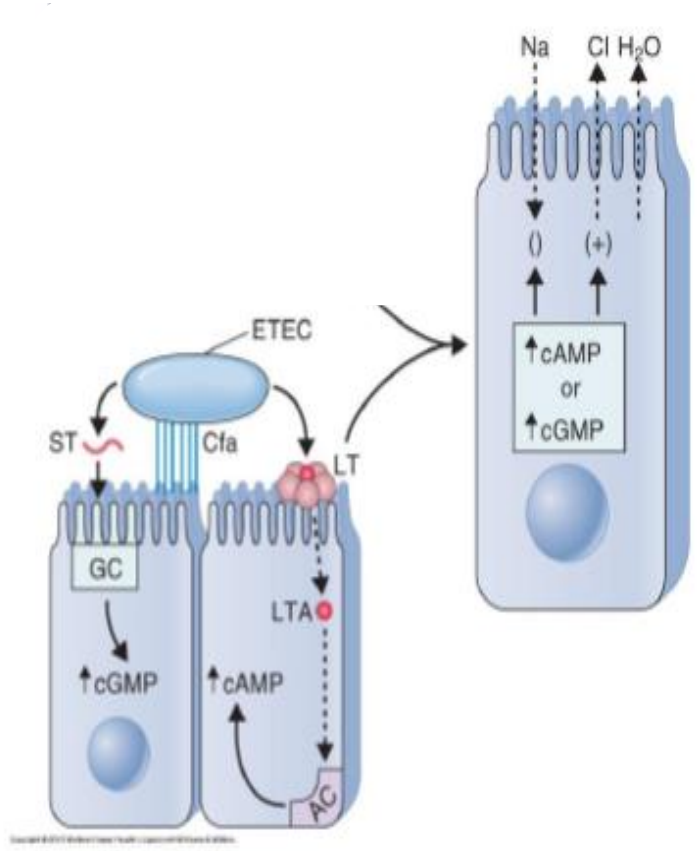
LT binds to its receptor, enters the vesicles. The **active toxin subunit** is transported to the basolateral membrane of the adenylate cyclase complex (AC)

Toxins transport ADP ribose to guanosine 5 triphosphate binding protein AC, increasing sAMP



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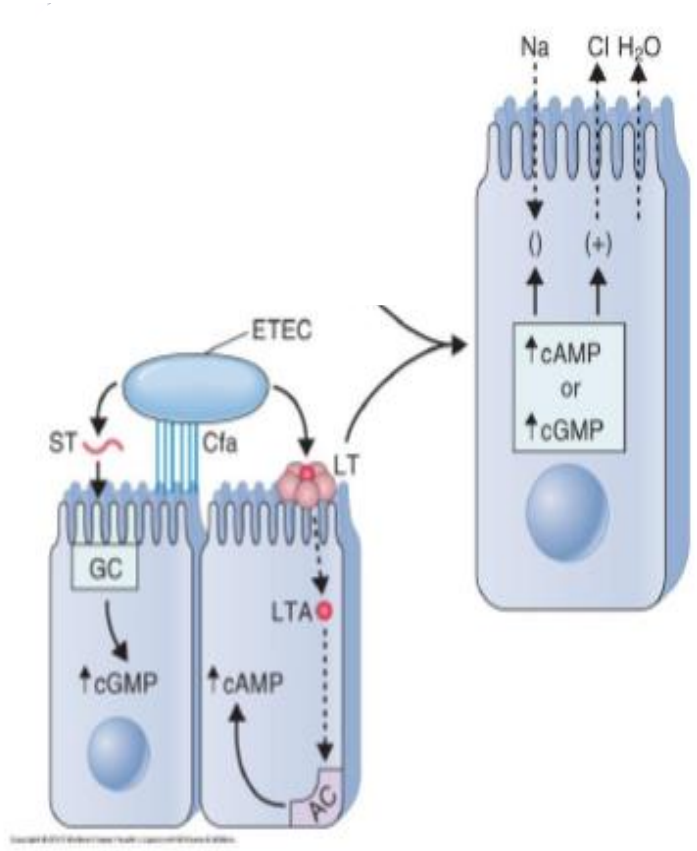
Toxins transport ADP ribose to guanosine 5 triphosphate binding protein AC, increasing sAMP

ST binds to membrane guanylate cyclase and increases the level of cyclic guanosine 5 monophosphate (cGMP)

Both cAMP and cGMP reduce sodium absorption in ciliated cells and increase chlorine secretion in goblet cells causing watery diarrhea

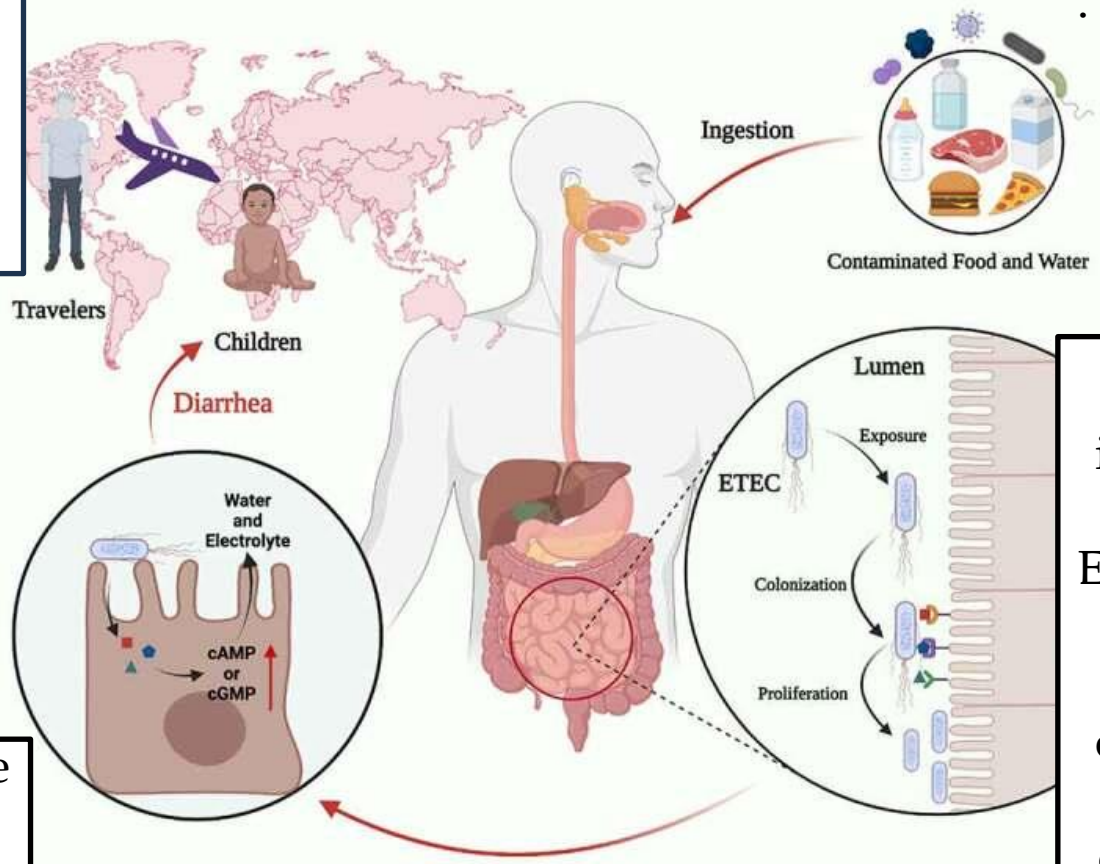


Characteristics of the ETEC infection

LET'S REPEAT

ETEC is a major cause of diarrhea in children and travelers in developing countries

ETEC infection is caused by ingestion of contaminated food and water.



ETEC through the gastrointestinal tract, and eventually colonization in the small intestine.

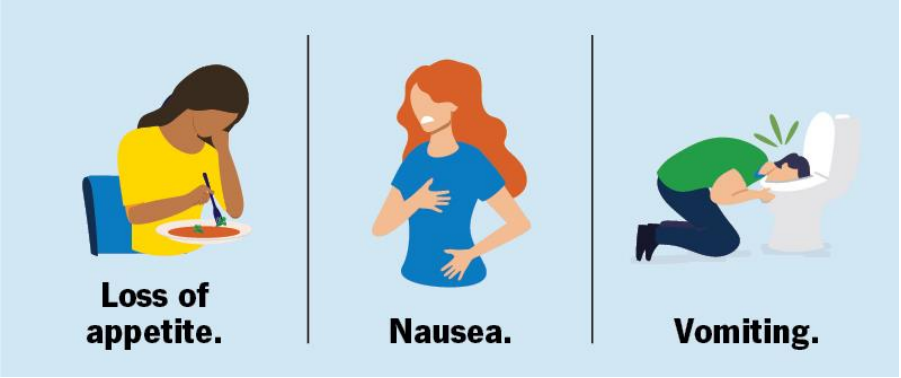
It colonizes intestinal epithelial cells via CFs, and ETEC proliferates on the intestinal epithelial after colonization. ETEC produces and delivers heat-labile (LT) and/or heat-stable (ST) enterotoxins to exert toxic effect

Symptoms of the ETEC infection

Illness develops 1-3 days after exposure and symptoms rarely last more than 3 weeks.

The characteristic symptoms include:

- Watery, non-bloody diarrhea
- Abdominal cramps
- Less commonly nausea and vomiting



Enteropathogenic *E. coli (EPECs)* -epidemiology

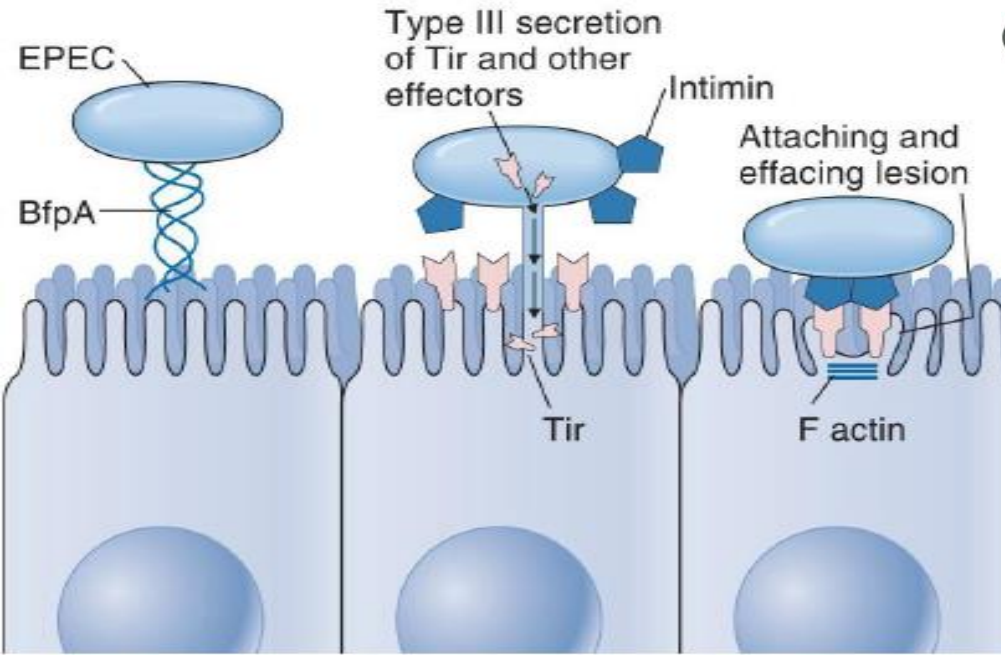
- They cause diarrhea in infants and young children in developing countries
- It has previously caused intrahospital epidemics in maternity and pediatric wards and in developed countries.

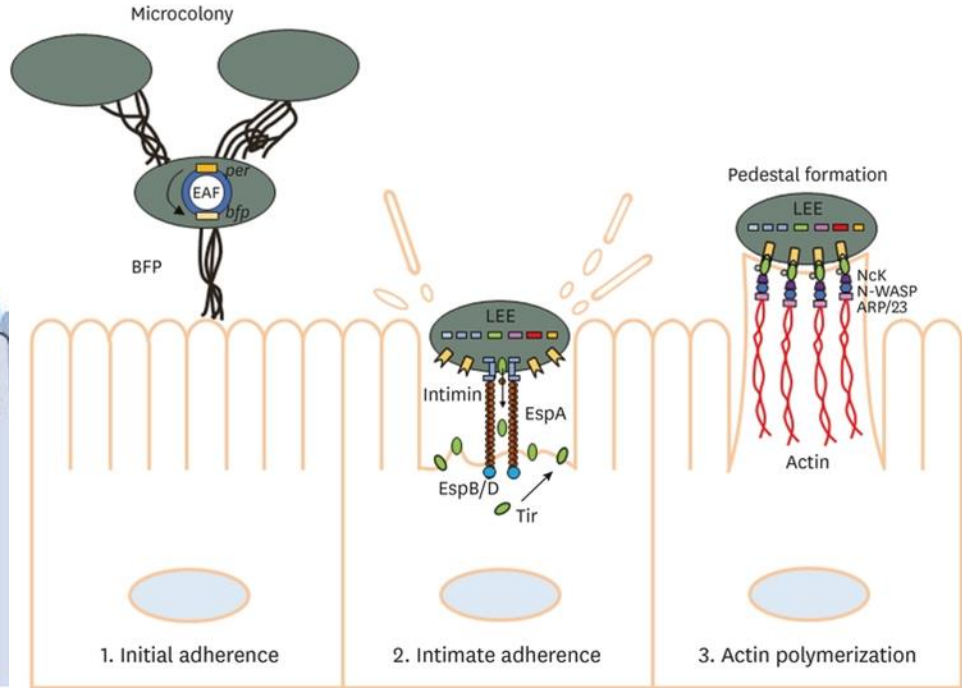
Mechanism of diarrhea

The bacterium binds to the epithelial cells of the small intestine using a "**bundle-forming pili" (BfpA**).

It delivers receptor protein, **Tir**, and other effector molecules inside the target cell

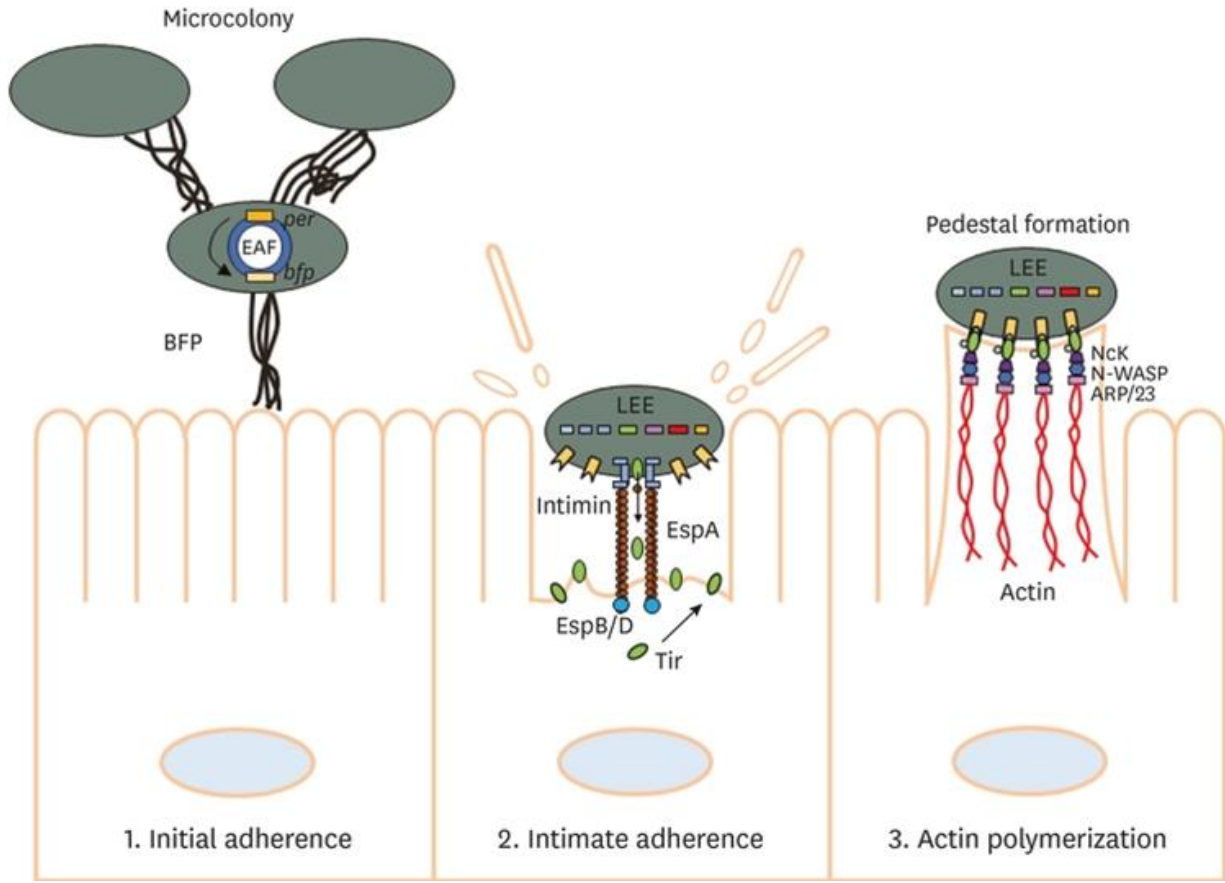
Intimin on the surface of the bacterial cell closely adheres to the target cell by binding to the inserted Tir receptor



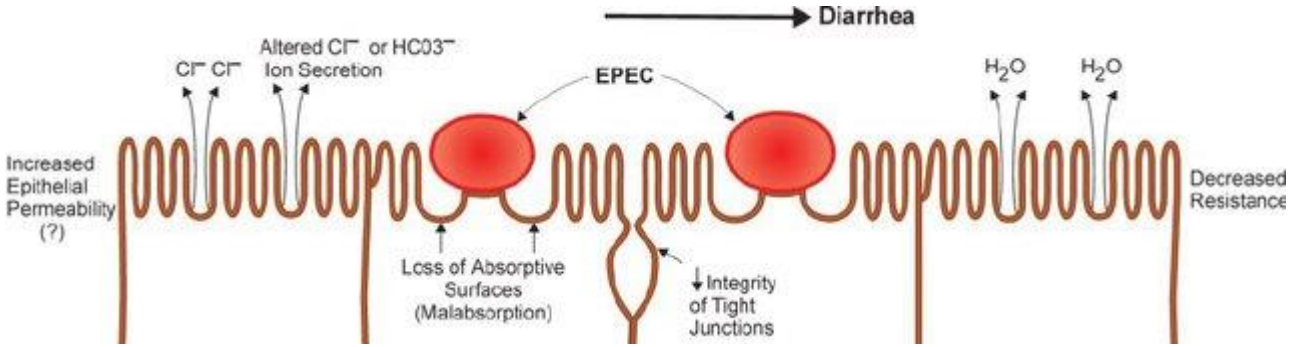


Mechanism of diarrhea

- Actin polymerization induces cytoskeletal rearrangement
- These processes result in the formation of “pedestal" important for EPEC adhesion and lesion formation



Malabsorption after microvilli rearrangement and disruption of interpitel bonds causes greater intestinal permeability and diarrhea



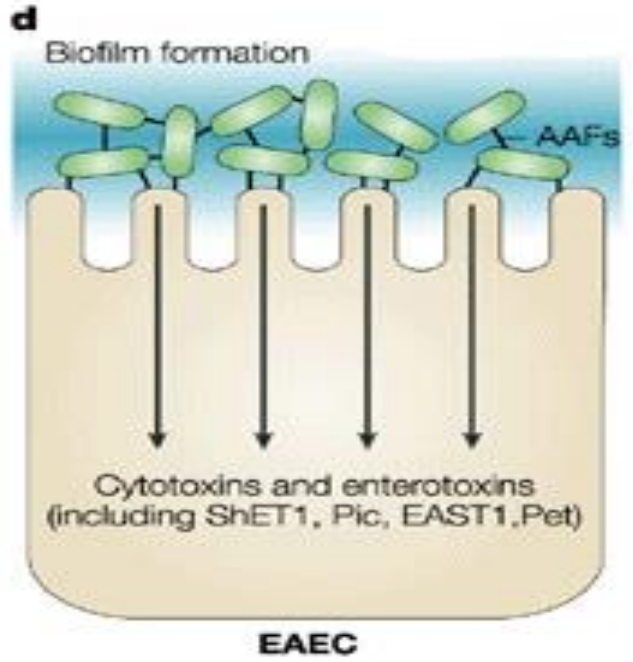
Symptoms of the EPEC infection

Watery diarrhea
Non-bloody stools
Vomiting
Fever

The onset of disease may be as rapid as a few hours after ingestion of EPEC.

Although most infections resolve after a few days, persistent diarrhea can occur that require hospitalization

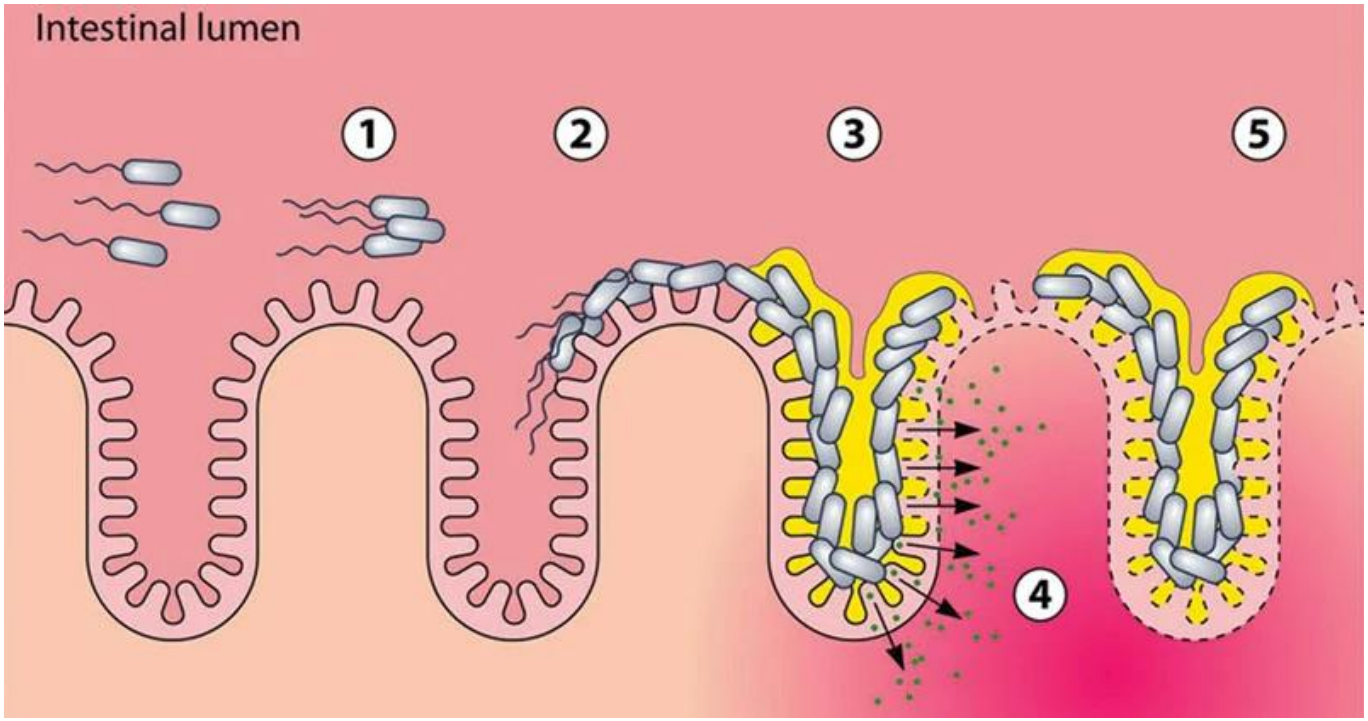
Enteroaggregative *E. coli (EAggEC)*



EAggEC agglutinates and forms aggregates in tissue culture and is the cause of diarrhea in children younger than 6 months, which often persists for weeks and causes malnutrition.

EAggEC may also be a cause of persistent diarrhea in some adult HIV patients

Stages of pathogenesis of *EAggEC*



1. Agglutination of planktonic EAEC bacteria.
2. Adherence to the intestinal epithelium and colonization of the gut.
3. Formation of biofilm.
4. Release of bacterial heat stabile enterotoxin 1, inducing damage to the epithelium and increased secretion.
5. Establishment of additional biofilm.

Extraintestinal infections caused by *E. coli*

E. coli are common causes of urinary tract infections

1 . Urinary tract infections

- 80% of cystitis in young women
- pyelitis and pyelonephritis

Endogenous infection

E. coli from the intestinal microflora through the perineum contaminates the urethra

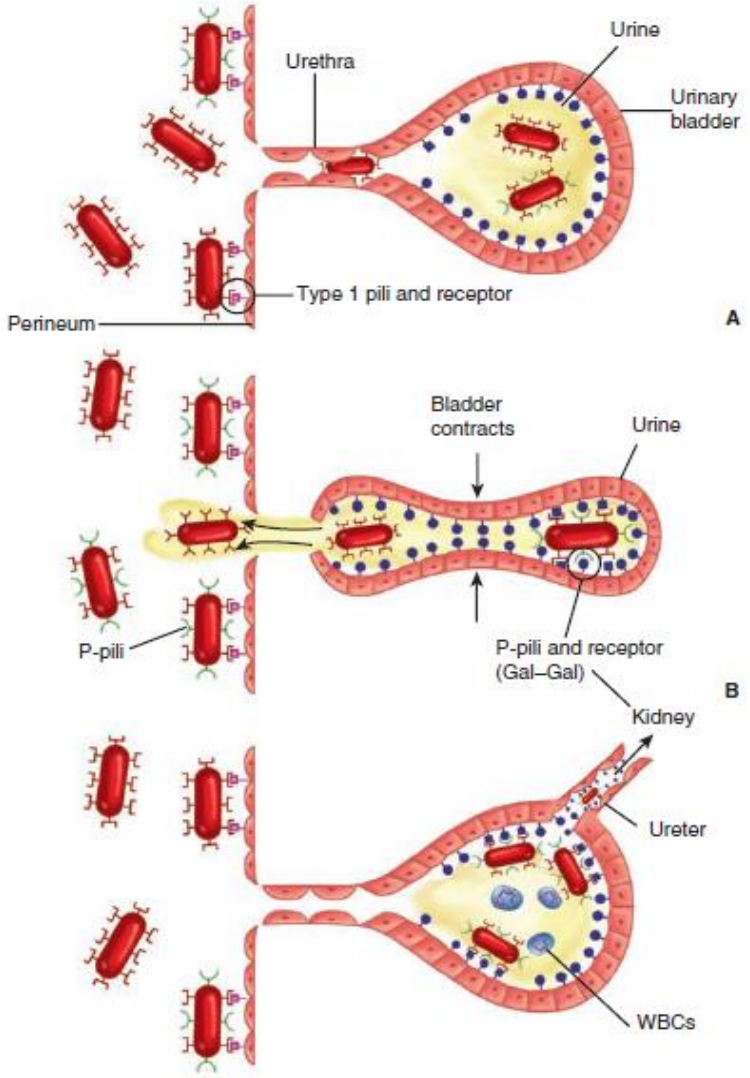
Differences in anatomical structure affect susceptibility to infection

Uropathogenic *E. coli (UPEC)* have the potential to cause urinary tract infections

- ability to produce **type 1 of pilli** (allows colonization of the perineum)

- **P pilli** play an important role in diseases of the upper urinary system and facilitate the development of pyelonephritis

- **flagella** allow their access to the bladder, as well as movement from the urethra to the kidneys



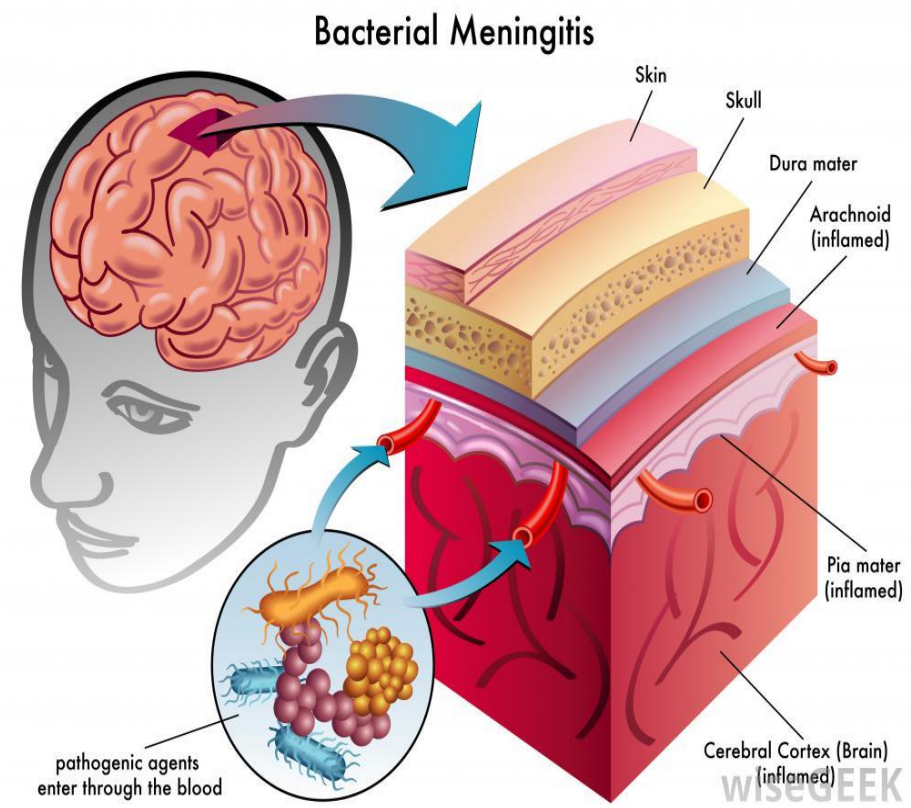
...

2. Sepsis - as a complication of urinary tract infection or infection of the digestive system (in newborns and immunodeficient persons)

...

2. Sepsis - as a complication of urinary tract infection or infection of the digestive system (in newborns and immunodeficient persons)

3. Neonatal meningitis-
one of the most common causes (similar as *S. agalactiae*). 75% cases were caused by strains possessing **K1 capsular polysaccharide**



Causes of invasive gastrointestinal infections

Shigella spp.
Salmonella spp.
Enterohemoragic *E. coli* (EHEC)
Campylobacter spp.

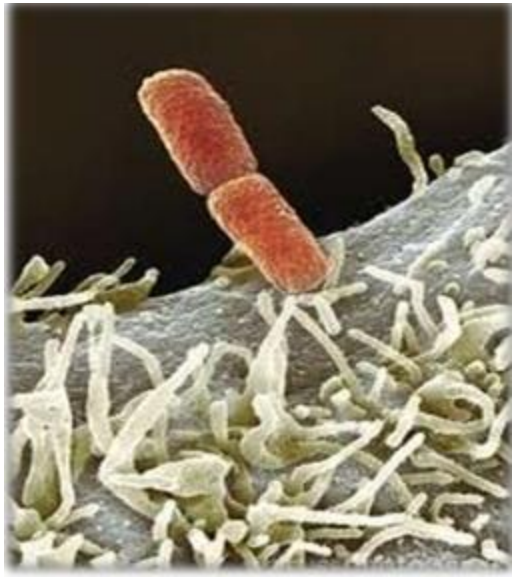
Gram-negative bacteria that cause watery diarrhea, hemorrhagic diarrhea or dysentery

Type	watery diarrhea	hemorrhagic diarrhea	Inflammatory diarrhea or dysentery	
			Ileitis	*Colitis*
Enterobacteriaceae				
ETEC	+			
EPEC	+		±	
EAggEC	+			
EIEC		+		+
EHEC		+		+
Shigella		+	±	+
Нетифоидна *Salmonella*	+	±	+	±
Salmonella typhi			+	
Yersinia enterocolitica	+	+	+	
Vibrionaceae				
Vibrio cholerae	+			
Vibrio parahaemolyticus	+	+	±	±
Campylobacter jejuni	+	+	±	+

Shigella spp...

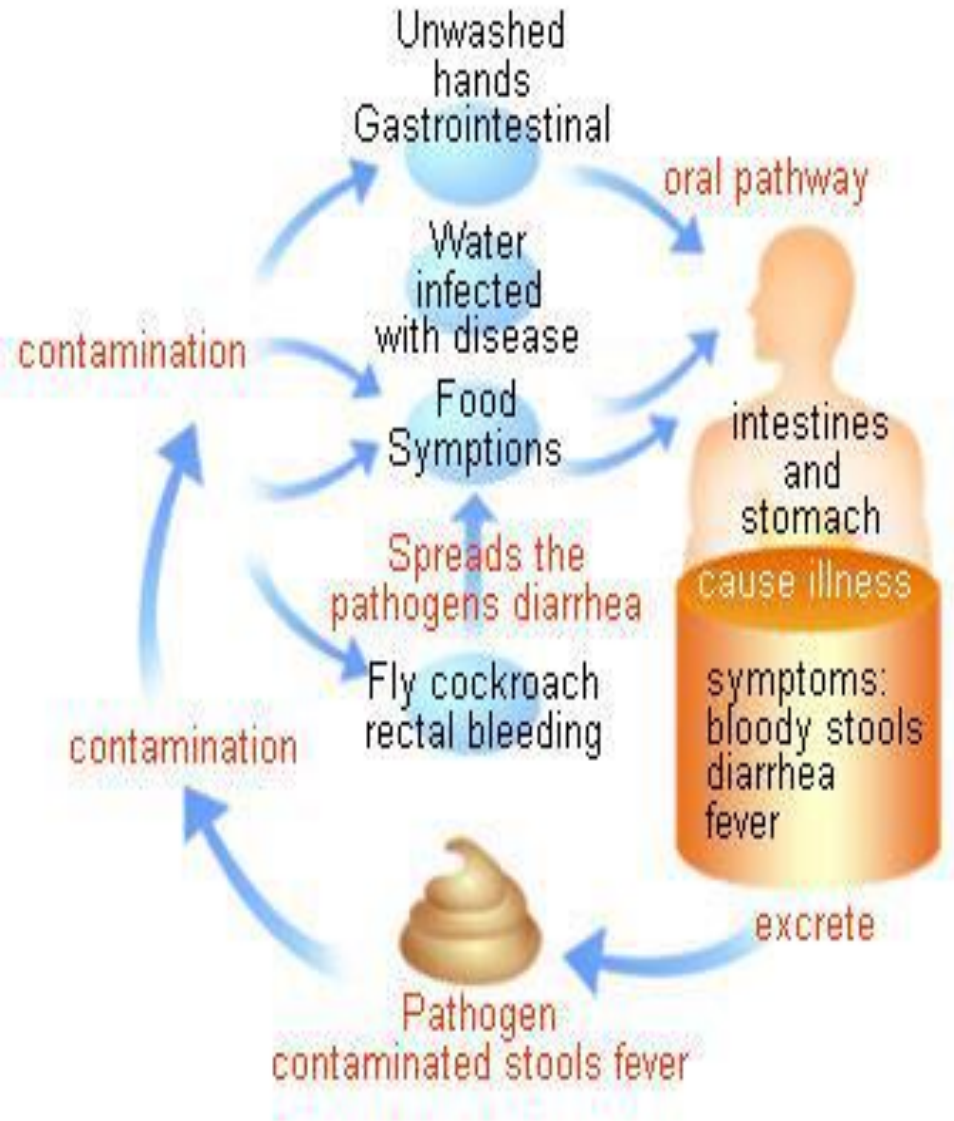
... causes of shigellosis (dysentery)

The genus Shigella consists of four species, which are serologically distinguished by the **O antigen of lipopolysaccharide**:



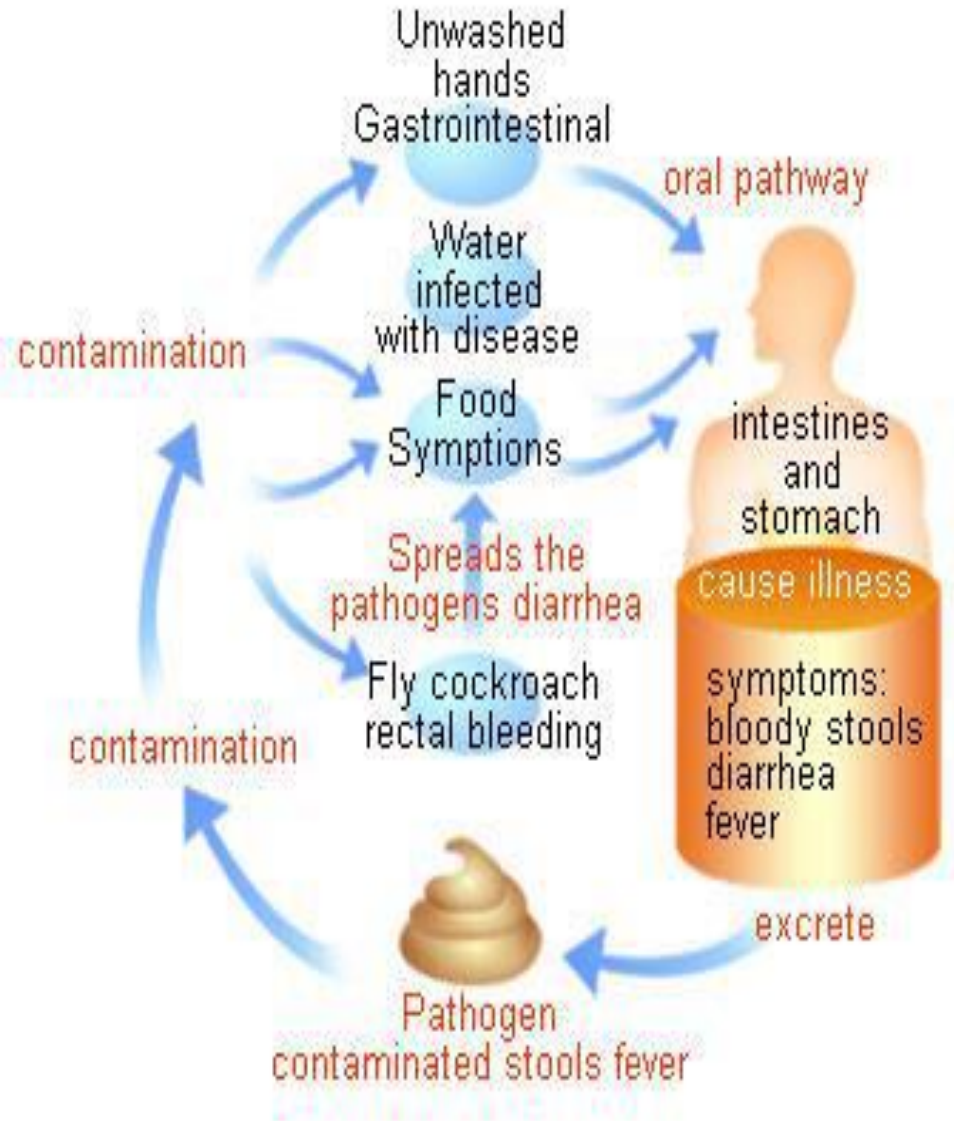
*S. **dysenteriae*** (serogruop A) тип 1	—	the most severe form of bacillary dysentery
*S. **flexneri*** (group B)	—	bacillary dysentery (most commonly isolated in developing countries
*S. **boydii*** (group C)		
*S. **sonnei*** (group D)	—	watery diarrhea in developed countries

Epidemiology



Shigella are **strictly pathogenic** to humans

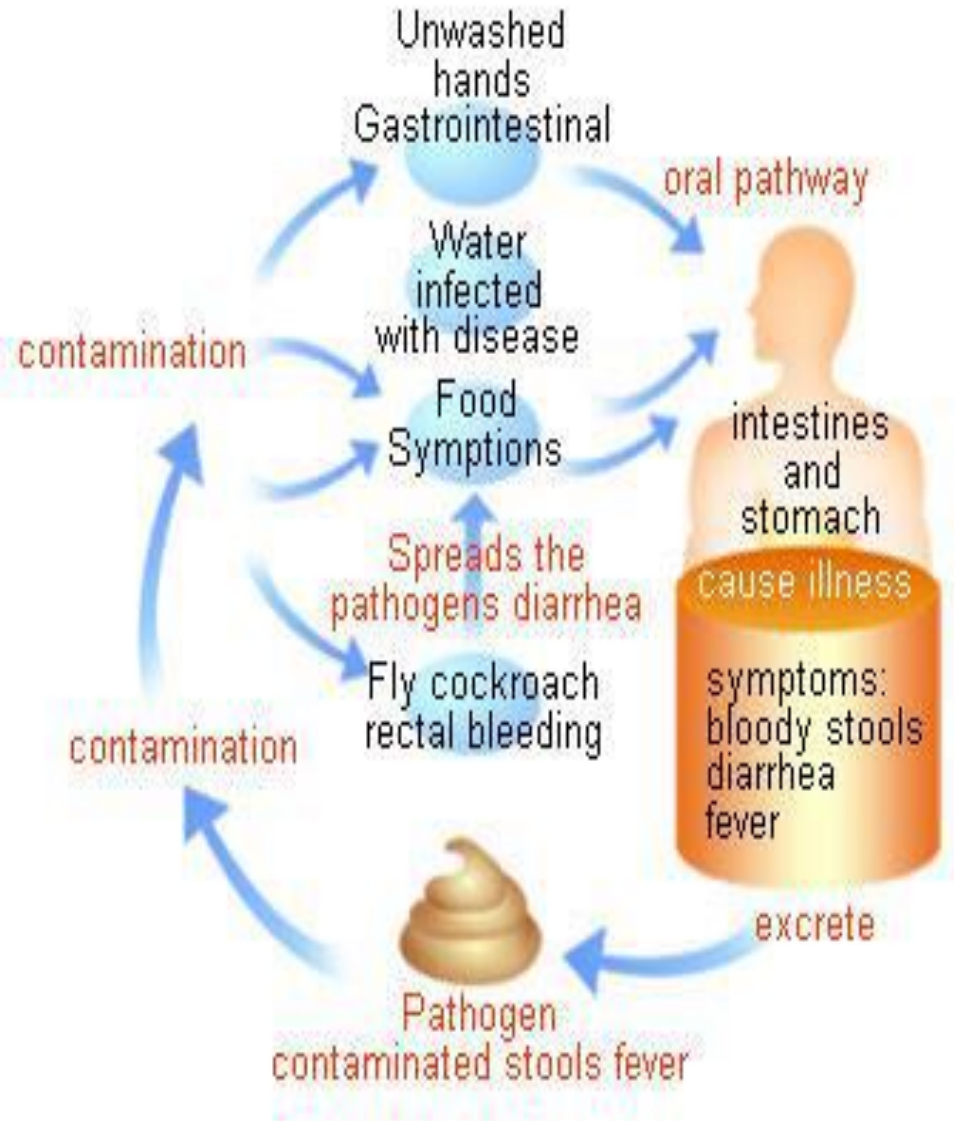
Epidemiology



Shigella are **strictly pathogenic** to humans

They are most often transmitted by **direct contact** (they are also transmitted through food and water contaminated with feces)

Epidemiology

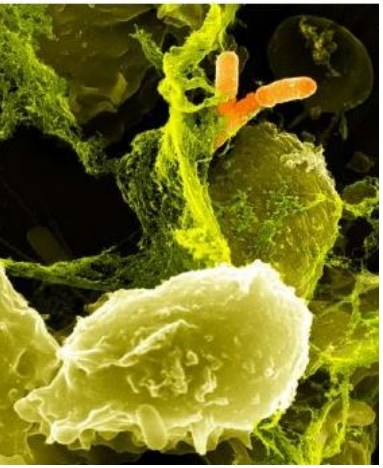


Shigella are **strictly pathogenic** to humans

They are most often transmitted by **direct contact** (they are also transmitted through food and water contaminated with feces)

The **infectious dose is small**: several hundred to several thousand bacteria, which allows the infection to spread easily from one person to another.

How does Shigella survive in the stomach, in conditions of **low pH value?**



When exposed to an acidic environment, they adapt thanks to **complex control of gene expression**, but are less able to attack cells

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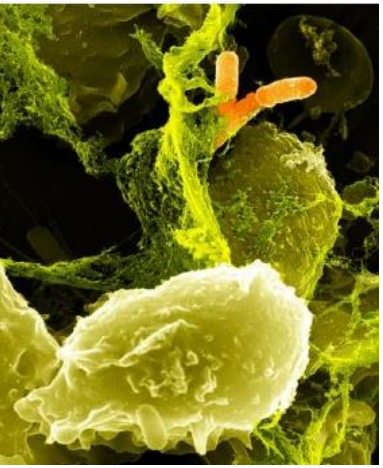

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In the small intestine (in an alkaline or neutral environment), shigella suppresses the genes responsible for their resistance to acids and **expresses an invasive phenotype**

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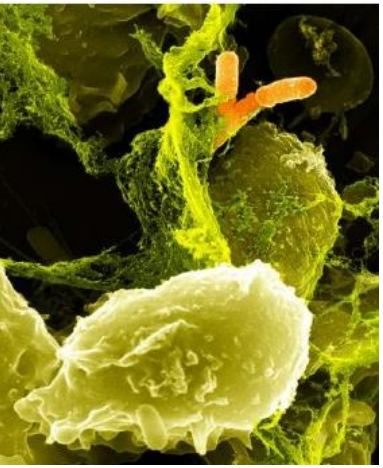

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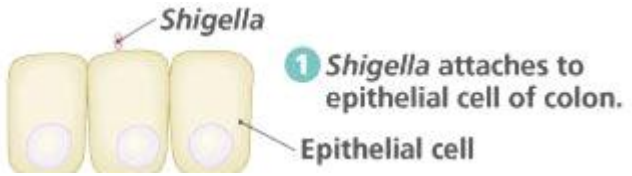
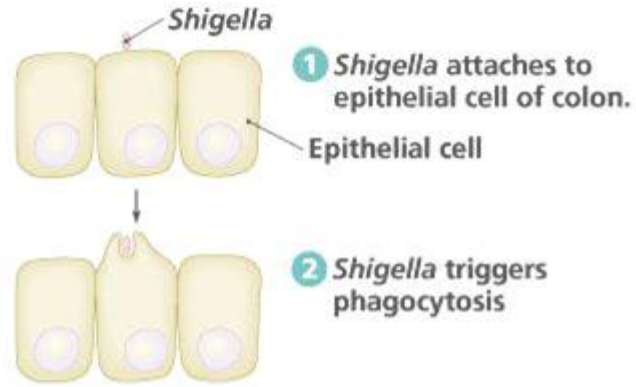
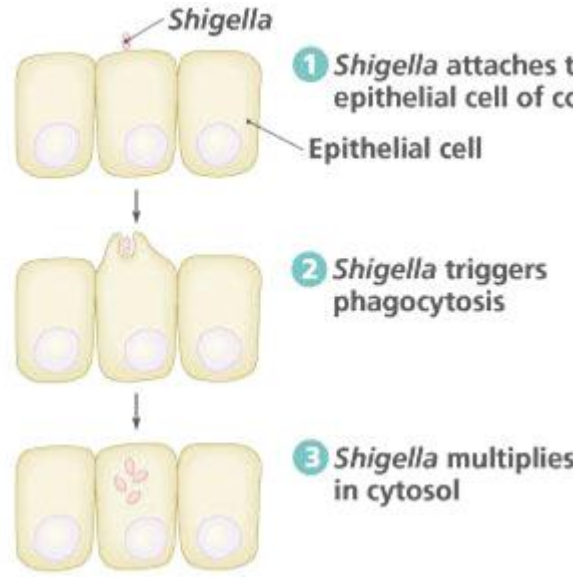
In the small intestine (in an alkaline or neutral environment), shigella suppresses the genes responsible for their resistance to acids and **expresses an invasive phenotype**

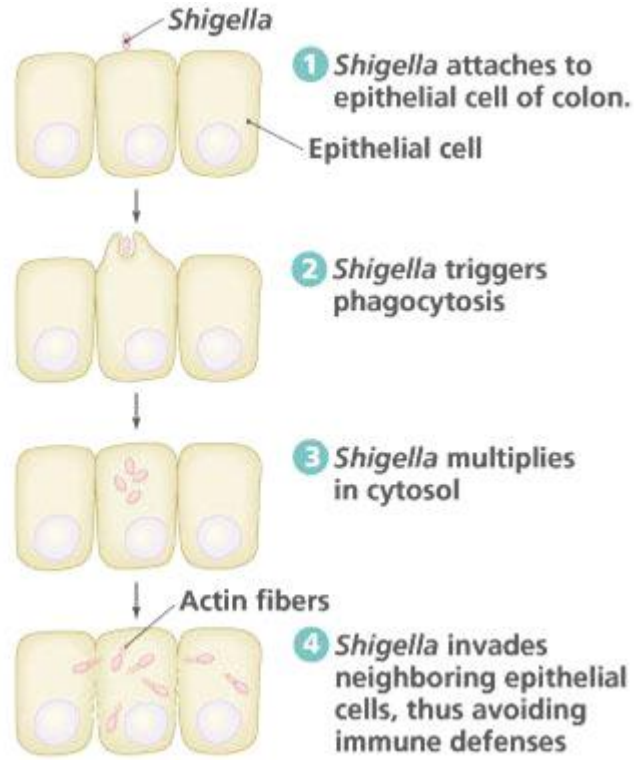
Acid resistance is active again when shigellae reach the large intestine



The main pathological event is invasion and damage to the mucous membrane of the colon. This activates an **intense acute inflammatory response** resulting in the formation of ulcers and abscesses


Shigella
1 *Shigella* attaches to epithelial cell of colon.
Epithelial cell
2 *Shigella* triggers phagocytosis


Shigella
1 *Shigella* attaches to epithelial cell of colon.
Epithelial cell
2 *Shigella* triggers phagocytosis
3 *Shigella* multiplies in cytosol


Shigella
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Epithelial cell
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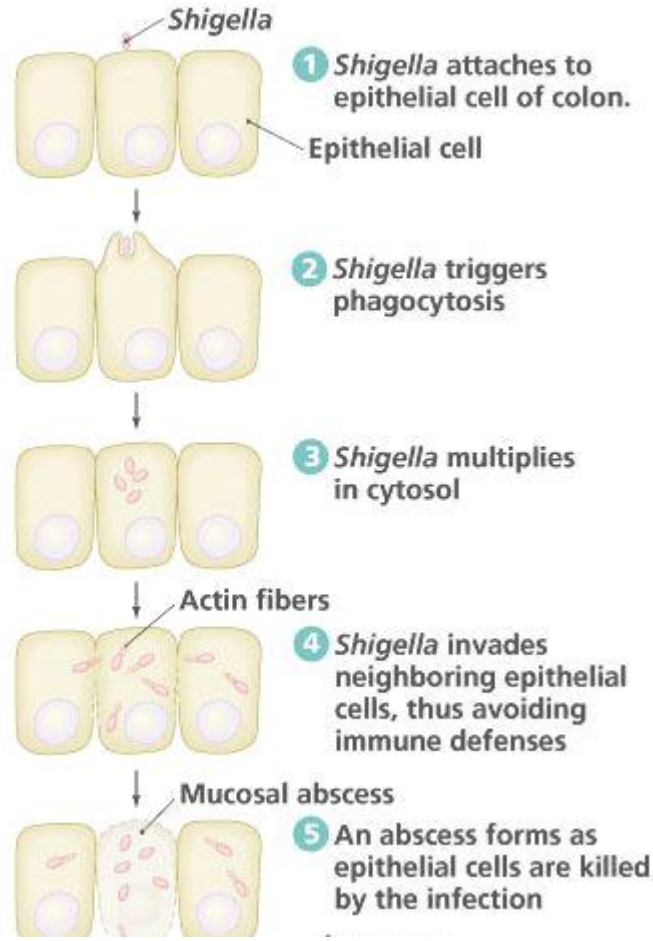
3 Shigella multiplies in cytosol
Actin fibers
4 Shigella invades neighboring epithelial cells, thus avoiding immune defenses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Epithelial cell
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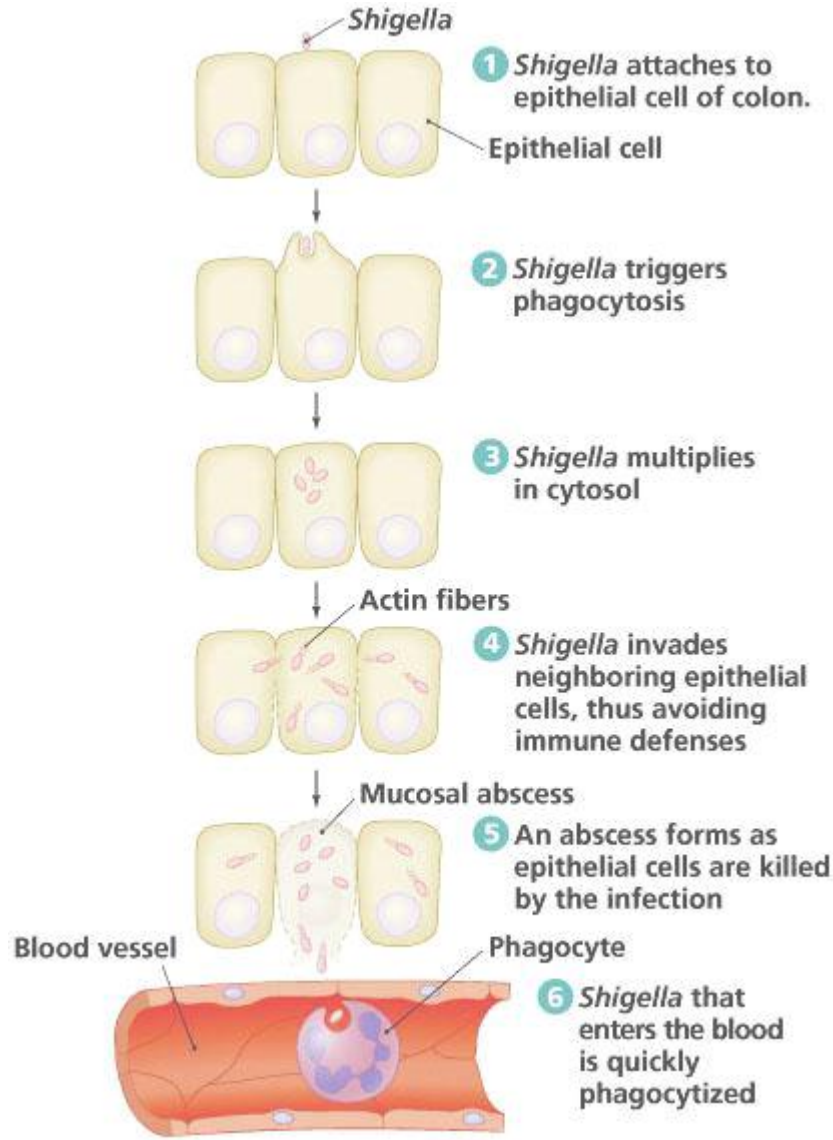
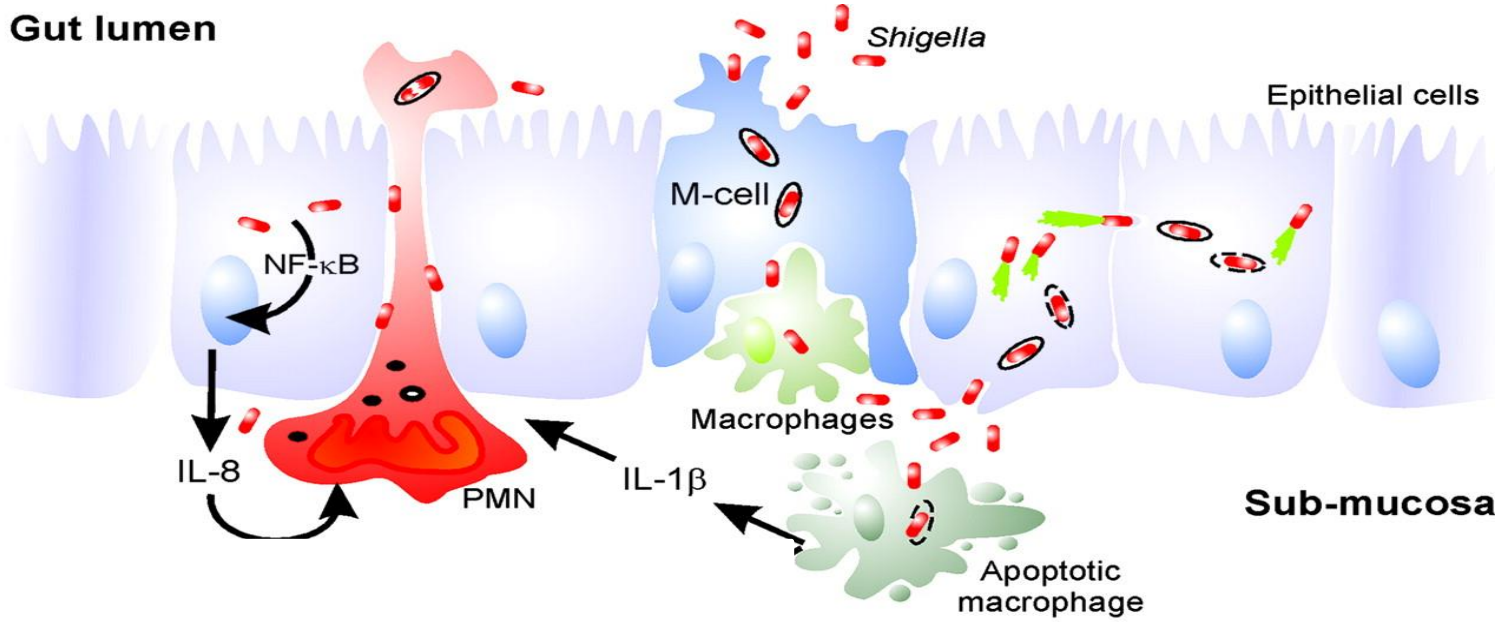
4 Shigella invades neighboring epithelial cells, thus avoiding immune defenses
Mucosal abscess
5 An abscess forms as epithelial cells are killed by the infection



Shigella never penetrates the blood

(exept *S. dysenteriae* type1)

Pathogenesis of bacillary dysentery



Shigella passes the EC barrier by transcytosis through M cells.

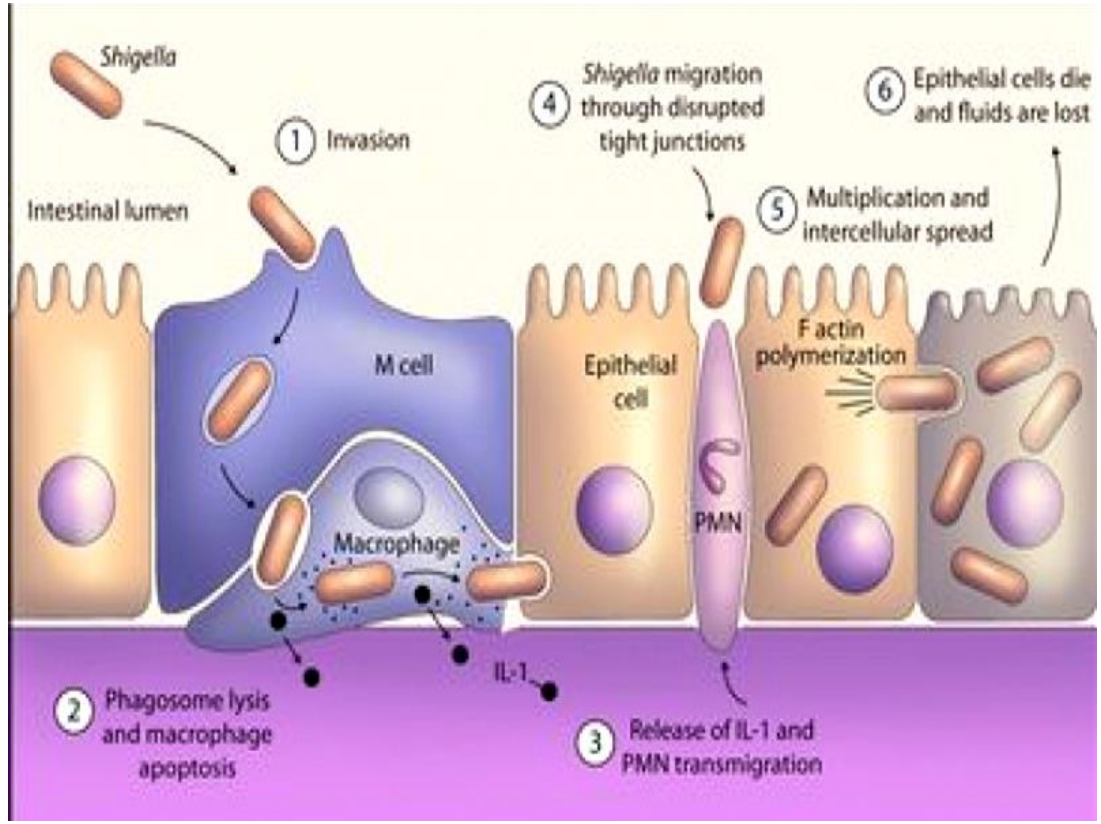
.... They quickly reach the lamina propria, where they are **phagocytosed by macrophages...**

The bacteria evade degradation in macrophages by inducing an apoptosis-like cell death which cause inflammatory response

... Macrophages produce IL-1 and IL-8 which cause strong inflammation and neutrophil attraction

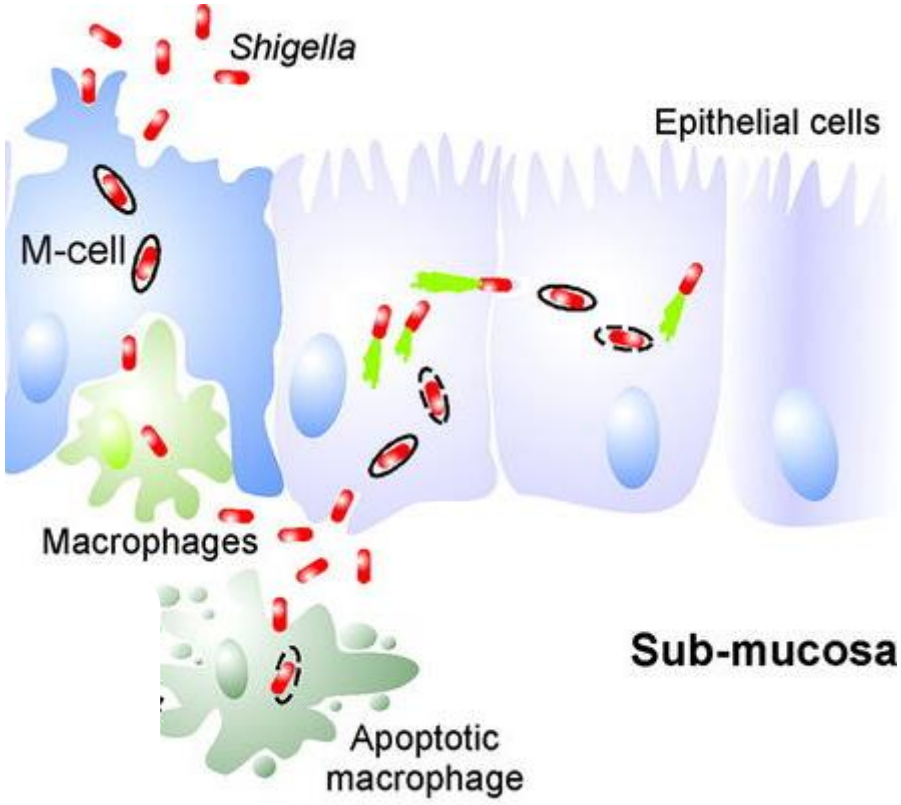
... The cascade of additional cytokines cause an influx of PMN, which migrate through the mucosa and **induce the separation of close bonds between cylindrical epithelial cells...**

... This separation consequently **allows bacteria to penetrate the damaged epithelium**.



... In the lamina propria, shigella activates **macrophage apoptosis** ...

... Free bacteria invade the EC from the basolateral side, move into the cytoplasm by vectorial actin polymerization, and spread to adjacent cells.



...IcsA causes polymerization of host cell actin. Rapid polymerization and depolymerization of actin filaments at one end pushes like a "propeller" bacteria forward

Mechanism of tissue damage in bacillary dysentery

Epithelial cell death causes **local ulceration** in the colon and **exudation of leukocytes and erythrocytes** into the intestinal lumen

The presence of blood and pus in the stool associated with **painful bowel movements** (tenesmus) are characteristic of bacillary dysentery

Rare bacteremia (except in *S. dysenteriae* type 1 infection)

Symptoms of Shigella infection

- Symptoms usually begin after 1 to 3 days of ingestion of bacterial cells.
- Typical symptoms include fever, loss of appetite, abdominal pain, bloody or watery diarrhea, inflammation of the colon, fatigue, fever.
- Due to the excretion of excess watery fluid, dehydration may occur but is usually rare and not a big concern.
- Anorexia and malnutrition require active management which is the main cause of death in children under 5 years of age.
- Neurological disorders may develop in some patients such as lethargy, irregular movement of the body and headache.
- The disease resolves itself within 5 to 7 days but an infected person may shed the bacteria in their feces for a long time being asymptomatic and may cause a threat of spreading the infection.

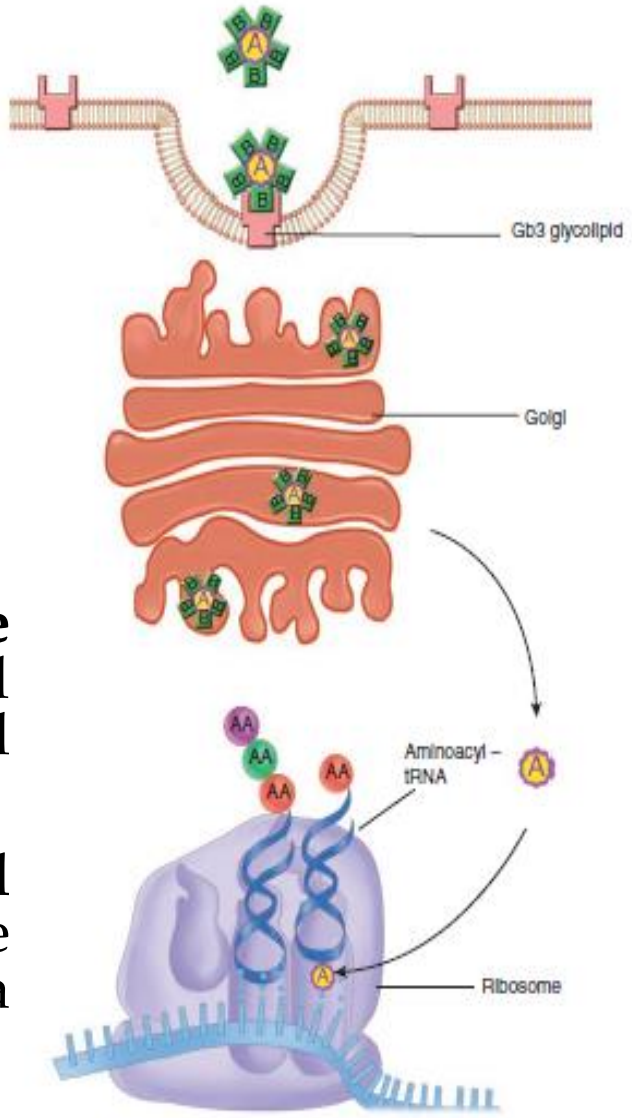
S. dysenteriae **type 1** causes the most severe clinical form of bacillary dysentery

It produces shiga toxin, a cytotoxin that kills intestinal epithelial and endothelial cells. Shiga toxin breaks down the 60S subunit of the ribosome and prevents protein synthesis

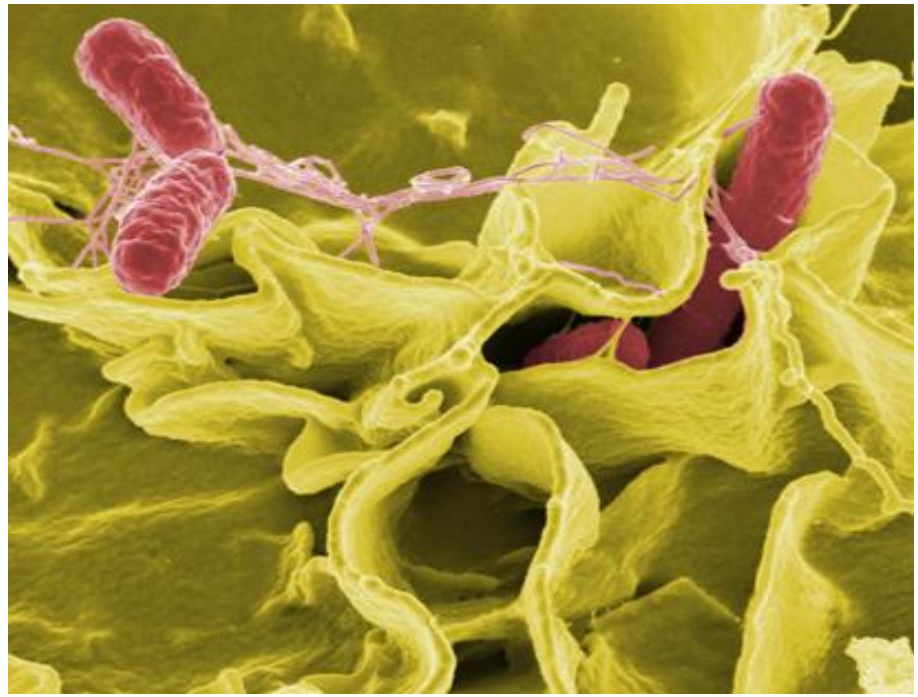
Shiga toxin has **two effects**:

... acts on the ciliated cells **and reduces the absorption of sodium**, which causes increased fluid loss in the stool

... has a **cytotoxic effect on intestinal endothelial cells**, which contributes to the development of hemorrhagic diarrhea

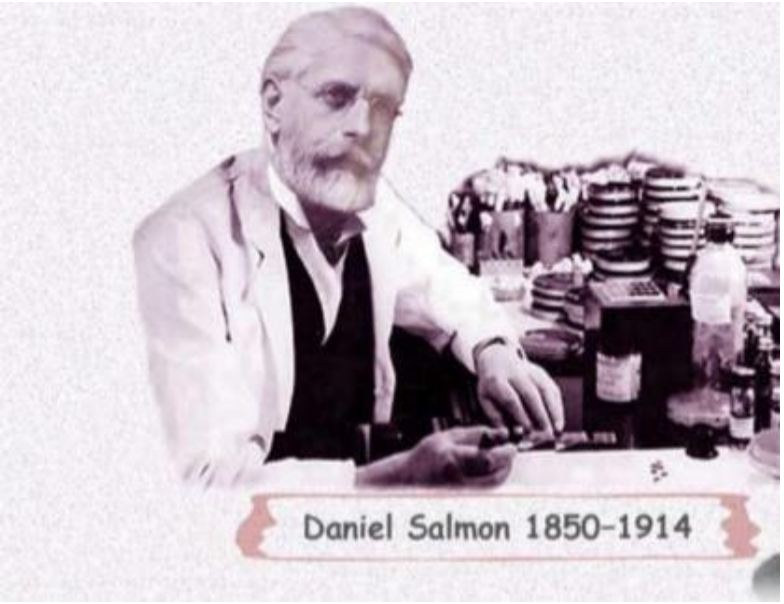


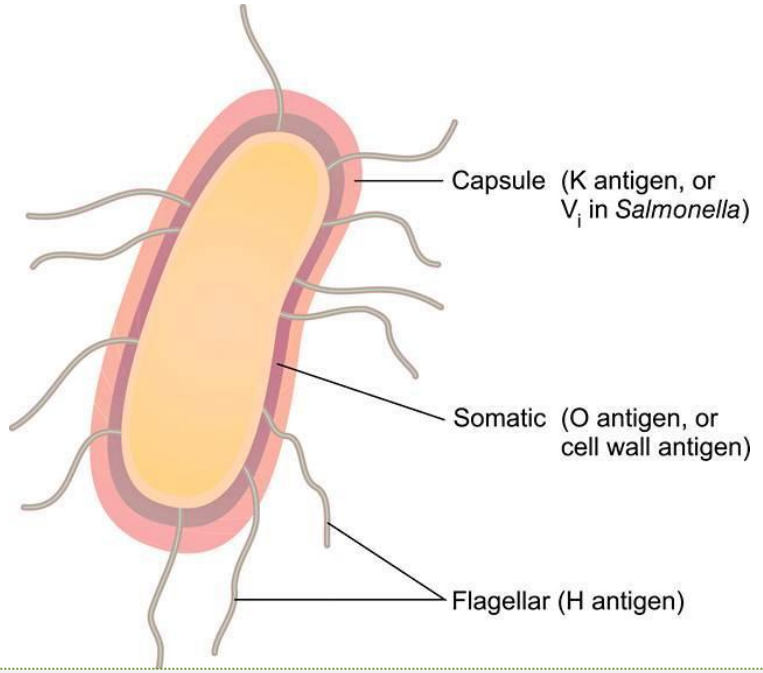
Salmonella spp...



... causes of gastroenteritis and typhoid fever

General characteristics of the causative agent





The genus *Salmonella* is huge and includes more than 2,300 different serological types or varieties

The main salmonella antigens used to distinguish serotypes are: **somatic (O), flagellar (N), and capsular (K).**

The enormous diversity of the genus stems from *Salmonella's* ability to alter its antigens

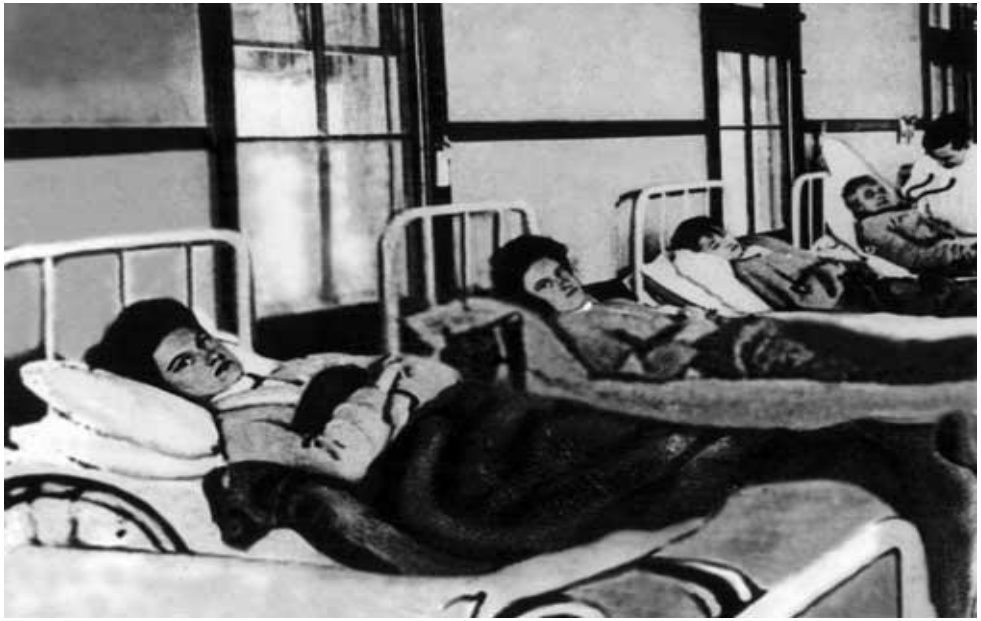
Most human pathogens are grouped within a species *S. enterica* subspecies *enterica*

Salmonella causes :

GERM CARRYING

gastroenteritis : mostly ***S. enterica* subspecies *enterica***

typhoid fever : mostly ***S. typhi*** и ***S. paratyphi* A** and **B** (they only infect humans)



<u>Other clinical syndromes are:</u>

focal vascular endothelial infection : caused by ***S. choleraesuis*** *and* ***S. typhimurium***

infection of some organ systems: osteomyelitis in patients with sickle cell anemia, most commonly caused ***S. typhimurium***

Epidemiology

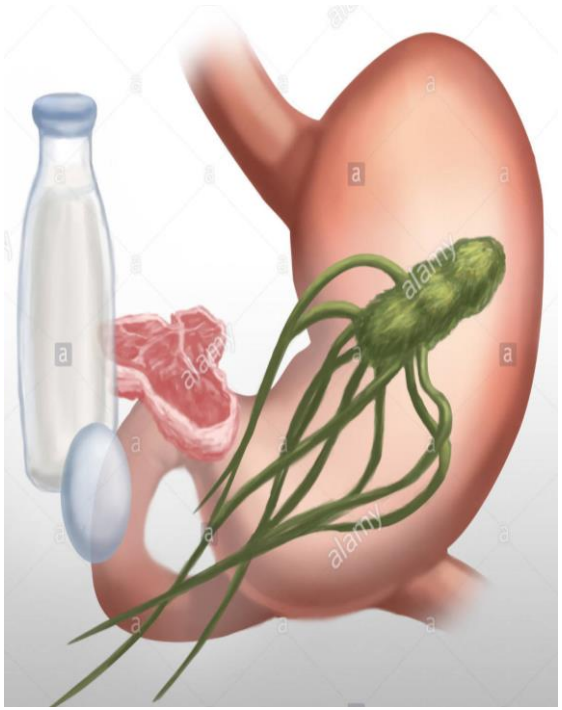
Salmonella are frequent inhabitants of the **physiological flora of many animals**, including chickens, cattle, and reptiles (e.g., turtles).

Leading causes of alimentary intestinal infections

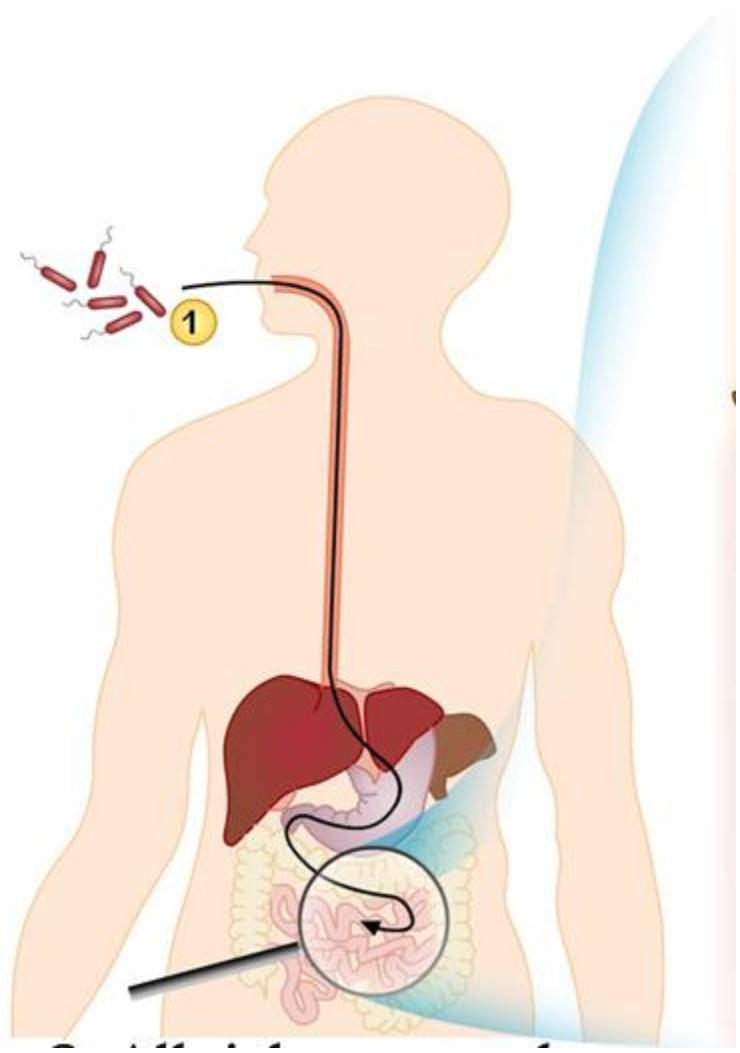
Outbreaks appear to be exacerbated during the summer months and are often associated with the ingestion of contaminated eggs, chicken salads and milk products.

People transmit typhoid fever although the mode of transmission often involves contaminated water or food

Germ carrying



Entry into the host organism



Salmonella is <u>more sensitive</u> to stomach acid than shigella

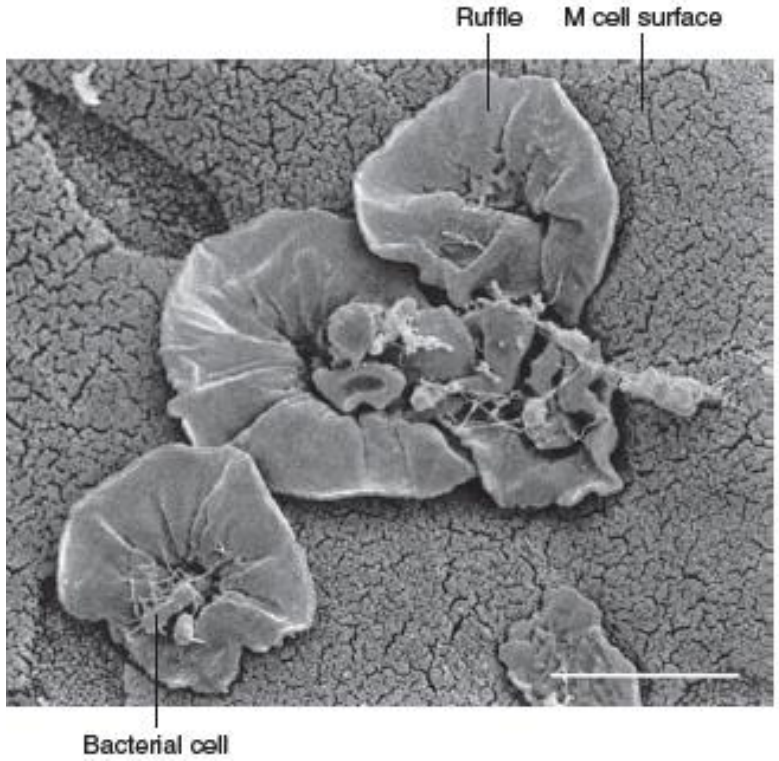
Relatively **<u>large inoculum</u>** (10 to 100 million bacteria)

Susceptible to salmonellosis are individuals who secrete little or no stomach acid (**with hypochlorhydria or achlorhydria**)

Bacteria that survived the passage through the stomach, continue their way through the small intestine, all the way to the **distal ileum and large intestine** ...

... Bacteria can enter **M cells or through the apical membrane of intestinal epithelial cells** ...

... Contact of salmonella with cells causes wrinkling cell membranes ("**ruffling**"). Visible rearrangement of the cytoskeleton allows bacteria to enter within the phagocytic vesicle, (**bacterial endocytosis**)



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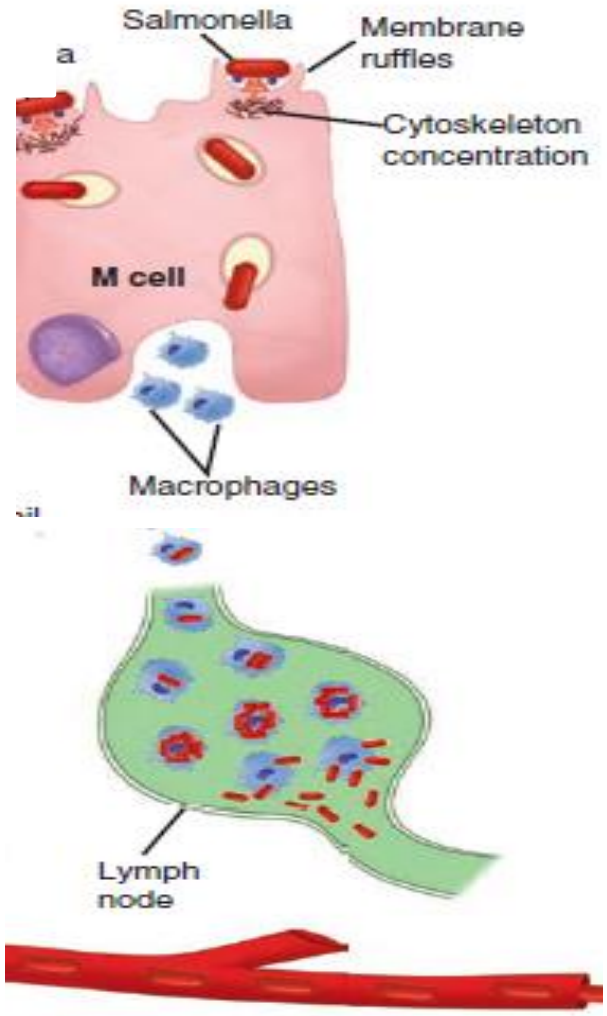


Salmonella remain within phagocytic vesicles

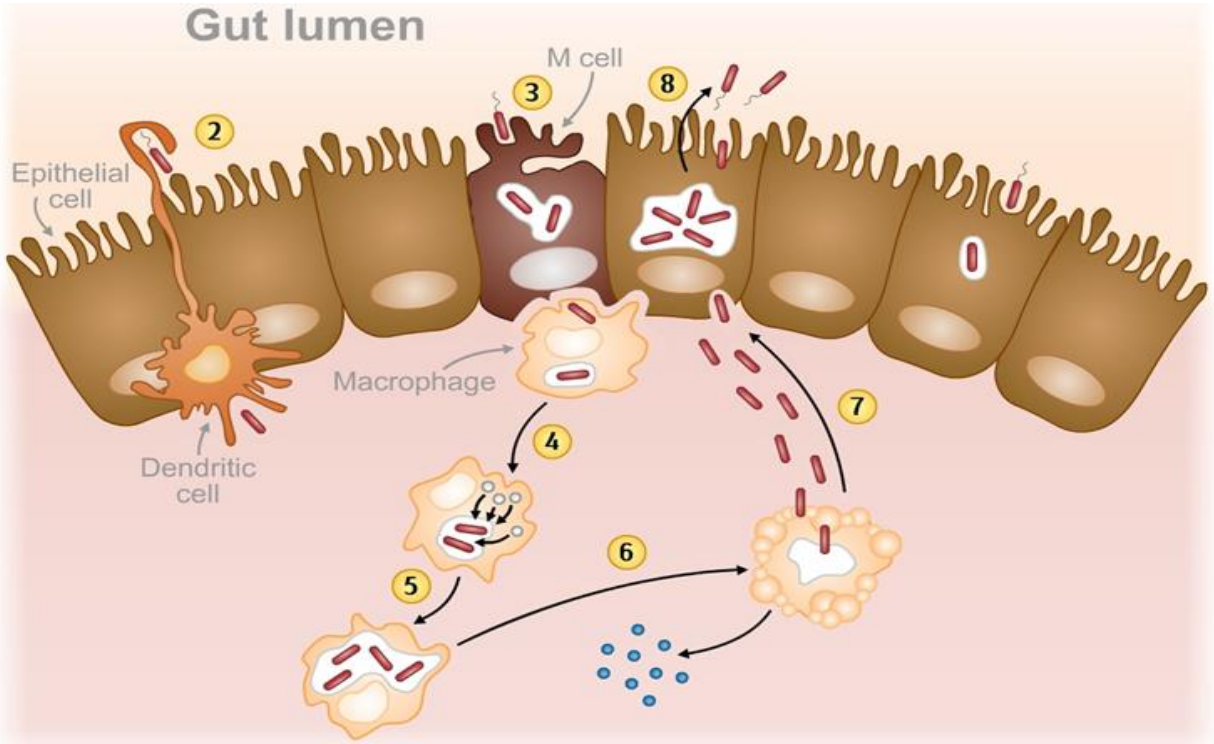
They are unusually resistant to lysosome enzymes and to antibacterial peptides- **cryptins** produced by intestinal epithelial cells.

The phagocytic vesicles, inside which the bacteria are, travel through the cell to the basement membrane, from where the bacteria go to the lamina propria.

Salmonella does not divide in the epithelial cells of the intestine, but only passes through them

During the infection, the bacteria activate MAP kinases and consequently the production of prostaglandins, leukotrienes and hepoxillins, and thus cause strong inflammation. The persistence of infection in lamina propria is aided by their ability to kill macrophages by multiple mechanisms, including induction of apoptosis.

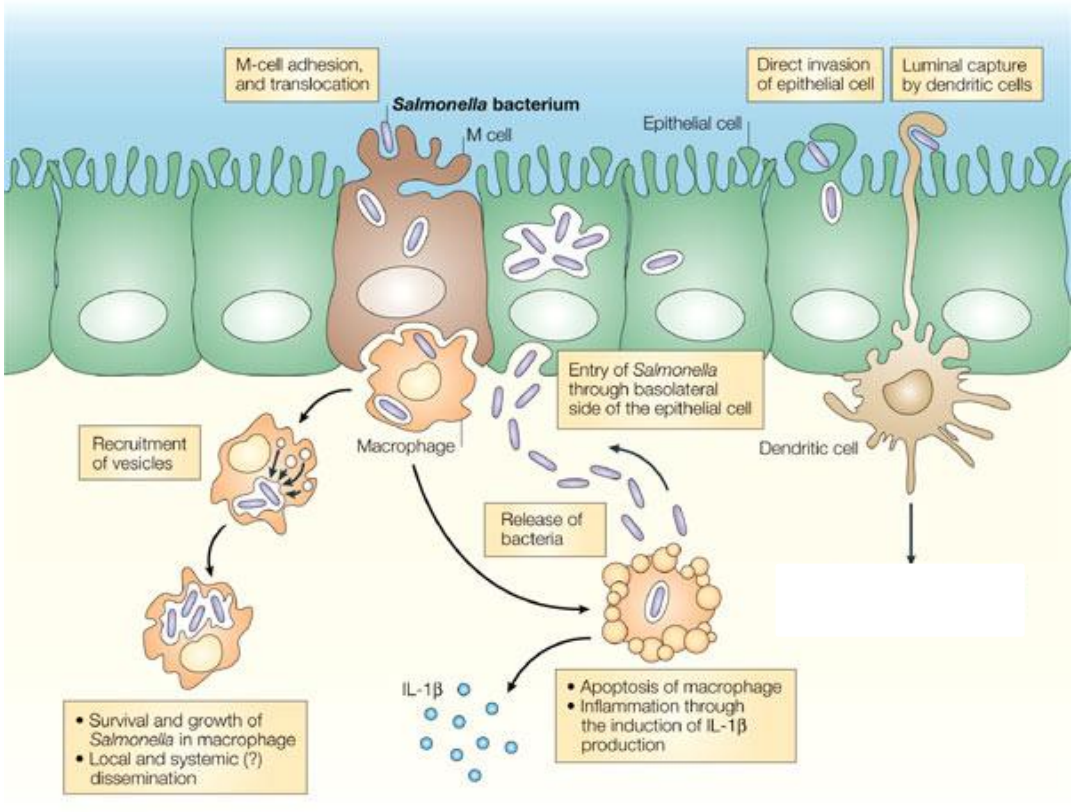
Dendritic cells also transport bacteria from the intestinal lumen to the mesenteric lymph nodes. Some bacteria go to the lymph nodes on their own, where they are phagocytosed by macrophages



Pathogenesis of gastroenteritis induced by *S. enterica*

Bacterial invasion and enterocyte transcytosis are accompanied by increased vascular permeability and inflammation (PMN influx). All of the above results in the appearance of diarrhea. **This inflammatory process remains localized in the mucosa and submucosa.** However, some strains invade deeper, entering the bloodstream from where they disseminate into distant organs.

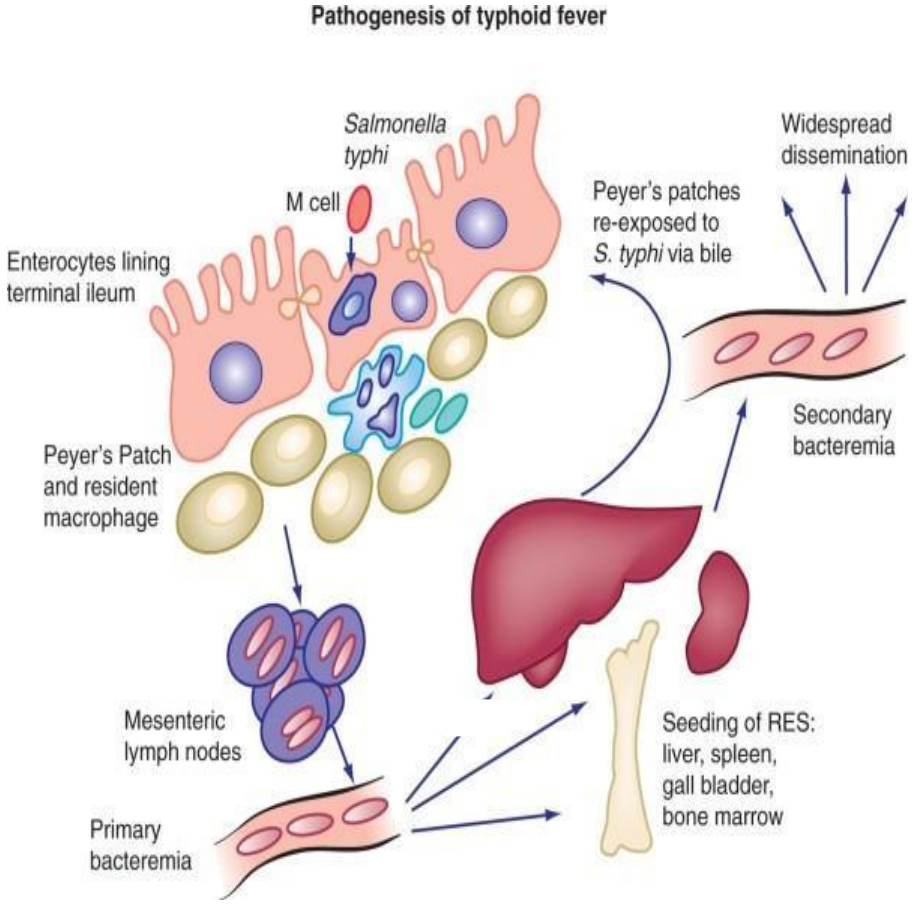
***S. enterica* has benefits from inflammation - ROS**



Pathogenesis of typhoid fever caused by *S. typhi*

The disease is characterized by **weak inflammation in the intestines and the spread of bacteria from the intestine into the cells of the monocyte-macrophage system.**

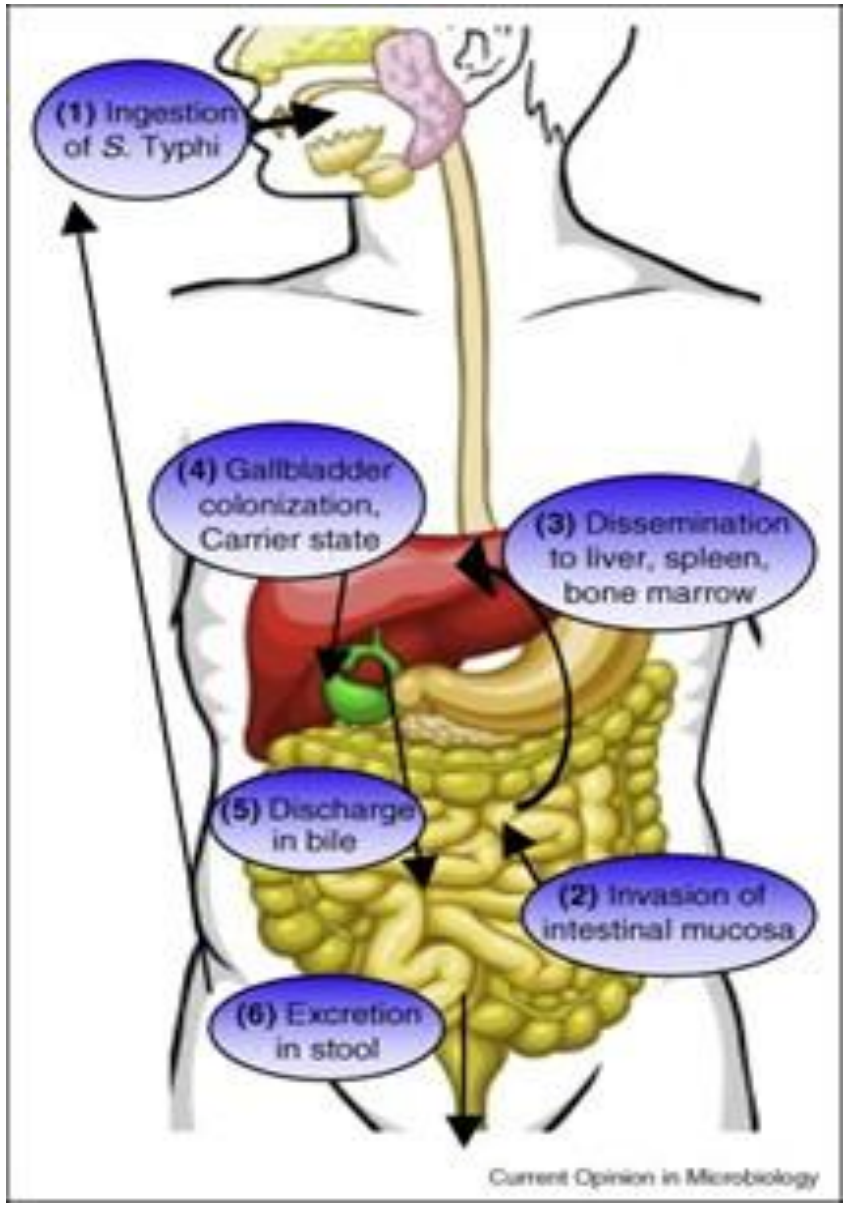
Salmonella that causes typhoid fever expresses the **Vi antigen**, which allows them to avoid the inflammatory response in the intestines and penetrate into the blood ...



... They multiply in the macrophages of the liver, spleen and mesenteric lymph nodes, and patients initially have no symptoms. When their number exceeds the threshold, they enter the bloodstream and cause continuous bacteremia. This event marks the beginning of a clinical illness, characterized by **high body temperature.**

Secondary bacteremia results in **invasion of the gallbladder and kidneys** and **re-invasion of the intestinal mucosa, especially the Payer's patches**. At this stage of the disease, bacteria can be isolated, not only from the blood, but also from the stool and urine

Germ carrying...



Chronic germ carriers are the primary reservoir of infection

Some patients have been carriers for years (due to a chronic infection of the biliary system, especially in the case of gallstones)

Let us remember...

Gastroenteritis- *S. enterica*

Epidemiology :

-disease of developed countries
- ingestion of contaminated food
-the reservoir are mostly animals
-the source is animal products, meat, milk, eggs

Pathogenesis :

- Bacterial invasion and transcytosis of enterocytes, increased vascular permeability and PMN influx, resulting in **diarrhea.**
- **Infection accompanied by inflammation generally remains localized in the mucosa and submucosa.**

Typhoid fever- *S. typhi*

Epidemiology :

- disease of underdeveloped countries
- feco-oral infection
-The reservoir is human
-the source is the stool of the patient or the carrier

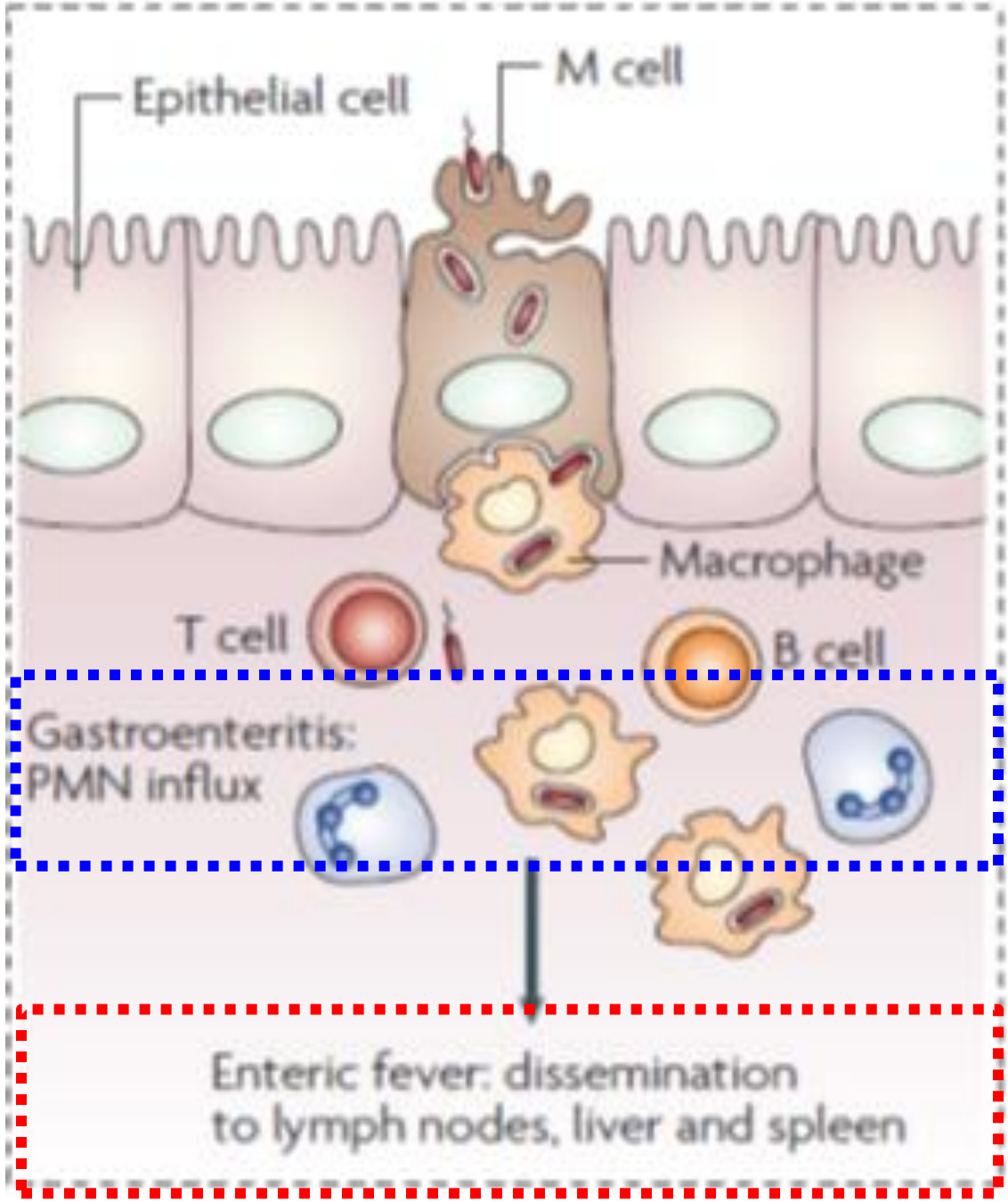
Pathogenesis :

- Weak inflammation in the intestines and the **spread of bacteria from the intestine to the cells of the monocyte-macrophage system**

When the number of bacteria exceeds the threshold, they **enter the bloodstream**, causing continuous bacteremia

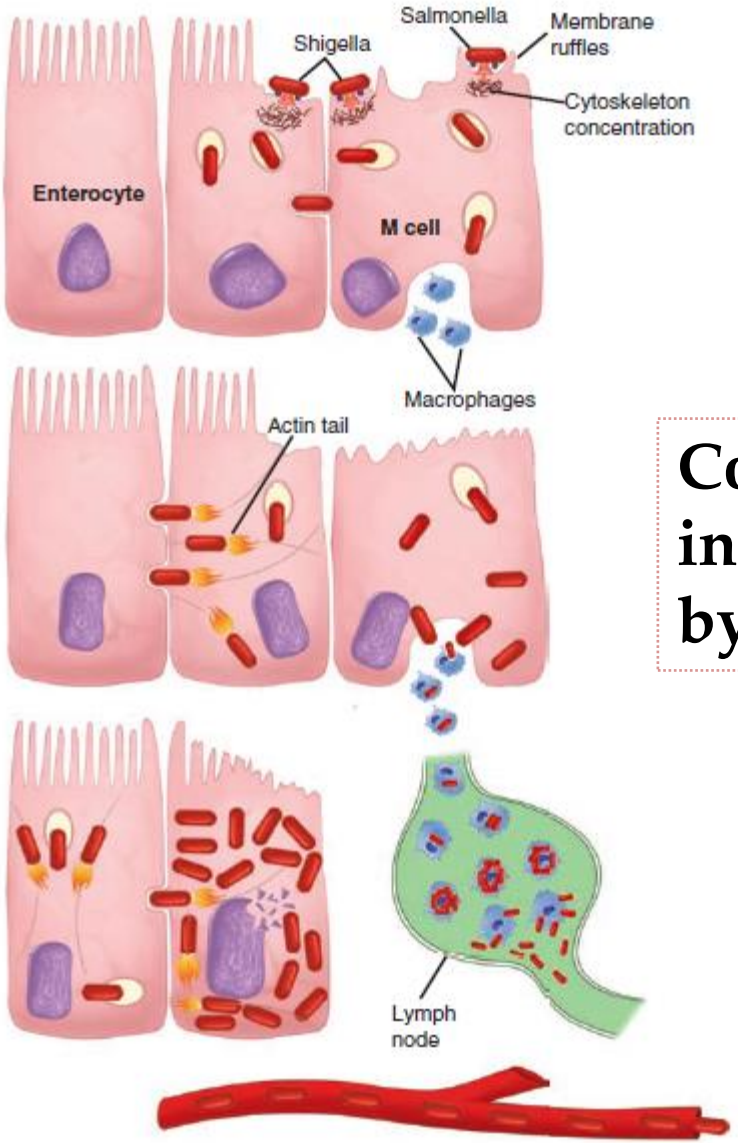
Metastatic infection in other organs (urinary and biliary system)

S. enterica



S. typhi

Let us remember once again...



Comparative presentation of intestinal epithelial invasion by Shigella and Salmonella

Diagnosis and therapy

Identification of the causative agent in the samples (blood, urin, stool, bone marrow)

Salmonela can not ferment lactosis

Identification of antibodies specific for **O** antigen and **Vi** antigen

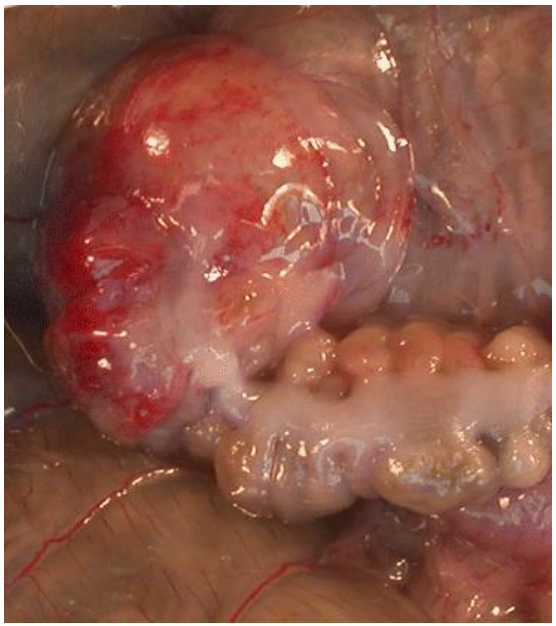
Antibiotics

Prevention

Other groups of E. coli that cause bloody diarrhea

Enterohemorrhagic *E. coli* *(EHEC)*

- The most commonly identified serotype is **O157: H7**
- They cause the characteristic afebrile bloody diarrhea (**hemorrhagic colitis**)
- A complication of hemorrhagic colitis is **hemolytic-uremic syndrome** (hemolytic anemia, thrombocytopenia and renal failure)



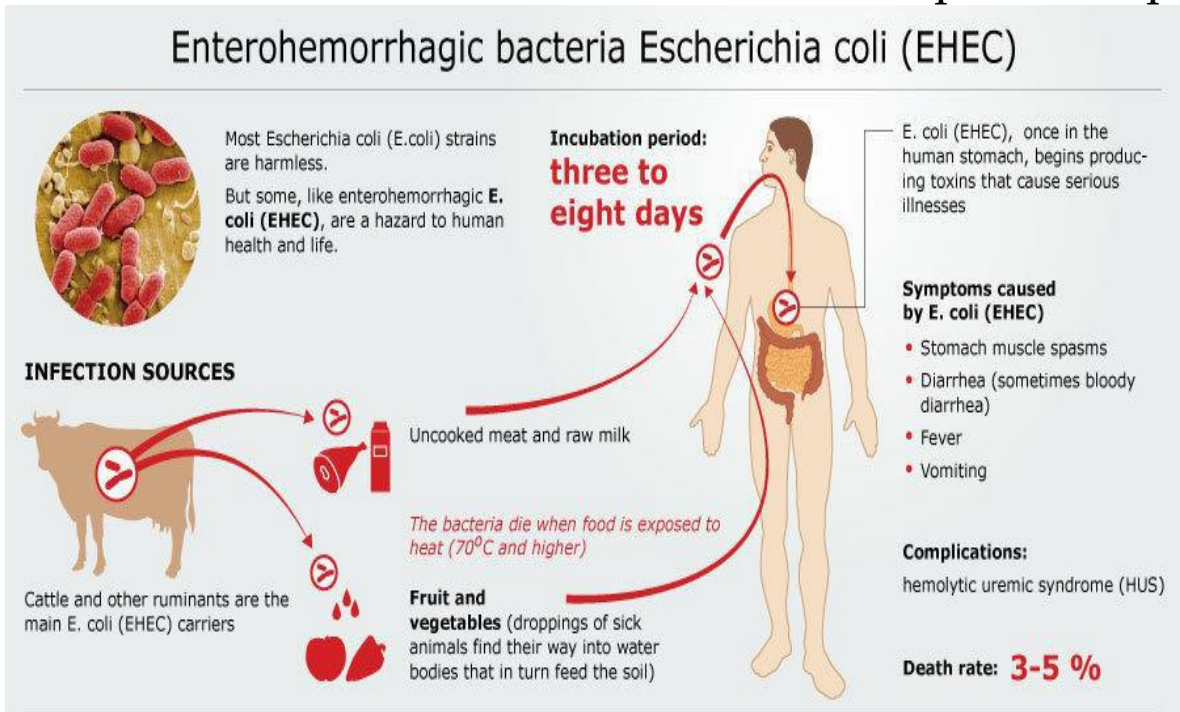
Epidemiology

O157: H7 causes both epidemics and sporadic diseases, primarily **zoonoses**. It occurs mainly after ingestion of **undercooked burgers** infected with the pathogen

It is most likely resistant to acids, and the **estimated infectious dose is about 50 bacteria per gram of hamburger**.

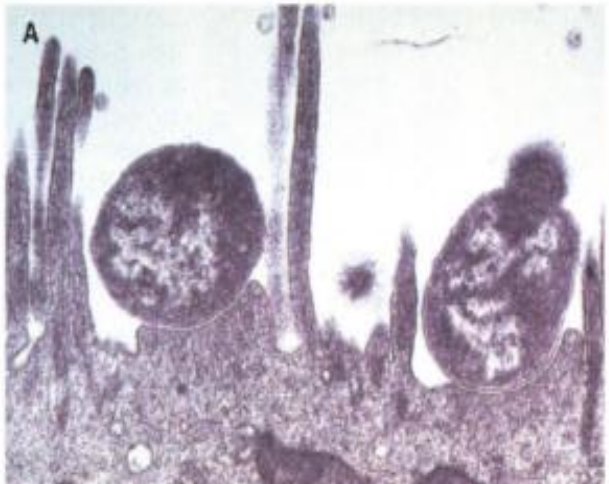
Contaminated groundwater, near an animal farm, can also affect the spread of the infection

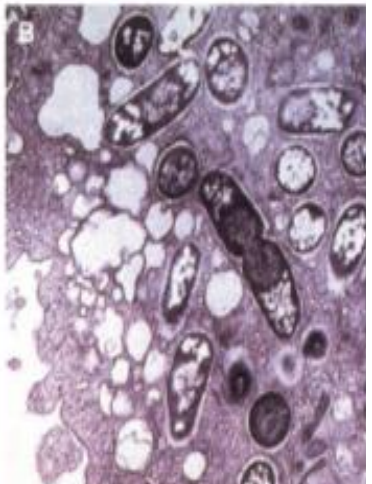
Direct transmission of E. coli O157: H7 from person to person was observed

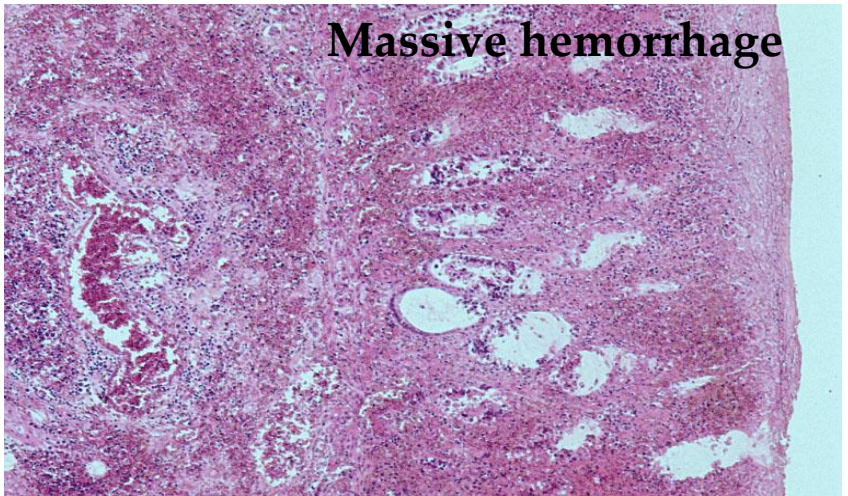


Establishment of infection and mechanism of damage

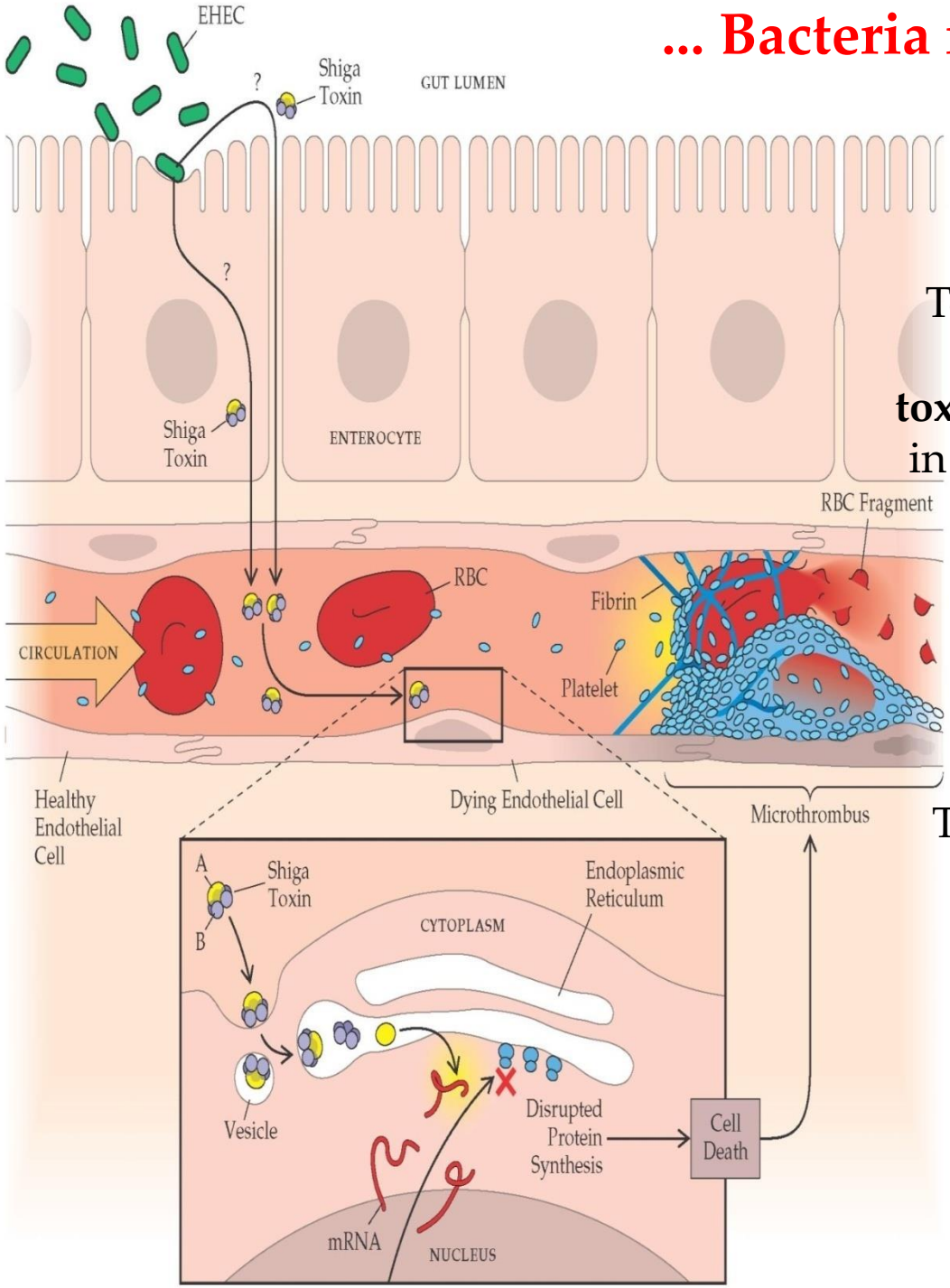
- After passing through the stomach, EHEC **colonize the terminal parts of the intestine** (bind to the surface of the intestinal mucosa) and then multiply locally (similar to EPEC)
- **ENES produce** one or two related but antigenically different toxins:
- **Shiga-like toxins 1 and 2** share the same enzyme specificity and binding sites on target cells as Shiga toxin S. dysenteriae type 1







... Bacteria never enter the bloodstream



Today, it is believed that the **interaction of inflammatory cytokines and shiga-like toxin**, which together damage blood vessels in the lamina propria, is responsible for the formation of profuse bleeding.

The main complication of EHEC (in about 5% of severe clinical cases) is **damage of small blood vessels** which, if it occurs in the renal glomeruli or in young children, most often results in the development of HUS

Diagnosis and therapy

Identification of the causative agent in the stool samples

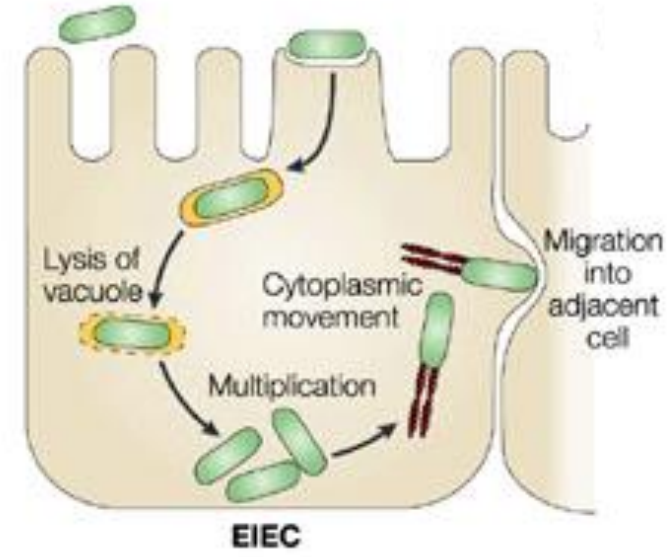
O157:H7 can not ferment sorbitol – way of identification

Enzyme immunoassay for the identification of Shiga like toxins or bacteria in the stool

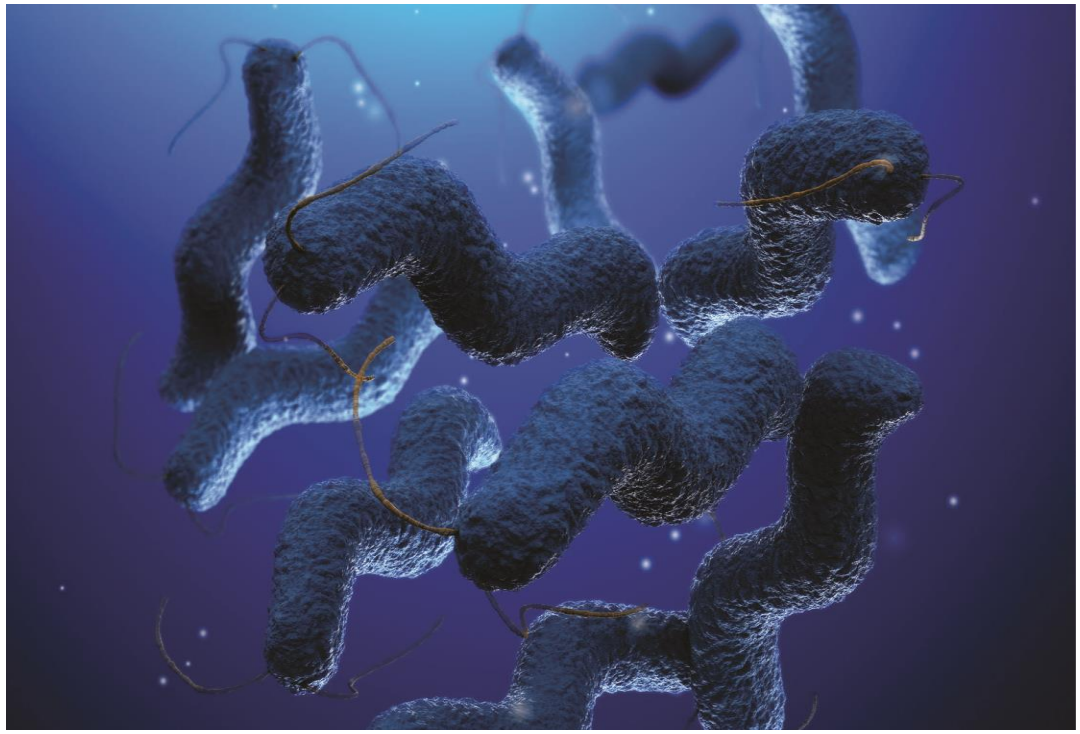
Antibiotics?
Rehydration
Dialysis
Transfusion

Enteroinvasive *E. coli (EIEC)*

- **Similar to shigella**
- They mainly cause infections in children under the age of 5 **in developing countries**
- Occasional epidemics in **developed countries** that are usually associated with the intake of contaminated food and water
- **Humans are the only known reservoir of infection**

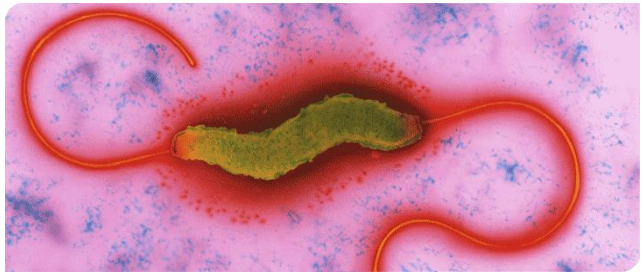


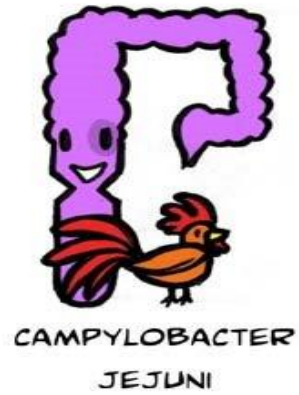
Campylobacter jejuni...



... one of the leading causes of acute diarrheal syndrome

Epidemiology

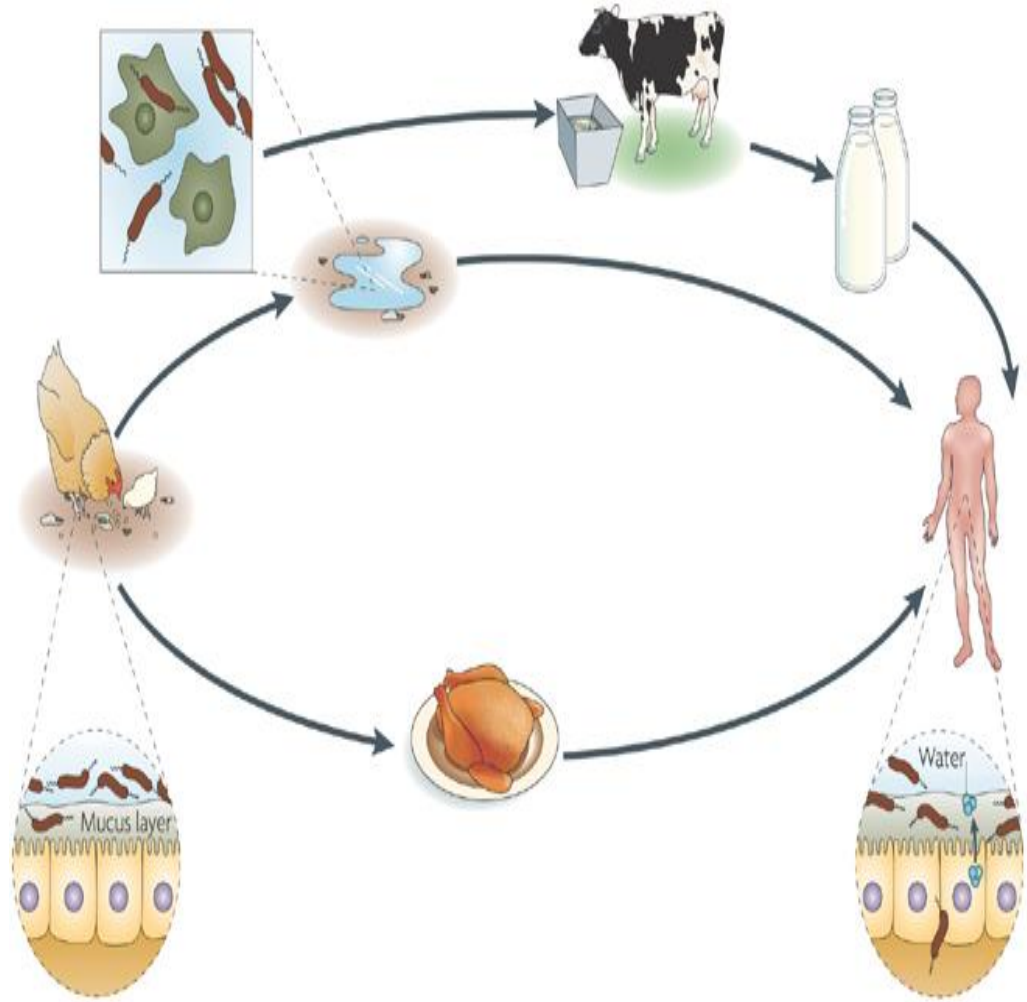




The reservoir of infection: domestic animals, and rarely humans

Source of infection: feces

It is transmitted indirectly by insufficiently heat-treated infected or contaminated meat (usually chicken), raw milk, contaminated water. Direct contact transmission is rare

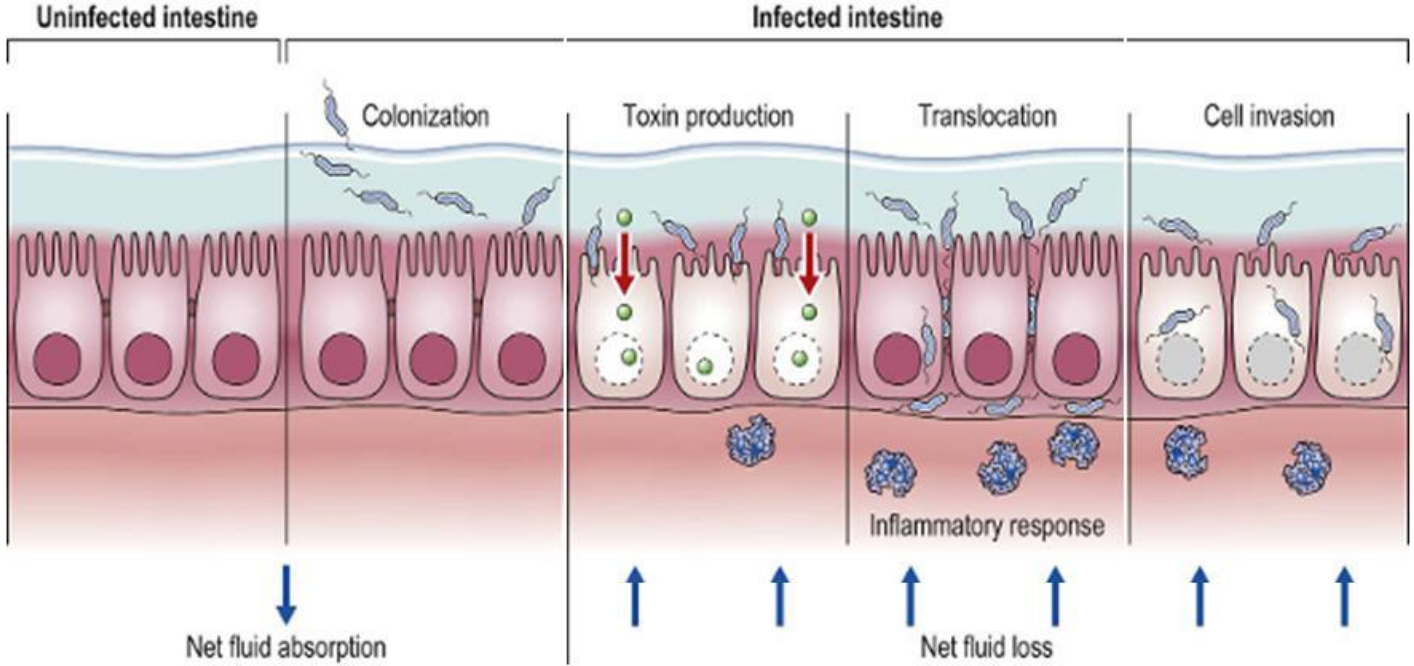


Mechanisms of enteritis

Adhesion and production of toxins that cause diarrheal syndrome manifested by **watery stools**
(mechanism similar to vibrio cholerae)

Invasion and replication in enterocytes, followed by inflammation
diarrheal syndrome manifested by **bloody-mucous stools**
(Shigella-like mechanism)

Epithelial transcytosis, bacteria replicates in the lymphatic tissue of the digestive system.This is followed by the **dissemination** of the causative agent and the generalization of the infection, and the so-called **enteric fever**
(salmonella-like mechanism)



Clinical manifestations

Enteritis or acute diarrheal syndrome: abdominal pain and fever (resembling appendicitis), followed by vomiting and diarrhea (watery stools, unpleasant odor, often containing a lot of bile, and mucus and blood may be present)

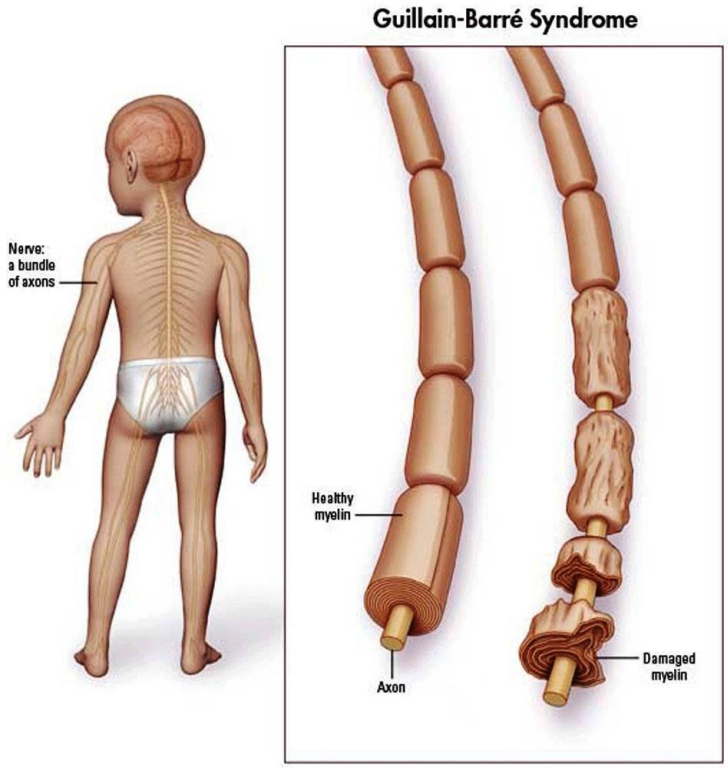
Bacteremia, often without previous gastrointestinal symptoms. The consequence can be **the spread of the infection to other tissues and organs**: endocarditis, liver abscess, meningitis, acute cholecystitis, cystitis and pancreatitis.

Complications: hemolytic-uremic syndrome and interstitial nephritis

...

Meningitis that most often occurs in newborns

Intrauterine fetal death and abortion (after infection of pregnant women)



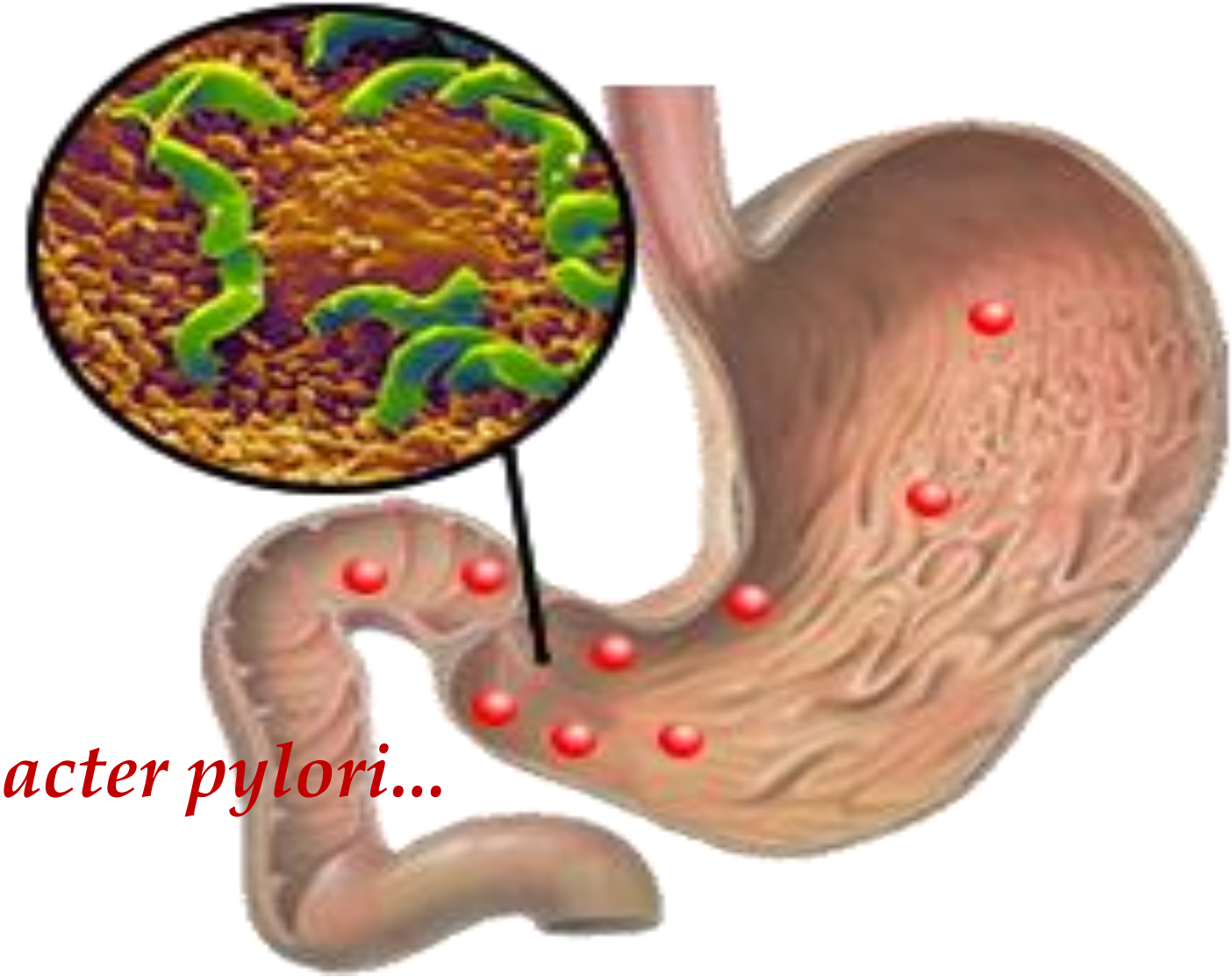
***Guillain-Barré* syndrome** (acute inflammatory demyelinating polyneuropathy). An asymptomatic or manifest infection caused by C. jejuni precedes Guillain-Barré syndrome in more than 40% of cases. A possible pathogenetic mechanism is molecular mimicry (production of antiglycoside antibodies)

Diagnosis and therapy

Identification of the causative agent in the stool samples or in blood or abscess during bacteriemia

Rehydration

Antibiotics



Helicobacter pylori...

... the cause of gastritis

In 1983, Barry Marshall and Robin Warren first identified *Helicobacter pylori* in the gastric epithelium of patients with chronic gastritis.

The Nobel Prize in Physiology or Medicine 2005

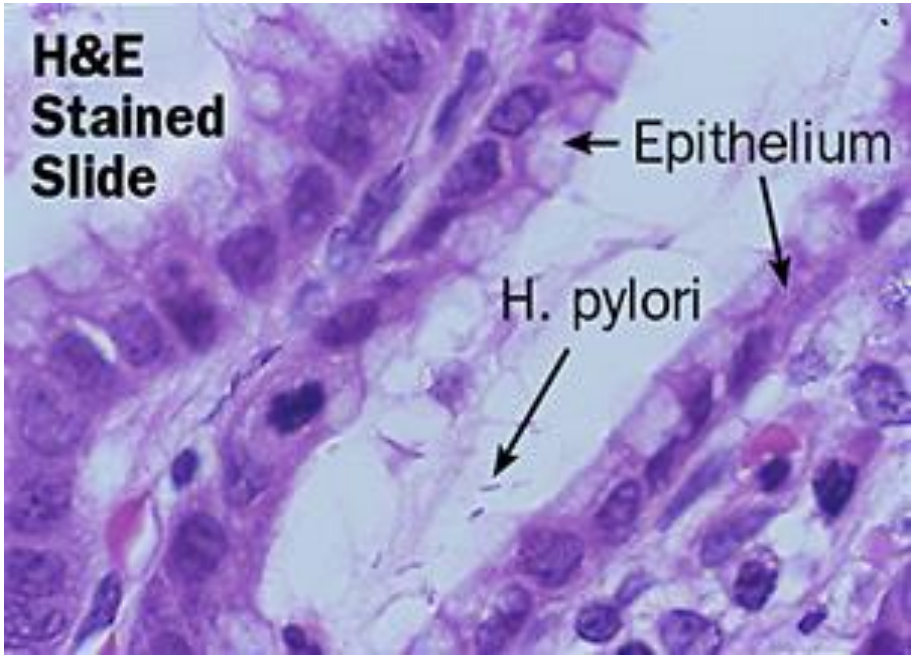
"for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"

Photo: C. Northcott

Barry J. Marshall

Photo: U. Montan

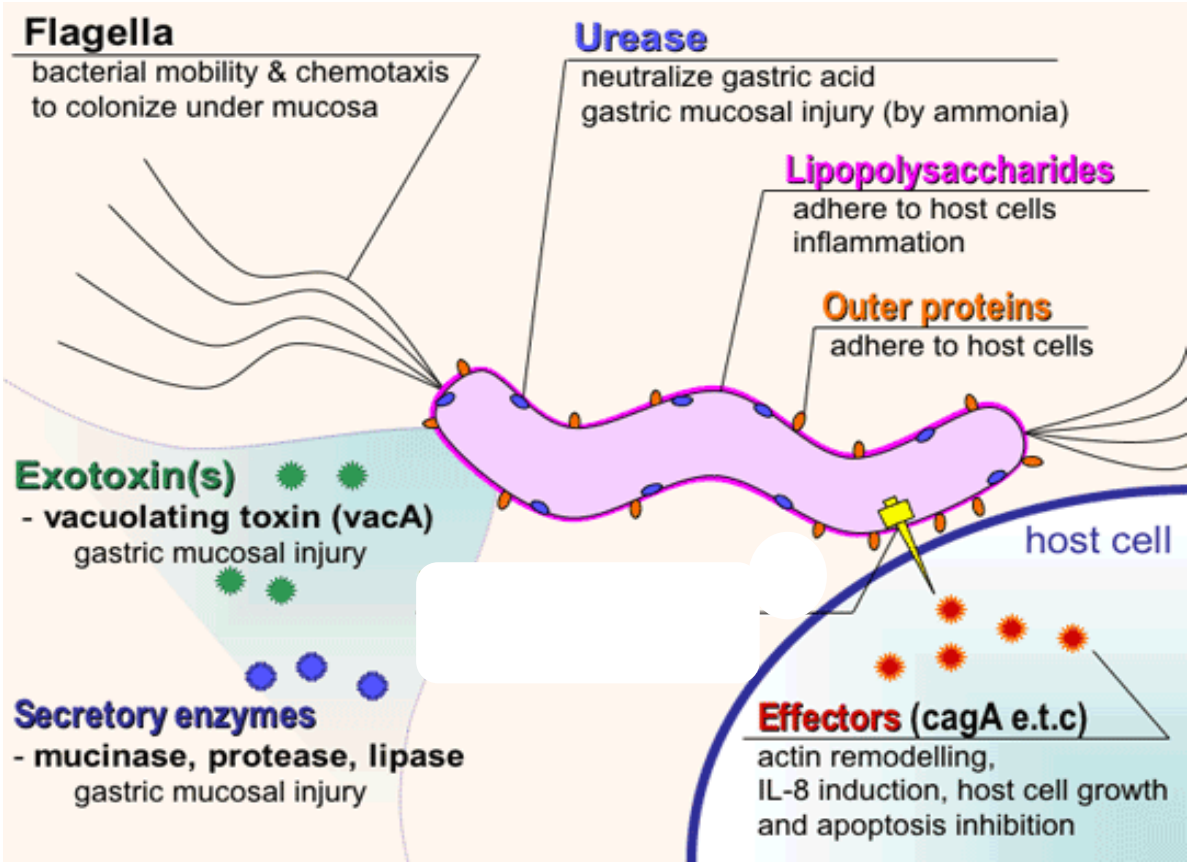
J. Robin Warren

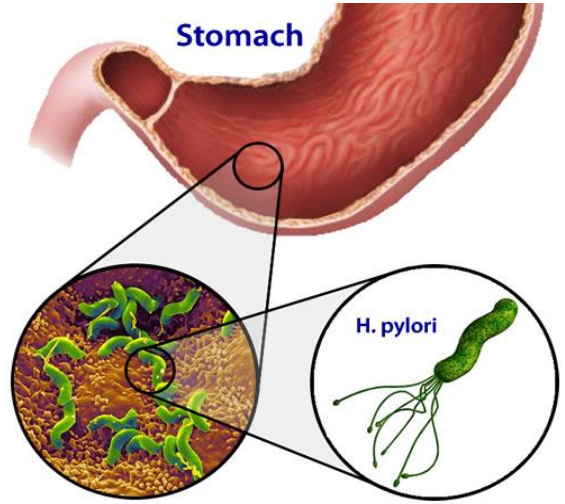


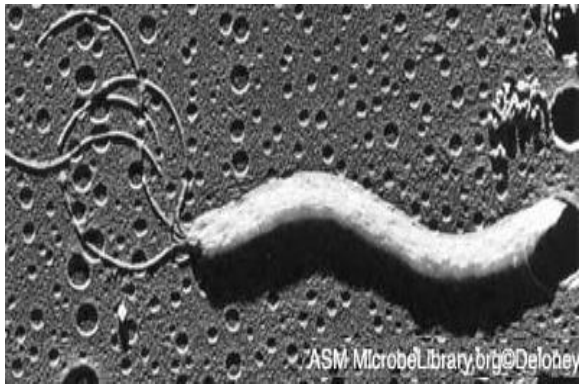
General characteristics

Gram- negative bacterium that selectively colonizes the stomach of humans

H. pylori infection is a prototype of persistent bacterial infection





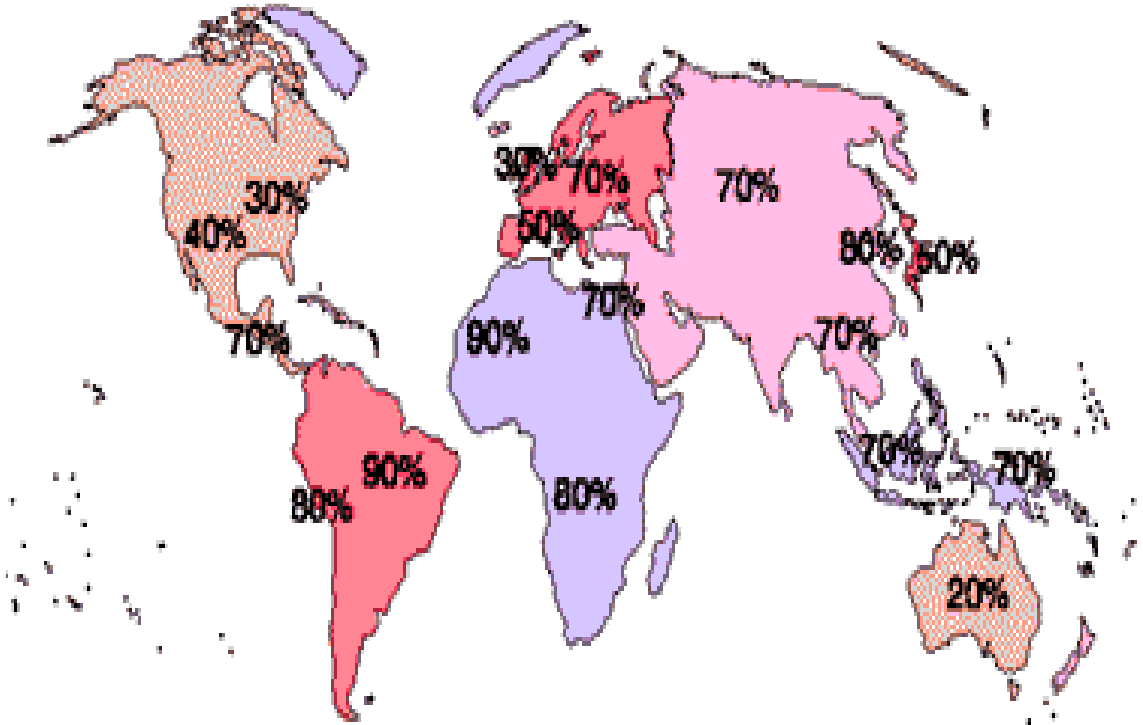


Epidemiology

One of the most common bacterial infections in humans (colonizes half of the world's population, but causes clinically manifest disease in only 10 to 15% of infected individuals)

Risk factors: poor socio-economic status, overpopulation, ethnicity ...

The infection is most likely acquired in childhood by **feco-oral or oral-oral transmission.**



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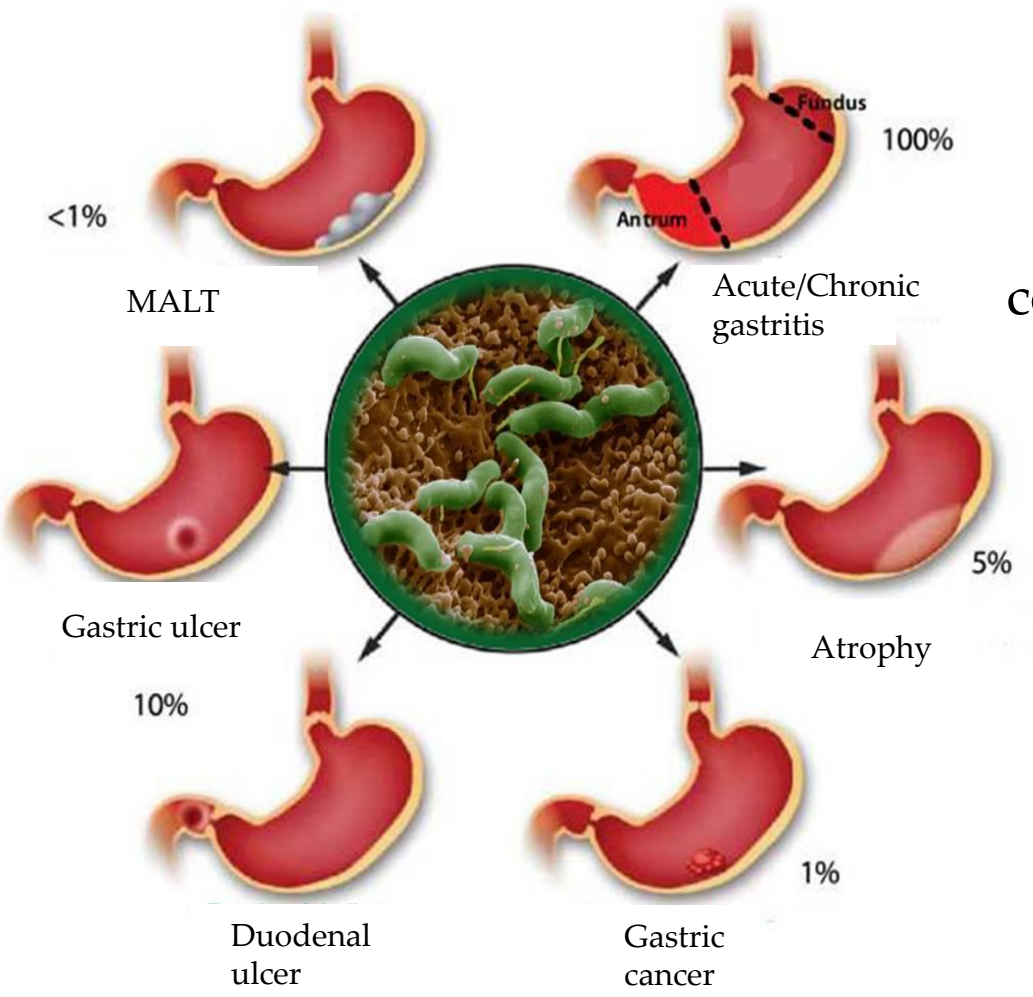
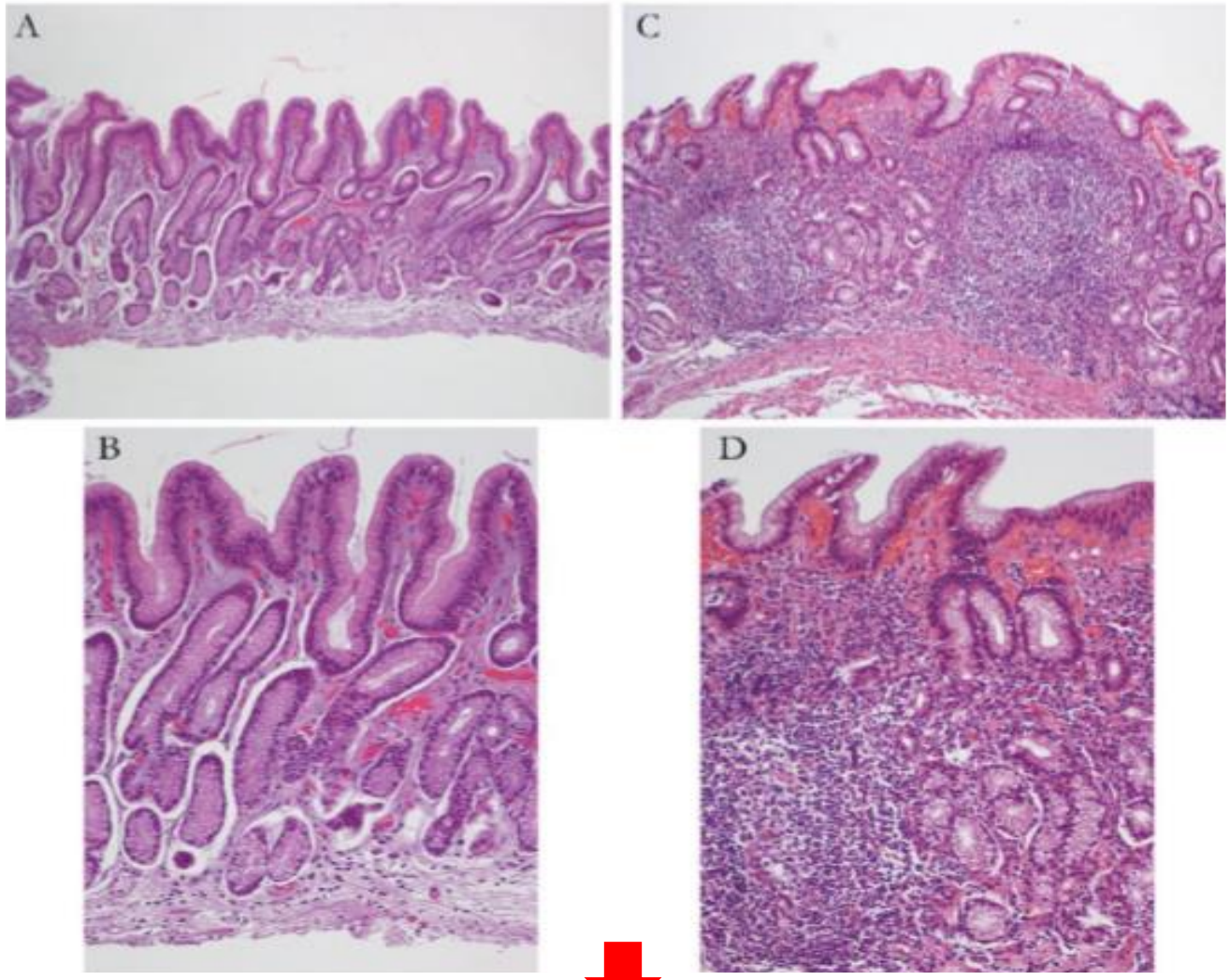


Helicobacter pylori colonizes the gastric mucosa and in a few weeks causes **superficial gastritis**

Prolonged colonization and chronic course of infection is accompanied by a **low degree of gastritis** and gradual progression of the disease

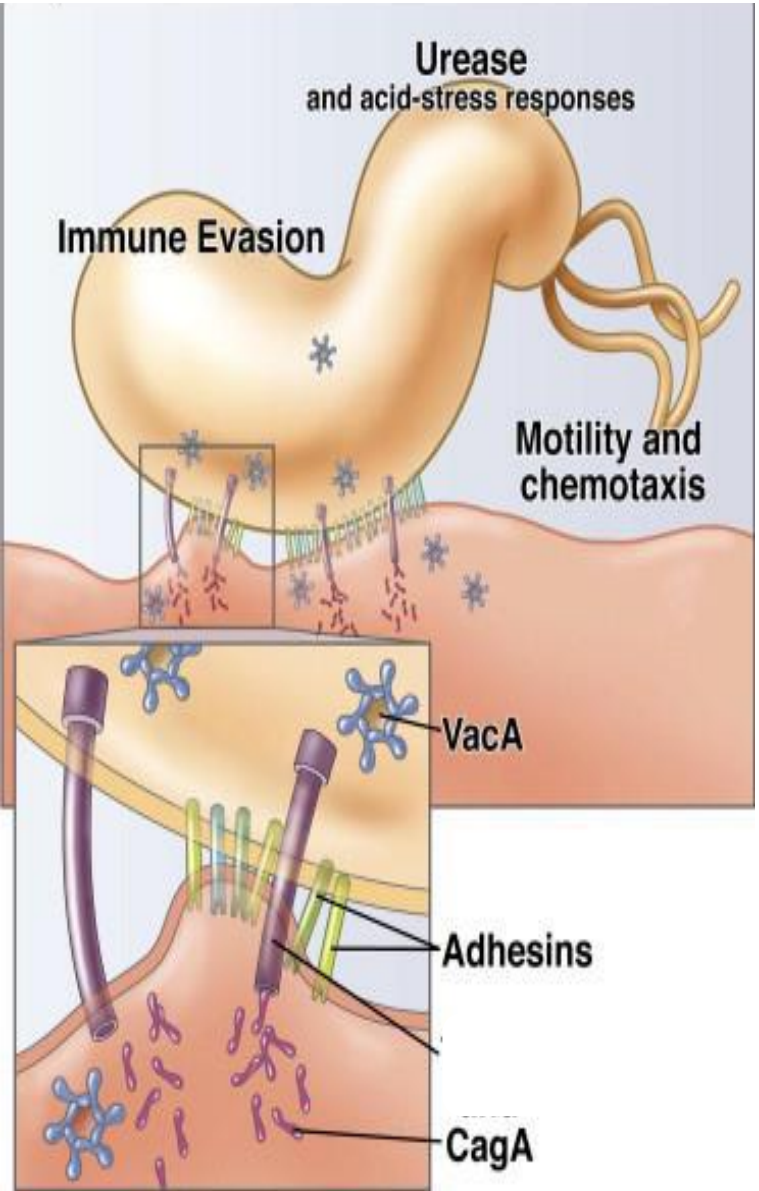
H. pylori gastritis can either remain clinically asymptomatic for years or progress to a variety of diseases including duodenal ulcer and gastric adenocarcinoma.

Gastritis



A. normal gastric epithelium (10×); **B.** normal gastric epithelium shown at higher magnification (20×); **C.** active gastritis with the appearance of a lymph follicle and infiltration of immune cells into the lamina propria (10×); **D.** active gastritis shown by higher magnification (20×).

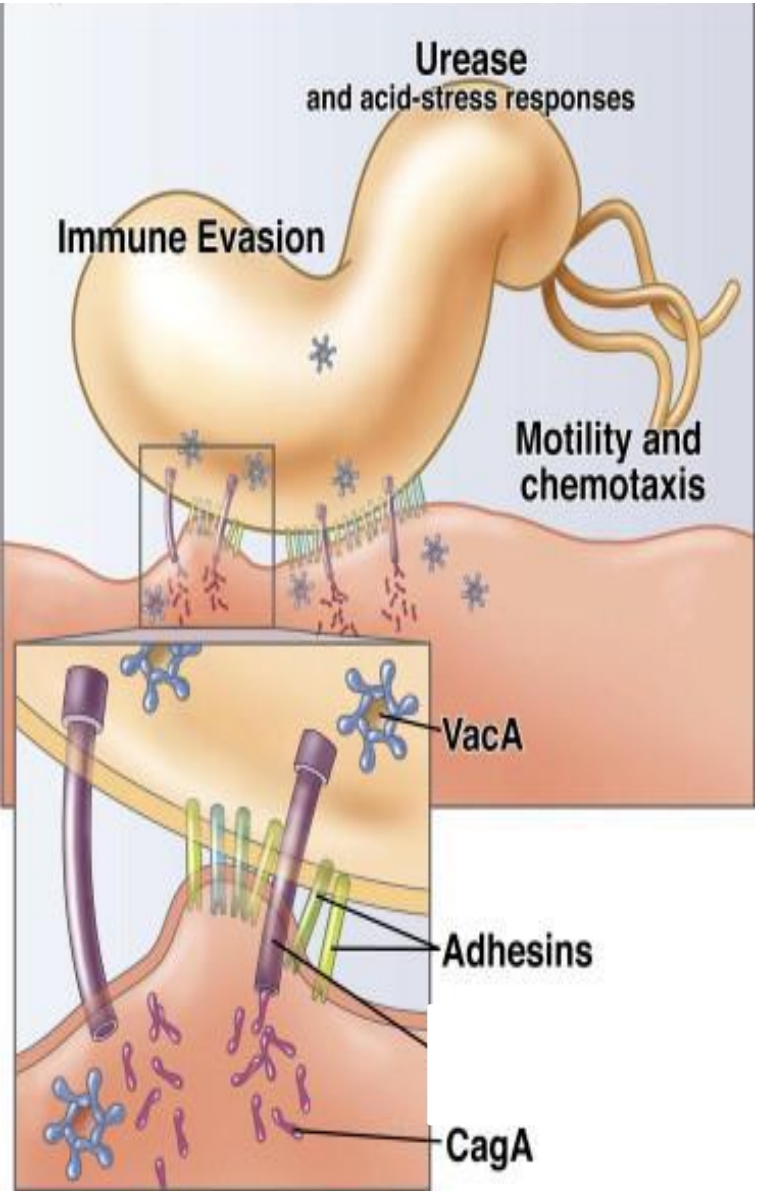
Establishment of infection



H. pylori **mass-produces urease,** which catalyzes the hydrolysis of urea to ammonia and carbon dioxide and thus neutralizes the acidic environment of the stomach
It has a large number of **polar flagella** which penetrate and colonize the layer of mucus in the stomach

It expresses a number of **outer membrane proteins** that are important for adhesion and persistent colonization of the gastric epithelium: **blood-group antigen-binding adhesin (BabA)** и **sialic acid–binding adhesin (SabA)**

H. pylory suppreses host's immune system

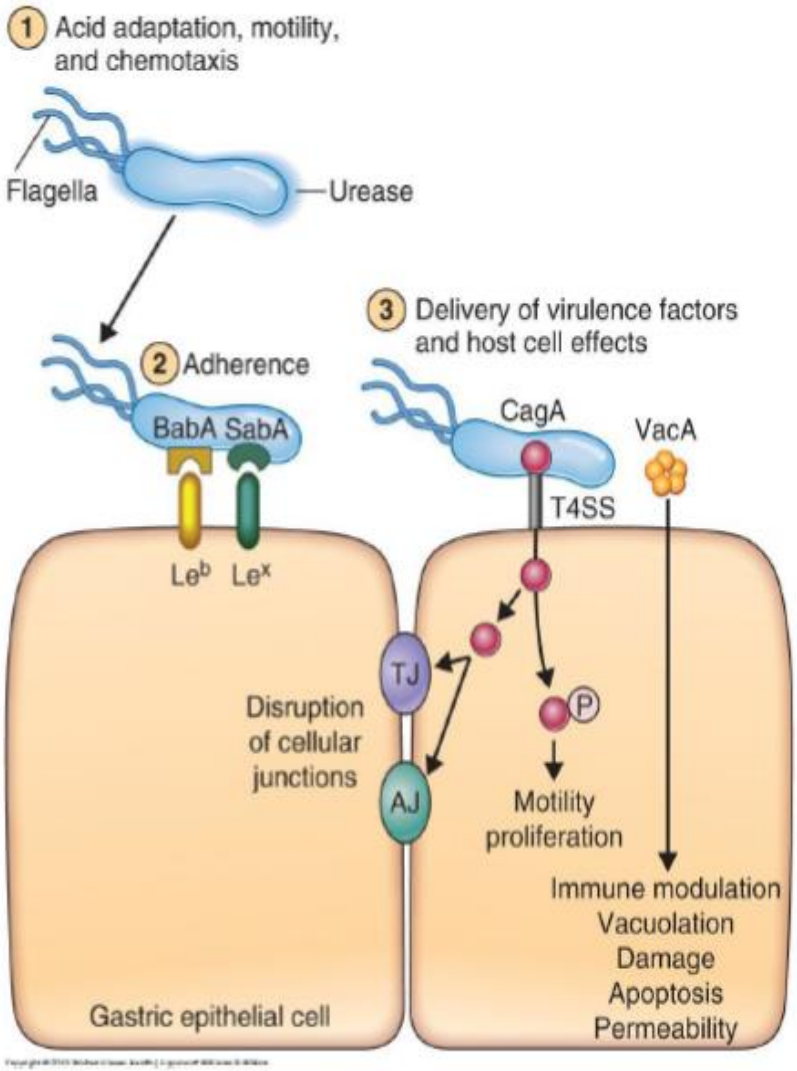


It expresses a repertoire of human antigens on LPS

LPS *H. pylori* is relatively anergic, it shows 10^3 times less activity than LPS of other *Gram-negative* bacteria

The vacuolizing cytotoxin, **VacA**, can modulate the host immune response by directly suppressing the T lymphocyte response

Mechanism of tissue damage



Cytotoxin-associated gene (CagA):
after adhesion of *H. pylori*, it transports to host epithelial cells, where it activates several intracellular signaling pathways which ultimately results in cell morphological changes, including disruption of intercellular connections, increased cell motility, and proliferation..

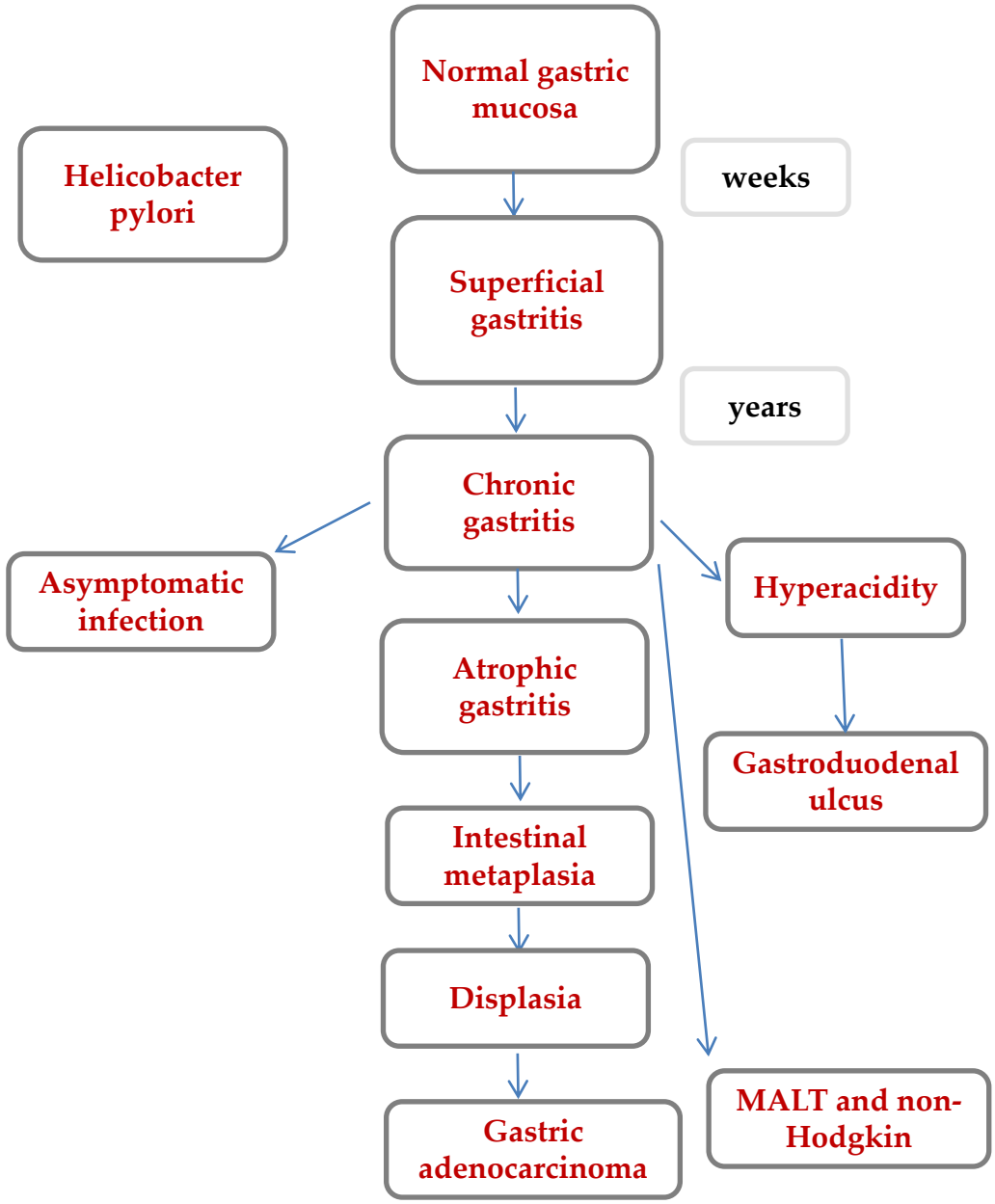
Vacuolating cytotoxin (VacA):
causes damage to epithelial cells
it functions through transmembrane pores, permeabilizing host epithelial cells for urea increases intercellular permeability to important nutrients

Pathogenesis of infection and possible consequences

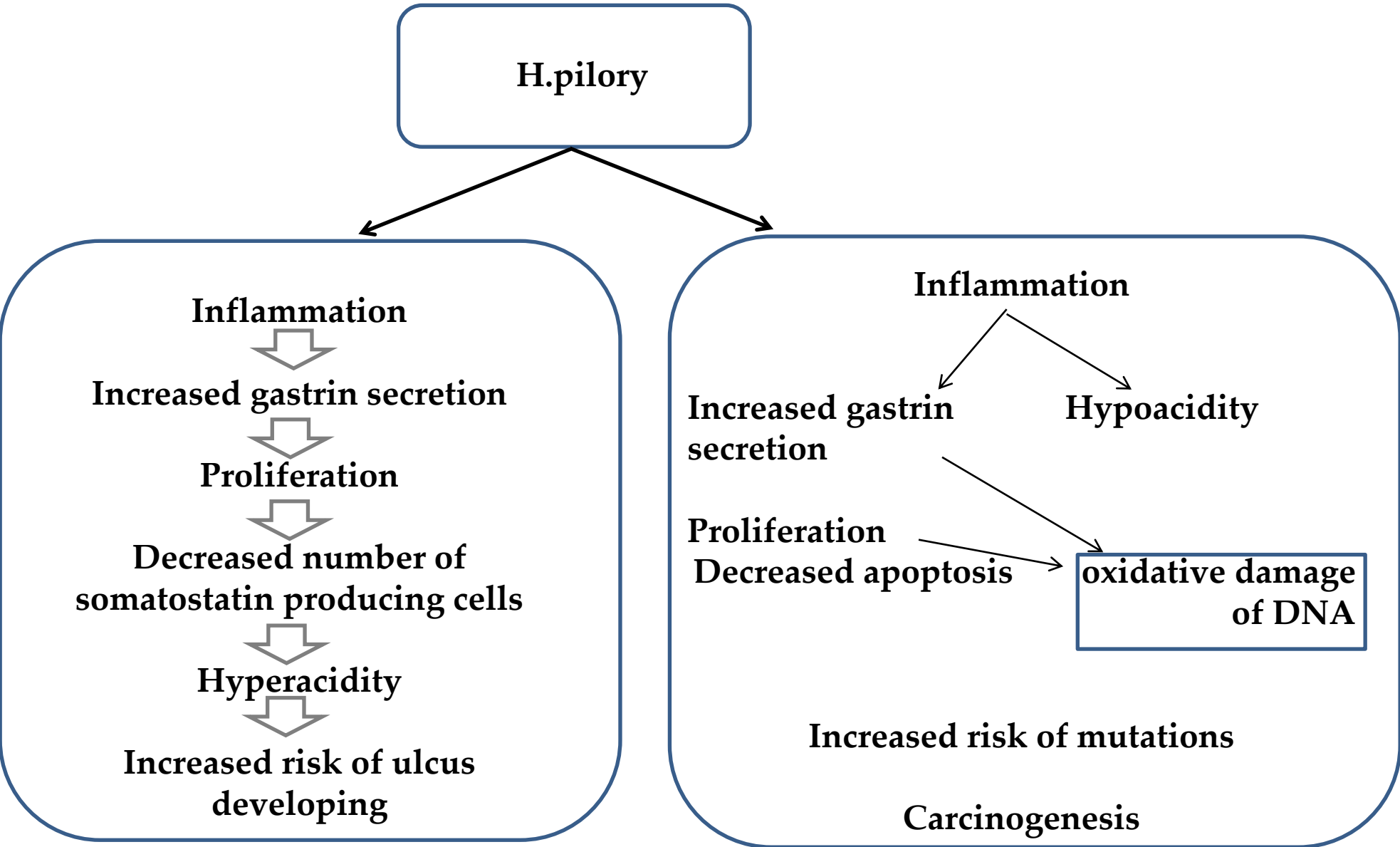
H. pylori infection results in a **reduced presence of somatostatin-secreting D cells**, which in turn causes inadequately **elevated gastrin levels and increased gastric acid secretion**, all of which increase the risk of **duodenal ulcers**.

H. pylori infection is also associated with the development of **gastric adenocarcinoma**

T lymphocytes involved in the chronic inflammatory process may react with *H. pylori* antigens. They produce proinflammatory cytokines causing uncontrolled growth and proliferation of B lymphocytes. Malignant transformation of lymphocytes is possible (**MALT lymphoma and non-Hodgkin's gastric lymphoma**)

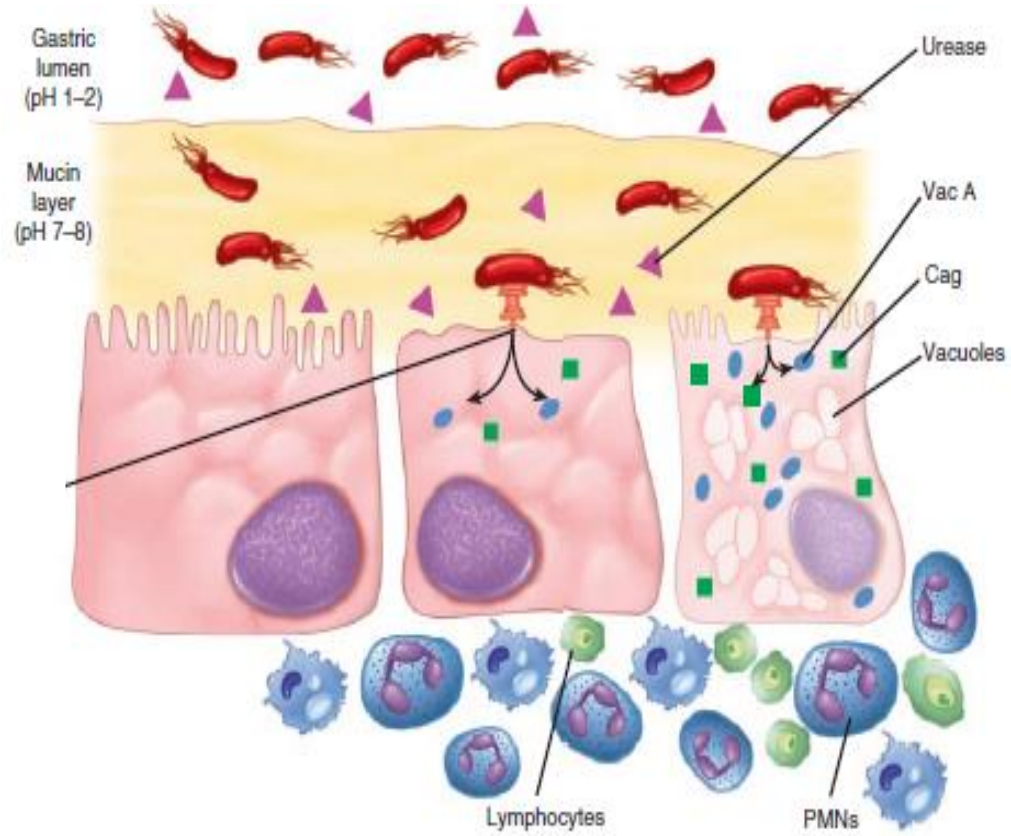


H. pylori infection and potential mechanisms involved in ulcer development and carcinogenesis



So let us remember...

The first steps in the pathogenesis of *H. pylori* infection include **adaptation to an acidic environment, motility, and chemotaxis** in the mucosal layer of the gastric epithelium.
This is followed by **colonization** of epithelial cells with the help of adhesins on the surface of the bacterium



Colonization is almost always accompanied by a cellular infiltrate in the range

from minimal infiltration of mononuclear cells in the lamina propria to extensive inflammation with neutrophils, lymphocytes, and microabscess formation.

H. pylori initiates epithelial damage by releasing and "delivering" several effector molecules **that induce a number of pathological processes in the gastric epithelium**

Diagnosis of the infection caused by *H. pylori*

Method	Sample	Sensitivity
Invasive tests		
Urease test	Gastric mucosal biopsy	High
Pathohistological analysis	Gastric mucosal biopsy	Extremely high
Cultivation	Gastric mucosal biopsy	Extremely high
Non-invasive tests		
Serology	Serum	High
Urea test in exhaled air	Exhale air	Extremely high
Stool antigen testing	Stool	Extremely high
Tests used in research		
Polymerase chain reaction (PCR)	Stool, gastric juice, gastric biopsy	High

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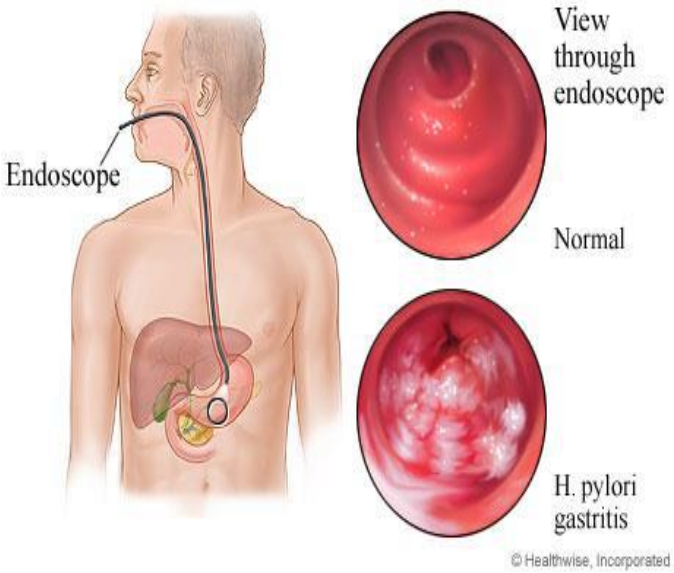
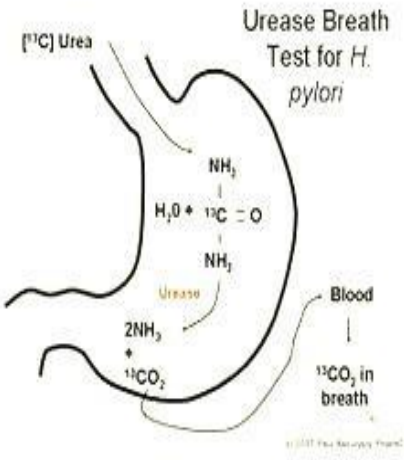
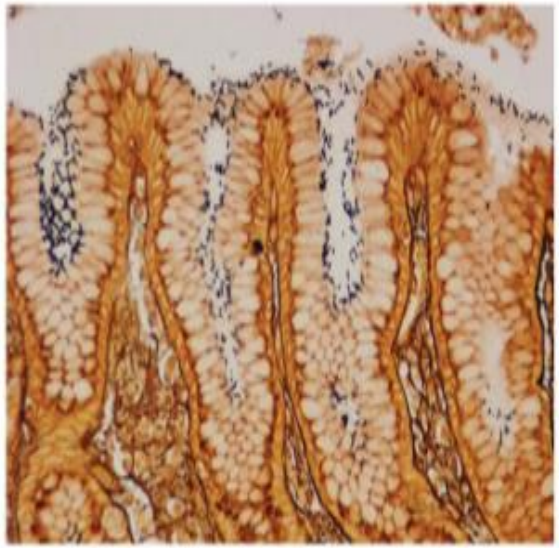

Endoscope
View through endoscope
Normal
H. pylori gastritis
© Healthwise, Incorporated


Urease Breath Test for H. pylori
[13C] Urea
NH2
H2O + 13C = O
NH2
Urease
2NH3
+
13CO2
Blood
13CO2 in breath




H.Pylori Antibody Test
Cassette
nbqihao.en.alibaba.com
www.bizrice.com
H.Pylori Antibody Test
PROCEDURE


Accurate H.pylori antigen test(stool)
Anti-H. Pylori
Rapid Test
ivdtest.en.alibaba.com

Therapy

- successful therapy - negative test for its presence 4 or more weeks after the end of therapy

- **triple therapy** (7 to 10 days) - **proton pump inhibitors (**PPI) and **two antibiotics** (usually clarithromycin with amoxicillin or metronidazole)

- **quadruple therapy** that combines **PPI**, **bismuth subsalicylate**, **metronidazole and tetracycline** for 14 days

- 10-day treatment regimen consists of administering **PPI** and **amoxicillin** twice daily for the first 5 days, after which the patient is treated with triple therapy: a combination of PPI, clarithromycin, and metronidazole twice daily for the remaining 5 days.

Non-invasive gastrointestinal and intra-abdominal infections

Pseudomonas aeruginosa
Bacteroides spp.

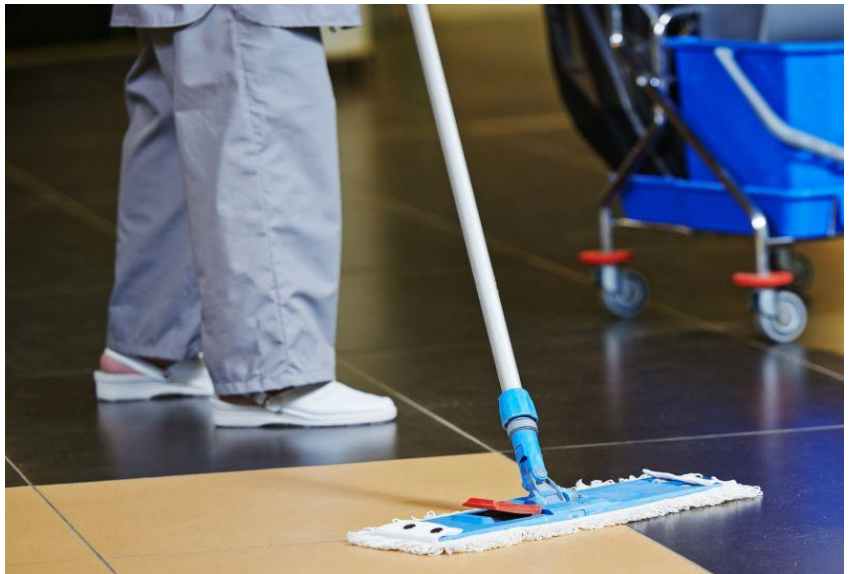
... cause of a wide range of infections (lung and urinary infections, soft tissue infections)

General characteristics

Pseudomonas spp. are aerobic mobile **Gram-negative bacteria that easily adapt to environmental conditions**. It lives in water and soil

Among them, ***Pseudomonas aeruginosa*** is the most common **opportunistic pathogen** that causes various infections in immunodeficient patients

Extremely resistant, can be found in disinfectants, infusion fluids, blood products, anesthesia kits, peritoneal dialysis ...



culture

Pigments, **piocyanin** and **pioverdin**, give them the characteristic blue-green and yellow-green color on agar

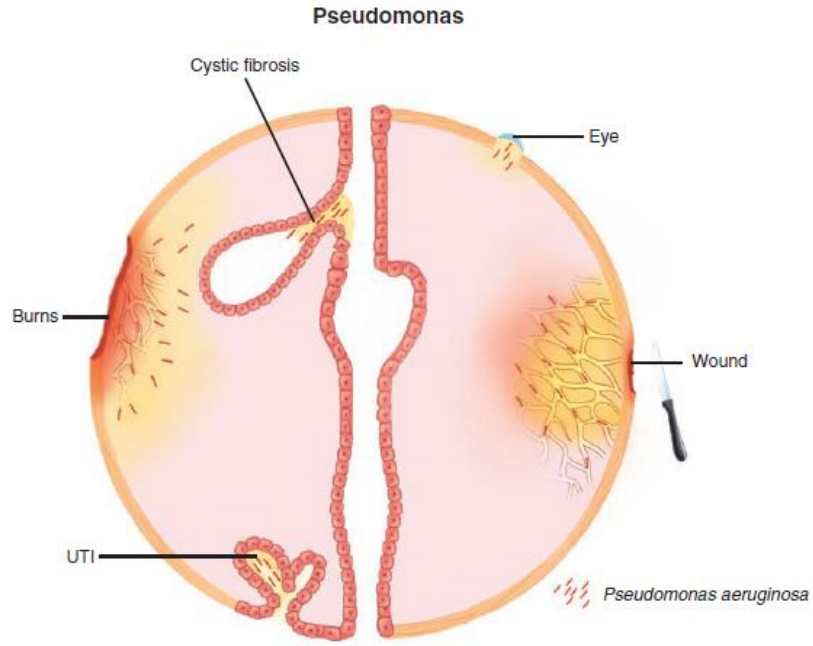
Colonies of this bacterium have a characteristic **odor** similar to fruit, grapes, or corn tortillas, which can sometimes be seen in infected wounds or other places massively infected with these bacteria.

It has numerous **virulence factors**

Causes infections of the lungs, wounds, burns, ears ...

Epidemiology

Because of its adaptability as well as innate and acquired resilience on many antibiotics, *P. aeruginosa* **often colonizes hospitalized patients**
P. aeruginosa mainly causes disease in humans only after local lesions or systemic immune system disorder
Folliculitis- hot tub
Otitis externa
Pneumonia, catheter related infection…
When bacteria enter the body, it is possible its dissemination into the bloodstream and the onset of sepsis



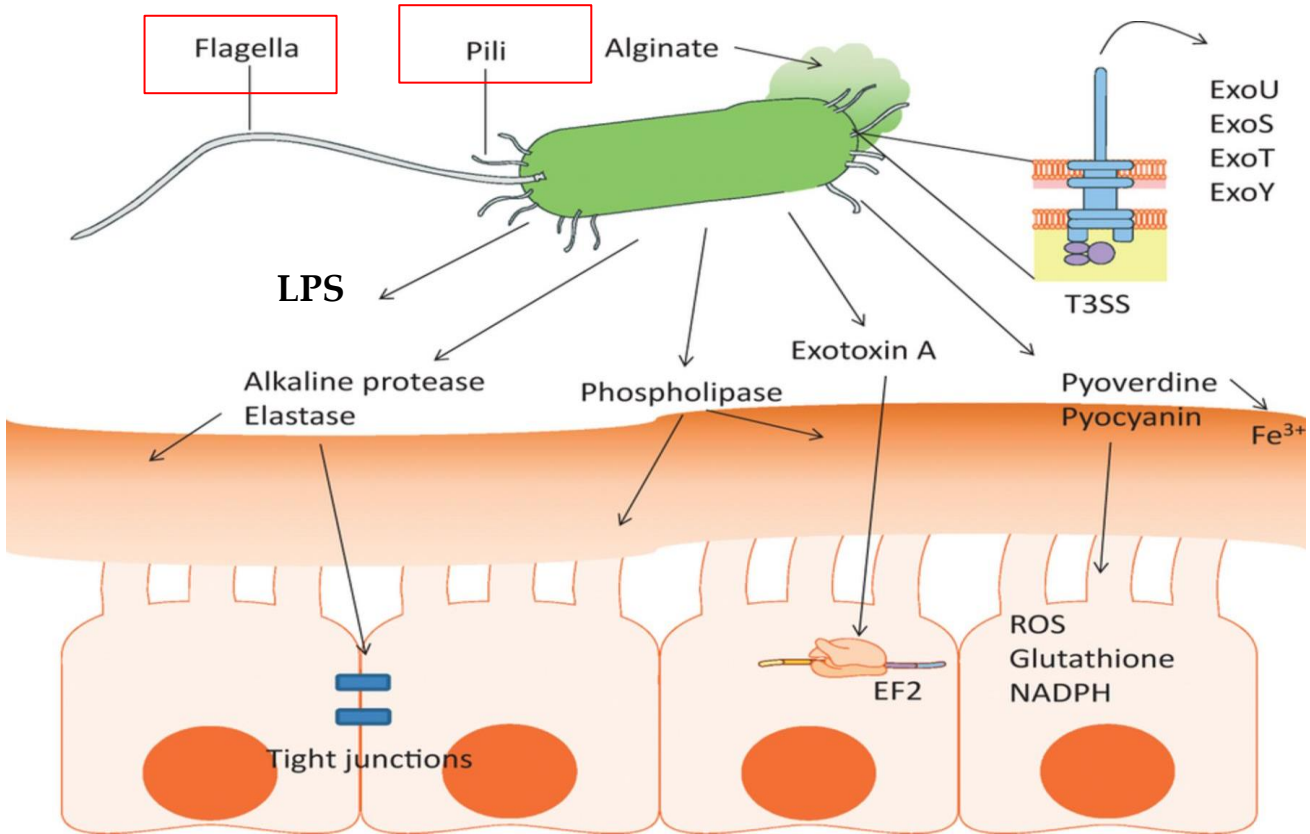
Establishing an infection

Moving: pili (wince), flagella (swimming), pili and flagella ("swarming")

Adhesion: flagella and pili are important in adhesion to epithelial cells

Flagella interacts with a TLR5 receptor present on innate cells, which can activate the immune response

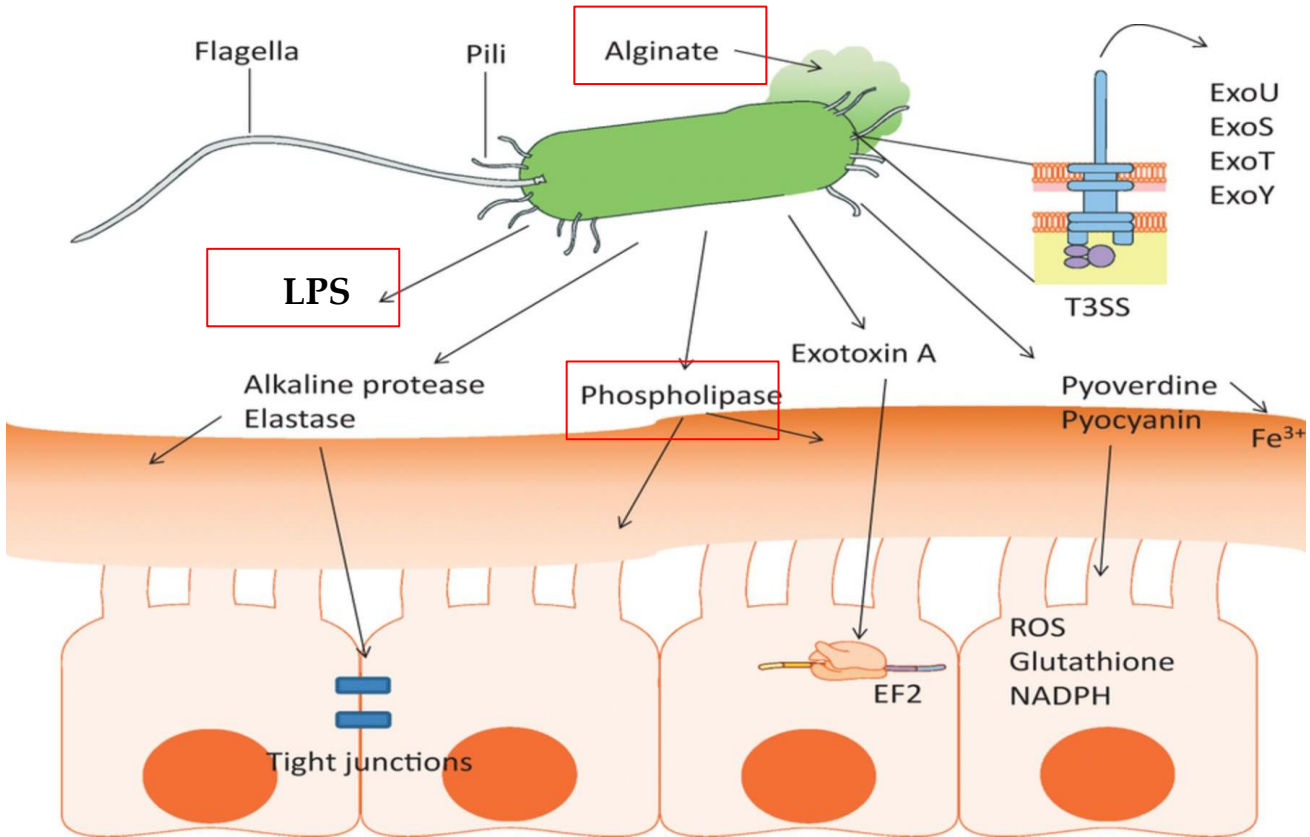
Type 4 pili are important for **biofilm formation** ...



... They form a **capsule composed of polysaccharides of alginate** that gives their colonies a recognizable **mucoid phenotype**. Alginate can also act as an adhesive. **Alginate is one of the main components of the biofilm in the isolates from the lungs** of patients with cystic fibrosis

... Lipopolysaccharide: long side chains of O-antigen responsible for bacterial resistance to serum, detergents and antibiotics

Siderophores, phospolipase C and **enzymes**

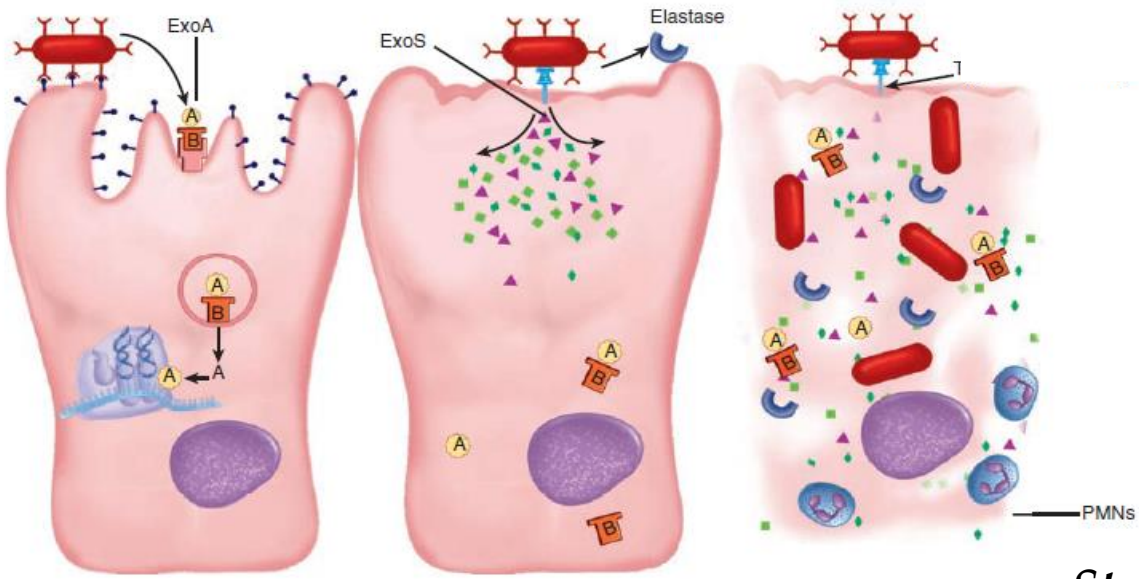


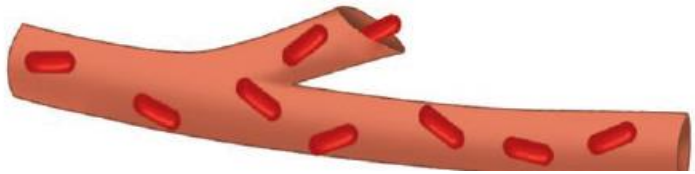
Mechanism of tissue damage

Exotoxin A –induces ADP-ribosalization of EF-2 which is necessary for protein synthesis

Extracellular proteases: elastase and phospholipases

Effector molecules : ExoS: causes rounding of cells; **ExoT**: allows internalization of P. aeruginosa into epithelial cells and macrophages ; **ExoY** has adenyl cyclase activity ; **ExoU** is a phospholipase that often causes lysis of the host cell (associated with severe infections)

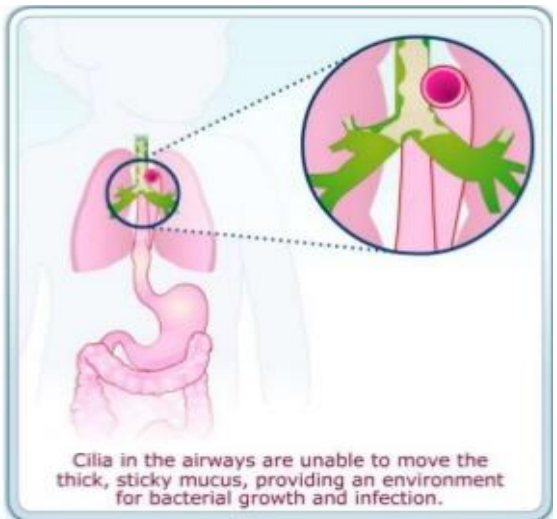


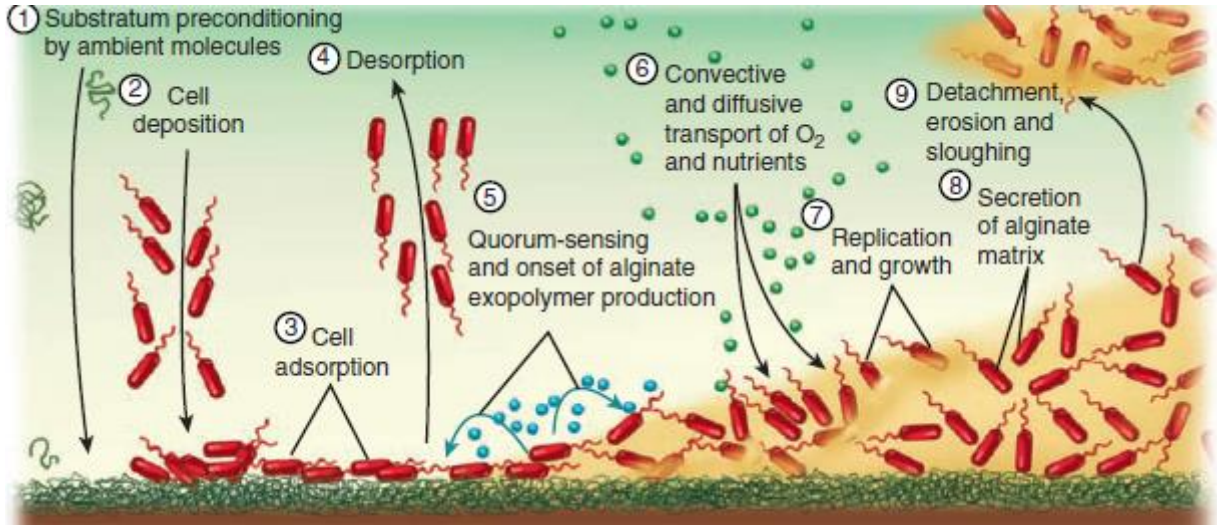


Strains that lack exotoxins and elastase are present locally, in burns and wounds, but fail to disseminate.

Pseudomonas aeruginosa and cystic pulmonary fibrosis

In this disease, ion transport through the respiratory epithelium is disrupted. Dehydration of respiratory secretions is partly responsible for the persistence of the infection, which results in a disorder of the mucociliary system.





Pseudomonas aeruginosa and cystic pulmonary fibrosis

In this disease, ion transport through the respiratory epithelium is disrupted. Dehydration of respiratory secretions is partly responsible for the persistence of the infection, which results in a disorder of the mucociliary system.

On the other hand, *P. aeruginosa* changes its characteristics during chronic lung infection in patients with cystic fibrosis.

The production of alginate increases, which gives the bacteria a mucoid appearance. **A biofilm is formed** that is consisted of bacterial microcolonies and cell debris, anchored in alginate. The strains have altered LPS (modified lipid structure A and impaired O antigen production)

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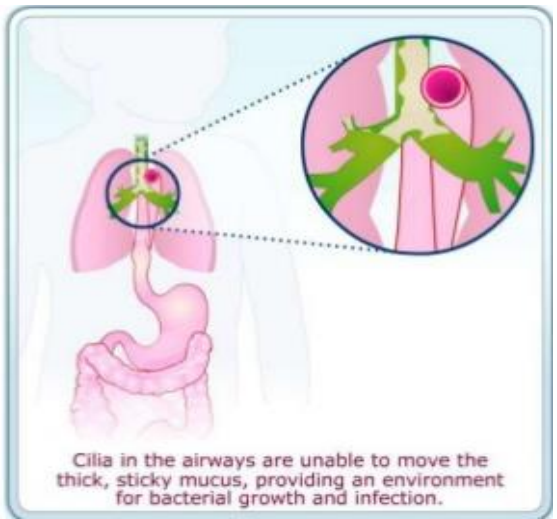
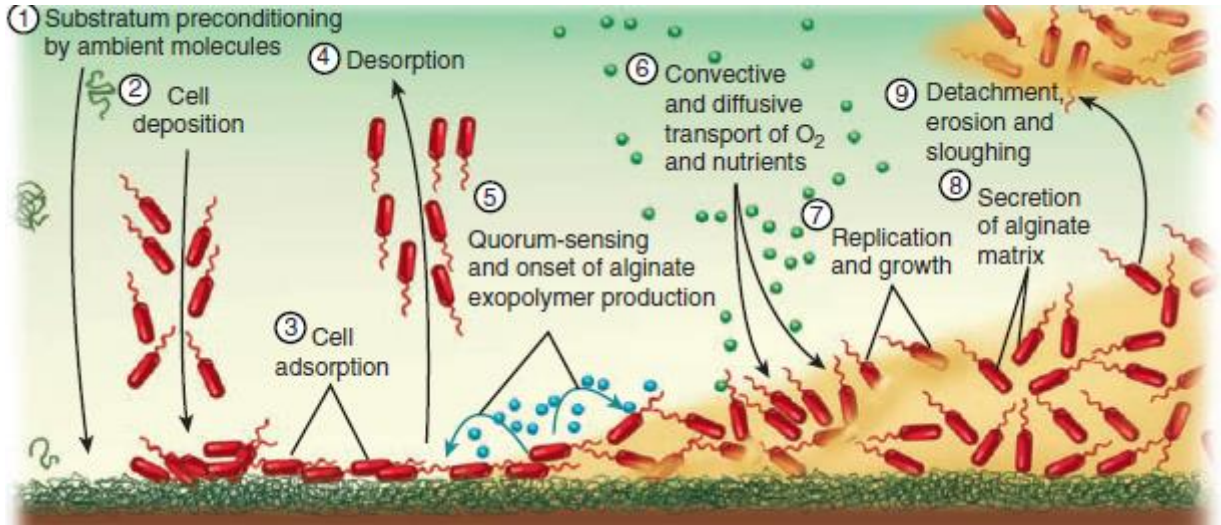




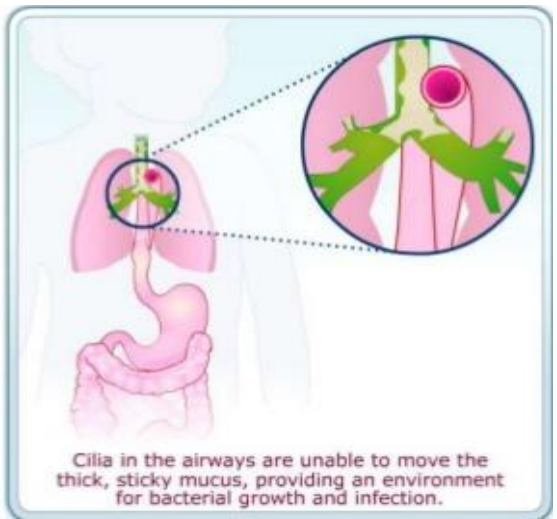
Pseudomonas aeruginosa and cystic pulmonary fibrosis

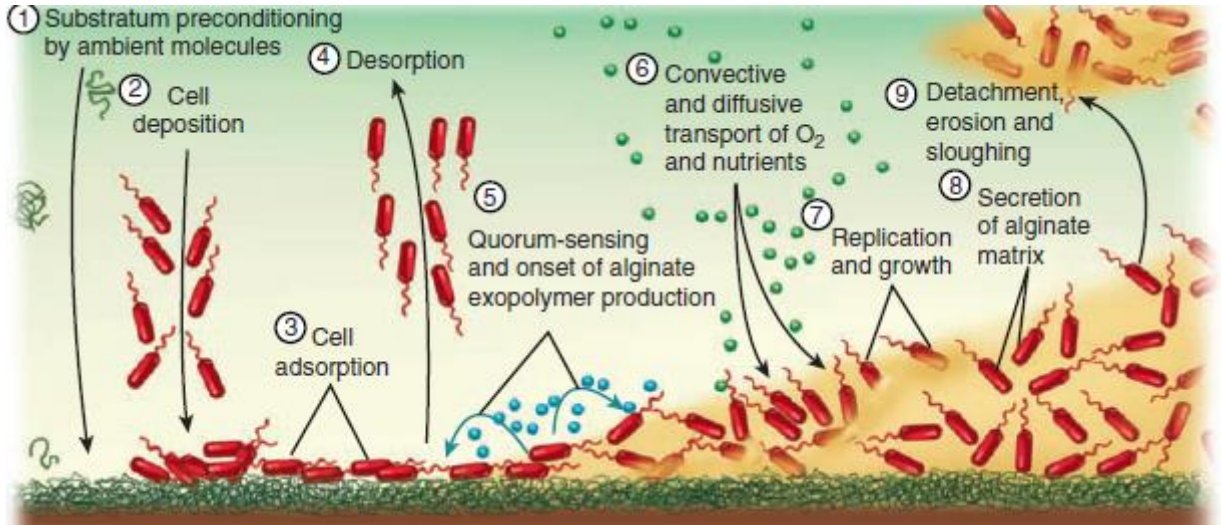
In this disease, ion transport through the respiratory epithelium is disrupted. Dehydration of respiratory secretions is partly responsible for the persistence of the infection, which results in a disorder of the mucociliary system.

On the other hand, *P. aeruginosa* changes its characteristics during chronic lung infection in patients with cystic fibrosis.

The production of alginate increases, which gives the bacteria a mucoid appearance. **A biofilm is formed** that is consisted of bacterial microcolonies and cell debris, anchored in alginate. The strains have altered LPS (modified lipid structure A and impaired O antigen production)

Bacteria that are isolated from the lungs of patients have fewer proteases, toxins and are immobile, which allows them to better hide from the cells of the immune system. This change, in the so-called "**chronic phenotype**", is regulated by a complex mechanism

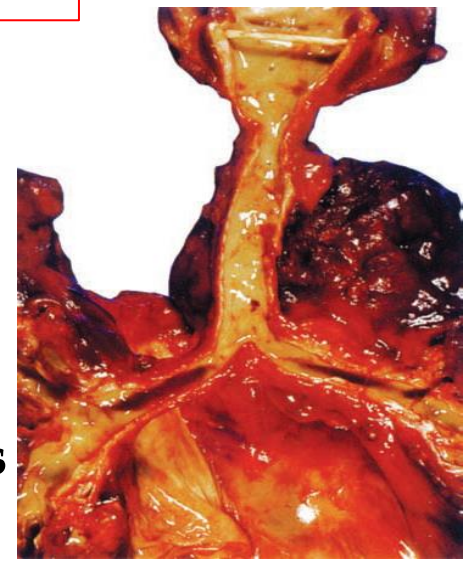




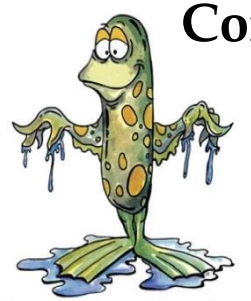
Clinical manifestations

Opportunistic infections anywhere
infections of burns, wounds, urinary system, skin, eyes, ears and respiratory infections

Complicates the outcome of cystic fibrosis of the lungs

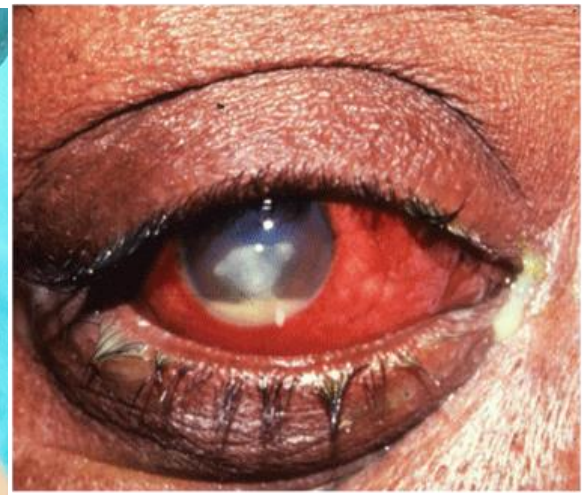


Cystic fibrosis of the lungs



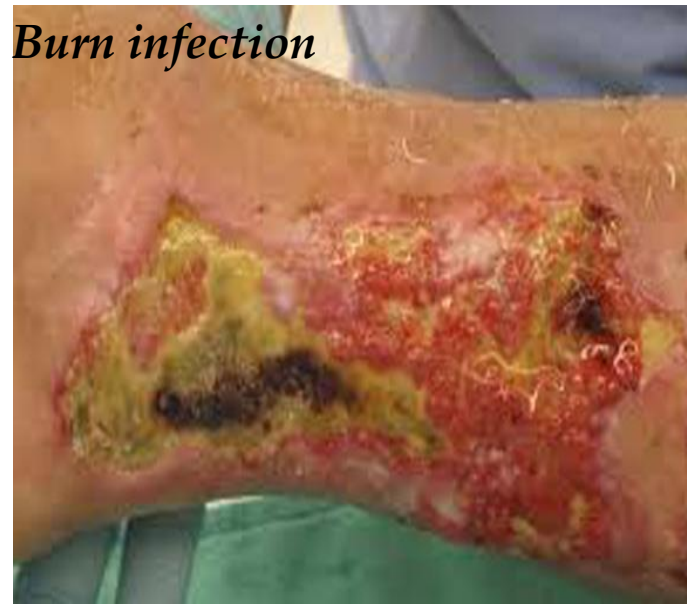
Pseudomonas aeruginosa

"The swimmer's ear"

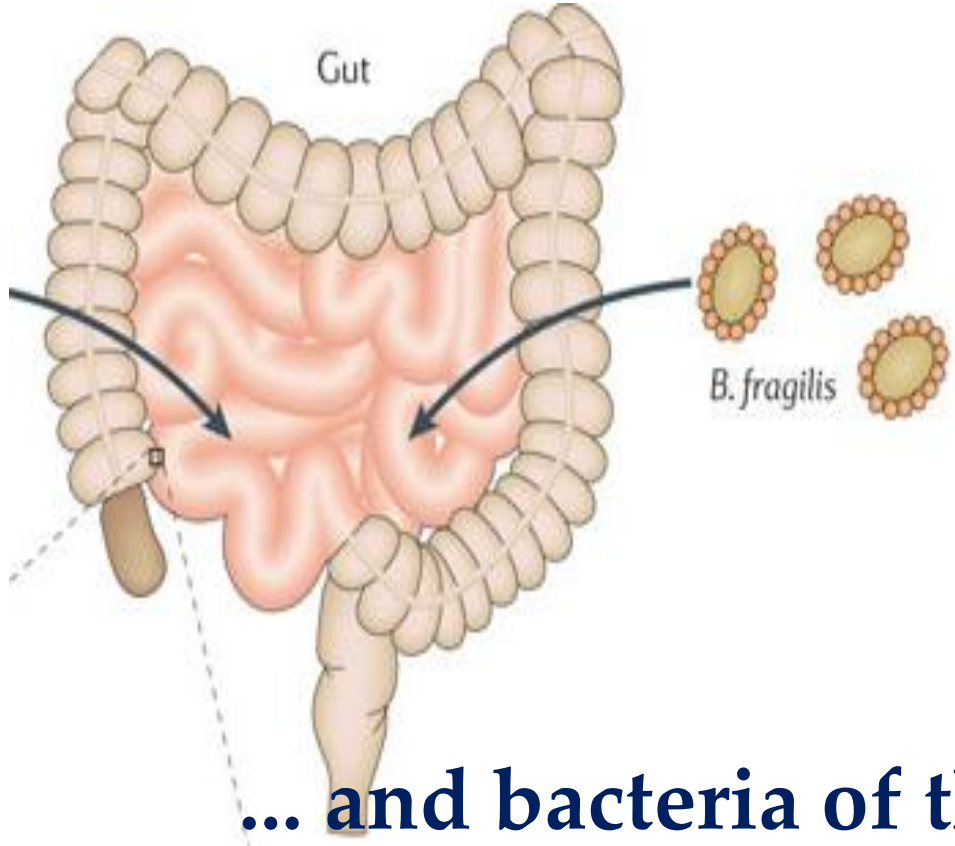


Microbial keratitis (MK) caused by *Pseudomonas aeruginosa*. Note the large central ulcer, hypopyon, gross hyperemia and mucopurulence.

Burn infection



Intraabdominal infections...



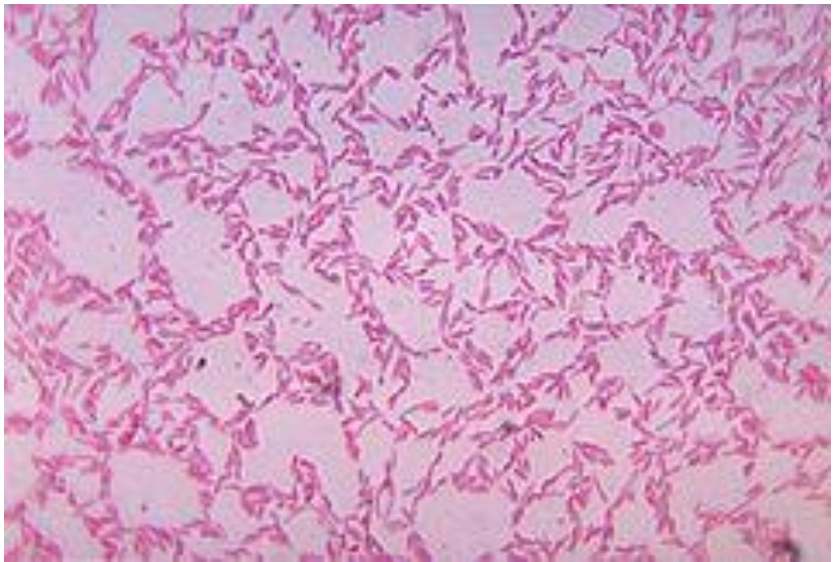
... and bacteria of the genus *Bacteroidales*

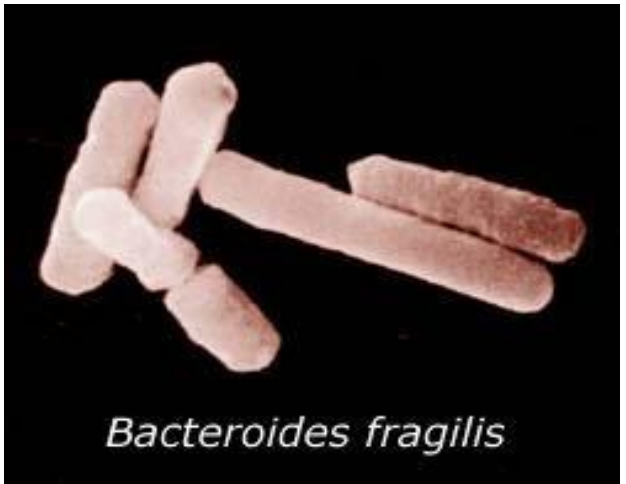
General characteristics

Bacteria from the order *Bacteroidales* - the most numerous Gram-bacteria in the large intestine.

They have **enzymes** that allow them to take and process undigested carbohydrates from the intestinal contents, which they then use as a source of energy for their metabolism.

... They are mostly commensals, while there are only a few species of the order *Bacteroidales* capable of surviving outside the colon, and represent a possible cause of opportunistic infections.

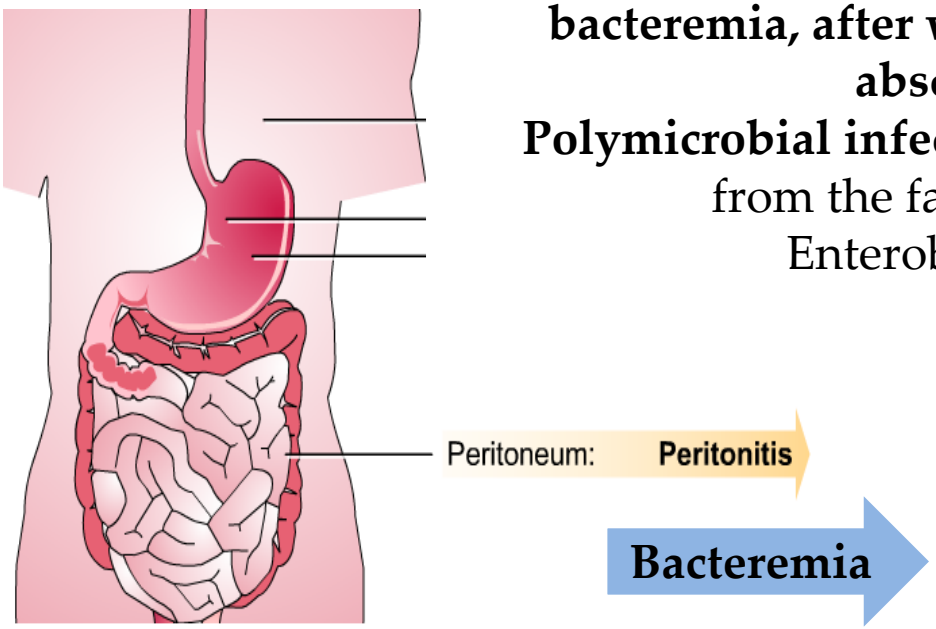




Epidemiology

<u>They cause opportunistic infections,</u> and occur due to the colonization of the peritoneum (after injury, rupture of the appendix and intestinal diverticula) or as a consequence of complications of surgical interventions in the abdomen.

Infections caused by bacteria of the order *Bacteroidales* occur after the penetration of bacteria from the intestine into the peritoneal cavity, so the **first manifestations are peritonitis and bacteremia, after which an intra-abdominal abscess is most often formed**. **Polymicrobial infections** (most often bacteria from the families Bacteroidaceae and Enterobacteriacea) **usually occur**.



Bacteroides fragilis

The most common causes of intra-abdominal infections and abscesses

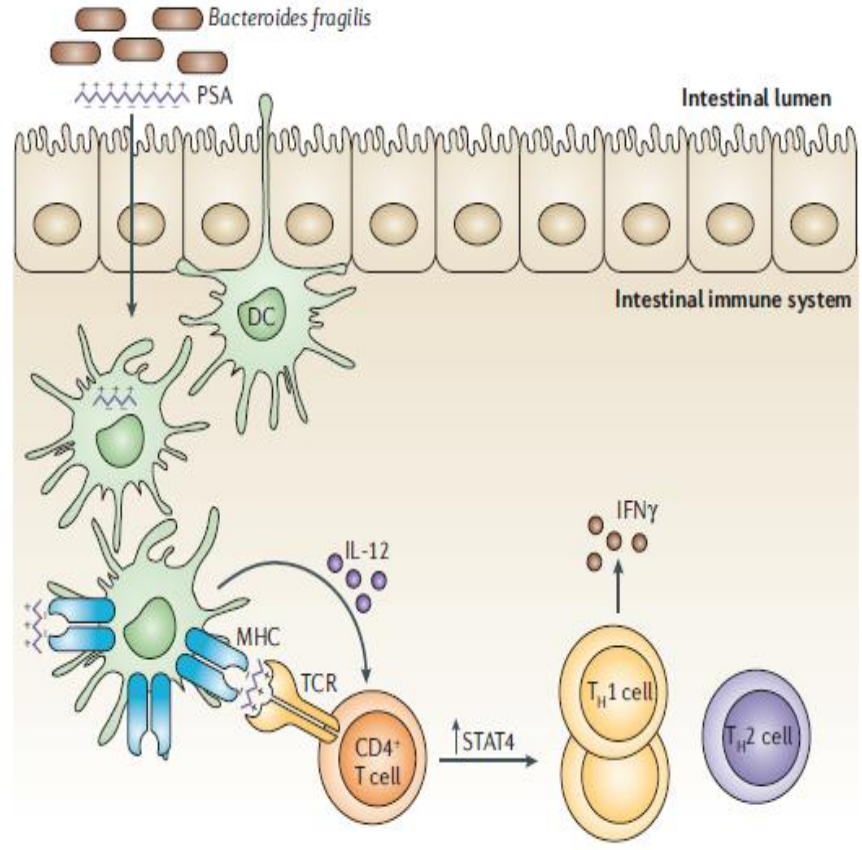
The aerotolerant bacterium survives in the peritoneal cavity, in the presence of oxygen because it possesses the enzymes **superoxide dismutase** (decomposes oxygen radicals) and **catalase** (decomposes hydrogen peroxide).

The toxic lipid A component of lipopolysaccharide is **less endotoxic compared to E. coli.**

Possibility of polysaccharide capsule synthesis

***Polysaccharide A* (PSA) is crucial in triggering an immune response (mediated by CD4 + T lymphocytes) and in the formation of abscesses**

Polysaccharide antigens are important for bacterial adhesion to the peritoneal mesothelium and for resistance to complement system proteins



Pathogenesis of infection

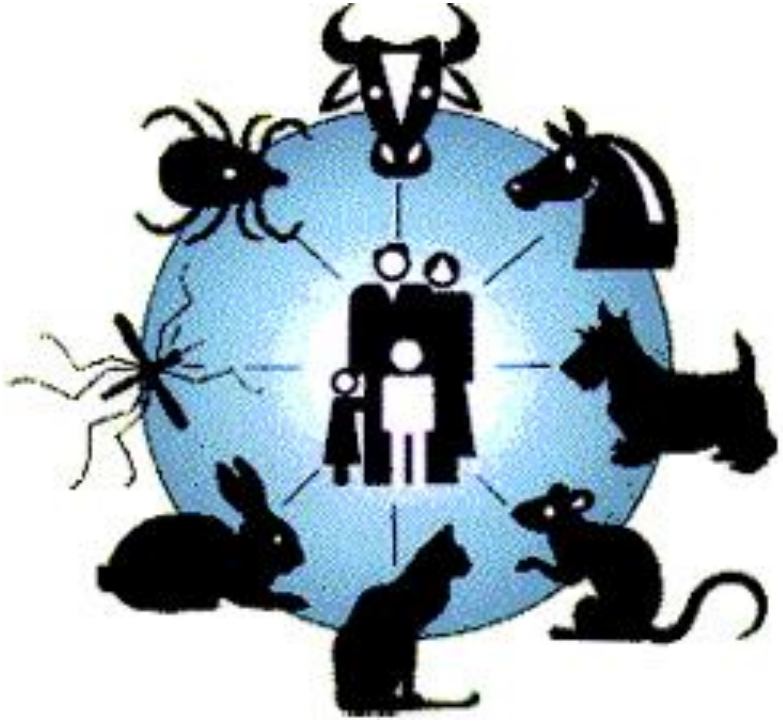
Most bacteria are drained by lymph vessels, while other bacteria are phagocytosed by peritoneal macrophages and neutrophils.

If the immune system fails to eliminate the bacteria, an abscess will form.

The penetration of bacteria into the peritoneal cavity causes **increased vascular permeability** and plasma release or **fibrin deposition**. Bacteria that bind to the peritoneum become "trapped" in the fibrin matrix. An **abscess forms**, bordered by a thin fibrin capsule rich in collagen.

Complications: intra-abdominal abscesses are dangerous due to the possible spread of the infection to the surrounding tissue or due to the possibility of bacteremia, their **metastatic spread** to distant organs and the possibility of developing **septic shock**.

Zoonoses

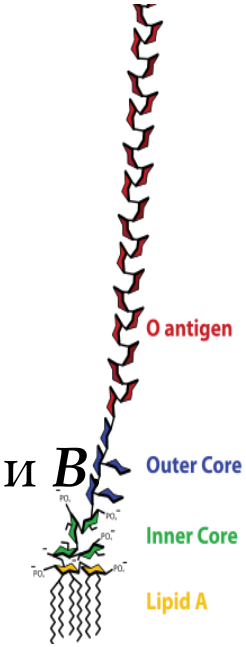


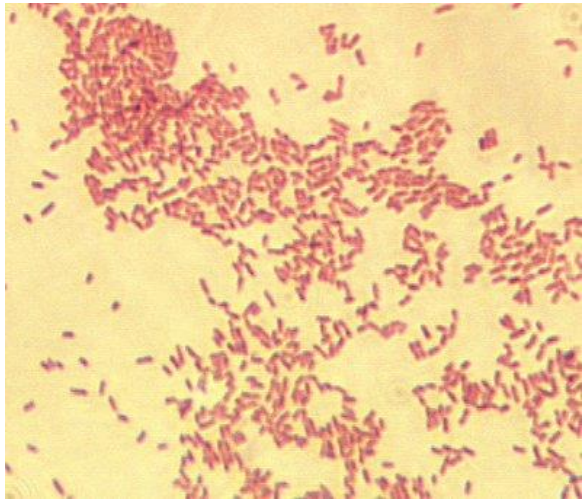
Brucellosis

Leptospirosis

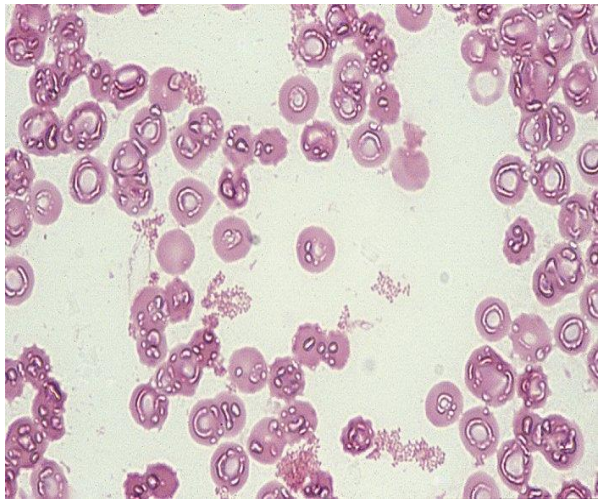
Brucella spp.
-general characteristics-

- *Brucellae* are Gram-negative cocobacilli or short bacilli
- It contains a **lipopolysaccharide** whose O-specific polysaccharide chain contains two main epitopes (A and M).
- The most important types: ***B. abortus, B. melitensis, B. canis*** и ***B. suis***.
- They grow slowly under aerobic conditions

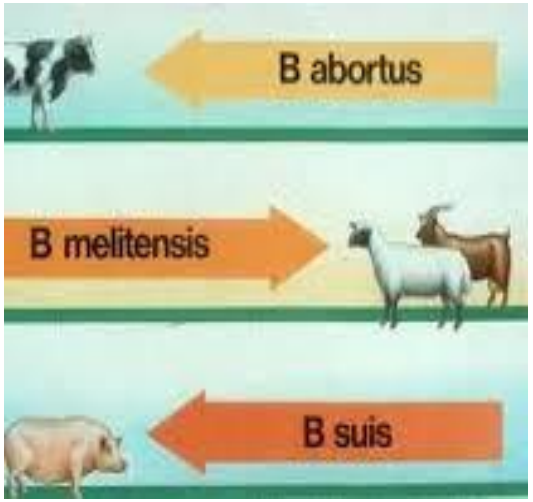




From culture

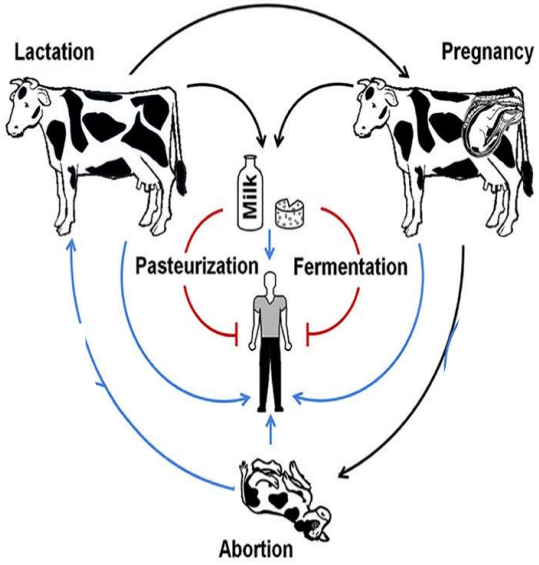


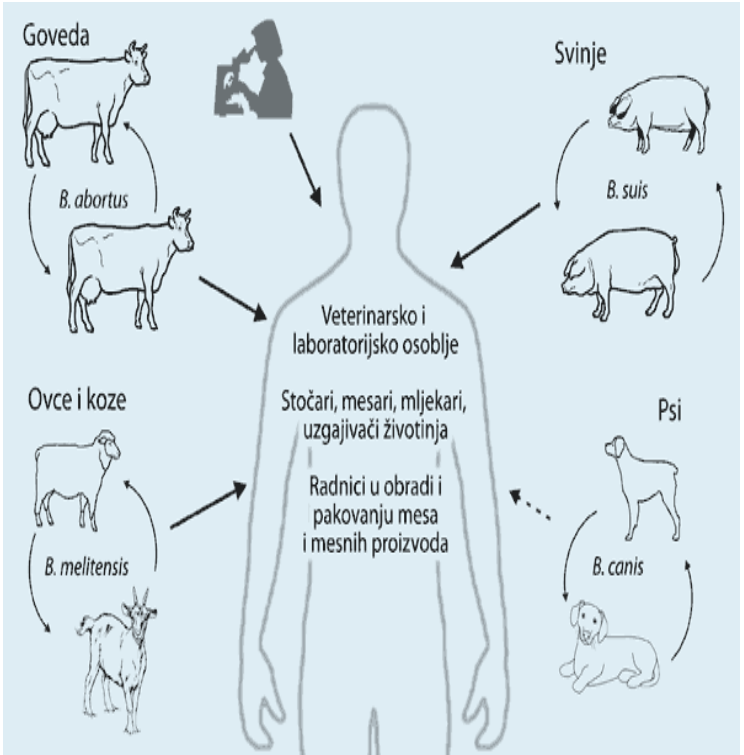
from blood culture

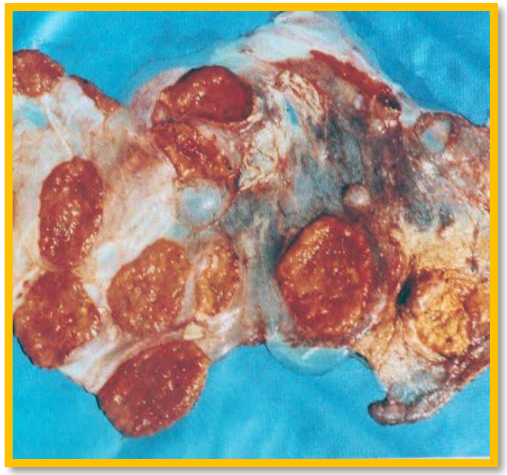


Brucellosis -epidemiology

- **Brucellosis** is typical zoonoses
- **In animals,** brucellosis is a genitourinary infection. *Brucellae* cause chronic infection of the mammary glands, uterus and placenta.
- **In humans,** brucellosis is a chronic disease characterized by fever, night sweats and weight loss over a period of weeks and months.

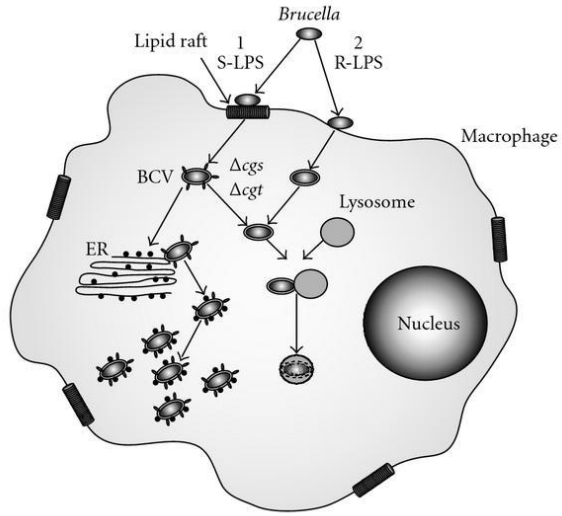






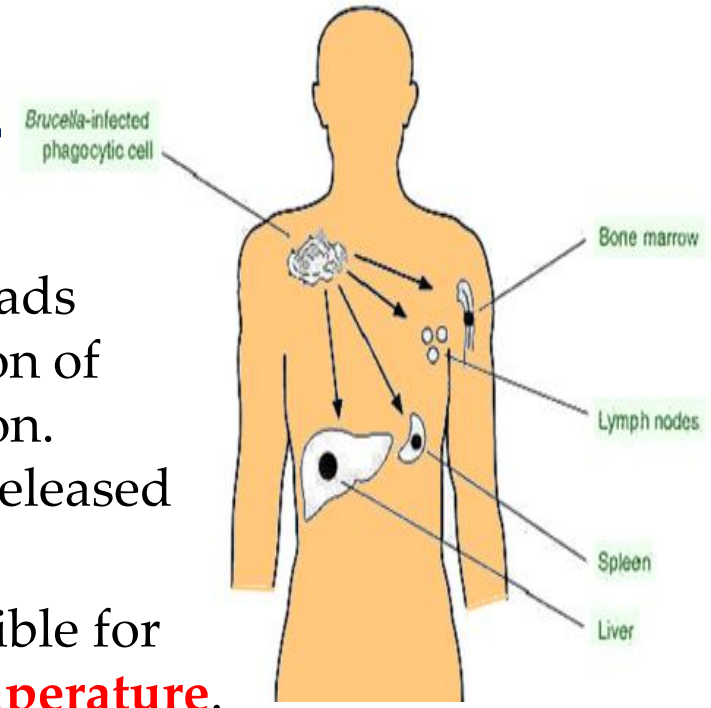
In animals, **erythriol** is present in the placenta and fetal membrane and significantly stimulates growth of ***Brucella*,** which is why in pregnant animals the infection is localized in this place and is accompanied by abortion. **Human placenta does not contain erythriol.**

Brucellae are **facultative intracellular bacteria** that infect **epithelial cells and cells of the mononuclear-phagocytic system** ...

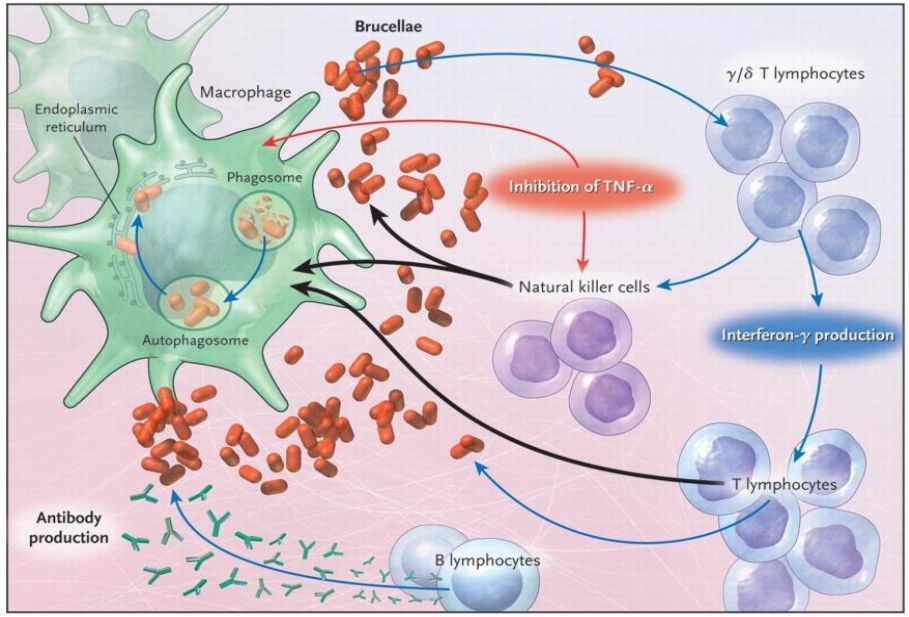


... **They survive within macrophages** by suppressing myeloperoxidase, inhibiting phagosome and lysosome fusion, and disrupting cytokine production.

Brucellosis
-pathogenesis-



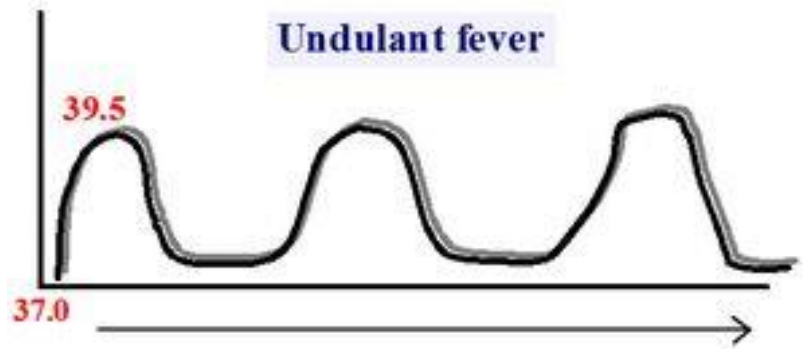
- If the local infection is uncontrolled, it spreads further and is accompanied by the formation of **small granulomas** at the site of reproduction. *Brucella*, and from there these bacteria are released into the systemic circulation.
- Episodes of bacteremia are mainly responsible for **recurrent shivering and a rise in body temperature**.



For infection control and elimination *Brucella* from macrophages is responsible T-cell immune response, and especially helper T lymphocytes that produce TNF-α, TNF-β, IL-1 and IL-2.

Brucellosis
-clinical manifestations-

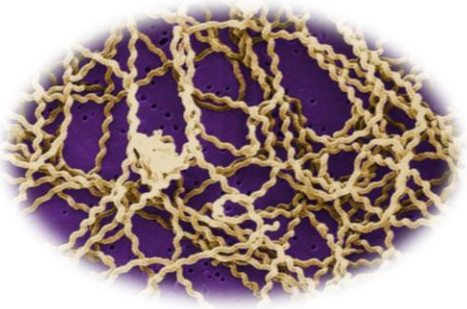
- **Brucellosis (*Bang* disease, *Febris undulens* - undulant fever, Maltese fever, Mediterranean relapsing fever...)**
- Periodic night fever (undulant fever) lasts for weeks, months, and even from the 1st to the 2nd year. Sweating, lymphadenopathy and hepatosplenomegaly are present. In the case of prolonged brucellosis, weight loss also occurs
- Occasionally, a localized infection develops in the lungs, bones, brain, heart, or genitourinary system.



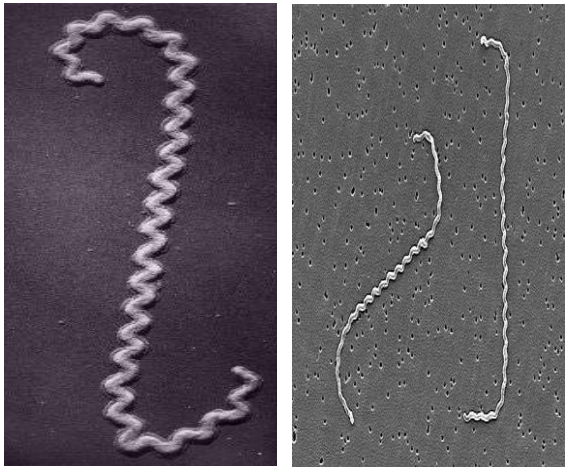
Prevention and treatment of brucellosis

- ✓ Prevention includes control and immunization of animals: live vaccine, attenuated *B. abortus* и *B. melitensis*
- ✓ Prevention of laboratory infections
- ✓ **Tetracyclines** are primarily used in the treatment of brucellosis. **Streptomycin**, **gentamicin** and **rifampin** are also used in severe diseases.

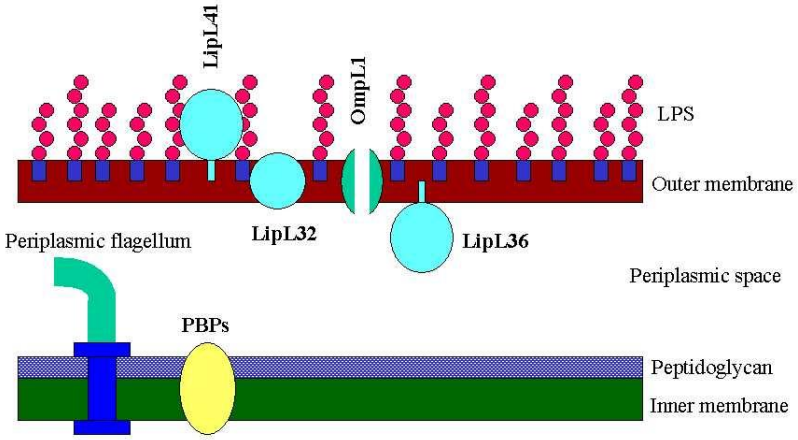
Leptospira spp.
- general characteristics-



- *Leptospirae* are **Gram-negative spiral bacilli.**
- Genus *Leptospira* includes two species...



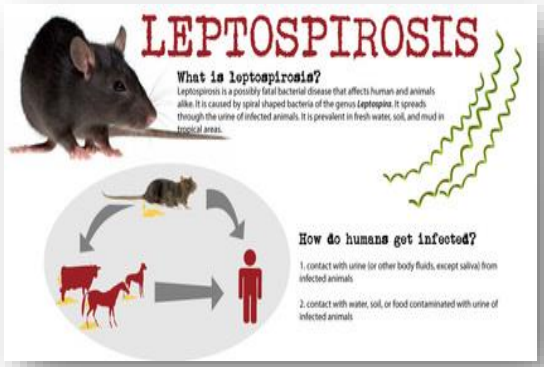
...***L. interrogans*** (pathogenic species)
L. biflexa (saprophytic species)

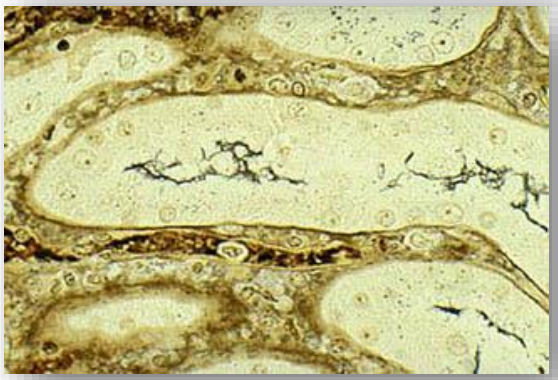


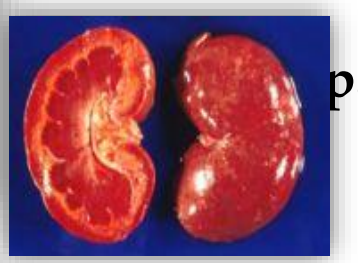
- **<u>They are sensitive to</u>**.

... drying
... extreme pH values (stomach acid)
... action of natural antibiotics
... low chlorine concentration
... temperature 40-60°C.

Leptospirosis
-epidemiology-







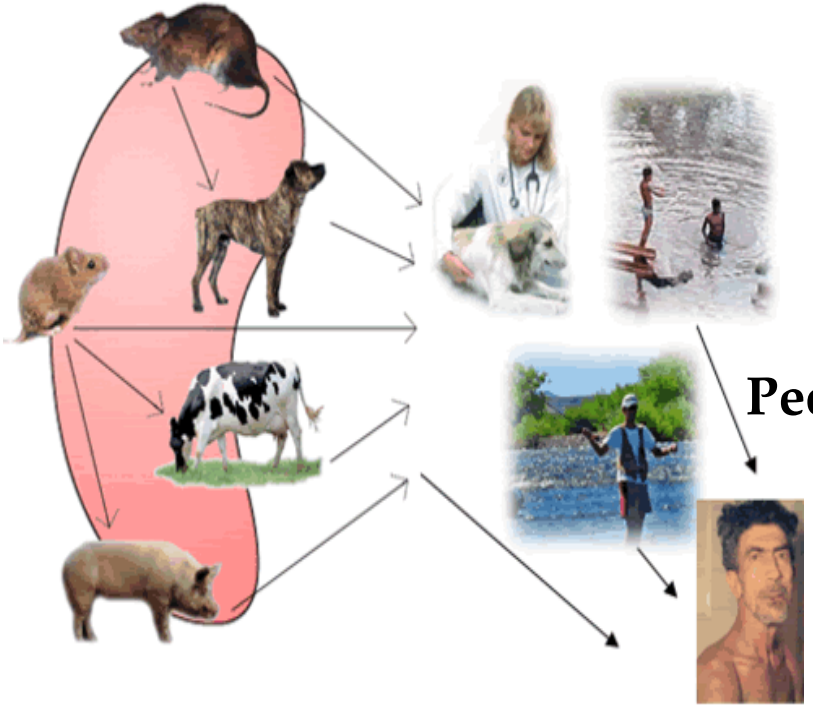
zoonoses

pathogenic leptospira: renal tubules of infected animals

urinary excretion

water and soil contamination

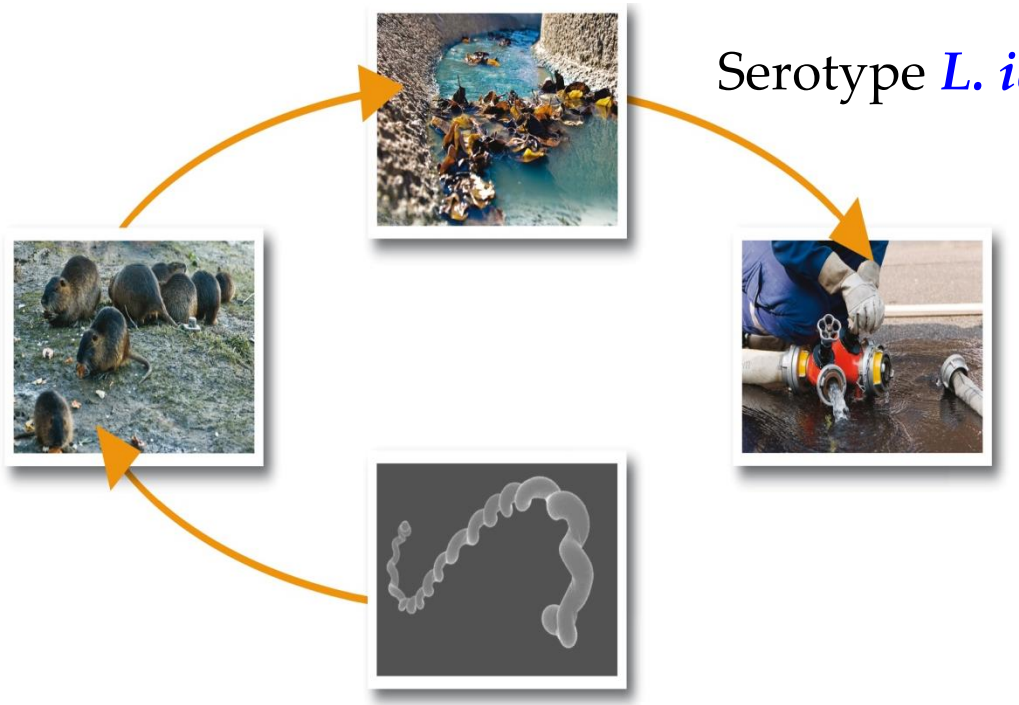
direct contact with urine or tissues of infected animals, water contaminated with urine of infected animals



Butchers, veterinary surgeons and animal breeders, as well as hunters and pet owners who are in direct contact with infected animals, are **professionally** affected by leptospirosis.

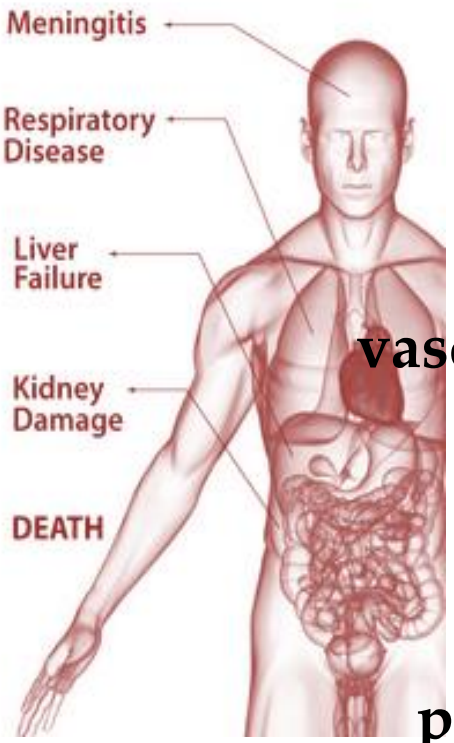
People can also become infected while working in stagnant and canal waters that are contaminated with leptospira.

Interhuman transmission is extremely rare.



Serotype ***L. icterohaemoragica*** often causes ***Well-ову disease*** , one of the most severe leptospirosis.

Leptospirosis
-pathogenesis-



Leptospires enter the body through small lesions on the skin, mucous membranes (conjunctiva)

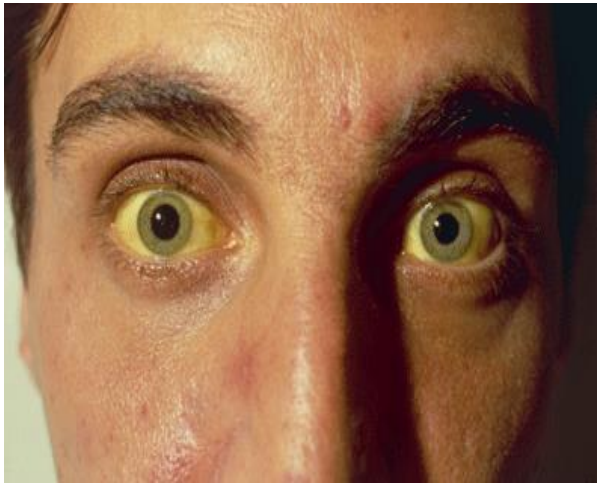
hematogenous dissemination

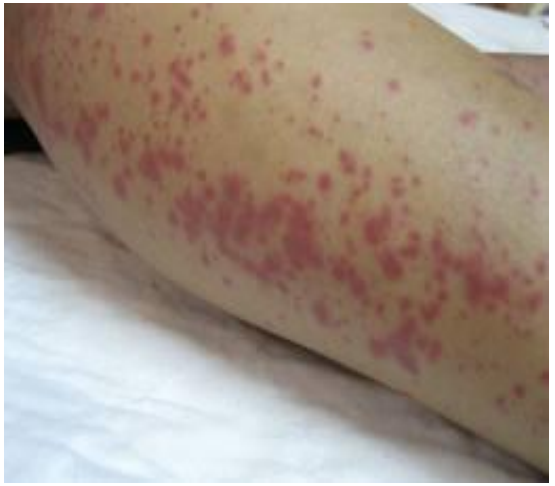
vasculitis and damage to the endothelium of small blood vessels

possible consequences: renal tubular necrosis, hepatocellular damage, meningitis, myositis, jaundice, bleeding

Leptospirosis
-clinical manifestations-

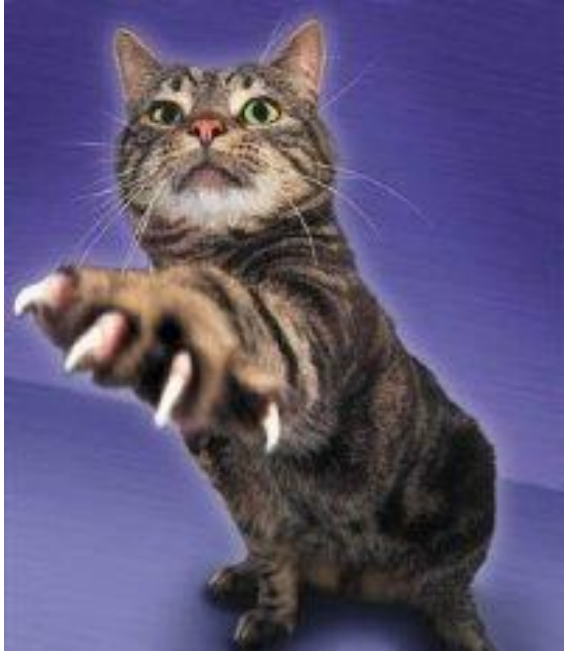
Leptospirosis may occur as a mild subclinical infection. Mild forms of leptospirosis are described as **anicteric leptospirosis.**





Severe forms are described as **icteric leptospirosis**. There is a difference between the bacteremia phase and the immune phase, which is characterized by the production of antibodies and the temporary disappearance of leptospira from the blood.

Severe icteric form of the disease **(*Weil* disease)**

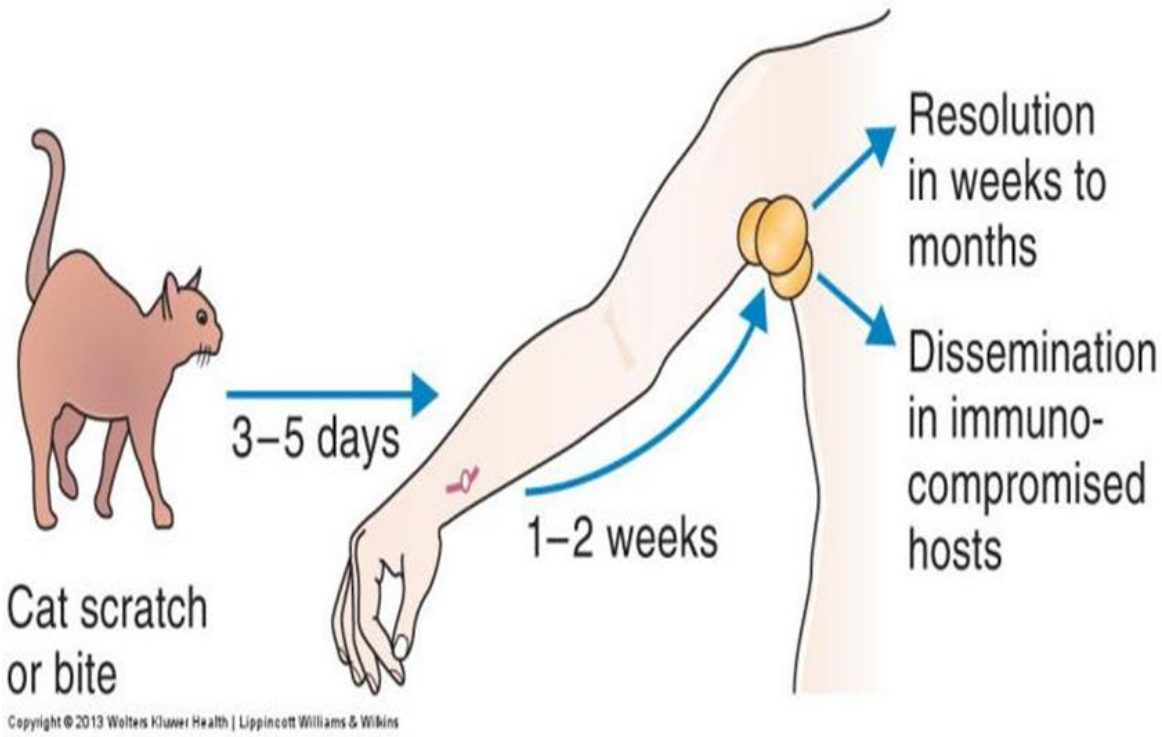


Cat Scratch Disease and Bacillary angiomatosis

Bartonella henselae

Bartonella henselae

It affects young adults and children (85% are under age 18) following a scratch or bite by a cat, which was infected by the microorganism *Bartonella henselae*



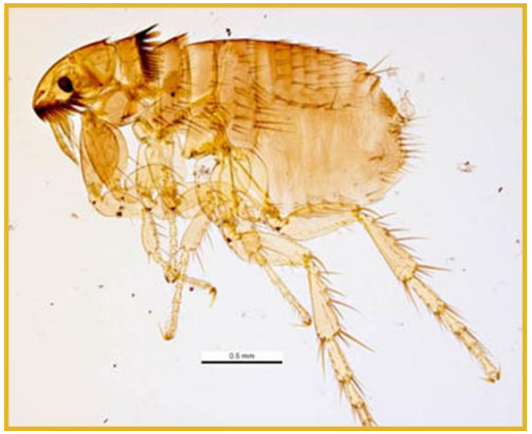
In immunocompetent people, *B. henselae* causes cat scratch disease, a mild to severe, self-limiting infection.

Immunocompromised individuals can develop *Bacillary angiomatosis*

Transmission

Transmission in Animals

- Vector-borne
- Cat flea (Ctenocephalides felis)
- Flea feces



Ctenocephalides felis

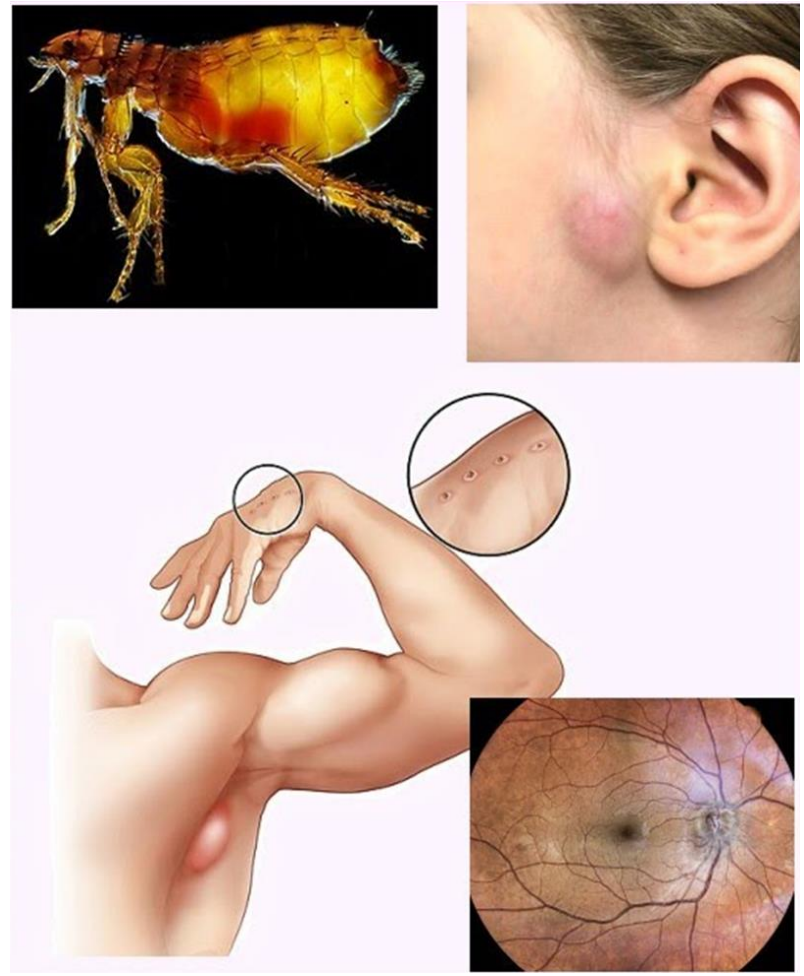
Transmission to humans

- Not well understood
- Patient history usually includes:
  - Cat scratch
  - Cat bite
  - Being licked by cats

It is possible that the source of infection is cat claws or teeth contaminated by flea feces.

Cat Scratch Disease

- Usually mild, self-limiting
  - Immunocompetent people
- Initial skin rash - consists of one or more small erythematous papules, pustules, macules, vesicles or ulcers at the site of inoculation.
- Lymph node enlargement- One to four weeks later, one or more lymph nodes become enlarged. The affected lymph nodes are usually painful or tender, and the skin over the nodes is warm. Occasionally, the nodes may suppurate. The lymphadenopathy usually lasts for a few weeks to a few months.
- Fever, malaise, fatigue

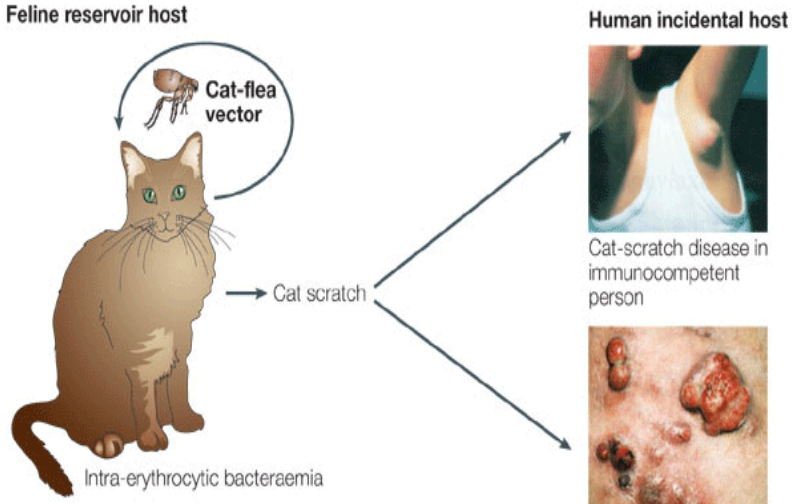


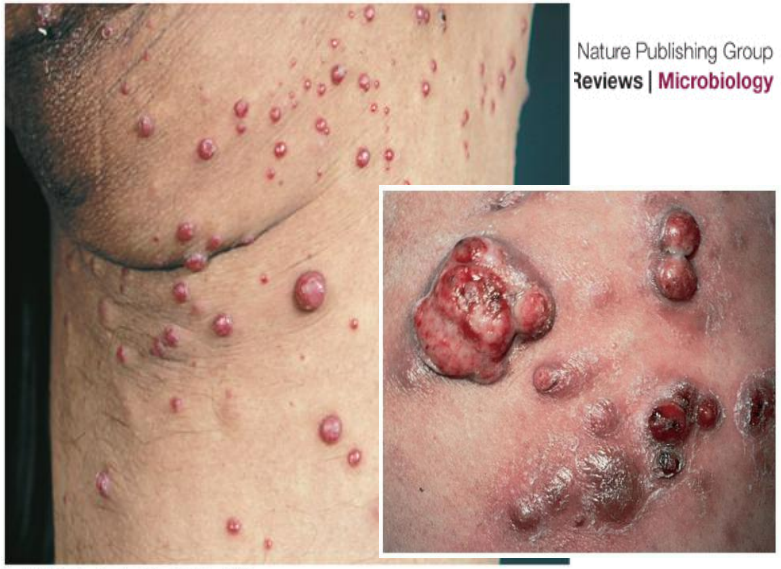
Bacillary angiomatosis

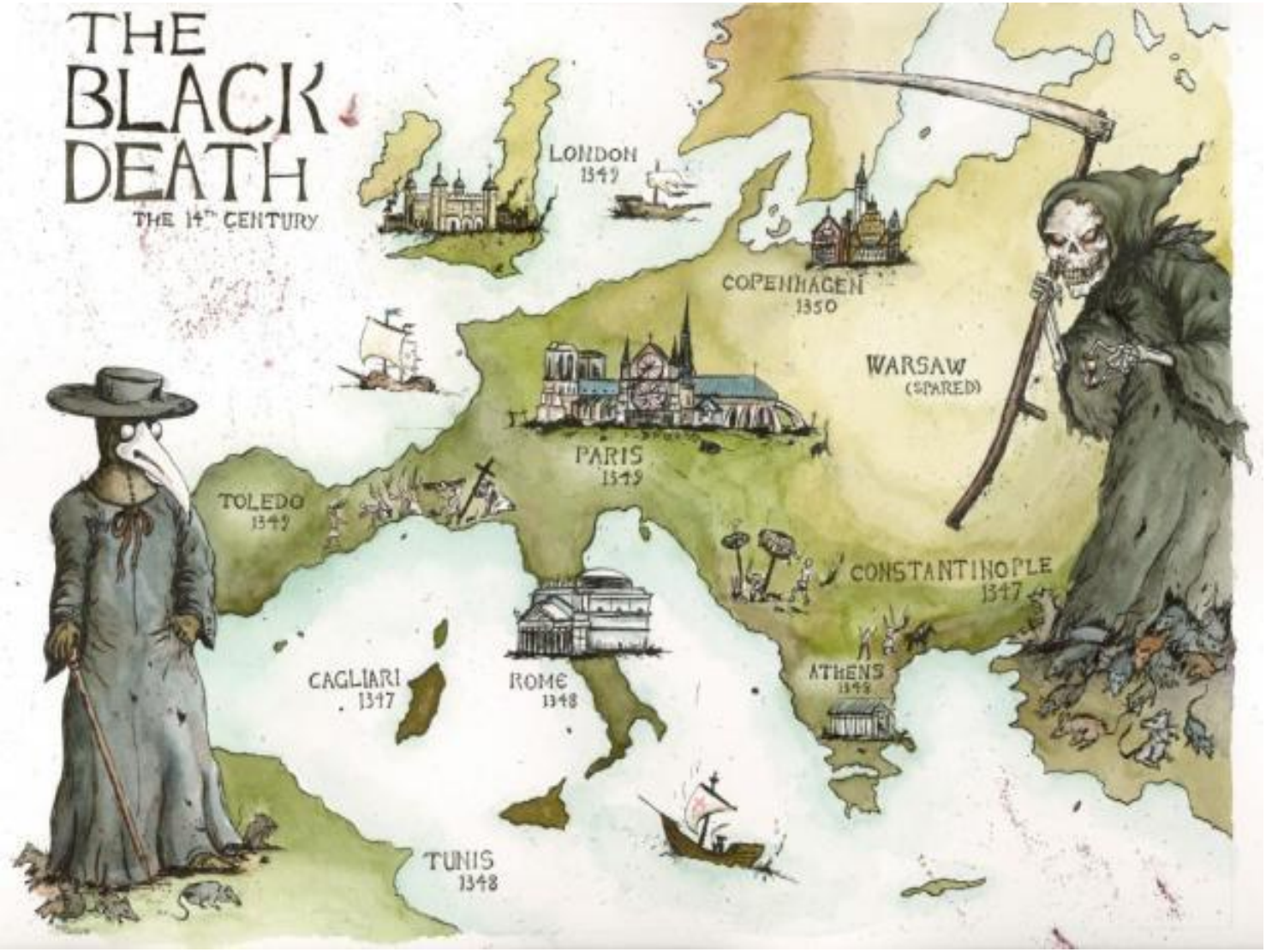
- **Vascular proliferative disease** of skin and/or internal organs
- Usually an **AIDS-related disease**
- **Bacteria** produce substances that stimulate the **production of cytokines,** which results in the **proliferation of small blood vessels**

Symptoms:

- one to hundreds of **cutaneous papules** and nodules.
- They are up to 10 cm in diameter. Subcutaneous nodules resembling a common abscess may also be seen.
- Bacillary angiomatosis can involve the internal organs, including the **heart, brain, liver, spleen, larynx, lymph nodes and gastrointestinal tract**

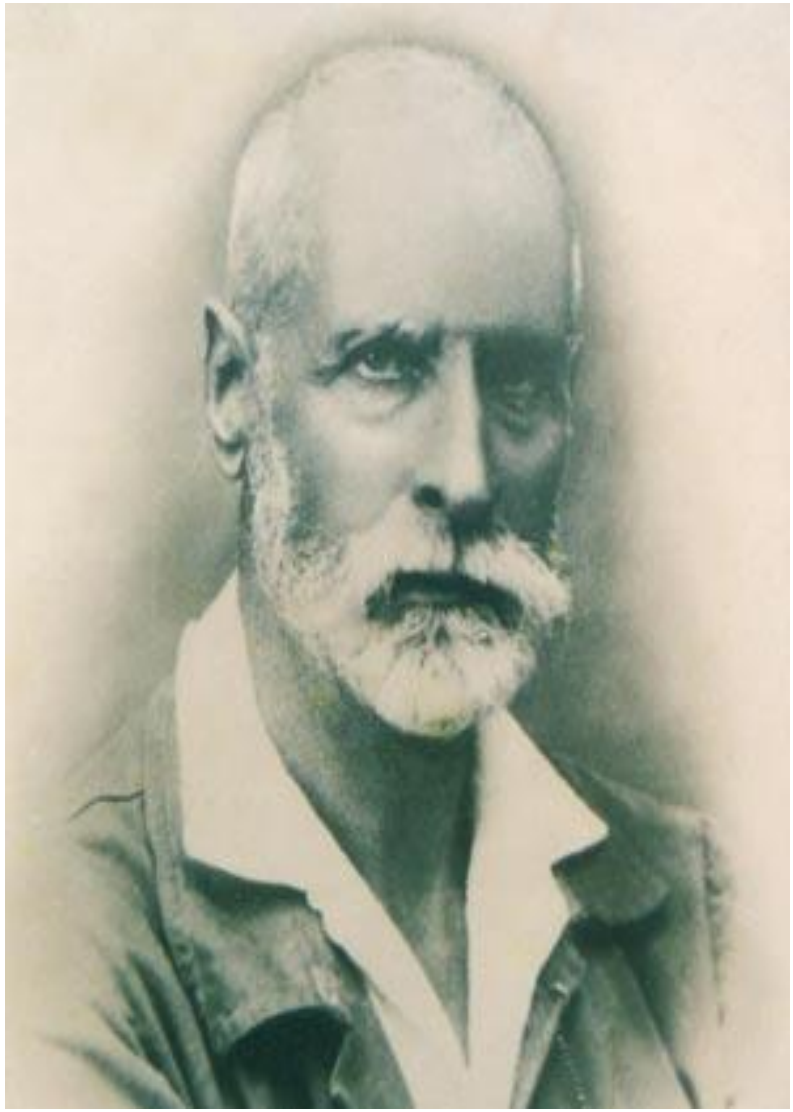






In the fourteenth century, a terrible catastrophe fell upon Asia, Europe the Middle East, and North Africa that would change the course of history- the **Black Death**

Yersinia pestis

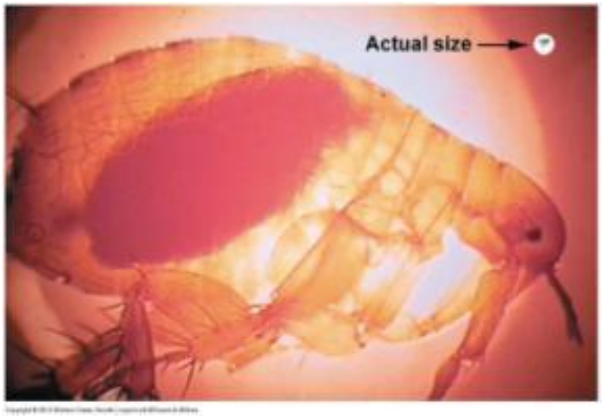


Alexander Yersin
(1863-1943)

- **Discovered the cause of the plague**
- **Yersinia pestis discovered in 1894 in Hong Kong**

Plague

- Plague is an infectious disease that affects people and animals.
- Plague is an infectious disease caused by the bacteria Yersinia pestis, a zoonotic bacteria, usually found in small mammals and their fleas. It is transmitted between animals through fleas. Humans can be infected through:
- the bite of infected vector fleas
- unprotected contact with infectious bodily fluids or contaminated materials
- the inhalation of respiratory droplets from a patient with pneumonic plague.

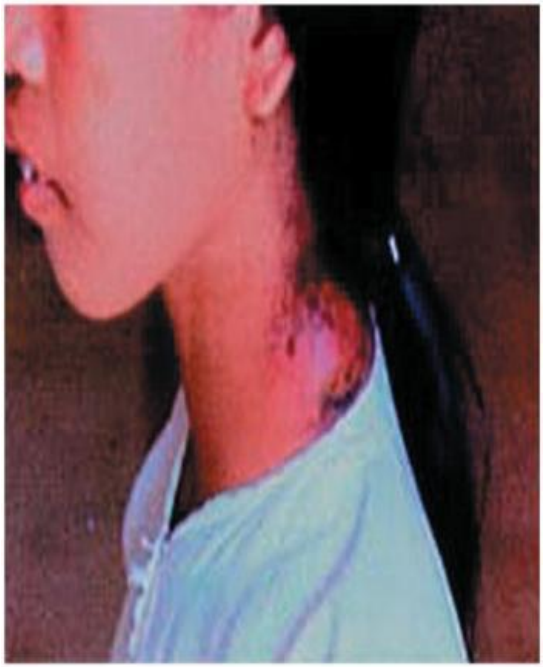


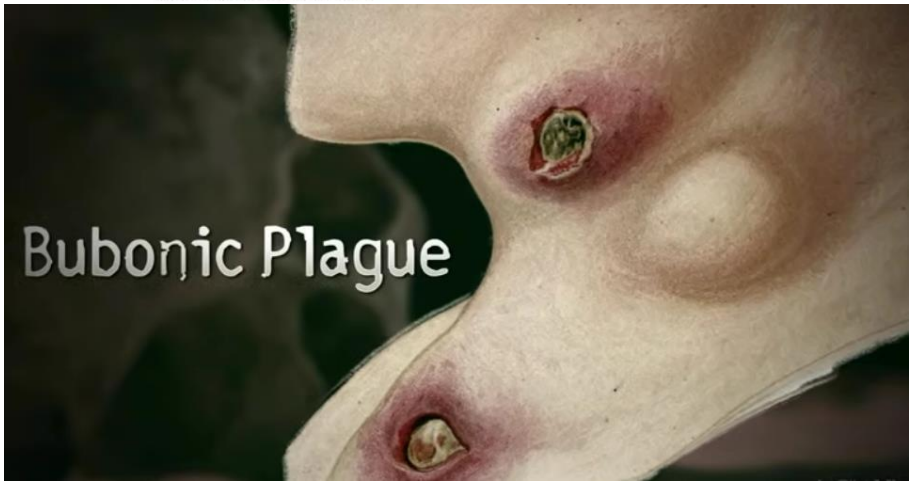
Xenopsylla cheopis

Pathogenesis:

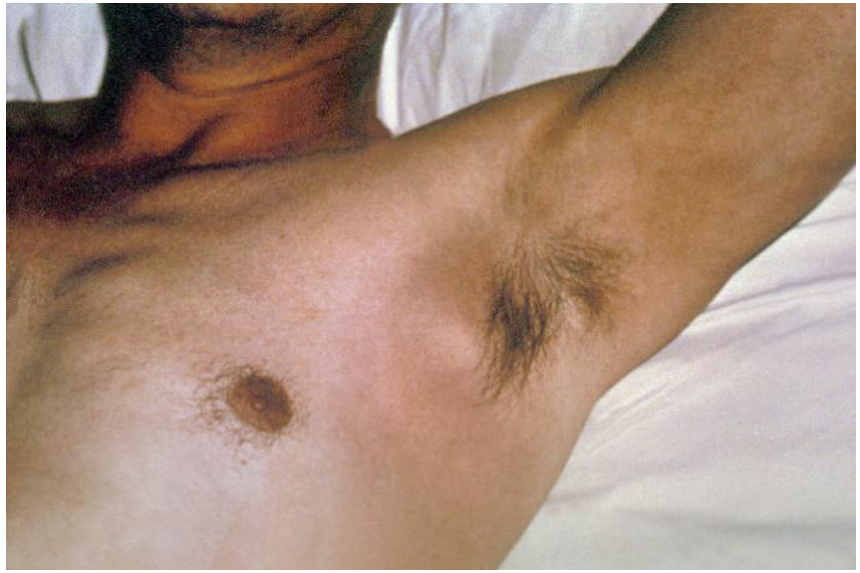
After the bite, the inoculated bacteria migrate to the **lymph nodes**, where they multiply in **mononuclear cells**. After an incubation period of 2 to 8 days from a flea bite, fever develops, and painful swelling of the lymph nodes, called buboes, is the most important characteristic of bubonic plague.

Buboes are usually found in the groin, axilla, or cervical lymph nodes..

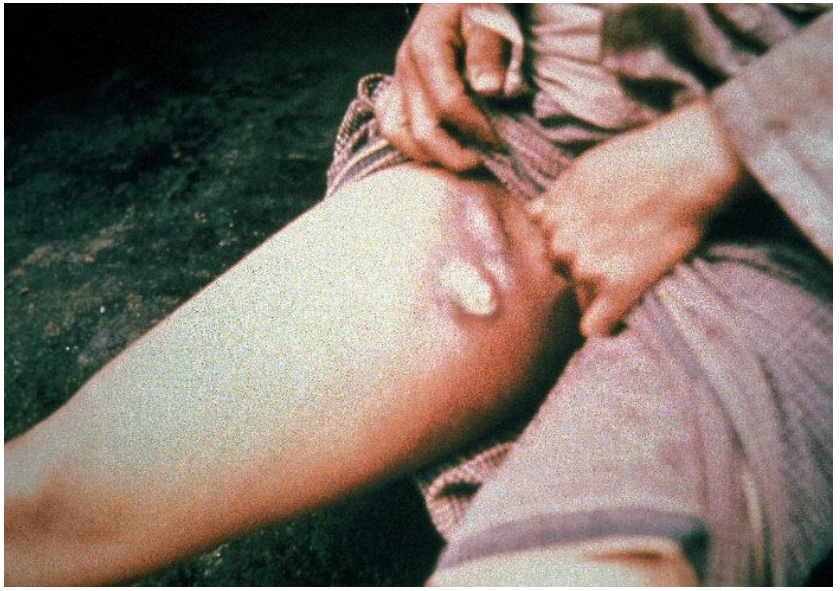




Bubonic plague



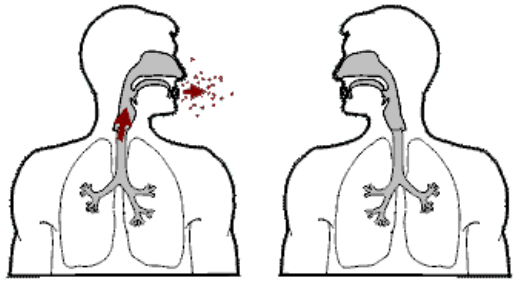
- enlarged lymph glands in the armpit area -



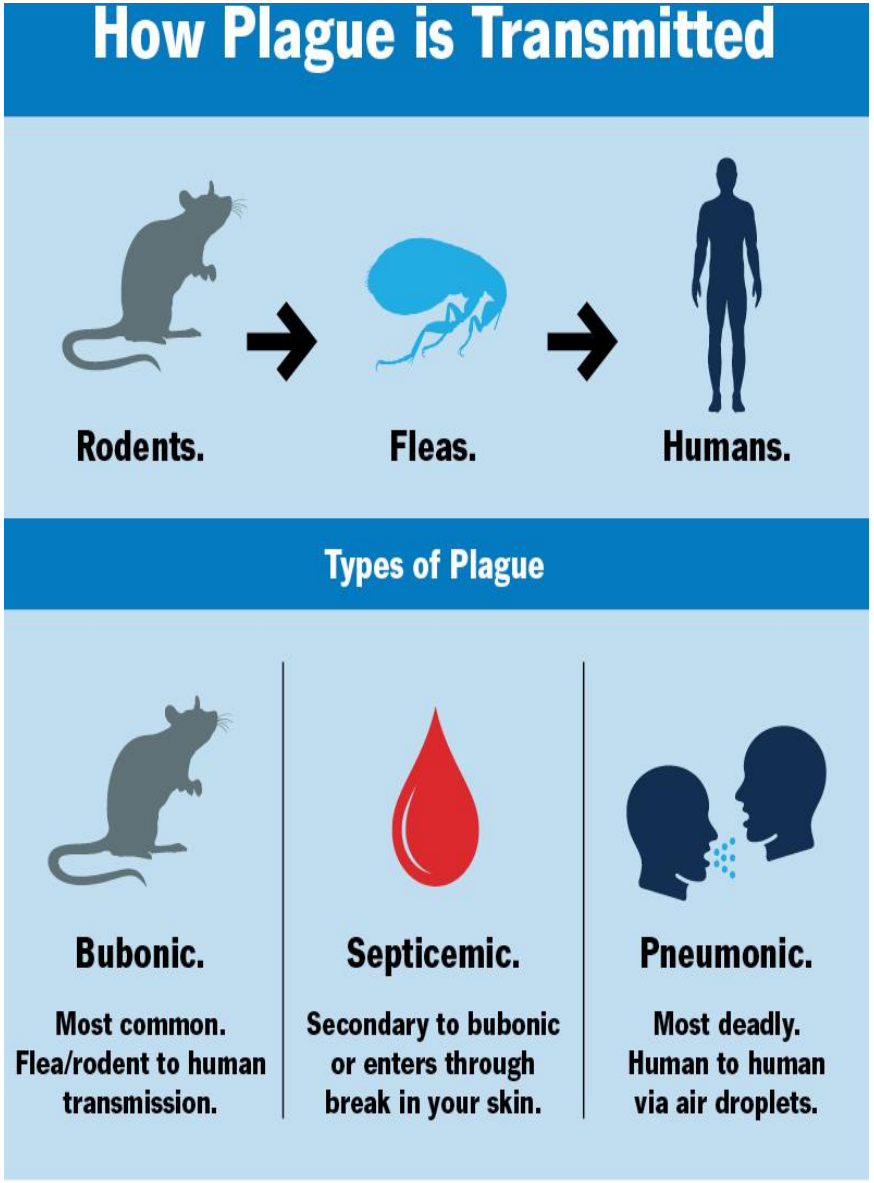
- enlarged lymph glands in the groin area-

... Pneumonic plague can be primary or secondary.

Primary pneumonic plague - after inhalation of plague bacilli

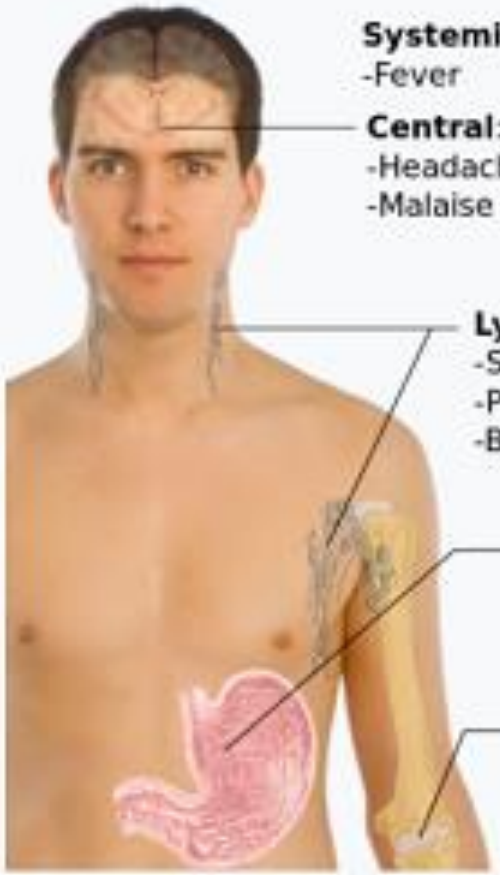


Secondary pneumonic plague - due to hematogenous spread of Y. pestis in the case of untreated forms of bubonic or septicemic plague..



Symptoms of

Bubonic plague



Systemic:
-Fever

Central:
-Headache
-Malaise

Lymph nodes:
-Swelling (buboes
-Pus exudation
-Bleeding

Gastric:
-Nausea
-Vomiting

Joints:
-Pain
-Ache

Main symptoms of

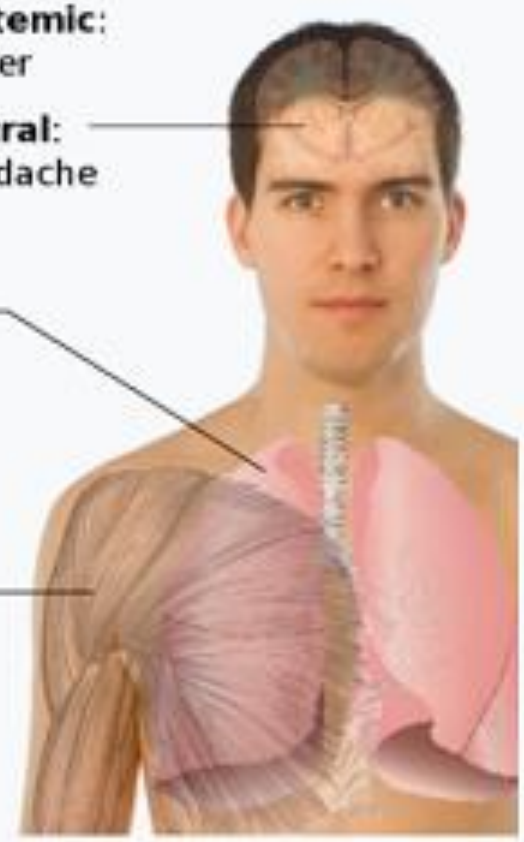
Pneumonic plague

Systemic:
-Fever

Central:
-Headache

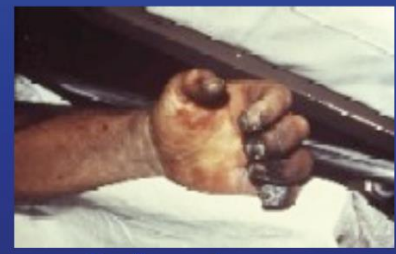
Respiratory:
-Cough
-Hemoptysis
-Dyspnea
-Chest pain

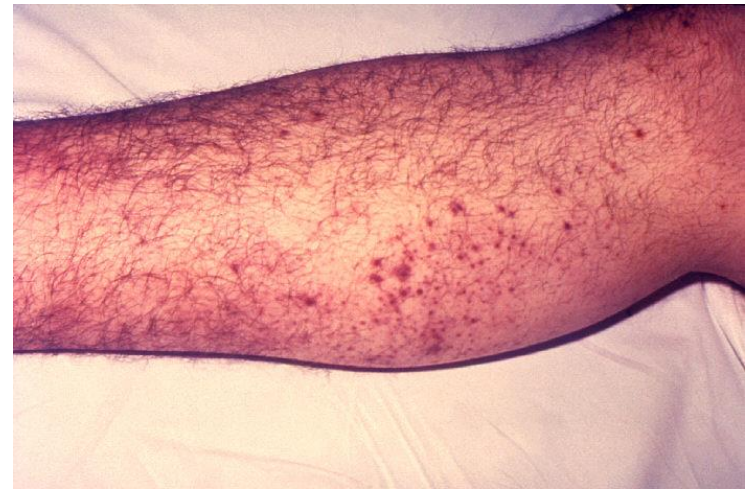
Muscular:
-Weakness

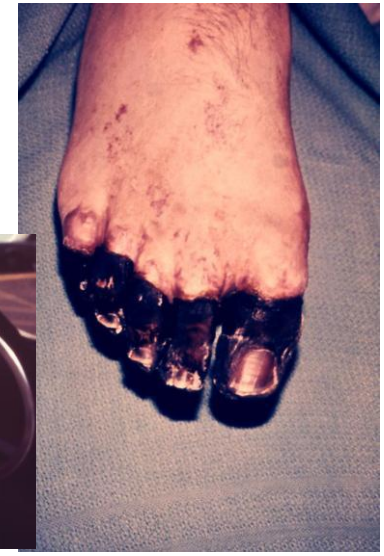


Septicemic Plague

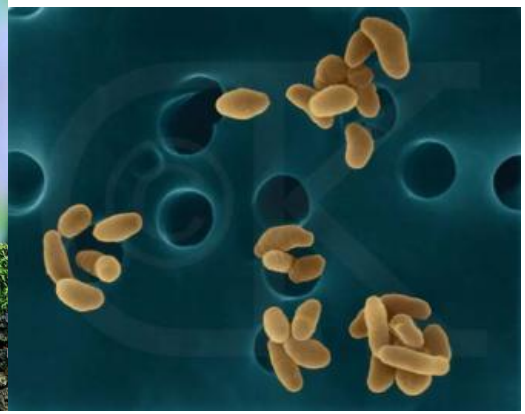
- Incubation: Most common as complication of pneumonic or bubonic plague
- Symptoms
  - Acute fever, chills, prostration, abdominal pain, nausea, vomiting
- Disease Progression
  - Purpura
  - DIC
  - Hypotension and other signs of shock
  - Fatal if not treated







Tularemia



Francisella tularensis

Francisella tularensis

- ❖ Gram negative
- ❖ Intracellular pathogen
  - **Macrophages**

- The bacterium multiplies within macrophages and the major target organs are the lymph nodes, lungs, spleen, liver, and kidney.

- **Reservoirs**
  - Ticks and rabbits most important
- **Infectious dose**
  - Small for inoculation or inhalation (10-50 organisms)
  - Large for oral (10^8 organisms)

Transmision

- ➢ **Direct**
- the bite of the tick

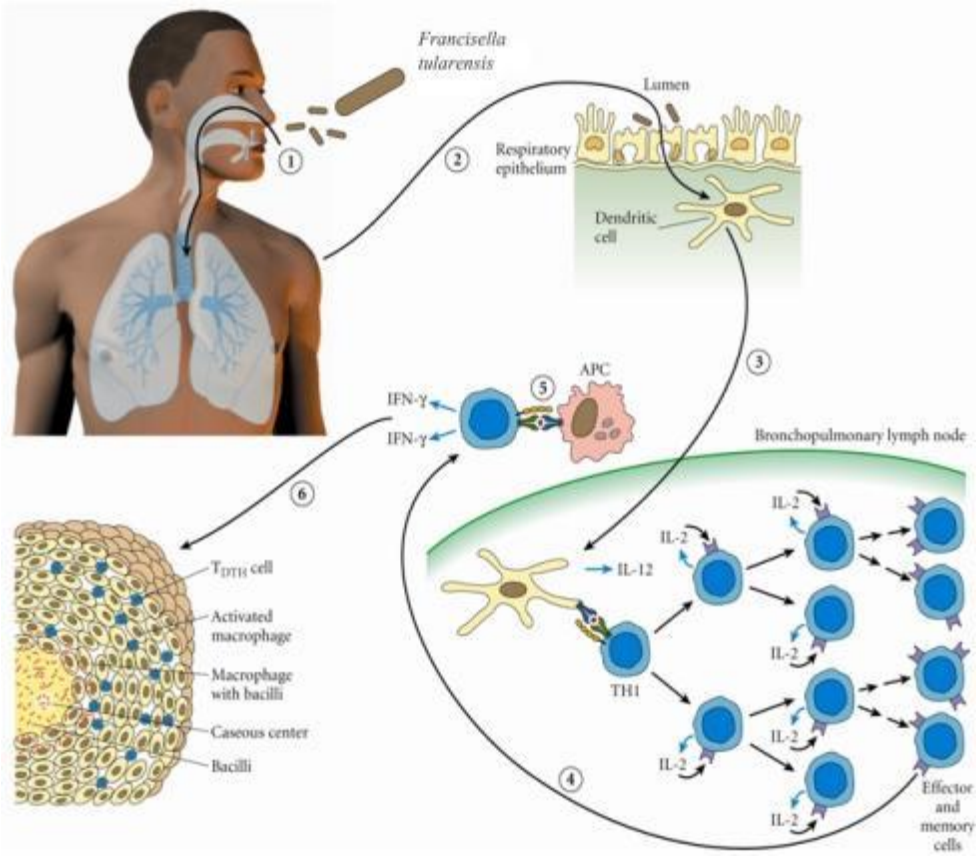
- ➢ **Ingestion**
- Undercooked meat
- Contaminated water

- ➢ **Aerosol**
- Contaminated dust

- ➢ **Not person-to-person**

Francisella tularensis* is an intracellular pathogen that infects *macrophages, hepatocytes* and *epithelial cells.

Virulence factors are the antiphagocytic capsule and the enzyme citrulline ureidase.



The dominant host response to infection is a **cellular immune response** with characteristic granulomatous infiltrates in the lymph nodes, liver, lungs, spleen and bone marrow.