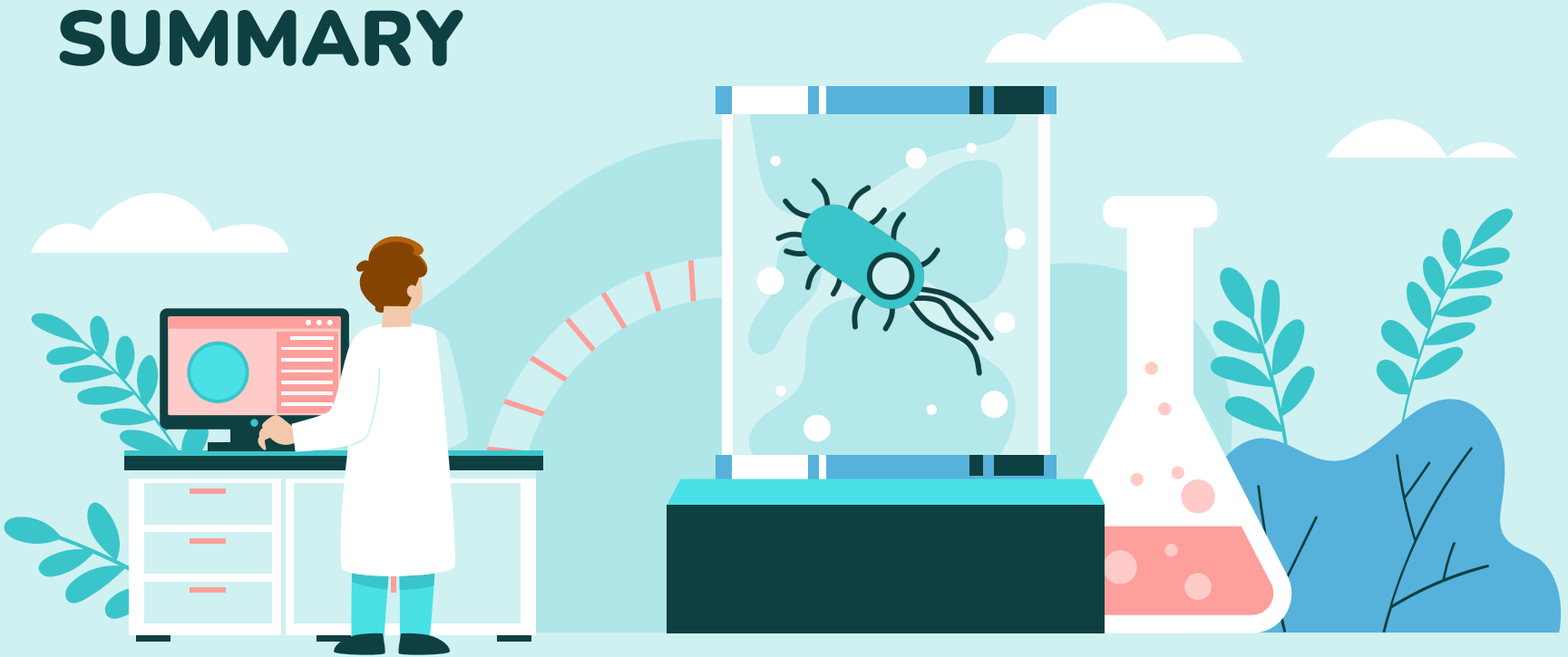
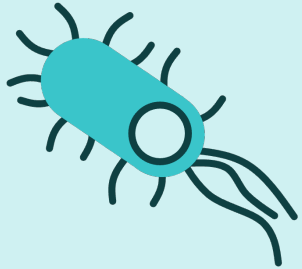
CASE 3
BACTERIAL PATHOGENESIS SUMMARY

Claire Sie

PATH417
2021W2





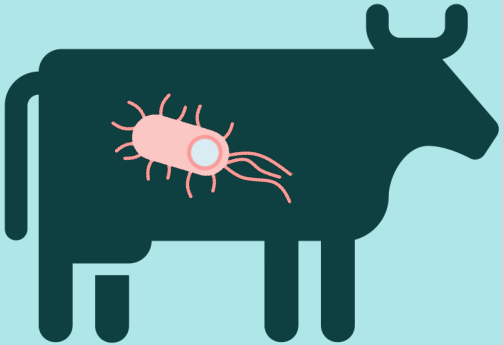
CASE SUMMARY

“10-year-old Ronnie has developed abdominal cramps, bloody diarrhea and a low-grade fever. His parents take him to see the family doctor. The doctor asks about what Ronnie has eaten in the past week. His parents recall that last weekend at a neighbor’s barbecue they were concerned that the hamburgers may not have been cooked thoroughly and Ronnie ate two burgers. The doctor performs a physical examination noting no rebound tenderness just some mild periumbilical tenderness. He asks the parents to collect a stool sample for the Microbiology Laboratory and also issues a requisition for routine bloodwork (to be performed at the local laboratory). The Microbiology Laboratory report comes back positive for *E.coli* 0157:H7.”

TABLE OF CONTENTS

E. COLI O157:H7 OVERVIEW

- Gram-negative enteric bacillus
- **Shiga toxin-producing** strain of *E. coli* (STEC)
- Transmitted via consumption of **contaminated food sources**[1]
    - Raw/undercooked meats
    - Contaminated fresh produce
    - Unpasteurized milk
- Causes **hemorrhagic diarrhea**



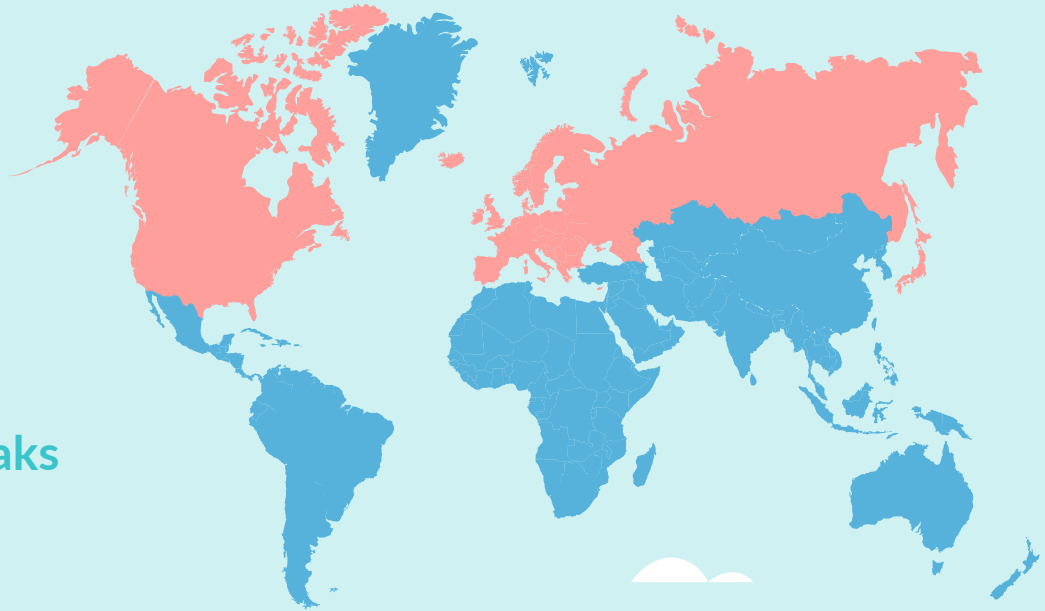
01

ENCOUNTER

Where does the organism normally reside, geographically and host wise, and what are the bacterial characteristics that leave it suited to these places of residence?

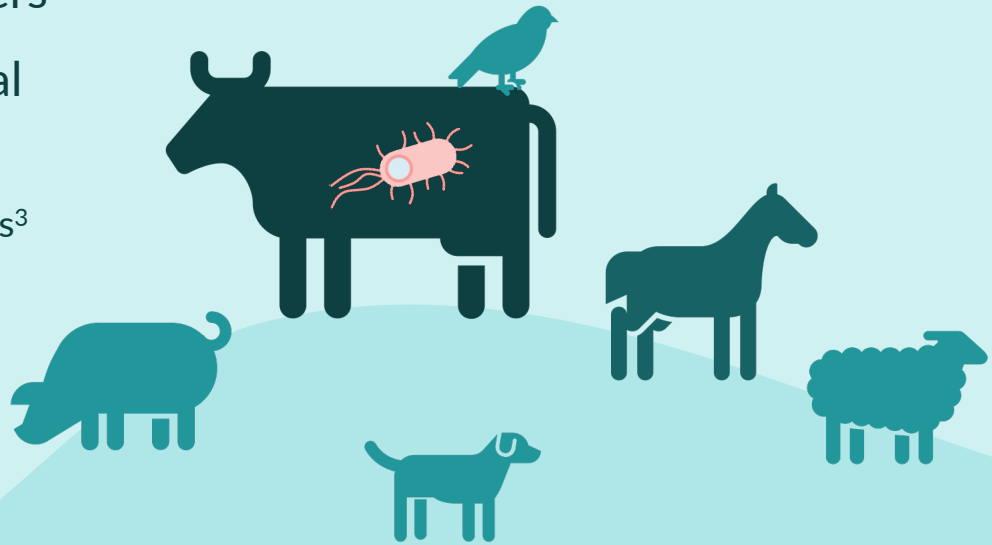
GEOGRAPHICAL LOCALIZATION

- **Industrialized** countries[2]
- More common in **western** Canada vs. eastern Canada[3]
- More common in **northern** US states vs. southern US states[3]
- **Prolonged community outbreaks** due to contaminated water or food sources[4]



ANIMALS AS RESERVOIRS FOR *E. COLI* O157:H7

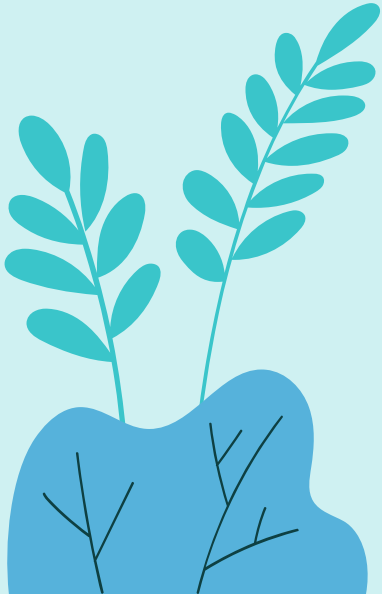
- **Cattle** are asymptomatic carriers[3]
- **Intermittent** and **seasonal** fecal shedding
    - Elevated during summer months[3]
- Other animal reservoirs:
    - Sheep
    - Pigs
    - Horses
    - Dogs
    - Deer
    - Birds



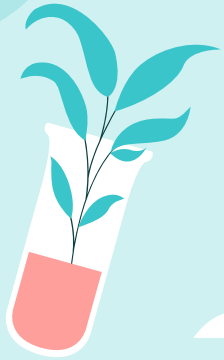
ENVIRONMENTAL RESERVOIRS[3]

- Farms
- Ponds
- Dams
- Wells
- Barns
- Water
- Water troughs
- Farm equipment
- Ground
- Pasture



E. COLI O157:H7 HAS BEEN FOUND TO BE ABLE TO SURVIVE UP TO:



12 months

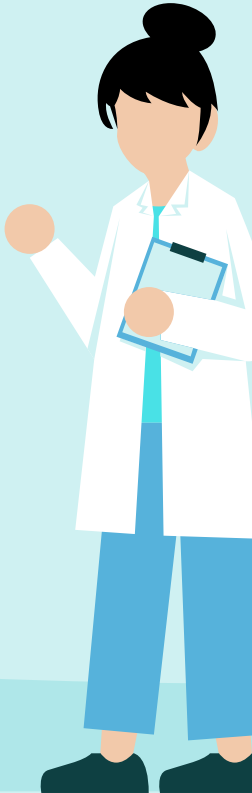
in manure-treated soil[5]

21 months

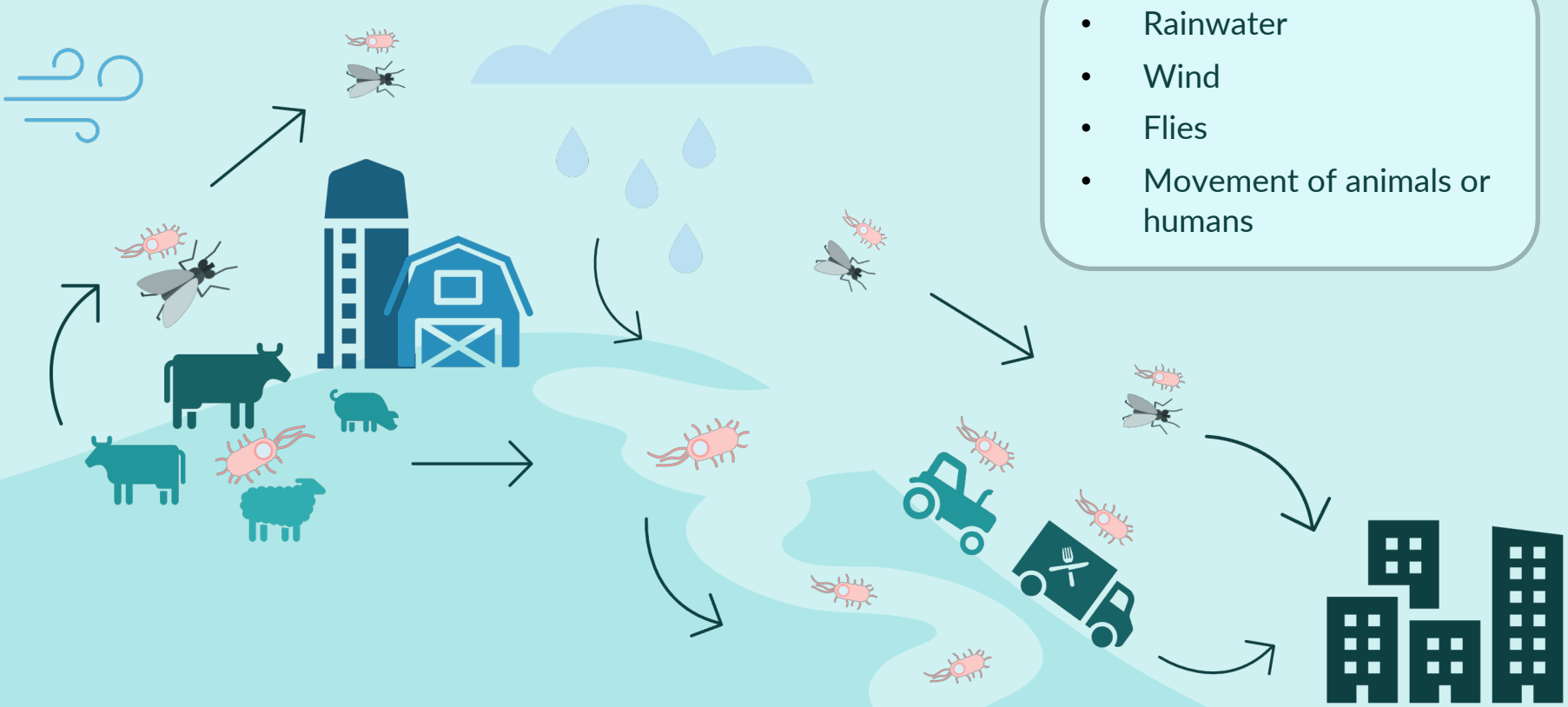
in raw, uncomposted manure[5]

10 months

in nutrient-deficient water sources[6]



SPREAD FROM AGRICULTURE[3]

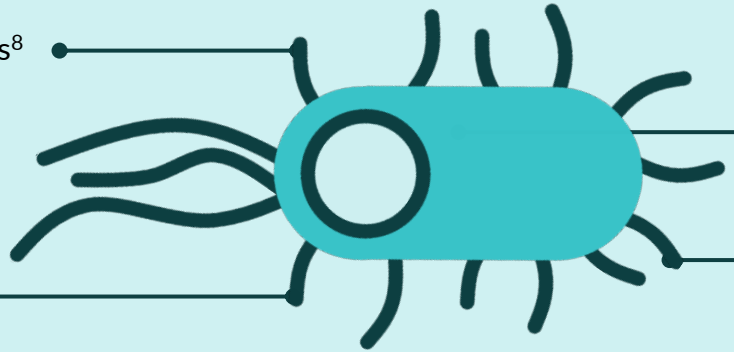


- Rainwater
- Wind
- Flies
- Movement of animals or humans

CHARACTERISTICS FOR ENVIRONMENTAL PERSISTENCE

↑ **enzymes** to catabolize nutrients[8]

↑ **toxins** and **antibiotics** to kill competitors[9,10]



Alter **membrane lipid composition** to adapt to temperature changes[5]

Exopolysaccharide for heat and acid tolerance[5]

Metabolic flexibility

In nutrient-rich conditions, able to utilize various carbon sources and store for later use[6]

Starvation-survival state

In nutrient-poor conditions, can reduce cell size for better nutrient uptake[7]

Survival state

Enhanced resistance to stressors and prolonged viability in absence of nutrients[11]

HOST LOCALIZATION

01 Ingestion

02 Attachment to microvilli in intestinal epithelium

03 Formation of attaching and effacing (AE) lesions[3,12]

04 Shedding and/or release of Shiga toxin[12]

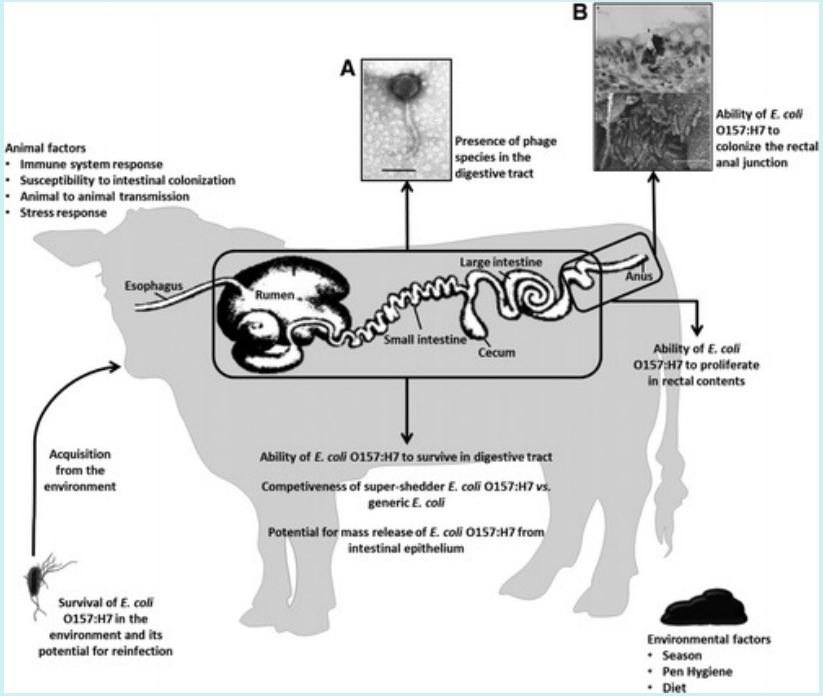


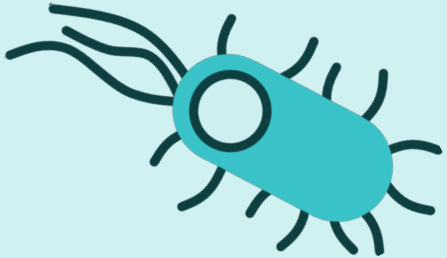
Figure 1. *E. coli* O157:H7 within the digestive tract of cattle, acquired from the environment. Reprinted from Munns et al. (1)

SURVIVAL IN THE STOMACH

E. coli O157:H7 must first survive this highly acidic environment before it can reach the intestine.

Barriers:

Low pH (2.0)
Stomach acid



Acid Resistance (AR) system 1

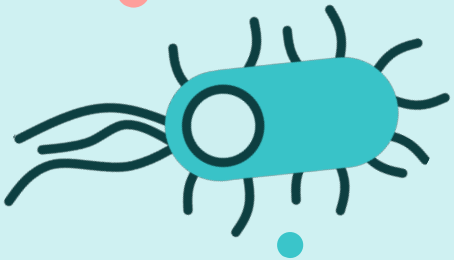
- rpoS sigma factor[13]
  - Regulates biofilm formation (adherence)
  - Regulates transition of motile cells during environmental stress[13]
- F1F0 ATPase[13]

Other acid-resistance mechanisms:

- Decarboxylase[13]
- Antiporter systems[13]
  - Export protons out of cells to increase intracellular pH

SURVIVAL IN THE INTESTINES

Colonization and utilization of complex nutrient sources



Upregulation of catabolic enzymes[14]

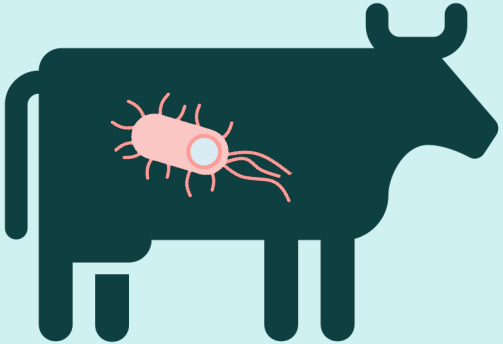
- Catabolism of **intestinal mucus-derived sugars**:
  - N-acetylglucosamine
  - Sialic acid
  - Glucosamine
  - Gluconate
  - Arabinose
  - Fucose
- Use of **multiple limiting sugars** for growth[15]
- Use of simple sugars derived from breakdown by **other commensal organisms**[16]

THE BUTCHERING PROCESS

Whole cuts

E. coli O157:H7 can be found on the **surface**

Cooking until the surface is no longer raw is enough to eliminate the pathogen



Ground/tenderized

E. coli O157:H7 can be transferred to the **inside** of the meat

Must be cooked thoroughly, until inside is no longer raw

More likely to cause illness[17]

In Ronnie's case:

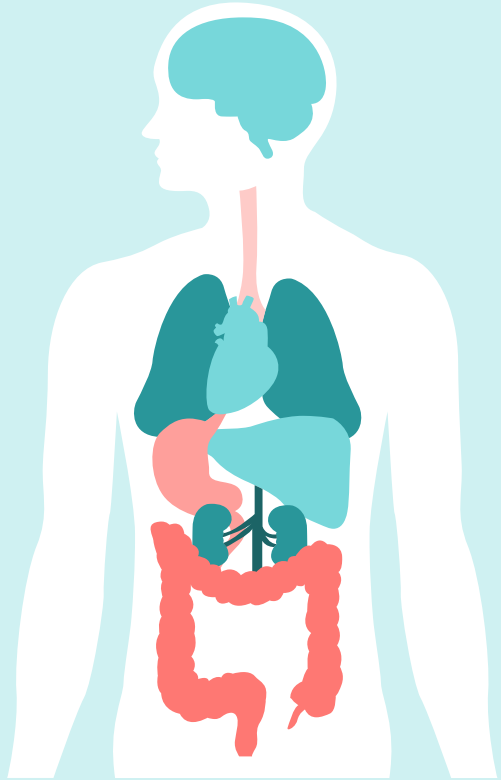
- Undercooked burger meat
- Improper handling or hand washing

02

ENTRY

How does the bacteria enter into the human host and take up residence? What are the molecular, cellular, and/or physiological factors at play?

PATH THROUGH DIGESTIVE SYSTEM



01

Ingestion

Pathogen is ingested from contaminated food source

02

Stomach

Pathogen resists acidic stomach environment

03

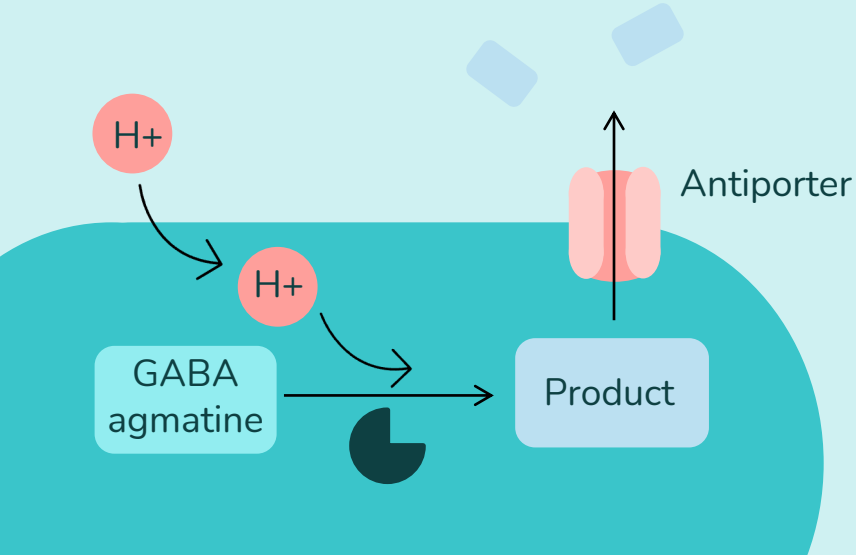
Intestines

Pathogen resists acid and bile to form AE lesions and establish infection

STOMACH ACID RESISTANCE

Alternative sigma factor

- Encoded by *rpoS*[18]
- See previous section for details



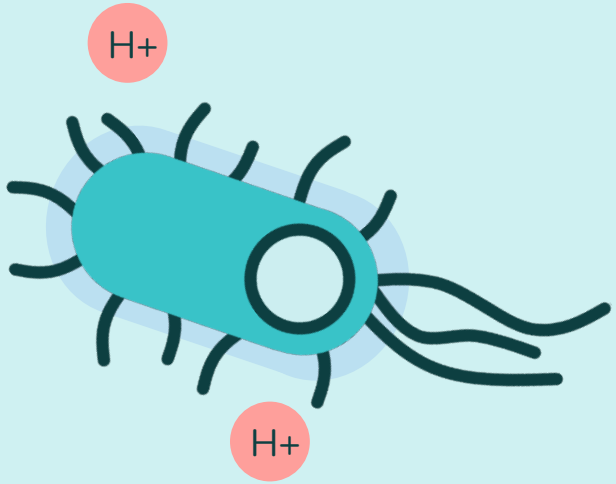
Decarboxylase systems

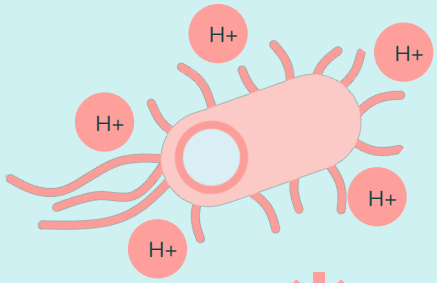
- Consumes protons during decarboxylation reaction[18]
- Products transported out of cell by antiporter systems[18]

1. Inducible glutamate decarboxylase
   - Produces γ-aminobutyric acid (GABA)[18]
2. Inducible arginine decarboxylase
   - Produces agmatine[18]

COLANIC ACID SECRETION

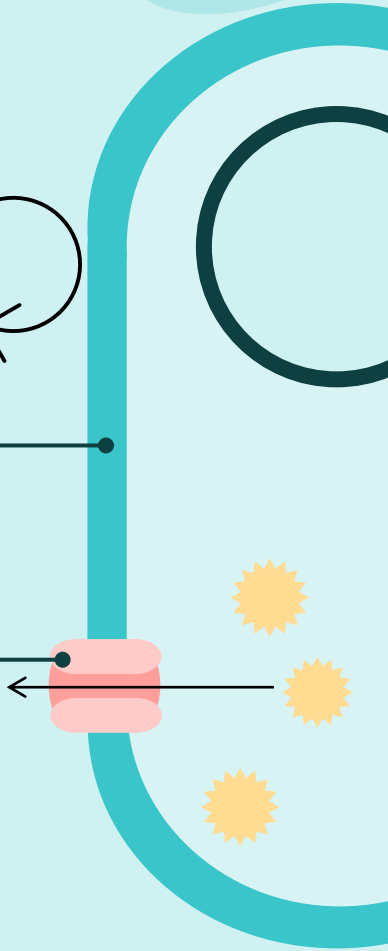
- **Colanic acid** (CA) is a type of exopolysaccharide secreted by *E. coli* (one of many)[19]
- **Negatively charged**
- **Neutralizes protons** at cell surface, preventing accumulation[19]





BILE RESISTANCE

- Bile secreted by **gallbladder** → duodenum
- Breaks down cell membrane of pathogens
- Causes **oxidative stress** and **DNA/protein damage**[20]



Membrane structure adaptations

Reduced permeability to prevent bile influx[20]

Efflux pumps

Remove intracellular bile

Upregulation of OmpF when bile sensed[20]

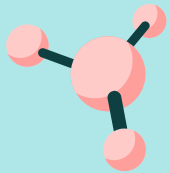
Bile

OTHER ADAPTATIONS

Aerobic respiration

Availability of **oxygen changes** throughout GI tract

Allows *E. coli* to **out-compete strictly anaerobic commensals**[20]



Iron scavenging

Iron is **required for growth**

Exposure to **bile** upregulates expression of genes involved in **iron acquisition**[20]

FORMATION OF AE LESIONS

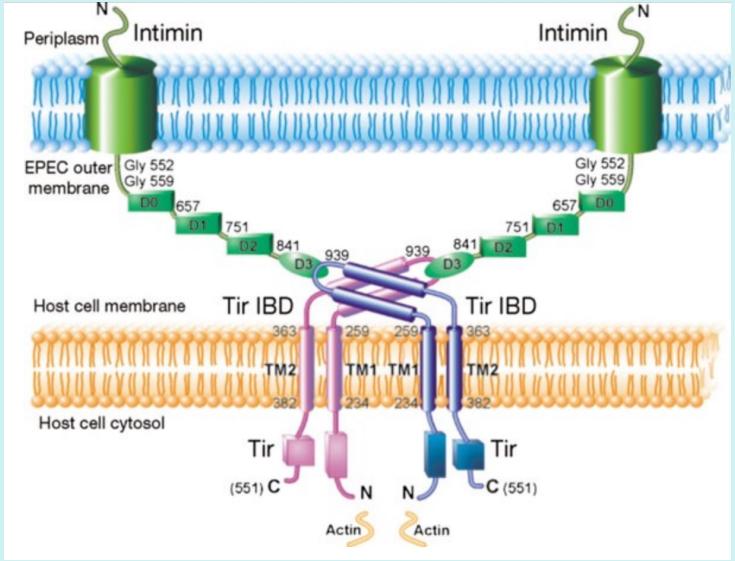


Figure 2. The bacterium/host-cell interface via proteins intimin and Tir. Reprinted from (2).

Controlled by **locus of enterocyte effacement (LEE)** pathogenicity island[21]

<u>41 genes organized into 3 regions:</u>

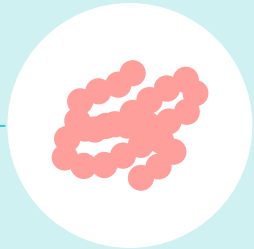
- **Type 3 secretion system (T3SS)**
  - Exports effector molecules
- **Intimin (adhesin) and Tir**[22]
  - Tir = translocated adhesin receptor
  - Inserted into host cell membrane, affects host cytoskeleton and signaling
- **Secreted proteins (Esp)**[23]

03

MULTIPLICATION AND SPREAD

Does the organism remain extracellular or do they enter into cells? Do the bacteria remain at the entry site, or do they spread beyond the initial site?

TIMELINE OF SPREAD[24]

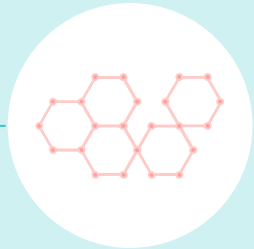


SMALL INTESTINE

Establishment of *E. coli* O157:H7 colony on intestinal surface

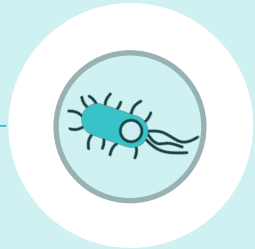
LARGE INTESTINE

Colonization spreads along large intestine



PRODUCTION OF SHIGA TOXIN

Shiga toxin secreted by T3SS, absorbed through intestinal epithelium → circulatory system



INTRACELLULAR INVASION

Invasion of intestinal epithelial cells, disrupting host cell signaling[25]

THE ROLES OF SHIGA TOXIN

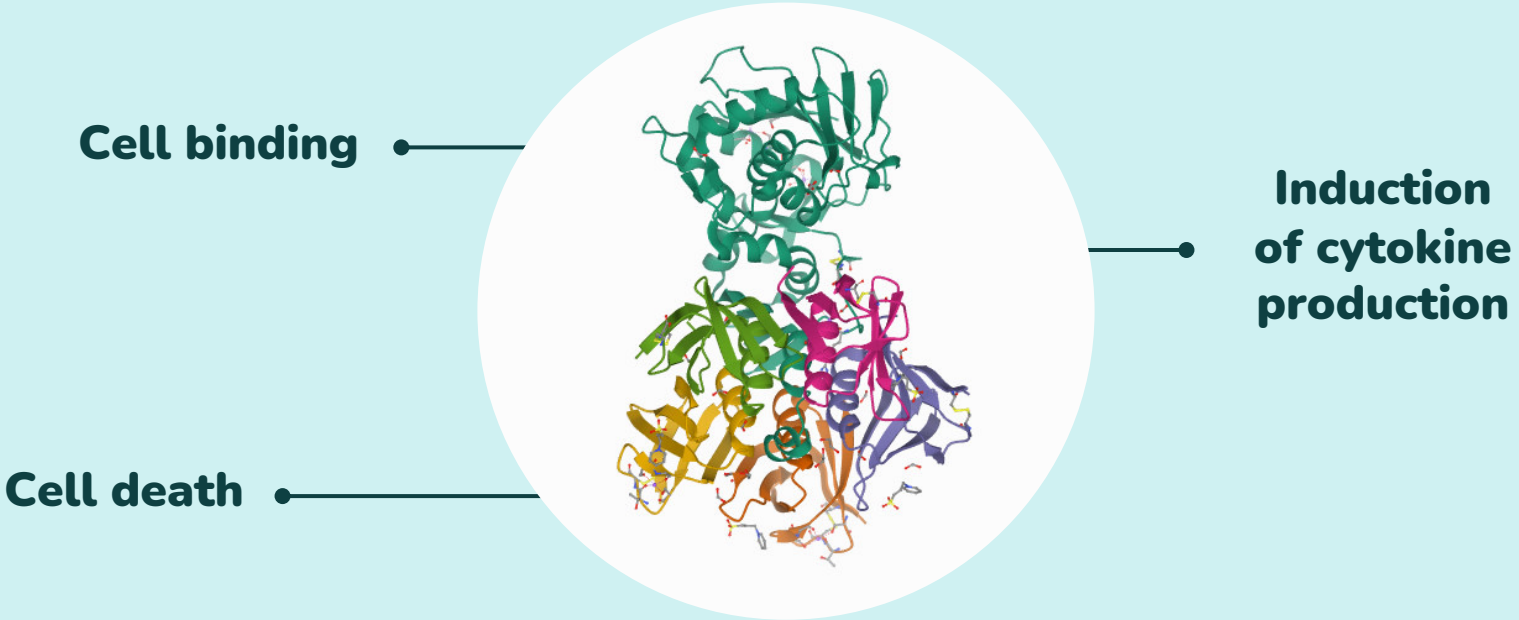
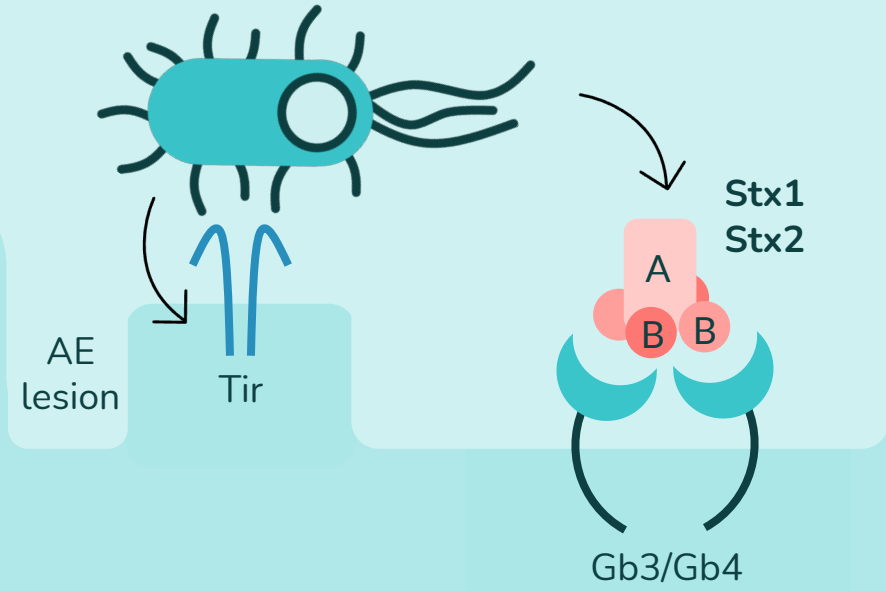


Figure 3. Crystal structure of Shiga toxin type 2. Reprinted from PDB (3).

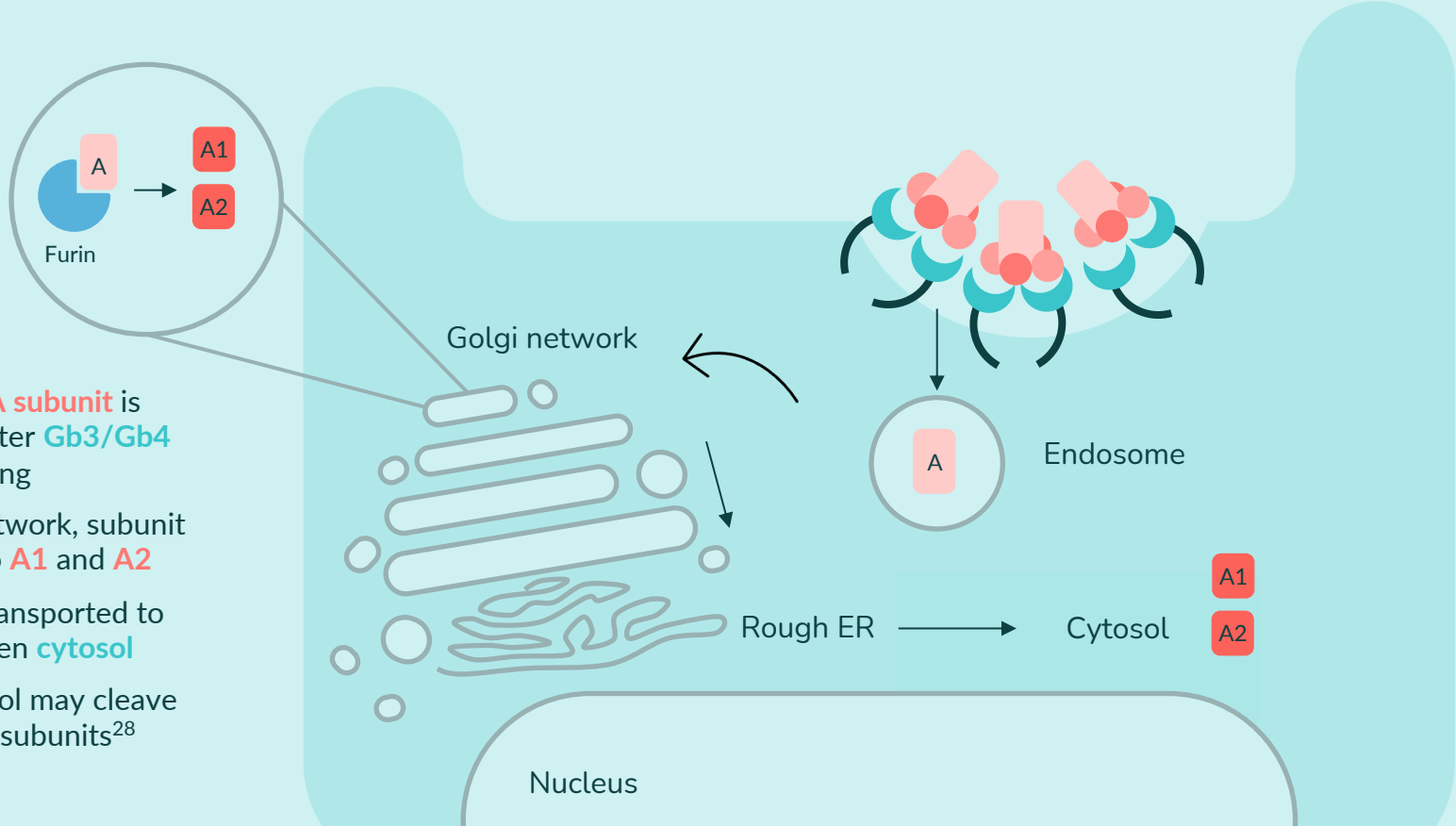
SHIGA TOXIN: CELL BINDING

The pentameric B subunits found on Stx1 and Stx2 bind the glycolipid receptors Gb3 and Gb4 (globotriaosylceramide 3 and 4)[26]

Gb3 and Gb4 are found on enterocytes[25] and across a wide variety of cell types[26,27]



SHIGA TOXIN: UPTAKE AND PROCESSING[25]



Monomeric A subunit is endocytosed after **Gb3/Gb4** binding

In *trans* Golgi network, subunit is cleaved into **A1** and **A2**

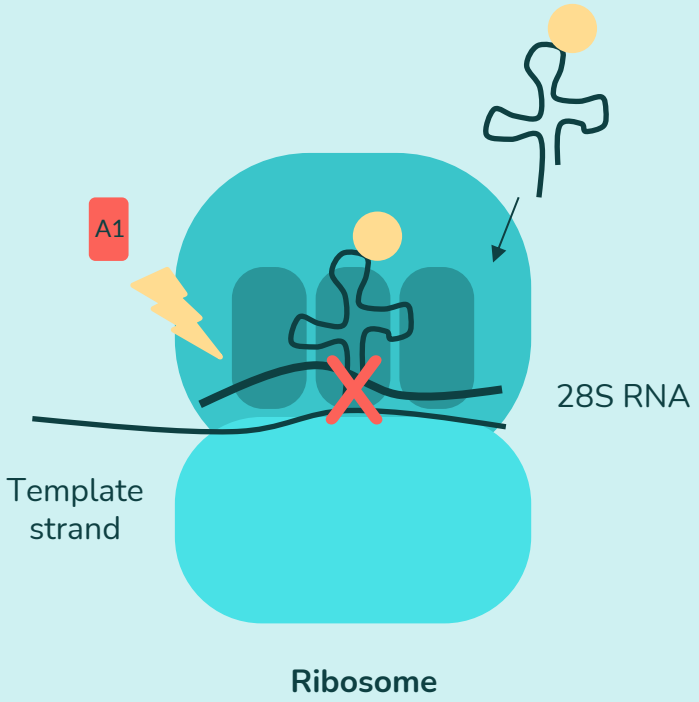
Subunits are transported to **rough ER**, then **cytosol**

Caplain in cytosol may cleave uncleaved A subunits[28]

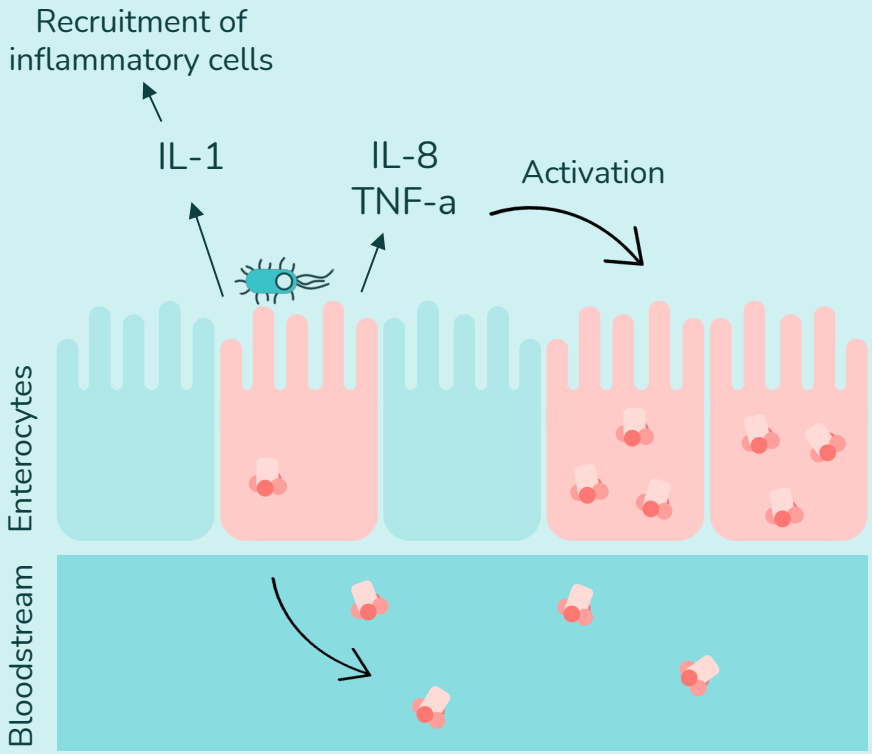
SHIGA TOXIN: CELL DEATH

A1 subunit

- Glycosidase
- Hydrolyzes an adenine-ribose bond in ribosomal 28S RNA[29]
- Cleavage renders 28S RNA unable to bind to aminoacyl-tRNA
- Ultimate inhibition of protein synthesis[29]



SHIGA TOXIN: CHEMOKINE SYNTHESIS



- Affects **intracellular signaling** of intestinal epithelial cells
- Production of **IL-8, IL-1, TNF-a**[27,30]
- TNF-a and IL-1 → **activation of endothelium**
- Activation = **increased susceptibility** to Stx[27]
    - Increased cell death
- Stx enters **bloodstream** as endothelial layer deteriorates
- Endothelial cell death → activation and aggregation of platelets, **clot formation**
- **Apoptosis** of supporting cells via inflammatory mediators[31]

THE SPREAD OF SHIGA TOXIN

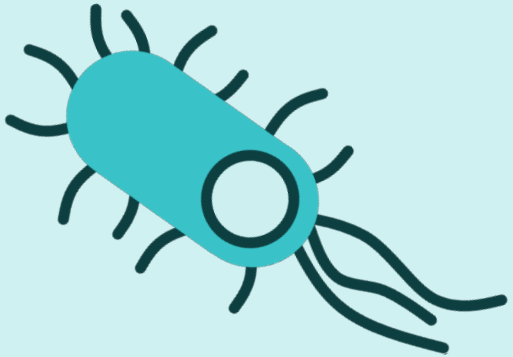
Propagation via circulation

- Shiga toxin able to **move across intestinal epithelium** without affecting cell function[32]
  - Entry into circulatory system
  - Travel to **kidneys** (sometimes brain)[32]
  - Stx **damages RBCs** and **blood vessels**[24]

Secondary uptake pathway

- Shiga toxin → **CXC chemokine production** in endothelium and mucosal epithelium cells[33]
- Induces **PMN infiltration**
  - PMNs thought to be involved in **spread to secondary sites**[33]
- Promotes **epithelial cell injury** and **increased Stx absorption**

Enterohemolysin

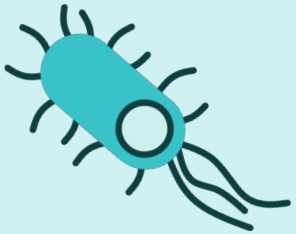


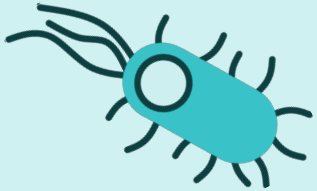
- Encoded on **pO157 plasmid**, in the hly operon[34]
- Allows for pathogen to **utilize blood** released into intestine as an **iron source**[35]

EspP

- **Protease**
- Cleaves **pepsin A** and **human coagulation factor V**
  - Contributes to **intestinal hemorrhaging**[36]
- Cleaves **complement system components**
  - **Immune evasion**[36]

SECONDARY SITES OF INFECTION





SUBMUCOSA

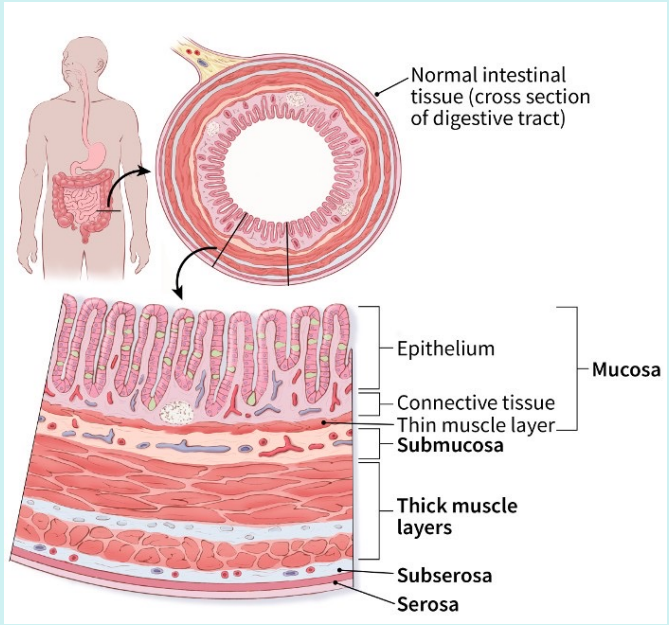


Figure 4. Layers of the small intestine. Reprinted from American Cancer Society (4).

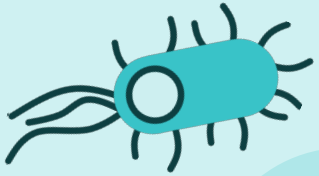
- Colonic vascular damage → allows LPS, inflammatory mediators into circulation[37]
- **Transcytosis** of *E. coli* O157:H7 through **microfold cells** → submucosa[38]
- Stx **disrupts tight junctions** between IECs
- **Actin network destabilization**/membrane ruffling caused by T3SS effectors[38]
  - **IpaC, IpaA, VirA, IpgD**
- **Evasion of innate immune responses** via various effectors[38]
  - **IpaB, PiaC, IpaD, IpaH**
  - **MAD2L2**
  - **OspE, OspF, OspG, OspB**

KIDNEYS

- Though Stx travels to lungs before kidneys, damage is not as severe
  - Kidney cells express Gb3/Gb4, are Stx-sensitive[39]
  - High blood flow/filtration rate increases chance of Stx interaction
- Damage to renal filtration barrier → Stx reaches Stx-sensitive cells of nephron
- Stx decreases VEGF production
  - VEGF required to support glomerular endothelium[39]

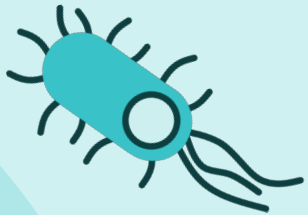
HEMOLYTIC UREMIC SYNDROME[12]

- Acute renal failure
- Perturbation of:
  - Fluid levels
  - Electrolyte imbalance
- Hemolysis
- Disruption of clotting cascade
- Risk of stroke



URINARY TRACT

- Infection can cause **cystitis** or **pyelonephritis** in kidneys (if untreated)[38]
  - Adhesion to uroepithelium via **fimbriae**
  - Fimbrial adhesin H (**FimH**) binds:
    - **Glycosylated uroplakin** Ia in the bladder[38]
    - **Alpha-3** and **beta-1 integrins** at site of invasion[38]



Secondary outcomes of UTIs[40]:

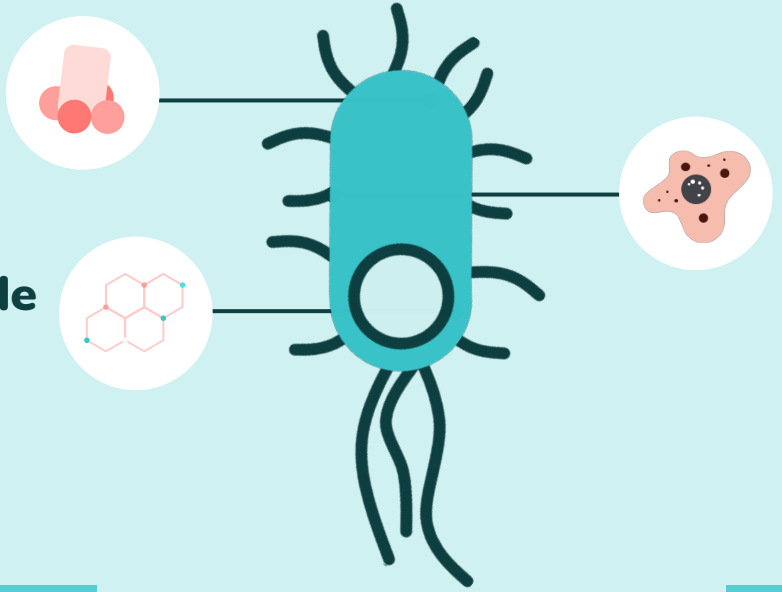
- Prostatitis (men)
- Pelvic inflammatory disease (women)

04

BACTERIAL DAMAGE

Do the bacteria cause any direct damage to the host, and, if so, what is the nature of the damage? Can it be linked to any of the signs and symptoms?

CAUSES OF BACTERIAL DAMAGE



Shiga toxin (Stx)

Lipopolysaccharide (LPS)

Stimulation of inflammatory response

Direct damage

Indirect damage

HEMORRHAGIC DIARRHEA

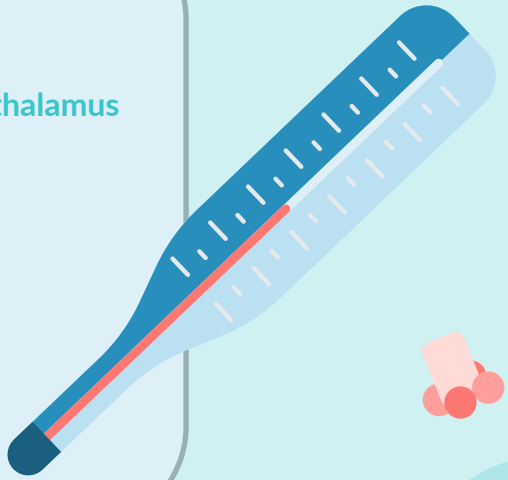
- **Shiga toxins** cause **direct damage** to host cells
  - Interruption of protein synthesis causes **apoptosis** via p38 mitogen-activated protein kinase (**p38 MAPK**) activation and other pathways[41]
- Cell death → **cell sloughing**
  - Cell sloughing also plays a role in bacterial propagation between hosts[12]
  - **Stool containing *E. coli* O157:H7** can contaminate food sources and other hosts

FEVER

- Caused by **inflammatory response** to *E. coli* O157:H7
- **Induction of cytokine** production in IECs → IL-8, IL-1, TNF-a

Mechanism for elevation of body temperature[42]

1. Inflammatory cytokines enter **anterior hypothalamus**
2. Stimulate production of **prostaglandin E2**
3. E2 diffuses into preoptic area
4. E2 **upturns thermostatic set point**
5. Efferent nerve signaling
6. Initiation of **heat conservation**
7. **Fever**

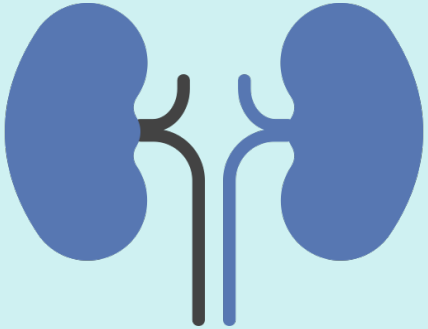


ABDOMINAL TENDERNESS

- May be caused by **inflammatory response** induced by Stx[12]
  - **Leukocyte** and **platelet aggregation**
  - Apoptosis (independent of Stx-mediated)
  - Microthrombi formation
  - **Hemolysis**
  - **Renal dysfunction**

Multiple organ systems can be affected by inflammatory response to Stx and other *E. coli* O157 features

HEMOLYTIC UREMIC SYNDROME



Classical Triad[43]

01 **Microangiopathic hemolytic anemia**

Fragmented RBCs on blood film

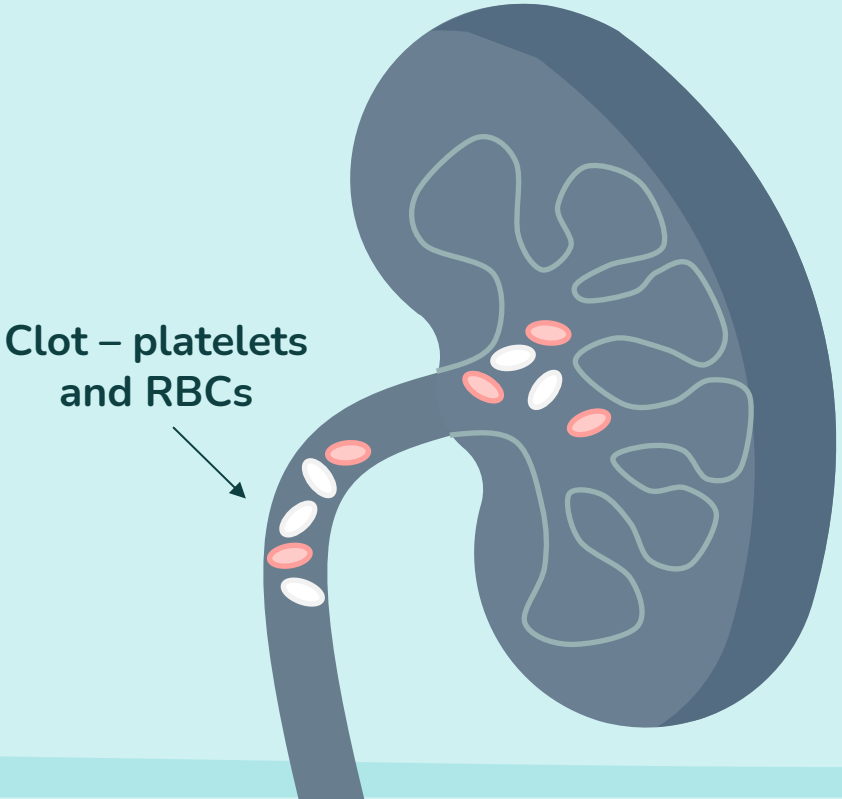
02 **Thrombocytopenia**

Low blood platelet count

03 **Renal failure**

HEMOLYTIC UREMIC SYNDROME

- Affects **kidneys**
- Affects blood clotting capabilities of infected individuals[44]
  - **Destruction of RBCs** and **platelets**, blood vessels
- **Glomeruli become clogged** with platelets and damaged RBCs[44]
- Filtration problems within renal cells
  - **Buildup of waste products**
- Prolonged HUS → **kidney failure**



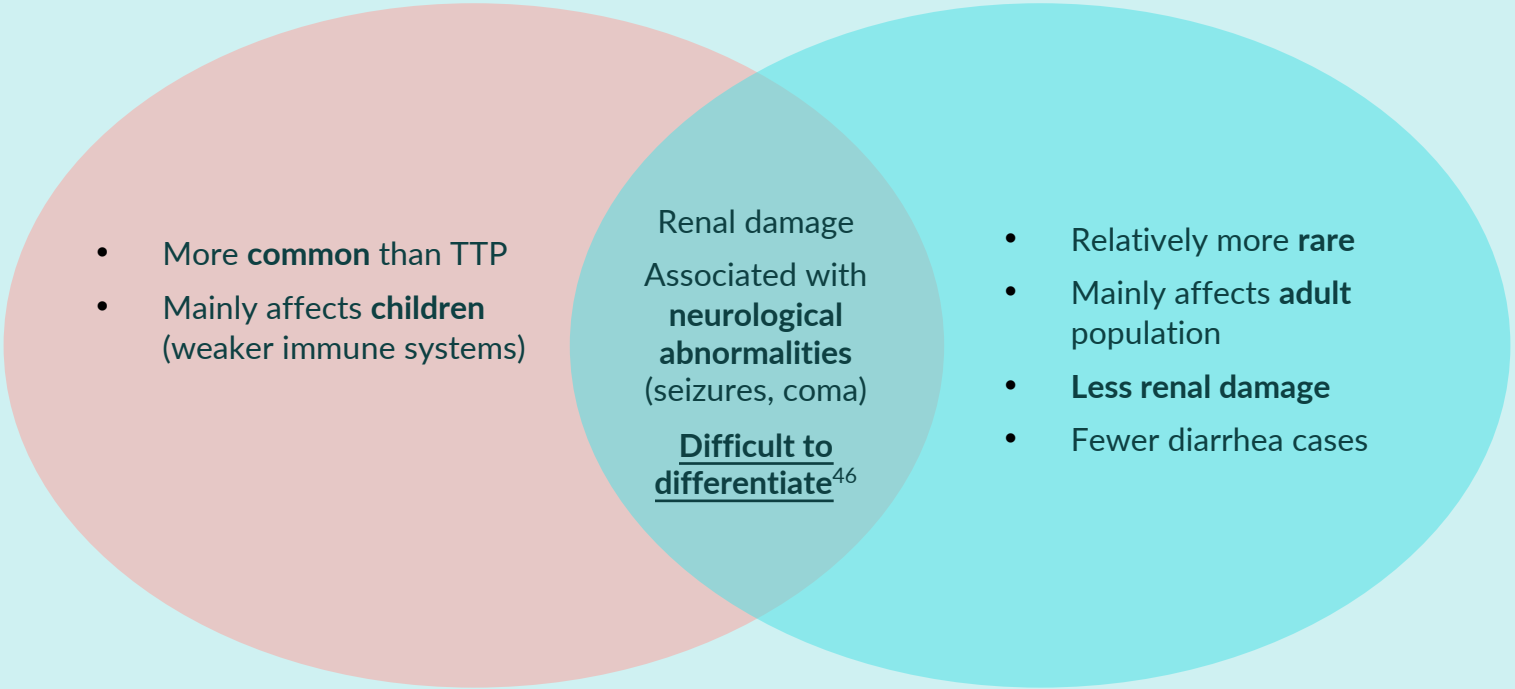
SYMPTOMS AND TREATMENT

Severe symptoms[45]

- Edema
- Albuminuria
- Decreased urination
- Bloody urine

Treatment[44]

- Hospitalization
- Dialysis (extreme cases)
- Blood transfusions
- Special diet


HEMOLYTIC UREMIC SYNDROME (HUS)
THROMBOTIC THROMBOCYTOPENIA PURPURA (TTP)[43]
More common than TTP
Mainly affects children (weaker immune systems)
Renal damage
Associated with neurological abnormalities (seizures, coma)
Difficult to differentiate[46]
Relatively more rare
Mainly affects adult population
Less renal damage
Fewer diarrhea cases

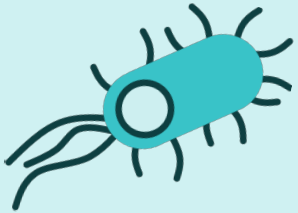
LIPOPOLYSACCHARIDE

Direct damage

- Damage to epithelial cells
- Induce production of **TNF-a**
- Activation of **platelets**
- Induce blood **coagulation cascade**

Indirect damage

- Increase production of **inflammatory cytokines**
  - **IL-8** → activation of **WBCs**
  - WBCs can damage tissues via **elastase**[27]



TREATMENT

- Rest and hydration recommended
- Antibiotic treatment not recommended
  - Can trigger **SOS-response** and **initiate lytic cycle of bacteriophages**[48]
  - Bacterial **lysis** → release large amounts of toxins
  - Reduces bacterial motility → can cause prolonged exposure and development of HUS (17-fold increase)[49]

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