Enterobacteriaceae and other bacterial agents of GIT infections

Content

- Taxonomy
- Physiology, structure and virulence factors
- Diseases
- Epidemiology
- Laboratory diagnosis
- Treatment, prevention and control

Taxonomy of family Enterobacteriae

- Family – *Enterobacteriaceae*, the largest, most heterogeous group of medically important bacteria
- Genera – more than 40
- Species – more than 150 (Euzéby, List of procaryotic names, http://www.bacterio.net/staphylococcus.html)
- Only around of 20 species are responsible for more than 95% infections

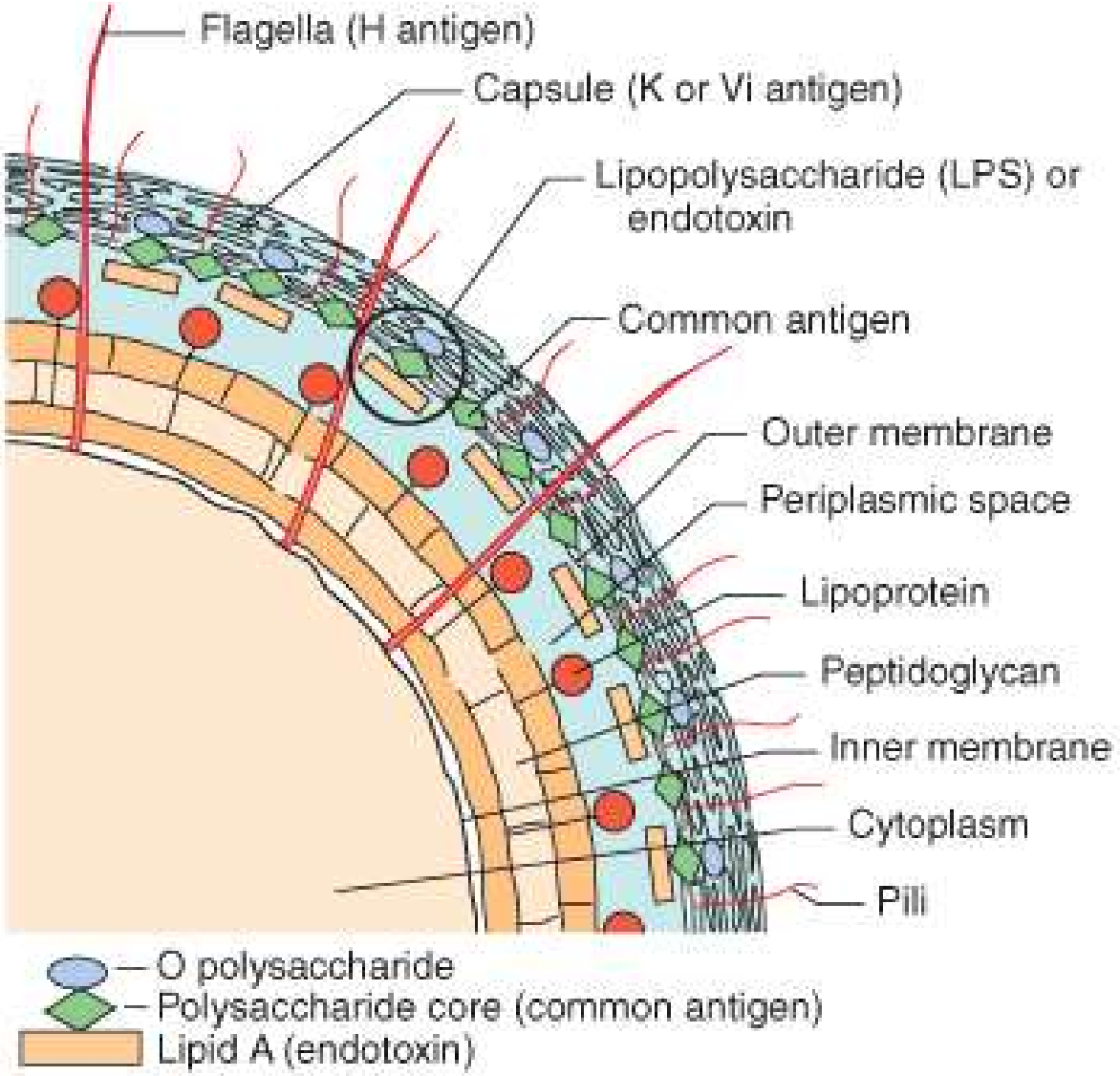
General properties

- family Enterobacteriaceae
- Gram-negative
- non–spore-forming
- facultative anaerobes that ferment glucose and other sugars
- most are motile by virtue of peritrichous flagellae (exceptions – Shigella, Klebsiella…)

Physiology structure and virulence factors

- *Enterobacteriaceae* are ubiquitous organisms, found worldwide in soil, water, and vegetation and are part of the normal intestinal flora of most animals, including humans.
- **moderately sized** (0.3 to 1.0 × 1.0 to 6.0 μm) gram-negative rods
- can grow rapidly, aerobically and anaerobically (facultative anaerobes)
- **The heat-stable lipopolysaccharide (LPS) is the major cell wall antigen and consists of three components: outermost somatic O polysaccharide, core polysaccharide** common to all *Enterobacte riaceae* (enterobacterial common antigen), and **lipid A**. The core polysaccharide is important **for classifying** and the O polysaccharide is important for the epidemiologic classification of strains within a species, and the **lipid A component of LPS** is responsible for **endotoxin activity**, an **important virulence factor**.

Physiology structure and virulence factors



Physiology structure and virulence factors

- **The epidemiologic (serologic) classification** of the Enterobacteriaceae is based on three major groups of **antigens**: **somatic O polysaccharides**, **K antigens** in the capsule (type-specific polysaccharides), and the **H proteins** in the bacterial **flagella**. Strain-specific O antigens are present in each genus and species, although cross-reactions between closely related genera are common (e.g., Salmonella with Citrobacter, Escherichia with Shigella). The antigens are detected by agglutination with specific antibodies.

Physiology structure and virulence factors

- Most Enterobacteriaceae are **motile**, with the exception of some common genera (e.g., Klebsiella, Shigella). The motile strains are surrounded with **flagella** (peritrichous). Many Enterobacteriaceae also possess **fimbriae** (also referred to as pili), which have been subdivided into two general classes: chromosomally mediated **common fimbriae** and **sex pili** that are encoded **on conjugative plasmids**. The common fimbriae are important for the ability of bacteria to **adhere** to specific host cell receptors, whereas the **sex** or **conjugative pili** facilitate **genetic transfer between bacteria**.

Epidemiology

- Although the natural habitat of many medically important members of the family Enterobacteriaceae is the **lower gastrointestinal tract of humans and other animals**, these organisms are actually quite **widespread in nature**
- Moreover, enterobacterial species rapidly **colonize the oropharynx of many hospitalized patients**
- The extended niche that Enterobacteriaceae may occupy under these circumstances is an important predisposing factor that allows subsequent **extraintestinal infections** to occur

Epidemiology

- They cause a **wide variety of infections** in both the community and the hospital setting, affecting **normal hosts** and **those with preexisting illnesses**. They comprise the vast majority of **urinary isolates** and a large proportion of isolates from the **blood**, the **peritoneal cavity**, and the **respiratory tract**. They may be isolated from numerous other sites.
- The proportion of **multiple antimicrobe-resistant isolates**, including those producing **extended-spectrum β-lactamases (ESBL)** and those resistant to fluoroquinolones, has increased steadily so that the majority of **nosocomial** and **many community-acquired isolates** are now resistant to several important antimicrobial classes.

Pathogenesis and immunity - virulence factors

- **Endotoxin** is a virulence factor shared among aerobic and some anaerobic gram-negative bacteria. The activity of this toxin depends on the **lipid A** component **of LPS, which is released at cell lysis**. Many of the systemic manifestations of gram-negative bacterial infections are initiated by **endotoxin-activation** of **complement**, release of **cytokines**, **leukocytosis**, **thrombocytopenia, disseminated intravascular coagulation (DIC), fever, decreased peripheral circulation, shock, and death**.

Pathogenesis and immunity - virulence factors

- **Capsule** - Encapsulated Enterobacteriaceae are **protected from phagocytosis** by the **hydrophilic capsular antigens**, which repel the hydrophobic phagocytic cell surface. These antigens **interfere with the binding of antibodies to the bacteria** and are **poor immunogens** or activators of complement.

Pathogenesis and immunity - virulence factors

- **Antigenic phase variation** - The expression of the somatic O antigens, capsular K antigens and flagellar H antigens is under the genetic control of the organism. Each of these antigens **can be alternately expressed** or **not expressed** (**phase variation**), a feature that **protects the bacteria from antibody-mediated cell death.**

Pathogenesis and immunity - virulence factors

- **Type III Secretion Systems.** A variety of bacteria (e.g., Yersinia, Salmonella, Shigella, enteropathogenic Escherichia, Pseudomonas, Chlamydia) have a common effector system for **delivering their virulence factors into targeted eukaryotic cells**. Think of the type III secretion system as a **molecular syringe** consisting of approximately **20 proteins** that **facilitate transfer of bacterial virulence factors into the targeted host cells.** Although the virulence factors and their effects differ among the various gram-negative rods, the general mechanism by which the virulence factors are introduced is the same. **In the absence of the type III secretion system, the bacteria have diminished virulence.**

Pathogenesis and immunity - virulence factors

- **Sequestration of Growth Factors.** Nutrients are provided to the organisms in enriched culture media, but the bacteria must become nutritional scavengers when growing in vivo. **Iron is an important growth factor** required by bacteria, but it is bound in heme proteins (e.g., hemoglobin, myoglobin) or in iron-chelating proteins (e.g., transferrin, lactoferrin). The bacteria counteract the binding by producing their own competitive **siderophores** or **iron-chelating compounds** (e.g., enterobactin, aerobactin). Iron can also be released from host cells by hemolysins produced by the bacteria.

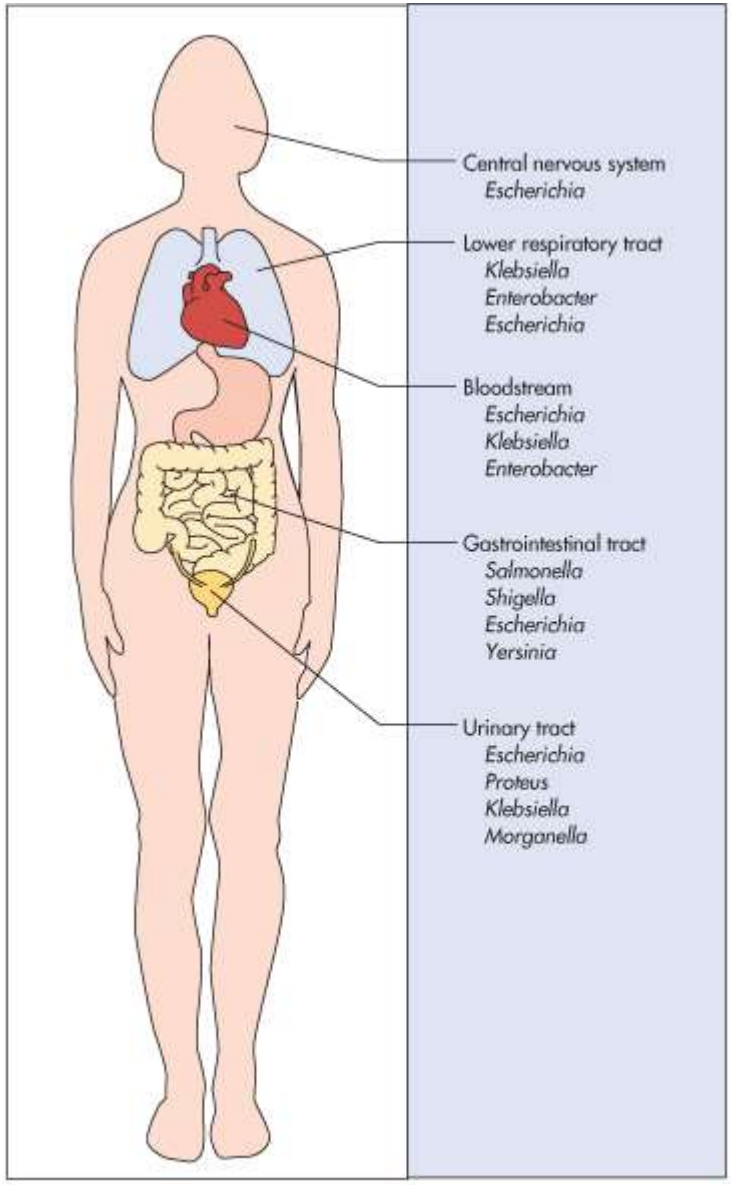
Pathogenesis and immunity - virulence factors

- **Resistance to Serum Killing.** Whereas many bacteria can be rapidly cleared from blood, virulent **organisms capable of producing systemic infections** are **often resistant to serum killing**. The bacterial capsule can protect the organism from serum killing as well as other factors that prevent the binding of complement components to the bacteria and subsequent complement-mediated clearance.

Pathogenesis and immunity - virulence factors

- **Antimicrobial Resistance.** As rapidly as new antibiotics are introduced, organisms can develop resistance to them. This resistance can be encoded on **transferable plasmids** and **exchanged among species, genera**, and even families of bacteria.

Enterobacterial infections



Sites of infections with common members of the Enterobacteriaceae listed in order of prevalence

Escherichia coli

- The **most common** and **important** member of the genus *Escherichia*. This organism is associated with a **variety of diseases**, including **gastroenteritis (enteroinvasive *E.coli* – EIEC)** and **extrainintestinal infections (**extraintestinal pathogenic *E.coli* – **ExPEC)**, such as UTIs, meningitis, and sepsis . A multitude of strains are capable of causing disease, with some serotypes associated with greater virulence

Escherichia coli

- **<u>Pathogenesis and Immunity.</u>** *E. coli* possesses a broad range of virulence factor. In addition to the general factors possessed by all members of the family *Enterobacteriaceae*, Escherichia strains (EAEC, Enteroaggregative E. coli; EHEC, enterohemorrhagic E. coli; EIEC, enteroinvasive E. coli; EPEC, enteropathogenic E. coli; ETEC, enterotoxigenic E. coli) possess **specialized virulence factors** that can be placed into two general categories: **adhesins** and **exotoxins**.

Escherichia coli

- **Epidemiology. Large numbers** of *E. coli* are present in the **gastrointestinal tract**. Although these organisms can be **opportunistic pathogens** when the intestines are perforated and the bacteria enter the peritoneal cavity, most *E. coli* that cause gastrointestinal and extraintestinal disease do so because they **have acquired specific virulence factors** encoded on plasmids or in bacteriophage DNA. The effectiveness of *E. coli* as a pathogen is illustrated by the fact the bacteria are (1) the **most common gram-negative rods isolated from patients with sepsis**; (2) responsible for causing more than **80% of all community-acquired UTIs**, as well as many **hospital-acquired infec-tions**; and (3) a **prominent cause of gastroenteritis**. **Most infections** (with the exception of neonatal meningitis and gastroenteritis) are **endogenous.**

Escherichia coli

- **Gastroenteritis.** The strains of *E. coli* that cause gastroenteritis are subdivided into **five major groups**:
- **Enterotoxigenic**
- **Enteropathogenic**
- **Enteroaggregative**
- **Enterohemorrhagic (zoonotic),** wider category **verotoxigenic *E. coli* (VTEC)** called also **Shiga-toxin producing *E. coli***
- **Enteroinvasive**
- **(Diffusely adherent** - DAEC)

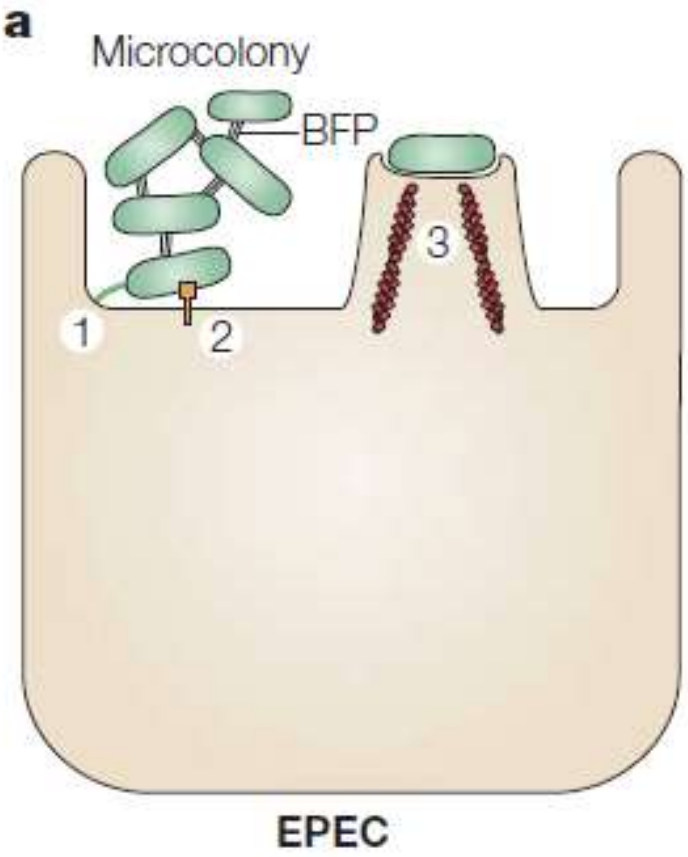
The first three groups primarily cause a **secretory diarrhea involving the small intestine**, while the **enterohemorragic and enteroinvasive primarily involve the large intestine**.

* **Identification** – growth characteristics (large colonies) and MALDI identification
* **Classification of various pathovars (pathogenic seroptypes)**: using O and H antigen and agglutination

Gastroenteritis caused by *Escherichia coli*

Organism	Site of Action	Disease	Pathogenesis	Diagnosis
Enterotoxigenic *E. coli* (ETEC)	Small intestine	Traveler's diarrhea; infant diarrhea in developing countries; watery diarrhea, vomiting, cramps, nausea, low-grade fever	Plasmid-mediated, heat-stable and/or heat-labile enterotoxins that stimulate hypersecretion of fluids and electrolytes	Most U.S. outbreaks caused by ST producing strains; two commercial immunoassays available for detecting ST in broth cultures; molecular probes for ST and LT from cultured bacteria available in research laboratories; PCR assays used with clinical specimens
Enteropathogenic *E. coli* (EPEC)	Small intestine	Infant diarrhea in developing countries; watery diarrhea and vomiting, nonbloody stools; believed to be rare in United States	Plasmid-mediated A/E histopathology, with disruption of normal microvillus structure resulting in malabsorption and diarrhea	Characteristic adherence to HEp-2 or HeLa cells; probes and amplification assays developed for the plasmid-encoded bundle-forming pili and gene targets on the "locus of enterocyte effacement" pathogenicity island
Enteroaggregative *E. coli* (EAEC)	Small intestine	Infant diarrhea in developing and probably developed countries; traveler's diarrhea; persistent watery diarrhea with vomiting, dehydration, and low-grade fever	Plasmid-mediated aggregative adherence of rods ("stacked bricks") with shortening of microvilli, mononuclear infiltration, and hemorrhage; decreased fluid absorption	Characteristic adherence to HEp-2 cells; DNA probe and amplification assays developed for conserved plasmid
Enterohemorrhagic *E. coli* (EHEC)	Large intestine	Initial watery diarrhea, followed by grossly bloody diarrhea (hemorrhagic colitis) with abdominal cramps; little or no fever; may progress to hemolytic uremic syndrome	EHEC evolved from EPEC; A/E lesions with destruction of intestinal microvilli resulting in decreased absorption; pathology mediated by cytotoxic Shiga toxins (Stx-1, Stx-2), which disrupt protein synthesis	Screen for O157:H7 with sorbitol-MacConkey agar; confirm by serotyping; immunoassays (ELISA, latex agglutination) for detection of the Stx toxins in stool specimens and cultured bacteria; DNA probes and amplification assays developed for Stx toxins
Enteroinvasive *E. coli* (EIEC)	Large intestine	Rare in developing and developed countries; fever, cramping, watery diarrhea; may progress to dysentery with scant, bloody stools	Plasmid-mediated invasion and destruction of epithelial cells lining colon	Sereny (guinea pig keratoconjunctivitis) test; plaque assay in HeLa cells; probes and amplification assays for genes regulating invasion (cannot discriminate between EIEC and *Shigella*)

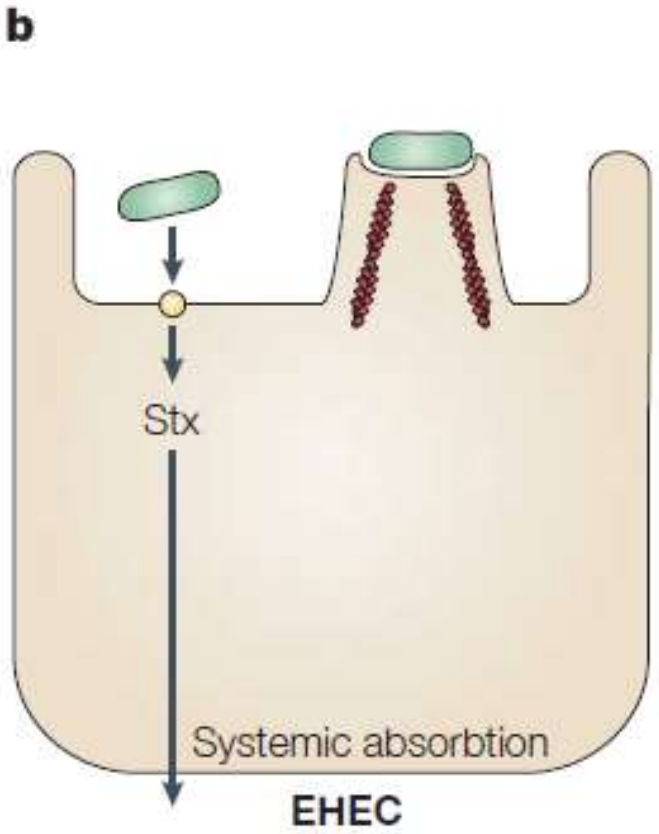
Pathogenic mechanism of enteropathogenic *E. coli* (EPEC) serotypes



a | EPEC adhere to small bowel enterocytes, but destroy the normal microvillar architecture, inducing the characteristic attaching and effacing lesion. Cytoskeletal derangements are accompanied by an inflammatory response and diarrhoea. 1. Initial adhesion, 2. Protein translocation by type III secretion, 3. Pedestal formation (BFP bundle forming pilus)

Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

Pathogenic mechanism of enterohemoragic *E. coli* (EHEC) serotypes



b | EHEC also induce the attaching and effacing lesion, but in the colon. The distinguishing feature of EHEC is the elaboration of Shiga toxin (Stx), systemic absorption of which leads to potentially life-threatening complications (HUS – hemolytic uremic syndrome, Stx – Shiga toxin)

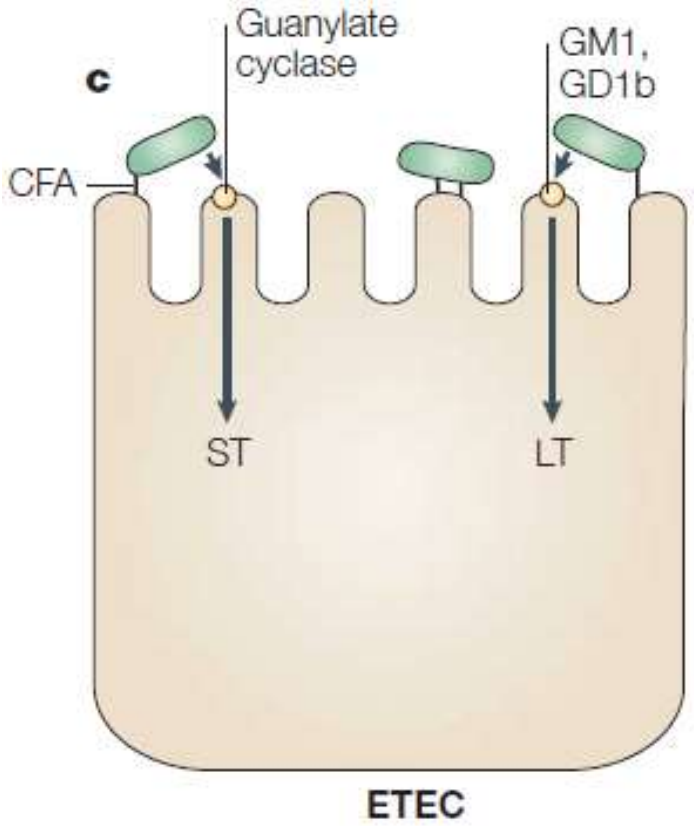
Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

Summary of E. coli O157:H7 Pathogenesis

1. Attachment of bacterial fimbriae to enterocyte
2. Bacterial Tir is translocated to enterocyte
3. Binding of Tir to intimin
4. Release of Shiga toxins
5. Binding of Shiga toxin to Gb3/Gb4 receptors
6. Shiga toxins enter the enterocytes and stops protein synthesis
7. Enterocyte damage and death
8. Shiga toxins enter circulation
9. Damage to RBCs, platelets, kidney, brain and possible death

See also: https://www.youtube.com/watch?v=w-zbjM8wruk

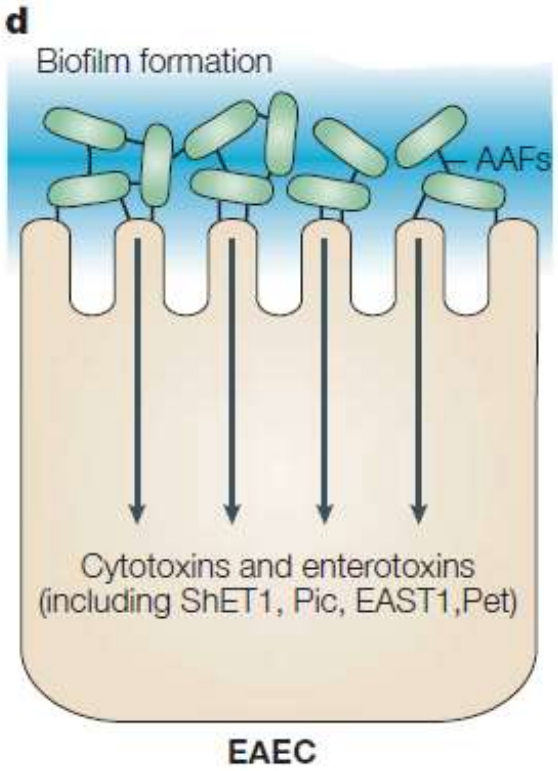
Pathogenic mechanism of enterotoxigenic *E. coli* (ETEC) serotypes



c | ETEC adhere to small bowel enterocytes and induce watery diarrhoea by the secretion of heat-labile (LT) and/or heat-stable (ST) enterotoxins (CFA, colonization factor antigen, GM1 and GD1b – host cell surface gangliosides)

Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

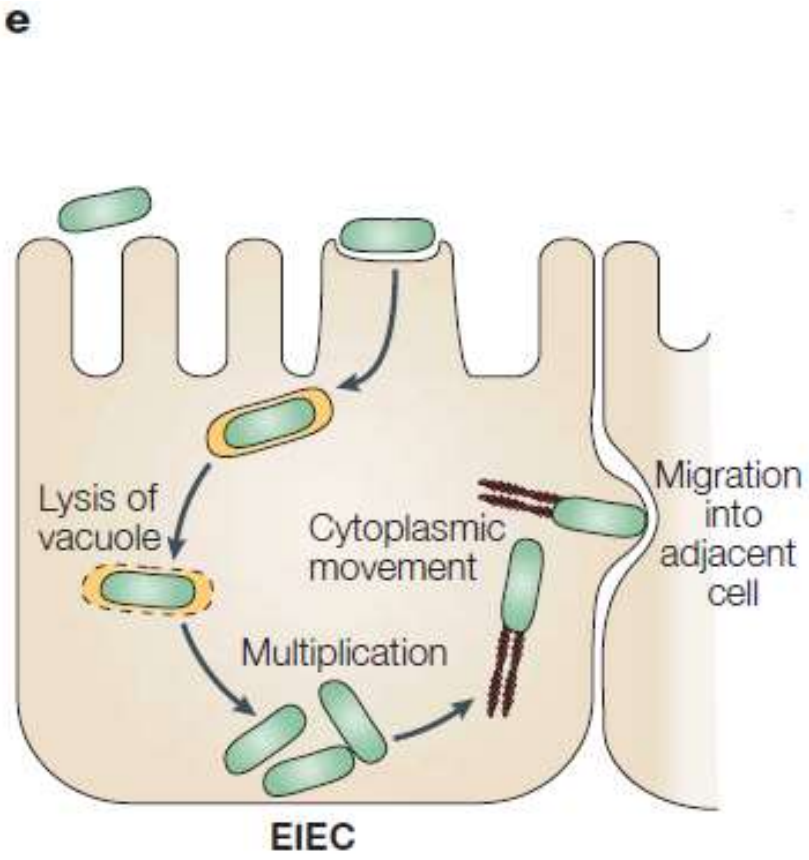
Pathogenic mechanism of enteroaggregative *E. coli* (EAEC) serotypes



d | EAEC adheres to small and large bowel epithelia in a thick biofilm and elaborates secretory enterotoxins and cytotoxins. (ShET1, *Shigella* enterotoxin 1, EAST1 enteroaggregative *E. coli* ST1, Pic autotransporter, Pet autotransporter, AAF, aggregative adherence fimbriae)

Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

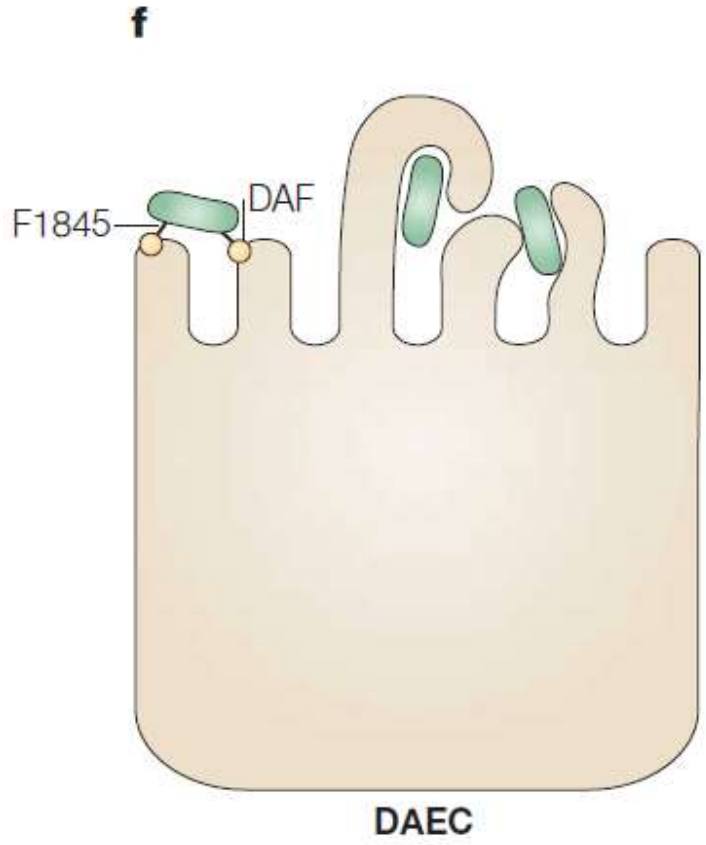
Pathogenic mechanism of enteroinvasive *E. coli* (EIEC) serotypes



e | EIEC invades the colonic epithelial cell, lyses the phagosome and moves through the cell by nucleating actin microfilaments. The bacteria might move laterally through the epithelium by direct cell-to-cell spread or might exit and re-enter the baso-lateral plasma membrane.

Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

Pathogenic mechanism of diffuselly adherent *E. coli (DAEC)* serotypes



f | DAEC elicits a characteristic signal transduction effect in small bowel enterocytes that manifests as the growth of long finger-like cellular projections, which wrap around the bacteria (DAF, decay-accelerating factor)

Kaper J.B. et al. Pathogenic *Escherichia coli, Nature Reviews Microbiology, 2, 2004*

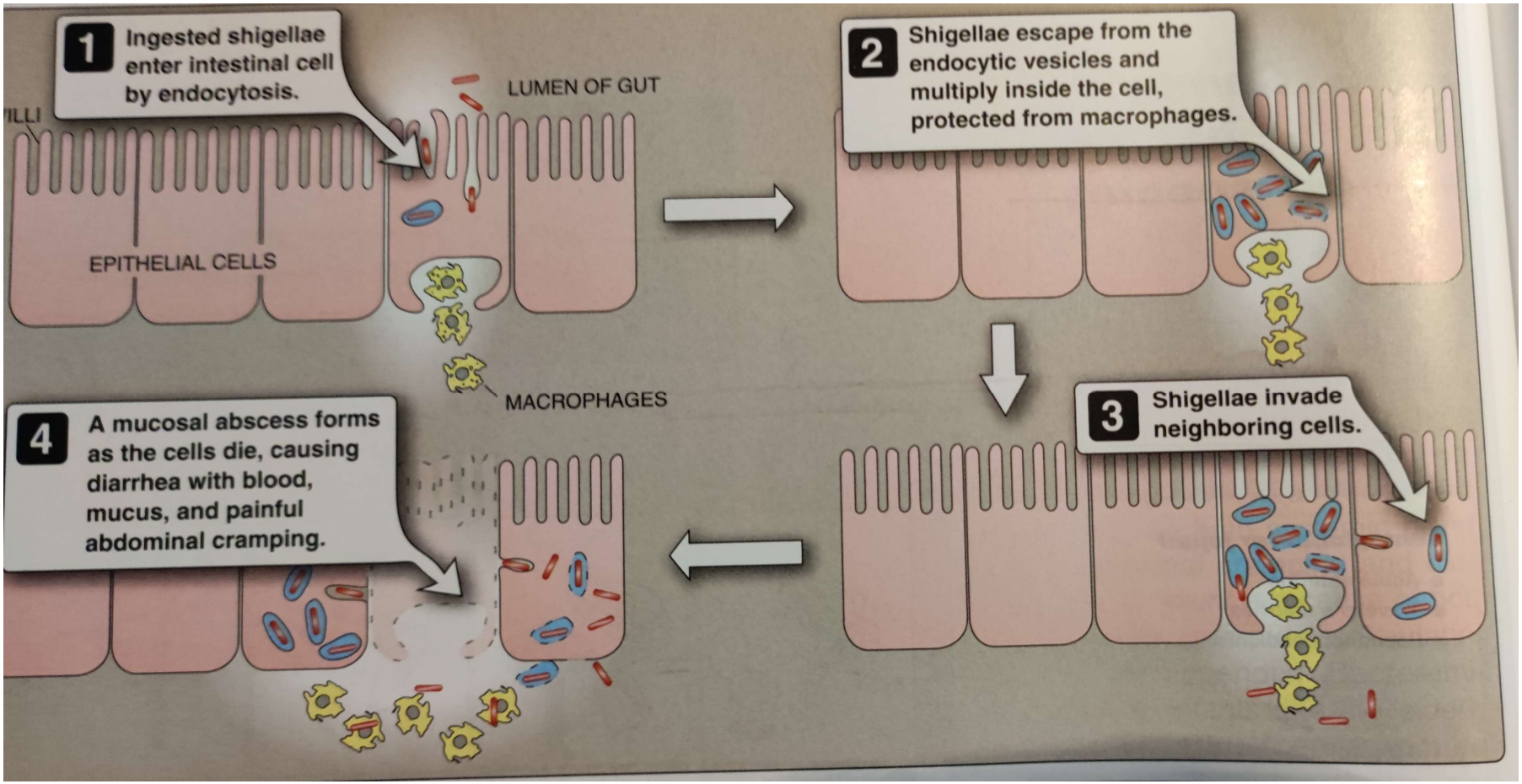
Shigella

Biology, Virulence, and Disease

- Gram-negative, facultatively anaerobic rods, **Fermenter;** oxidase negative, **Four species** recognized: ***S. sonnei*** responsible for most infections in **developed countries**; ***S. fexneri*** for infections in **developing countries**; ***S. dysenteriae*** (shiga toxin)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**.
- **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, HUS); asymptomatic carriage develops in a small number of patients (reservoir for future infections)

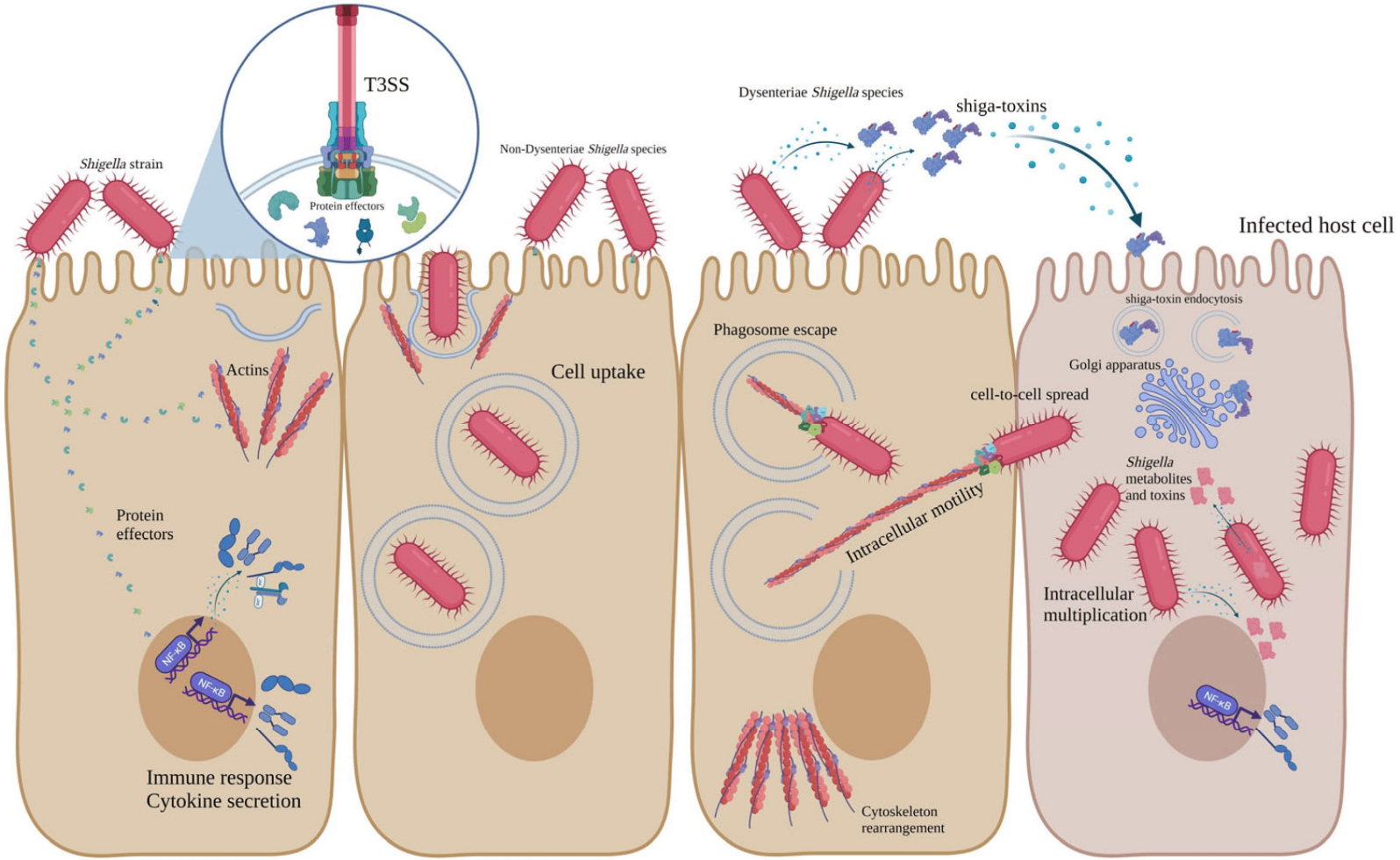
See aslo: ttps://www.youtube.com/watch?v=BEAwYmBMqrU

Shigella pathogenesis



References: Harvey et al. Lippincott´s Illustrated Reviews, Microbiology

Schematic representation of pathogenesis mechanisms of Dysenteriae and non-Dysenteriae species of Shigella.



Note: non-dysenteriae shigellosis – main causes *S. sonnei, S.flexneri*

See also: https://www.youtube.com/watch?v=CtsQ6lZ3RI4

References: Pakbin B et al. Molecular Mechanisms of Shigella Pathogenesis, Int J of Mol Sci, 24, 2448

Epidemiology

Humans are only reservoir for these bacteria. Disease **spread person to person** by **fecal-oral route (food, water).** Patients at highest risk for disease are young children in daycare 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)(160 mil. patients, 1 mil. mortality)

Diagnosis. Isolation from stool specimens requires use of selective media

Treatment, Prevention, and Control. Rehydratation and ions replacement in uncomplicated infections. Antibiotic therapy shortens the course of symptomatic disease and fecal shedding. Treatment should be guided by in vitro susceptibility tests. Empiric therapy can be initiated with a **fluoroquinolone** or **trimethoprim-sulfamethoxazol**e Appropriate infection control measures should be instituted to **prevent spread** of the organism, including hand washing and proper disposal of soiled linens.

Extraintestinal infections of *Escherichia coli*

- **Urinary Tract Infection.** Most gram-negative rods that produce UTIs **originate in the colon**, contaminate the urethra, ascend into the bladder, and may migrate to the kidney or prostate. Although most strains of ***E. coli*** can produce UTIs, disease is more common with certain **specific serogroups**. These bacteria are particularly **virulent** because of their ability to produce **adhesins** (primarily P pili, AAF/I, AAF/III, and Dr) that **bind to cells lining the bladder** and upper urinary tract (preventing the elimination of the bacteria in voided urine) and **hemolysin HlyA** that lyses erythrocytes and other cell types (leading to cytokine release and stimulation of an inflammatory response).
- **Neonatal Meningitis.** E. coli and group B streptococci cause the majority of CNS infections in infants **younger than 1 month**. Approximately 75% of the *E. coli* strains possess the K1 capsular antigen. This serogroup is also commonly present in the gastrointestinal tracts of pregnant women and newborn infants.
- **Septicemia.** Typically, septicemia caused by gram-negative rods, such as *E. coli*, **originates from infections in the urinary or gastrointestinal tract** (e.g., intestinal leakage leading to an intraabdominal infection). The **mortality** associated with E. coli septicemia is **high** for patients in whom immunity is compromised or the primary infection is in the abdomen or CNS.

Treatment, prevention and control

- Enteric pathogens are treated **symptomatically** unless disseminated disease occurs.
- Antibiotic therapy is guided by in vitro susceptibility tests
- 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 EHEC infections, EAEC, Enteroaggregative *E. coli*; EHEC, enterohemorrhagic *E. coli*

Salmonella

- The **taxonomic classification** of the genus *Salmonella* is **problematic**. DNA homology studies have revealed that exist only 2 species *Salmonella enterica* and *Salmonella bongori* (causing lizard inf.) most clinically significant isolates belong to the species ***Salmonella enterica***. More than **2500 unique serotypes** have been described **for this single species**; however, these serotypes are commonly listed as individual species (e.g., *Salmonella Typhi, Salmonella choleraesuis, Salmonella Typhimurium, Salmonella Enteritidis*). These designations are incorrect for example, the correct nomenclature is ***Salmonella enterica subspecies enterica* serovar Typhi**. In an effort to prevent confusion and **still retain the historical terms**, individual serotypes are now commonly written with the serotype name capitalized and not in italics. For example, Salmonella enterica, serovar. Typhi is **commonly designated** as **Salmonella Typhi**. For the sake of consistency, this nomenclature will be used in this chapter.

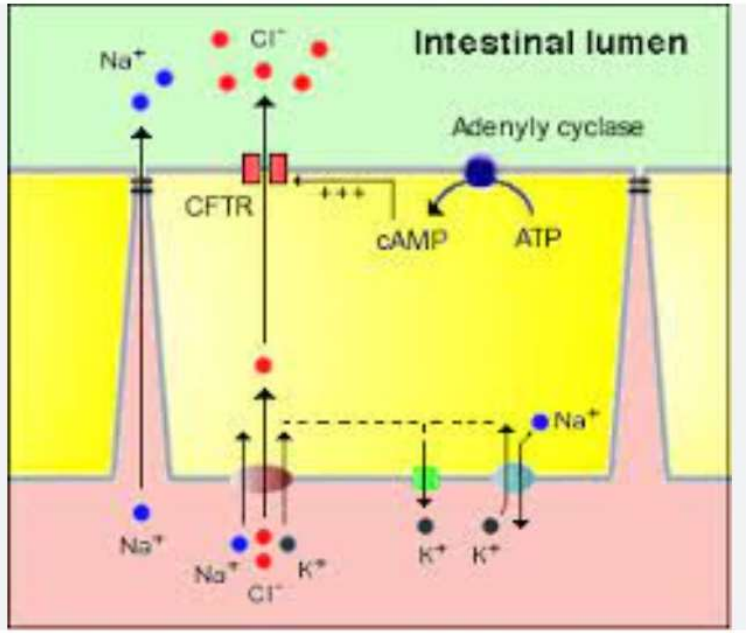
Pathogenesis and immunity

- After ingestion and passage through the stomach, salmonellae **attach** to the mucosa of the **small intestine** and **invade** into the **M (microfold) cells** located **in Peyer patches**, as well as **into enterocytes**. The bacteria **remain in endocytic vacuoles**, where they replicate. The bacteria **can also be transported across the cytoplasm and released into the blood** or **lymphatic circulation**. Regulation of the attachment, engulfment, and replication is controlled primarily by two large clusters of genes (**pathogenicity island I and II**) on the bacterial chromosome.

See also:
https://www.youtube.com/watch?v=puAV0ZvWrZg
https://micro.biol.ethz.ch/research/hardt.html

Pathogenesis and immunity

- **Pathogenicity island I** encodes **salmonella-secreted invasion proteins (Ssps)** and a **type III secretion system** that **injects the proteins into the host cell**. **Pathogenicity island II** contains genes that allow the bacteria to **evade the host's immune response** and a second type III secretion system for this function. **The inflammatory response** confines the infection to the gastrointestinal tract, mediates the release of prostaglandins, and **stimulates cAMP** and **active fluid secretion.**



Diseases

- **Enteritis** (fever, nausea, vomiting, bloody or nonbloody diarrhea, abdominal cramps), **6-48hours after consumption** of contaminated food or water, with the initial presentation consisting of **nausea**, **vomiting**, and **nonbloody diarrhea**. Fever, abdominal cramps, myalgias, and headache are also common. **Colonic involvement** can be demonstrated in the acute form of the disease. **Symptoms** can persist from **2 to 7 days** before **spontaneous resolution**.

- **Asymptomatic colonization** - primarily with ***Salmonella* Typhi** and ***Salmonella* Paratyphi** which are maintained by human colonization. **Chronic colonization** for more than 1 year after symptomatic disease develops in **1% to 5% of patients**, the **gallbladder** being the **reservoir** in most patients. Chronic colonization with other species of Salmonella occurs in less than 1% of patients and does not represent an important source of human infection.

Diseases

- **Septicemia. All *Salmonella* species can cause bacteremia**, although infections with ***Salmonella* Typhi**, ***Salmonella* Paratyphi**, and ***Salmonella* Choleraesuis more commonly lead to a bacteremic phase**. The **risk** for *Salmonella* bacteremia is **higher** in **pediatric** and **geriatric patients** and in immuno-compromised patients (HIV infections, sickle-cell disease, congenital immunodeficiencies). The clinical presentation of *Salmonella* bacteremia is like that of other gram-negative bacteremias; however, localized **suppurative infections** (e.g., **osteomyelitis, endocarditis, arthritis)** can occur in as many as 10% of patients.

Diseases

- **Enteric Fever**. *Salmonella* Typhi produces a **febrile illness** called typhoid fever. A **milder form** of this disease, referred to as paratyphoid fever, is produced by ***Salmonella* Paratyphi A**, Salmonella Schottmuelleri (formerly ***Salmonella* Paraty-phi B**), and Salmonella Hirschfeldii (formerly ***Salmonella* Paratyphi C**)(other serotypes rarely). The bacteria responsible for enteric fever **pass through the cells lining the intestines** and are **engulfed by macrophages**. They **replicate after being transported to the liver, spleen, and bone marrow**. Ten to **14 days after ingestion** of the bacteria, patients experience **gradually increasing fever**, with nonspecific complaints of **headache, myalgias, malaise,** and **anorexia**. These symptoms **persist for 1 week or longer** and are followed by **gastrointestinal symptoms**. This cycle corresponds to an **initial bacteremic phase** that is **followed by colonization of the gallbladder** and then **reinfection of the intestines**. Enteric fever is a **serious clinical disease** and must be suspected in febrile patients who have recently traveled to **developing countries** where disease is endemic.

Diseases

- **Diagnosis**

Enteric fever – prefered blood culture, serology (Widal reaction)

NTS infection - Isolation from stool specimens requires use of selective media, **specific PCR from stool**

- **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

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

Yersinia

Biology, Virulence, and Disease Gram-negative, facultatively anaerobic rods, Fermenter; oxidase negative. ***Y. pestis*** is covered with a **protein capsule**. **Some species** (e.g., *Y. enterocolitica*) can **grow at cold temperatures** (e.g., can grow to high numbers in contaminated, refrigerated food or blood products).

Virulence - **capsule** on *Y. pestis* is **antiphagocytic**; Y. pestis is **resistant to serum killing**; **genes for adherence**, **cytotoxic activity**, inhibition of phagocytic migration and engulfment, and inhibition of platelet aggregation.

Disease - ***Y. pestis*** causes **bubonic plague** (most common) and **pulmonary plague**, both having a **high mortality rate**; **other *Yersinia*** species cause **gastroenteritis** (**acute watery diarrhea or chronic diarrhea**) and transfusion-related sepsis; enteric disease in children **may manifest as enlarge mesenteric lymph nodes** and **mimic acute appendicitis**

See also: https://www.youtube.com/watch?v=ZCE6U75nt8s

Yersinia

Epidemiology

Y. pestis is a **zoonotic** infection with **humans** the **accidental host**; **natural reservoirs** include **rats, squirrels, rabbits, and domestic animals** Disease is **spread** by **flea bites** or **direct contact** with infected tissues or person to person by **inhalation** of infectious aerosols from a patient with pulmonary disease.

Other *Yersinia* infections are spread through exposure to contaminated food products or blood products (***Y. enterocolitica***). Colonization with other *Yersinia* species can occur.

See also: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9076465/

Yersinia

Diagnosis. Organisms grow on most culture media; prolonged storage at 4° C can selectively enhance isolation.

Treatment, Prevention, and Control *Y. pestis* infections are treated with **streptomycin**; **tetracyclines, chloramphenicol, or trimethoprim-sulfamethoxazole** can be administered as alternative therapy. **Enteric infections** with **other *Yersinia*** species are **usually self-limited**; if antibiotic therapy is indicated, most organisms are susceptible to **broad-spectrum cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, and trimethoprim-sulfamethoxazole.** **Plague** is **controlled by reduction of the rodent population and vaccination** of individuals at risk. Other *Yersinia* infections are controlled by the proper preparation of food products.

Other Enterobacteriaceae

Klebsiella. Members of the genus *Klebsiella* have a **prominent capsule** that is responsible for the **mucoid appearance** of isolated colonies and the **enhanced virulence** of the organisms in vivo. The most commonly K. pneumoniae and ***Klebsiella oxytoca***, which can cause **community- or hospital-acquired primary lobar pneumonia**. Pneumonia caused by *Klebsiella* species frequently involves the necrotic destruction of alveolar spaces, formation of cavities, and the production of blood-tinged sputum. These bacteria **also cause wound, soft-tissue, and UTIs. *K. granulomatis*** is the etiologic agent of **granuloma inguinale**, a granulomatous disease affecting the **genitalia and inguinal area** (donovanosis). It can be **transmitted** after repeated exposure **through sexual intercourse** or **nonsexual trauma to the genitalia**. After a prolonged incubation of weeks to months, **subcutaneous nodules** appear on the **genitalia** or in the inguinal area. The nodules subsequently **break down**, revealing one or more **painless granulomatous lesions** that can extend and coalesce into ulcers resembling syphilitic **lesions. Two other *Klebsiella* species** of clinical importance are ***Klebsiella rhinoscleromatis***, cause of a **granulomatous disease of the nose**, and ***Klebsiella ozaenae***, cause of chronic atrophic rhinitis (both diseases are relatively uncommon).

Other enterobacteria – e.g. from genera *Proteus, Enterobacter, Citrobacter, Morganella, Serratia* – causing UTIs but also various infections

Campylobacter (e.g. *C. jejuni*)

TAXONOMY

***Gramnegative rod,** motile, **spiral**, microaerophilic, nutritionally demanding

DISEASE

- **Intestinal - infect intestine (incubation – 1-7 days, lasts few weeks, usually selflimiting),** can cause **ulcerative, inflammatory lesion in the jejunum, ileum** or **colon**
- **Systemic – fever, myalgia, pseudoappendicitis**
- **Complications – septic abortion, reactive artritis, Guillain-Barré syndrom** (rare condition in which a person's immune system attacks the peripheral nerves)

EPIDEMIOLOGY

* **Fecal/oral route –** usually **contaminated meat** (especially **poultry)**

- **the most common bacterial cause of human ganstroenteritis worldwide**

TREATMENT AND PREVENTION

- **diarrhea - fluid and electrolyte replacement**
- **Bloody diarrheae and sytemic - antibiotics** (e.g. ciprofloxain, cephalosporinds 3rd generation)

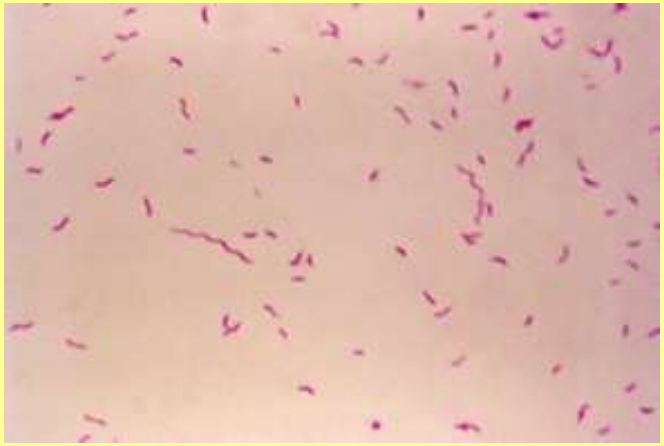
see also : https://www.youtube.com/watch?v=rKRkOwOpAO8

Campylobacter and campylobacteriosis

MATERIAL AND DIAGNOSIS

- **intestinal infections – rectal swab, stool and culture (identification using MALDI-TOF) or PCR identification**
- **Sytemic infections** – blood culture (poor sensitivity), **PCR** diagnosis, **serology** (reactive artritis, Guillain-Barré syndrom)

Karmali culture media



Gramnegative spiral rods

https://pathologyboardreview.com/ELSBRP/a/samplecase/2286

Helicobacter pylori

TAXONOMY

***Gramnegative rod,** motile, **spiral**, microaerophilic, nutritionally demanding

DISEASE

- Agent of acute gastritis and duodenic and gastric ulcers
- Untreated – chronic infection affecting gastric epithelium leading to chronic inflammation, risk factor for development gastric carcinoma
- Helicobacter urease produces ammonia ions neutralizing stomach acid in the vicinity of the organism and Helicobacter produce a cytotoxin
- **SYMPTOMS**
- Gastritis – epigastric discomfort
- Gastric carcinoma or gastric B-cell lymphoma

EPIDEMIOLOGY

*** Common worldwide**

TREATMENT AND PREVENTION

*** Ampicillin + clarithromycin + proton pump inhibitor (omeprazol)**

See also: https://www.youtube.com/watch?v=uhYGG0uNmZ8

Helicobacter pylori

TAXONOMY

***Gramnegative rod,** motile, **spiral**, microaerophilic, nutritionally demanding

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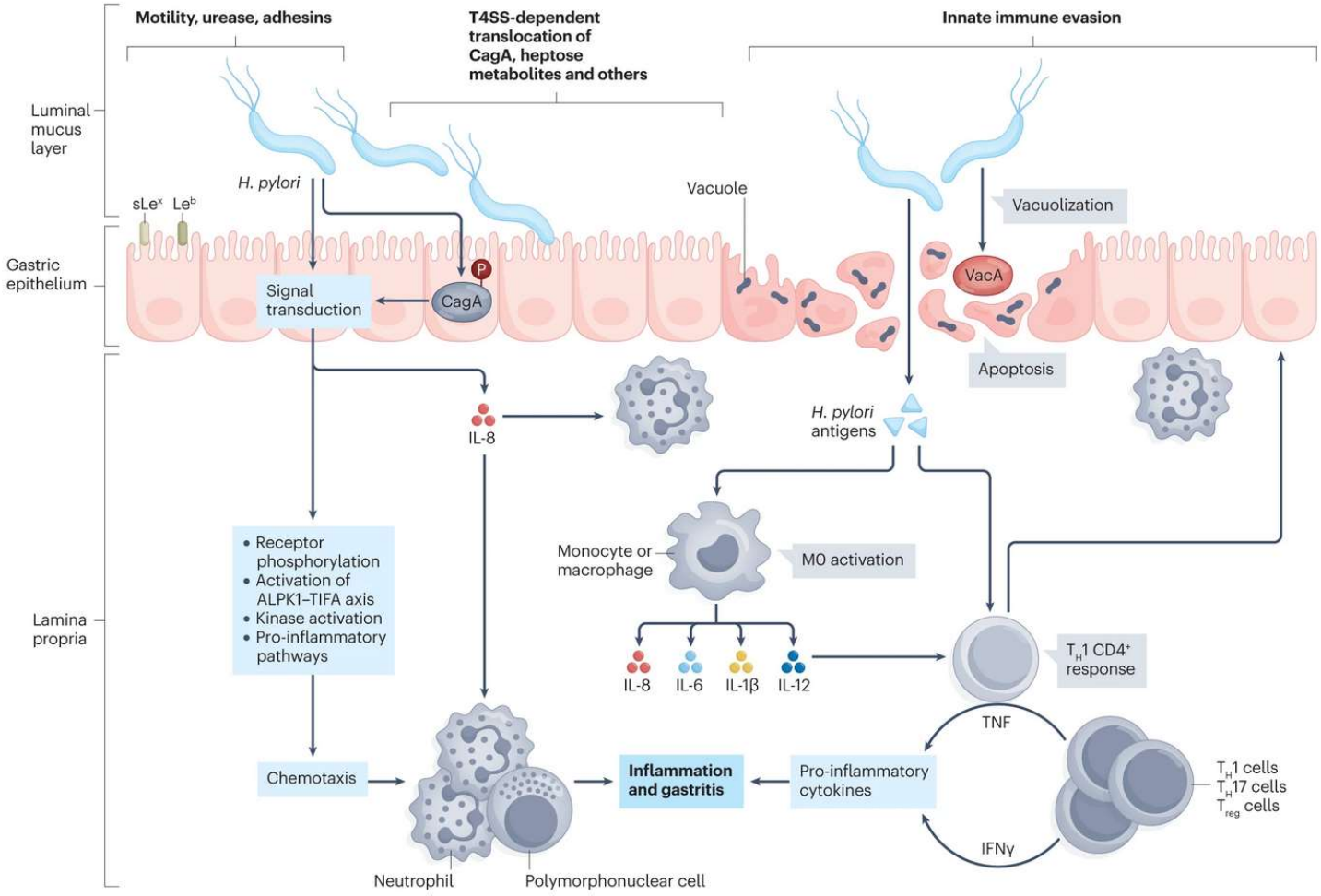
EPIDEMIOLOGY

- **Common worldwide**
- **Source of infection – human**
- Once individuals acquire *H. pylori* infection, the pathogen usually persists throughout their *pylori* does often occur in patients with advanced atrophic gastritis. The global prevalence of *H. pylori* infection in adults has declined from 50–55% to 43% during 2014–2020.

See also: https://www.youtube.com/watch?v=uhYGG0uNmZ8

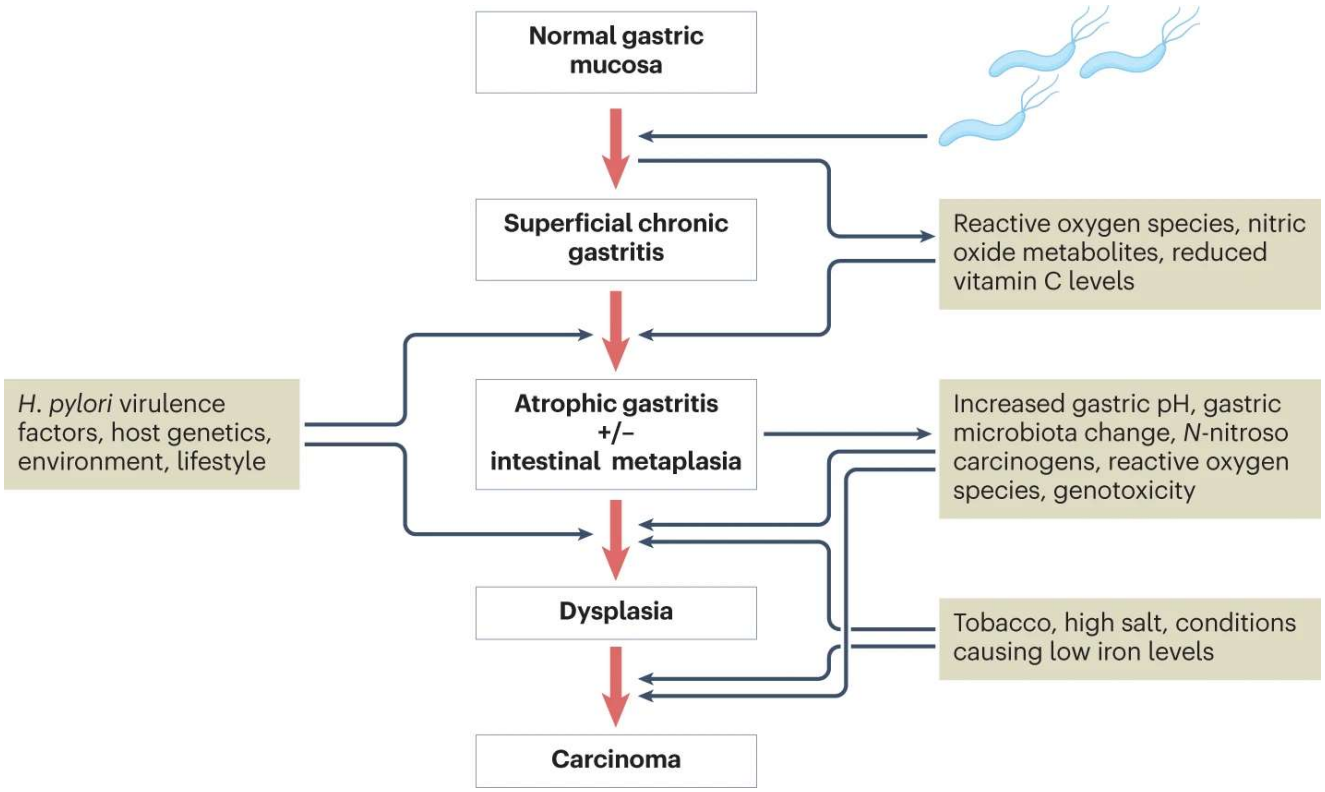
Helicobacter pylori - pathogenesis



Key aspects of bacterial colonization involve flagellar motility, urease activity, mechanisms of adhesion and damage to the gastric epithelium via vacuolization. The *Helicobacter pylori* pathogenicity island exerts a key role in inflammation, composes a type IV secretory system (T4SS) and promotes the intracellular injection of cytotoxin-associated gene A (CagA) antigen. The host immune response is characterized by initial mucosal invasion with polymorphonuclear cells followed by activation of the innate and adaptive immune system with complex T helper 1 (T_H1), T_H17 and regulatory T (T_{reg}) cell interactions. Le^b, Lewis b blood group antigen; sLe^x, sialyl-Lewis x antigen.

See also: https://www.nature.com/articles/s41572-023-00431-8

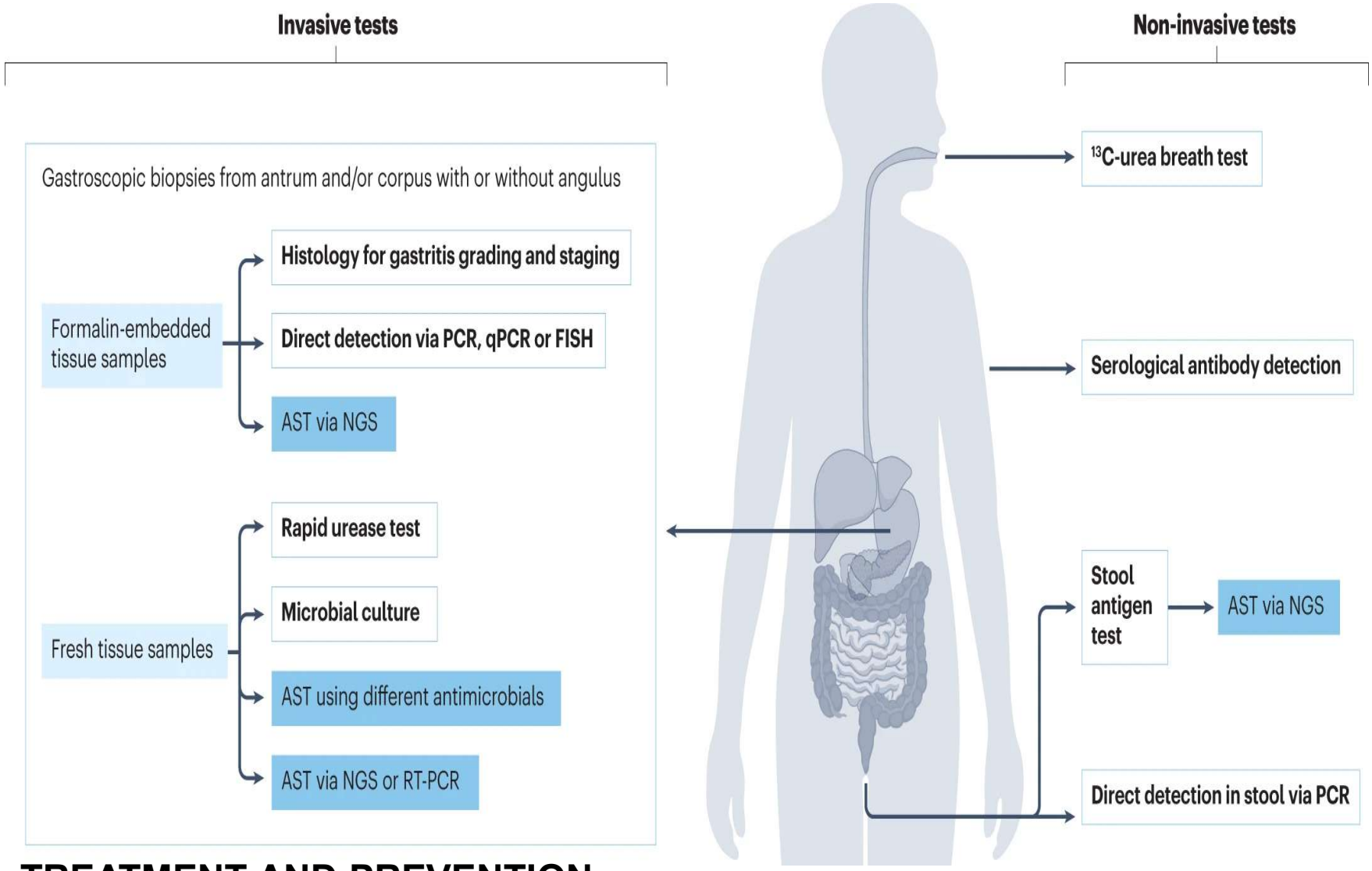
Pathogenesis of gastric adenocarcinoma triggered by *H. pylori*.



The dynamic progress of gastric carcinogenesis along the stepwise evolution of chronic gastritis initiated by *Helicobacter pylori* infection. *H. pylori* causes chronic gastritis that is associated with the generation of reactive oxygen species and nitric oxide metabolites and a reduction in antioxidant vitamin C levels. The risk of gastric cancer is highest in individuals who have infection by more virulent *H. pylori* strains, have pro-inflammatory host genetic factors, poor diet (high salt, smoked foods), low iron levels, unhealthy lifestyle and/or smoking habit. In these individuals, sustained chronic inflammation leads to damage and loss of acid-producing parietal cells, which leads to hypochlorhydria and finally achlorhydria. The loss of acidity facilitates colonization by harmful pro-inflammatory gastric microbiota, which in turn may produce more genotoxic pro-inflammatory metabolites and carcinogens that act directly on malignant epithelial cell transformation in the stomach.

See also: https://www.nature.com/articles/s41572-023-00431-8

Helicobacter pylori diagnosis and treatment



TREATMENT AND PREVENTION

*** Ampicillin + clarithromycin + proton pump inhibitor (omeprazol)**

See also: https://www.nature.com/articles/s41572-023-00431-8

Vibrio cholerae

TAXONOMY

***Gramnegative curved rod,** halophilic organisms

DISEASE

- ***Vibrio cholerae* O1 (classic and El Tor strains)– epidemic cholera**
- ***Vibrio cholerae* non-O1 – sporadic cholera like illness, milder illnesss**
- ***V. parahemolyticus, V. vulnificus* – gastroenteritis and extraintestinal inf. – soft tissue inf., septicemia**

PATHOGENESIS (see also: https://www.youtube.com/watch?v=QDp7a8yIHpc

*** Adhesion to small intestine, cholera toxin (enterotoxin A, B) – initiates an outpouring of fluid (adenylate cyclese elevate level of intracellular cAMP)**

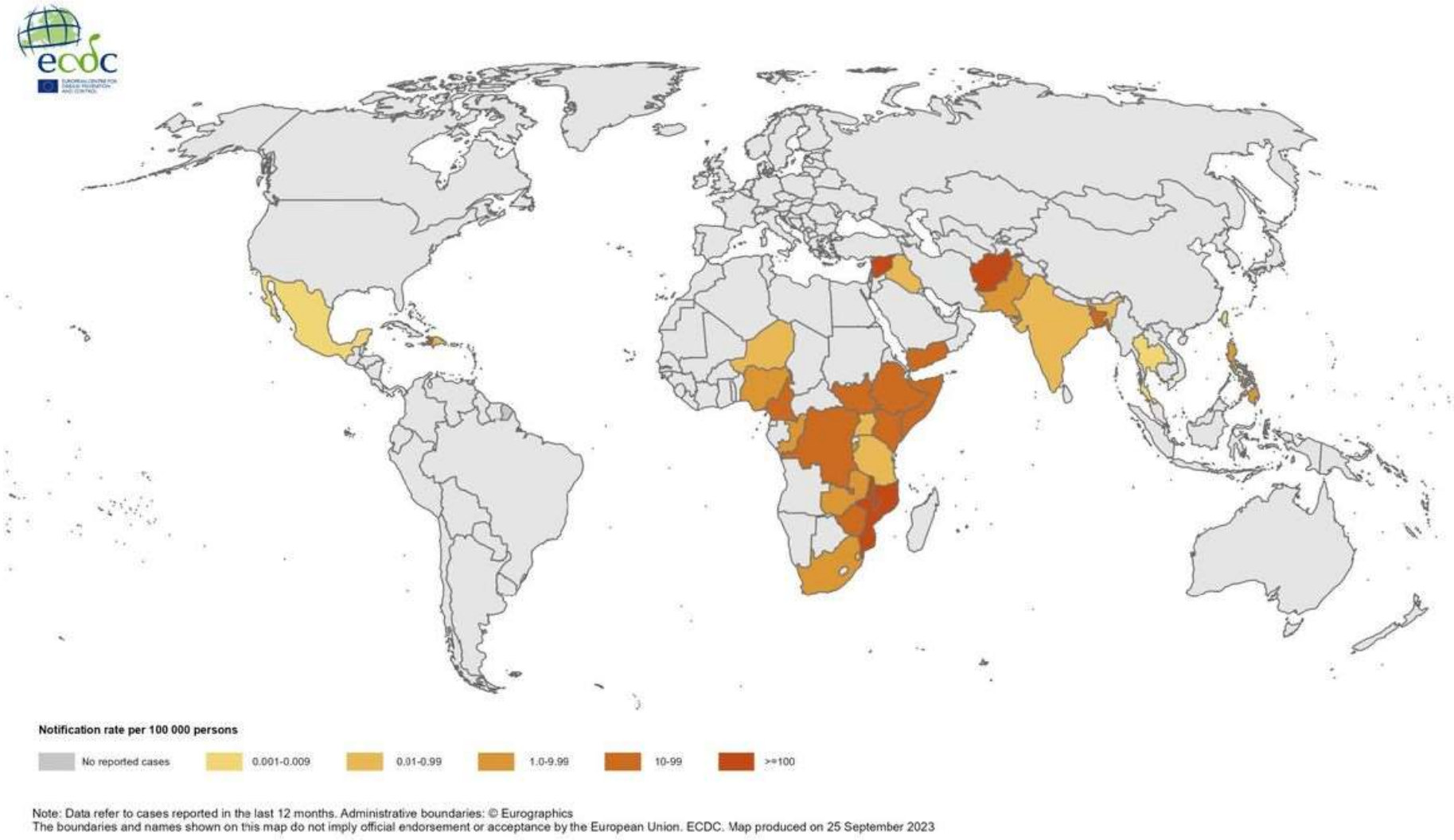
EPIDEMIOLOGY

*** Fecal/oral route –** usually **contaminated water (food)**

- **Cholera – profuse watery diarrhea, massive loss of fluid and electrolytes – hypovolemic shock and death**

- **See also: https://www.pbslearningmedia.org/resource/envh10.sci.life.nathis.johnsnow/john-snow-pioneer-of-epidemiology/**

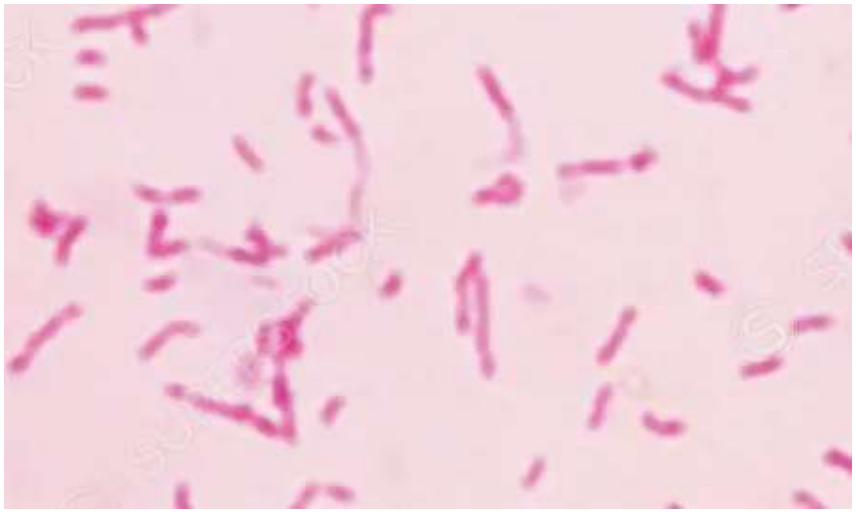
Geographical distribution of cholera cases reported worldwide, from July to September 2023



Vibrio cholerae

MATERIAL AND DIAGNOSIS

- **Rectal swab, stool – culture (blood agar, Mac-Conkey agar or a diagnostic agar) and identification using MALDI-TOF**
- **Stool - PCR**



Vibrio cholerae growing on thiosulphate citrate bile salt sucrose (TCBS) agar plates and microscopy using Gram stained bacteria

TREATMENT AND PREVENTION

•diarrhea - fluid and electrolyte replacement

•Doxycyclin can can shorten the duration of diarrhea. If resistance to doxycycline is documented, azithromycin and ciprofloxacin