

Invasive infections of the digestive tract

Asso. Prof Biljana Popovska Jovičić

Invasive infections

- ◉ The common feature of invasive microorganisms of the digestive tract is that they invade the mucosa of the gastrointestinal tract
- ◉ Possible mechanisms of fluid production:
 - ◉ Endotoxin
 - ◉ Synthesis of prostaglandins
 - ◉ Impaired resorption due to damage to the epithelium

The influence of the invasiveness of microorganisms on the clinical picture

INVASIVENESS OF MICROORGANISMS	INFLUENCE ON THE CLINICAL PICTURE
Non-invasive microorganisms	<p>Short incubation - usually a few hours</p> <p>The disease starts suddenly without warning or prodrome</p> <p>The temperature is usually not elevated</p> <p>Illness is short-lived, ends spontaneously (except for cholera)</p>
Invasive microorganisms	<p>Length of incubation - at least 24-48 hours</p> <p>The disease begins gradually</p> <p>The temperature is always present, over 38°</p> <p>The disease lasts longer and treatment is often necessary</p> <p>Propensity for complications</p>

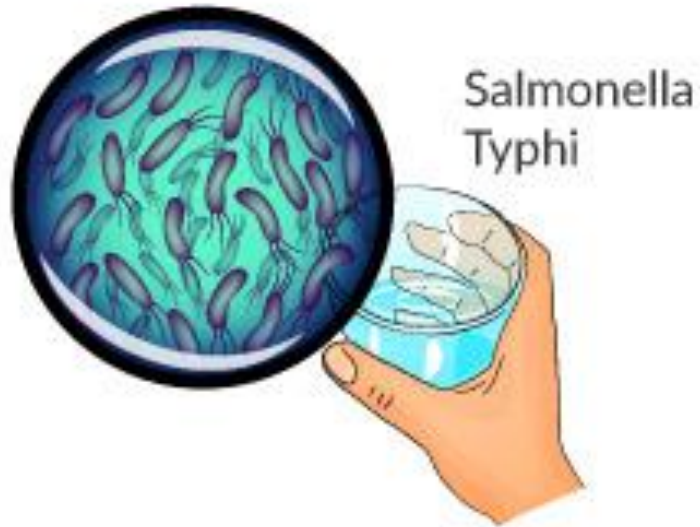
Segmentation of lesions of the digestive tract

Segment of the digestive tract	Type of stool	Characteristics of stool
Proximal part of the small intestine	Enteric type 1	Very voluminous from beginning to end Watery consistency Mostly colorless Undigested food particles
Distal small intestine	Enteric type 2	Voluminous Pulpy consistency Green or brown in color
Large intestine (left half)	Colitic stool	Initially voluminous, later scanty First few stools feculent, later scanty, with increasing mucus content, blood in stool

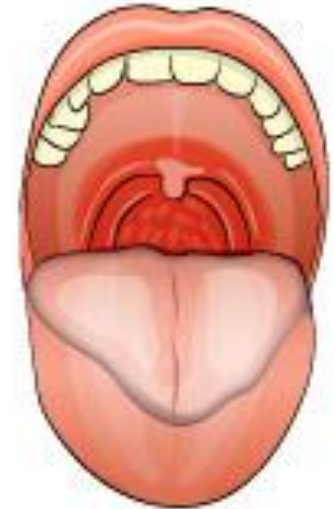
Invasive intestinal infections

- ◉ Typhoid fever
- ◉ Salmonellosis
- ◉ Campylobacter jejuni
- ◉ Yersiniosis
- ◉ Enterohemorrhagic Escherichia coli
- ◉ Intestinal infection caused by Cl. Difficile

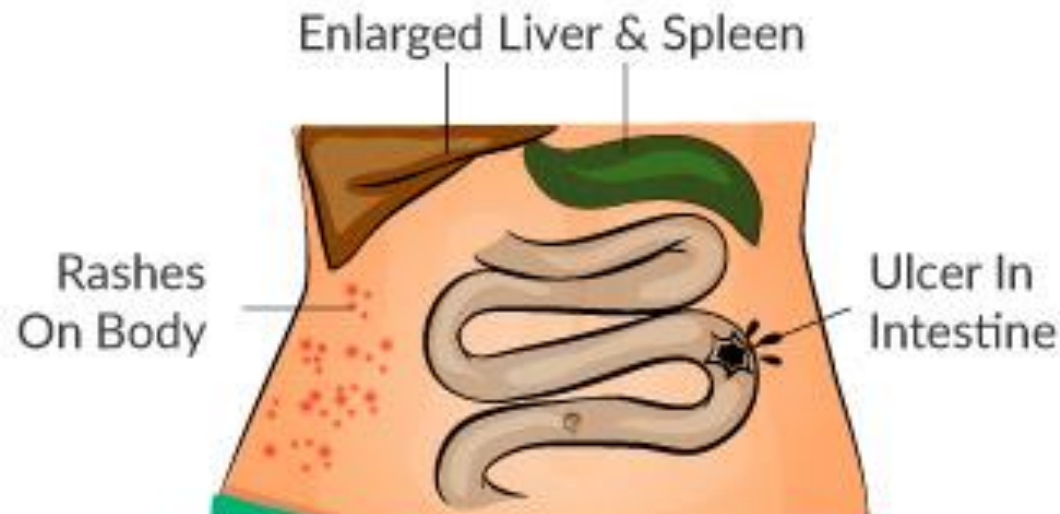
TYPHOID FEVER



White Coating
On Tongue

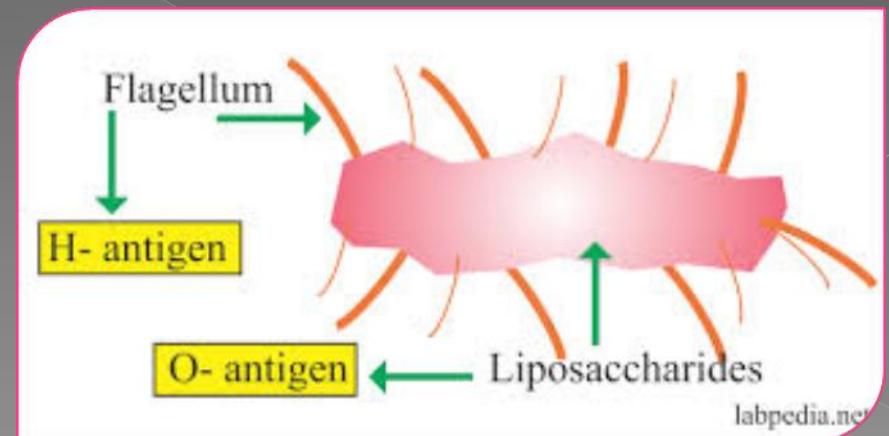


Septic toxic disease



Typhoid fever

- Severe, acute, contagious, septic-toxic
- The causative agents are *Salmonella typhi*, *Salmonella paratyphi* A, B, C
- Antigenic structure of typhus bacillus
- Somatic O antigen (endotoxin)
- Vi antigen (envelope)
- Flagellar H antigen

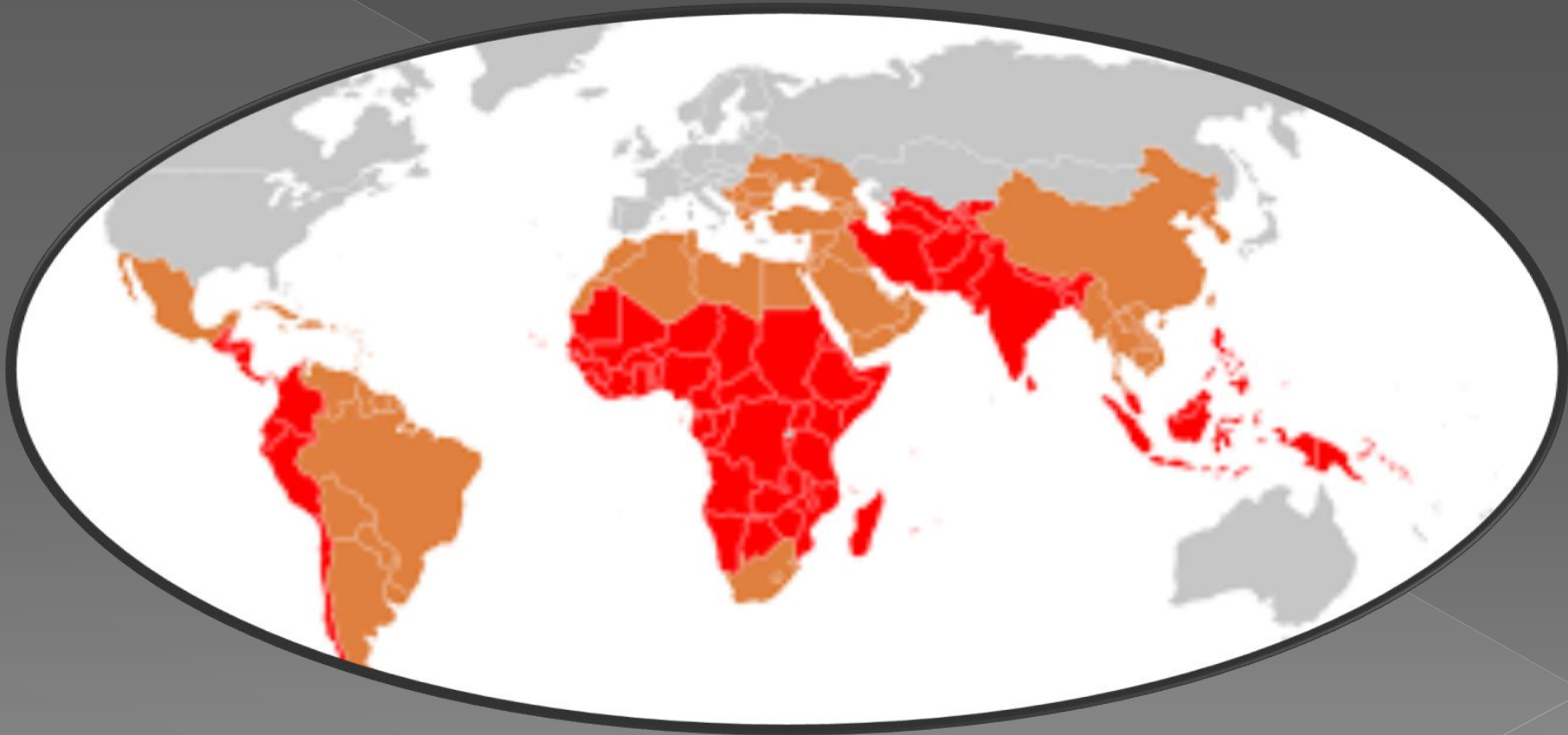


Epidemiological characteristics of typhus

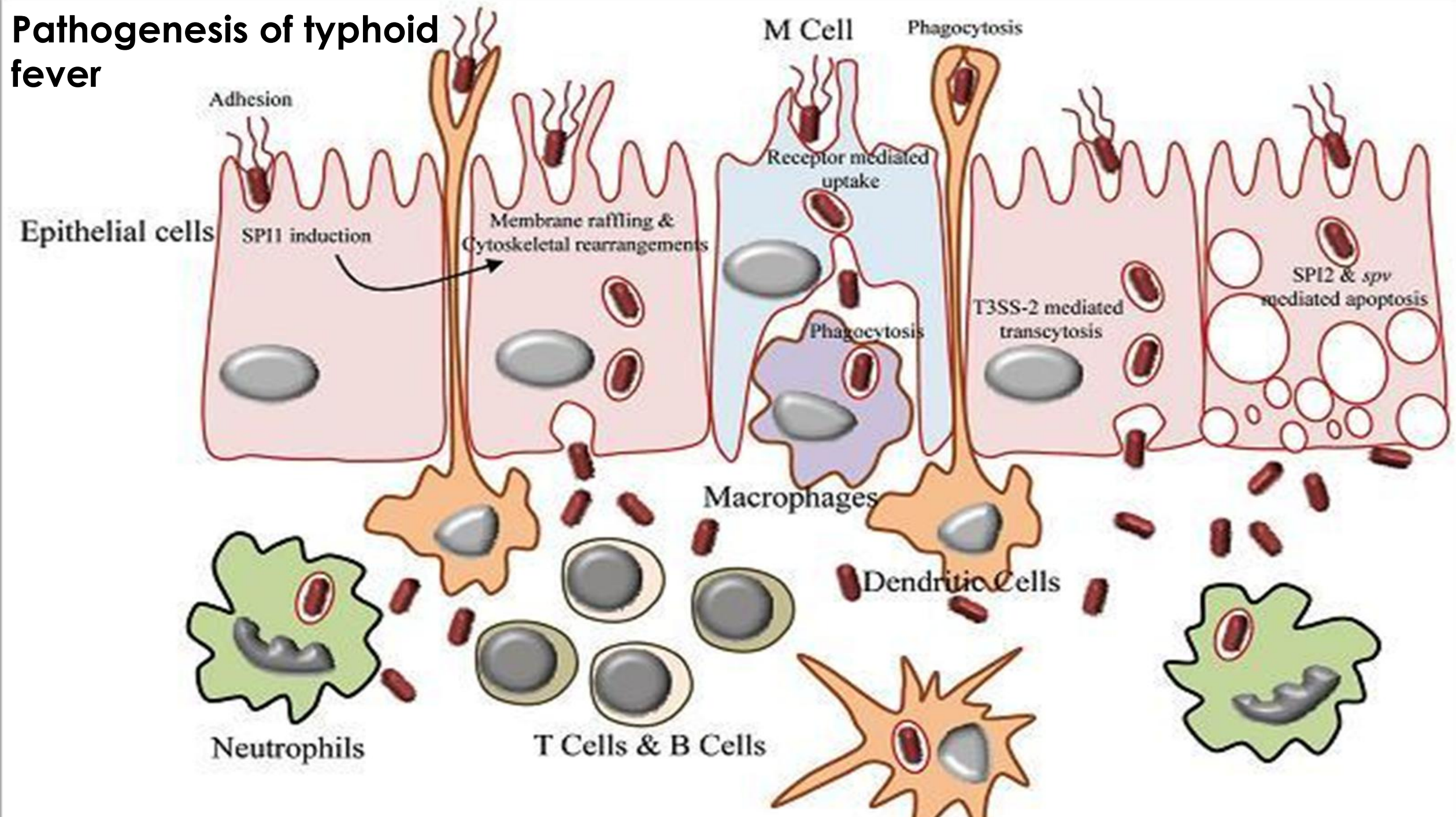
- ◉ A typical **fecal-oral** infection
- ◉ The source of infection is exclusively human (**sick or carrier**)
- ◉ It is excreted in **stool and urine**
- ◉ **Transmission of infection**
 - Direct
 - Indirect



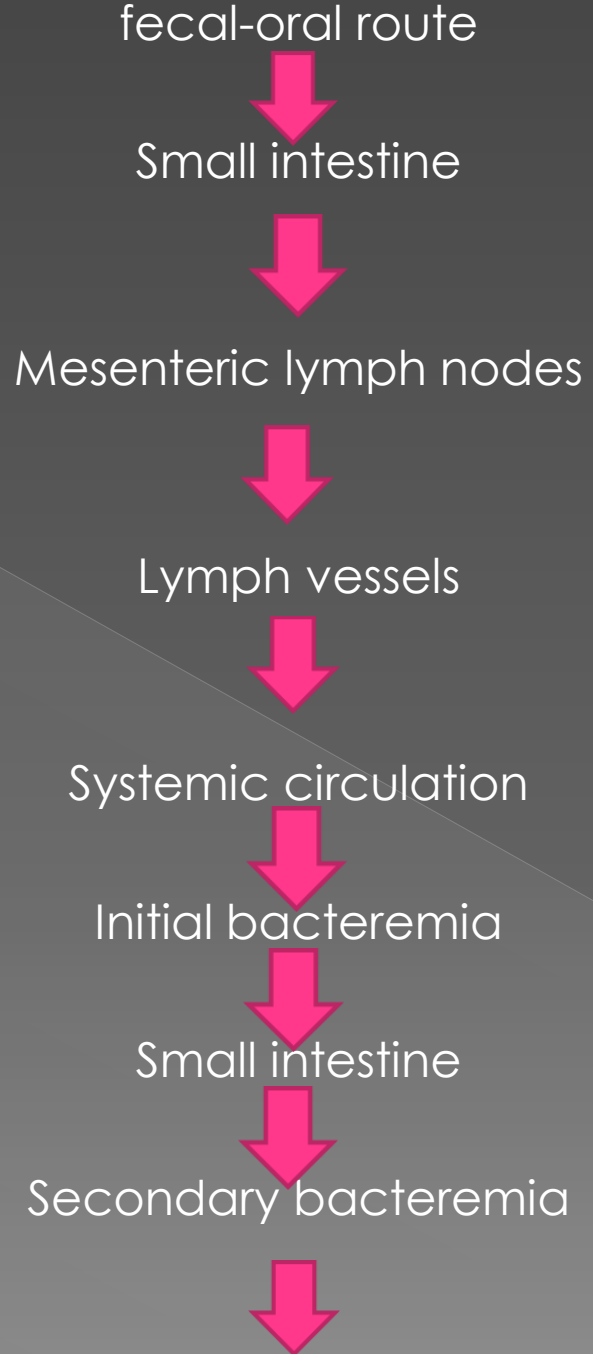
Prevalence of typhoid fever in the world



Pathogenesis of typhoid fever



**Pathogenesis of
typhoid - incubation
10-14 days**

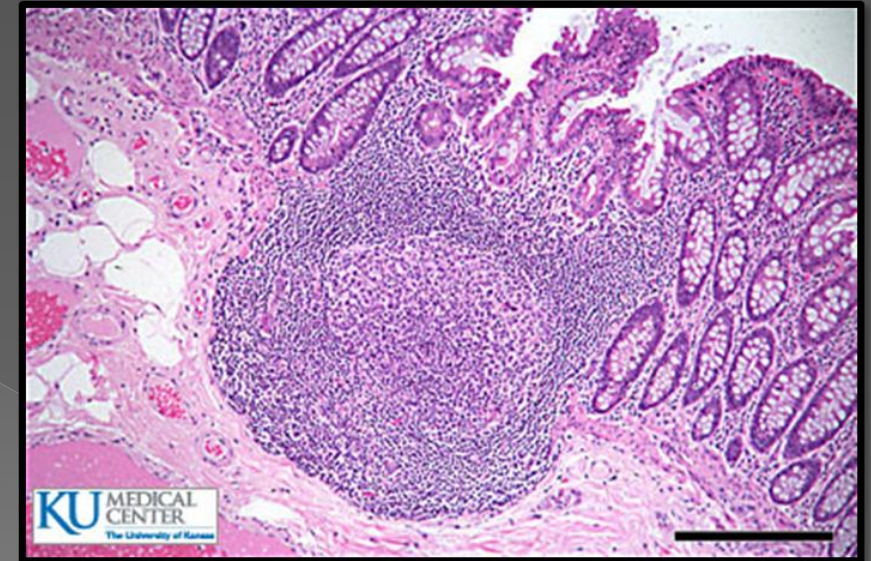


Symptomatic phase of infection and infection of many organs

Changes in the lymphatic tissue of the ileocecal region

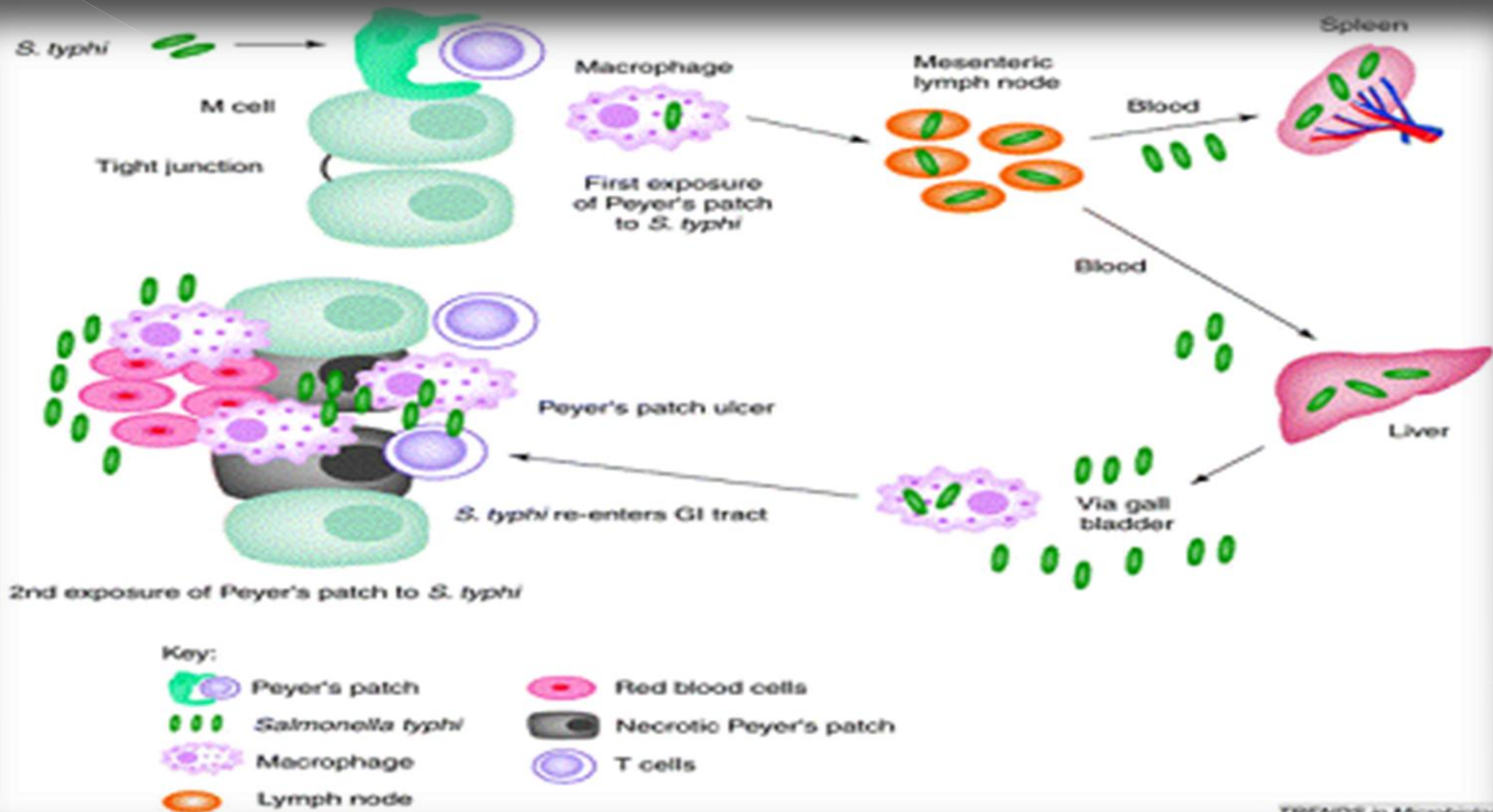
The four stages through which the lymphatic tissue in the ileocecal region passes:

- ✓ Hyperplasia
- ✓ Necrosis
- ✓ Ulcerations
- ✓ Ulceration healing



Hyperplasia of lymph nodes in the ileocecal region during typhoid fever

Pathogenesis of typhoid fever



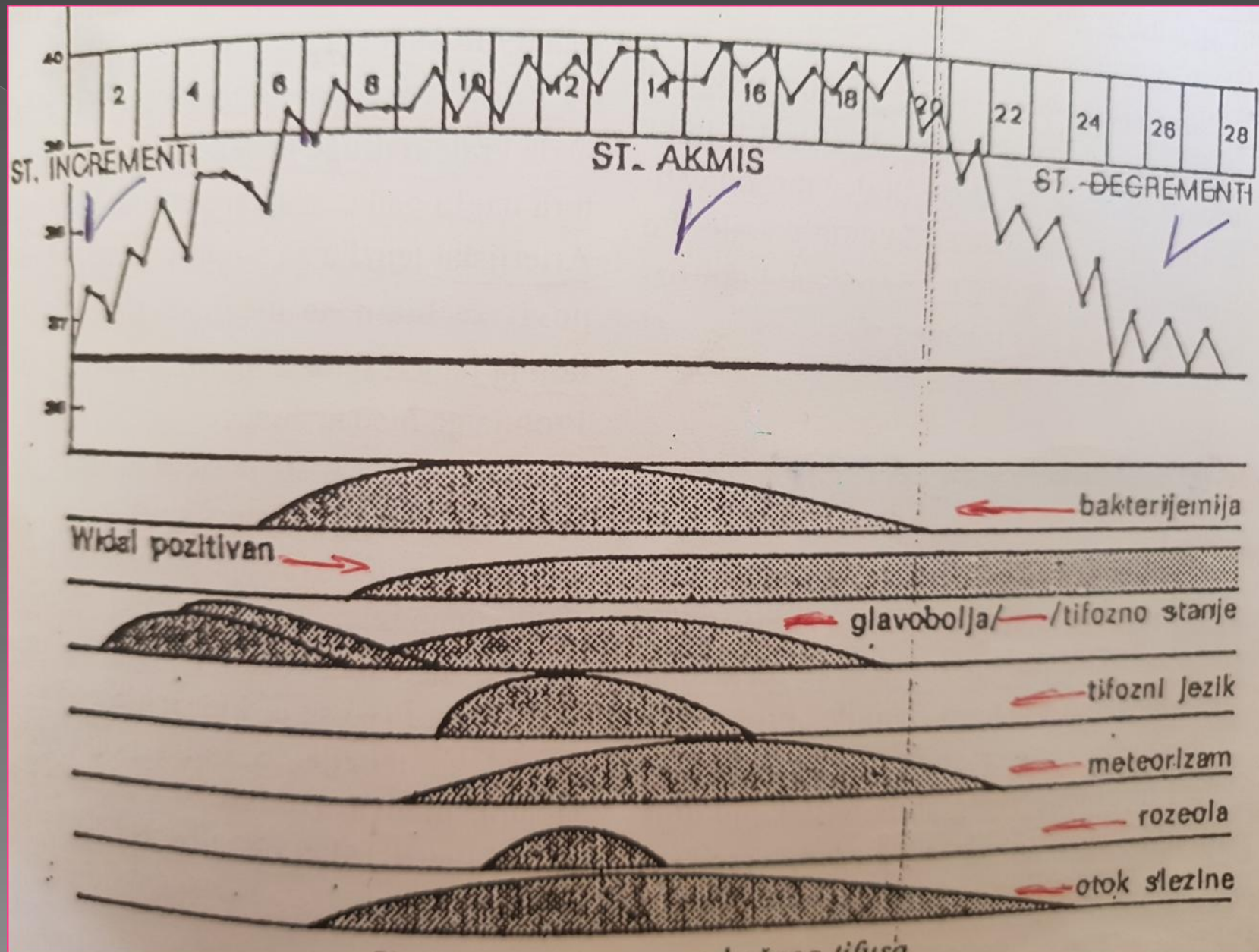
Objective examination of a typhoid patient

- ◉ The patient is febrile in the continuous type, pale, adynamic
- ◉ Conscious but in prostration, confused, bradypsychic
- ◉ The tongue is coated and cracked,
- ◉ The abdomen is above the plane of the chest, meteoric, diffusely sensitive to palpation
- ◉ Liver and spleen slightly enlarged under the rib cage
- ◉ Maculopapular rare measles of the roseola type



The typhoid state includes apathy, disinterest up to dullness, inversion of sleep, nocturnal deliriums with hallucinations.

Temperature curve in typhoid fever

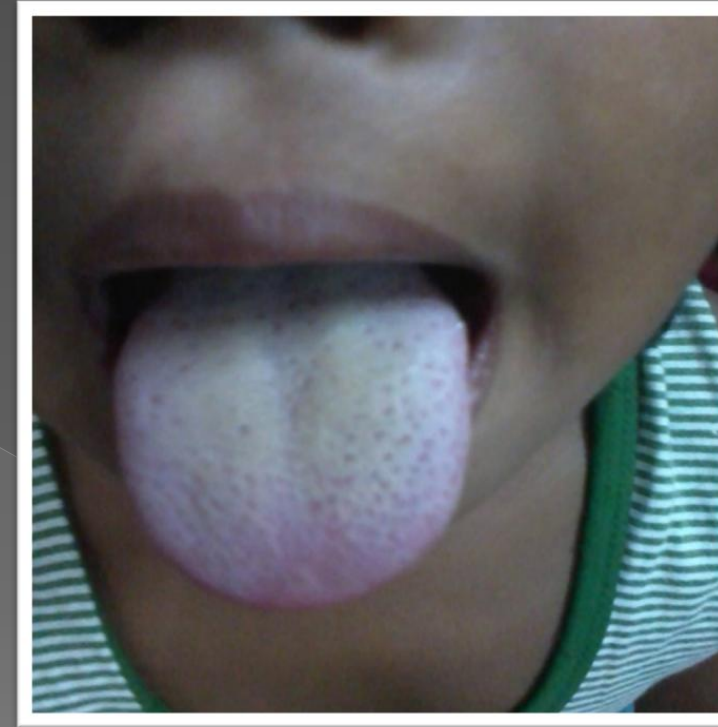


Clinical manifestations of typhoid fever



**Roseola - occurs in 30% of patients, on the front abdominal wall in the form of macules or maculopapules, pale pink in color
They are lost on vitropression, they last 3-5 days**

Clinical manifestations of typhoid fever



The tongue is coated, cracked and white, resembling oak bark, extremely dry and rough

Complications of typhoid fever

Toxic-cardiovascular collapse, myocarditis, hyperpyrexia, bone marrow damage

Local-enterorrhagia, perforation, pneumonia, decubitus

Bacterial-meningitis, endocarditis, osteomyelitis, arthritis, abscesses

Iatrogenic - agranulocytosis, allergy

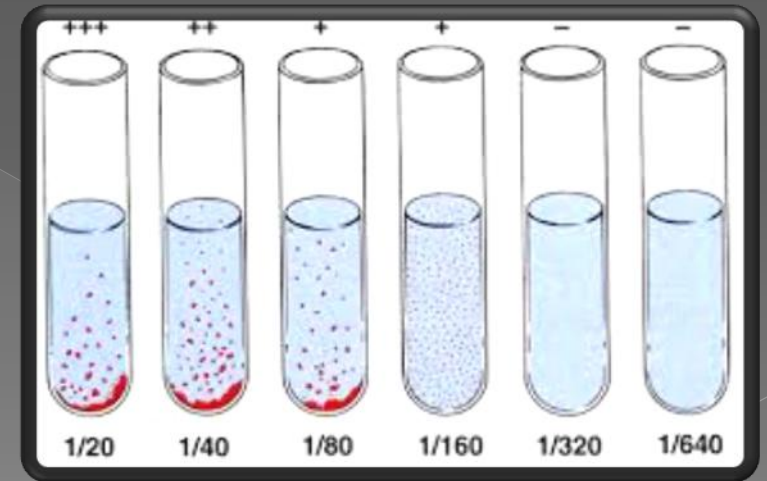
Diagnosis of typhoid fever

- ◉ Laboratory analyses-leukopenia with neutropenia
- ◉ Bacteriological tests
 - Blood culture
 - Coproculture
 - Urine culture
 - Culture from hair marrow
 - Biculture



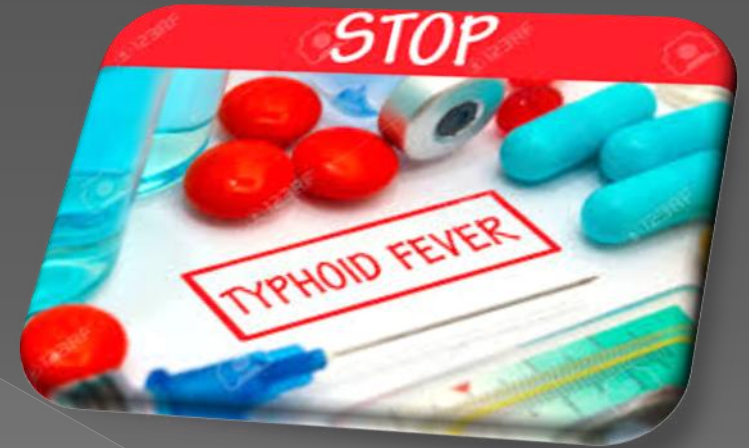
Serological reactions

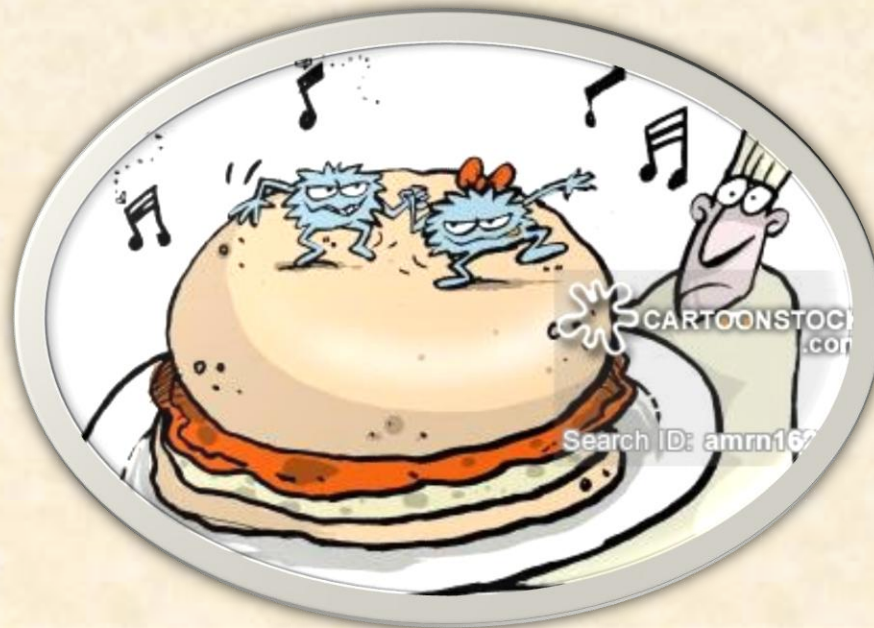
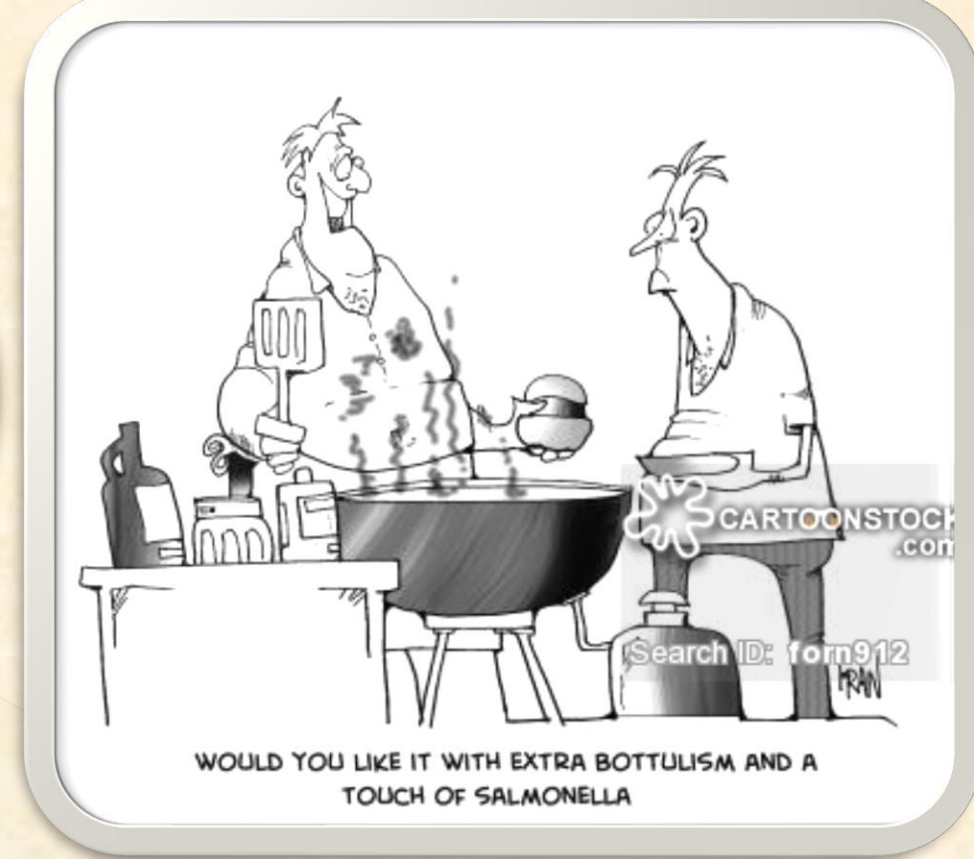
- Widal's agglutination reaction (indirect increase)
- Specific antibodies to *Salmonella typhi* and paratyphi antigens are sought
- Detection of antibodies to O and N antigens
- Antibodies appear from the 7th day of the disease
- The rise in titer is monitored for 7 to 10 days



Treatment of typhoid fever

- Antibiotic therapy
 - Cephalosporins
 - Chloramphenicol
 - Quinolones
 - Amoxicillin
- Corticosteroids (short-term use)
- Symptomatic therapy
- Prophylaxis
 - Inactive parenteral vaccine
 - Oral live vaccine (Ty21)





Salmonellosis

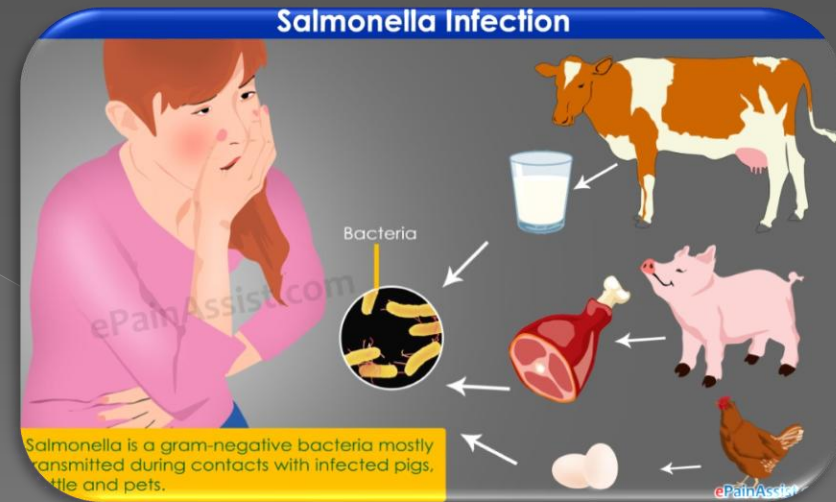
Etiology

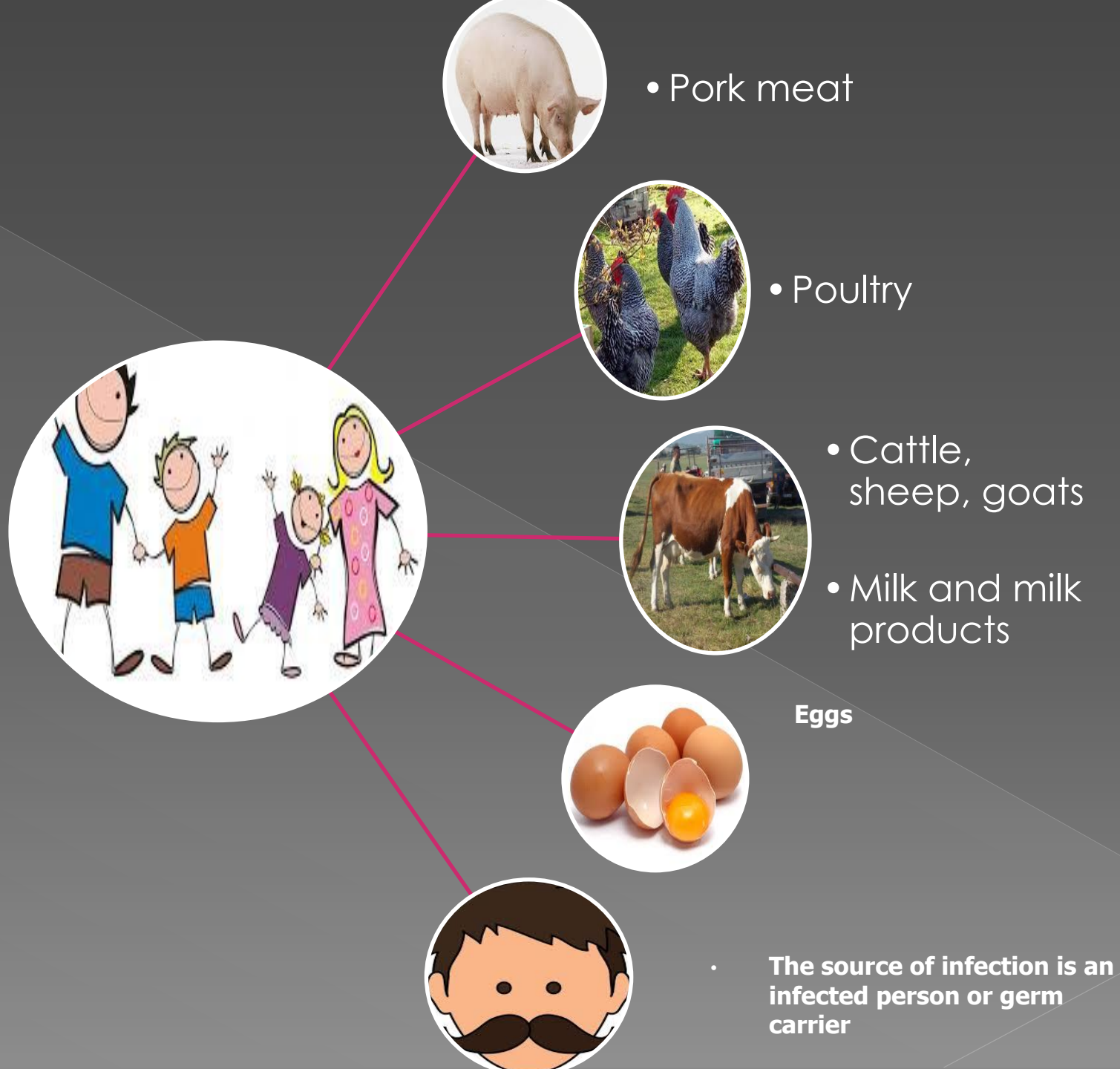
- The causative agents of salmonellosis are gram-negative bacteria from the Enterobacteriaceae family
- About 2000 serotypes are pathogenic for humans
- The most common serotypes in our area are:
 - *Salmonella enteritidis*
 - *Salmonella typhi* murium
- Typing is done on the basis of the antigenic structure: O and N
- They tolerate low temperatures well, but are destroyed by temperatures above 65°



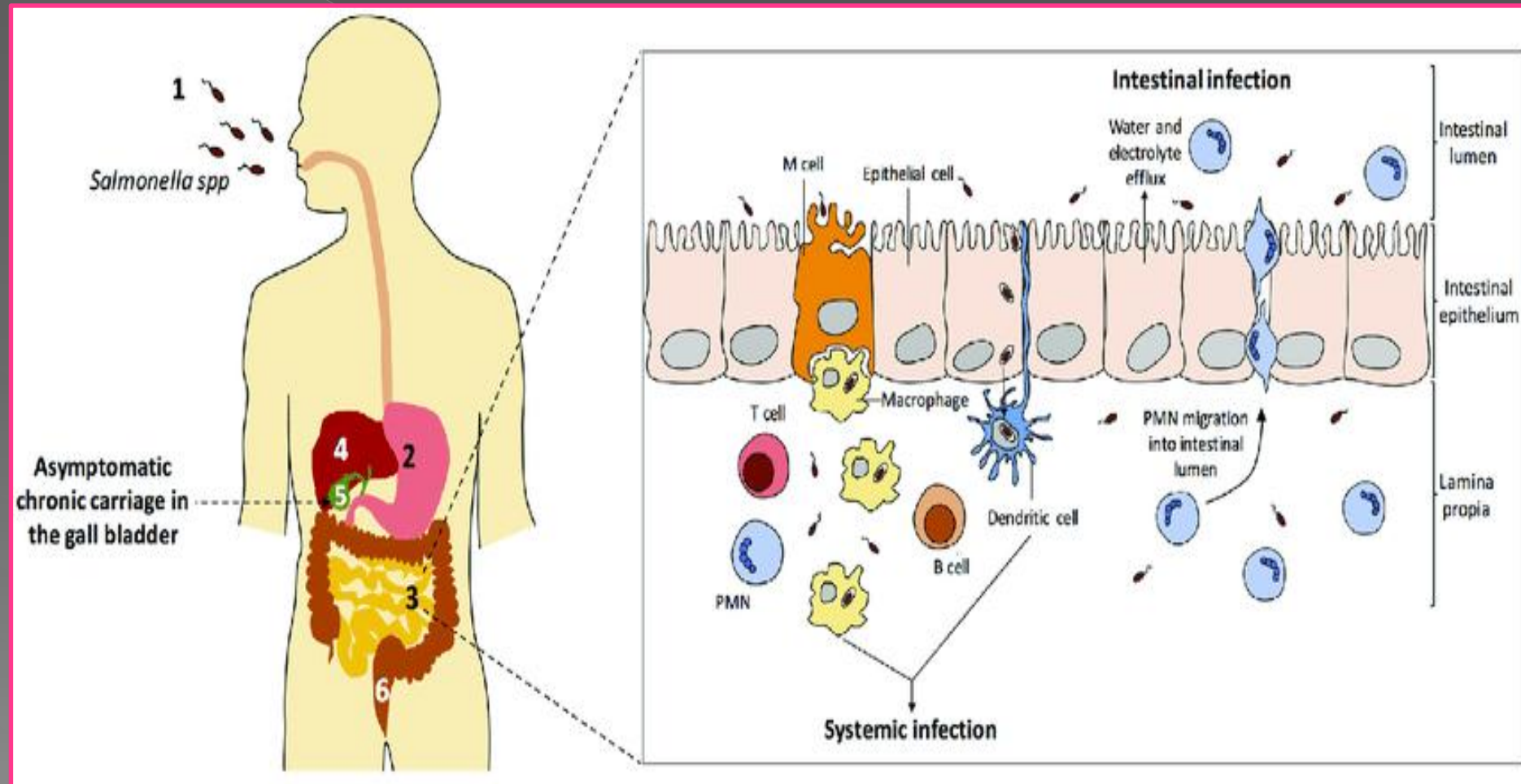
Epidemiology

- ◉ Salmonella belongs to zoonoses
- ◉ The reservoir is the digestive tract of domestic animals
- ◉ Eating food of animal origin contaminated with salmonella
- ◉ Infectious dose **100000**
- ◉ The clinical picture depends on the infectious dose and the immune status of the patient
- ◉ Summer and early autumn



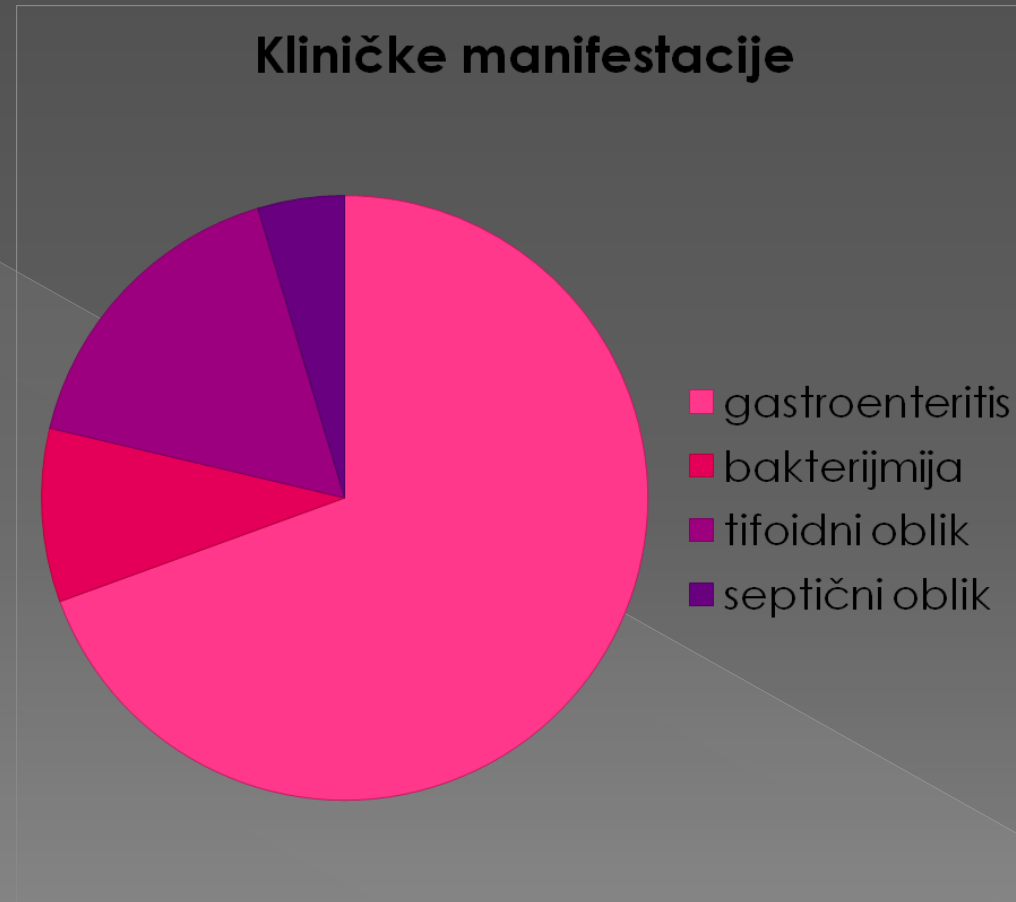


Pathogenesis of salmonellosis infection



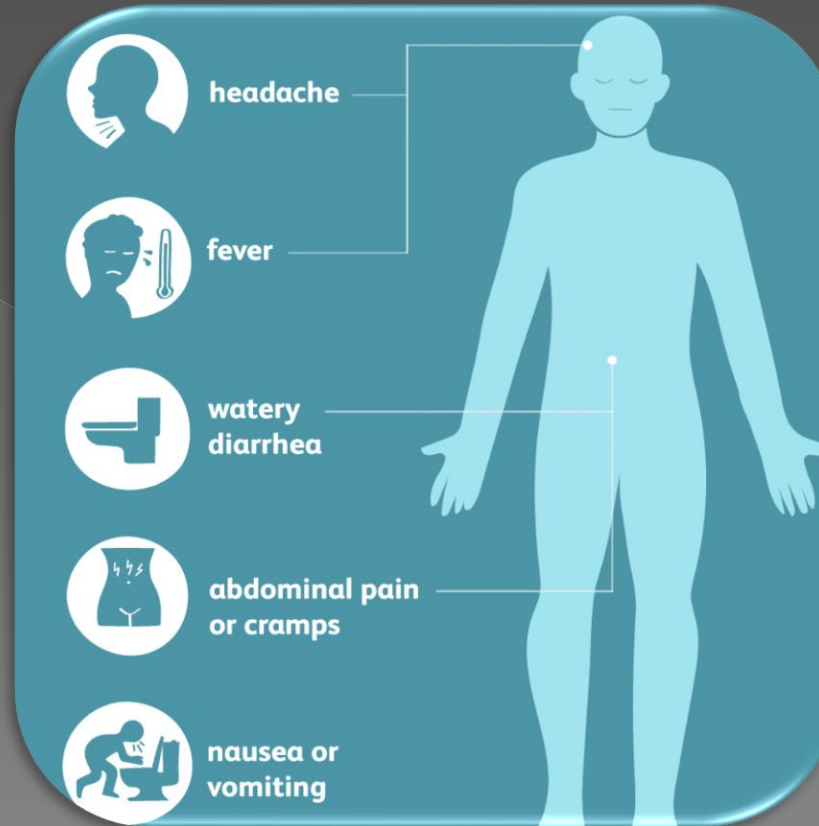
Clinical syndromes of salmonellosis infection

- Gastroenteritis
(Toxiinfectio alimentaris)
- Bacteremia
- Typhoid form
- Septic form
- Clergy

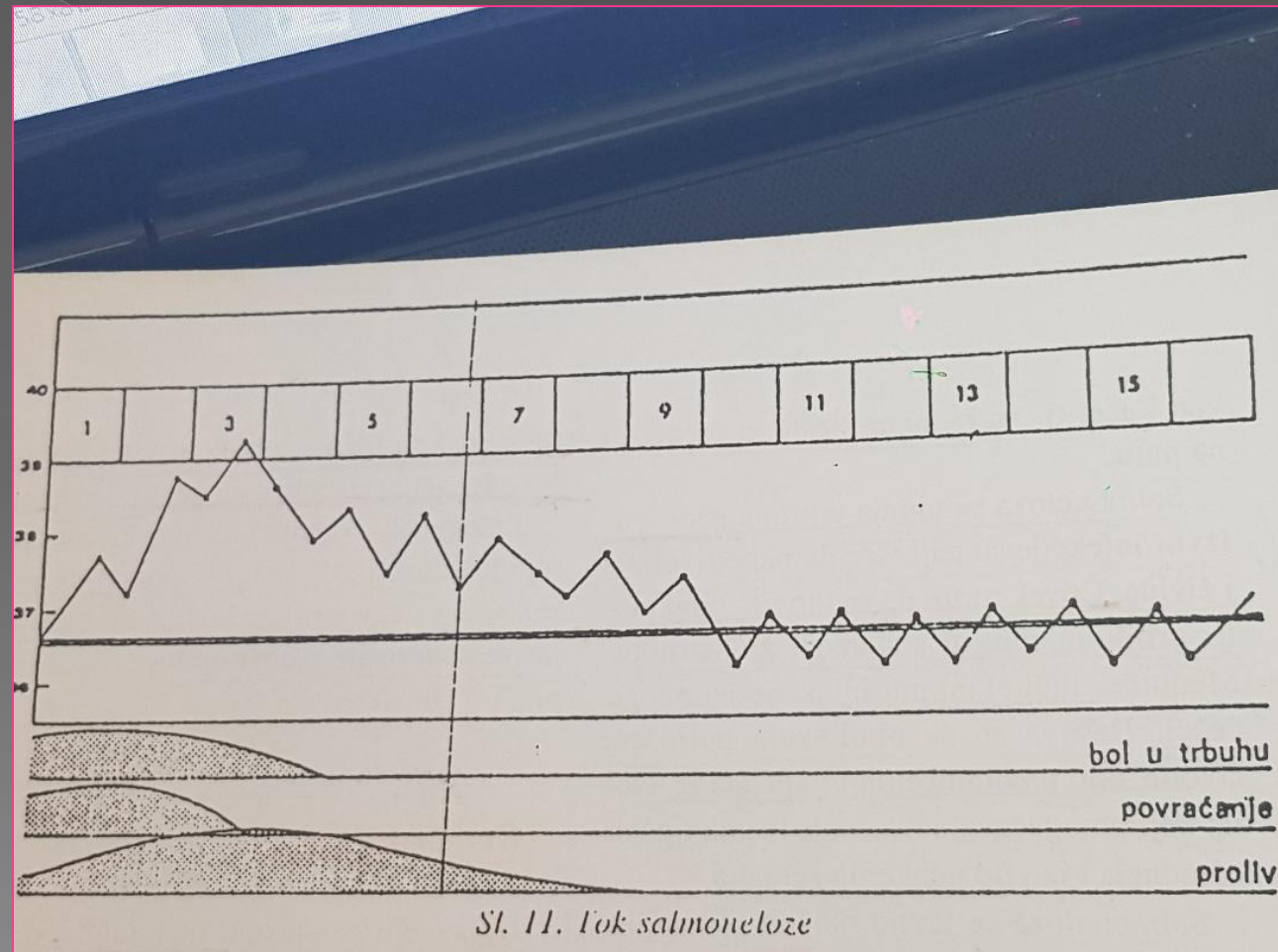


Salmonellosis gastroenteritis (Toxiinfectio alimentaris)

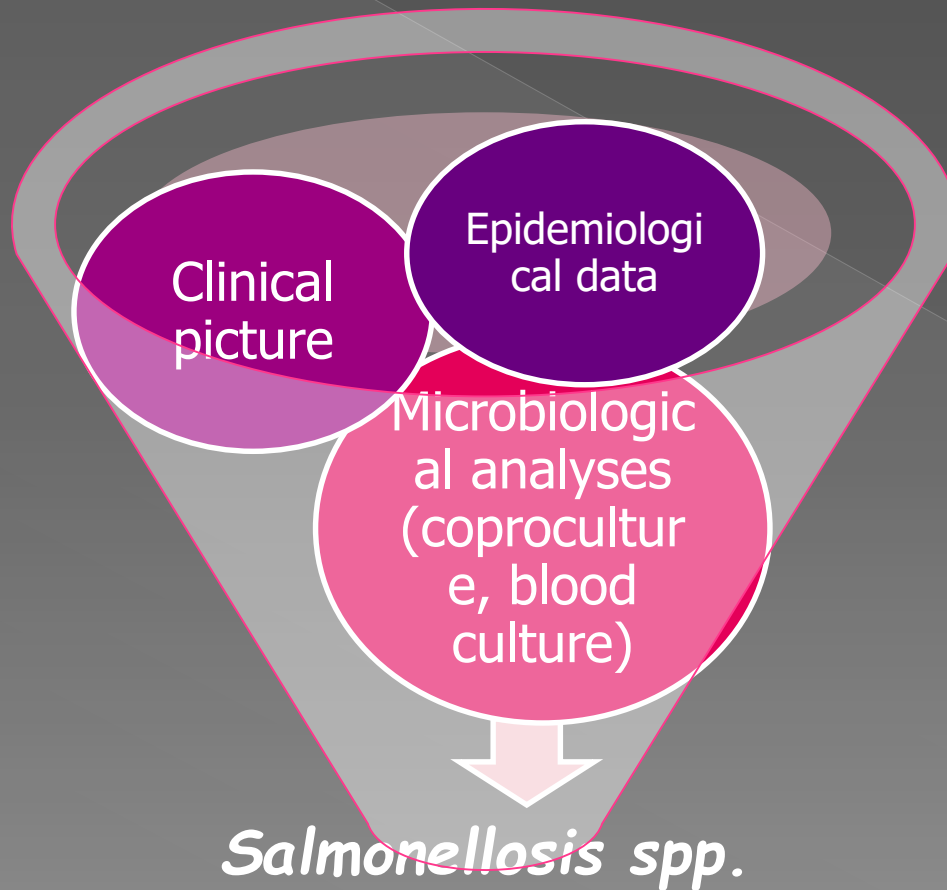
- Length of incubation - at least 24-48 hours, it can be longer
- It lasts 7 to 10 days
- The disease begins gradually
- General symptoms of infection
- The temperature is always present,
over 38°
- Nausea, vomiting
- Diarrheal syndrome (type II enteric stools, can also be colitic)



Clinical manifestations in salmonellosis gastroenteritis



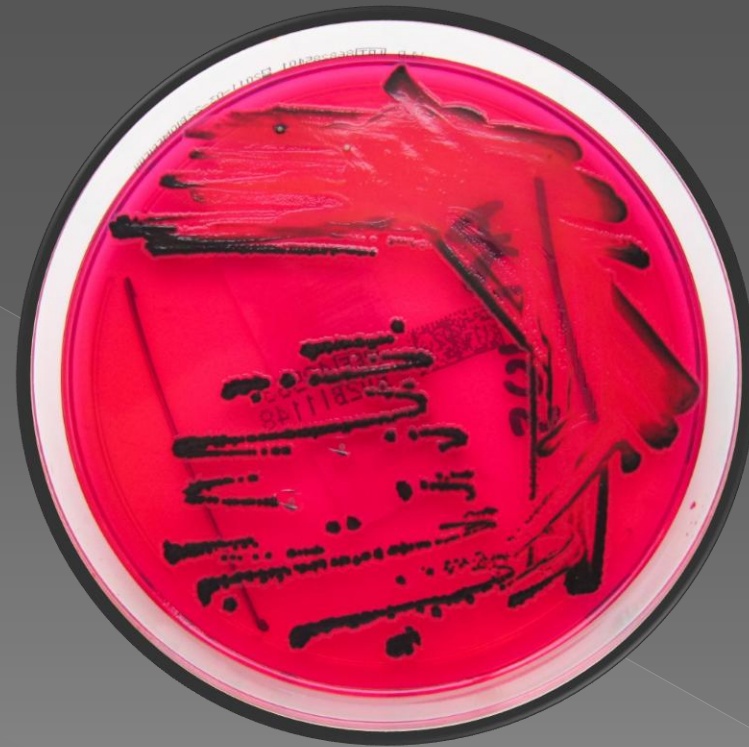
Diagnosis of salmonellosis infections

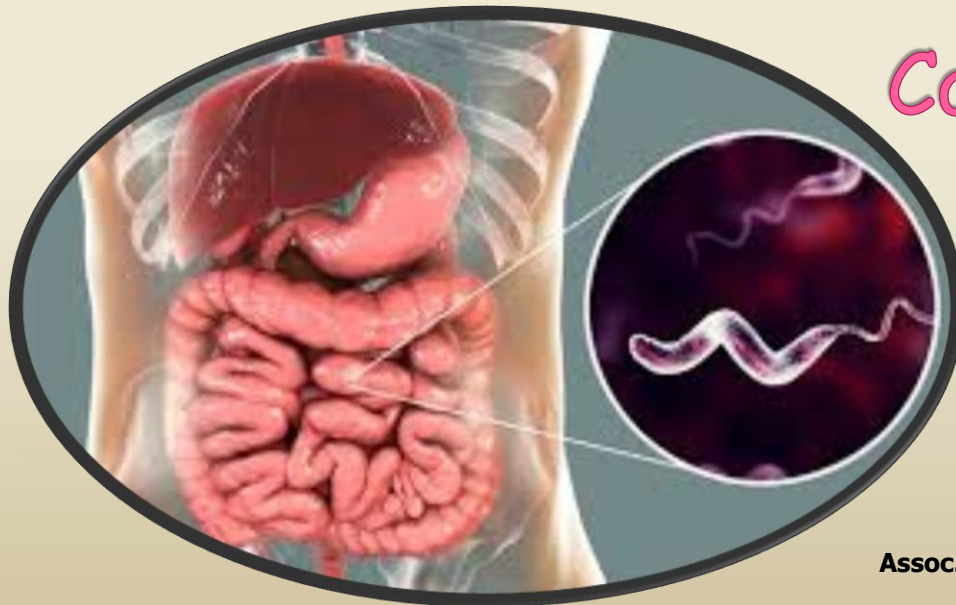


Salmonella enteritidis
Salmonella typhimurium
Salmonella heidelberg
Salmonella newport
Salmonella hadar

Therapy of salmonellosis

- Symptomatic therapy includes replacement of water and electrolytes
- Antibiotic therapy for certain categories
- Ampicillin
- Trimethoprim-sulfamethoxazole
- Ciprofloxacin





Campylobacteriosis

Etiology

- Acute intestinal and septic disease
- *Campylobacter* spp.- curved gram negative rod
- It grows on special substrates with 5 to 10% oxygen
 - *Campylobacter jejuni*
 - *Campylobacter coli*
 - *Campylobacter fetus*
 - *Campylobacter hepaticus*

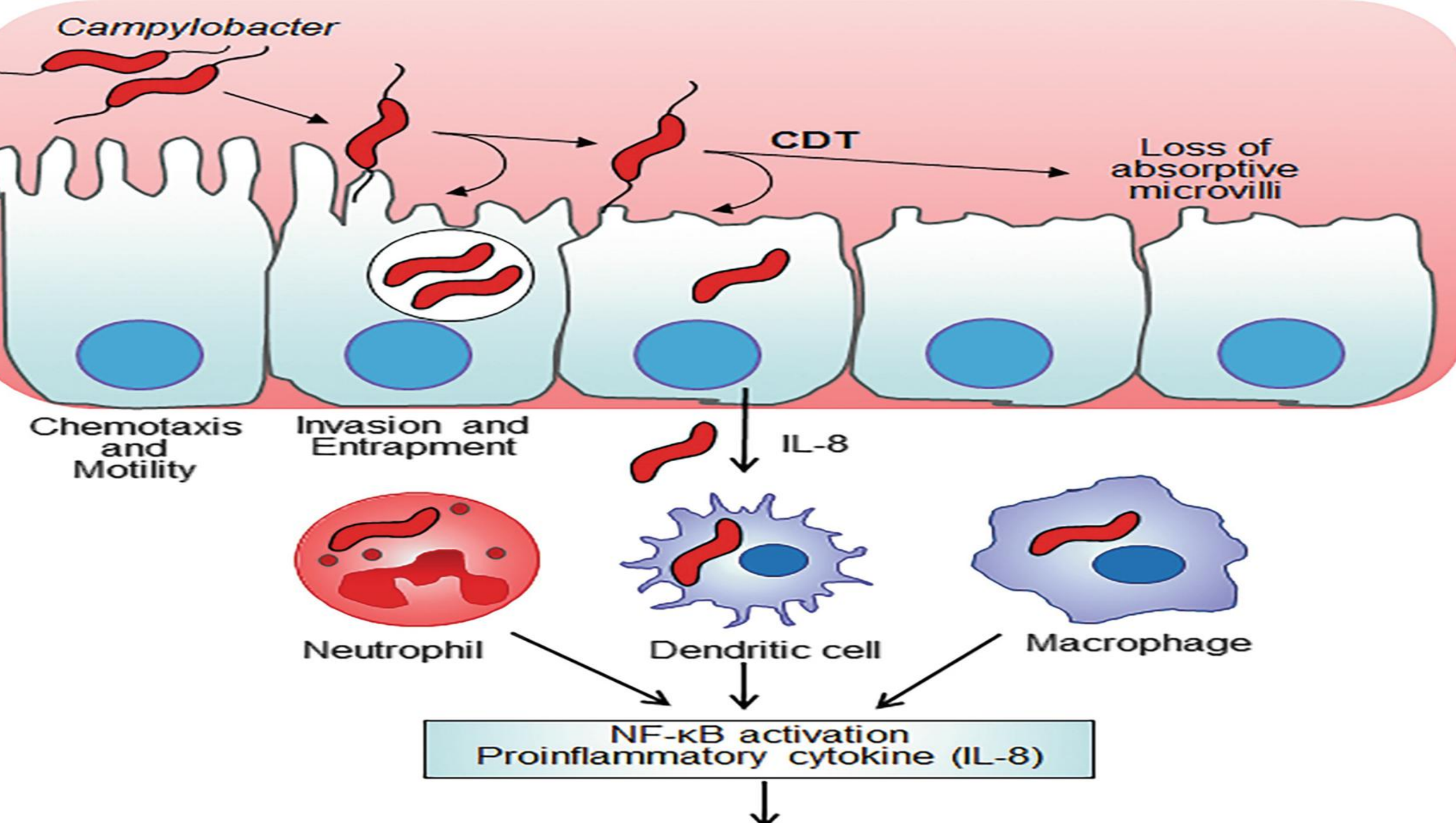


Epidemiology

- Campylobacteriosis are zoonoses
- The reservoir of infection is the digestive tract of domestic and wild animals
- Fecal-oral infection
- The source of infection is fresh pork and beef

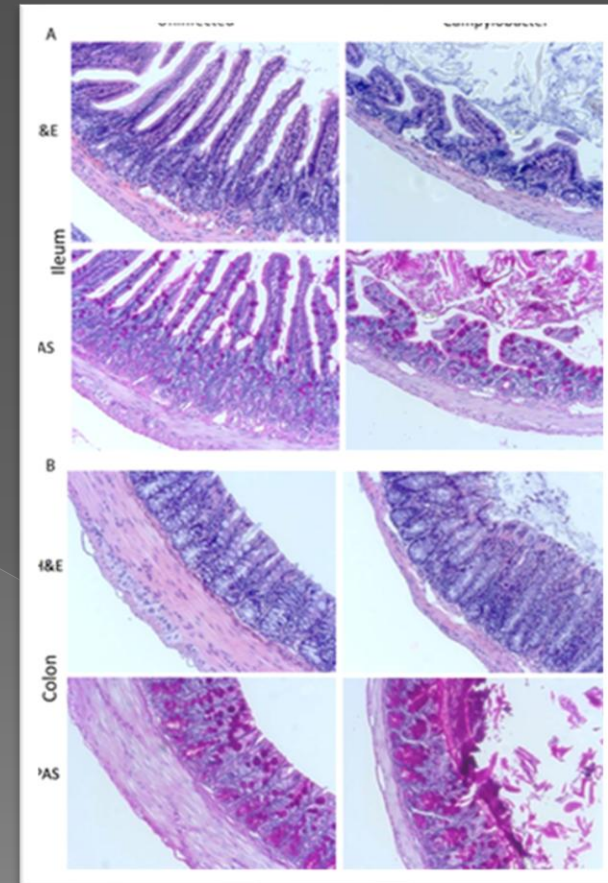


ECDC data from 2016 in Europe
The largest number of patients in Sweden, Germany, the Czech Republic and the UK



Clinical manifestations-Acute gastroenteritis

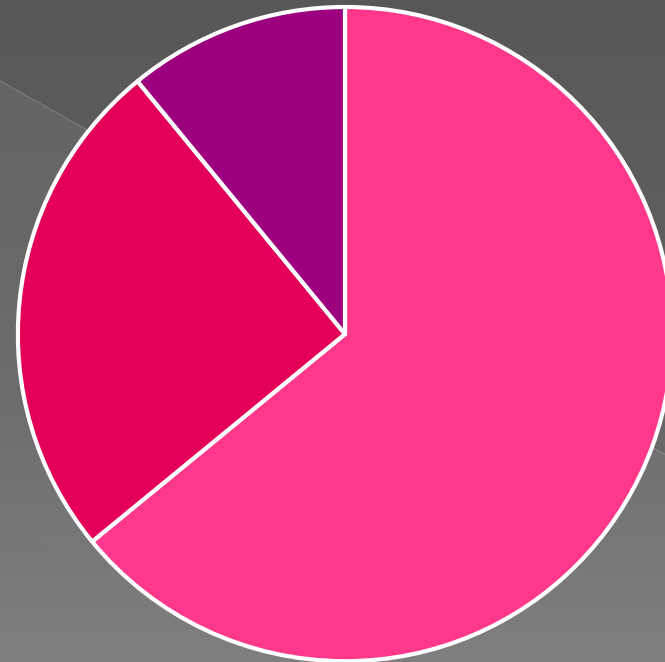
- Incubation 1-7 days, on average 2 to 4 days
- The disease lasts on average 7 days, it can be 14 days
- Prodromal stage
- Diarrheal syndrome, enteric type II or colitic type
- Terminal ileitis with mesenteric lymphadenopathy
- Differential diagnosis - intussusception or acute appendicitis



Clinical manifestations - extraintestinal forms

□ Guillain-Barre syndrome-
postinfectious radiculopathy

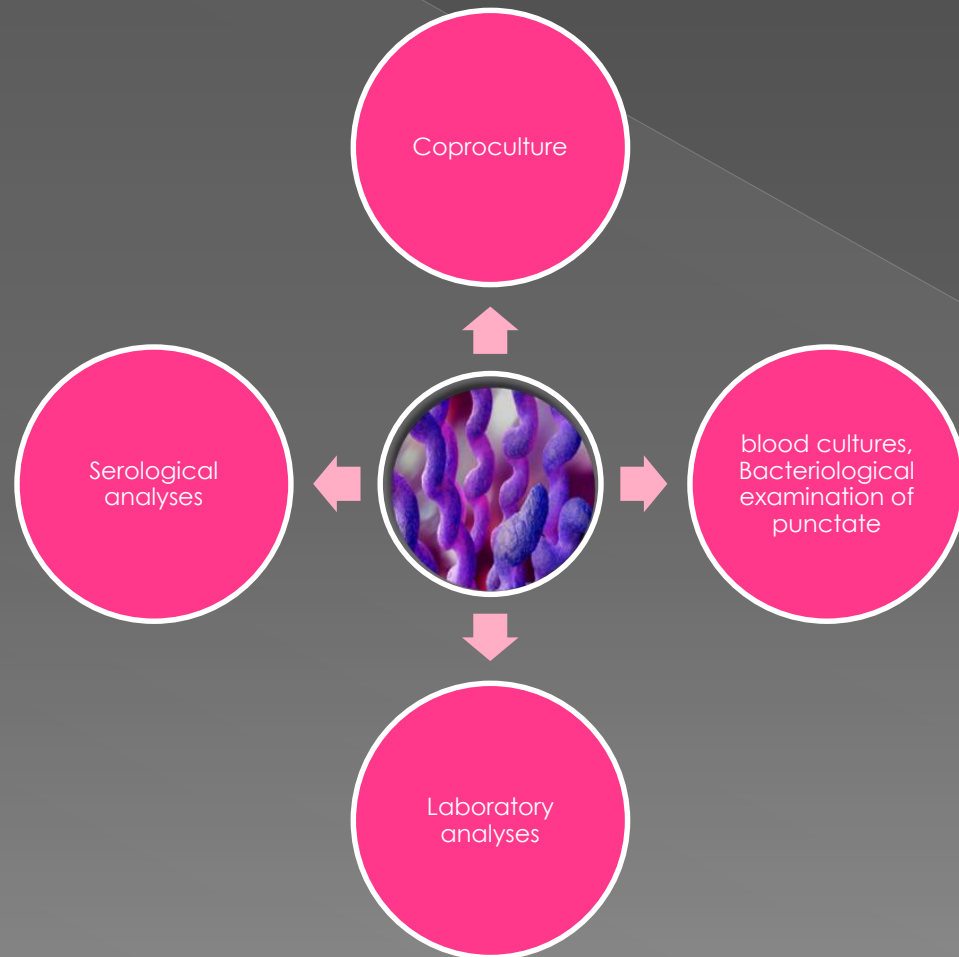
Septic diseases



■ Septic febrile condition with or without diarrhea
■ Infection of pregnant women and fetal death

■ Septic disease with febrile rash
■

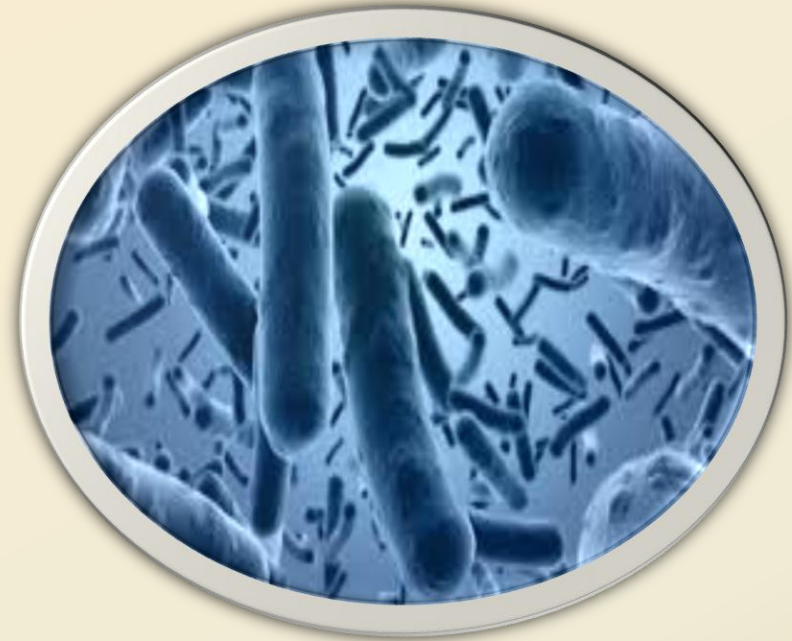
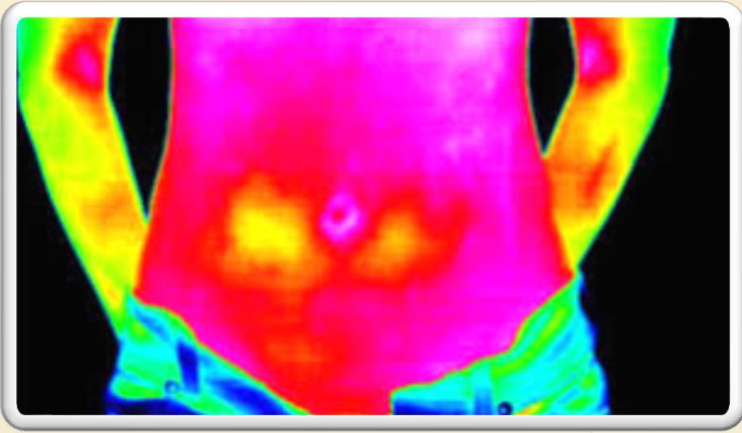
Diagnosis of campylobacteriosis



- ⊙ Differential diagnosis
 - Inflammatory bowel diseases
 - Acute gastroenteritis of other etiology
 - Acute surgical diseases

Campylobacteriosis therapy

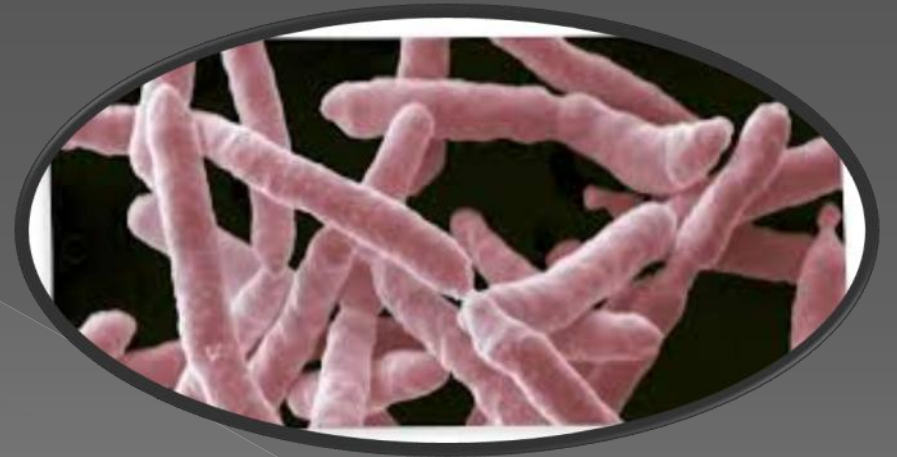
- Symptomatic therapy is the basic method of treatment (replenishment of water and electrolytes)
- In some cases, antibiotic therapy is indicated
- Erythromycin caps. 500mg/6h
- Ciprofloxacin tbl. 500mg 2x1
- In case of systemic infections, aminoglycosides, chloramphenicol and carbapenems are given



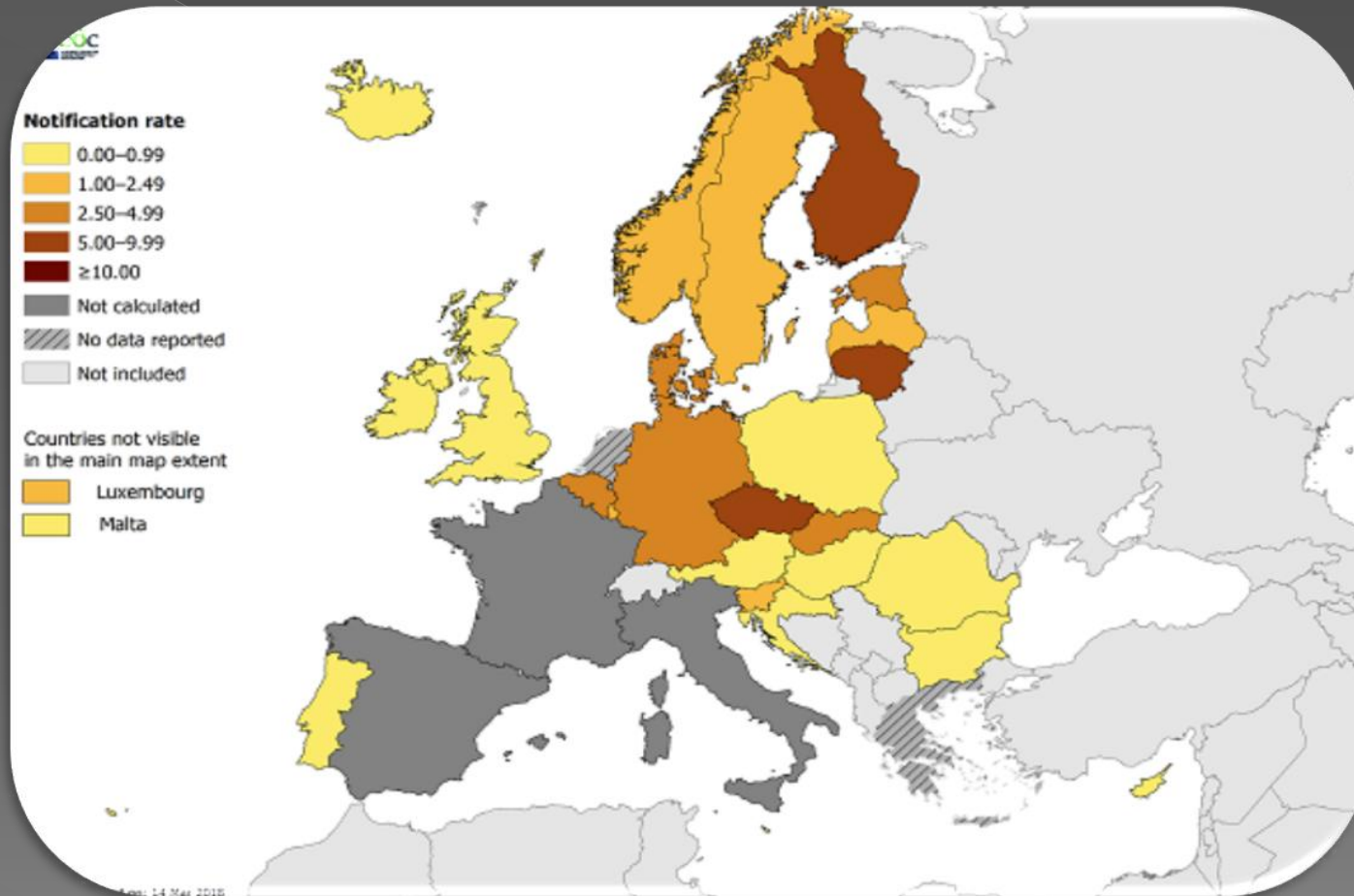
Yersiniosis

Yersiniosis

- ◉ It belongs to the relatively rare causes of acute intestinal infections
- ◉ Etiological agent *Yersinia enterocolitica*
- ◉ Gram-negative bacillus with multiple serotypes
- ◉ In Europe, serotypes O:3 and O:9 are represented
- ◉ In addition to intestinal infections, it also causes septic conditions, arthritis, erythema nodosum



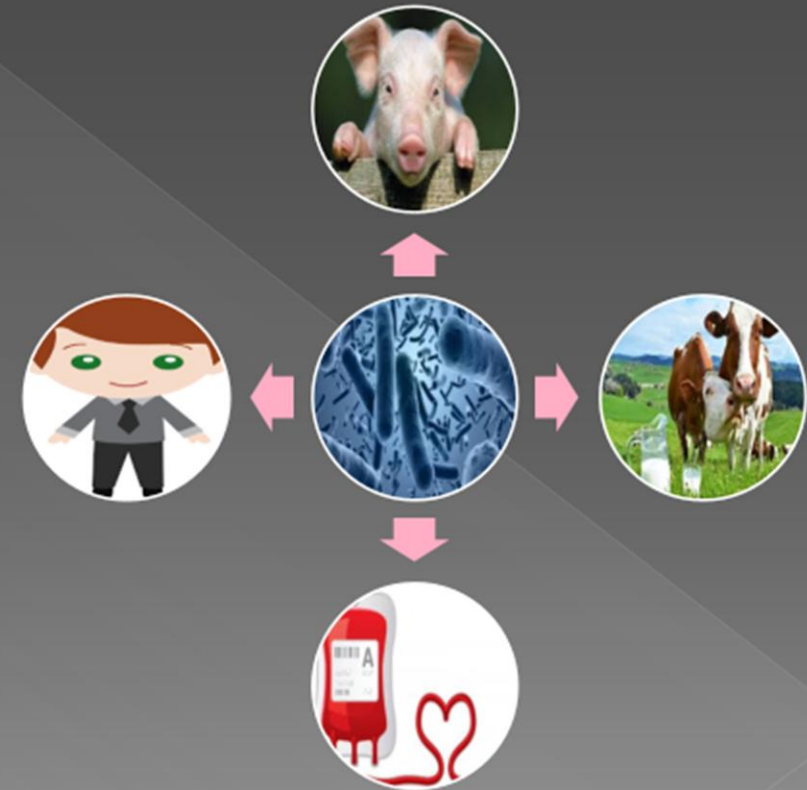
Epidemiology of yersiniosis

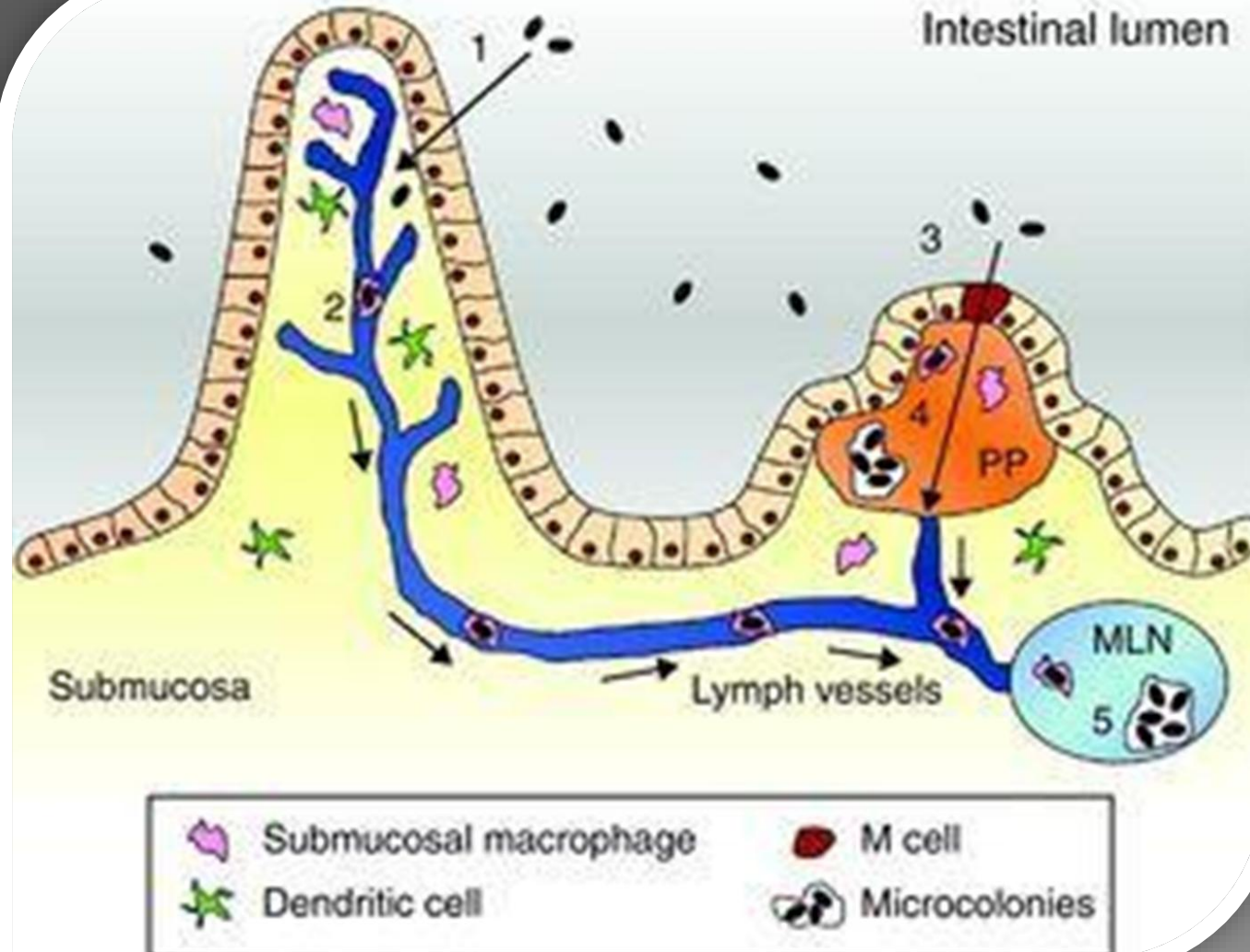


- *Yersinia enterocolitica* grows better at low temperatures, so it can multiply even at +4°C
- More frequent infection in the winter months

Epidemiology of yersiniosis

- Yersiniosis is a zoonosis
- The reservoir of infection is the digestive tract of domestic and wild animals
- Source contaminated meat or milk
- Interhuman transmission is also possible, as well as through blood transfusion





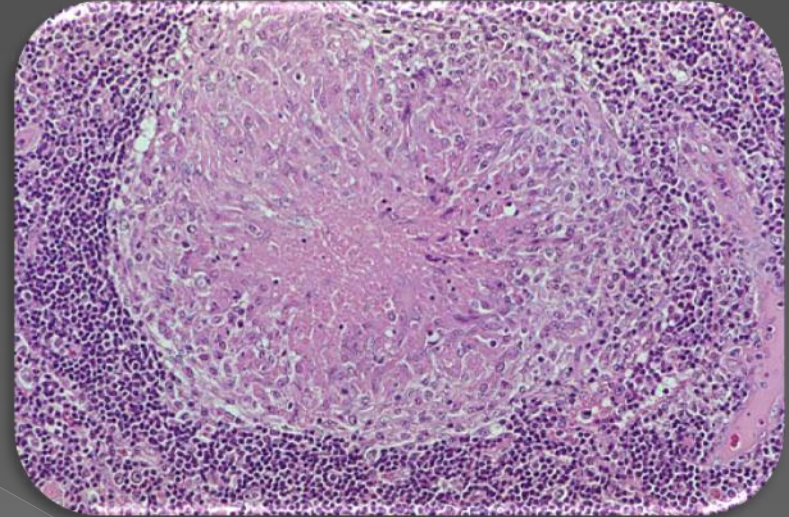
- ✓ Pathogenesis model of *Yersinia enterocolitica*
- ✓ *Yersinia* cells traverse the intestinal epithelium via epithelial cells to the submucosa
- ✓ Submucosal macrophages phagocytose the pathogen and enter into the lymphatic system thereby reaching the MLN
- ✓ Alternatively, bacteria can be engulfed by M cells
- ✓ Once in the PP *Yersinia* forms microcolonies and starts replication
- ✓ Eventually, bacterial cells are located in the MLN and can equally form microcolonies to allow replication

Clinical manifestations of yersiniosis

- ◉ Acute enteritis
- ◉ Other clinical forms
(extraintestinal
manifestations)
- ◉ Post-infectious manifestations

Clinical manifestations - Acute enteritis

- Incubation 4 to 7 days
- The disease lasts from 7 to 21 days
- Pronounced general symptoms of infection
- Diarrheal syndrome-Enteric type II
- Pseudoappendicitis
- Complications-rectorrhagia, perforation of the ileum



Mesenteric lymphadenitis with suppurative granuloma in enteritis caused by *Yersinia enterocolitis*

Clinical manifestations

◉ Other clinical manifestations

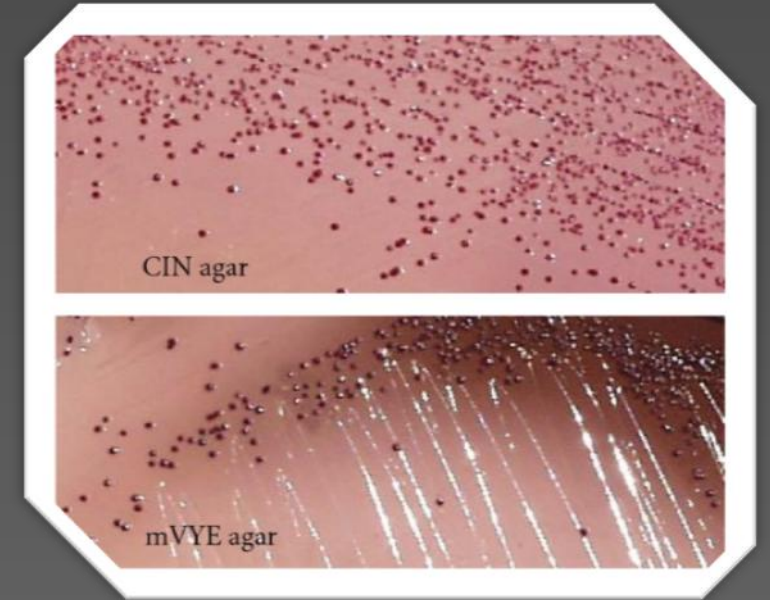
- Acute pharyngitis without intestinal disorders
- Septicemia
- Focal infections of various organs

◉ Post-infectious manifestations

- Reactive arthritis
- Erythema nodosum
- Thyroiditis

Diagnosis of yersiniosis

- Microbiological analyses-isolation from coproculture, blood culture, lymph nodes, punctate
- Serological analyses
- Agglutination reaction (specific O antigen)
- ELISA, Wblot IgM and IgG



Yersiniosis therapy

- Enteritis is generally a self-limiting disease
- Symptomatic therapy (probiotics, replacement of fluids and electrolytes, hygienic and dietary regime)
- Patients with disseminated forms must be treated with antibiotic therapy
- amp. Gentamicin 5mg/kg body weight
- amp. Chloramphenicol 50mg/kg bw



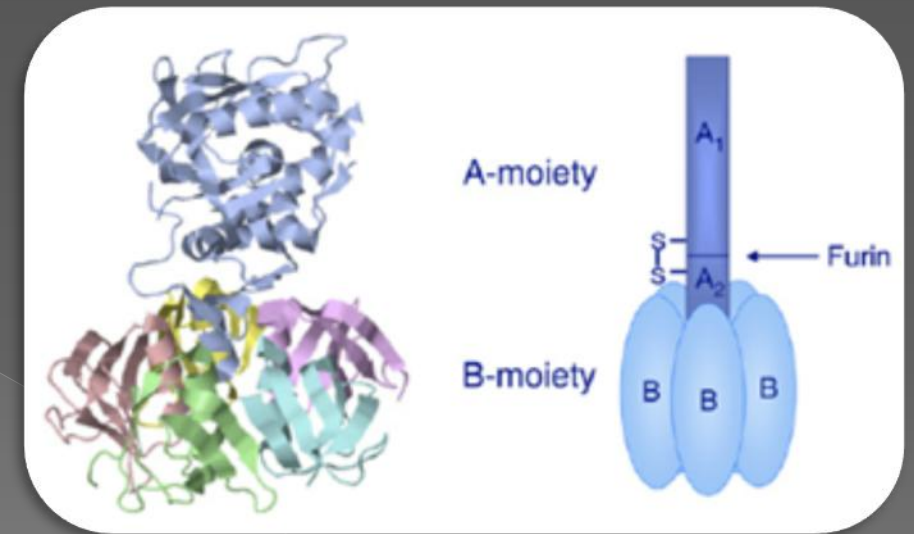
Enterohemorrhagic Escherichia coli (EHEC)

0157:H7



Ентерохеморагична E. Coli (EHEC)

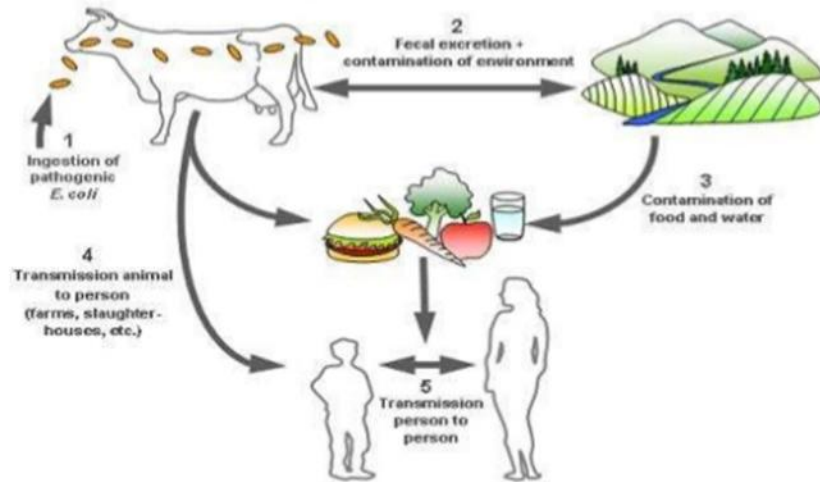
- EHEC causes hemorrhagic colitis and hemolytic uremic syndrome
- Fecal-oral infection
- Reservoir of infection, domestic animals
- 10² enough to cause infection
- The most dangerous serotype O157:H7
- It has the ability to produce a Shiga-like toxin



❑ Shiga-like toxin - has two A subunits and 5 identical B subunits

Enterohemorrhagic E. Coli (EHEC)

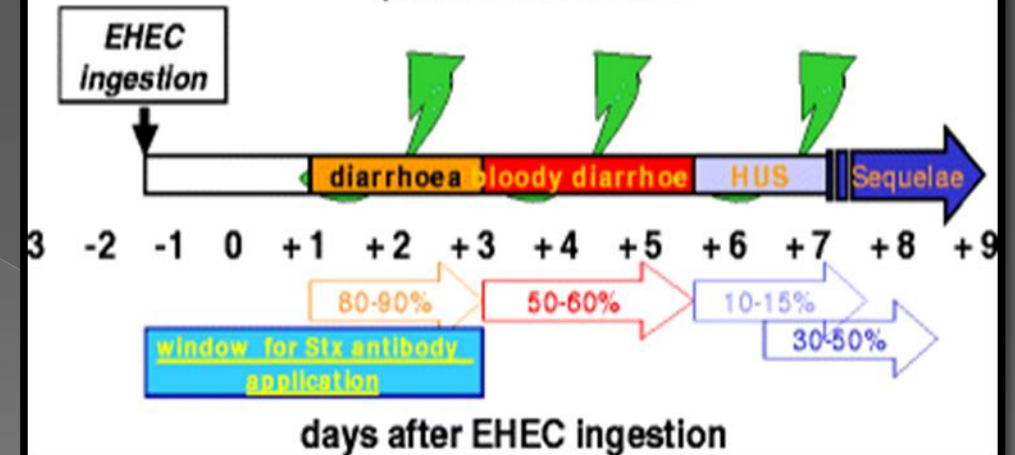
TRANSMISSION



- ✓ Transmission of enterohemorrhagic *E. coli* via infected domestic animals

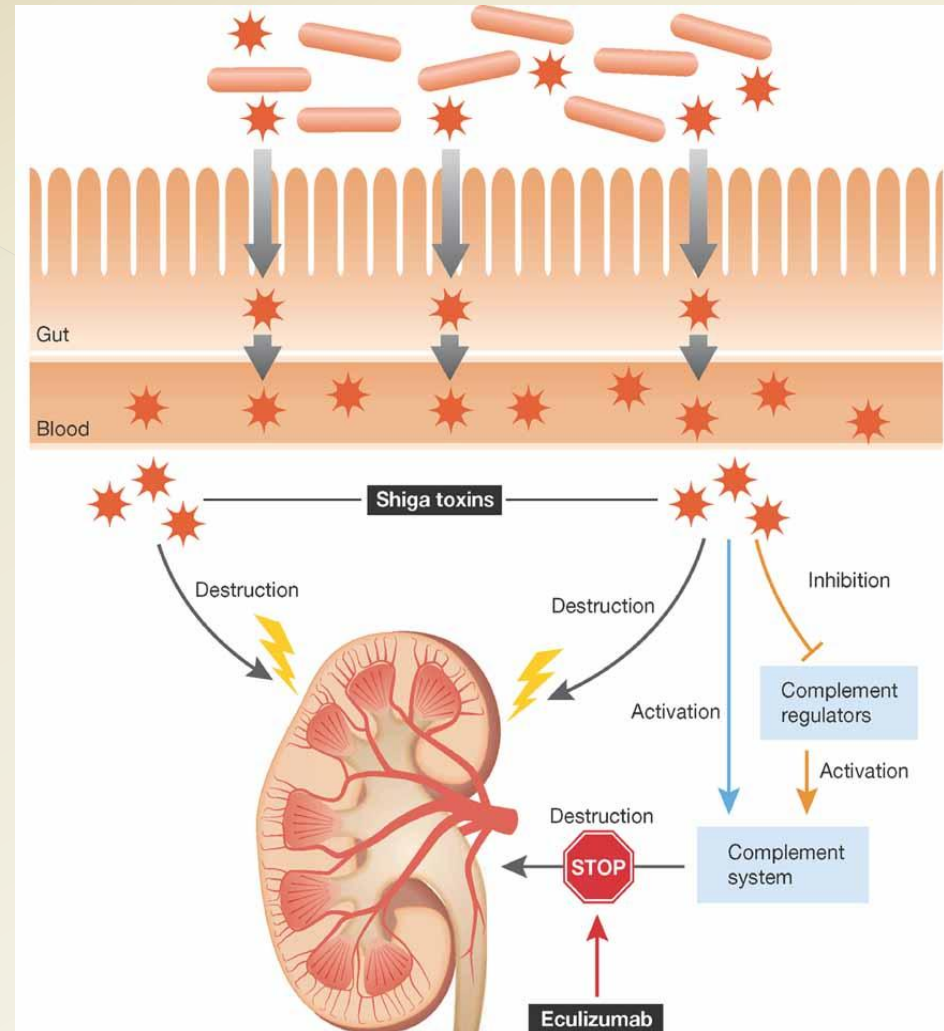
Pathophysiology of EHEC infection

RECOVERY-spontaneous resolution



- ✓ Clinical manifestations - watery stools appear first, then bloody stools, while hemolytic uremic syndrome develops 2-14 days after diarrheal syndrome

After an EHEC infection, the bacterium remains in the digestive tract, but releases Shiga toxin that goes into the circulation and attacks numerous organs, primarily the kidneys.



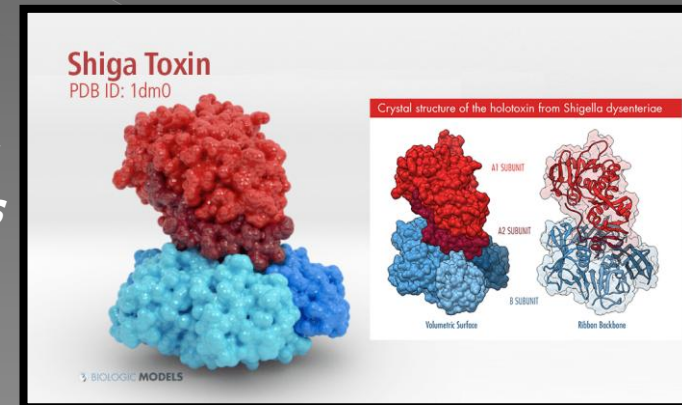
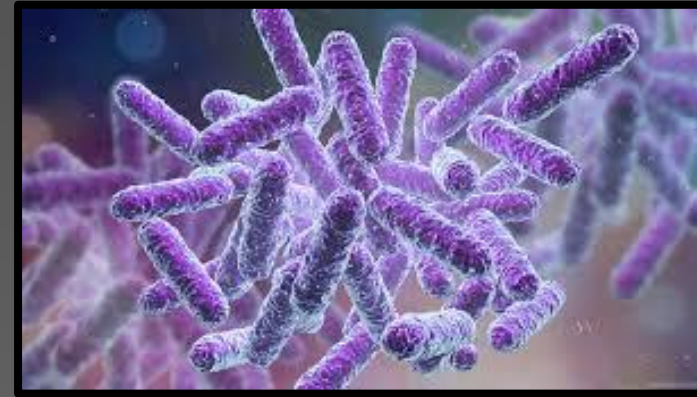
Dorothea Orth-Höller et al. EMBO Mol Med. 2011;3:617-619



Bacillary dysentery

Bacillary dysentery

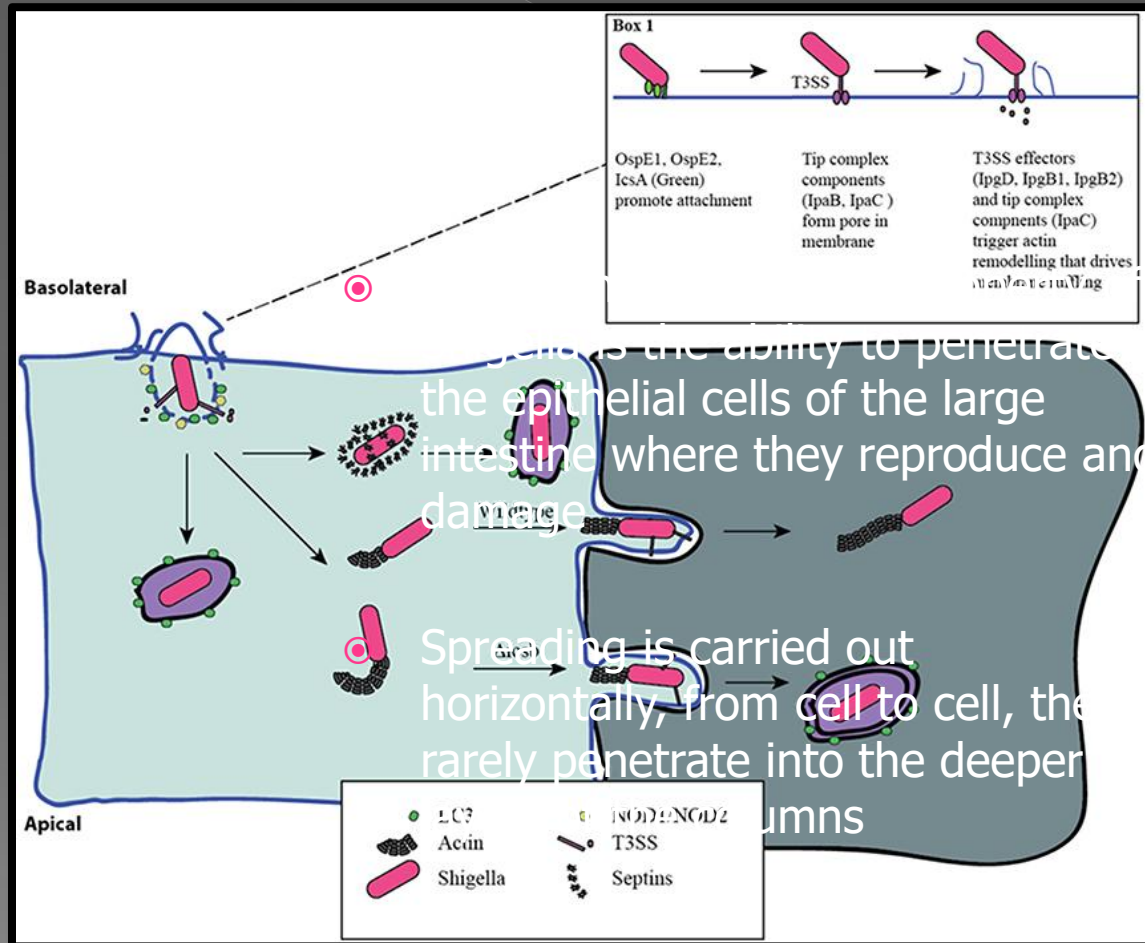
- *Disease of the large intestine, with mucous-bloody stools*
- *There are 4 subgroups of Shigellae:*
 - ***S. dysenteriae***
 - *S. flexneri*
 - *S. boydii*
 - *S. sonnei*
- *Gram-negative bacilli, motile and without capsule*
- ***S. Dysenteriae secretes an exotoxin that has cytotoxic, enterotoxic and neurotoxic effects***



Epidemiological data

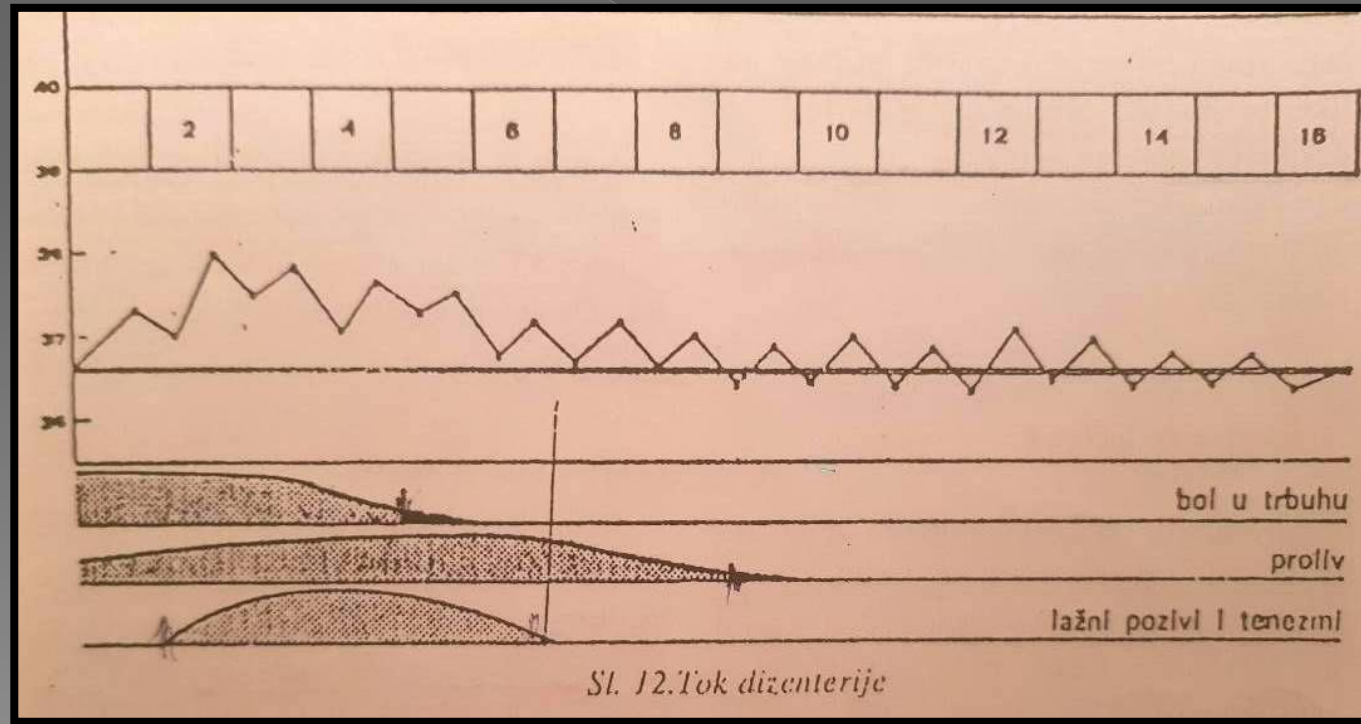
- A cosmopolitan disease, it occurs sporadically, while in extraordinary circumstances, epidemics of a larger scale are possible
- Frequent infection in children under five years of age, during the summer months
- Dysentery is common in poor hygienic and economic conditions, so it is prevalent in third world countries
- It represents a fecal-oral infection
- The source of the infection is exclusively man, and that as a patient, convalescent and carrier

Pathogenetic mechanisms of Shigella



Clinical picture

- ◉ Incubation is usually on the 3rd day (1 to 7 days)
- ◉ Sudden onset of the disease, stools first feculent, then slimy-feculous and finally scanty slimy-bloody stools, dysenteric sputum
- ◉ False stool calls and tenesmus
- ◉ Toxic dysentery rarely occurs



Digestive tract complications in bacillary dysentery

- Most often in children under the age of five and the elderly
- Toxic megacolon
- Intestinal perforation



Extraintestinal manifestations of bacillary dysentery

- ◉ Leukemoid reaction
- ◉ Sepsis is a rare manifestation
- ◉ Neurological manifestations - delirium, convulsions, meningeal syndrome
- ◉ Urotract-hemolytic-uremic syndrome
- ◉ Post-infectious manifestations-**Reiter's syndrome**(**urethritis**, conjunctivitis, arthritis, mucocutaneous changes)



Diagnosis of bacillary dysentery

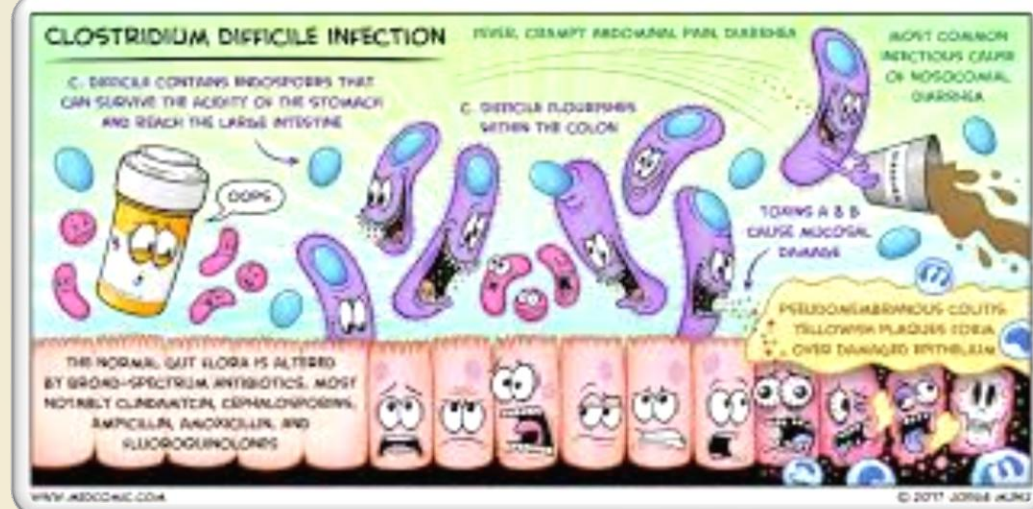
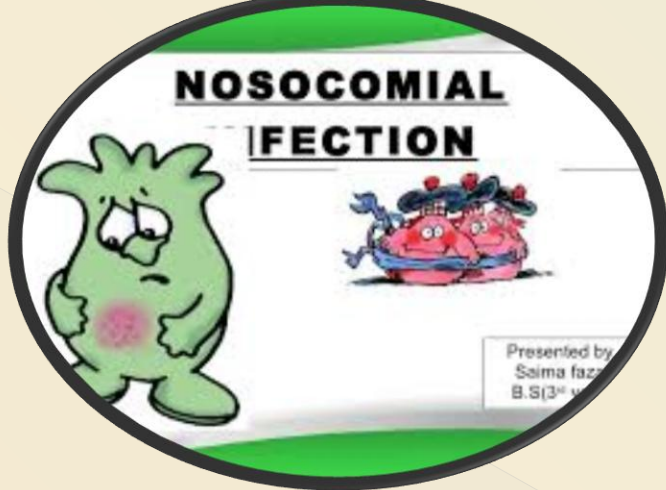
- Basic laboratory analyses
- Epidemiological survey
- Microbiological examination of the stool - extremely resistant in the external environment
- The pathohistological findings do not differ from ulcerative colitis



Treatment of bacillary dysentery

- Symptomatic therapy
- Rehydration involves infusion replacement of sodium, potassium and glucose
- Diet

Drugs	Doses
Ampicilin	500mg /6 h per os, 1gr/6h i.v.
Trimetoprim-sulfametoksazol	Trimetoprim 10mg/kg tt i sulfametoksazol 50mg/kg tt per os
Ciprofloksacin	500mg 2x1 per os



Infection caused by
Clostridium difficile



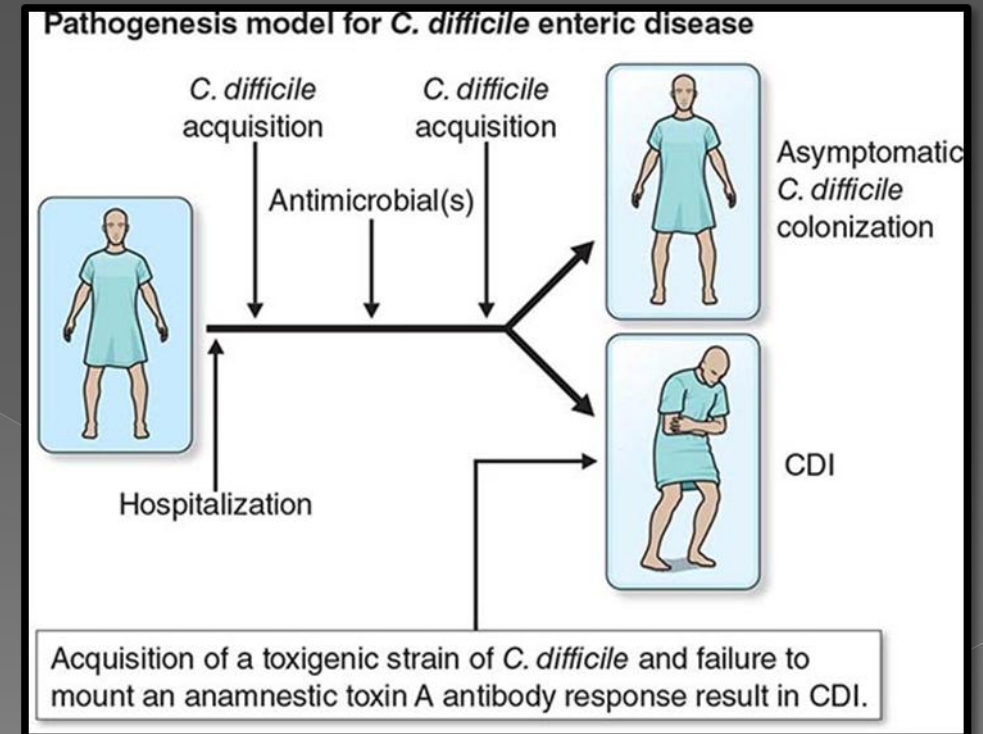
Infection caused by Clostridium difficile

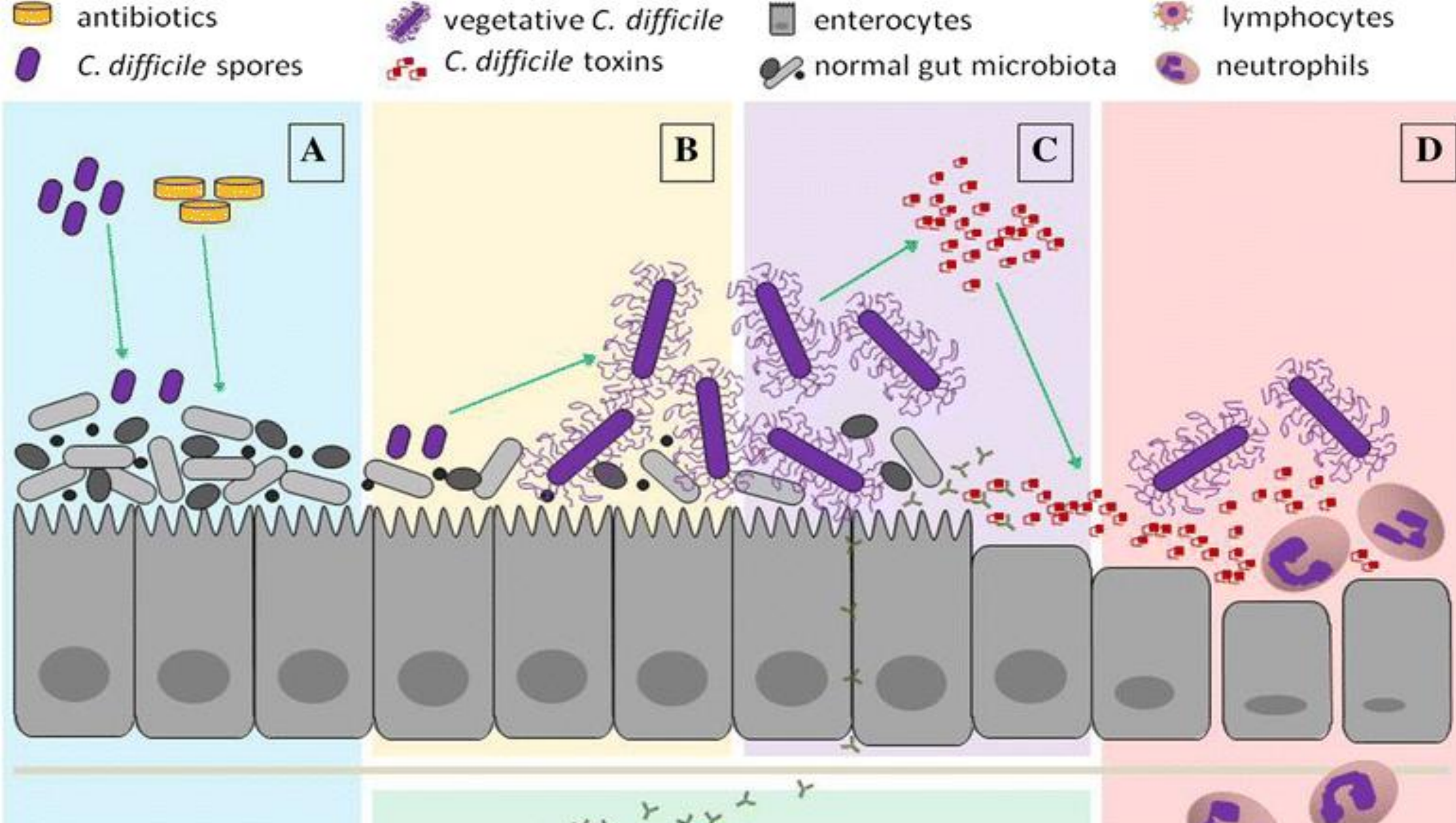
- Colon infection caused by the bacterium Clostridium difficile
- Postantibiotic or pseudomembranous colitis
- Clostridium difficile gram positive, sporogenous, anaerobic bacillus
- The bacterium produces toxins A and B
- A recorded increase in the number of patients and deaths since 2000
- Intrahospital infection



Risk factors for transmission of infection

- Use of antibiotics
- Hospitalization, especially intensive care units
- Older age
- Surgical intervention
- Comorbidities
- Horizontal transmission - contaminated hands of patient staff





Medicines responsible for the appearance of the disease:

Common

- Cephalosporins II and III of the third generation
- Ampicillin, Amoxicillin and other beta lactams
- Clindamycin
- Fluoroquinolones (Ciprofloxacin, Levofloxacin)
- Macrolides

Less common

- Amphotericin B
- Rifampicin
- Aminoglycosides
- Chloramphenicol
- Cytostatics

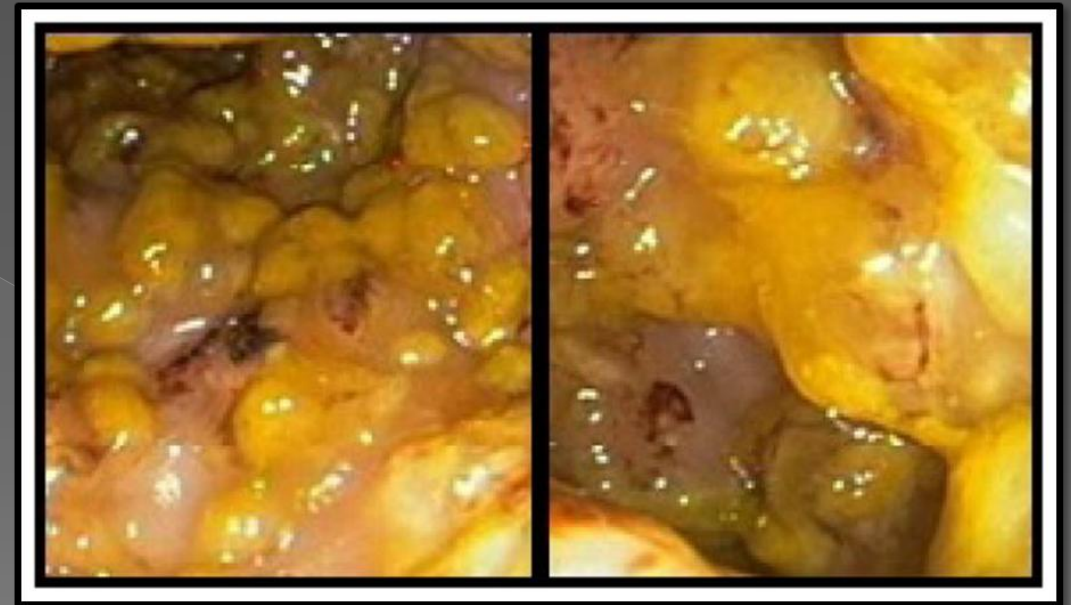
Clinical picture

- **Diarrhea without colitis**-liquid mucous stools, no more than 10 in 24 hours
- **Diarrhea with colitis** - watery stools more than 10 in 24 hours, fecal leukocytes, occult bleeding from the colon, abdominal distension and pain / cramps, temperature, anorexia, nausea and dehydration
- **Pseudomembranous colitis**- symptoms and signs of colitis with endoscopically or biopsy-proven pseudomembranes
- **Toxic megacolon or paralytic ileus** with or without diarrhoea, marked abdominal distension and pain/cramps
- **Asymptomatic carrier**

Severe clinical manifestations

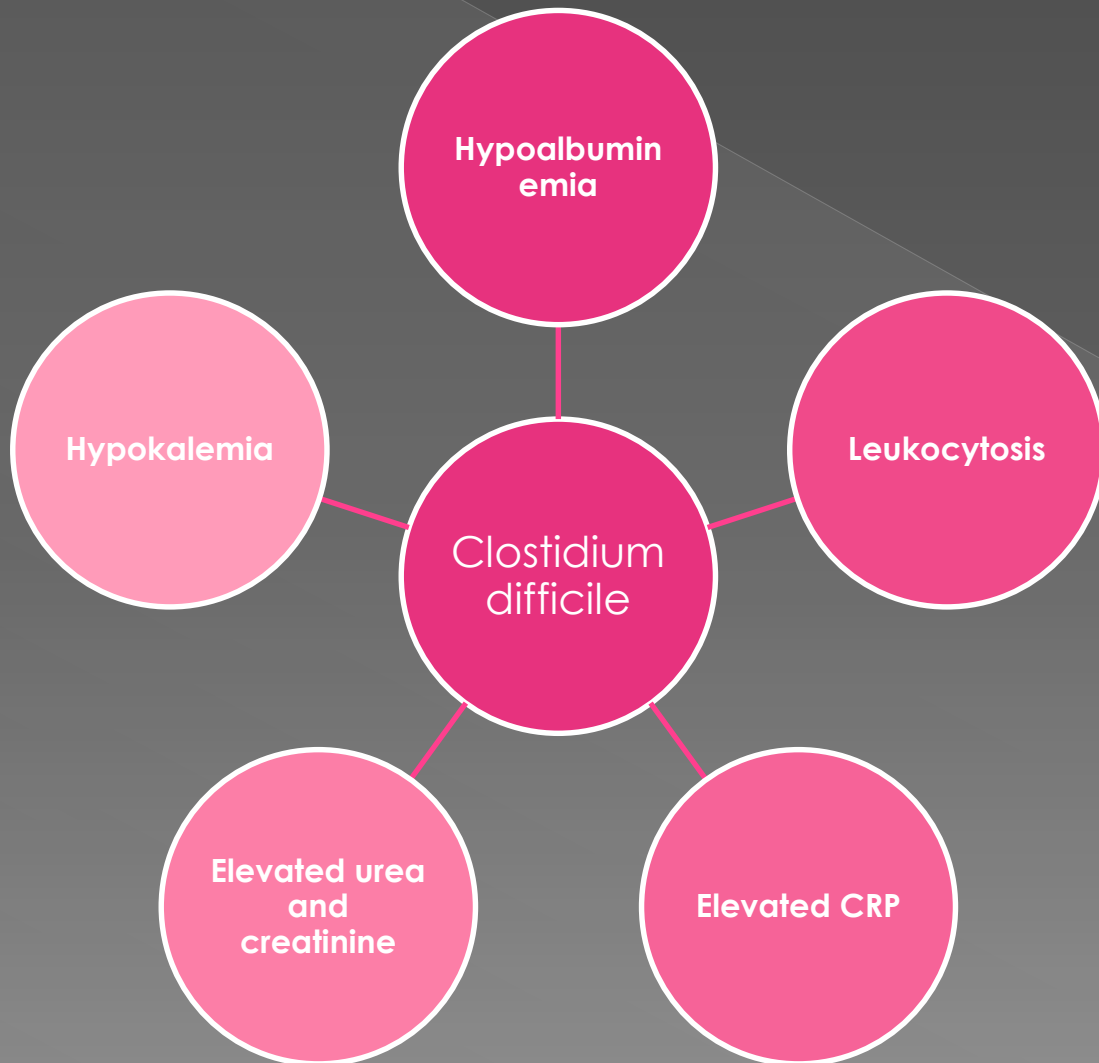


- ✓ Radiographic finding of toxic megacolon in a patient with pseudomembranous colitis



- ✓ Flexible sigmoidoscopy showing diffuse pseudomembranous colitis of the rectosigmoid part of the colon

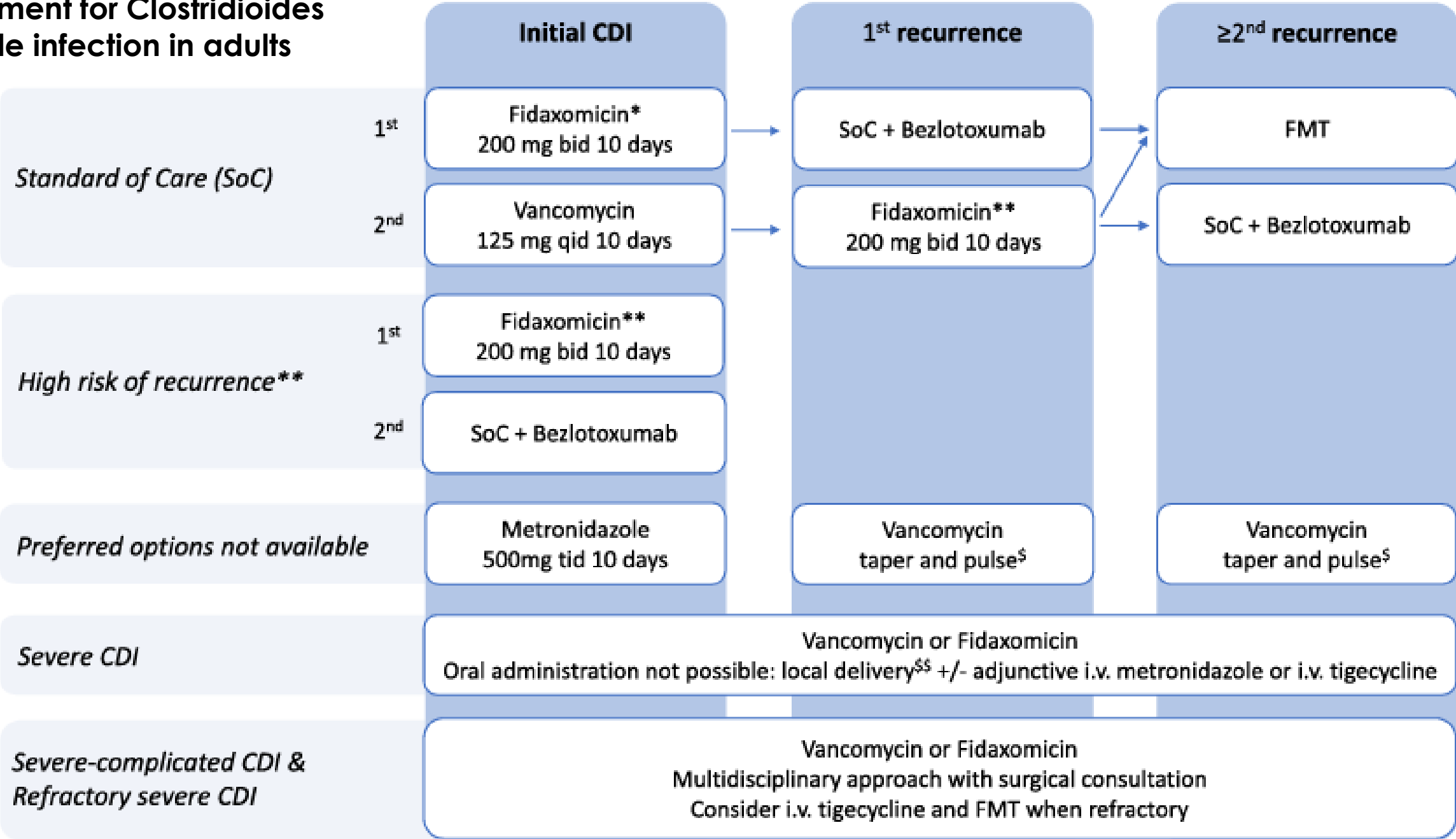
Pathological finding in usual laboratory analyses



Etiological diagnosis

- Cell culture, cytotoxicity test
- Toxogenic culture - toxogenic and non-toxigenic C.diff, sensitive, enables typing of strains in epidemics
- Enzyme immunoassay detects toxin A or B or GDH
- Real-time PCR

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.

** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA):2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	<p>Preferred: Fidaxomicin 200 mg given twice daily for 10 days</p> <p>Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days</p> <p>Alternative for nonsevere CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days</p>	<p>Implementation depends upon available resources</p> <p>Vancomycin remains an acceptable alternative</p> <p>Definition of nonsevere CDI is supported by the following laboratory parameters: White blood cell count of 15 000 cells/μL or lower and a serum creatinine level <1.5 mg/dL</p>
First CDI recurrence	<p>Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days</p> <p>Alternative: Vancomycin by mouth in a tapered and pulsed regimen</p> <p>Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days</p> <p>Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics^a</p>	<p>...</p> <p>Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks</p> <p>Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode</p> <p>Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure^b</p>
Second or subsequent CDI recurrence	<p>Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days</p> <p>Vancomycin by mouth in a tapered and pulsed regimen</p> <p>Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days</p> <p>Fecal microbiota transplantation</p> <p>Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics^a</p>	<p>...</p> <p>...</p> <p>...</p> <p>The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation</p> <p>Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure^a</p>
Fulminant CDI	<p>Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present</p>	<p>Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon</p>

