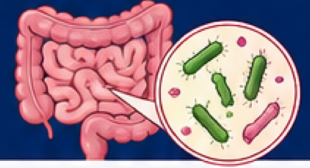


GRAM-NEGATIVE ENTEROBACTERIACEAE CAUSING GASTROINTESTINAL INFECTIONS



- Enterobacteriaceae family members are ubiquitous organisms and are **part of the normal intestinal flora** of most animals, including humans.
- Some organisms (e.g., *Salmonella* serotype Typhi; *Shigella* species, *Yersinia pestis*) are always associated with human disease.
- Others (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*) are members of the normal commensal flora that can cause opportunistic infections.
- Other commensal organisms can become pathogenic when they acquire virulence genes (e.g., *E. coli*)

GENERAL PROPERTIES OF ENTEROBACTERIACEAE



- Enterobacteriaceae are moderate-sized non spore forming Gram-negative, **facultative anaerobic** rods.
- All members ferment glucose, reduce nitrate, and are **catalase positive**, but they are **oxidase negative**.
- Most members grow readily on nonselective (e.g. blood agar) and selective (e.g. MacConkey agar) media, which is important for stool and blood culture diagnosis.
- Selective and differential media, such as **MacConkey agar**, help **separate lactose fermenters** from **non-lactose fermenters**.

LACTOSE FERMENTERS

(pink colonies on MacConkey agar)

Escherichia coli
Klebsiella
Enterobacter



NON-LACTOSE FERMENTERS

(colorless colonies on MacConkey agar)

Salmonella
Shigella
Yersinia
Proteus



BIOCHEMICAL IDENTIFICATION

(May include)

- **Carbohydrate fermentation**
- **Indole production**
- **Urease activity**
- **Citrate use**
- **Motility**
- **Hydrogen sulfide production**



MOTILITY

- Most Enterobacteriaceae are motile (coated with flagella), with the exception of some common genera (e.g., *Klebsiella*, *Shigella*, *Yersinia*).



Non-motile genera

- *Klebsiella*
- *Shigella*
- *Yersinia*

MODERN LABORATORY IDENTIFICATION

- Modern laboratories often use **automated** identification systems, **MALDI-TOF MS**, **molecular assays**, and **culture-based susceptibility testing**.



COMPARISON OF COMMON ENTEROBACTERIACEAE

Feature	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Enterobacter spp.</i>	<i>Salmonella spp.</i>	<i>Shigella spp.</i>	<i>Yersinia spp.</i>	<i>Proteus mirabilis</i>
Lactose Fermentation (on MacConkey agar)	Lactose fermenter (pink colonies)	Lactose fermenter (pink, mucoid)	Lactose fermenter (pink)	Non-lactose fermenter (colorless)	Non-lactose fermenter (colorless)	Non-lactose fermenter (colorless)	Non-lactose fermenter (colorless)
Motility	Motile	Non-motile	Motile	Motile	Non-motile	Non-motile (at 37°C)	Motile (swarming)
H ₂ S Production	-	-	-	+	-	-	+
Indole Production	+	-	+/-	-	-	-	+/-
Urease Activity	-	+	-/+	-	-	+/-	+
Citrate Utilization	-	+	+	+	-	+	+
Typical Habitat	Human & animal intestine	Human intestine	Environment, hospital	Human & animal intestine	Humans only (intestine)	Animals, humans (some species)	Human & animal intestine
Associated Disease	UTIs, diarrhea, sepsis, neonatal meningitis	Pneumonia, UTIs, sepsis	UTIs, sepsis, nosocomial infections	Gastroenteritis, typhoid fever, bacteremia	Bacillary dysentery (shigellosis)	Yersiniosis (gastroenteritis, plague - <i>Y. pestis</i>)	UTIs, struvite stones, wound infections

ANTIGENIC STRUCTURE OF ENTEROBACTERIACEAE: O, K, AND H ANTIGENS

O ANTIGEN (Somatic)

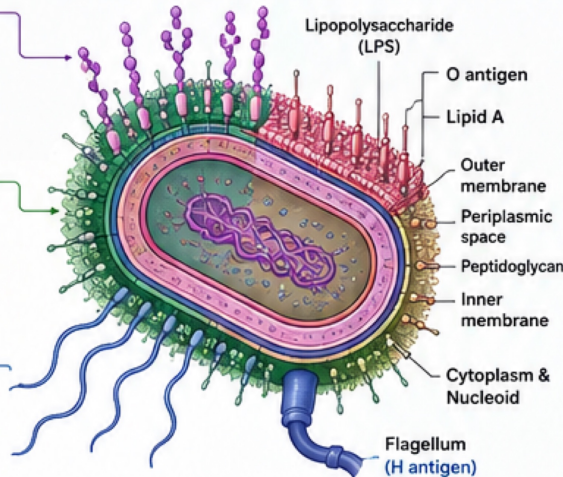
Outer polysaccharide component of lipopolysaccharide (LPS). Useful for **serologic classification**.

K ANTIGEN (Capsular)

Capsular polysaccharide antigen. Can contribute to **immune evasion** and **virulence**.

H ANTIGEN (Flagellar)

Flagellar antigen. Present in motile organisms.



- The **O antigen (somatic)** is the outer polysaccharide component of lipopolysaccharide and is useful for serologic classification.



- The **K antigen** is the capsular polysaccharide antigen and can contribute to immune evasion and virulence.



- The **H antigen** is the flagellar antigen and is present in motile organisms.



- **Serotyping** remains important for organisms such as *Salmonella*, *Shigella*, and some diarrheagenic *E. coli* strains.



- Antigenic variation of these antigens helps these organisms evade host immune responses and complicates epidemiologic classification.

WHY ANTIGENS MATTER



Help bacteria evade host immune responses



Aid in epidemiologic tracking and outbreak investigation

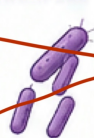


Important for vaccine development and diagnostic tests

EXAMPLES OF SEROTYPING



Salmonella
Uses O and H antigens (e.g., *S. Typhi* O9, H:d)



Shigella
Primarily O antigen (e.g., *S. flexneri* serotypes)

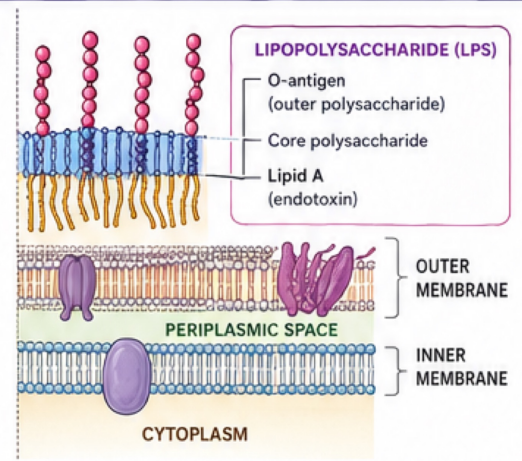


E. coli
(O, H, and K antigens used in pathotype typing e.g., O157:H7)

MAJOR VIRULENCE FACTORS

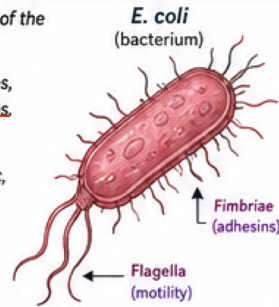


- Many Enterobacteriaceae are **harmless colonizers**, but pathogenic strains acquire **virulence genes** that allow them to attach, invade, produce toxins, or survive host defenses.
- **Endotoxin**, or **lipid A** of lipopolysaccharide, is shared by aerobic Gram-negative rods and can trigger fever, inflammation, shock, and disseminated intravascular coagulation.
- **Capsules** protect organisms from phagocytosis and may interfere with complement-mediated killing.
- **Adhesins** allow organisms to bind host epithelial surfaces and are essential for **colonization** of the intestinal tract.
- **Exotoxins**, including enterotoxins and Shiga toxins, explain many of the diarrheal syndromes caused by these organisms.
- **Antimicrobial resistance** and resistance to serum killing.



ESCHERICHIA COLI

- *E. coli* is the most common and important member of the genus *Escherichia*.
- This organism is associated with a variety of diseases, including **gastroenteritis** and **extraintestinal infections**.
- The strains of *E. coli* that cause gastroenteritis are subdivided into a number of groups: enterotoxigenic, enteropathogenic, enteroaggregative, Shiga toxin-producing, and enteroinvasive *E. coli* (EIEC).
- *Escherichia* strains possess specialized **virulence factors**: **adhesins** and **exotoxins**.



ASSOCIATED DISEASES

GASTROENTERITIS



EXTRAI NTESTINAL INFECTIONS



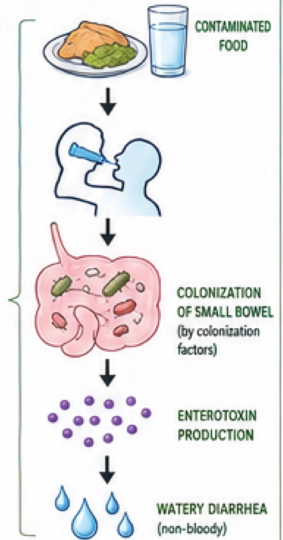
Urinary tract infections

Septicemia

Pneumonia (neonates)

ENTEROTOXIGENIC E. COLI (ETEC)

- **ETEC** is one of the most common causes of bacterial diarrheal disease in developing countries and a major cause of **traveler's diarrhea**.
- It is usually acquired by **ingestion of contaminated food or water**.
- Disease is mediated by bacterial attachment to the small bowel by colonization factors followed by production of enterotoxins.
- The diarrheal is usually **watery and non-bloody**, with abdominal cramps, nausea, and **sometimes low-grade fever**.
- **ETEC** causes disease **without prominent tissue invasion**, which explains the absence of dysentery in typical cases.

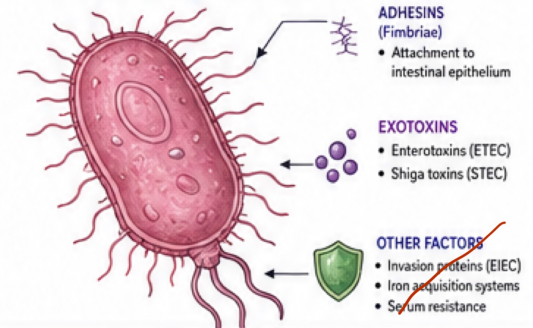


PATHOTYPES OF DIARRHEAGENIC E. COLI

Pathotype	Abbreviation	Key Virulence Factors	Typical Clinical Features	Commonly Affects
Enterotoxigenic <i>E. coli</i>	ETEC	Colonization factors (fimbriae), heat-labile toxin (LT), heat-stable toxin (ST)	Watery diarrhea, traveler's diarrhea	All ages, travelers, developing countries
Enteropathogenic <i>E. coli</i>	EPEC	Attaching and effacing lesions, intimin, BFP pili	Watery diarrhea (infants), vomiting	Infants and children
Enteroaggregative <i>E. coli</i>	EAEC	Aggregative adherence fimbriae, EAST1 toxin	Persistent watery diarrhea	Children, developing countries
Shiga toxin-producing <i>E. coli</i>	STEC	Shiga toxin (Stx1, Stx2), LEE pathogenicity island	Bloody diarrhea, HUS*	All ages
Enteroinvasive <i>E. coli</i>	EIEC	Invasion plasmid antigens, Shigella-like invasion	Dysentery-like illness (bloody diarrhea)	Developing countries

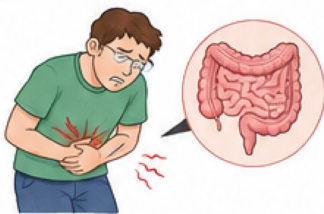
*HUS = Hemolytic uremic syndrome

VIRULENCE FACTORS IN E. COLI

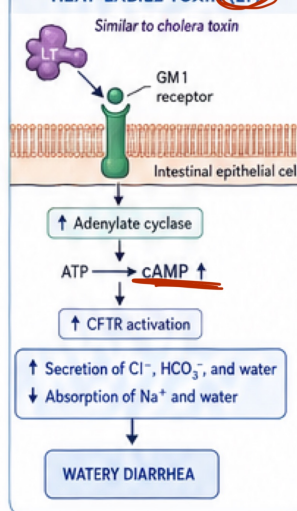


ETEC TOXINS

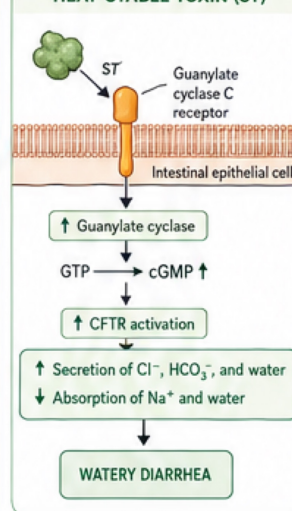
- **ETEC** produces **heat-labile toxin**, **heat-stable toxin**, or both.
- **Heat-labile toxin** is functionally similar to cholera toxin and increases intracellular **cyclic AMP**.
- **Heat-stable toxin** increases **cyclic GMP** and promotes intestinal fluid secretion; more commonly responsible for severe disease.
- Both mechanisms result in **impaired absorption and increased secretion of water and electrolytes into the intestinal lumen**.
- Clinically, this produces watery diarrhea that can resemble mild cholera but is usually self-limited.



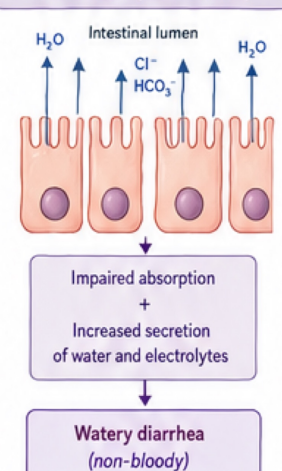
HEAT-LABILE TOXIN (LT)



HEAT-STABLE TOXIN (ST)



NET EFFECT (BOTH TOXINS)



ENTEROPATHOGENIC E. COLI (EPEC)

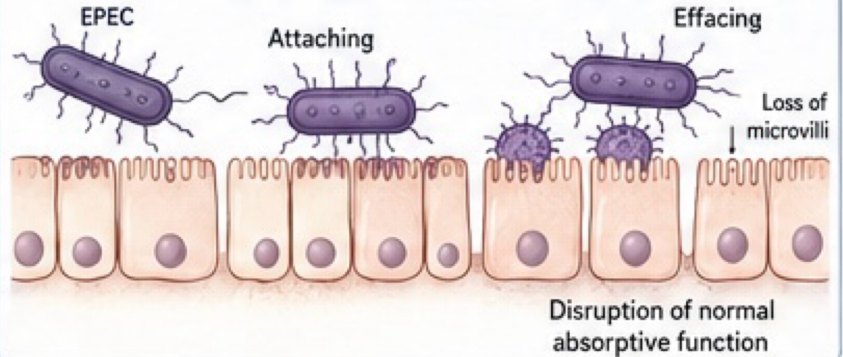
- **EPEC** is an important cause of diarrhea in infants, especially in developing countries.
- Posses a cluster of virulence genes located on a chromosomal pathogenicity island called the **locus of enterocyte effacement (LEE)**.
- It causes disease by attaching to enterocytes and producing **attaching and effacing lesions**.
- These lesions are associated with loss of microvilli and disruption of normal absorptive function.
- transmitted by **fecal-oral exposure** to contaminated surfaces or food products.
- The diarrhea is usually **watery** and may be prolonged in infants.
- Most infections resolve after a few days; persistent diarrhea requiring hospitalization can occur.
- Unlike ETEC, EPEC disease is mainly due to **epithelial injury and altered absorption** rather than classic enterotoxin production.

THE LEE PATHOGENICITY ISLAND

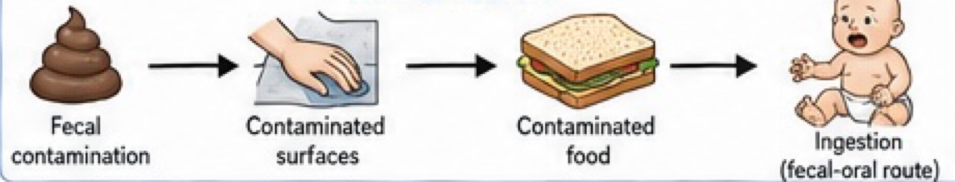


LEE encodes proteins for adhesion, type III secretion system, and effector molecules.

ATTACHING AND EFFACING LESIONS



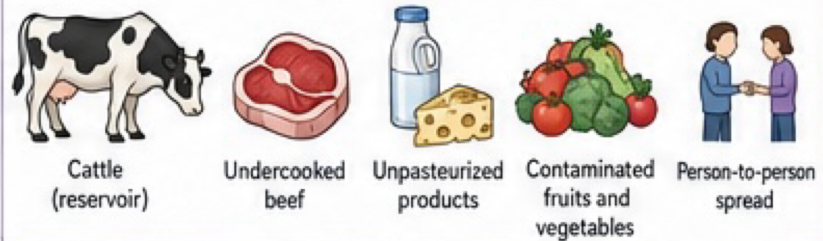
TRANSMISSION



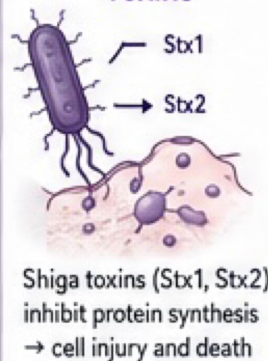
SHIGA TOXIN-PRODUCING E. COLI (STEC)

- **STEC**, also called verocytotoxin-producing *E. coli* (**VTEC**) or **enterohemorrhagic E. coli (EHEC)**, when associated with hemorrhagic colitis, is an important cause of bloody diarrhea.
- Disease is strongly associated with **Shiga toxins**, especially **Stx1** and **Stx2**.
- Important reservoirs include cattle and transmission may occur through undercooked beef, unpasteurized products, contaminated fruits and vegetables, or person-to-person spread.
- The most **common serotype** associated with sever human disease is **O157:H7**.
- The illness often begins with abdominal cramps and watery diarrhea that can progress to bloody diarrhea and hemorrhagic colitis.
- Fever may be absent or low-grade, which can help distinguish **STEC** from some invasive bacterial dysenteries.

RESERVOIRS AND TRANSMISSION



TOXINS



CLINICAL COURSE



KEY POINT

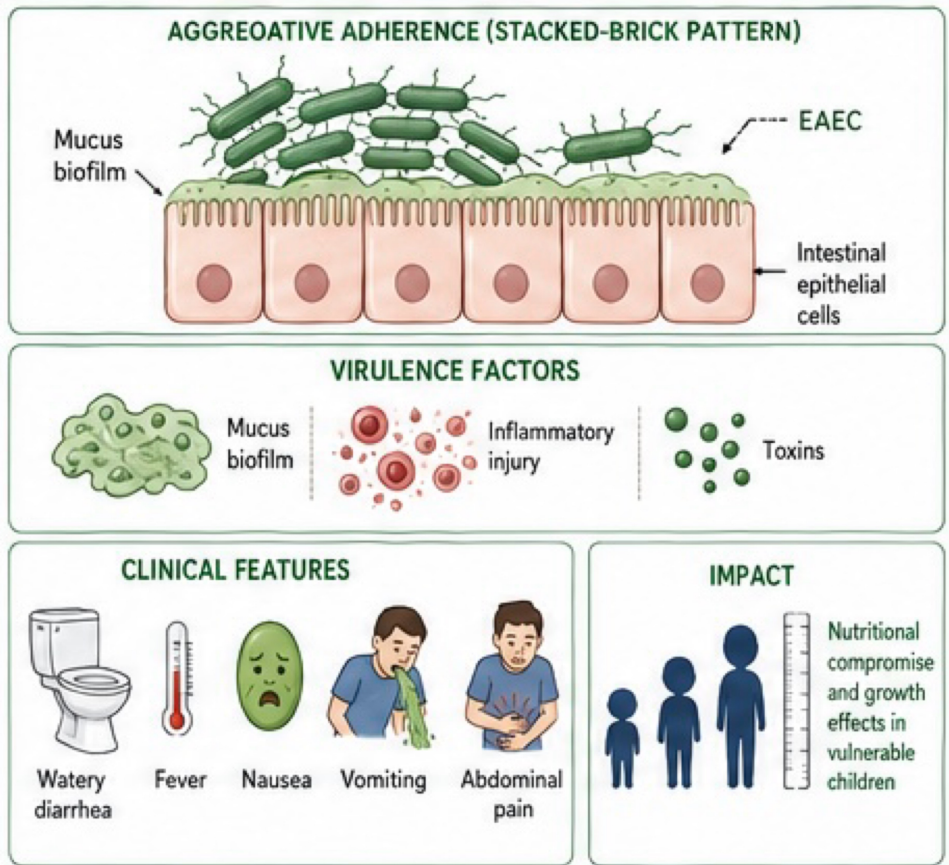
Fever may be absent or low-grade

COMMON SEROTYPE

O157:H7

ENTEROAGGREGATIVE E. COLI (EAEC)

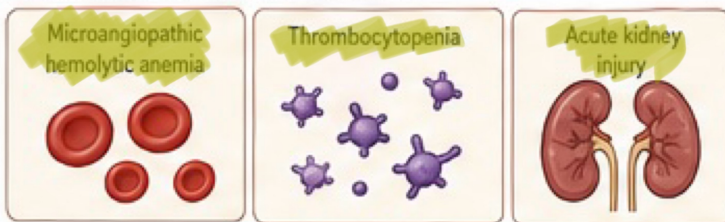
- EAEC is associated with acute or persistent diarrhea, especially in children and immunocompromised patients.
- It adheres to intestinal epithelial cells in an aggregative, stacked-brick pattern.
- EAEC may produce mucus biofilm, inflammatory injury, and toxins that contribute to prolonged disease.
- The clinical illness is commonly watery diarrhea, often with fever, nausea, vomiting, and abdominal pain.
- EAEC is important because its chronicity can contribute to nutritional compromise and growth effects in vulnerable children.



STEC COMPLICATIONS AND MANAGEMENT

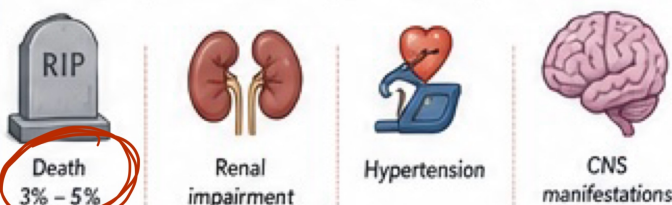
COMPLICATION: HEMOLYTIC UREMIC SYNDROME (HUS)

- The most feared complication of STEC infection is hemolytic uremic syndrome, especially in children younger than 10 (5-10%) and older adults - STX2 preferentially.
- HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.



OUTCOMES

- Resolution of symptoms occurs in uncomplicated disease after 4 to 10 days in most untreated patients; however, death can occur in 3% to 5% of patients with HUS, and severe sequelae (e.g., renal impairment, hypertension, CNS manifestations) can occur in as many as 30% of HUS patients.



Severe sequelae in up to 30% of HUS patients

MANAGEMENT

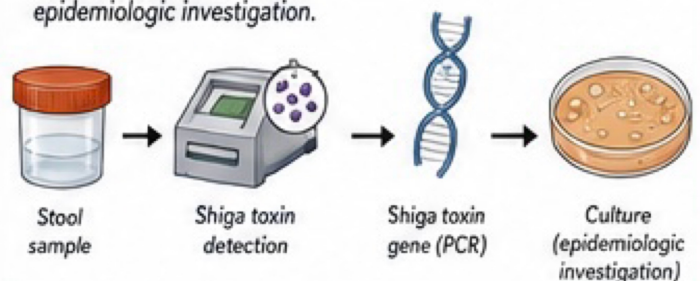
- Antibiotics and antimotility agents are generally avoided when STEC infection early intravenous fluids may reduce renal failure risk in children with STEC O157 infection.



Early intravenous fluids may reduce renal failure risk in children (STEC O157)

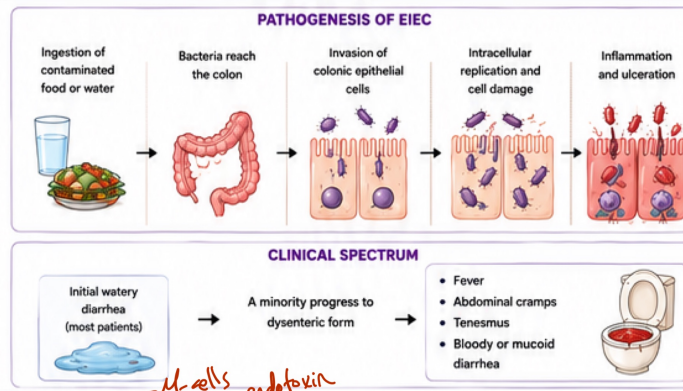
DIAGNOSIS

- Diagnosis requires detection of Shiga toxin or Shiga toxin genes, often combined with culture for epidemiologic investigation.



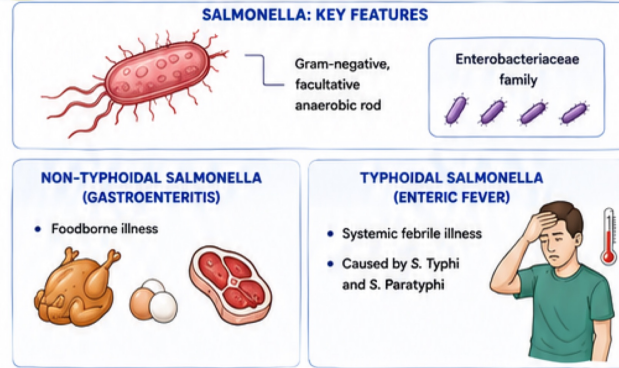
ENTEROINVASIVE E. COLI (EIEC)

- EIEC causes an invasive diarrheal illness resembling shigellosis.
- It invades and replicates within colonic epithelial cells initially producing watery diarrhea.
- A minority progress to dysenteric form with fever, abdominal cramps, tenesmus, and bloody or mucoid diarrhea.
- EIEC is less commonly identified than other diarrheagenic *E. coli* pathotypes in routine clinical practice.
- Its pathogenesis is important because it shows that not all *E. coli* diarrhea is toxin-mediated or watery.

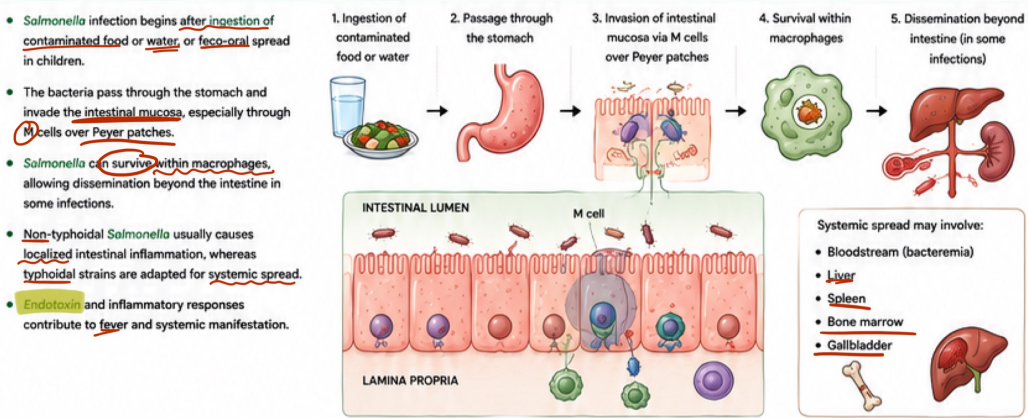


SALMONELLA SPP

- Salmonella* are Gram-negative, facultative anaerobic rods within Enterobacteriaceae.
- Clinically, *Salmonella* infections are divided into non-typhoidal *Salmonella* gastroenteritis and typhoidal *Salmonella* enteric fever.
- Non-typhoidal *Salmonella* commonly causes foodborne gastroenteritis.
- Salmonella Typhi* and *Salmonella Paratyphi* cause enteric fever, a systemic febrile illness.
- This classification is essential because gastroenteritis and enteric fever differ in pathogenesis, clinical course, diagnosis, treatment, and prevention.

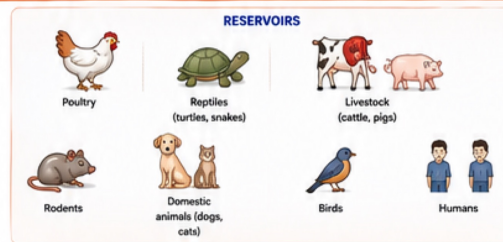


PATHOGENESIS



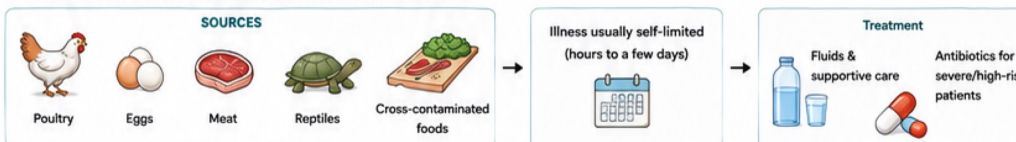
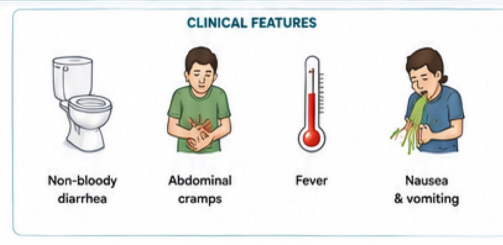
EPIDEMIOLOGY

- Salmonella* can colonize virtually all animals, including poultry, reptiles, livestock, rodents, domestic animals, birds, and humans.
- Serotypes such as *Salmonella Typhi* and *Salmonella Paratyphi* are highly adapted to humans and do not cause disease in nonhuman hosts.
- Salmonella Typhi* and *Salmonella Paratyphi* can survive in the gallbladder and establish chronic carriage (chronic colonization).
- Salmonella Typhi* infections occur when food or water contaminated by infected food handlers is ingested.
- The infectious dose for *Salmonella Typhi* infections is low unlike other serovars, so person-to-person spread is common.



NON-TYPHOIDAL SALMONELLA GASTROENTERITIS

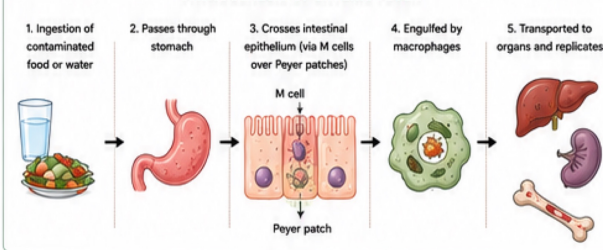
- Non-typhoidal *Salmonella* gastroenteritis is commonly associated with contaminated poultry, eggs, meat, reptiles, and cross-contaminated foods.
- Symptoms usually include non-bloody diarrhea, abdominal cramps, fever, nausea, and vomiting.
- The incubation period is commonly hours to a few days, and illness is often self-limited.
- Stool may be inflammatory, and bacteremia can occur, especially in infants, older adults, and immunocompromised patients.
- Most uncomplicated cases are treated with fluids and supportive care, while antibiotics are reserved for severe disease or high-risk patients.



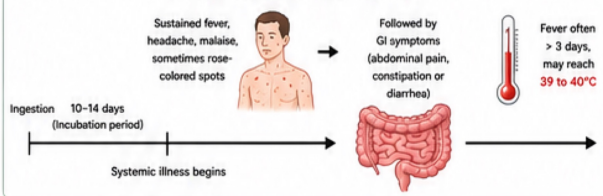
ENTERIC FEVER

- Enteric fever is caused by *Salmonella Typhi* and *Salmonella Paratyphi A, B, C* (Typhoid and Paratyphoid fever respectively).
- The disease is endemic in **Africa, south Asia and Latin America**.
- It is acquired by ingestion of food or water contaminated with **human feces**.
- The bacteria pass through the cells lining the intestines and are engulfed by macrophages. They replicate after being transported to the liver, spleen, and bone marrow.
- The illness is systemic and typically presents **10-14 days after ingestion** with **sustained fever**, headache, malaise, and sometimes **rose-colored spots**, followed by GI symptoms.
- Typhoid fever often produces fever lasting more than **three days** and may reach **39 to 40°C**.
- Diagnosis is often by blood culture early in disease, while stool culture may become positive later

PATHOGENESIS OF ENTERIC FEVER



CLINICAL COURSE (TYPICAL TIMELINE)



DIAGNOSIS, TREATMENT, AND PREVENTION

CLINICAL AND PUBLIC-HEALTH APPROACH

DIAGNOSIS

Stool culture is useful for suspected **non-typhoidal Salmonella gastroenteritis**.

Blood culture is important when **enteric fever** or **invasive Salmonella** infection is suspected.

Antimicrobial susceptibility testing is important because resistance affects treatment choices.

TREATMENT

First-line treatments often include:

- Ciprofloxacin (for susceptible strains)
- Azithromycin
- Ceftriaxone

Treatment choice depends on:

- Susceptibility pattern
- Severity of illness
- Patient factors (age, pregnancy, allergies, local resistance)

PREVENTION (FOOD SAFETY)

- Safe food handling
- Cooking poultry and eggs thoroughly
- Avoiding cross-contamination
- Proper sanitation
- Clean drinking water

TYPHOID PREVENTION

- Safe water
- Sanitation
- Identification of carriers
- Vaccination for travelers to endemic regions

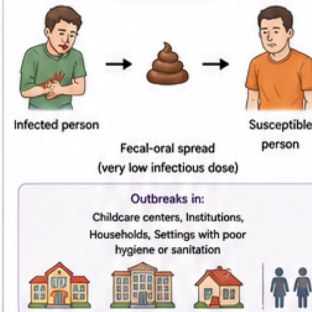
SHIGELLA SPP

- Shigella* are nonmotile **highly infectious** Gram-negative rods that cause shigellosis or bacillary dysentery.
- Humans are the only reservoir, and transmission occurs by **fecal-oral spread**.
- Shigella* has a **very low infectious dose**, so person-to-person transmission is common.
- Outbreaks occur in **childcare centers, institutions, households**, and settings with poor hygiene or sanitation.
- The major species include *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*.

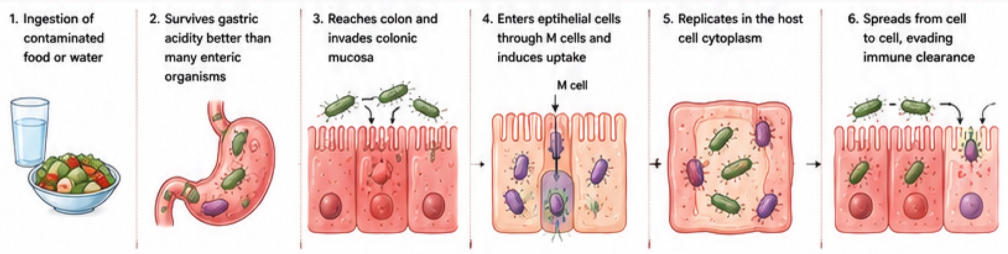
SHIGELLA: KEY FACTS

- Nonmotile
- Gram-negative rods
- Highly infectious
- Cause shigellosis (bacillary dysentery)
- Humans are the only reservoir

TRANSMISSION

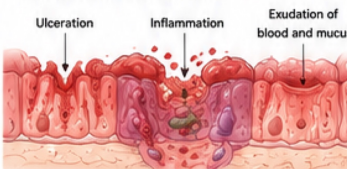


SHIGELLA PATHOGENESIS AND CLINICAL MANIFESTATIONS



MECHANISMS AND-EFFECTS

- Invades the colonic mucosa and spreads from cell to cell, replicating in the host cell cytoplasm, evading immune clearance.
- Invasion causes mucosal ulceration, intense inflammation, and exudation of blood and mucus.



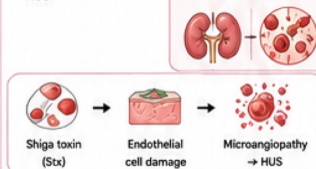
CLINICAL MANIFESTATIONS

- Abdominal cramps
- Fever
- Tenesmus
- Frequent small-volume stools

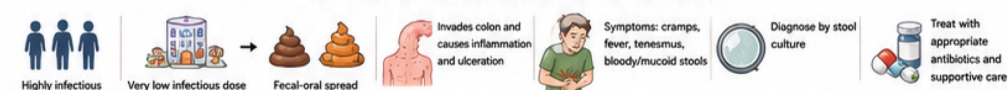
VIRULENCE FACTORS

- Shiga toxin, especially from *S. dysenteriae* type 1, can contribute to severe disease and HUS.

Possible complication:
HUS (Hemolytic Uremic Syndrome)

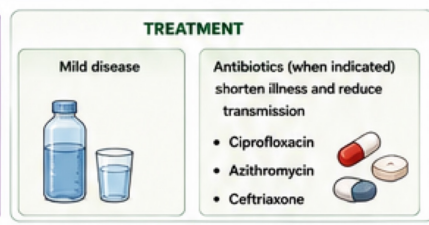
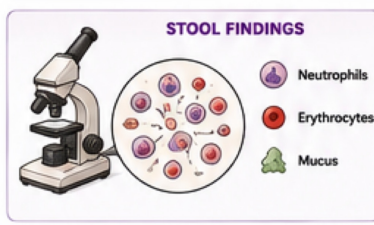
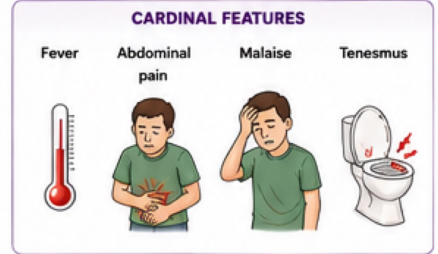
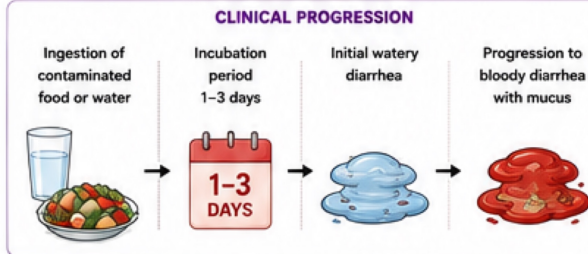


SUMMARY: SHIGELLOSIS (BACILLARY DYSENTERY)



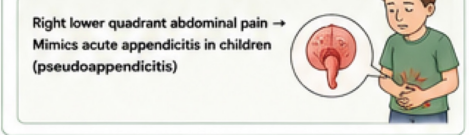
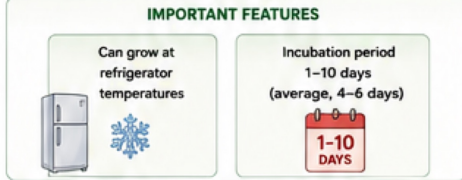
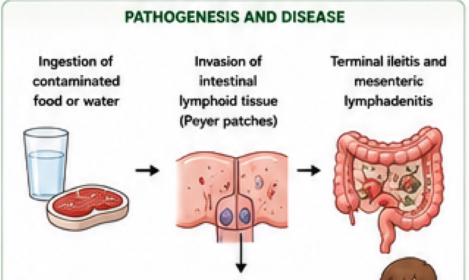
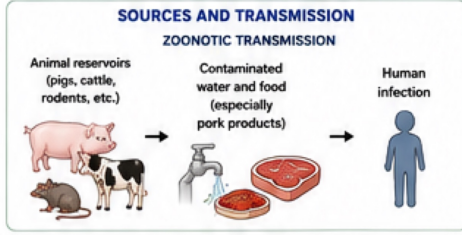
SHIGELLOSIS – DYSENTERY SYNDROME

- *Shigellosis* may begin 1–3 days after ingestion with watery diarrhea but can progress to bloody diarrhea with mucus.
- Cardinal features include fever, abdominal pain, malaise, and tenesmus.
- Abundant neutrophils, erythrocytes, and mucus are found in the stool.
- Mild disease may resolve with fluids and supportive care, but antibiotics can shorten illness and reduce transmission when indicated (ciprofloxacin, azithromycin, or ceftriaxone).
- Antimotility agents should be avoided because they may worsen invasive diarrhea.

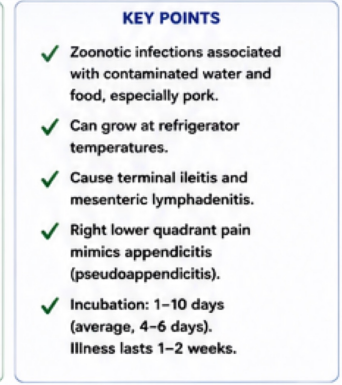
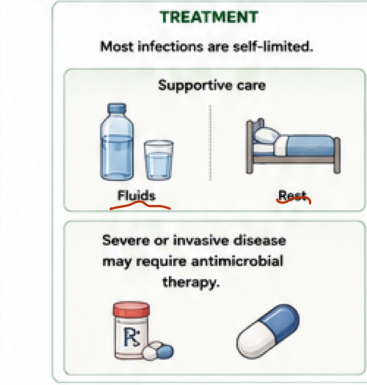
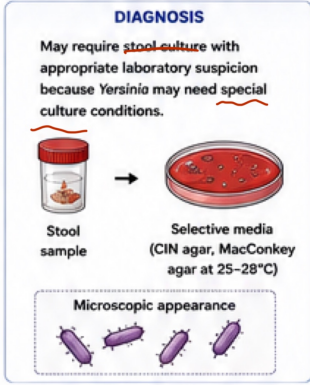
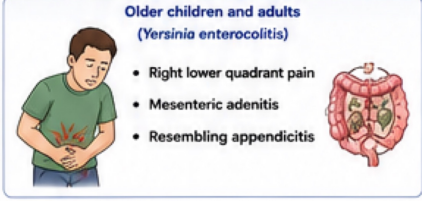
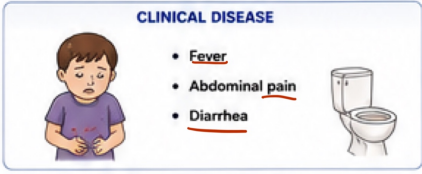


YERSINIA ENTEROCOLITICA AND YERSINIA PSEUDOTUBERCULOSIS

- *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* can cause gastrointestinal disease in humans.
- *Yersinia* infections are often zoonotic and are associated with contaminated water and food, especially pork products.
- Incubation period of 1 to 10 days (average, 4 to 6 days), and disease can last as long as 1 to 2 weeks.
- *Y. enterocolitica* can grow at refrigerator temperatures, which is an important food safety point.
- The organisms can invade intestinal lymphoid tissue and cause terminal ileitis and mesenteric lymphadenitis.
- Because of right lower quadrant abdominal pain, *Yersinia* infection can clinically mimic acute appendicitis in children (pseudoappendicitis).

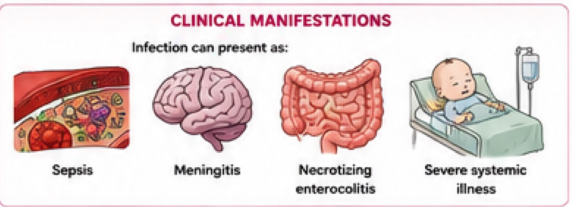
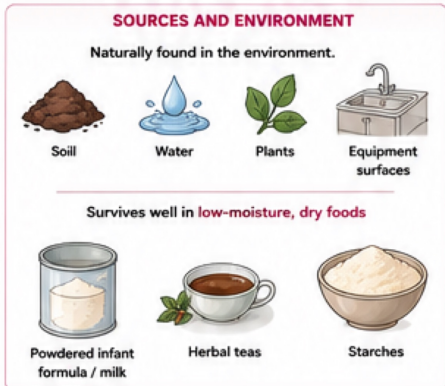


CLINICAL DISEASE, DIAGNOSIS, AND TREATMENT



CRONOBACTER SAKAZAKII

- *Cronobacter sakazakii* (formerly *Enterobacter sakazakii*) is an Enterobacteriaceae member of special importance in neonates and young infants.
- Important cause of neonatal gastrointestinal and systemic infection.
- *Cronobacter* is naturally found in the environment and is particularly good at surviving in low-moisture, dry foods, such as powdered infant formula/milk, herbal teas, and starches.
- Infection can present as sepsis, meningitis/necrotizing enterocolitis, or severe systemic illness.
- Premature infants, low-birth-weight infants, and immunocompromised neonates are at greatest risk.
- Prevention focuses on safe preparation, storage, and handling of powdered infant formula, especially in neonatal units.



PREVENTION: SAFE PREPARATION, STORAGE, AND HANDLING OF POWDERED INFANT FORMULA



Cronobacter infections are rare but can be life-threatening in neonates and young infants. Strict adherence to safe preparation and handling practices is essential, especially in neonatal units.

High-risk groups: premature infants, low-birth-weight infants, and immunocompromised neonates.