Enterobacteriaceae

This family includes genera and species that cause **well-defined diseases with typical clinical symptoms** (typhoid fever, dysentery, plague) as well as many opportunists that cause **mainly nosocomial infections** (urinary tract infections, pneumonias, wound infections, sepsis).

Enterobacteriaceae are **Gram-negative, usually motile, facultatively anaerobic rod bacteria**. The high levels of metabolic activity observed in them are made use of in identification procedures.

The species are subdivided into epidemiologically significant serovars based on O, H, and K antigens.

The most important pathogenicity factors of Enterobacteriaceae are *colonizing factors, invasins, endotoxin,* and *various exotoxins*.

Enterobacteriaceae are the most significant contributors to intestinal infections, which are among the most frequent diseases of all among the developing world populace.

Definition and significance

Together with the families *Vibrionaceae* and others, the Enterobacteriaceae form the group of *Gram-negative, facultatively anaerobic rod bacteria*. Their natural habitat is **the intestinal tract of humans and animals**. Some species cause characteristic diseases. While others are *facultatively pathogenic*, they are still among the bacteria most frequently isolated as pathogens. They are often responsible for nosocomial diseases.

Taxonomy

The taxonomy of the Enterobacteriaceae has seen repeated changes in recent decades and has doubtless not yet assumed its final form. The family includes 41 genera with hundreds of species.

The taxonomic system applied to Enterobacteriaceae is based on varying patterns of metabolic processes. One of the important characteristics of this bacterial family is **lactose breakdown** (presence of the *lac* operon). The *lac* operon includes the genes *lacZ* (codes for β-galactosidase), *lacY* (codes for β-galactoside permease), and *lacA* (codes for transacetylase). **Lactose-positive** Enterobacteriaceae are grouped together as **coliform Enterobacteriaceae.** **Salmonellae** and most of the **shigellae** are **lactose-negative**.

Enterobacteriaceae

Genera/species/var	Disease	Remarks
Salmonella enterica		
S. Typhi	Typhus abdominalis (syn. typhoid fever)	Generalized septic infection
S. Typhimurium	Gastroenteritis (diarrhea)	Profuse watery diarrhea
S. Enteritidis and others		
Shigella	Bacterial dysentery	Diarrhea, abdominal cramping, tenesmus, stool frequently contains blood and mucus
Klebsiella pneumoniae	Pneumonia (Friedländer's)	Severe pneumonia in predisposed persons
Escherichia coli *Citrobacter* *Klebsiella* *Enterobacter* *Serratia* *Proteus* *Providencia*	Sepsis, wound infections, infections of the urinary tract and respiratory tract	Facultatively pathogenic bacteria; disease only manifests if host organism immune defenses are weakened; often cause nosocomial infections; frequently resistant to

Yersinia		
Y. pestis	Plague	Generalized systemic infection; rare
Y. enterocolitica *Y. pseudotuberculosis*	Enterocolitis, lymphadenitis of the mesenteric lymph nodes	Pseudoappendicitis, reactive arthritis, erythema nodosum
Escherichia coli	Intestinal infections	
Enteropathogenic *E. coli* (EPEC)	Classic infant diarrhea	Epidemics in hospitals, children's homes
Enterotoxic *E. coli* (ETEC)	Diarrhea, choleralike	Cause of travelers' diarrhea (50%)
Enteroinvasive *E. coli* (EIEC)	Dysenterylike	Invasion and verocytotoxins
Enterohemorrhagic *E. coli* (EHEC)	Hemorrhagic colitis	Hemolytic–uremic syndrome (HUS) in 5% of EHEC cases
Enteroaggregative *E. coli* (EAggEC)	Watery diarrhea, mainly in infants	Adhesion to small intestine mucosa; production of a toxin

Salmonella (Gastroenteritis, Typhoid Fever, Paratyphoid Fever)

All salmonellae are classified in the species *Salmonella enterica* with seven subspecies. Nearly all human pathogen salmonellae are grouped under *S. enterica*, subsp. *enterica*. Salmonellae are further subclassified in over **2000 serovars** based on their O and H antigens, which used to be (incorrectly) designated as species.

Typhoid salmonelloses are caused by the serovars *typhi* and *paratyphi A, B*, and *C.* The salmonellae are taken up orally and the invasion pathway is through the intestinal tract, from where they enter lymphatic tissue, first spreading lymphogenously, then hematogenously.

A generalized septic clinical picture results. Human carriers are the only source of infection. Transmission is either direct by smear infection or indirect via food and drinkingwater. Anti-infective agents are required for therapy (ampicillin, cotrimoxazole, 4-quinolones). An active vaccine is available to protect against typhoid fever.

Enteric salmonelloses develop when pathogens are taken up with food. The primary infection source is usually livestock. These relatively frequent infections remain restricted to the gastrointestinal tract. Treatment with anti-infective agents is necessary in exceptional cases only.

Excerpt from the Kauffmann–White Scheme which Covers Over 2000 Serovars

Group	Serovar	O antigens	H antigens Phase 1	Phase 2
A	*Paratyphi A*	1, **2**, 12	a	–
B	*Schottmuelleri* (syn. *Paratyphi B*)	1, **4**, (5), 12	b	1, 2
	Typhimurium	1, **4**, (5), 12	i	1, 2
C1	*Hirschfeldii* (syn. *Paratyphi C*)	**6**, 7, (Vi)	c	1, 5
	Choleraesuis	**6**, 7	(c)	1, 5
C2	*Newport*	**6**, 8	e, h	1, 2
D1	*Typhi*	**9**, 12, (Vi)	d	–
	Enteritidis	1, **9**, 12, (Vi)	g, m	(1, 7)
	Dublin	1, **9**, 12, (Vi)	g, p	–
	Gallinarum	1, **9**, 12	–	–
	Panama	1, **9**, 12	l, v	1, 5
E1	*Oxford*	**3**, 10	a	1, 7

H Phase Variation in Salmonellae

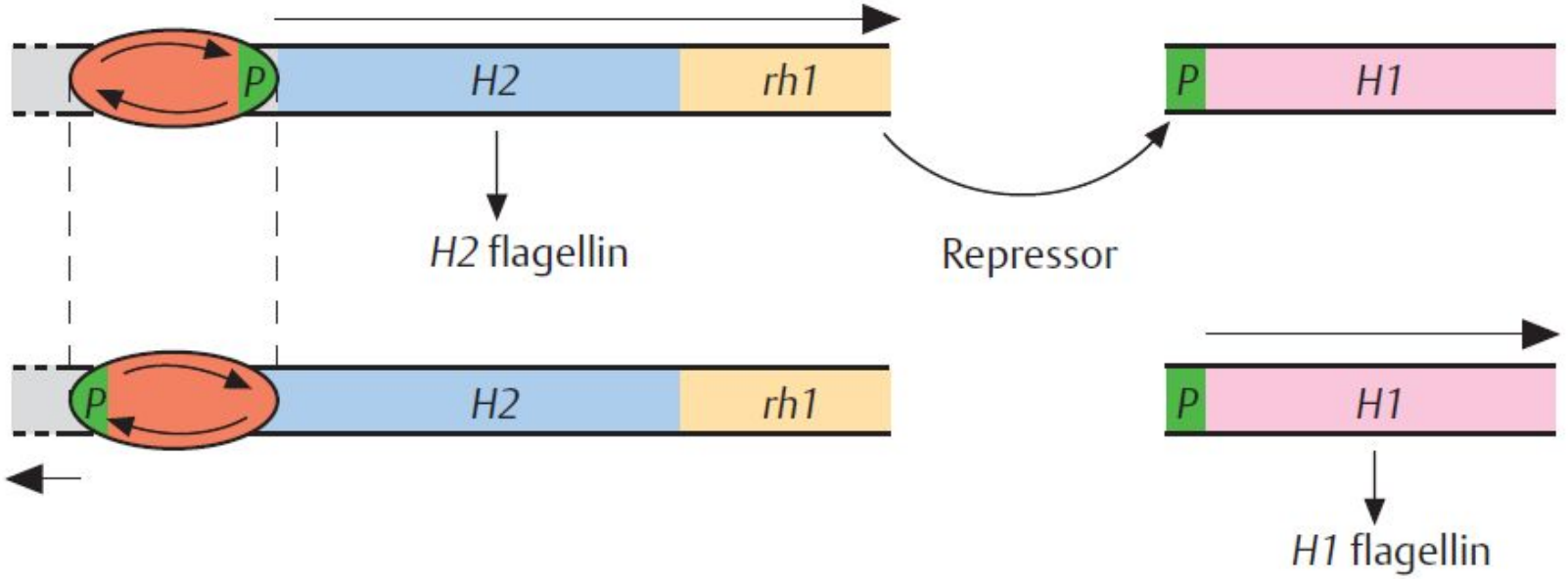


Fig. 4.**18** *P* = promoter, *H2* = H2 phase gene, *H1* = H1 phase gene, *rh1* = regulator gene for *H1*, *hin* = gene coding for the DNA invertase. The horizontal arrows show the direction in which the genetic information is read off.

Overview of the Most Important Differences between Typhoid and Enteric Salmonellae and Salmonelloses

Parameter	Typhoid salmonellae/salmonelloses	Enteric salmonellae/salmonelloses
Serovars	*Typhi*; *Paratyphi A*, *B*, *C* (see Table 4.**7**)	Often *Enteritidis* and *Typhimurium*; more rarely: numerous other serovars
Infection spectrum	Humans	Animals and humans
Source of infection	Humans: infected persons, chronic carriers	Mainly livestock; possibly humans as well
Mode of infection	Oral	Oral
Transmission	Indirect: water, contaminated food Direct: smear infection	Indirect: contaminated food
Infective dose	Small: 10^2–10^3 bacteria	Large: $>10^6$ bacteria; in most cases proliferation in food

Parameter	Typhoid salmonellae/salmonelloses	Enteric salmonellae/salmonelloses
	Sepsis	Fever. Self-limiting infection in most cases
Diagnosis	Identification of pathogen in blood, stool, urine. Antibody detection using Gruber-Widal quantitative agglutination reaction	Identification of pathogen in stool
Therapy	Antibiotics: aminopenicillins, 4-quinolones	Symptomatic therapy: loperamide, replacement of water and electrolyte losses as required (WHO formula)
Occurrence	Sporadic; usually imported from countries with endemic typhoid fever	Endemic, epidemics in small groups (family, cafeteria, etc.) or as mass infection
Prevention	**Exposure prophylaxis:** Drinking water and food hygiene; elimination of pathogen in chronic carriers. **Immunization prophylaxis:**	**Exposure prophylaxis:** Food hygiene

Epidemiology

The cases of **typhoid salmonelloses seen in northern and central Europe are imported by travelers**. Cases arise only sporadically or in form of an epidemic because of a chain of unfortunate circumstances. Humans are the only primary source of infection. By contrast, enteric salmonelloses occur in this population both endemically and epidemically. Case counts are steadily increasing. Exact morbidity data are hard to come by due to the large numbers of unreported cases. Livestock represents the most important source of infection. The pathogens are transmitted to humans in food.

Shigella (Bacterial Dysentery)

Shigella is the causative pathogen in bacterial dysentery. The genus comprises the species *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*. Shigellae are nonmotile. The three primary species can be classified in serovars based on the fine structure of their O antigens. Shigellae are characterized by invasive properties. They can penetrate the colonic mucosa to cause local necrotic infections. Humans are the sole source of infection since shigellae are pathologically active in humans only. The pathogens are transmitted directly, more frequently indirectly, via food and drinking water. Antibiotics can be used therapeutically.

Pathogenesis

Shigellae are only pathogenic in humans. The pathogens are ingested orally. Only a few hundred bacteria suffice for an infective dose. Shigellae enter the terminal ileum and colon, where they are taken up by the M cells in the intestinal mucosa, which in turn are in close vicinity to the macrophages. Following phagocytosis by the macrophages, the shigellae lyse the phagosome and actively induce macrophage apoptosis. The shigellae released from the dead macrophages are then taken up by enterocytes via the basolateral side of the mucosa (i.e., retrograde transport).

Pathogenesis

The invasion is facilitated by outer membrane polypeptides, the invasins, which are coded by *inv* genes localized on 180–240 kb plasmids. Adjacent enterocytes are invaded by means of lateral transfer from infected cells. In the enterocytes, the shigellae reproduce, finally destroying the cells. *Shigella dysenteriae* produces shigatoxin, the prototype for the family of shigalike toxins (or verocytotoxins), which also occur in several other Enterobacteriaceae. The toxin inhibits protein synthesis in eukaryotic cells by splitting the 23S rRNA at a certain locus. Shigatoxin contributes to the colonic epithelial damage, the small intestine diarrhea with watery stools at the onset of shigellosis and (less frequent) the hemolytic-uremic syndrome (HUS).

Therapy

Anti-infective agents are the first line of treatment (aminopenicillins, 4-quinolones, cephalosporins). Losses of water and electrolytes may have to be replaced.

Epidemiology and prevention

Bacterial dysentery occurs worldwide, although it is usually seen only sporadically in developed countries. In developing countries, its occurrence is more likely to be endemic and even epidemic. The source of infection is always humans, in most cases infected persons whose stools contain pathogens for up to six weeks after the disease has abated. Transmission is by direct contact (smear infection) or indirect uptake via food, surface water, or flies. Control of dysentery includes exposure prophylaxis measures geared to prevent susceptible persons from coming into contact with the pathogen.

Yersinia (Plague, Enteritis)

Y. pestis is the causative pathogen of plague (black death, bubonic plague). Plague is a classic rodent zoonosis. It occurred in epidemic proportions in the Middle Ages, but is seen today only sporadically in persons who have had direct contact with diseased wild rodents. The pathogens penetrate into the skin through microtraumata, from where they reach regional lymph nodes in which they proliferate, resulting in the characteristic buboes. In the next stage, the pathogens may enter the bloodstream or the infection may generalize to affect other organs. Laboratory diagnosis involves isolation and identification of the organism in pus, blood, or other material. Therapy requires use of antibiotics.

Y. enterocolitica and *Y. pseudotuberculosis* cause generalized zoonoses in wild animals and livestock. Diseased animals contaminate their surroundings. Humans then take up the pathogens orally in water or food. The organisms penetrate the mucosa of the lower intestinal tract, causing enteritis accompanied by mesenteric lymphadenitis.

Extramesenteric forms are observed in 20% of infected persons (sepsis, lymphadenopathies, various focal infections). Secondary immunopathological complications include arthritis and erythema nodosum. Diagnosis involves identification of the pathogen by means of selective culturing.

Yersinia pestis

Morphology and culture

Y. pestis is a nonflagellated, short, encapsulated, Gram-negative rod bacteria that often shows bipolar staining. This bacterium is readily cultured on standard nutrient mediums at 30°C.

Pathogenesis and clinical picture

The plague is primarily a disease of rodents (rats). It spreads among them by direct contact or via the rat flea. Earlier plague epidemics in humans resulted from these same transmission pathways. The rare human infections seen today result from contact with rodents that are infected with or have died of plague. The pathogen breaches the skin through dermal injuries. From such a location, the bacteria reach regional lymph nodes in which they proliferate. Two to five days after infection, hemorrhagically altered, blue, and swollen lymph nodes (buboes) are observed.

Diagnosis. The pathogen must be identified in bubo punctate, sputum, or blood by means of microscopy and culturing.

Therapy. In addition to symptomatic treatment, antibiotics are the primary method (streptomycin, tetracyclines, in the case of meningitis, chloramphenicol). Incision of the buboes is contraindicated.

Epidemiology and prevention. Plague still occurs **endemically** in wild rodents over large areas of Asia, Africa, South America, and North America. Human plague infections have been reduced to sporadic instances. The sources of infection are mainly diseased rodents. Transmission of the disease is mainly via direct contact with such animals. Prevention involves exposure prophylactic measures. Persons with manifest disease, in particular the pulmonary form, must be isolated. Contact persons must be quarantined for six days (= incubation period). Cases of plague infection must be reported to health authorities.

Yersinia enterocolitica and *Yersinia pseudotuberculosis*

Occurrence and significance

Y. enterocolitica and *Y. pseudotuberculosis* cause generalized infections in domestic and wild animals, especially rodents. The pathogens can be transmitted from animals to humans. *Y. enterocolitica* is responsible for about 1% of acute enteritis cases in Europe. *Y. pseudotuberculosis* is insignificant in terms of human pathology.

Escherichia coli

The natural habitat of *E. coli* is the intestinal tract of humans and animals. It is therefore considered an indicator organism for fecal contamination of water and foods. E. coli is the most frequent causative pathogen in human bacterial infections. Extraintestinal infections include urinary tract infections, which occur when the tract is obstructed or spontaneously caused by the pathovar UPEC. The most important other coli infections are cholecystitis, appendicitis, peritonitis, postoperative wound infections, and sepsis. Intestinal infections are caused by the pathovars EPEC, ETEC, EIEC, EHEC, and EAggEC. EPEC and EAggEC frequently cause diarrhea in infants. ETEC produce enterotoxins that cause a choleralike clinical picture. EIEC cause a dysenterylike infection of the large intestine. EHEC produce verocytotoxins and cause a hemorrhagic colitis as well as the rare hemolytic-uremic syndrome. E. coli bacteria infections are diagnosed by means of pathogen identification

General characteristics

The natural habitat of *E. coli* is the intestines of animals and humans. This bacterium is therefore used as an indicator for fecal contamination of drinking water, bathing water, and foods. Guideline regulations: 100 ml of drinking water must not contain any *E. coli*. Surface water approved for bathing should not contain more than 100 (guideline value) to 2000 (absolute cutoff value) E. coli bacteria per 100 ml. *E. coli* is also an important human pathogen. It is the bacterial species most frequently isolated from pathological materials

Morphology, culture, and antigen structure

The Gram-negative, straight rods are peritrichously flagellated. Lactose is broken down rapidly. The complex antigen structure of these bacteria is based on O, K, and H antigens. Fimbrial antigens have also been described. Specific numbers have been assigned to the antigens, e.g., serovar O18:K1:H7.

Vibrio cholerae (Cholera)

Morphology and culture. Cholera vibrios are Gram-negative rod bacteria, usually slightly bent (comma-shaped), 1.5–2 lm in length, and 0.3–0.5 lm wide, with monotrichous flagellation.

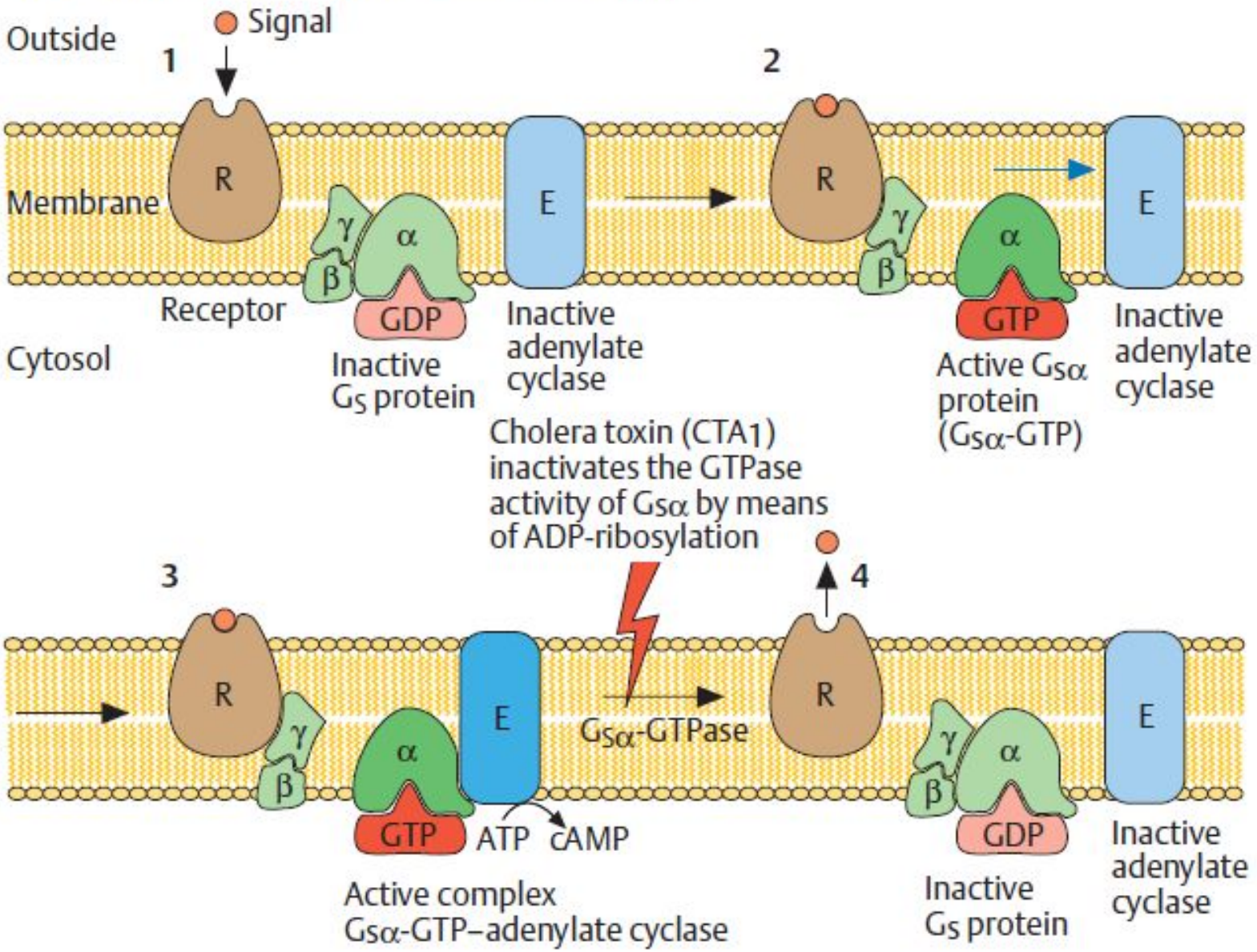
Culturing of *V. cholerae* is possible on simple nutrient mediums at 37°C in a normal atmosphere. Owing to its pronounced alkali stability, *V. cholerae* can be selectively cultured out of bacterial mixtures at pH 9.

Antigens and classification.

V. cholerae bacteria are subdivided into serovars based on their O antigens (lipopolysaccharide antigens). The serovar pathogen is usually serovar O:1. Strains that do not react to an O:1 antiserum are grouped together as nonO:1 vibrios. NonO:1 strains were recently described in India (O:139) as also causing the classic clinical picture of cholera. O:1 vibrios
are further subclassified in the biovars cholerae and eltor based on physiological characteristics. The var *eltor* has a very low level of virulence.

Comma-shaped rod bacteria with monotrichous flagellation (SEM image)

Mechanism of Action of Cholera Toxin



Pathogenesis and clinical picture

Infection results from oral ingestion of the pathogen. The infective dose must be large (>10^8), since many vibrios *are killed by* the *hydrochloric acid* in gastric juice. Based on their pronounced stability in alkaline environments, vibrios are able to colonize the mucosa of the proximal small intestine and secrete **cholera toxin**. The pathogen does not invade the mucosa.

The incubation period of cholera is two to five days.

The clinical picture is characterized by voluminous, watery diarrhea and vomiting. The amount of fluids lost per day can be as high as 20 l. Further symptoms derive from the resulting exsiccosis: *hypotension, tachycardia, anuria, and hypothermia*. Lethality can be as high as 50% in untreated cases.

Diagnosis

Diagnosis requires identification of the pathogen in stool or vomit. Sometimes a rapid microscopical diagnosis succeeds in finding numerous Gram-negative, bent rods in swarm patterns. Culturing is done on liquid or solid selective mediums, e.g., alkaline peptone water or taurocholate gelatin agar. Suspected colonies are identified by biochemical means or by detection of the O:1 antigen in an agglutination reaction.

Therapy

The most important measure is restoration of the disturbed waternand electrolyte balance in the body. Secondly, tetracyclines and cotrimoxazole can be used, above all to reduce fecal elimination levels and shorten the period of pathogen secretion.

Epidemiology and prevention

Nineteenth-century Europe experienced several cholera pandemics, all of which were caused by the classic cholerae biovar. An increasing number of cases caused by the biovar eltor, which is characterized by a lower level of virulence, have been observed since 1961. With the exception of minor epidemics in Italy and Spain, Europe, and the USA have been spared major outbreaks of cholera in more recent times. South America has for a number of years been the venue of epidemics of the disease.

Epidemiology and prevention

Humans are the only source of infection. Infected persons in particular eliminate large numbers of pathogens. Convalescents may also shed *V. cholerae* for weeks or even months after the infection has abated. Chronic carriers as with typhoid fever are very rare. Transmission of the disease is usually via foods, and in particular drinking water. This explains why cholera can readily spread to epidemic proportions in countries with poor hygiene standards.

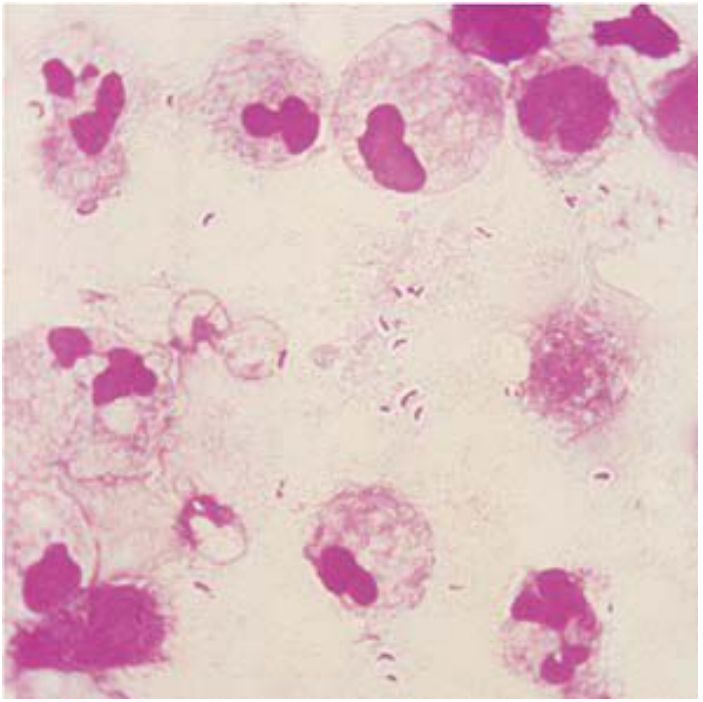
Epidemiology and prevention

Protection from exposure to the pathogen is the main thrust of the relevant preventive measures. In general, control of cholera means ensuring adequate food and water hygiene and proper elimination of sewage. In case of an outbreak, infected persons must be isolated. Infectious excreta and contaminated objects must be disinfected. Even suspected cases of cholera must be reported to health authorities without delay. The incubation period of the cholera vibrio is reported in international health regulations to be five days. A vaccine containing killed cells as well an attenuated live vaccine are available. The level of immunization protection is, however, incomplete and lasts for only six months.

Haemophilus influenzae

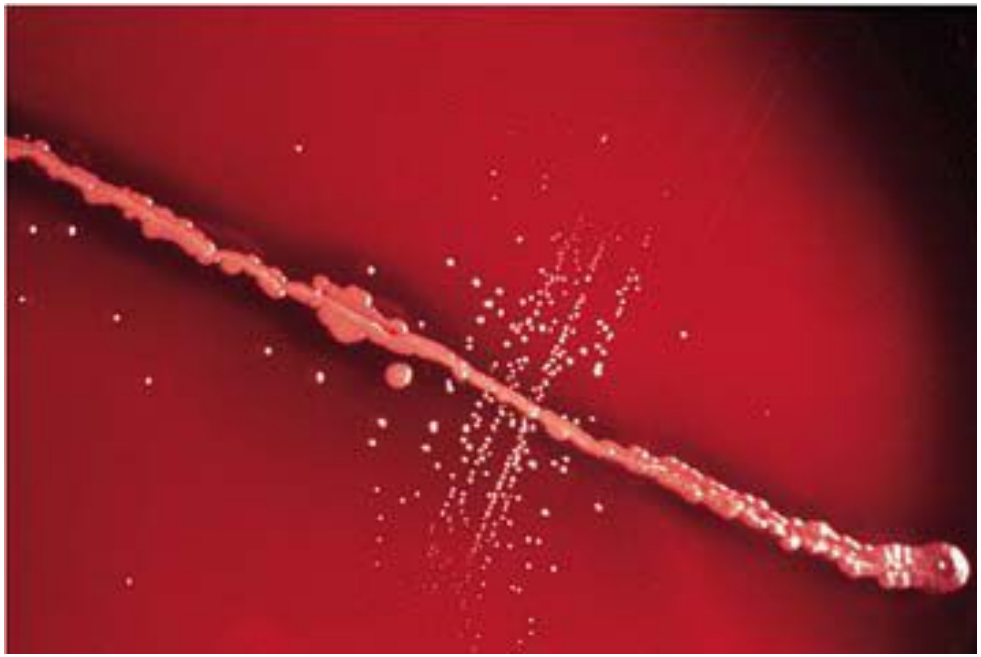
Hemophilic bacteria are so designated because they require growth factors contained in blood. The most important human pathogen in this genus is *H. influenzae*. Other *Haemophilus* species either infect only animals or are found in the normal human mucosal flora. These latter include *H. parainfluenzae, H. hemolyticus, H. segnis, H. aphrophilus*, and *H. paraphrophilus*. These species can cause infections on occasion.

Morphology and culture. *Haemophilus* are small (length: 1.0–1.5 lm, width: 0.3 lm), often encapsulated, nonmotile, Gram-negative rods. The encapsulated strains are subclassified in serovars a-f based on the fine structure of their capsule polysaccharides. Serovar b (Hib) causes most Haemophilus infections in humans.



a Gram-stained cerebrospinal fluid sediment preparation. Fine, Gram-negative rods surrounded by a capsule (serovar b). Clinical diagnosis: purulent meningitis.

b Satellite colonies of *Haemophilus influenza*e surrounding the *Staphylococcus aureus* streak. *S. aureus* provides small amounts of V factor. The blood agar contains free X factor.



Pathogenesis and clinical pictures

H. influenzae is a mucosal parasite of the upper respiratory tract present in 30–50% of healthy persons. The strains usually found are nonencapsulated and therefore hardly virulent. The capsule protects the cells from phagocytosis and is thus the primary determinant of pathogenicity. Others include the affinity of H. influenzae to respiratory tract mucosa and meninges and production of an IgA1 protease.

H. influenzae infections are seen frequently in children aged from six months to four years of age due to the low levels of anticapsule antibodies in this age group. Maternal antibodies still protect children during the first months of life. The body has built up a sufficient store of antibodies by the age of four. Any list of potential clinical developments must begin with meningitis, followed by epiglottitis, pneumonia, empyema, septic arthritis, osteomyelitis, pericarditis, cellulitis, otitis media, and sinusitis.

Pathogenesis and clinical pictures

Haemophilus infections in adults are usually secondary complications of severe primary illnesses or the result of compromised immune defenses. The most frequent complication is an acute exacerbation of chronic bronchitis. Pneumonias caused by *H. influenzae* are also observed, often as superinfections following viral influenza. In immunocompromised adults, even the nonencapsulated strains can cause infections of the upper and lower respiratory tract.

Diagnosis

The method of choice is identification of the pathogen in cerebrospinal fluid, blood, pus, or purulent sputum using microscopy and culture assays. Satelliting on blood agar is an indication of a V factor requirement. An X factor requirement is confirmed most readily by the porphyrin test, with a negative result in the presence of *H. influenzae*.

Therapy

In view of the increasing number of betalactamase-producing *H. influenzae* strains observed in recent years, penicillinase-stable betalactam antibiotics should be used to treat these infections. The likelihood that a strain produces betalactamase is 5–30% in most countries. 4-quinolones are an alternative to betalactams that should not, however, be used in children. The agent of choice in meningitis is ceftriaxone

Epidemiology and prevention

H. influenzae is found only in humans. The incidence of severe invasive infections (meningitis, sepsis, epiglottitis) in children has been reduced drastically – to about one in 10 of the numbers seen previously—since a vaccination program was started, and will continue to fall assuming the vaccinations are continued .

Immunization is achieved with the conjugate vaccine Hib in which the capsule polysaccharide epitope “b” conferring immunity is conjugated to protein. Such a conjugate vaccine can be administered as early as the first month of life. The immune system does not respond to pure polysaccharide vaccines until about the age of two, since polysaccharides are T-independent antigens against which hardly any antibodies are produced in the first two years of life. There is also no booster response. A four-day regimen of rifampicin has proved to be an effective chemoprophylactic treatment for non-vaccinated small children who have been exposed to the organism.

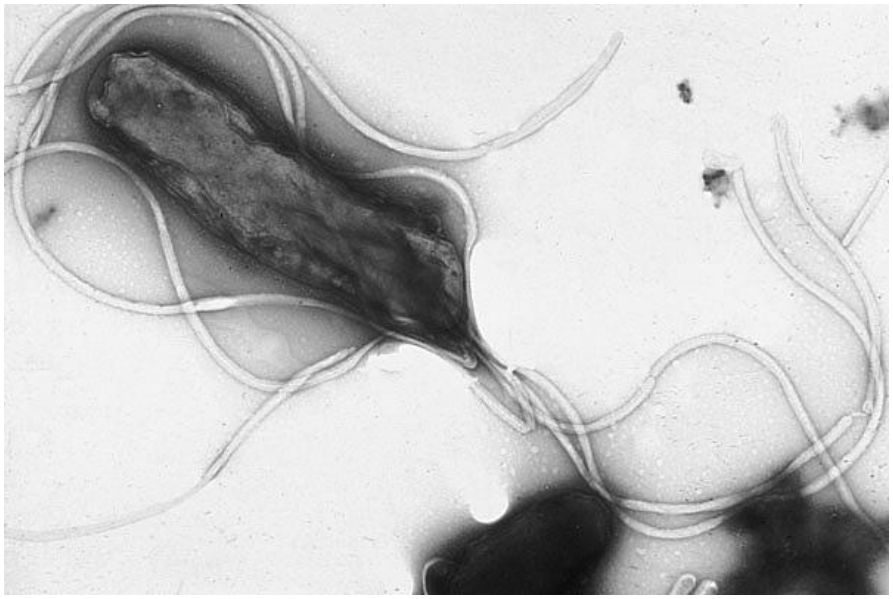
Campylobacter, Helicobacter, and *Spirillum* belong to the group of spiral, motile, Gram-negative, microaerophilic bacteria. *C. jejuni* causes a form of enteritis. The sources of infection are diseased animals. The pathogens are transmitted to humans in food. The diseases are sometimes also communicable among humans. The pathogens are identified for diagnostic purposes in stool cultures using special selective mediums. *Helicobacter pylori* contribute to the pathogenesis of type B gastritis and peptic ulcers. *Spirillum minus* causes rat bite fever, known as sodoku in Japan where it is frequent.

Campylobacter

Campylobacter (meaning "curved bacteria") is a genus of Gram-negative bacteria. *Campylobacter* typically appear comma or s-shaped and motile. Most *Campylobacter* species can cause disease and can infect humans and other animals. The bacterium's main reservoir is poultry; humans can contract the disease from eating food contaminated with *Campylobacter* species. Another source of infection is contact with infected animals, which often carry *Campylobacter* asymptomatically. At least a dozen species of *Campylobacter* have been implicated in human disease, with *C. jejuni* and *C. coli* being the most common. *C. jejuni* is now recognized as one of the main causes of bacterial foodborne disease in many developed countries.*C. jejuni* infection can also spread to the blood in individuals with AIDS, while *C. lari* is a known cause of recurrent diarrhea in children. *C. fetus* is a cause of spontaneous abortions in cattle and sheep, as well as an opportunistic pathogen in humans. This genus has been found to be part of the salivary microbiome.

Helicobacter pylori

Morphology and culture



H. pylori are spirally shaped, Gram-negative rods with lophotrichous flagellation. Cultures from stomach biopsies are grown on enriched mediums and selective mediums under microaerobic conditions (90% N_2, 5% CO_2, and 5% O_2) for three to four days. Identification is based on detection of oxidase, catalase, and urease.

Pathogenesis and clinical pictures

H. pylori occurs only in humans and is transmitted by the fecal-oral pathway. The pathogen colonizes and infects the stomach mucosa. The pathogenicity factors include pronounced motility for efficient target cell searching, adhesion to the surface epithelial cells of the stomach, urease that releases ammonia from urea to facilitate survival of the cells in a highly acidic environment and a vacuolizing cytotoxin (VacA) that destroys epithelial cells.

Once the pathogen has infected the stomach tissues an acute gastritis results, the course of which may or may not involve overt symptoms. Potential sequelae include:

1. Mild chronic gastritis type B that may persist for years or even decades and is often asymptomatic.

2. Duodenal ulceration, sometimes gastric ulceration as well.

3. Chronic atrophic gastritis from which a gastric adenocarcinoma sometimes develops.

4. Rarely B cell lymphomas of the gastric mucosa (MALTomas).

Diagnosis. Histopathological, cultural and, molecular identification of the bacteria in stomach lining biopsies. Antigen detection in stool. Antibodies can be identified with an ELISA or Western Blotting.

Therapy. In patients with ulcers and/or gastritis symptoms, a triple combination therapy with omeprazole (proton pump blocker), metronidazole, and clarithromycin lasting seven days is successful in 90% of cases.

Epidemiology. Based on seroepidemiological studies we know that *H. pylori* occur worldwide. Generalized contamination of the population begins in childhood and may reach 100% in adults in areas with poor hygiene. The contamination level is about 50% among older adults in industrialized countries. Transmission is by the fecal-oral route.

Legionella (Legionnaire's Disease)

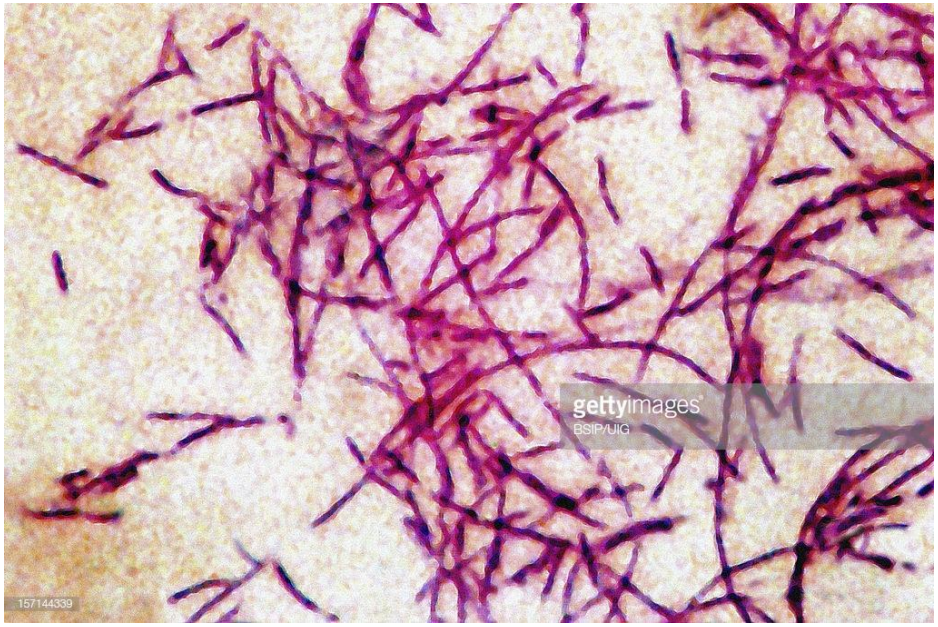
Legionella is the only genus in the family Legionellaceae. The species *Legionella pneumophila* is responsible for most legionelloses in humans. Legionellae are difficult to stain. They are Gram-negative, aerobic rod bacteria. Special mediums must be used to grow them in cultures. Infections with Legionella occur when droplets containing the pathogens are inhaled. Two clinically distinct forms are on record: legionnaire's disease leading to a multifocal pneumonia and nonpneumonic legionellosis or Pontiac fever.

Legionella bacteria were discovered in 1976, occasioned by an epidemic among those attending a conference of American Legionnaires (former professional soldiers). They are now classified in the family Legionellaceae, which to date comprises only the genus *Legionella*. This genus contains numerous species not listed here. Most human infections are caused by *L. pneumophila*, which species is subdivided into 12 serogroups. Human infections are caused mainly by serogroup 1.

The persons most likely to contract legionnaire's disease are those with a primary cardiopulmonary disease and generally weakened immune defenses. Laboratory diagnostic methods include microscopy with direct immunofluorescence, culturing on special mediums and antibody assays. The antibiotics of choice are the macrolides. The natural habitat of legionellae is damp biotopes. The sources of infection listed in the literature include hot and cold water supply systems, cooling towers, moisturizing units in air conditioners, and whirlpool baths. Legionelloses can occur both sporadically and in epidemics.

Morphology and culture

L. pneumophila is a rod bacterium 0.3–1 lm wide and 2–20 lm long. Its cell wall structure is of the Gram-negative type, but gram staining hardly "takes" with these bacteria at all. They can be rendered visible by means of direct immunofluorescence.



Pathogenesis and clinical picture

The pathomechanisms employed by legionellae are not yet fully clarified. These organisms are facultative intracellular bacteria that can survive in professional phagocytes and in alveolar macrophages. They are capable of preventing the phagosome from fusing with lysosomes. They also produce a toxin that blocks the oxidative burst. Two clinical forms of legionellosis have been described:

Legionnaire's disease. Infection results from inhalation of droplets containing the pathogens. The incubation period is two to 10 days. The clinical picture is characterized by a multifocal, sometimes necrotizing pneumonia. Occurrence is more likely in patients with cardiopulmonary primary diseases or other immunocompromising conditions. Lethality >20%.

Pontiac fever. Named after an epidemic in Michigan. Incubation period one to two days. Nonpneumonic, febrile infection. Self-limiting. Rare.

Diagnosis. Specific antibodies marked with fluorescein are used to detect the pathogens in material from the lower respiratory tract. For cultures, special culture mediums must be used containing selective supplements to exclude contaminants. The mediums must be incubated for three to five days. A gene probe can also be used for direct detection of the nucleic acid (rDNA) specific to the genus *Legionella* in the material. Antibodies can be assessed using the indirect immunofluorescence technique.

Therapy. Macrolide antibiotics are now the agent of choice, having demonstrated clinical efficacy. Alternatively, 4-quinolones can be used.

Epidemiology and prevention. Legionellosis can occur in epidemic form or in sporadic infections. It is estimated that one third of all pneumonias requiring hospitalization are legionelloses. Soil and damp biotopes are the natural habitat of Legionella. Sources of infection include hot and cold water supply systems, cooling towers, air moisturizing units in air conditioners, and whirlpool baths. Human-to-human transmission has not been confirmed. *Legionella* bacteria tolerate water temperatures as high as 50°C and are not killed until the water is briefly heated to 70°C.

Treponema pallidum
***Borrelia* (Relapsing Fever, Lyme Disease)**
***Leptospira* (Leptospirosis, Weil Disease)**
Rickettsia
Chlamydia
Mycoplasma

Thank you for your attention!