**Lecture 2.**

**The causative agents of gastro-intestinal bacterial infections (genus of *Escherichia, Shigella, Salmonella, Vibrio, Campilobacter, Helicobacter*)**

**The purpose of the lecture:** Morpho-biological characteristics of bacteria that cause gastrointestinal infections (Escherichia, Shigella, Salmonella, Vibrio, Campilobacter, Helicobacter species), pathogenic factors, diseases they cause, pathogenesis, main clinical signs, microbiological diagnosis, specific treatment and prevention principles. To inform them about broad-spectrum beta-lactamase-resistant bacteria.

**Note.** In this lecture, the teacher should try to explain the importance of the properties of these microorganisms in the pathogenesis, microbiological diagnosis, treatment and prevention of diseases caused by them.

**Lecture plan:**

• Bacteria that cause gastrointestinal infections:

- Genus of *Escherichia*, morpho-biological characteristics of Escherichia, pathogenic factors, diseases they cause, antibiotic-resistant forms, microbiological diagnosis, specific treatment and prevention.

- Genus of *Shigella*, morpho-biological characteristics, pathogenic factors, diseases they cause, antibiotic-resistant forms, microbiological diagnosis, specific treatment and prevention.

- Classification of pathogenic bacteria belonging to the genus of *Salmonella*, morpho-biological characteristics, pathogenic factors, pathogenesis of diseases caused by these bacteria, the main clinical signs, microbiological diagnosis, specific principles of treatment and prevention. Broad-spectrum beta-lactamase-resistant bacteria.

• *Vibrios*. Classification. Cholera vibrio, morpho-biological characteristics. Biovar: classic plague vibrio and El-Tor. Pathogenesis of cholera, main clinical signs, microbiological diagnosis, specific principles of treatment and prevention

• *Campylobacteria*, their morpho-biological characteristics. Pathogenic factors. Diseases caused by. Pathogenesis, main clinical signs and microbiological diagnosis

• *Helicobacter pylori*, their morpho-biological characteristics. Pathogenic factors. Diseases caused by. Pathogenesis, main clinical signs and microbiological diagnosis

***Enterobacteriaceae***

***ESCHERICHIA COLI***

**Trigger Words**

Gastroenteritis, EAEC, EIEC, EPEC, ETEC, STEC, neonatal meningitis, urinary tract infection

**Biology and Virulence**

Gram-negative, facultative anaerobic rods

Fermenter; oxidase negative

 Lipopolysaccharide consists of outer somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin)

**Epidemiology**

Most common aerobic gram-negative rods in the gastrointestinal tract

Most infections are endogenous (patient’s microbial flora), although strains causing gastroenteritis are generally acquired exogenously

**Diagnosis**

ᑏᑏOrganisms grow rapidly on most culture

media

ᑏᑏ Enteric multiplex NAATs considered gold

standard diagnostic

**Diseases**

At least five different pathogenic groups cause gastroenteritis: EAEC, EIEC, EPEC, ETEC, and STEC

Most cause diseases in developing countries, although STEC is an important cause of hemorrhagic colitis and hemolytic uremic syndrome

Extraintestinal disease includes bacteremia, neonatal meningitis, urinary tract infections, and intraabdominal infections

**Treatment, Prevention, and Control**

Enteric pathogens are treated symptomatically unless disseminated disease occurs

Antibiotic therapy is guided by in vitro susceptibility tests; increased resistance to penicillins and cephalosporins mediated by ESBLs

Appropriate infection-control practices are used to reduce the risk of nosocomial infections (e.g., restricting use of antibiotics, avoiding unnecessary use of urinary tract catheters)

Maintenance of high hygienic standards to reduce the risk of exposure to gastroenteritis strains

Proper cooking of beef products to reduce risk of STEC infections

***SHIGELLA***

**Trigger Words**

Gastroenteritis, dysentery, Shiga toxin

**Biology and Virulence**

Gram-negative, facultatively anaerobic rods

Fermenter; oxidase negative

Lipopolysaccharide consists of somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin)

Four species recognized: *S. sonnei* responsible for most infections in developed countries, *S. flexneri* for infections in developing countries, *S.dysenteriae* for the most severe infections, and *S.boydii* not commonly isolated

Virulence: exotoxin (Shiga toxin) produced by *S. dysenteriae* disrupts protein synthesis and produces endothelial damage

**Epidemiology**

Humans are the only reservoir for these bacteria

Disease spread person to person by fecal-oral route

Patients at highest risk for disease are young children in day-care centers, nurseries, and custodial institutions; siblings and parents of these children; male homosexuals

Relatively few organisms can produce disease (highly infectious)

Disease occurs worldwide with no seasonal incidence (consistent with person-to-person spread involving a low inoculum)

**Diseases**

Disease: most common form of disease is gastroenteritis (shigellosis), an initial watery diarrhea progressing within 1 to 2 days to abdominal cramps and tenesmus (with or without bloody stools); severe form of disease is caused by *S. dysenteriae* (bacterial dysentery); asymptomatic carriage develops in a small number of patients (reservoir for future infections)

**Diagnosis**

ᑏᑏ Isolation from stool specimens requires

use of selective media

ᑏᑏ Enteric multiplex NAATs considered gold

standard diagnostic

**Treatment, Prevention, and Control**

Antibiotic therapy shortens the course of symptomatic disease and fecal shedding

Treatment should be guided by in vitro susceptibility tests

Empirical therapy can be initiated with a fluoroquinolone or trimethoprim, sulfamethoxazole

Appropriate infection control measures should be instituted to prevent spread of the organism, including hand washing and proper disposal of soiled linens

***SALMONELLA***

**Trigger Words** Gastroenteritis, enteric fever, antibiotic treatment

**Biology and Virulence**

Gram-negative, facultative anaerobic rods

Fermenter; oxidase negative

Lipopolysaccharide consists of outer somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin)

More than 2500 O serotypes

Virulence: refer to Box 25.2; tolerant of acids in phagocytic vesicles

Can survive in macrophages and spread from the intestine to other body sites

**Epidemiology**

Most infections are acquired by eating contaminated food products (poultry, eggs, and dairy products are the most common sources of infection)

Direct fecal-oral spread in children

*Salmonella* Typhi and *Salmonella Paratyphi* are strict human pathogens (no other reservoirs); these infections are passed person to person; asymptomatic long-term colonization occurs commonly

Individuals at risk for infection include those who eat improperly cooked poultry or eggs, patients with reduced gastric acid levels, and immunocompromised patients

Infections occur worldwide, particularly in the warm months of the year

**Diseases**

Diseases: enteritis (fever, nausea, vomiting, bloody or nonbloody diarrhea, abdominal cramps); enteric fever (typhoid fever,

paratyphoid fever); bacteremia (most commonly seen with *Salmonella* serotype Typhi, *Salmonella* serotype Paratyphi, *Salmonella* serotype Choleraesuis); asymptomatic colonization (primarily with *Salmonella* Typhi and *Salmonella* Paratyphi)

**Clinical Diseases Induced by Salmonellae**

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**Diagnosis**

ᑏᑏ Isolation from stool specimens requires

use of selective media

ᑏᑏ Enteric multiplex NAATs considered gold

standard diagnostic

**Treatment, Prevention, and Control**

Antibiotic treatment not recommended for enteritis because this may prolong the duration of disease

Infections with *Salmonella* Typhi and *Salmonella* Paratyphi or disseminated infections with other organisms should be treated with an effective antibiotic (selected by in vitro susceptibility tests); fluoroquinolones (e.g., ciprofloxacin), chloramphenicol, trimethoprim sulfamethoxazole, or a broad-spectrum cephalosporin may be used

Most infections can be controlled by proper preparation of poultry and eggs (completely cooked) and avoidance of contamination of other foods with uncooked poultry products

Carriers of *Salmonella* Typhi and *Salmonella* Paratyphi should be identified and treated

Vaccination against *Salmonella* Typhi can reduce the risk of disease for travelers into endemic areas

*EAEC,* Enteroaggregative *E. coli*; *EIEC,* enteroinvasive *E. coli*; *EPEC,* enteropathogenic *E. coli*; ESBL, extended-spectrum \_-lactamase; *ETEC,* enterotoxigenic *E. coli*; *NAAT,* nucleic acid amplification test; *STEC,* Shiga toxin–producing *E. coli*.

Important Enterobacteriaceae

**Organism Historical Derivation**

*Escherichia coli - escherichia,* named after Escherich; *coli,* of the colon

*Salmonella enterica - salmonella,* named after Salmon; *enteron*, gut; pertaining to the gut

*Salmonella* Typhi - *typhi,* of typhoid; disease is typhoid fever

*Salmonella* Paratyphi - *paratyphi,* of a typhoid-like infection

*Salmonella* Choleraesuis - *cholera,* cholera; *sus,* hog; cholera of a hog

*Salmonella* Typhimurium - *typhi,* of typhoid; *murium,* of mice; *typhimurium,* typhoid of mice

*Salmonella* Enteritidis - *enteris,* gut; *idis,* inflammation

*Shigella dysenteriae - shigella,* named after Shiga; *dysenteriae,* dysentery

*S. flexneri - flexneri,* named after Flexner

*S. boydii - boydii,* named after Boyd

*S. sonnei - sonnei,* named after Sonne

*Yersinia pestis - yersinia,* named after Yersin; *pestis,* plague

*Y. enterocolitica - enterocolitica,* pertaining to the intestine and colon

*Y. pseudotuberculosis - tuberculum,* a small swelling; *pseudotuberculosis,* false swelling

**Common Medically Important Enterobacteriaceae**

*Citrobacter freundii, C. koseri*

*Enterobacter cloacae*

*Escherichia coli*

*Klebsiella pneumoniae, K. oxytoca*

*Morganella morganii*

*Proteus mirabilis*

*Salmonella serotype Typhi, Salmonella nontyphoidal serotypes*

*Serratia marcescens*

*Shigella sonnei, S. flexneri*

*Yersinia pestis, Y. enterocolitica, Y. Pseudotuberculosis*

**Common Virulence Factors Associated with Enterobacteriaceae**

Endotoxin

Capsule

Antigenic phase variation

Type III secretion systems

Sequestration of growth factors

Resistance to serum killing

Antimicrobial resistance

**Specialized Virulence Factors Associated with *Escherichia coli***



**Gastroenteritis Caused by *Escherichia coli***



**Vibrio *and Related Bacteria***

**VIBRIO CHOLERAE**

**Trigger Words**

Serogroup O1, cholera, cholera toxin, shellfish, gastroenteritis

**Biology and Virulence**

Curved gram-negative rods

Fermentative, facultative anaerobic; require salt for growth

Strains subdivided into more than 200 serogroups (O–cell wall antigens)

*V. cholerae* serogroup O1 is further subdivided into serotypes (Inaba, Ogawa, and Hikojima) and biotypes (Classical and El Tor)

Disease mediated by cholera toxin (complex A-B toxin) and toxin coregulated pilus

**Epidemiology**

Serotype O1 is responsible for major pandemics (worldwide epidemics), with significant mortality in developing countries; O139 can cause similar diseases

Organism found in estuarine and marine environments worldwide (including along the coast of the United States); associated with chitinous shellfish

Organism can multiply freely in water

Bacterial levels in contaminated waters increase during the warm months

Most commonly spread by consumption of freshly contaminated water

Direct person-to-person spread is rare because the infectious dose is high; the infectious dose is high because most organisms are killed by stomach acids

**Diseases**

Infection can range from asymptomatic colonization or mild diarrhea to severe, rapidly fatal diarrhea

**The Medically Important Vibrios**

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**Diagnosis**

ᑏᑏMicroscopic examination of stool can be useful in acute infections in the setting of an epidemic but rapidly becomes negative as the disease progresses

ᑏᑏ Immunoassays for cholera toxin or O1 and O139 lipopolysaccharides can be useful, although the analytical performance of the assays is quite variable

ᑏᑏMultiplex nucleic acid amplification tests can be used to detect many enteric pathogens (bacteria, viruses, and parasites) and are the diagnostic test of choice

ᑏᑏCulture should be performed early in course of disease with fresh stool specimens maintained in a neutral to alkaline pH

**Treatment, Prevention, and Control**

Fluid and electrolyte replacement are crucial

Antibiotics (e.g., azithromycin) reduce the bacterial burden and exotoxin production, as well as duration of diarrhea

Improved hygiene is critical for control

Combination inactivated whole cell and cholera toxin B subunit vaccines provide limited protection and herd immunity

**VIBRIO PARAHAEMOLYTICUS**

**Trigger Words**

Kanagawa hemolysin, shellfish, gastroenteritis

**Biology and Virulence**

Curved gram-negative rods

Fermentative, facultative anaerobic; require salt for growth

Production of thermostable direct hemolysin (Kanagawa hemolysin) associated with pathogenic strains

**Epidemiology**

Organism found in estuarine and marine environments worldwide

Associated with consumption of contaminated raw shellfish

Most common cause of bacterial gastroenteritis in Japan and Southeast Asia

Most common cause of seafood-associated gastroenteritis in United States

**Diseases**

Most symptomatic infections are selflimited diarrhea

**Treatment, Prevention, and Control**

Self-limited disease, although antibiotics can shorten length of symptoms and fluid loss

Disease prevented by proper cooking of shellfish

No vaccine is available

**VIBRIO VULNIFICUS**

**Trigger Words**

Septicemia, wound infections, hepatic disease

**Biology and Virulence**

Curved gram-negative rods

Fermentative, facultative anaerobic; require salt for growth

Virulence associated with presence of polysaccharide capsule and hydrolytic enzymes

**Epidemiology**

Infection associated with exposure of a wound to contaminated salt water or ingestion of improperly prepared shellfish

**Diseases**

High mortality associated with primary septicemia and wound infections, particularly in patients with underlying hepatic disease

**Diagnosis**

ᑏᑏCulture wounds and blood

**Treatment, Prevention, and Control**

 Life-threatening illnesses that must be promptly treated with antibiotics

Minocycline or doxycycline combined with a ceftriaxone or cefotaxime is the treatment of choice

No vaccine is available

**Important *Vibrio* and *Aeromonas* Species**

*Vibrio vibrio,* move rapidly or vibrate (rapid movement caused by polar flagella)

*V. cholerae cholera,* cholera or an intestinal disease

*V. parahaemolyticus para,* by the side of; *haema,* blood; *lyticus,* dissolving (dissolving blood; Kanagawa toxin–positive strains are hemolytic)

*V. vulnificus vulnificus,* inflicting wounds (associated with prominent wound infections)

*Aeromonas aero,* gas or air; *monas,* unit or monad (gasproducing bacteria)

*A. caviae cavia,* guinea pig (first isolated in guinea pigs)

*A. hydrophila hydro,* water; *phila,* loving (water loving)

*A. veronii veron,* named after the bacteriologist Veron

***Vibrio* Species Most Commonly Associated with Human Disease**

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**Virulence Factors of *Vibrio* Species**

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***Vibrio cholerae***

**Cholera:** it begins with an abrupt onset of watery diarrhea and vomiting and can progress to severe dehydration, metabolic

acidosis and hypokalemia, and hypovolemic shock.

**Gastroenteritis:** milder forms of diarrheal disease can occur in toxin-negative strains of *V. cholerae* O1 and in non-O1 serotypes.

***Vibrio parahaemolyticus***

**Gastroenteritis:** it is generally self-limited, with an explosive onset of watery diarrhea and nausea, vomiting, abdominal cramps, headache, and low-grade fever.

**Wound infection:** it is associated with exposure to contaminated water.

***Vibrio vulnificus***

**Wound infection:** severe, potentially fatal infections characterized by erythema, pain, bullae formation, tissue necrosis, and septicemia.

**CAMPYLOBACTER**

**Trigger Words**

Curved rods, gastroenteritis, Guillain-Barré syndrome

**Biology and Virulence**

Thin, curved, gram-negative rods

ᑏ Factors that regulate adhesion, motility, and invasion into intestinal mucosa are poorly defined

**Epidemiology**

Zoonotic infection; improperly prepared poultry is a common source of human infections

Infections acquired by ingestion of contaminated food, unpasteurized milk, or contaminated water

Person-to-person spread is unusual

Dose required to establish disease is high unless the gastric acids are neutralized or absent

Worldwide distribution with enteric infections seen throughout the year

**Diseases**

Most common disease is acute enteritis with diarrhea, malaise, fever, and abdominal pain

Guillain-Barré syndrome is believed to be an autoimmune disease caused by antigenic cross-reactivity between oligosaccharides in the bacterial capsule and glycosphingolipids on the surface of neural tissues

Most infections are self-limited but can persist for a week or more

*C. fetus* is associated with septicemia and is disseminated to multiple organs

**Diagnosis**

ᑏᑏMicroscopic detection of thin, S-shaped, gram-negative rods in stool specimens is specific but insensitive

ᑏᑏCommercial multiplex nucleic acid amplification assays are highly sensitive and specific for enteric pathogens and particularly useful for detection of *C.* *jejuni* and *C. coli* infections

ᑏᑏCulture requires use of specialized media incubated with reduced oxygen, increased carbon dioxide, and (for thermophilic species) elevated temperatures requires incubation for 2 or more days and is relatively insensitive unless fresh media are used

ᑏᑏDetection of *Campylobacter* antigens instool specimens is moderately sensitive and very specific compared with culture

**Treatment, Prevention, and Control**

For gastroenteritis, infection is self-limited and is managed by fluid and electrolyte replacement

Severe gastroenteritis and septicemia are treated with erythromycin or azithromycin

Gastroenteritis is prevented by proper preparation of food and consumption of pasteurized milk; preventing contamination of water supplies also controls infection

Experimental vaccines targeting the outer capsular polysaccharides are promising for control of infections in animal reservoirs

***H*ELICOBACTER PYLORI**

**Trigger Words**

Gastritis, peptic ulcers, gastric cancer, lymphoid tissue lymphoma, urease

**Biology and Virulence**

Curved gram-negative rods

Urease production at very high levels is typical of gastric helicobacters (e.g., *H. pylori;* important diagnostic test for *H. pylori*) and uncommon in intestinal helicobacters

Multiple factors contribute to gastric colonization, inflammation, alteration of gastric acid production, and tissue destruction

**Epidemiology**

Infections are common, particularly in people in a low socioeconomic class or in developing nations

Humans are the primary reservoir

Person-to-person spread is important (typically fecal-oral)

Ubiquitous and worldwide, with no seasonal incidence of disease

**Diseases**

*H. pylori* is an important cause of acute and chronic gastritis, peptic ulcers, gastric adenocarcinoma, and mucosa associated Lymphoid tissue lymphoma

**Diagnosis**

ᑏᑏMicroscopy: histologic examination of biopsy specimens is sensitive and specific

ᑏᑏUrease test relatively sensitive and highly specific; urea breath test is a noninvasive test

ᑏᑏ*H. pylori* antigen test is sensitive and specific; performed with stool specimens

ᑏᑏCulture requires incubation in microaerophilic conditions; growth is slow; relatively insensitive unless multiple biopsies are cultured

ᑏᑏ Serology useful for demonstrating exposure to *H. pylori*

**Treatment, Prevention, and Control**

Multiple regimens have been evaluated for treatment of *H. pylori* infections. Combined therapy with a proton pump inhibitor (e.g., omeprazole), a macrolide (e.g., clarithromycin), and a \_-lactam (e.g., amoxicillin) for 2 weeks has had a high success rate

Prophylactic treatment of colonized individuals has not been useful and potentially has adverse effects, such as predisposing patients to adenocarcinomas of the lower esophagus

Human vaccines are not currently available

**Important *Campylobacter* and *Helicobacter* Species**

*Campylobacter kampylos,* curved; *bacter,* rod (a curved rod)

*C. jejuni jejuni,* of the jejunum

*C. coli coli,* of the colon

*C. fetus fetus,* refers to the initial observation that these bacteria caused fetal infections

*C. upsaliensis upsaliensis,* original isolates recovered fromthe feces of dogs at an animal clinic in Uppsala, Sweden

*Helicobacter helix,* spiral; *bacter,* rod (a spiral rod)

*H. pylori pylorus,* lower part of the stomach

*H. cinaedi cinaedi,* of a homosexual (the organism was first isolated from homosexuals withgastroenteritis)

*H. fennelliae fennelliae,* named after C. Fennell, who first

isolated the organism

**Common *Campylobacter* Species Associated with Human Disease**

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***Helicobacter* Species Associated with Human Disease**

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**Rapid, Presumptive Identification of Gram-Negative Enteric Bacteria**

**Lactose fermented rapidly**

*Escherichia coli*: metallic sheen on differential media; motile; flat, nonviscous colonies

*Enterobacter aerogenes*: raised colonies, no metallic sheen; often motile; more viscous growth

*Enterobacter cloacae*: similar to *Enterobacter aerogenes*

*Klebsiella pneumoniae*: very viscous, mucoid growth; nonmotile

**Lactose fermented slowly**

*Edwardsiella, Serratia, Citrobacter, Arizona, Providencia, Erwinia*

**Lactose not fermented**

*Shigella* species: nonmotile; no gas from dextrose

*Salmonella* species*:* motile; acid and usually gas from dextrose

*Proteus* species*:* “swarming” on agar; urea rapidly hydrolyzed (smell of ammonia)

*Pseudomonas* species (see Chapter 16): soluble pigments, blue-green and fluorescing; sweetish smell