Lesson 12

Microbiological diagnosis of infections caused by gram-negative bacteria (genus Escherichia, Salmonella, Shigella, Vibrio, Helicobacter, Campylobacter

family Enterobacteriaceae

(species of medical importance)

Family Enterobacteriaceae

(most commonly affected biotopes)

Enterobacteriaceae

Opportunistic pathogens

Escherichia coli

Klebsiella pneumoniae

Enterobacter aerogenes

Serratia marcescens

Proteus spp.

Providencia spp.

Citrobacter spp.

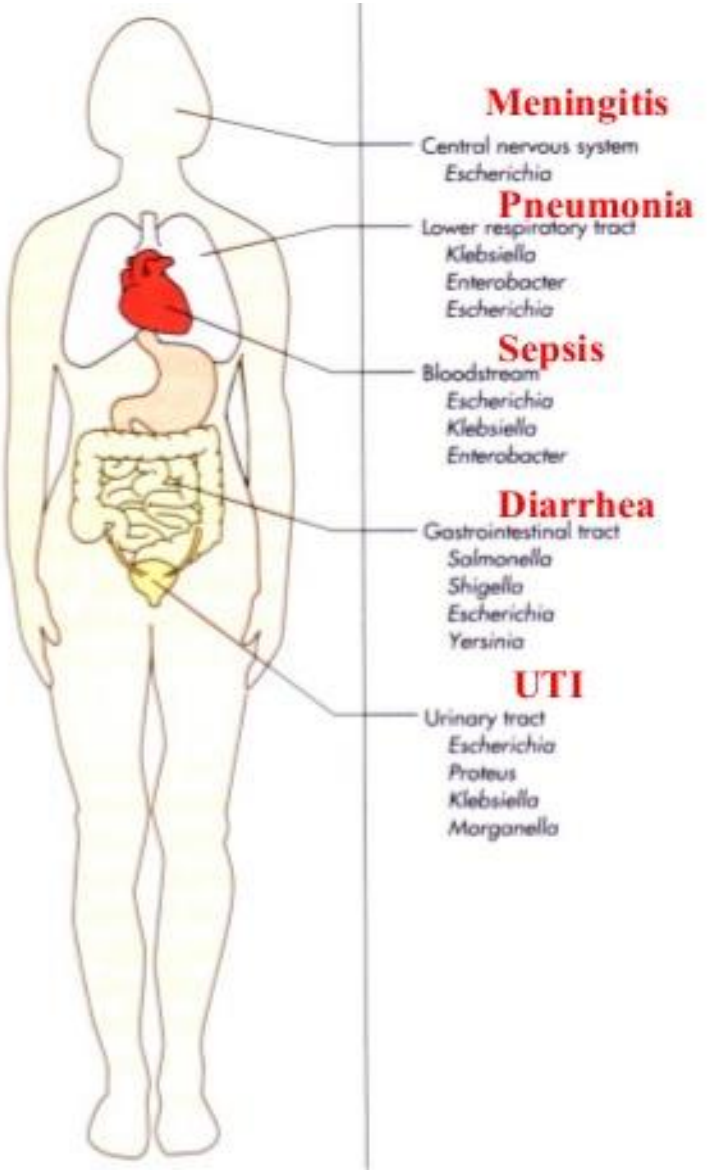
Obligate pathogens

Salmonella spp.

Shigella spp.

Yersinia spp.

Some *E. coli* strains



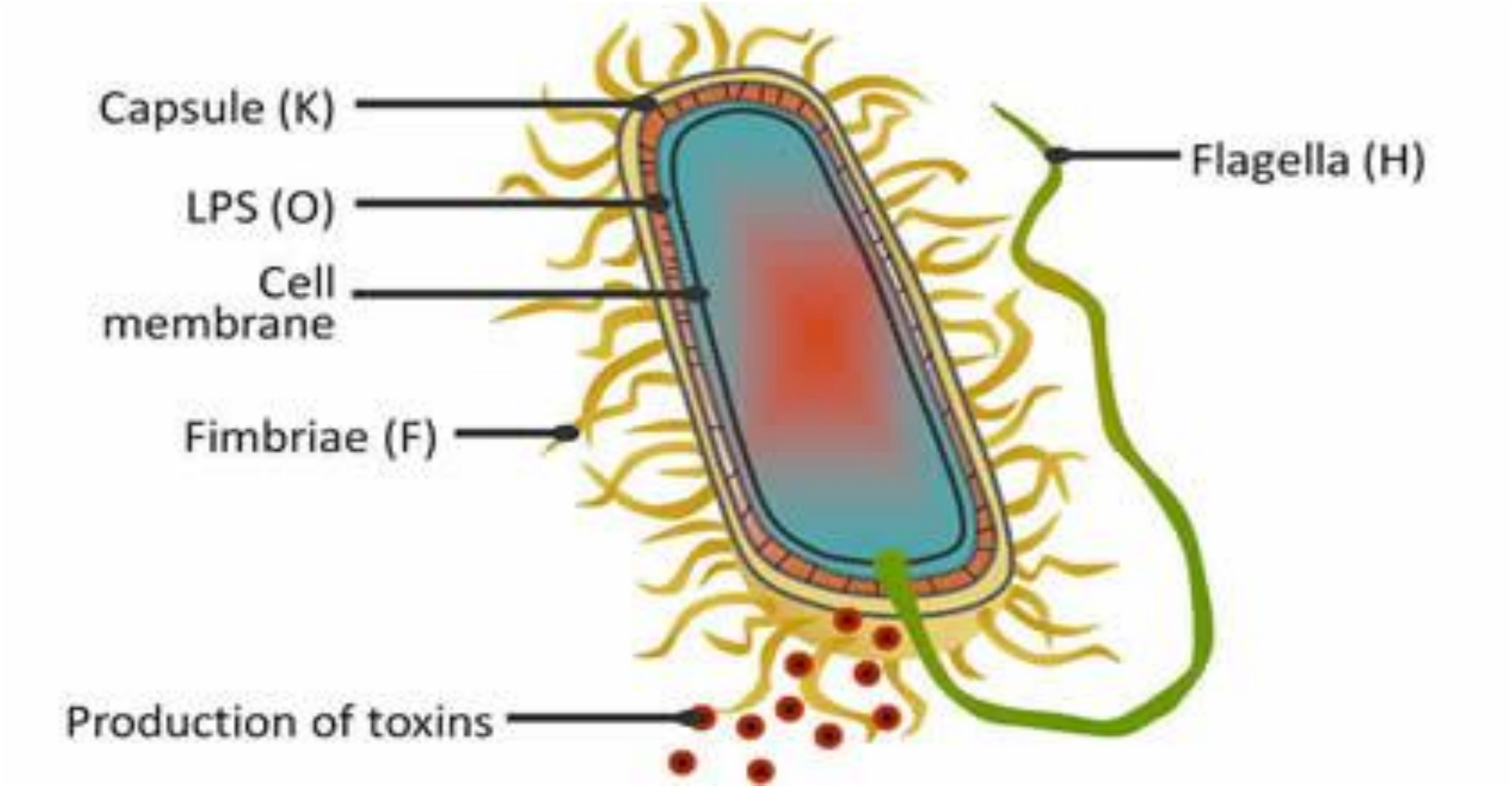
Classification

Escherichia coli

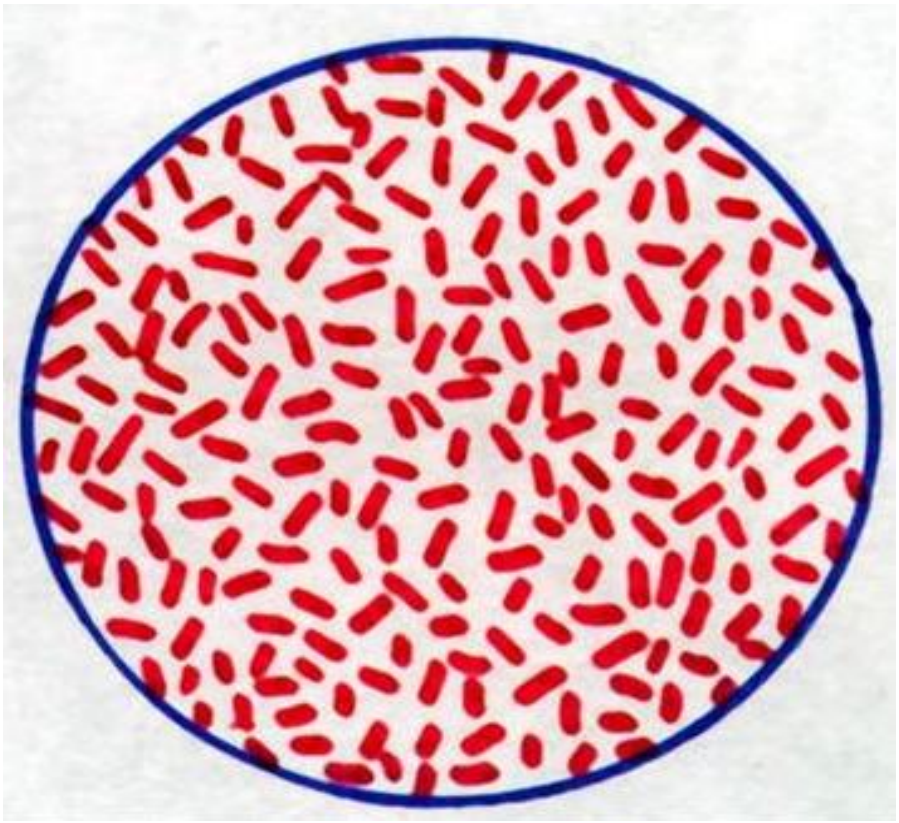
Family: Enterobacteriaceae
Genus: Escherichia
Species: E.coli

Morphology

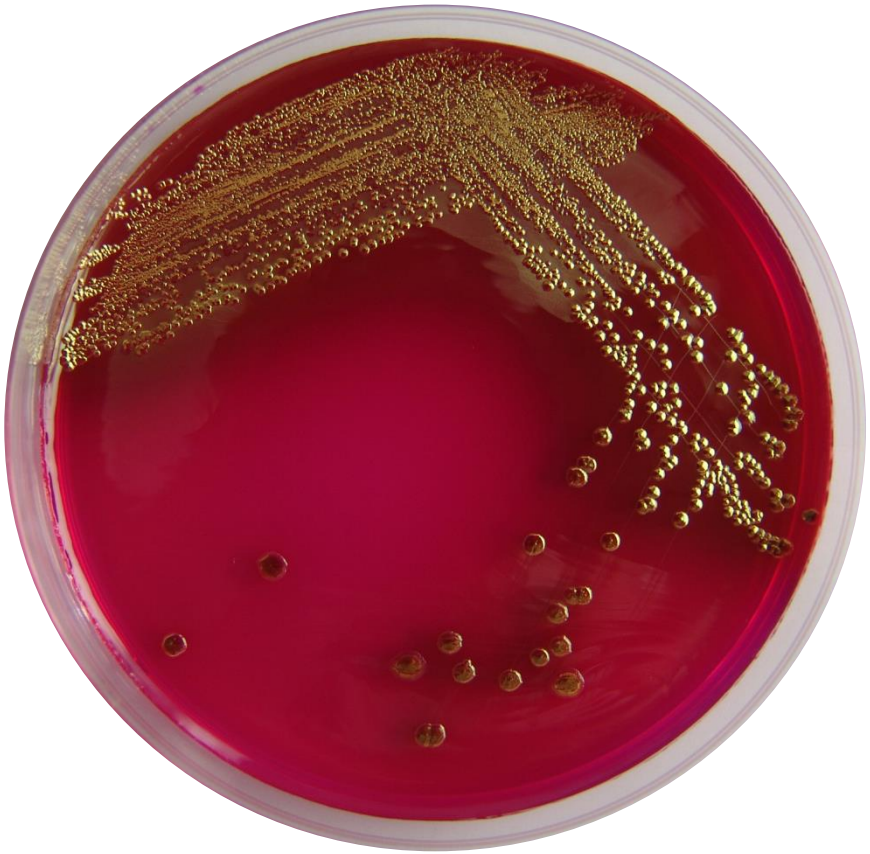
Escherichia coli - Gram-negative, motile (peritrichous), microencapsulated, non-spore forming, short rods



genus Escherichia



Escherichia coli - Lactose-positive raspberry-red colonies with a metallic sheen on Endo's medium

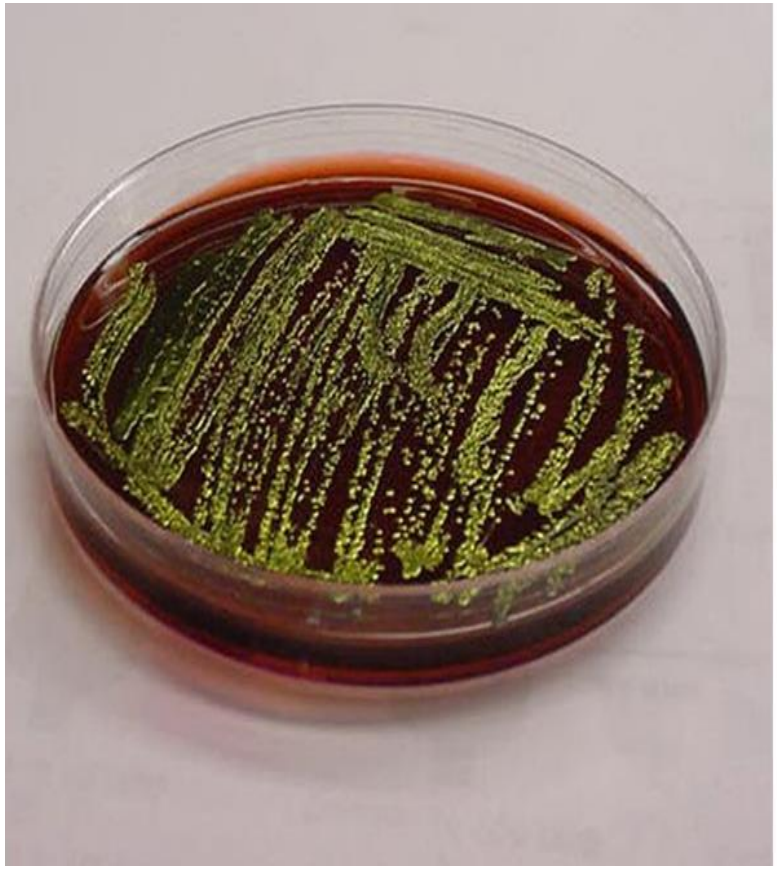


Escherichia coli

pink lactose-positive colonies on MacConkey agar

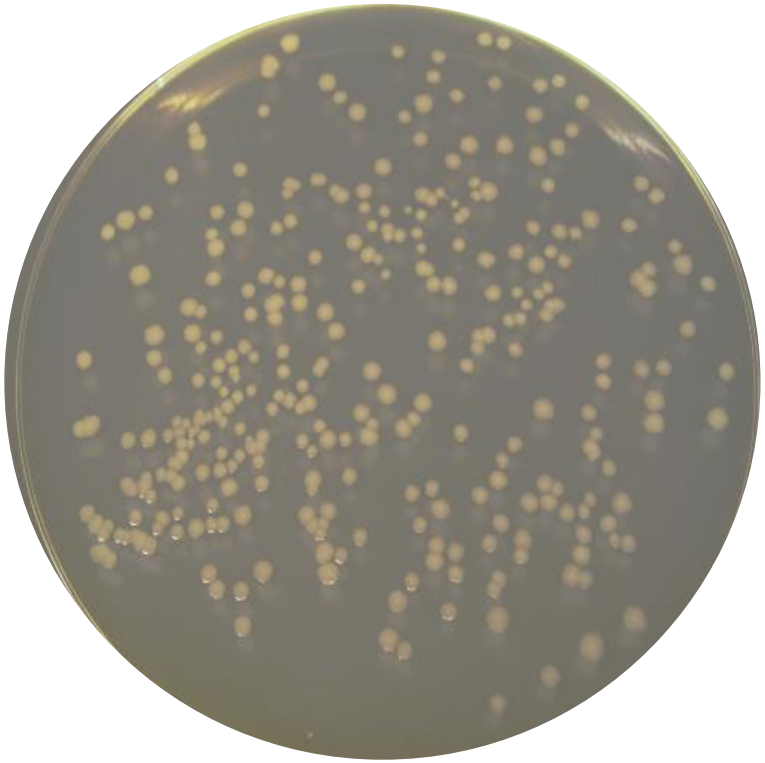
Escherichia coli –

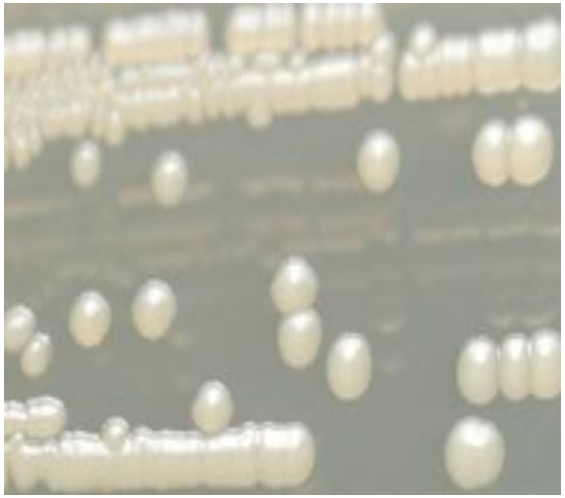
dark purple colonies (EMB-agar (Eosin Methylene Blue) (Levin's Medium)



Escherichia coli

form smooth, convex, shiny, translucent S-colonies on meat-peptone agar





Escherichia coli

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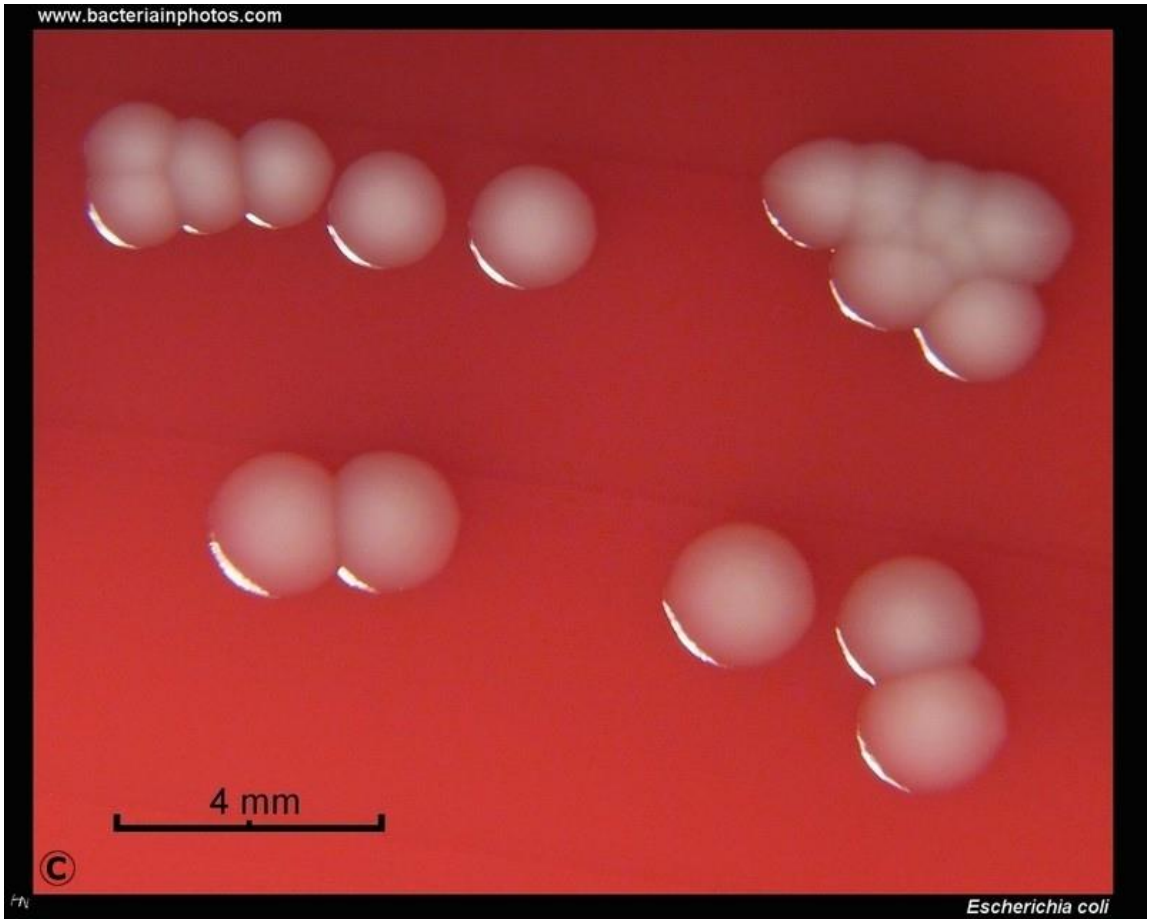


Escherichia coli

(biochemical properties)

- Break down glucose, lactose, mannitol, maltose, sucrose to acid and gas
- Form indole
- Does not produce hydrogen sulfide

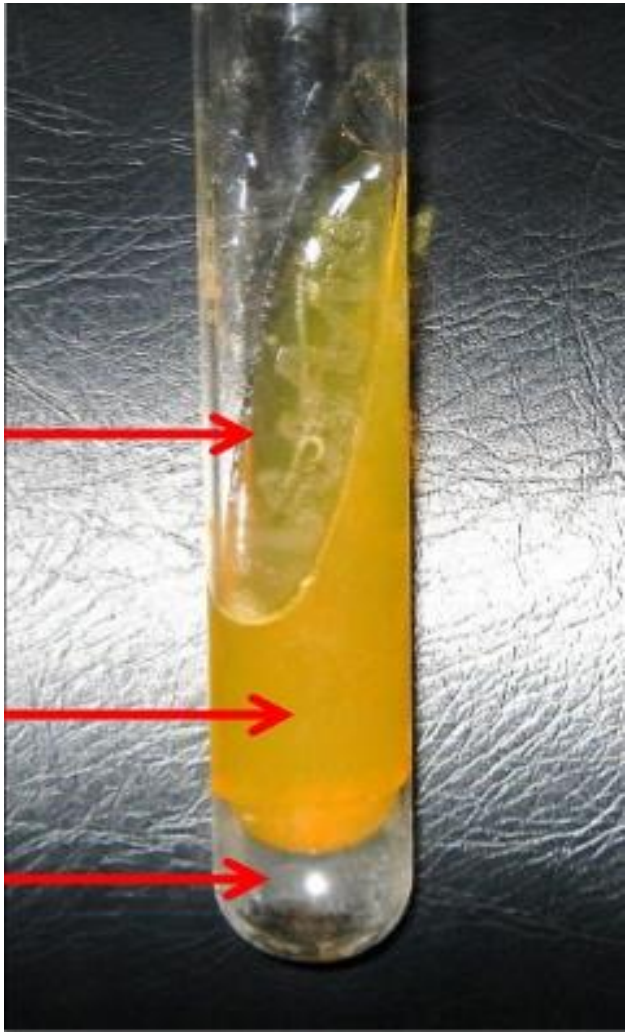
Escherichia coli –
(biochemical properties)

Agar Kligler

AGAR SLOPE: ACID(+)

AGAR COLUMN: ACID(+)

GAS PRODUCTION (+)



Escherichiosis:

➢ Extraintestinal escherichiosis

- **Sepsis**
- **Suppuration of wounds**
- **Secondary pneumonia**
- **Meningitis**
- **Urinary tract infections**
- **Nosocomial infections**

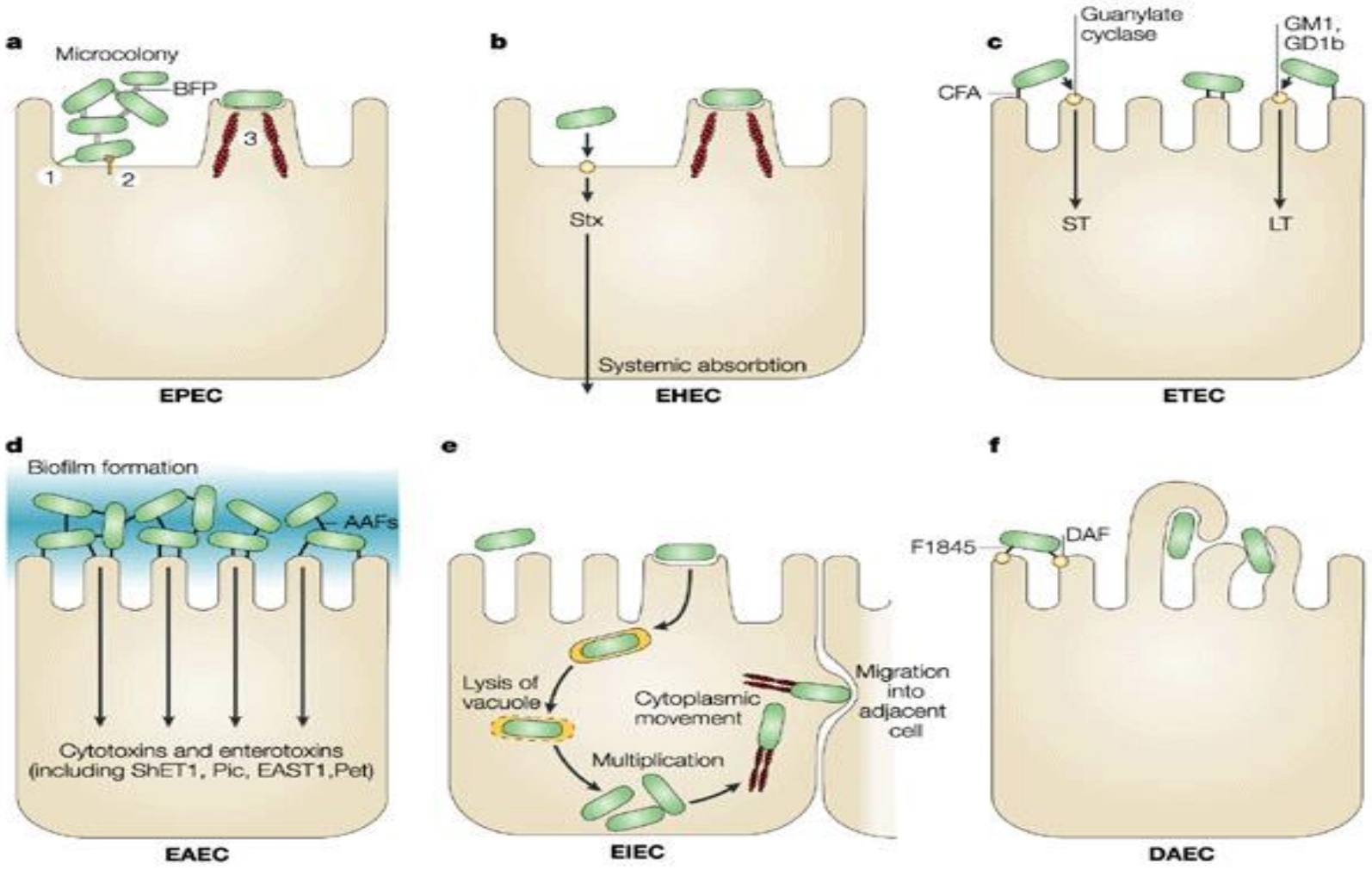
➢ Intestinal escherichiosis

- **Diarrheogenic strains**

Diarrheal strains of Escherichia coli

1. ETCP - ENTEROTOXIGENIC
2. EICP – ENTEROINVASIVE
3. EHEC – ENTEROHEMORRAGIC
4. EACP – ENTEROADHESIVE
5. EPK – ENTEROPATHOGENIC

Mechanism of pathogenicity of diarrheagenic strains



Microbiological diagnostics:

Materials for research:

1. Excrements (with intestinal escherichiosis)
2. Urine (with parenteral escherichiosis)
3. Cerebrospinal fluid
4. Wound discharge
5. Blood

Microbiological diagnostics

➢ Bacteriological (cultural) method

- primary inoculation of the test material (except for blood) on lactose-containing differential media (Endo, SS-agar). Blood culture in sugar broth at a ratio of 1:10, and cultivation of samples under aerobic and anaerobic conditions
- incubation 18-24 hours at 37ºC
- identification of grown colonies based on biochemical properties. Determination of serovars using polyvalent OK
- sera antibiotic susceptibility testing

Classification

Genus Salmonella

Family: Enterobacteriaceae

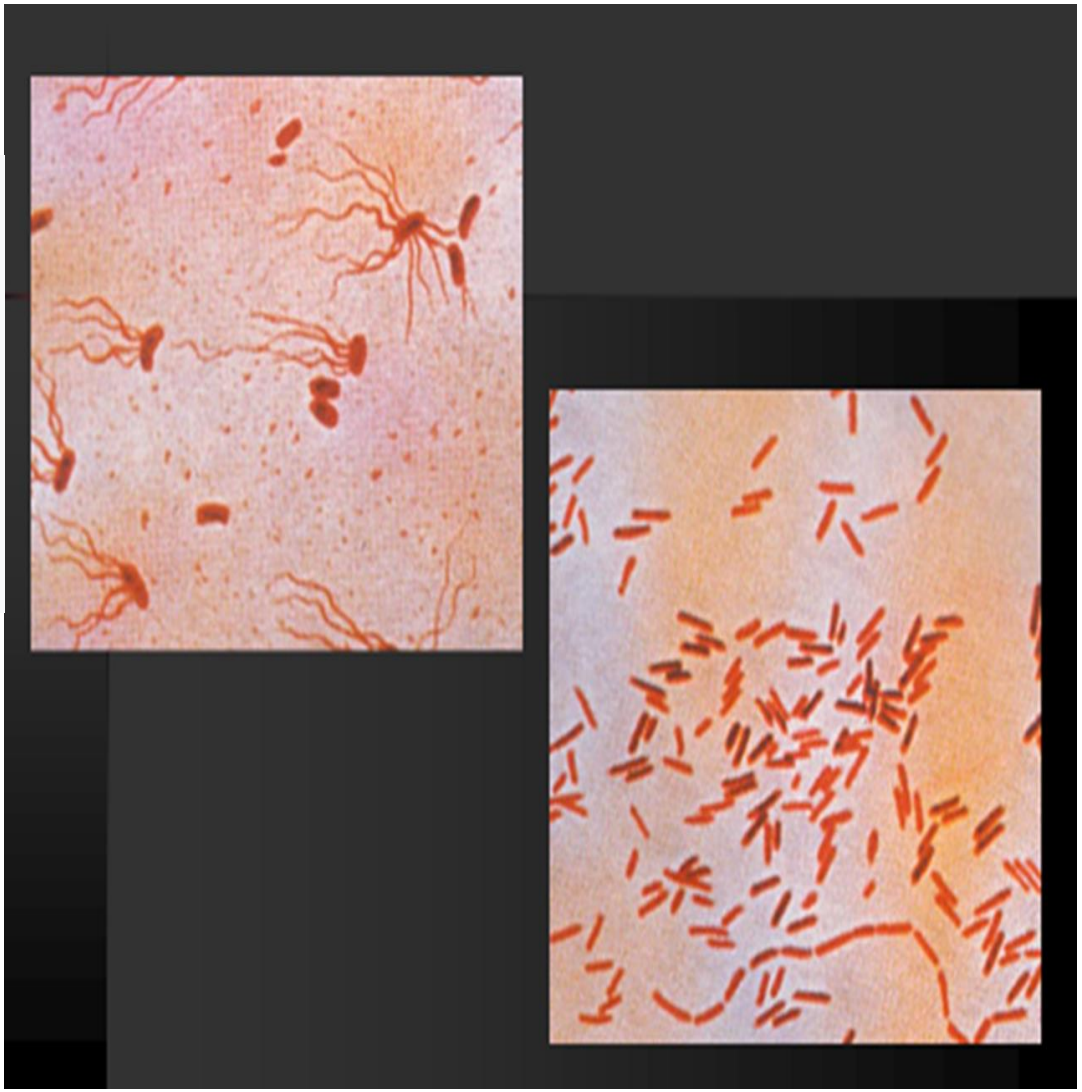
Genus: Salmonella

Species: S.typhi, S.paratyphi A, S.paratyphi B

Morphology

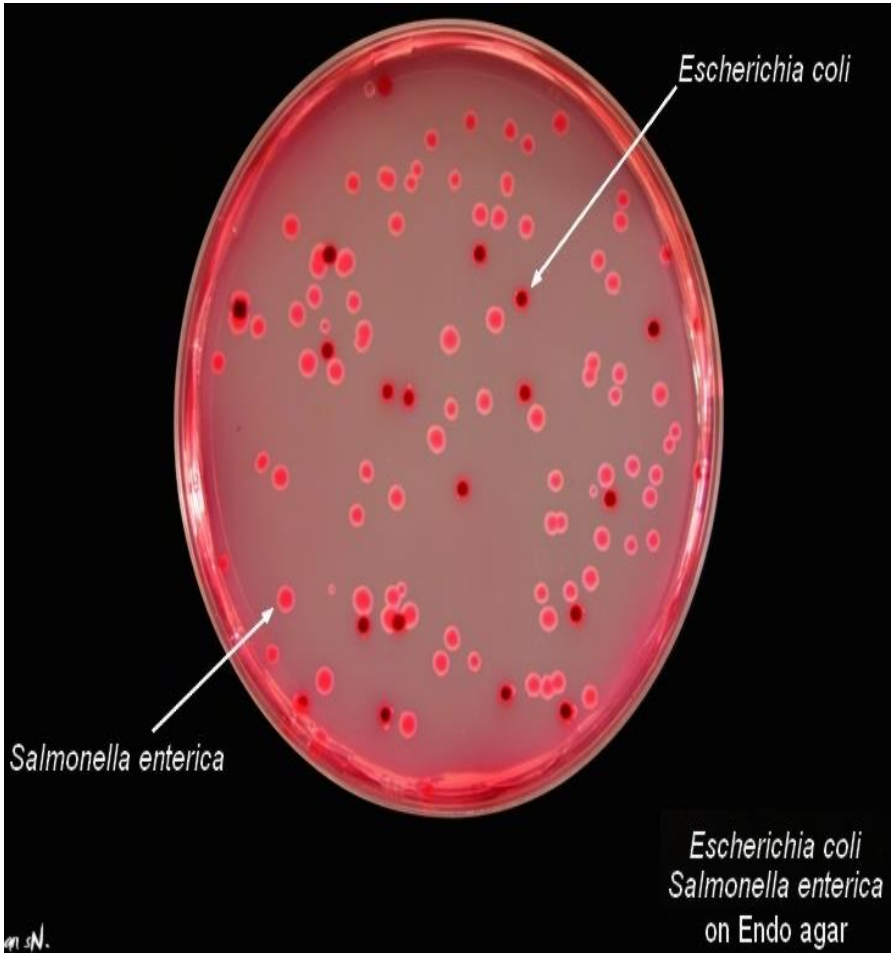
Genus Salmonella –

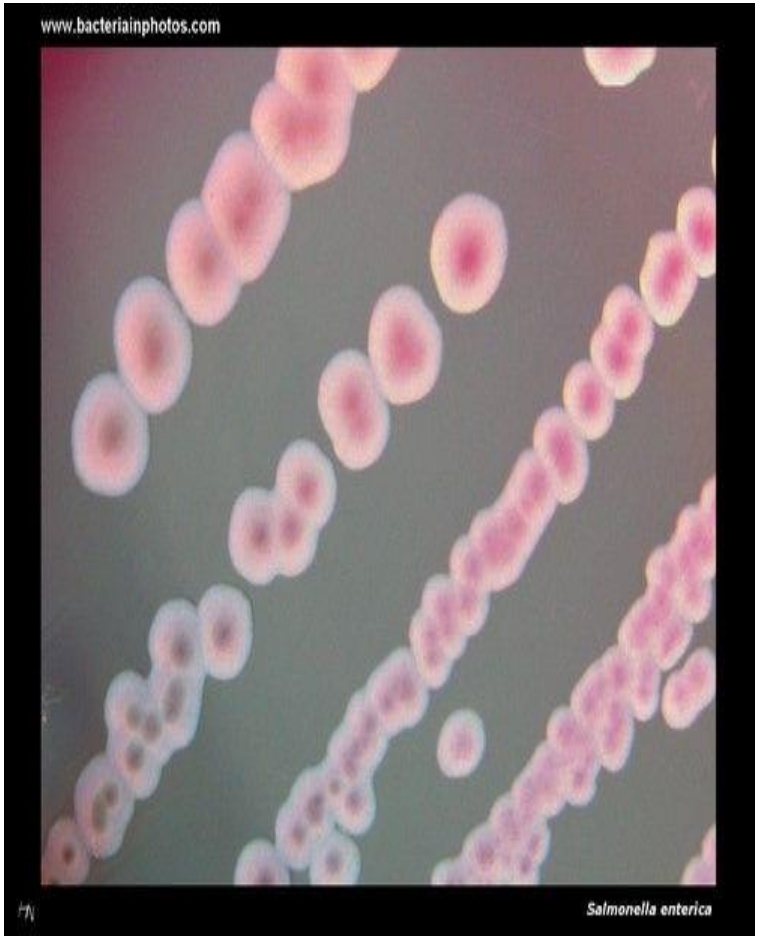
Gram-negative motile (peritrichous), rods with rounded ends that do not form a capsule and spore



Genus Salmonella

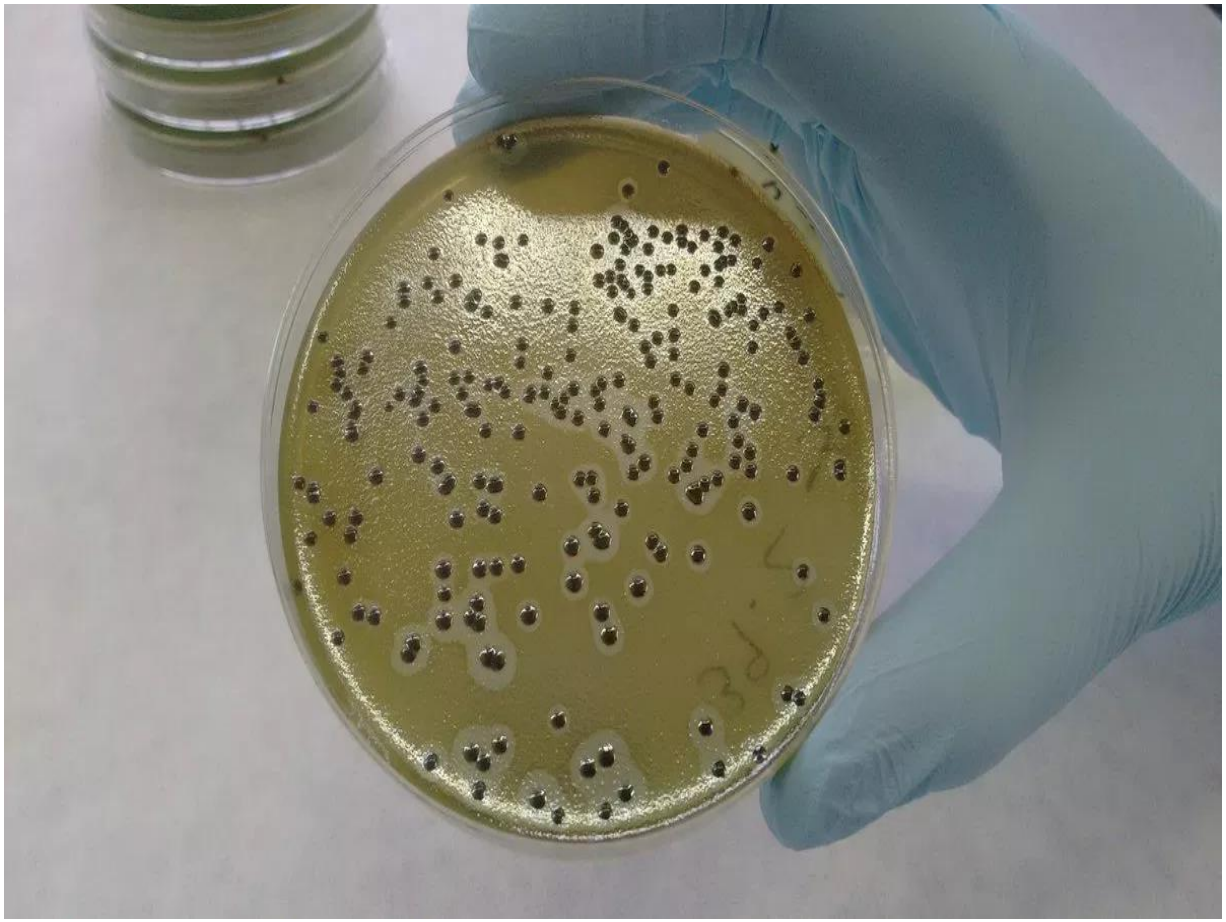
On Endo's medium, they form lactose-negative colorless colonies.





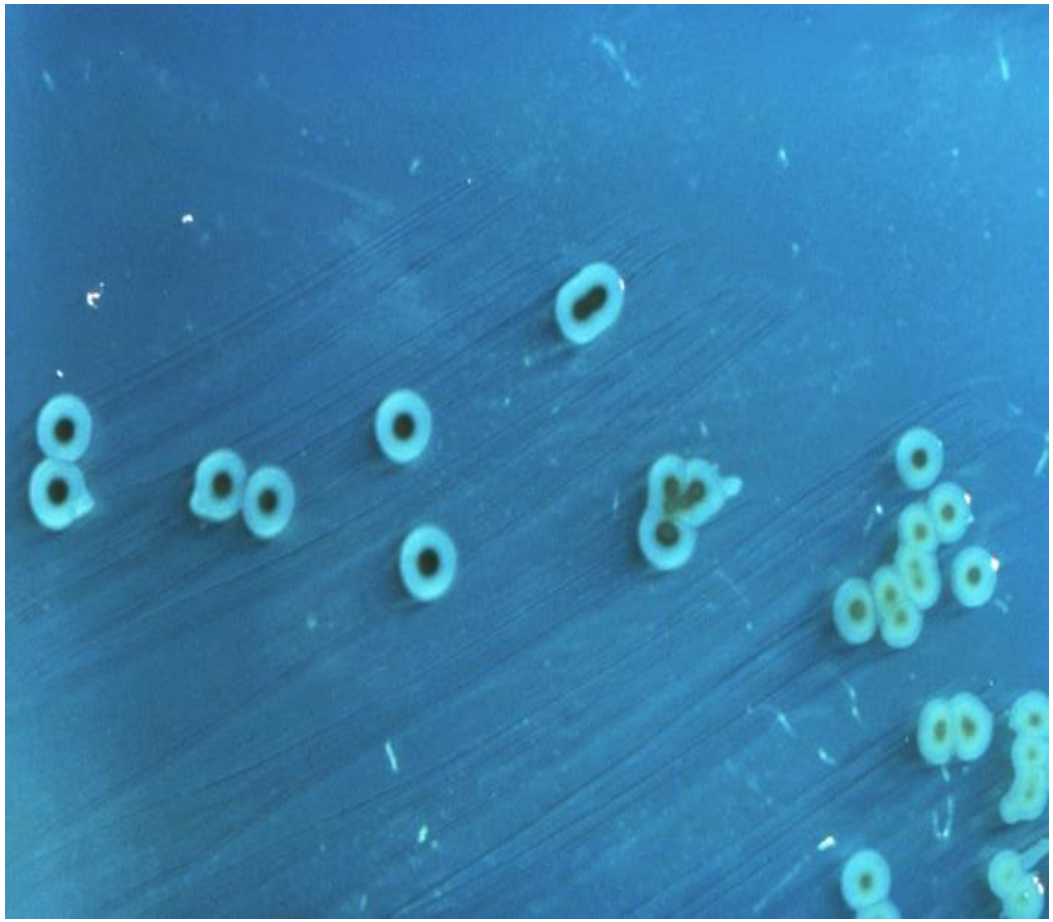
Salmonella

(black colonies on bismuth sulfite agar)



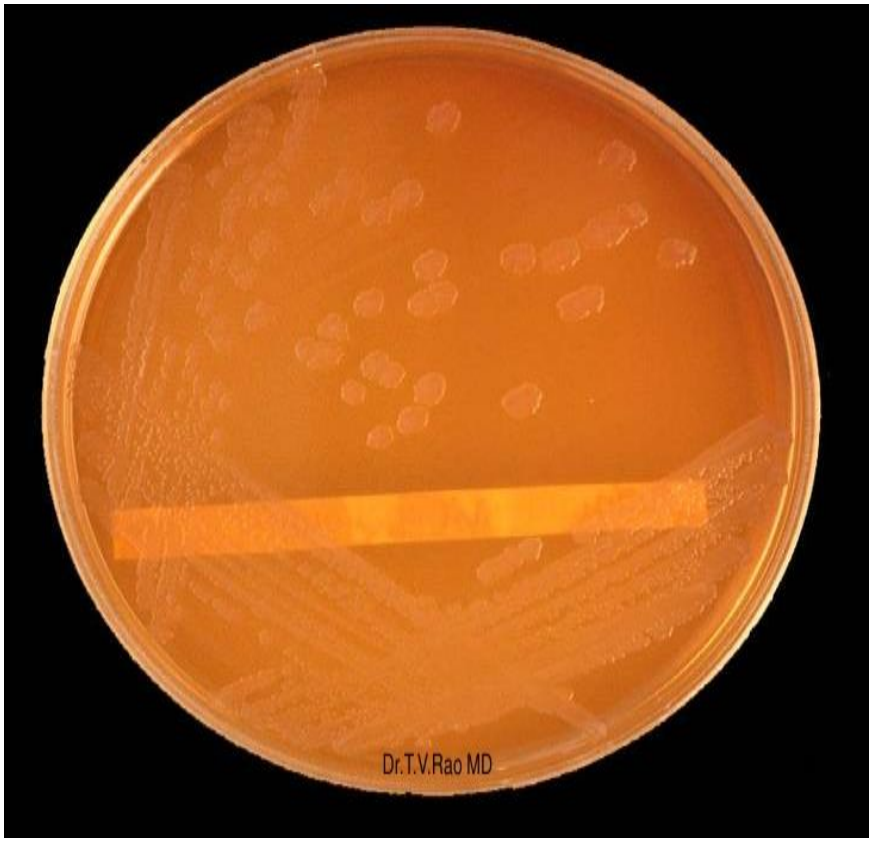
Salmonella paratyphi B

when growing on dense nutrient media, they form mucous ridges



Genus Salmonella

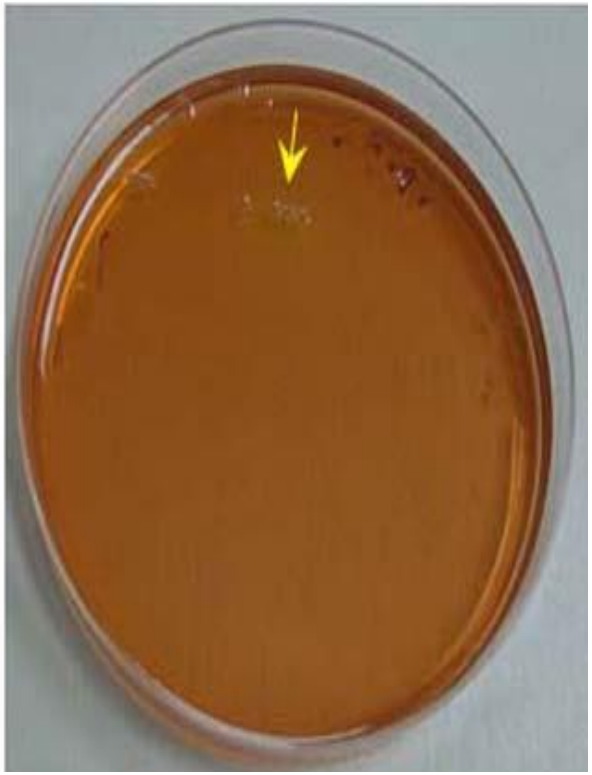
(lacto-negative colorless colonies on MacConkey agar)



Genus Salmonella –

colonies on salmonella-shigella (SS) agar

Genus Salmonella
(black colonies)



Genus Shigella
(colorless colonies)

Genus Salmonella

(pathogenicity factors)

- **mechanism of transcytosis**
- **invasives**
- **resistance to phagocytosis**
- **endotoxin**

Genus Salmonella

(biochemical properties)

break down glucose, mannitol, maltose to acid and gas (S.typhi only to K), do not break down lactose and sucrose form hydrogen sulfide (except S. paratyphi A) do not form indole does not liquefy gelatin

Genus Salmonella
(biochemical properties)

TSİ – Triple Sugar İron agar –

Growth on three-sugar (glucose, lactose, sucrose) agar with iron salts

TSİ agar – before sowing

SKOS AGAR:
Lactose / sucrose (-)

Hydrogen sulfide (+)

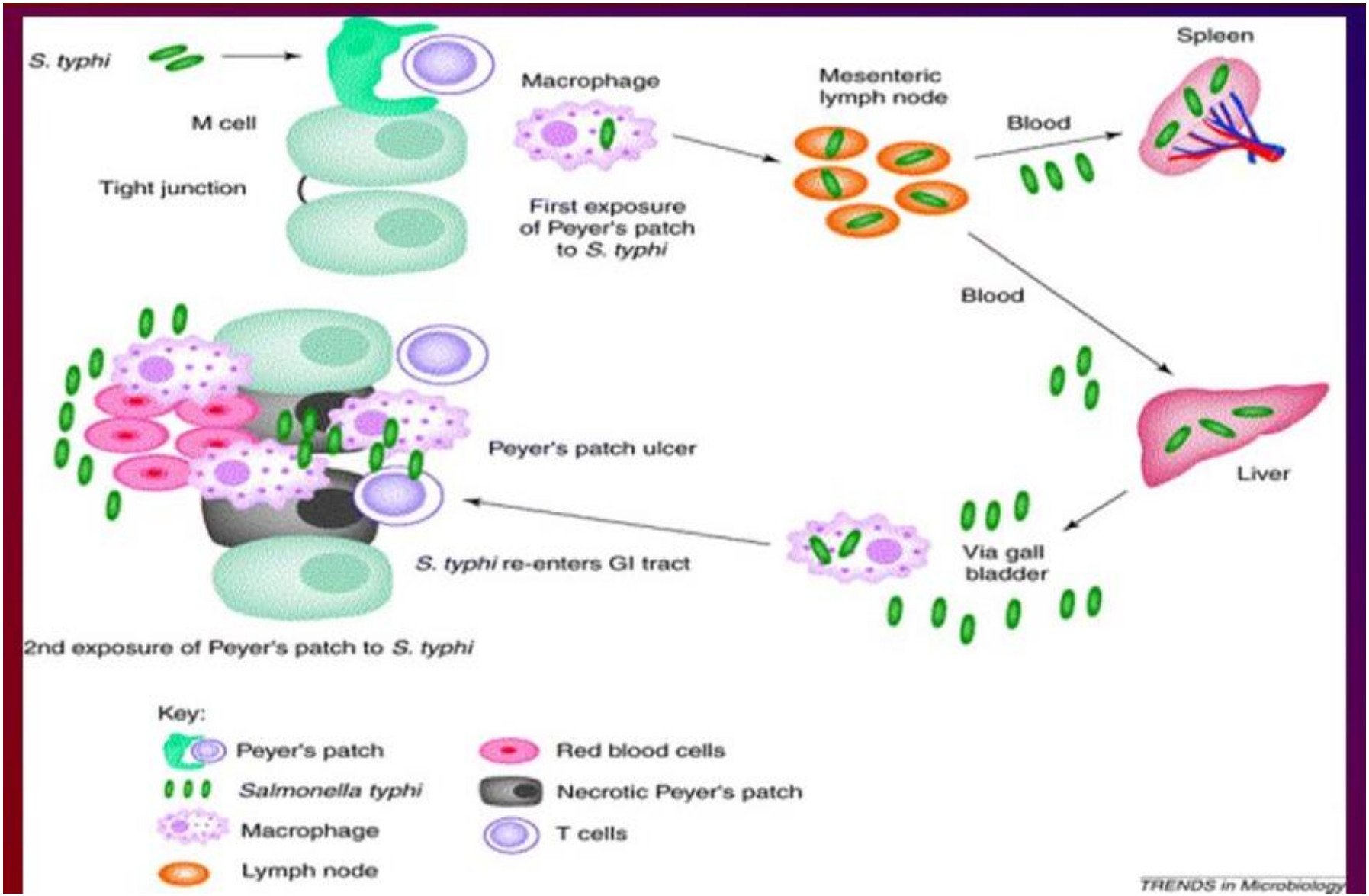
GAS (+)

AGAR COLUMN: Breakdown o
glucose to acid (+)

Diseases caused by members of the genus Salmonella

- Typhoid fever (S.typhi)
- Paratyphoid (S.paratyphi A və B)
- Salmonellosis (food poisoning) - S.enteritidis, S.typhimurium, S.choleraesuis)
- Septicemia (S.choleraesuis)
- Nosocomial salmonellosis (S.typhimurium)

Genus Salmonella
(pathogenesis of typhoid fever)



Microbiological diagnostics

Materials for research:

- Blood (to obtain a blood culture in the first 2 weeks of the disease)
- Defecation (coproculture)
- Urine (urine culture)
- Duodenal contents (with bacteriocarrier)

Microbiological diagnostics

Bacteriological method (cultural)

- During the febrile period, blood is taken and sown in the bile broth, followed by subculture on differential media (Endo, Ploskireva, ICA) in order to obtain a pure culture.
- Identification of grown colonies by biochemical properties and antigenic structure
- Antimicrobial susceptibility testing

➢ Serological method

- Vidal reaction - starting from the 2nd week of the disease, antibodies to the pathogen are determined in the blood serum. Using the Vidal reaction, antibodies to O- and H-antigens are determined.
- RPHA with O-, H-, Vi- diagnosticums

Salmonellosis (food poisoning)

- ***S.enteritidis***
- ***S.typhimurium***
- ***S.choleraesuis***

Microbiological diagnostics

Materials for research

- Wash water of the stomach
- Vomit
- Excreta
- Bile
- Urine
- Blood (with generalized forms)

Microbiological diagnostics

Bacteriological (cultural)

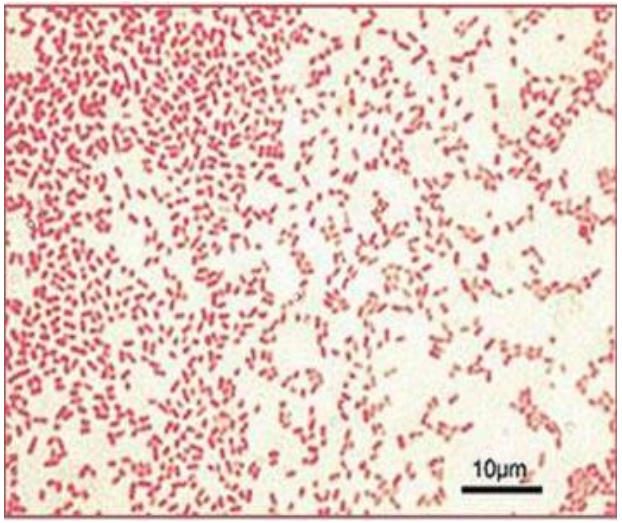
inoculation of the test material on lactose-containing differential media (Endo, SS-agar, Levin, Ploskireva, Mac Konki) incubation 18-24 hours at 37ºC identification of grown lactose-negative colonies by morphological, biochemical properties and antigenic structure antibiotic susceptibility testing

Genus SHIGELLA

Family: Enterobacteriaceae
Genus: Shigella
Species: S.dysenteriae, S.flexneri, S.sonnei, S.boydii

Morpho-biological properties:

Shigella are gram-negative immobile rods 0.5-0.7x2-3 µm in size. Spores and capsules do not form

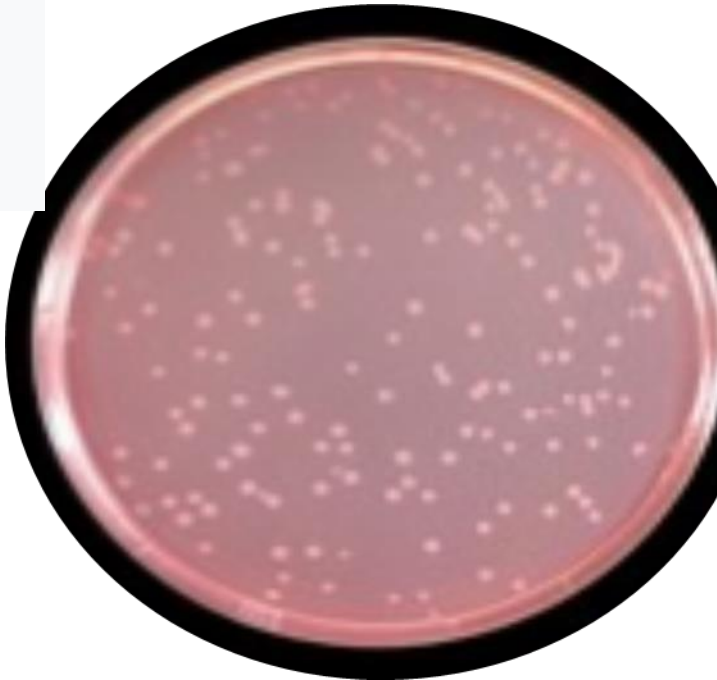


Genus Shigella
(cultural properties)

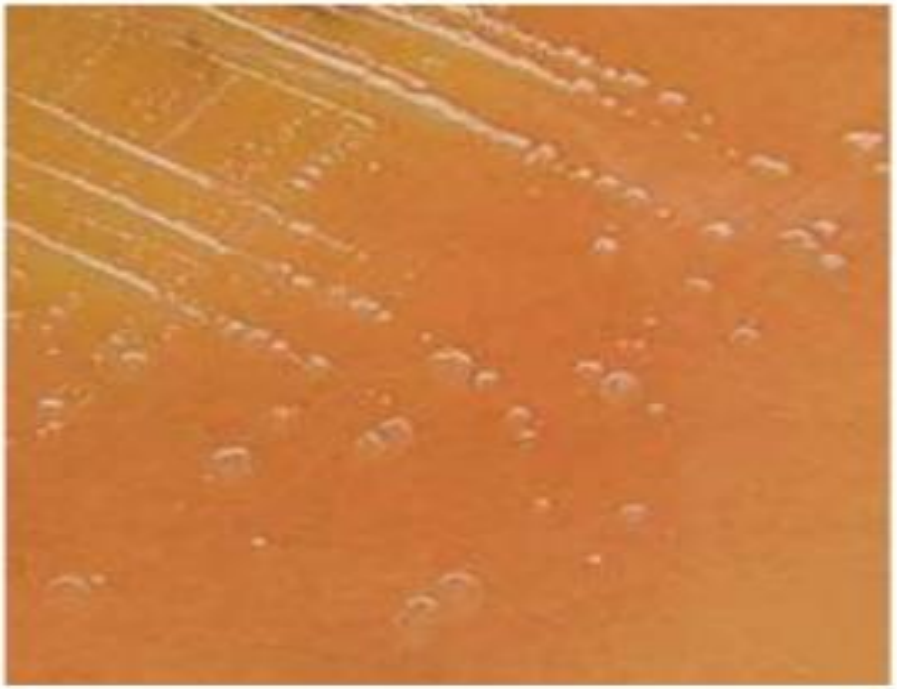
On dense nutrient media they form small, shiny, smooth, translucent S-colonies 1-2 mm in diameter.

On liquid nutrient media - cause diffuse turbidity.

The genus Shigella - form colorless colonies on Endo, Levin, Ploskirev, MacConkey media; do not ferment lactose. The enrichment liquid medium is selenite broth.



The genus Shigella forms transparent or translucent colorless colonies on SS (Salmonella-Shigella) medium

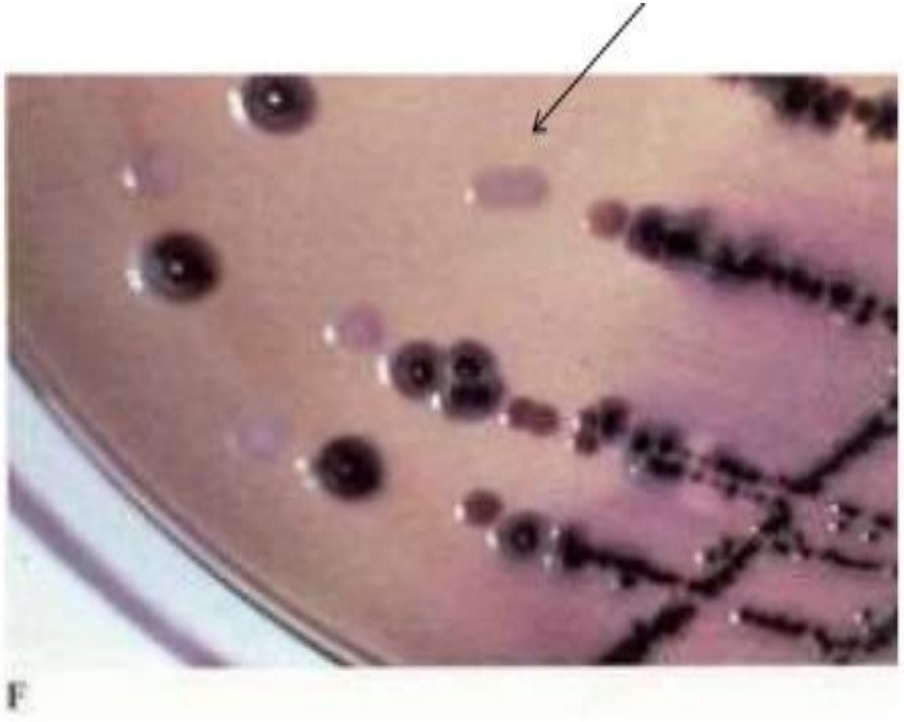


S. sonnei –

(forms non-hemolytic colonies on blood agar)

The genus Shigella

forms colorless colonies on EMB (eosin methylene blue) agar



Biochemical properties of bacteria of the genus Shigella

Subgroups	Fermentation					Indole formation	H2S Education
	lactose	glucose	mannitol	dulcite	sucrose		
Sh.dysenteriae	-	+К	-	-	-	-	-
Sh.flexneri	-	+ К	+	±	-	±	-
Sh.boydii	-	± К	+	+	-	+	-
Sh.sonnei	+gradually	+ К	+	-	+gradually	+	-

Genus Shigella
(antigenic structure)

Shigella have a somatic O-antigen, on the basis of which the genus is divided into A, B, C, D serogroups, and these, in turn, into serotypes.

Serogroup A: Shigella dysenteriae (12 serotypes)
Serogroup B: Shigella flexneri (9 serotypes)
Serogroup C: Shigella boydii (18 serotypes)
Serogroup D: Shigella sonnei (1 serotype)

Genus Shigella
(pathogenicity factors)

Invasiveness - intercellular distribution and reproduction in the epithelium of the intestinal mucosa is due to: ipa-BCD - invasive TTSS - systems Proteins of intracellular distribution Endotoxin Shiga toxin (exotoxin produced by S. dysenteria serotype 1) Shiga-like toxins (excluding S. dysenteria serotype 1)

Epidemiology:

Source of infection: sick persons and bacteria carriers Way and mechanism of transmission: alimentary route, fecal-oral mechanism

Caused diseases:

Bacterial dysentery (bloody diarrhea)

The pathogenesis of dysentery

Action of exotoxin (Shiga toxin)

Enterotoxic: Shiga toxin interacts (adhesion) with intestinal cell receptors, prevents the absorption of glucose, electrolytes, amino acids from the intestinal lumen

Cytotoxic: The B component of Shiga toxin causes the binding of the toxin to the cellular receptor on the surface of the microvilli. A component that inactivates the 60-S subunit of ribosomes inhibits protein synthesis and causes cell death, which leads to damage to the microvascular system of the intestine and the development of hemorrhages (appearance of blood and leukocytes in stool)

Pathogenesis

The Sereny test is used to test the invasiveness of Shigella species. This is done by inoculating a suspension of bacteria into the guinea pig's eye. Severe mucopurulent conjunctivitis and severe keratitis indicate a positive test result.

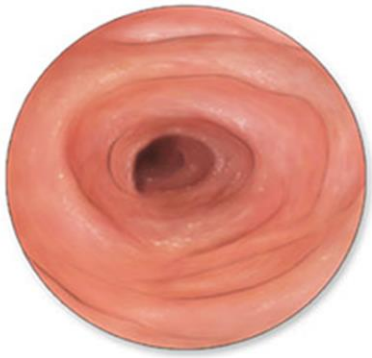
Neurotoxic effects: fever and spasmodic abdominal pain (convulsions)

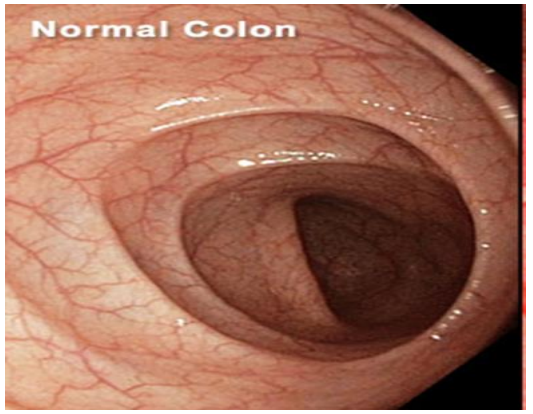
Clinical manifestations

diarrhea (with blood or mucus) spasmodic abdominal pain (cramps) tenesmus (false urge to defecate) fever (neurotoxic effect) ulcers - virulent shigella, interacting with the epithelium of the colon mucosa, penetrate through M-cells into the submucosa, where they multiply in macrophages, which leads to the death of the latter. Apoptosis of macrophages initiates the development of inflammation in the submucosa and the development of diarrhea. Intercellular distribution of shigella leads to the development of erosions. As a result of the death of Shigella, exotoxins are released, the action of which leads to the development of bloody mucous diarrhea.

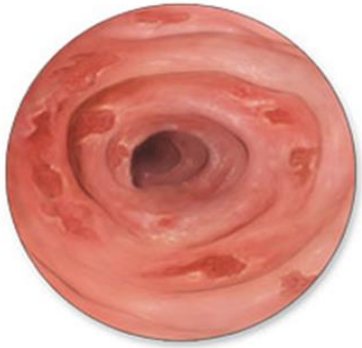
Colon ulcers

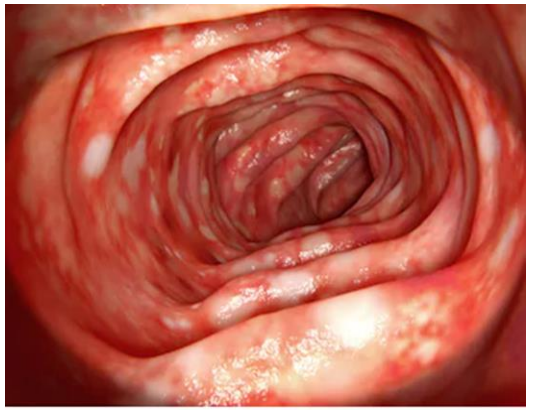
The mucous membrane of the colon intestines (normal)





The mucous membrane of the large intestine (ulcers)





Microbiological diagnostics:

➢ Research materials:

- excreta
- rectal
- Scraping
- blood (to detect antibodies in chronic dysentery)

➢Bacteriological (cultural)

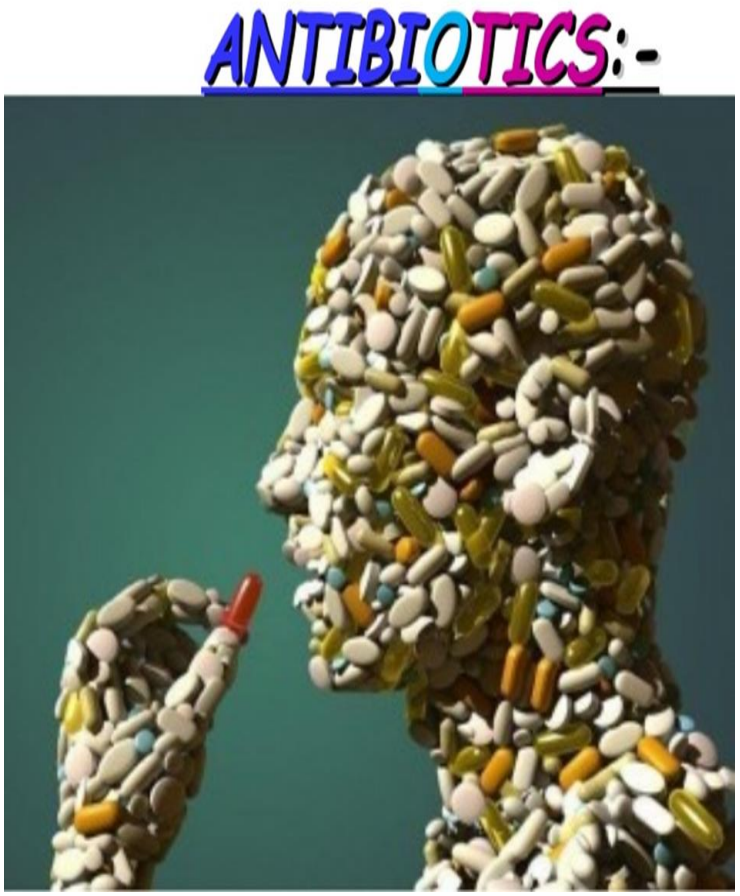
Sowing pathological material on lactose-containing differential nutrient media (Endo, Levin, Ploskireva, McConkey) Incubation at 37ºC for 18-24 hours. Identification of grown lactose-negative colonies by morphological, biochemical and antigenic properties Determination of sensitivity to antibiotics Note: because specific antibodies to the pathogen are formed after 2 weeks, the ongoing serological tests have no diagnostic value.

Definition of bacteriocarrier

Excrements (material with a bacteriocarrier is taken with a cotton swab directly from the rectum from a depth of 5-10 cm.) Bacteriological method Serological method (similar to the Vidal reaction) Put a test of lysis of bacterial culture with polyvalent dysenteric phage. A positive response confirms the diagnosis.

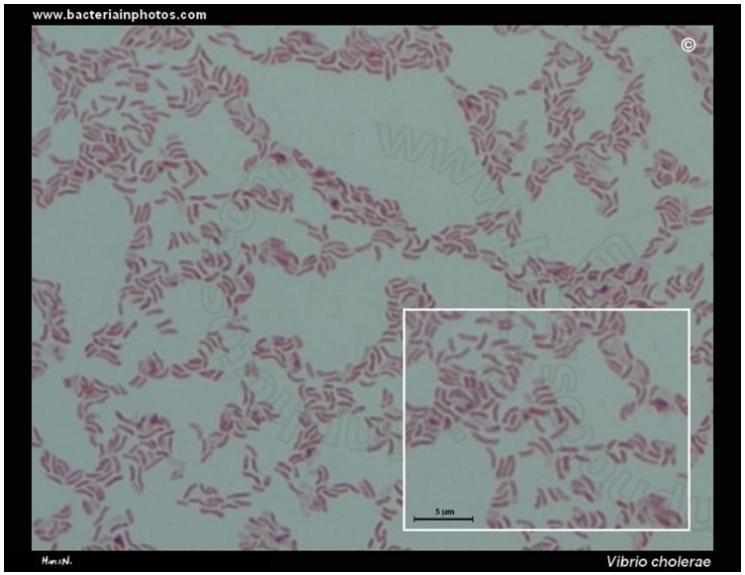
Treatment and prevention:

- The drugs of choice are tetracycline, doxycycline, and quinolones. According to epidemiological indications, bacteriophages are used, in case of dysbacteriosis, probiotics are used to correct the microflora.
- Restoration of water-salt balance
- There is no specific prevention!

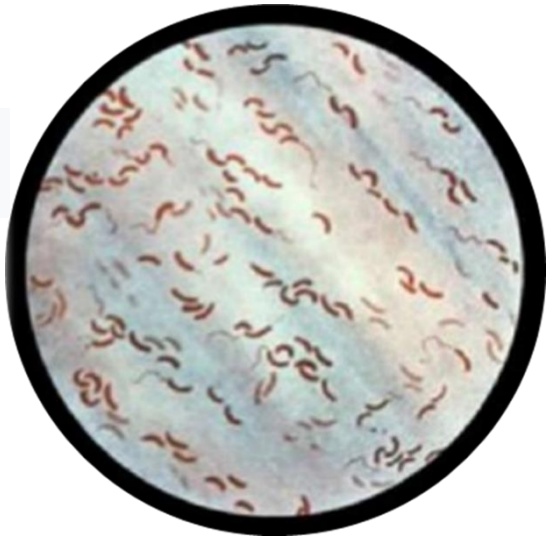


Vibrios

Family: Vibrionaceae
Genus: Vibrio, Aeromonas, Plesiomonas
Species: V. cholerae, V. parahaemoliticus, V. vulnificus

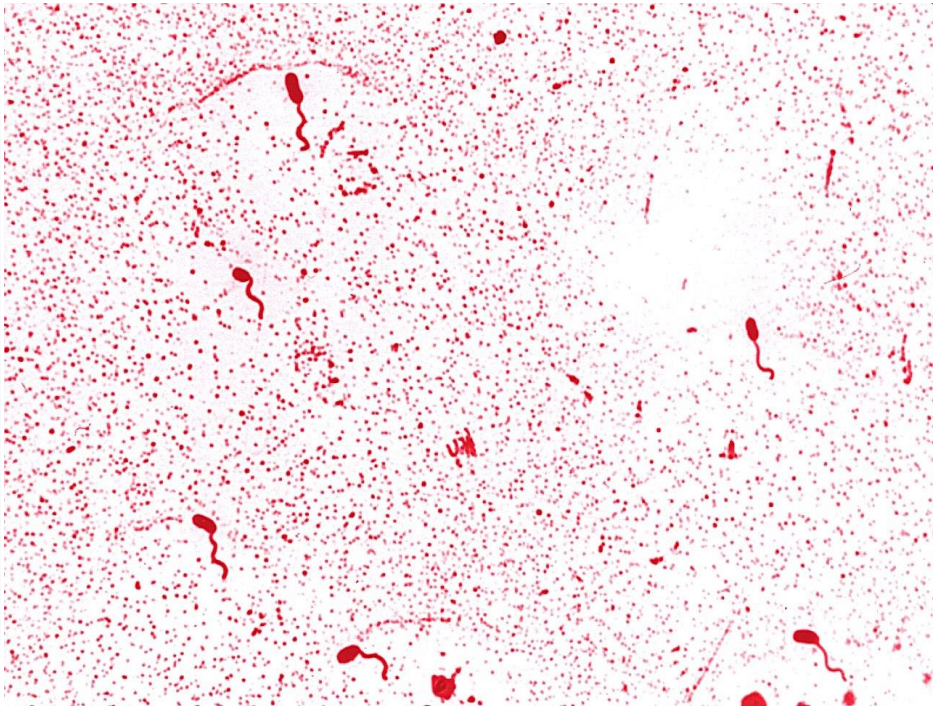


Genus Vibrio (smear from pure culture. Gram method, x100)

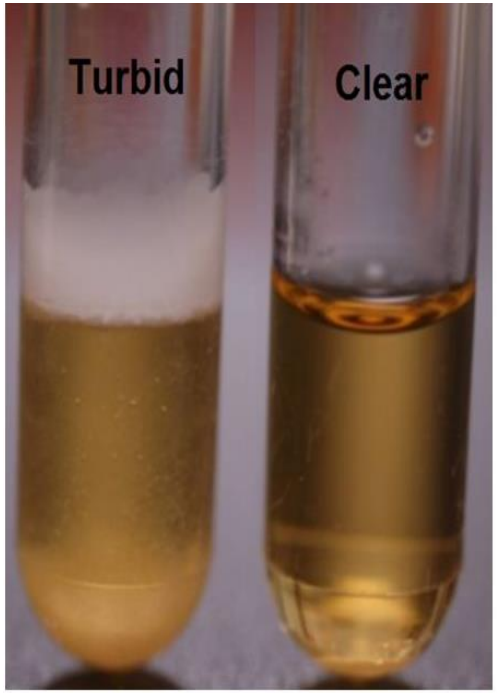


Morpho-biological properties:

The genus Vibrio is a Gram-negative, curved, polymorphic, motile (monotrich) rod-shaped bacterium that does not form spores or capsules. alkaline, optimum pH 7.6-9.0

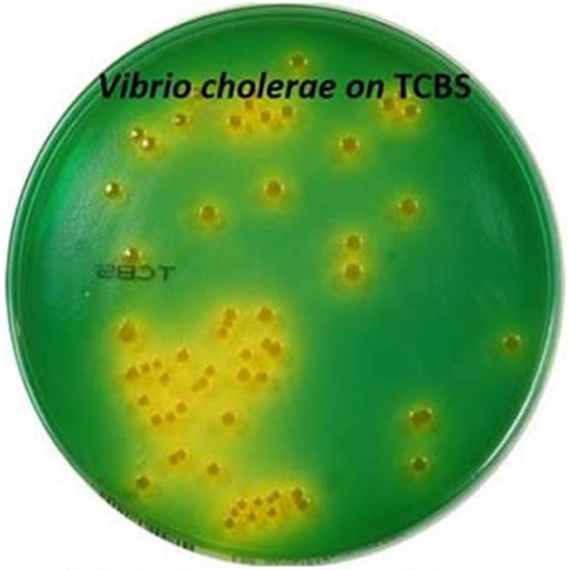


Genus Vibrio - (cultural properties)



1% peptone water

Growth on alkaline blood agar



TCBS-agar

V.cholerae - yellow colonies

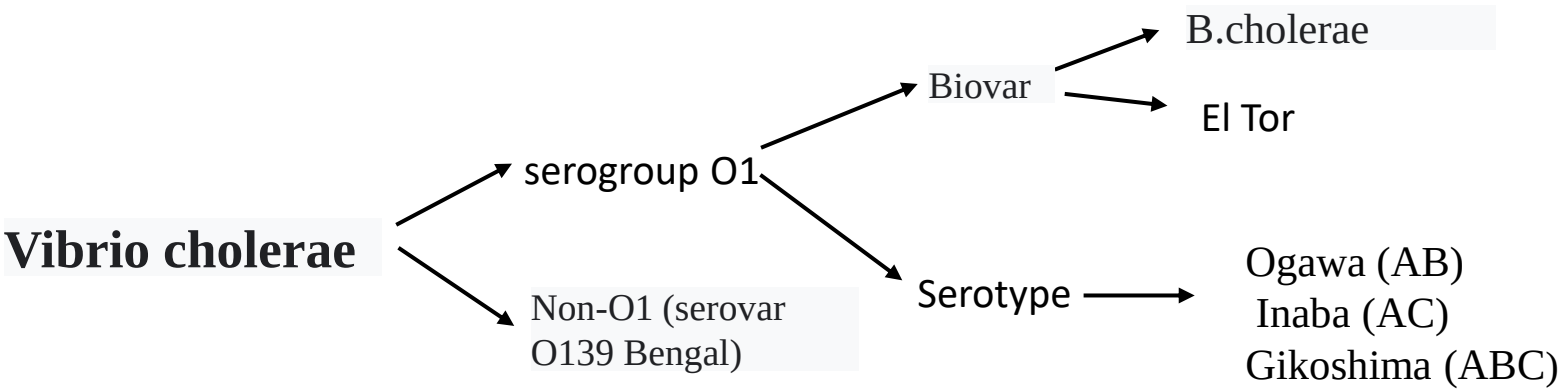
Genus Vibrio –
(biochemical properties)

- Possess saccharolytic activity: Carbohydrates are fermented with the formation of acid (glucose, sucrose, maltose, mannose)
- Possess proteolytic activity: form indole hydrolyze casein liquefy gelatin do not form hydrogen sulfide
- Oxidase-positive

Differential signs of cholera pathogens:

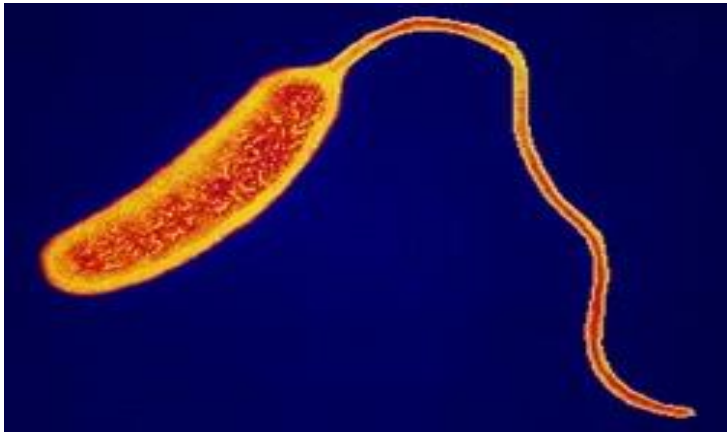
sign	Cholerae biovar	El Tor biovar	B.cholerae O139
Voges-Proskauer reaction	+	+	+
Phage sensitivity.	+	-	-
Sensitivity to phage El Tor	-	+	-
Agglutination of chicken erythrocytes	-	+	+
Sheep erythrocyte hemolysis	-	+	-
Sensitivity to polymyxin	+	-	-

Vibrio cholerae

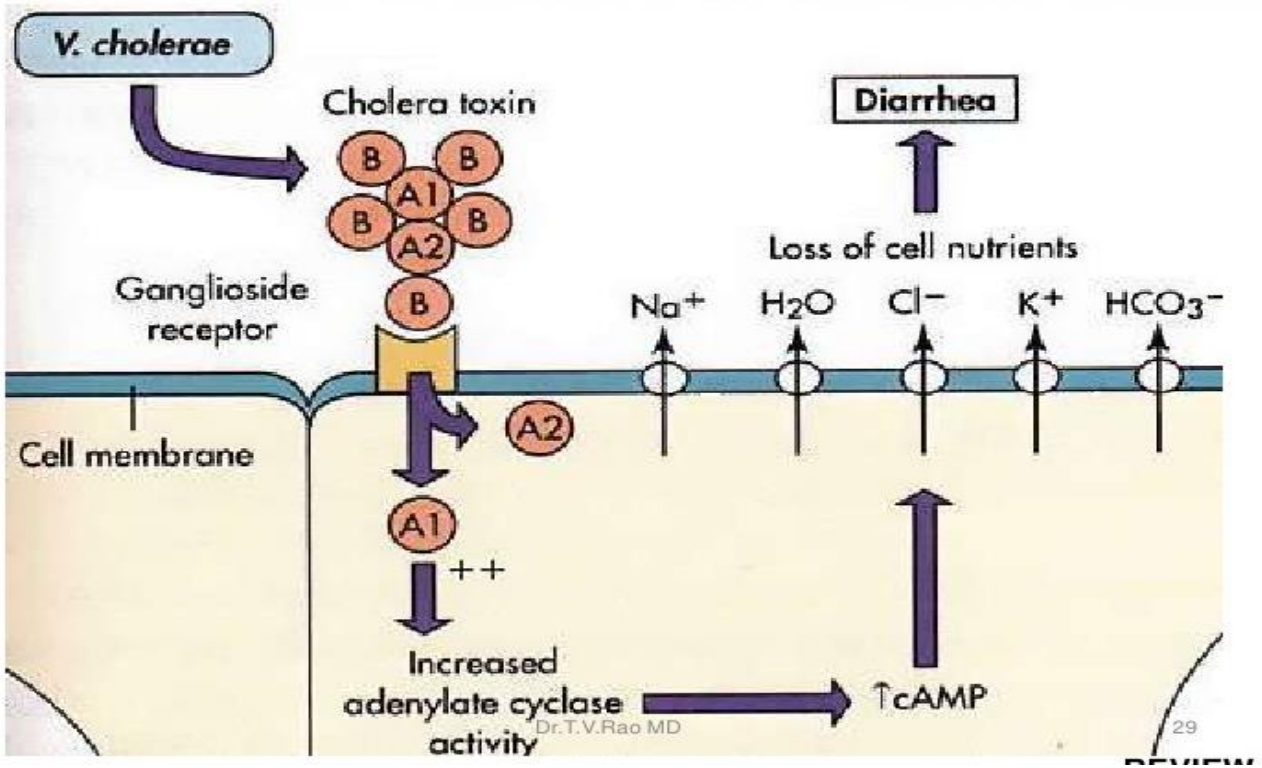


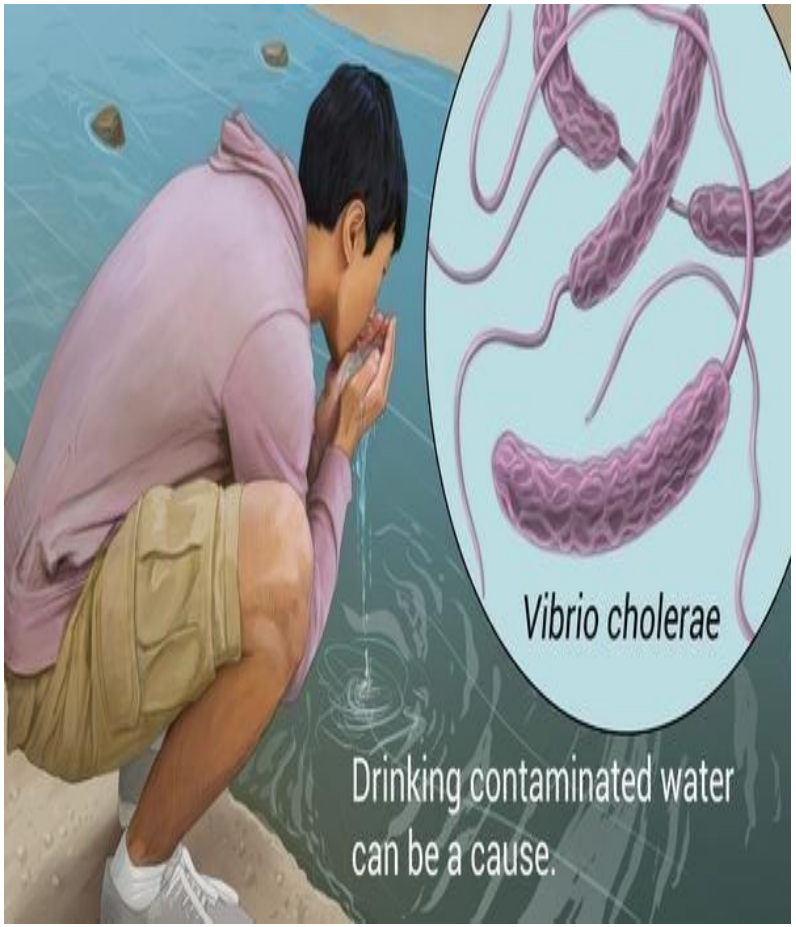
Genus Vibrio –
(pathogenicity factors)

flagellum adhesive pili (colonization of microvilli, biofilm formation) mucinase, neuraminidase (contribute to the implementation of the action of the toxin) endotoxin (starts the synthesis of prostaglandins, causing smooth muscle contraction and tenesmus soluble hemagglutinin protease exotoxin (cholerogen) – activation adenylate cyclase, increased cAMP synthesis



Mechanism of action of cholera toxin (cholerogen toxin):





CHOLERA

It is characterized by toxic damage to the small intestine, a violation of the water-salt balance and high mortality. Most vibrios die in the acidic environment of the stomach. Cholera is not an invasive infection, the pathogen does not enter the bloodstream. Cholera is one of the most dangerous quarantine infections.

infectious dose:

with water - 109 - 1010
with food - 102 - 104

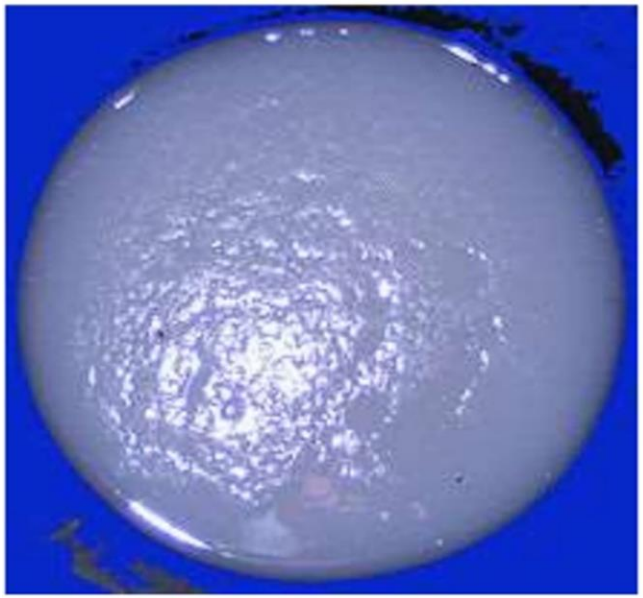
Clinical manifestations:

Enteritis - diarrhea (the stool looks like "rice water") gastroenteritis (the entry of a toxin into the blood along with diarrhea is accompanied by vomiting) dehydration (loss of water and electrolytes) I degree up to 3% II degree up to 6% III degree up to 9% IV degree more than 10% (hypovolemic shock, anuria, metabolic acidosis, death (if untreated)

"hands of the laundress" "symptom of the setting sun" "hippocratic face" "choleric algid" body temperature is lower 34oC

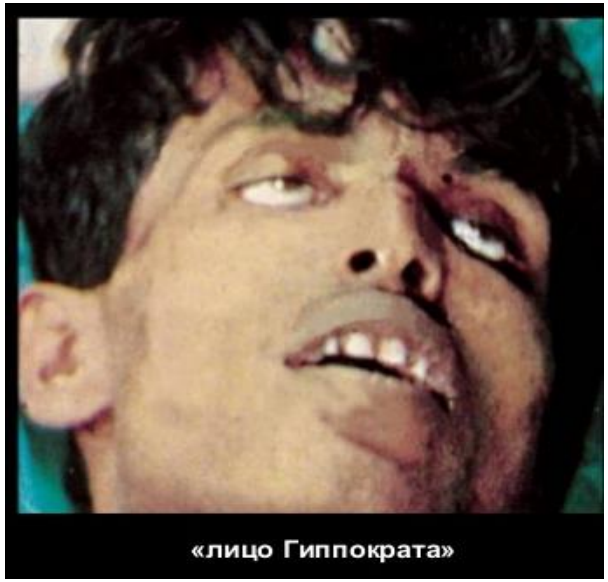
Clinical manifestations:

"washerwoman's hand" "symptom of the setting sun" "hippocratic face" "cholera algid" (decrease in body temperature up to 34o C)

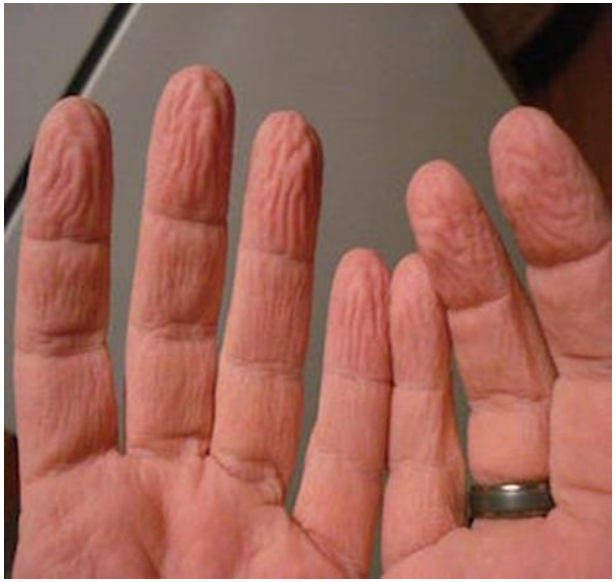


The stool has the character of "rice water"

Clinical manifestations:

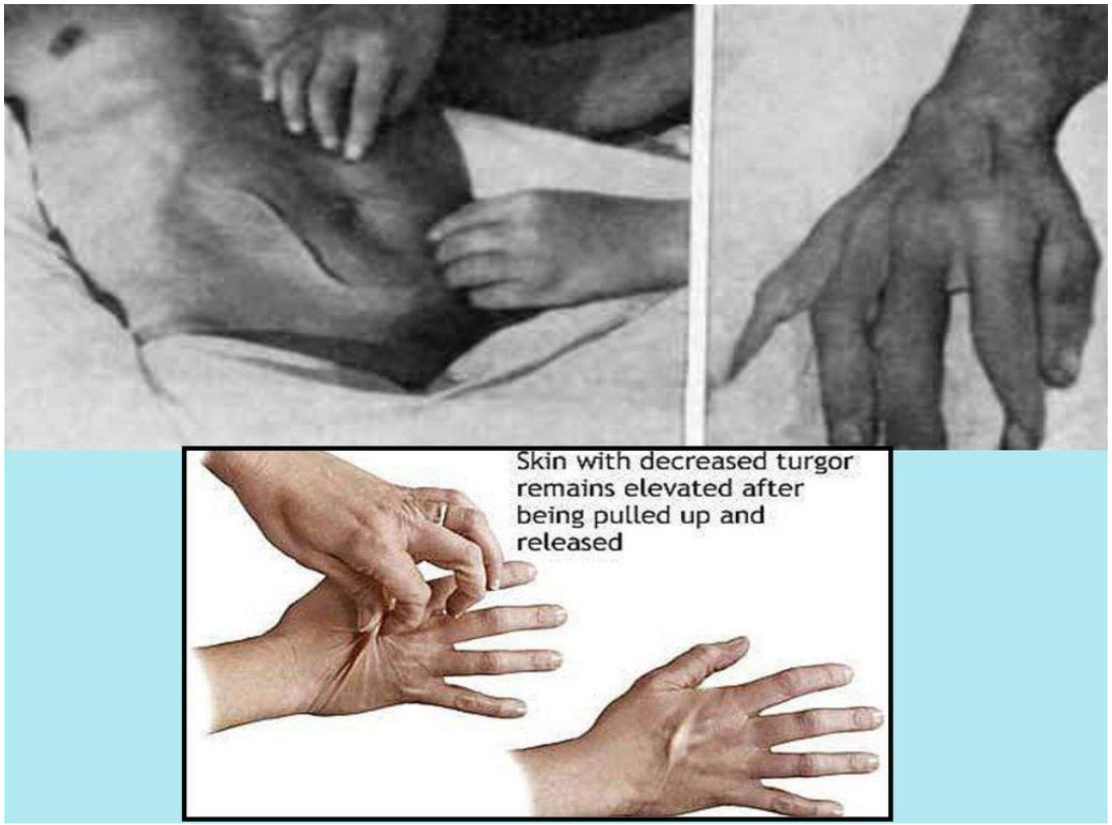


"hippocratic face"



"washerwoman's hand"

Clinical manifestations:



As a result of dehydration, elasticity (turgor) of the skin is lost.

World Health Organization

!!!

According to WHO data, 1.3-4 million cases of cholera infection and 210,000 to 143,000 deaths are registered annually in the world.

Microbiological diagnosis of cholera:

Research materials:

excreta vomit section material during mass examinations, they take 1 ml of water and 200 g of food when examining for vibriocarrier, laxatives are prescribed, liquid intestinal discharge is examined by inoculation in 1% peptone water Note: research is carried out in special regime laboratories!

Microbiological diagnosis of cholera:

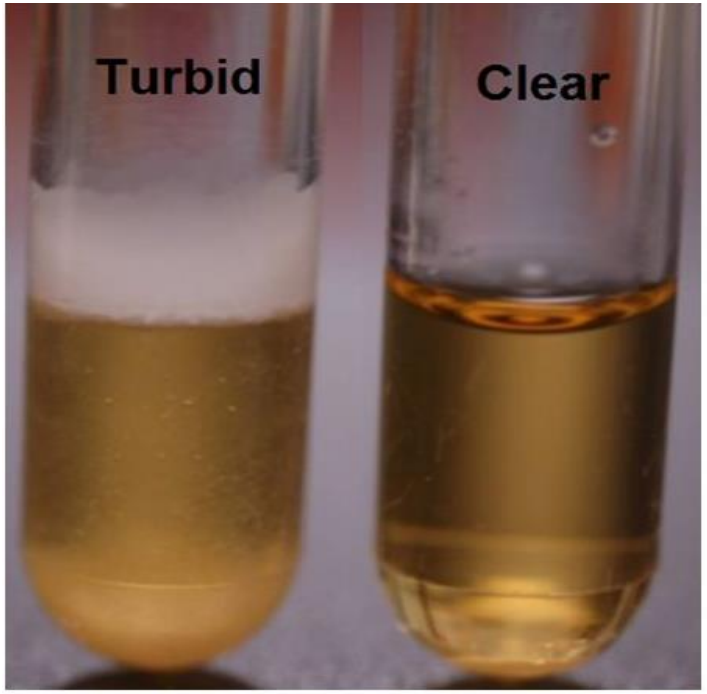
Microscopic method –preparation of smears from pathological material, Gram stain, determination of mobility by the method of "crushed", "hanging" drop

Bacteriological (cultural)

inoculation of the material in 1% alkaline peptone water, TBCS agar, alkaline blood agar (pH-9.0), cultivation at 37o C. 4 hours after cultivation, a film forms on the surface of 1% peptone water. Hanging-drop smears are prepared from the film to study bacterial motility. Gram staining is also carried out. After 10-12 hours, grown colonies are examined on dense nutrient media.

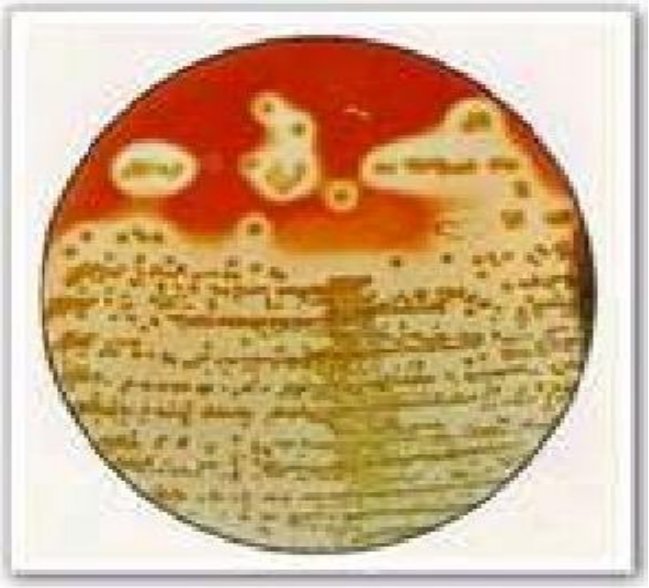
Genus Vibrio - (cultural properties)

1% alkaline peptone water - It is an elective medium for vibrios. After 4-6 hours, a film forms on the surface of the medium, which is destroyed by shaking. Smears are prepared from film samples and examined for mobility.



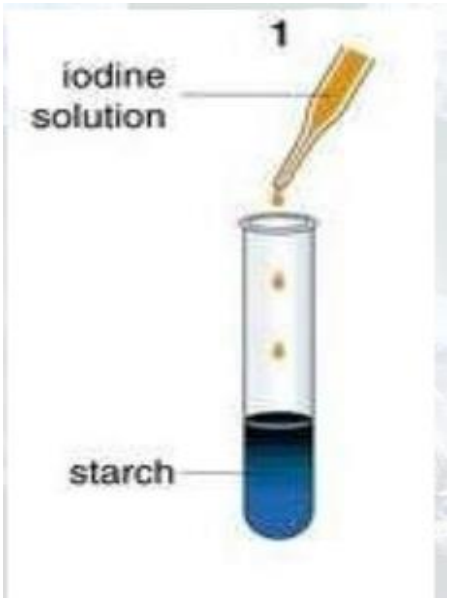
1% alkaline peptone water

Growth on alkaline blood agar
(Biovar El-Tor causes hemolysis. biovar cholerae does not show hemolytic activity)

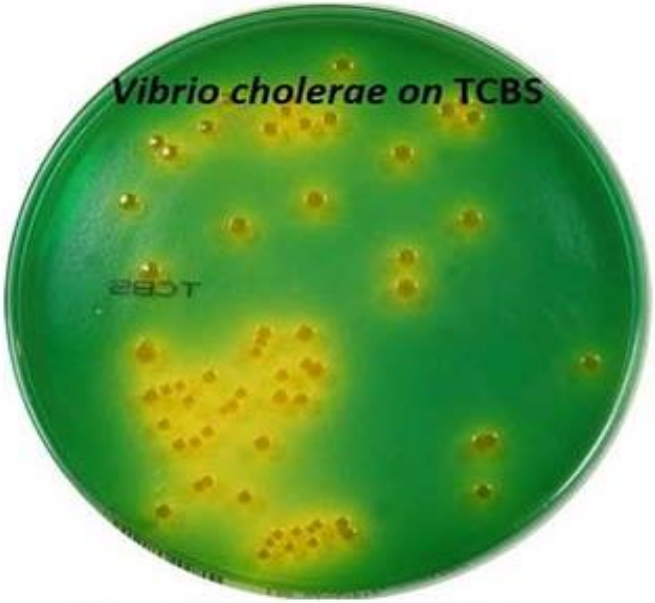


starch test

Suspicious colonies are inoculated by injection into test tubes with liquid starch. (V. cholerae, El-Tor) break down starch and therefore, when iodine solution is added, the color of the medium does not change (does not turn blue). A color change in the test tube indicates the absence of cholera vibrios.



TCBS - thiosulfate citrate sucrose bile agar On TCBS agar, V. cholerae forms yellow colonies due to sucrose degradation. From the grown colonies, preparations are prepared using the “crushed” and “hanging” drop method and studied for mobility.



Yellow colonies of V.cholerae

- Serological method - carried out by setting up a detailed agglutination reaction with specific O-serum and an immobilization reaction (15-20 minutes) with an isolated culture. These methods for diagnosing cholera are indicative and require further research. As an accelerated method, the immunofluorescence method (RIF) is used.

- Molecular genetic method - PCR (polymerase chain reaction)

To detect bacteriocarrier, it is recommended to inoculate feces (taken from 10 individuals) in 200 ml of peptone water and O-agglutinating serum, which are kept in a thermostat for 3-4 hours. In the case of growth of vibrios at the bottom of the test tube, growth is observed in the form of a lump of cotton wool, from which the “hanging drop” preparation is prepared, and when the mobility of the pathogen is established, the feces of 10 persons are subjected to additional examination

Treatment and prevention:

Treatment : restoration of water-salt balance solutions enriched with electrolytes (to prevent seizures)
Antibiotics (tetracycline)

Specific prevention: A complex preparation has been developed, consisting of cholerogen-anatoxin and O-antigen of both biovars Cholerae and El-Tor.

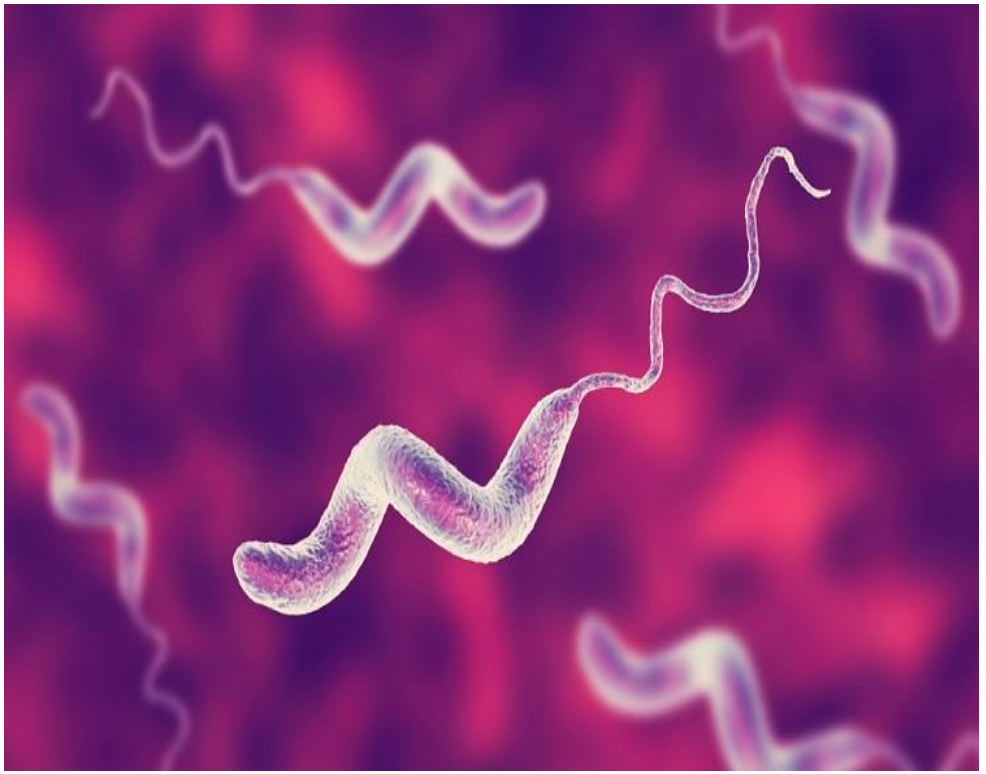
Campylobacter

Genus Campylobacter -

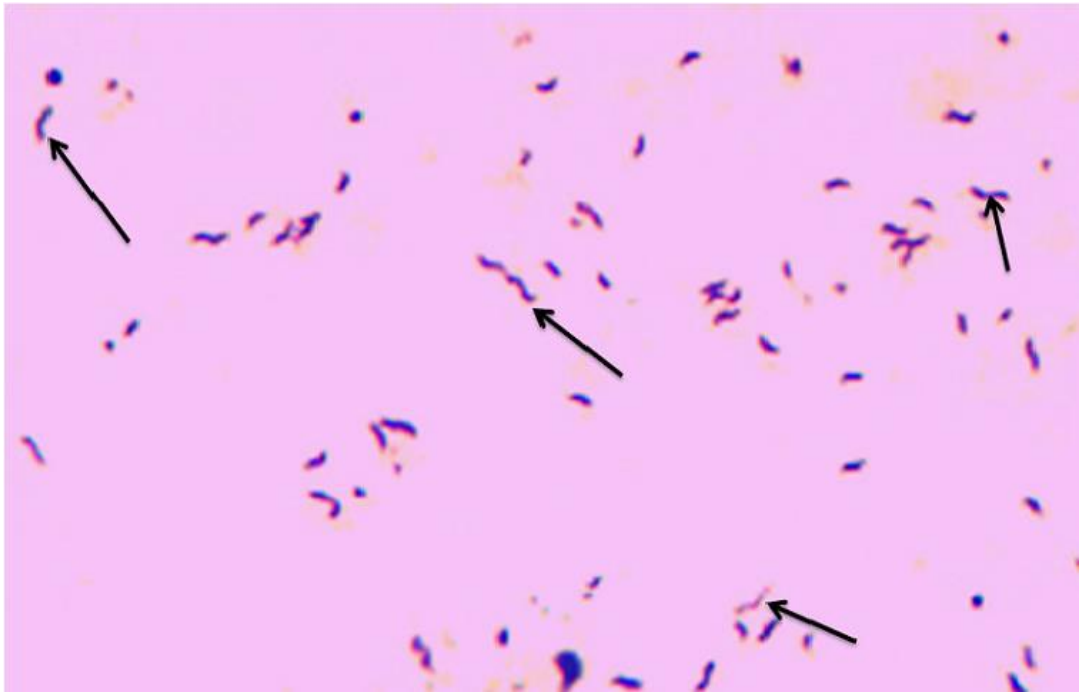
Family: Campylobacteraceae

Genus: Campylobacter

Species : C.jejuni

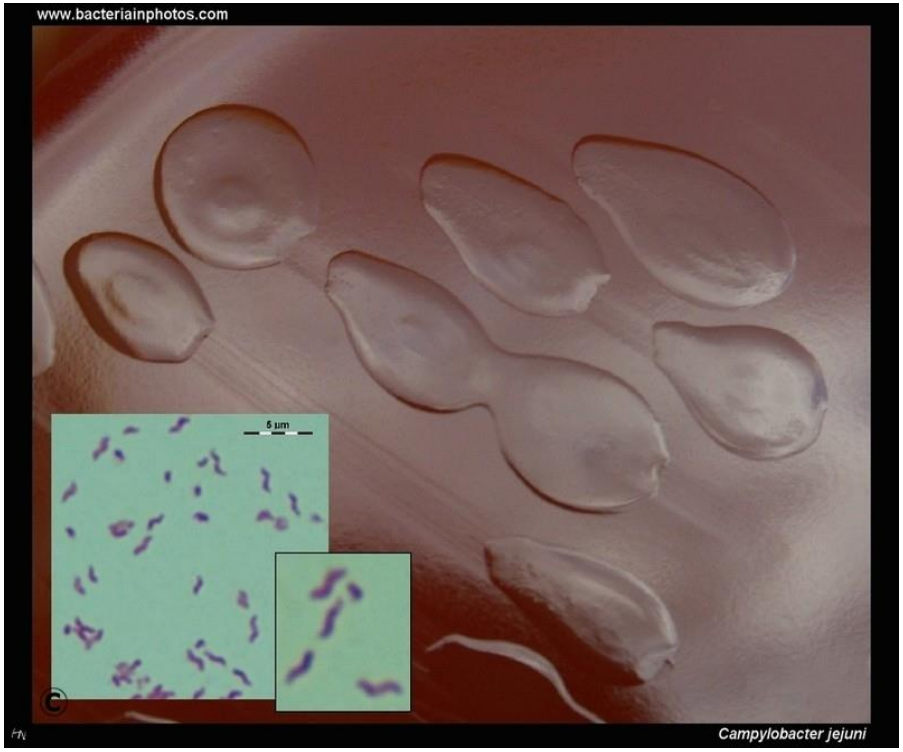


Genus Campylobacter - curved, Gram-negative S-shaped bacteria, mobile, do not form spores and capsules.



gull wings (Campylobacter jejuni, Gram stain, x100)

Campylobacter jejuni - (blood agar colonies)



Genus Campylobacter - (biochemical properties)

Weak saccharolytic activity: Sugar is not fermented Proteolytically active: Restore nitrates Form hydrogen sulfide Oxidase-, catalase-positive.

Genus Campylobacter - (pathogenicity factors)

- Specific adhesins flagella
- thermolabile
- enterotoxin
- cytotoxin
- endotoxin

Genus Campylobacter - (diseases caused)

Clinical manifestations:

Enterocolitis Meningitis
Diseases of the oral cavity GVZ
Polyradiculoneuritis syndrome Reactive arthritis

Microbiological diagnosis of campylobacteriosis:

research material - feces Microscopic method Detects gull-wing bacteria in a Gram-stained stool smear. Dark-field and phase-contrast microscopy can be used to identify motile campylobacter. Bacteriological (cultural) The research material is feces, inoculated on selective media (Skirrow medium, with blood, hemin, growth factors, protein hydrolysates, amino acids, etc.). For species differentiation, they are cultivated under various temperature conditions. C.jejuni grows at 420C. Determination of sensitivity to antibiotics

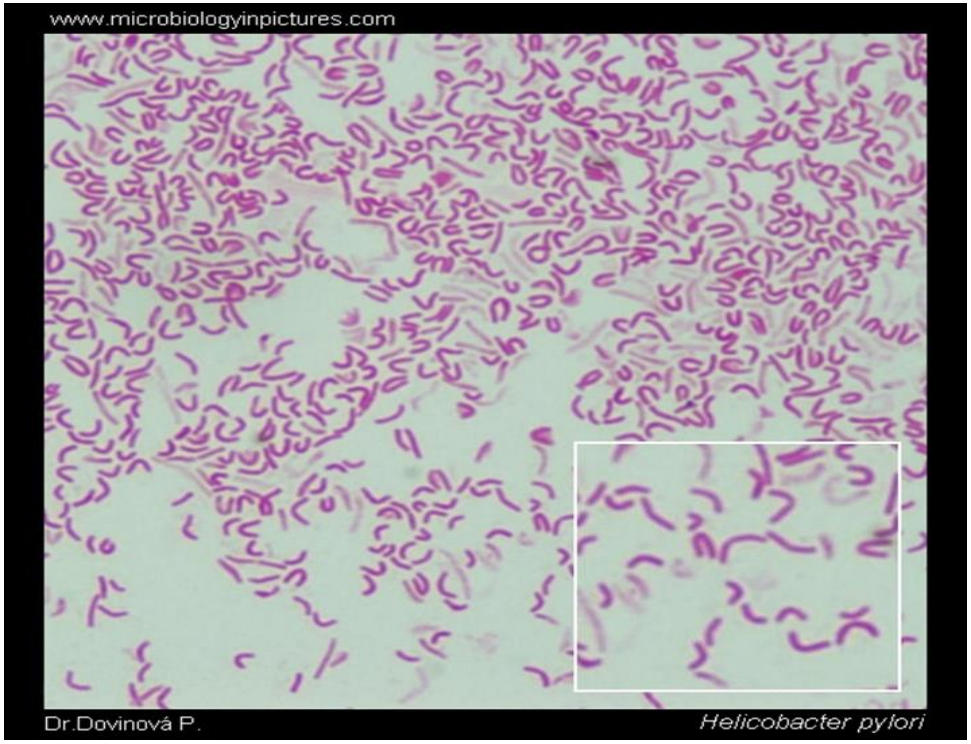
Treatment and prevention:

Treatment: in most cases there is no need for treatment, but if there is a threat of serious complications, erythromycin, tetracycline, levomycetin and ciprofloxacin should be used.
Specific prophylaxis has not been developed!
Nonspecific prophylaxis is similar to that for intestinal infections.

Genus Helicobacter

Family: Helicobacteriaceae
Genus: Helicobacter
Species: H. pylori

The genus Helicobacter is a gram-negative, curved or S-shaped, motile, non-capsular bacterium that does not form spores.



“flying swallow” (Helicobacter pylori, Gram method, x100)

Helicobacter pylori - (3 day old colonies on blood agar)

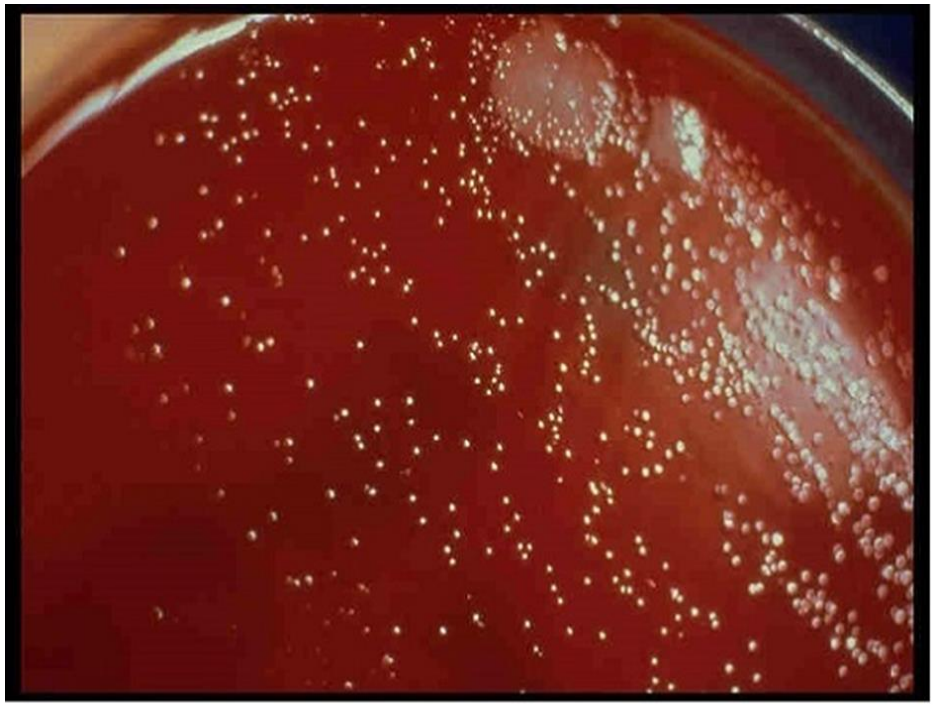


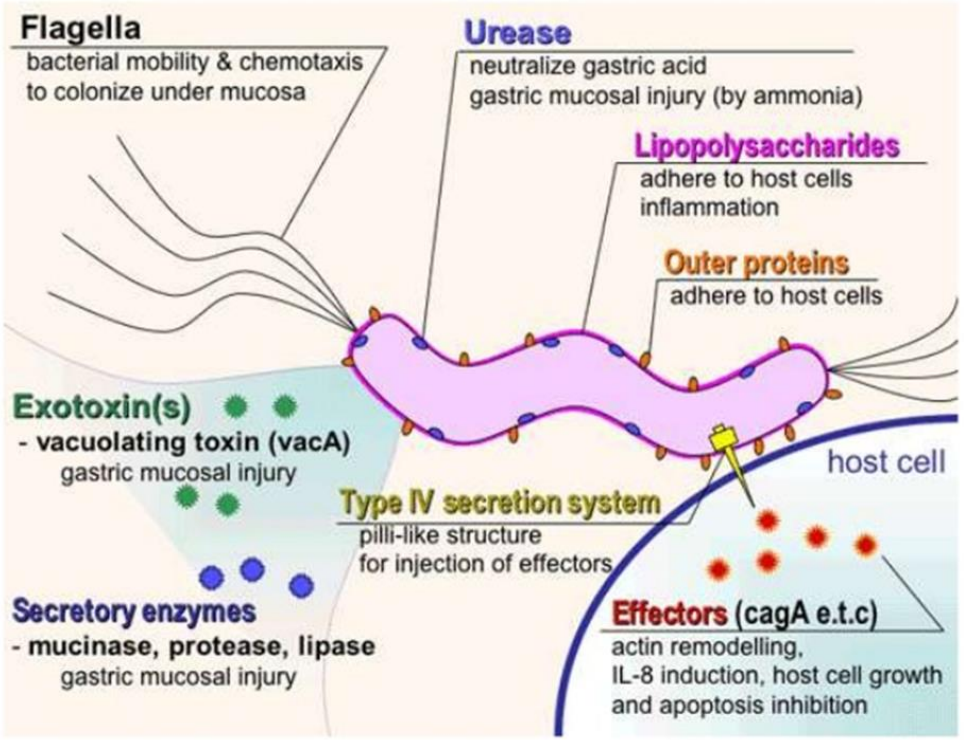
Fig. 3 day culture of *Helicobacter pylori* on blood agar

Helicobacter pylori - (biochemical properties)

Weak saccharolytic activity: Sugar is not fermented Weak proteolytic activity: Does not restore nitrates forms hydrogen sulfide oxidase- and catalase-positive has urease, transpeptidase and phosphatase activity

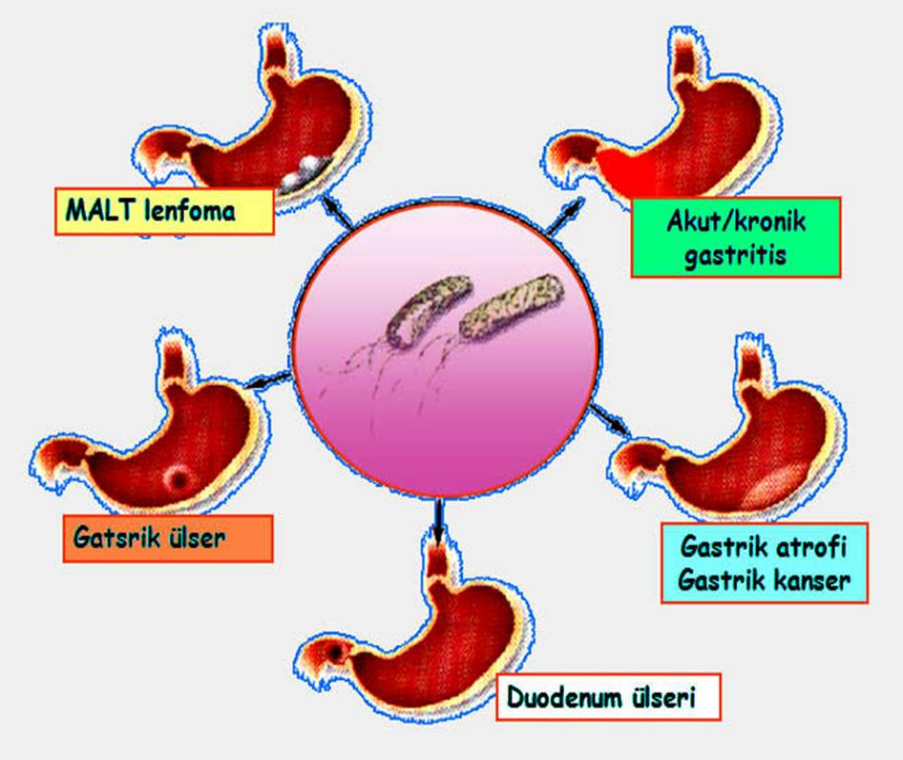
Helicobacter pylori - (pathogenicity factors)

urease enzyme
flagellum protease
cytotoxins (polypeptide cytotoxin (CagA), vacuolating cytotoxin (VacA) adhesins outer membrane proteins
peptidoglycans
lipopolysaccharide (LPS)

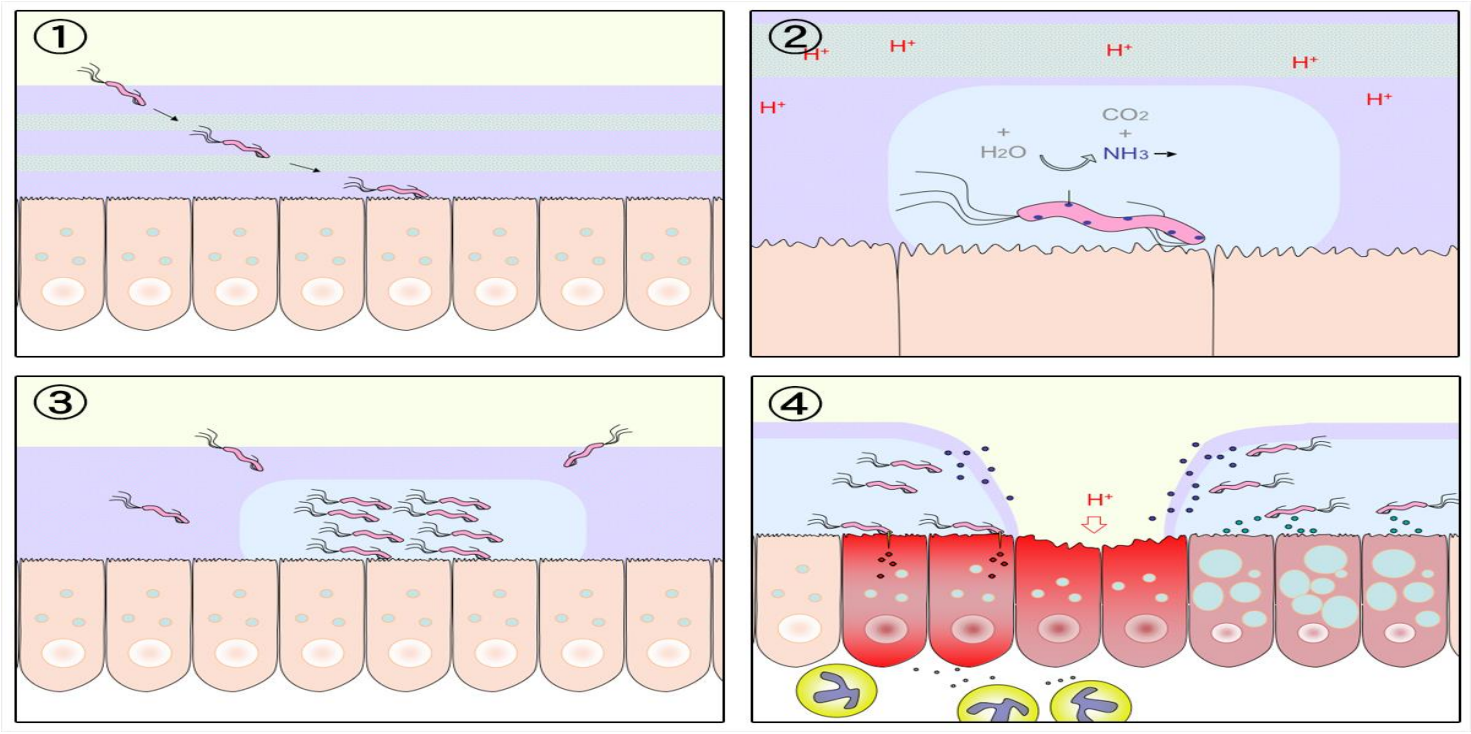


Helicobacter pylori– (diseases caused)

Gastroduodenitis (acute infection) Chronic gastritis stomach ulcer Duodenal ulcer Stomach cancer MALT - lymphoma (mucosa-associated lymphatic tissue)

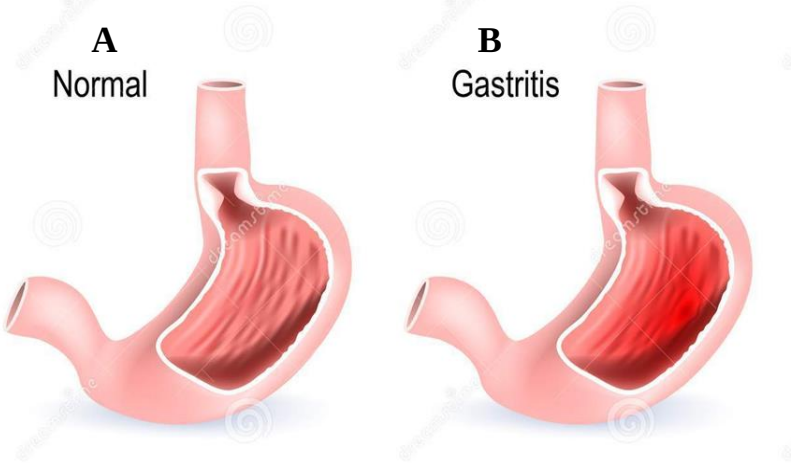


PATHOGENESIS:

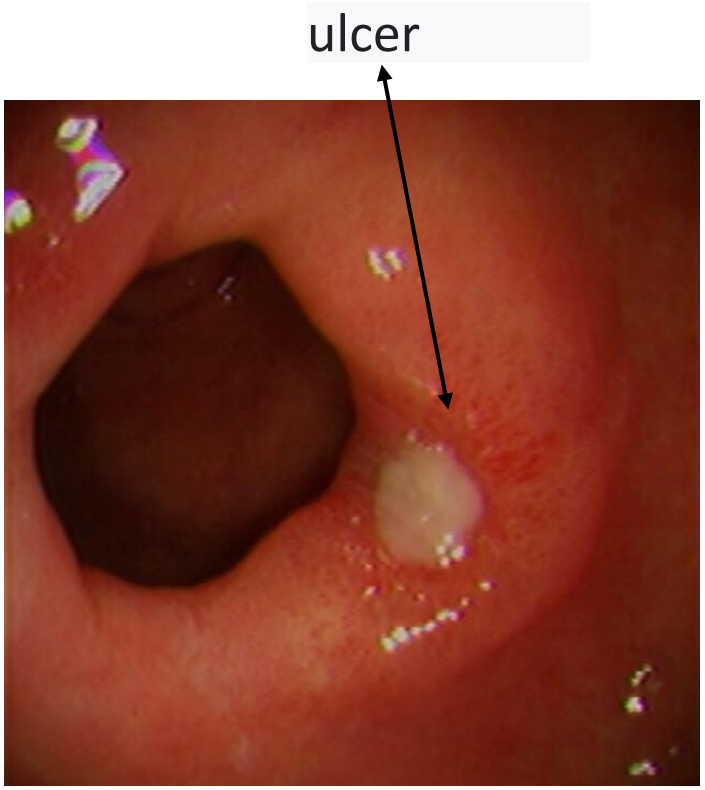


1. The introduction of H. pylori into the mucous membrane.
2. H. pylori urease production creates an ammonia cloud around the bacterium
3. H. pylori colonization
4. The mucosa is exposed to the action of gastric juice and pepsin. As a result, a chemical burn of this area of the mucous membrane develops, which further leads to the development of inflammation.

Endoscopy



Endoscopy of the stomach Gastric mucosa - normal Gastric mucosa - with gastritis



Ulcer of the pyloric canal of the stomach

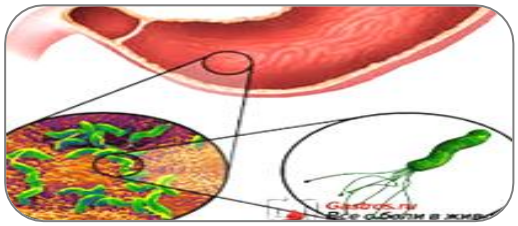
Microbiological diagnosis of helicobacteriosis:

Research materials: biopsy from the mucous membrane of the stomach and duodenum gastric juice excreta blood

DIAGNOSIS

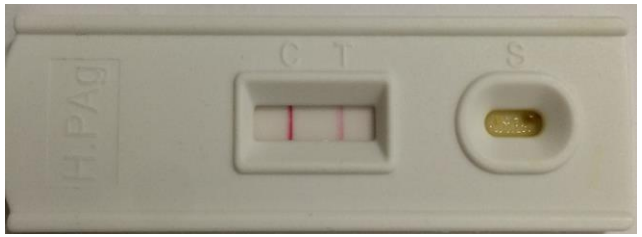
invasive

- endoscopy.
- histological
- accelerated urease test
- cultural
- molecular genetic method



non-invasive

- urea respiratory
- serological
- test for antigens in feces
-molecular-genetic-
- cue method



Cultural method

The method of isolating a pure culture of H. pylori from gastric biopsy samples is highly specific, but characterized by low sensitivity (100% specific, 85%-95% sensitive). The causative agent is demanding on cultivation media, therefore, when it is cultivated in vitro, it is necessary to use special transport media and incubation conditions. For example, biopsy specimens can be stored in Stuart's transport medium for 24 hours at 4°C.

Cultural method

Nutrient media:

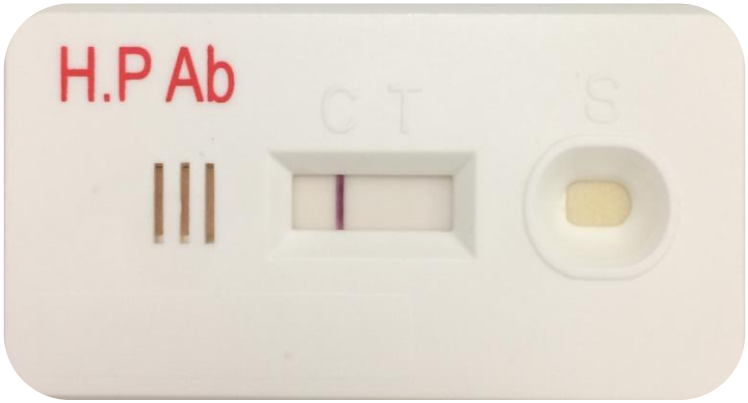
- Skirrow agar - Columbia agar with blood - Pylori agar (enriched with sheep or horse blood) Brain Heart Agar Trypticase Soy Agar

On blood agar, they form small transparent colonies 1-2 mm in size. Some strains exhibit hemolytic activity (alpha hemolysis). Microaerophiles (80-90% N2, 5-10% CO2, 5-10% O2). Grow on complex nutrient media at 35-37°C for 5-7 days. In liquid media, they form a bluish-gray surface film.

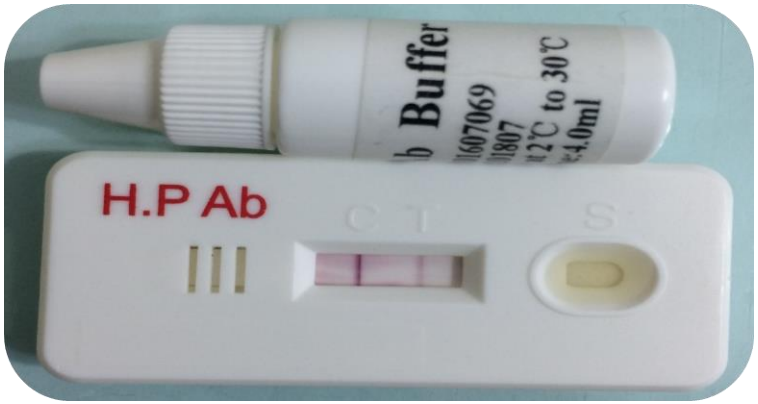
Serological method:

- ELISA (enzyme-linked immunosorbent assay)
- Western Blot Immunofluorescence reaction (RIF)
- Complement fixation reaction (CFR)
- Latex agglutination Rapid antibody test (in serum)

Rapid test for antibodies in blood serum:



Negative result

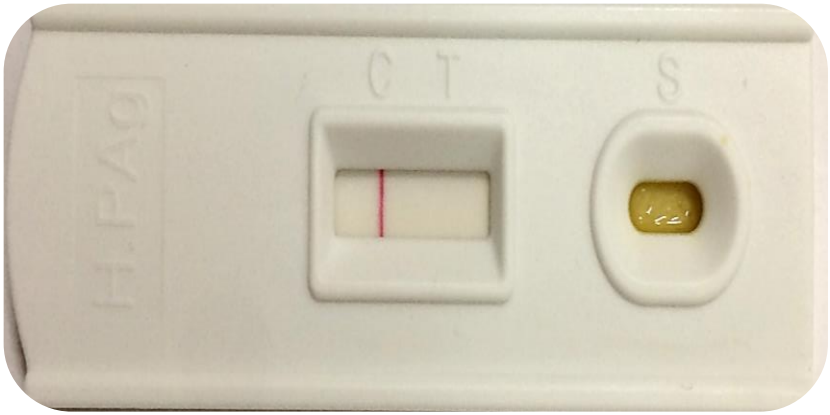


Positive result

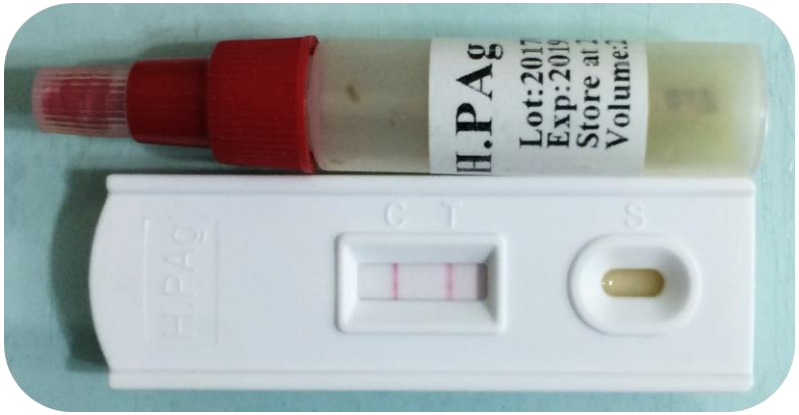
Method for determining antigens in feces

The non-invasive test for H. pylori antigen in feces is simple and easy to perform, and allows detection of active infection. This test is used in epidemiological studies to detect the incidence of H. pylori infection in asymptomatic individuals, as well as to monitor the effectiveness of treatment (after 4 weeks). Sensitivity and specificity of the method up to 95%

Rapid test for antigens in feces:



Negative result



Positive result

CLO test with stomach biopsy (Campylobacter-like organism)

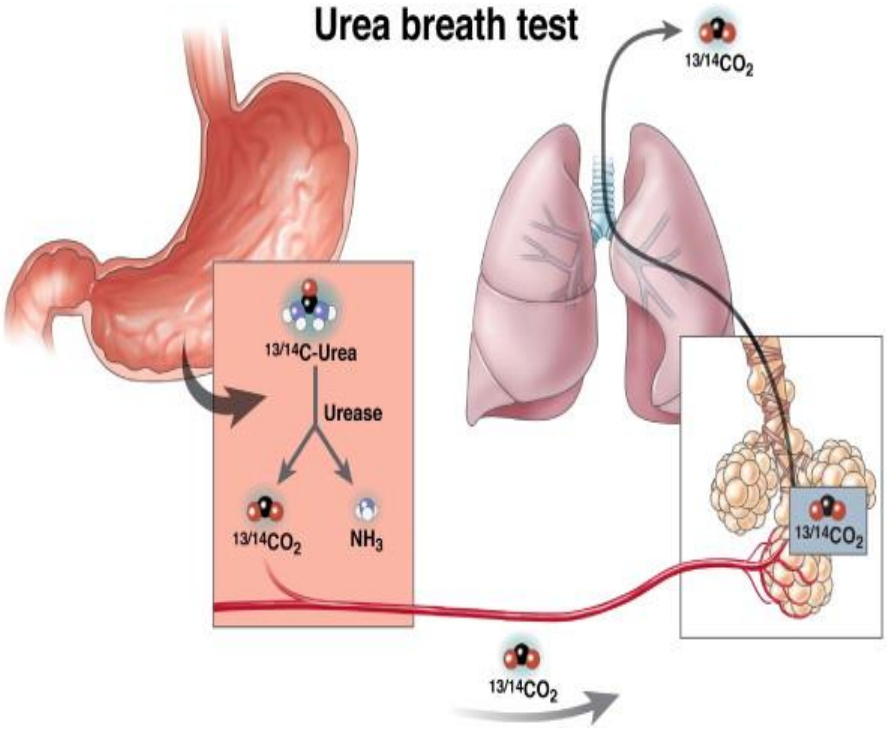
Negative result

Positive result

Helicobacter pylori (diagnosis)

Urease breath test

The patient is given to drink a solution of urea labeled with the carbon isotope 13C. Under the action of the pathogen urease, urea is hydrolyzed to ammonia and carbon dioxide containing labeled carbon. Isotopically labeled carbon dioxide enters the bloodstream, then enters the lungs, and then into the air exhaled by the patient



Treatment and prevention:

- Treatment - use two groups of drugs: antacids (omeprazole) and antibiotics (metronidazole, clarithromycin, amoxicillin, etc.).
- Specific prophylaxis has not been developed!