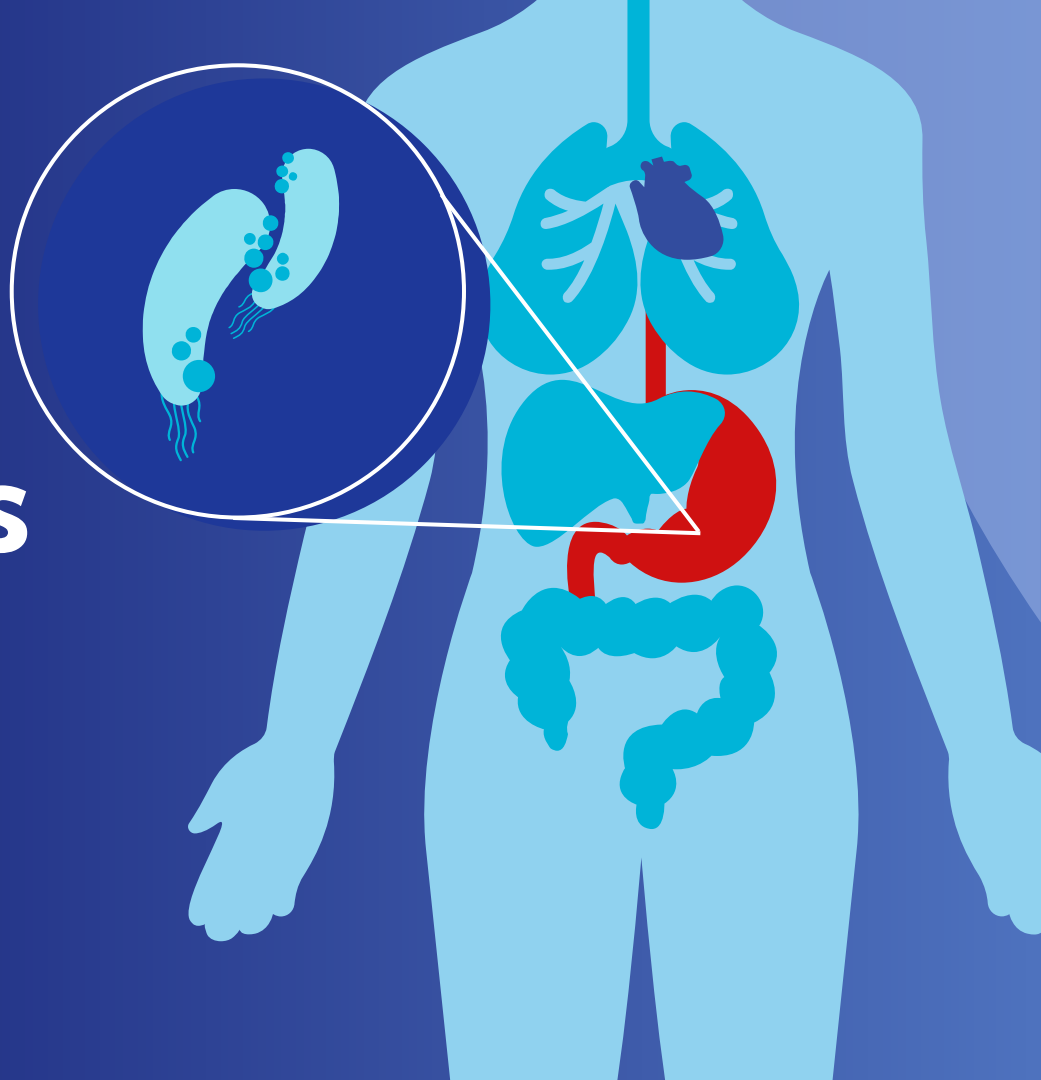
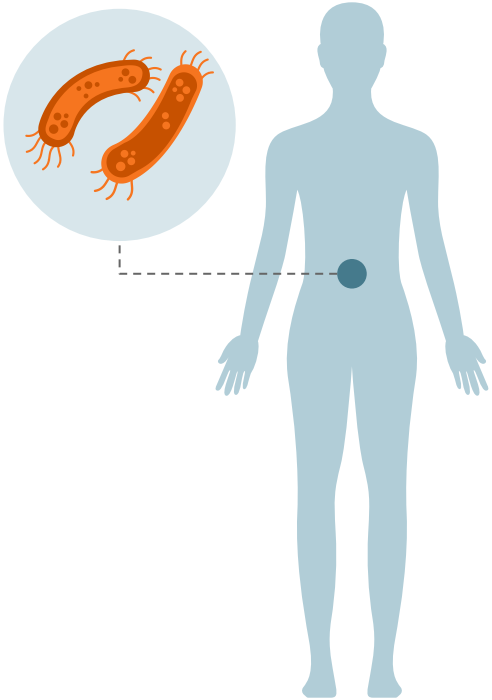
Bacterial Pathogenesis Summary

Yisa Yu





Patient Overview

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 blood work** (to be performed at the local laboratory). The Microbiology Laboratory report comes back **positive for E.coli O157:H7.**

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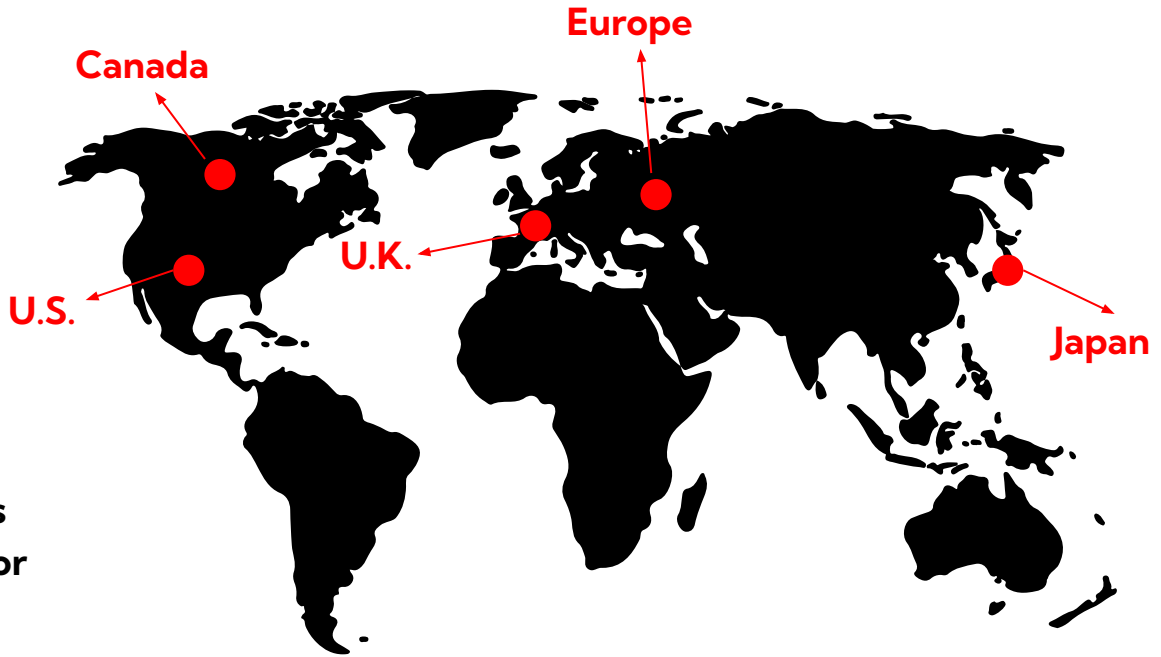
01
ENCOUNTER

Geographical Locations

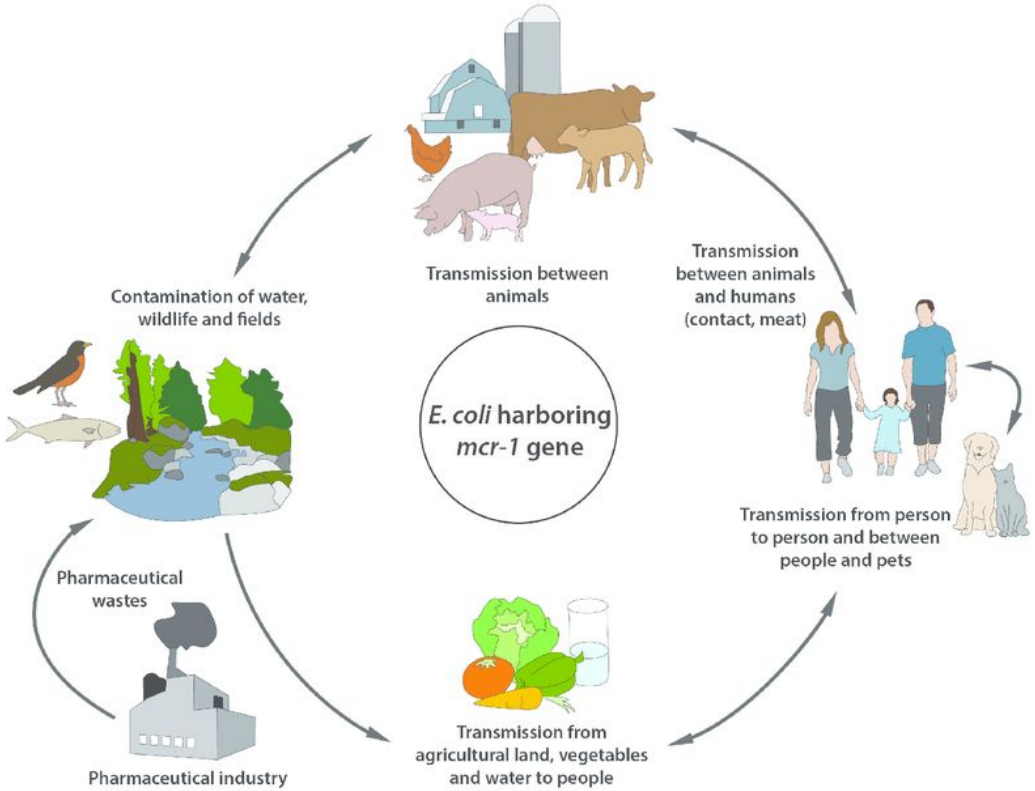
Within Canada and the U.S.

- More common in western provinces of Canada
- More common in northern states in the U.S.
    - Commonly found in cattles (asymptomatic carriers)
    - Fecal shedding intermittent and seasonal
- can result in a large number of cases due to outbreaks from waterborne or food origin within a community
- sheep, pigs, horses, dogs, deer, and feces of birds may also carry *E. coli* O157:H7



Environmental Locations

1. Farms
2. Ponds
3. Dams
4. Wells
5. Barns
6. Water and water troughs
7. Farm equipment
8. Ground
9. Pasture



ENVIRONMENTAL LOCATIONS

WATER

- Large presence in water due to low temperatures
- Water trough sediments can be contaminated with cattle feces

ANIMAL MOVEMENT

- Animals may come into contact with E. Coli via drinking contaminated water

SOIL

- Survive up to a year in manure-treated soil
- Up to 21 months in raw manure (not composted)

NATURAL EVENTS

- Rainwater, wind can contribute to the spreading and transmission of E. Coli

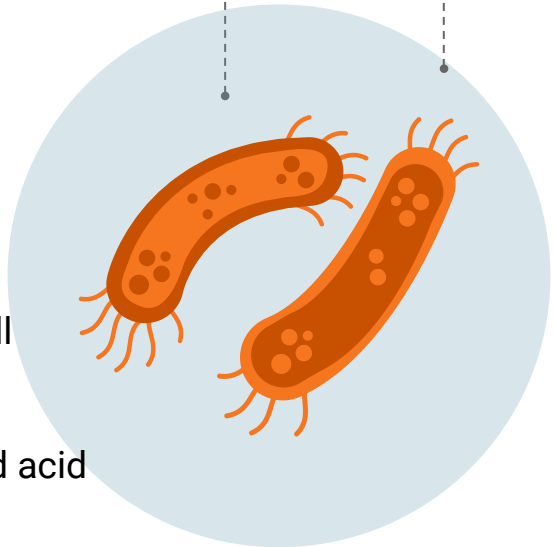
FLIES

- May encounter contaminated animals
- Transmitted onto food
- Potential effective vectors

PERSISTENCE IN ENVIRONMENT

NUTRIENT-DEFICIENT CONDITIONS

- Can survive up to 10 months in aquatic environments
- Can reduce cell size to allow more efficient nutrient uptake (aka starvation-survival state)
- Activate catabolic enzymes
- Increase production of toxins to kill competitors
- Exopolysaccharide (EPS): heat and acid tolerance
- Lipid membranes can be altered in response to heat stress

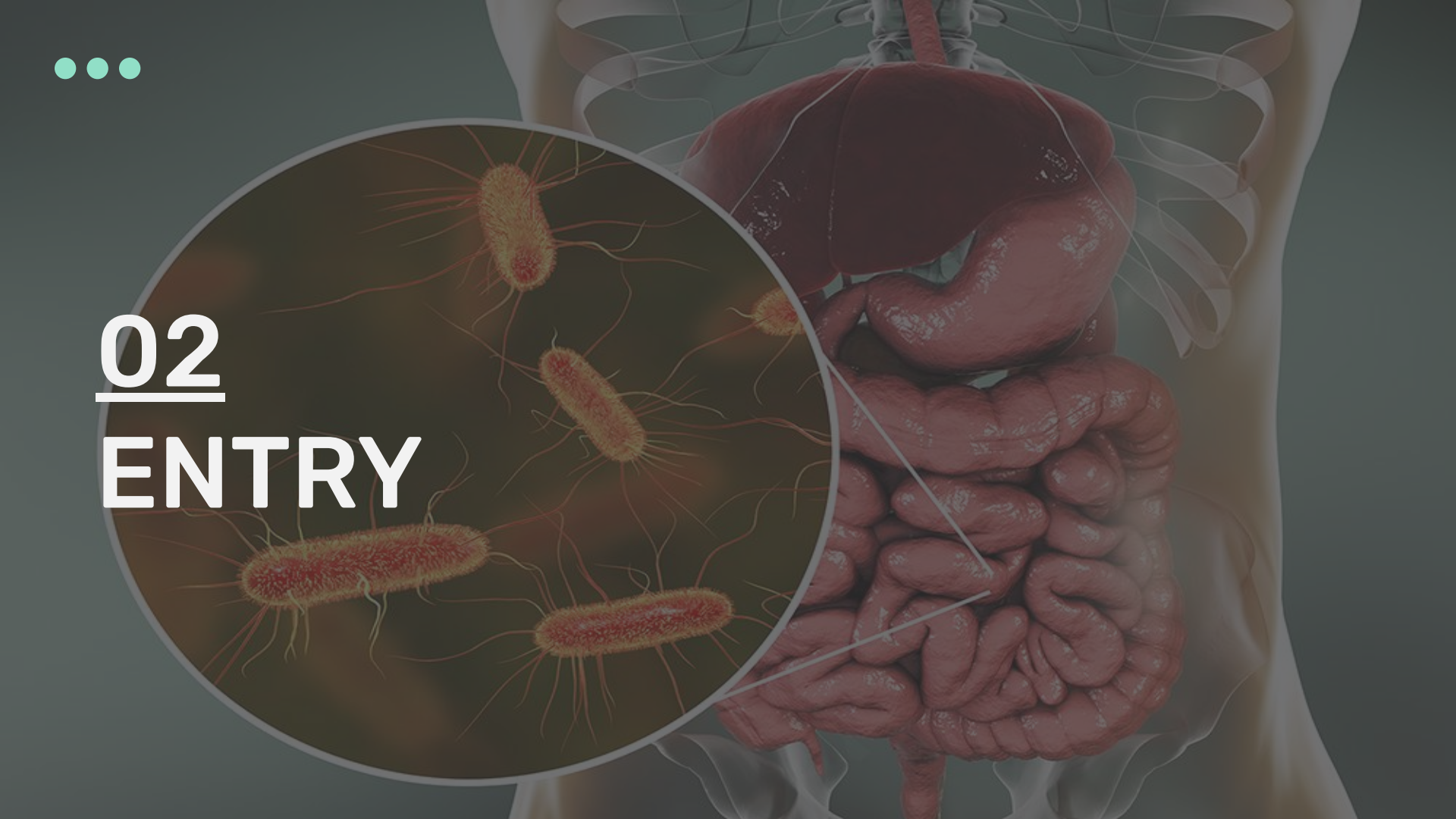


NUTRIENT-SUFFICIENT CONDITIONS

- Accumulate reserve carbon sources that are stored for use in nutrient-poor environment

HOST LOCATIONS

01	INTESTINAL CELLULAR WALLS	- Attaches onto the microvilli of intestinal epithelial cells via attaching and effacing (AE) lesions
02	LOW pH ENVIRONMENT IN STOMACH	- Expresses an acid resistance (AR) system, utilizing a rpoS sigma factor and F1F0 ATPase - rpoS for better adherence to surfaces and transition of motile cells during environmental stress - Other AR mechanisms: decarboxylase and antiporter systems
03	HOST INTESTINE	- upregulates enzymes involved in the catabolism of N-acetylglucosamine, sialic acid, glucosamine, gluconate, arabinose and fucose - uses multiple limiting sugars for growth in the intestine and grows using simple sugars released upon breakdown of complex polysaccharides
04	BUTCHERING PROCESS	- Whole cuts of meat only have *E. coli o*n the surface, so easier to kill by cooking - grounded meat: *E. coli* can be transferred to the inside of the meat - Ronnie may have come into contact through the contaminated, undercooked, or raw burger meat - Can be contaminated via improper handling or hand washing



02
ENTRY

BACTERIAL ENTRY

CONSUMING UNCOOKED FOOD

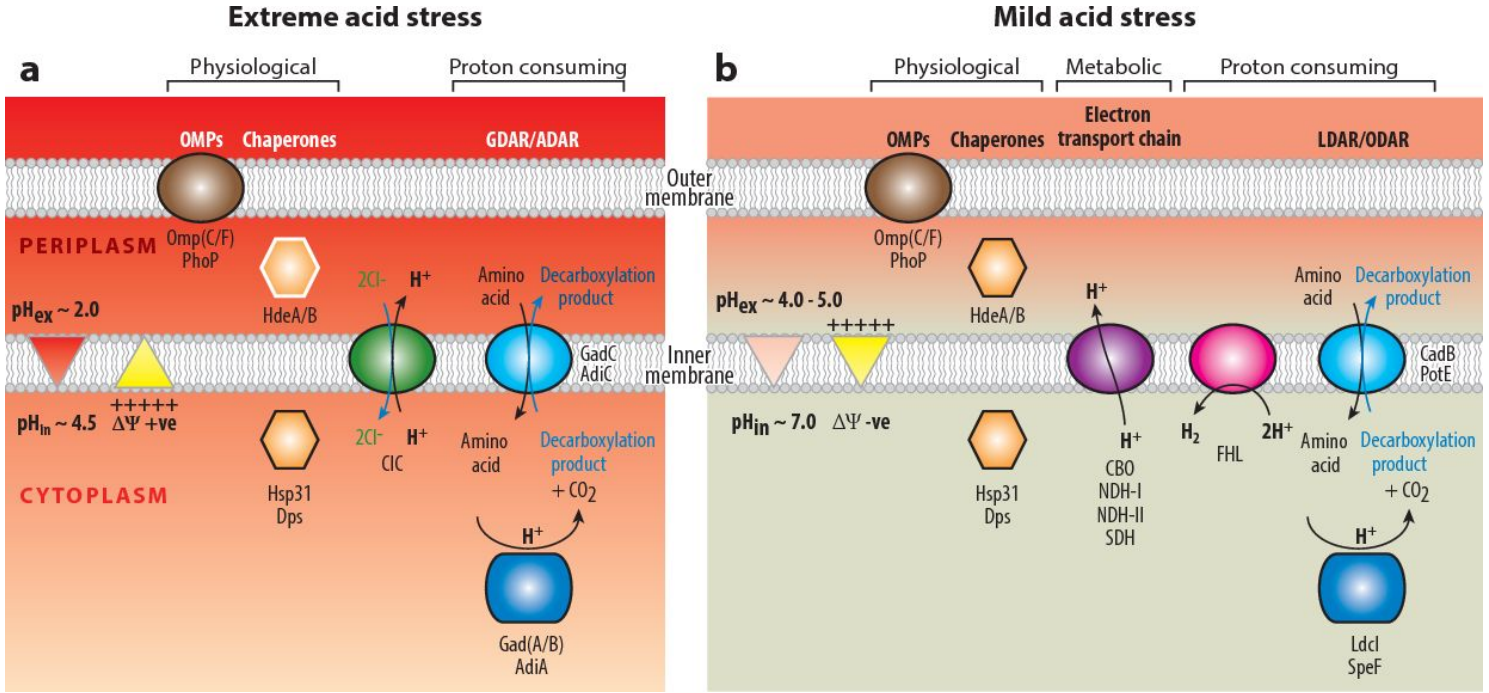
FOOD TRAVELS DOWN DIGESTIVE TRACT

ENTER INTESTINES

INTESTINAL ADHESION

IN THE STOMACH

- Acid resistance (AR) : allows the organism to survive gastric acidity and volatile fatty acids
- colonize and establish a commensal relationship with mammalian hosts
- Three systems that protect the bacterial cells against pH 2 to 2.5



3 SYSTEM THAT PROTECT E.COLI AGAINST LOW pH

- Dependent on the alternative sigma factor, encoded by the rpoS gene

rpoS Sigma Factor

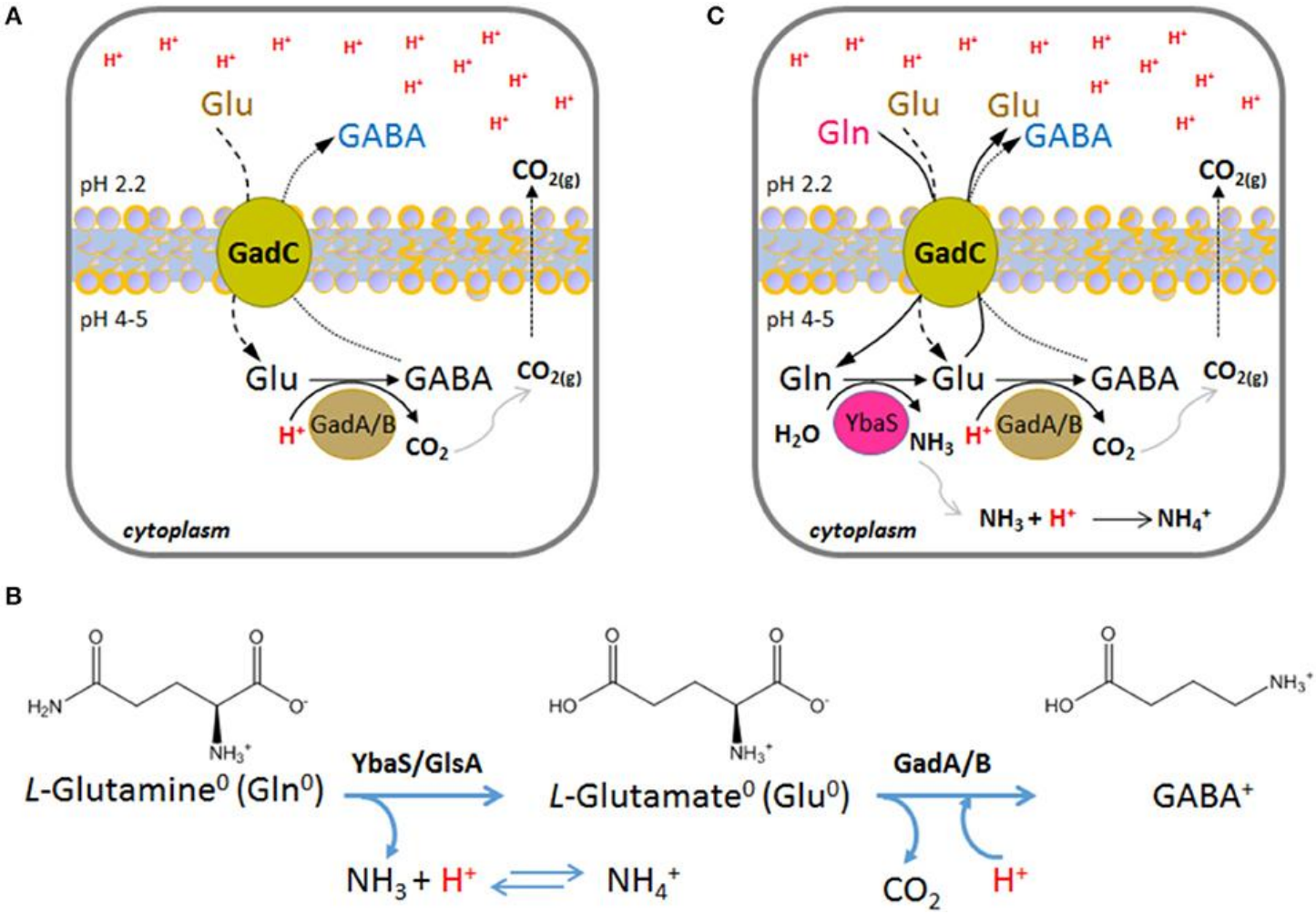
Glutamate Dependent Acid Resistance

- Requires glutamic acid
- Consume protons
- End products, γ-aminobutyric acid (GABA, formed from glutamate decarboxylase [GAD]) transported out of the cell via GadC in exchange for the new substrate

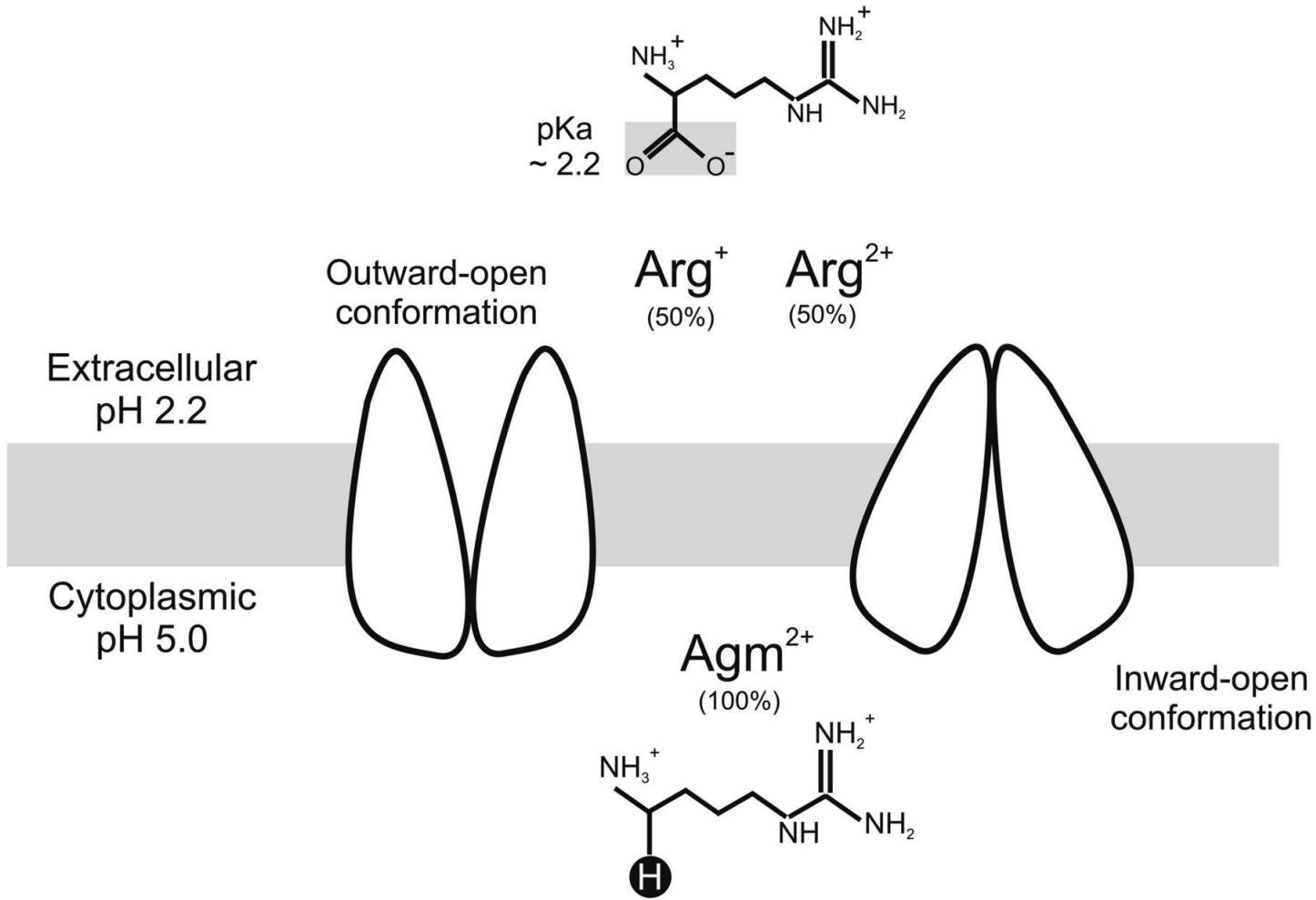
- Requires arginine
- End products, agmatine (formed from arginine decarboxylase), transported out of the cell via unknown antiporter in exchange for the new substrate

Arginine Dependent Acid Resistance

Glutamate Dependent Acid Resistance



Arginine Dependent Acid Resistance



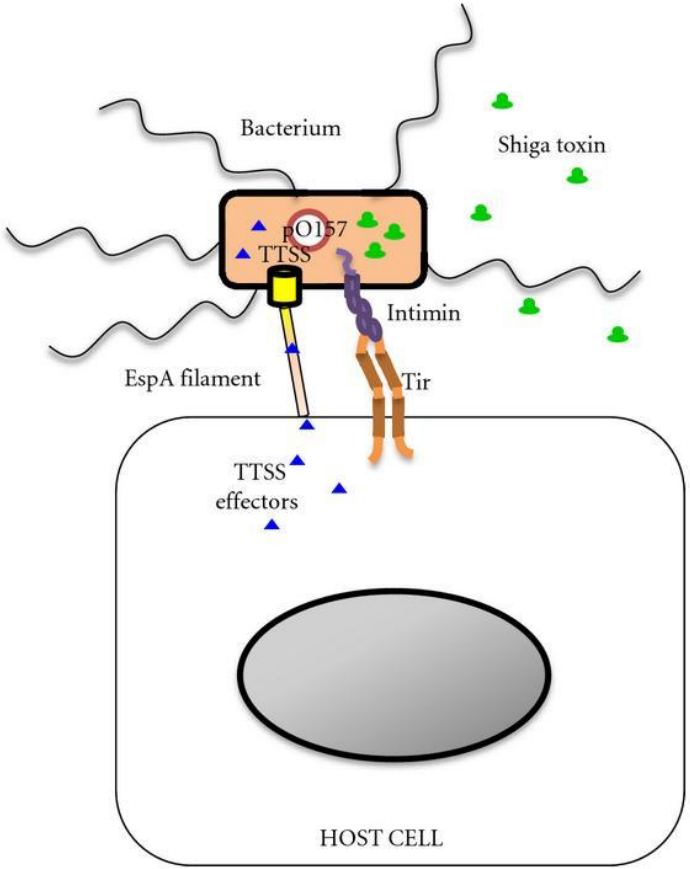
COLANIC ACID SECRETION

- E. coli secretes a variety of EPS, including colanic acid
- E. coli O157:H7 cells are inactivated during acidic conditions due to proton accumulation
- CA serve as a buffer by neutralizing protons at the cell surface
- prevents the positively charged protons from accumulating and penetrating cells
- Without CA, the protons will accumulate and enter the bacteria, causing an imbalance of intracellular charge and ultimately causing cell death

IN THE INTESTINE

GENES	SIGNIFICANCE
arcA arcB arcR micF marB marR	• Bile can cause **oxidative stress** and result in the d**amage of DNA and proteins**, as well as **breaking down the cell membrane** of bacterial cells • Genes regulate **ompF expression and bile efflux** to increase two-fold in E. coli O157:H7 cells • Aerobic respiration allows the bacteria to continue providing energy so that it can successfully grow and colonize within the host • The bacteria increase mRNA for **17 genes** which play a role in the acquisition of **iron** once the bacteria are exposed to bile

IN THE INTESTINE

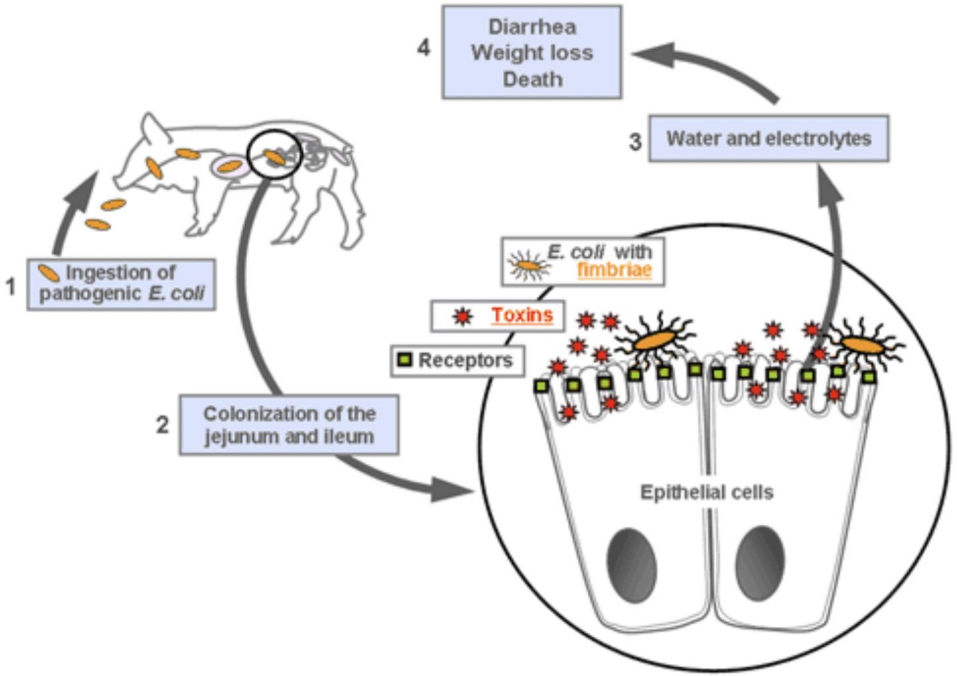


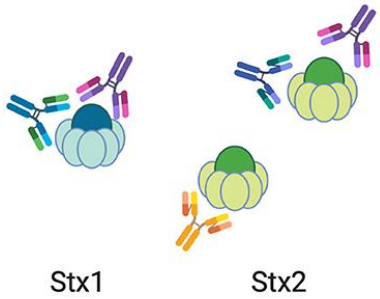
- The genes responsible for A/E lesions are due to the locus of enterocyte effacement (LEE)
- The LEE is composed of at least 41 different genes organized into three major regions
    - type III secretion system that exports effector molecules
    - an adhesion called intimin and its translocated receptor, Tir
    - several secreted proteins (Esp) as a part of TTSS
- The Tir protein is also capable of interacting with host cytoskeletal and signalling components

03 MULTIPLICATION & SPREAD

MULTIPLICATION AND SPREAD

- First location of spread: large intestine
- The pathogen does not only remain extracellularly, but actively invades the intestinal epithelial cells, pumping proteins and toxins into the body's circulatory system
    - Shiga toxins absorbed through the intestinal epithelium
    - Then join the circulatory system
- Disrupt host cell processes
    - Hijacking and altering host cell signaling pathways
    - coordinated host cell invasion
    - evasion of host immune responses
    - efficient colonization
- In animals (eg. cattles), initial colonization of the large intestine often spreads to the rectum.





SHIGA TOXINS

Shiga toxins Stx1 and Stx2 bind to enterocytes

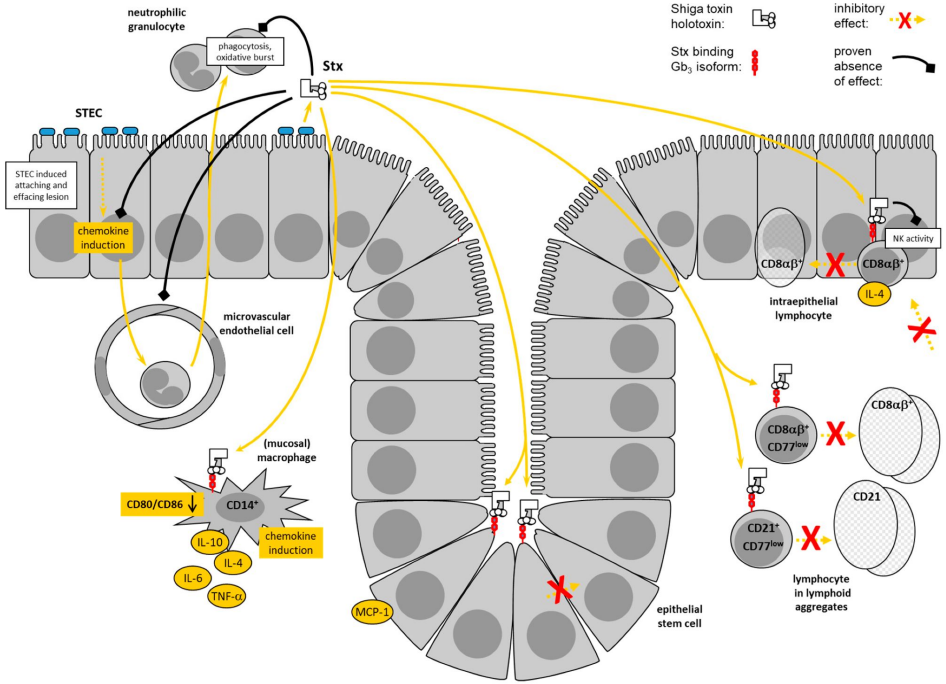
Pentameric B portion of the Shiga toxin

- binds to the cellular glycolipid receptor globotriaosylceramide (Gb3) and globotriaosylceramide (Gb4)
- Binds to various other cell types:
  - Aortic
  - brain endothelial cells
  - mesangial cells
  - renal tubular and lung epithelial cells
  - cells of the monocytic lineage
  - polymorphonuclear cells
  - Platelets
  - erythrocytes

Monomeric A subunit of the Shiga toxin

- endocytosed into the enterocyte and transported to the rough ER by the Golgi apparatus
- In the TGN, the toxin is cleaved by the enzyme furin into the A1 and A2 subunits
- If toxin was not cleaved by furin, then the cytosolic enzyme caplain may cleave the molecule
- A1 is a glycosidase that hydrolyzes a specific adenine-ribose bond in the ribosomal 28S RNA.
- cleaved ribosomal 28S RNA inhibits protein synthesis, resulting in cell death

SHIGA TOXINS



Stx induces chemokine synthesis

↓

Increase in toxin receptor expression and breach intestinal epithelium

↓

Stx enters blood; capillary endothelial cells killed

↓

Activation and aggregation of platelets

↓

initiates leukocyte adherence, cytokine secretion, and vasoconstriction

↓

apoptosis of supporting cells such as inflammatory mediators

SHIGA TOXINS

Brain + Kidney

- Move across the intestinal epithelium without affecting cell function for further propagation into the circulatory system
- toxin starts to cause damage breaking down red blood cells and the vessels
- In very rare cases does the E. coli continue to spread to the brain.

Secondary Pathway

- Shiga toxins causing CXC chemokine production in human endothelium and intestinal mucosal epithelial cells
- promotes intestinal epithelial injury and increased Stx absorption into the systemic circulation by inducing PMN infiltration into the intestinal epithelium

SHIGA TOXINS

SLOUGHING

Caused by shiga toxins and is a form of bacterial propagation amongst animals

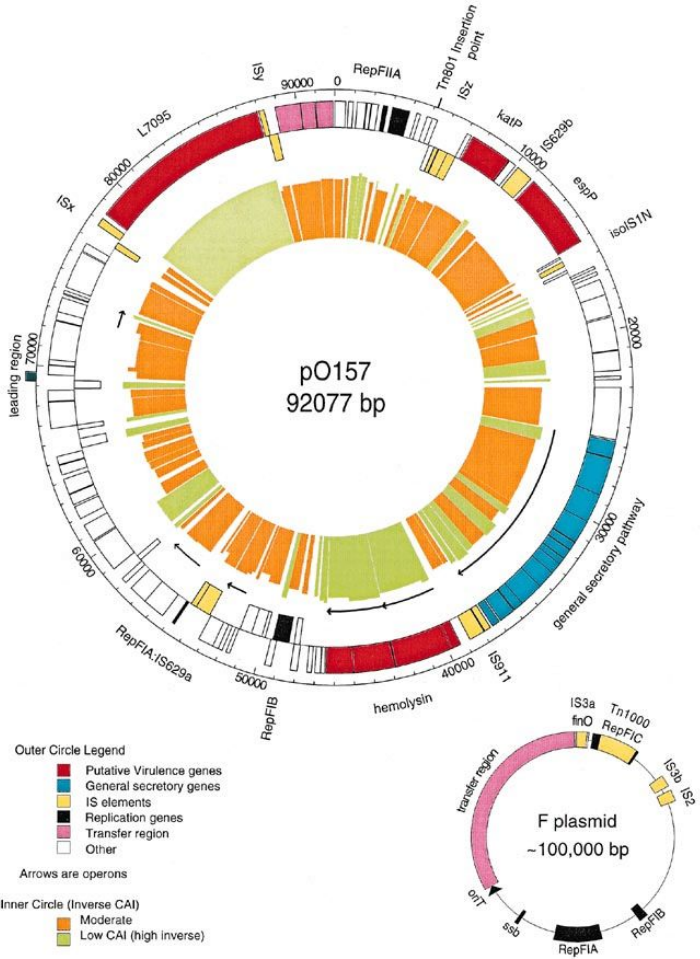
DIARRHEA

Expel a substantial amount of E.coli in the stool

HYGIENE

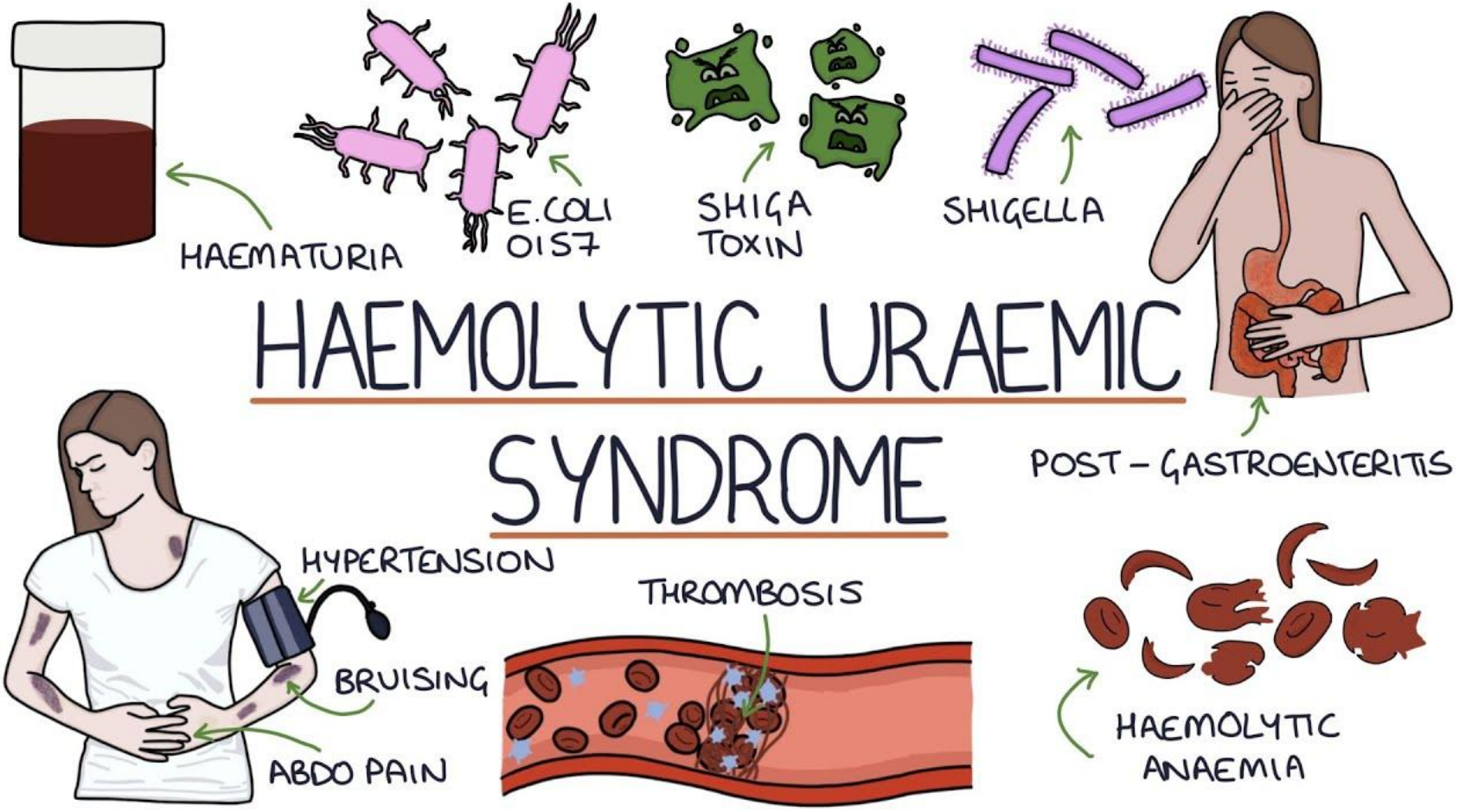
Ensure infected animals do not contaminate communal apparatuses or expose to other individuals

pO157 plasmid

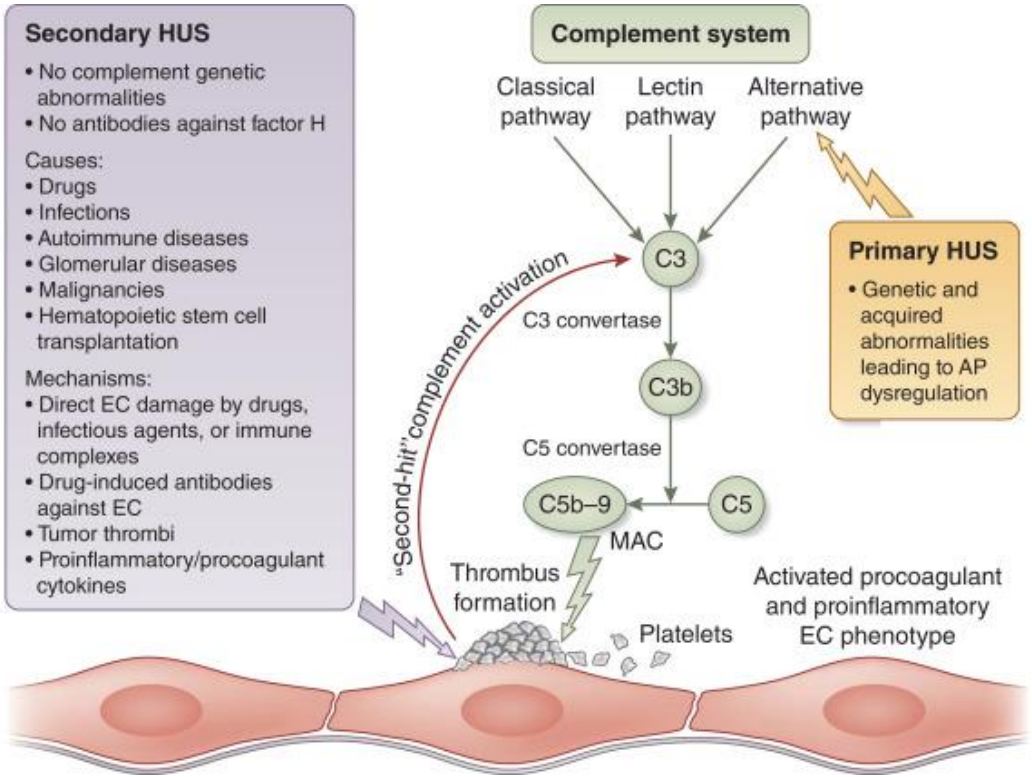


- Contains the hly operon that encodes enterohemolysin
- This hemolysin allows E. coli O157:H7 to utilize the blood released into the intestine as a source of iron
- Some strains of E. coli O157:H7 also have EspP
    - cleaves pepsin A and human coagulation factor V, contributing to hemorrhage into the intestinal tract
    - cleaves several complement system components, protecting the bacteria from immune system-mediated elimination

SECONDARY SITES OF INFECTION



COLONIC VASCULAR DAMAGE



- Stx are uptake into resident macrophages and released from dead macrophages to invade the basolateral side of colonocytes
- T3SS effectors cause actin polymerization and ruffle formation and recruit ARP2/3 complex to aid in the process of bacterial entry
- IpaA, VirA, and IpgD: destabilize actin
- IpaB, PiaC, IpaD, and IpaH: escape phagosomes
- IpgD: allow the bacteria to avoid apoptosis
- IpaB: mediate cell cycle rest through the targeting of an inhibitor of anaphase
- MAD2L2 and OspE: prevente epithelial cell attachments via interacting with integrin-linked kinase (ILK)

COLONIC VASCULAR DAMAGE

Four effectors allowing the evasion of innate immune responses

1) OspF and IpaH
    - targets the nucleus to irreversibly dephosphorylate protein kinases important for nuclear factor-KB (NF-KB) regulated transcription genes and interferes with the expression of inflammatory cytokines by interacting with splicing factors respectively
2) OspG
    - inhibits NF-KB activation
3) OspB
    - plays a role in reducing interleukin-8 (IL-8) through recruitment of host factors to help remodel chromatin

Ultimately, it is with these mechanisms that allow the bacteria to persist, survive and maintain infection by reducing the host's inflammatory responses.

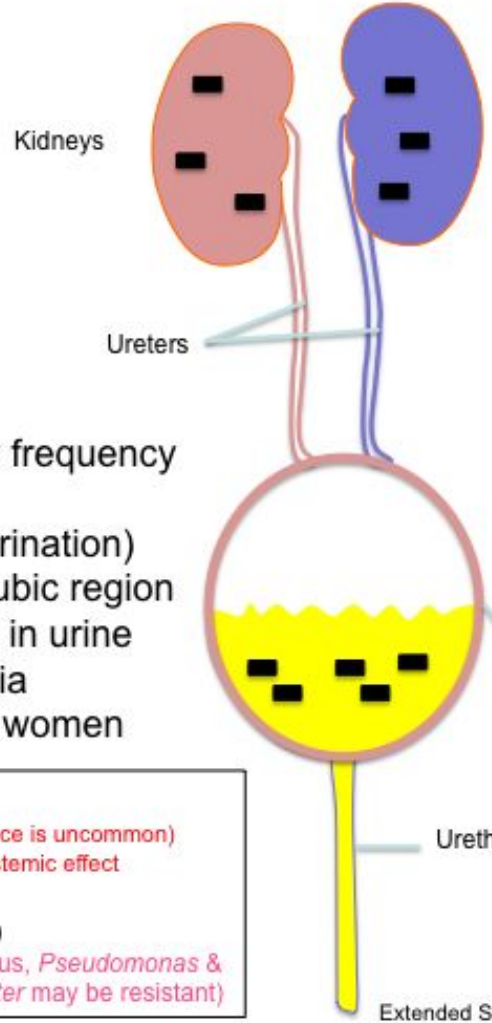
INFECTION IN KIDNEY

- Polymorphonuclear leukocytes (PMN) are involved in the spread of Shiga-toxin-related injury by delivering Stx to kidneys
- Damage to the lungs is not as severe as in the kidneys because many kidney cells express the Stx receptor and contain Stx-sensitive cells
- High volume of blood flow and filtration rate of blood in kidneys increases the chance of Stx interaction
- if the renal filtration barrier is damaged, Stx can then interact with tubular epithelial cells of the nephron, leading to further damage
- Globotriaosylceramide (Gb3)
    - acts as the cellular receptor for Stx
    - renal microvascular endothelial cells express a large amount of Gb3
    - expressed by the proximal tubules
- Stx2 has been shown to decrease VEGF production by human podocytes

URINARY TRACT INFECTIONS

- Occur through adhesion to the uroepithelium, in which most adhesins generate separate morphological features termed pili (or fimbriae)
- The adhesion to the uroepithelium is mediated by fimbrial adhesin H (FimH) binding to glycosylated uroplakin Ia in the bladder
- FimH can also bind to alpha-3 and beta-1 integrins at the site of invasion, and destabilization of microtubule can also occur to further assist with invasion into the urinary tract
- Prostatitis in men and pelvic inflammatory disease (PID) in women may be secondary outcomes of UTI’s
- Bacteria may eventually reach the bloodstream and make its way further to other tissues of the host

UTIs



Pyelonephritis
(Kidney infection)
- **flank pain**
- **high fever**
- malaise
- WBCs & bacteria in urine
- urinary symptoms similar to cystitis

Empiric Rx:
IV ceftriaxone (3rd Gen Ceph)
- penetrates tissue, ~good spectrum

Alternative:
Piperacillin/Tazobactam (Zosyn ®)

Cystitis
(Bladder infection)
- increased urinary frequency
- urgency
- dysuria (painful urination)
- pain above the pubic region
- WBCs & bacteria in urine
- possible hematuria
- more common in women

Empiric Rx:
Nitrofurantoin (resistance is uncommon)
- localized to urine, little systemic effect

Alternatives:
TMP/SMX (if not resistant)
Fosfomycin (less efficacious, *Pseudomonas* & *Acinnetobacter* may be resistant)

Pathogens:
- *E. coli* (75-95%)
- *Proteus*
- *Klebsiella*
- *Enterobacter*
- *Staph* (less common)

ESBLs: Rx Carbapenems
(meropenem, ertapenem)

Extended Spectrum Beta Lactamases – inactivate Pen's,Ceph's & Aztreonam

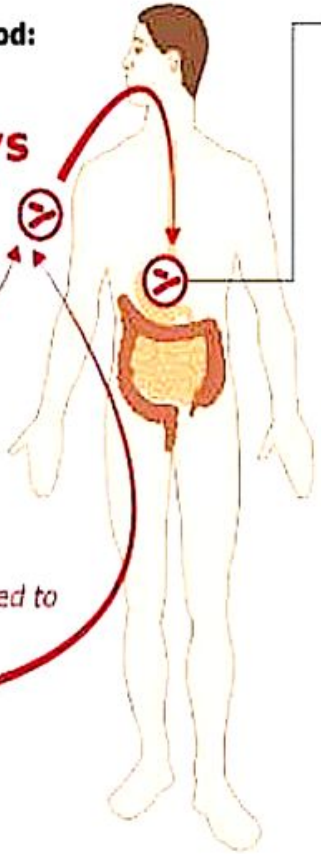
04
BACTERIAL DAMAGE

Most Escherichia coli (E.coli) strains are harmless.

But some, like enterohemorrhagic **E. coli (EHEC)**, are a hazard to human health and life.

Incubation period:

three to eight days



E. coli (EHEC), once in the human stomach, begins producing toxins that cause serious illnesses

Symptoms caused by E. coli (EHEC)

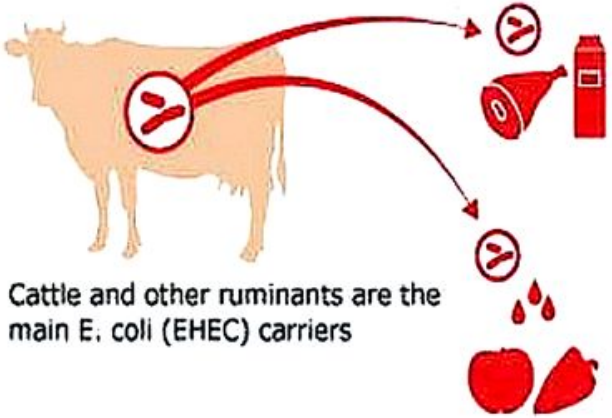
- Stomach muscle spasms
- Diarrhea (sometimes bloody diarrhea)
- Fever
- Vomiting

Complications:

hemolytic uremic syndrome (HUS)

Death rate: **3-5 %**

INFECTION SOURCES



Cattle and other ruminants are the main E. coli (EHEC) carriers

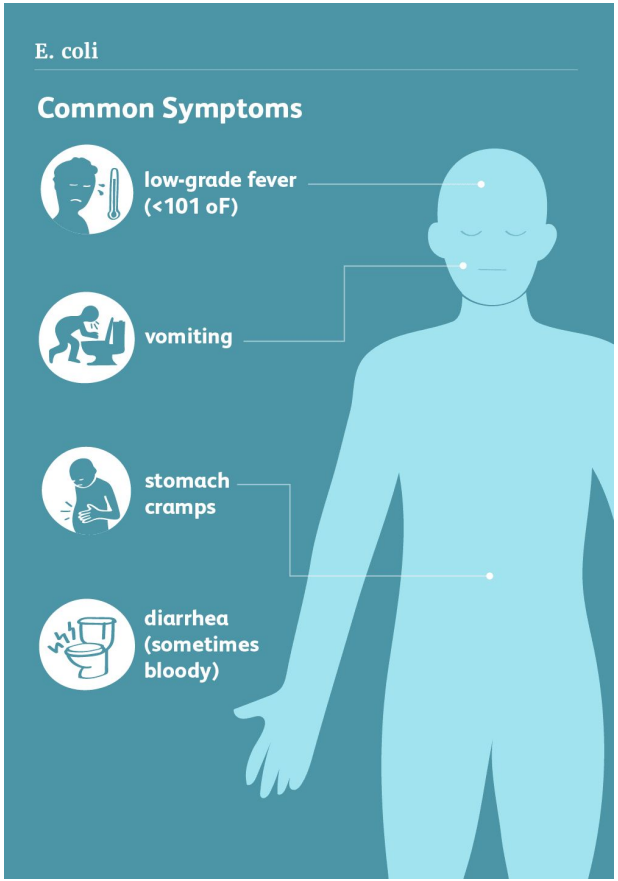
Uncooked meat and raw milk

The bacteria die when food is exposed to heat (70^{0}C and higher)

Fruit and vegetables (droppings of sick animals find their way into water bodies that in turn feed the soil)

DIRECT DAMAGES

1) Shiga toxin causes damage to the intestine by killing cells
2) Stx enters enterocytes expressing globotriaosylceramide (Gb3) and globotriaosylceramide (Gb4) via endocytosis
3) inhibit protein translation and trigger the ribotoxic and endoplasmic reticulum stress responses
4) leads to cell apoptosis through p38 mitogen-activated protein kinase (p38 MAPK) activation and other apoptotic pathways
5) leads to the sloughing off of intestinal mucosa cells, which results in hemorrhagic diarrhea
6) Shiga toxin also has systemic effects on vascular endothelial cells, resulting in vasculitis, and manifests in HUS, abdominal pain, and in rare cases, thrombotic thrombocytopenic purpura



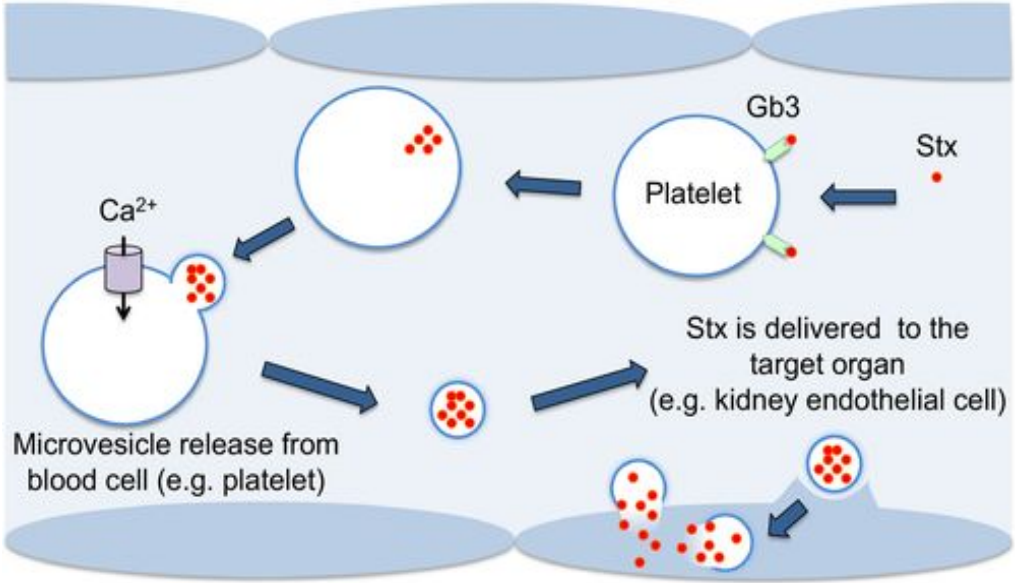
HOST INFLAMMATORY RESPONSES

- Fever
  - Shiga toxins induce an increase in chemokine synthesis from intestinal epithelial cells
    - release of interleukins, such as IL-8 and IL-1
    - Release of Tumor Necrosis Factor (TNF), as known as pyrogens
  - pyrogens can enter the organum vasculosum of the lamina terminalis (OVLT) within the anterior hypothalamus
  - cells are then stimulated to produce prostaglandin E2 which diffuses into the adjacent preoptic area to upturn the temperature set point and cause fever
- Abdominal tenderness may be more severe if there is hemorrhagic vasculitis
- inflammatory response also leads to
  - leukocyte aggregation
  - apoptosis of the affected cells
  - platelet aggregation
  - microthrombi formation
  - Hemolysis
  - renal dysfunction
  - multiple organ failures in more severe cases

HUS vs. TTP

	Characteristics	Renal damage	Diarrhea	Other damages
Hemolytic Uremic Syndrome (HUS)	Classical triad of microangiopathic hemolytic anemia (fragmented RBCs on blood film), thrombocytopenia, and renal failure	More	More	Neurological abnormalities such as seizures, coma, and hemiparesis
Thrombotic thrombocytopenia purpura (TTP)	More rare; mainly affects the adult population	Less	Less	

Hemolytic Uremic Syndrome (HUS)

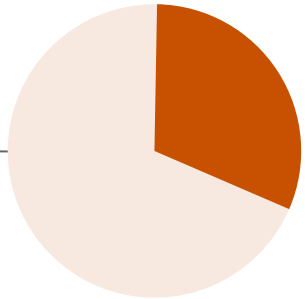


- Children under the age of 5 are particularly susceptible for developing HUS due to a weak immune system

- Additional filtrate load on the glomeruli which become clogged with platelets and damaged red blood cells
- Can lead to kidney failure
- Once the Kidney is severely affected, individuals may experience edema, albuminuria, decreased urine output, hypoalbuminemia and blood in the urine
- Treatment options
  - Hospitalization
  - dialysis in extreme cases
  - Blood transfusions and special diets

HEMOLYTIC UREMIC SYNDROME (HUS)

Brain present CNS dysfunction in HUS cases



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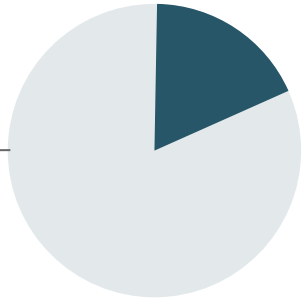
Seizures in pediatric patients



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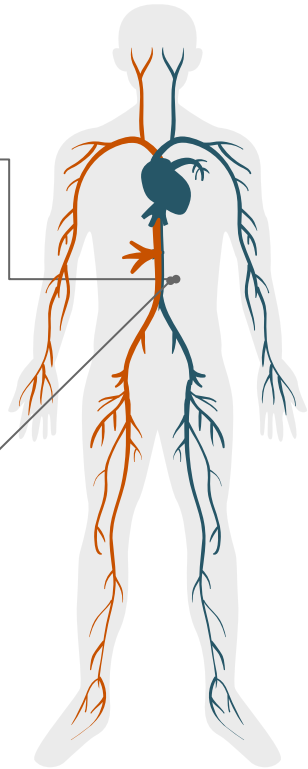
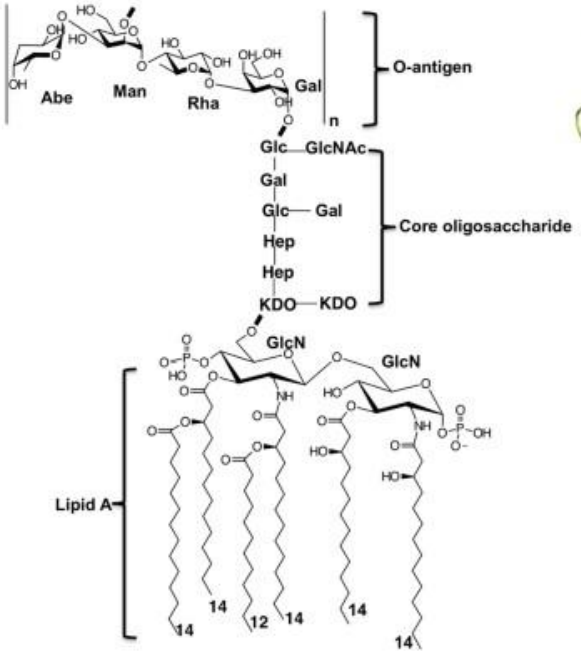
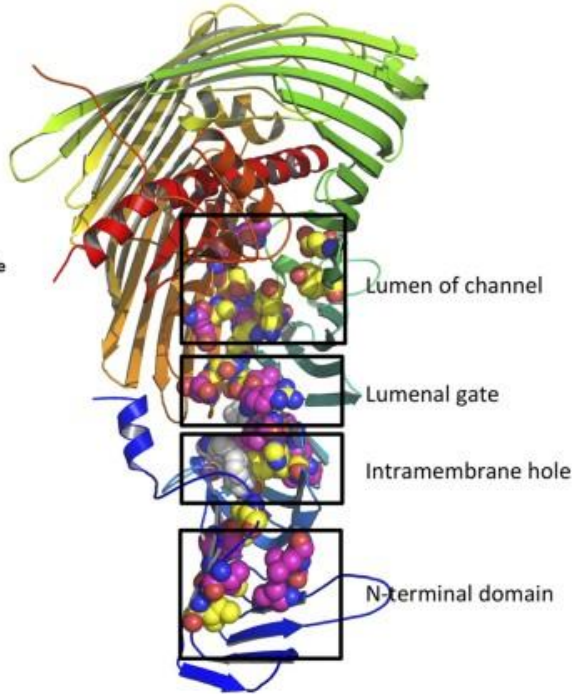


LIPOPOLYSACCHARIDE (LPS)

- Can damage endothelial cells, increase TNF levels, activate platelets, and induce the blood coagulation cascade
- Can lead to an increased levels of interleukins such as IL-8, which can activate white blood cells (WBCs). The host WBCs can then cause damage to the host by producing tissue-damaging enzymes





TREATMENT OPTIONS

- Hydration
- Antibiotics not recommended
  - may trigger an SOS-response and initiate the lytic cycle of bacteriophages
  - May lead to antibiotic-induced injury and release large amounts of toxins
  - lead to more HUS cases as the bacterial motility is decreased
- Antibiotic use is only recommended in cases of sepsis

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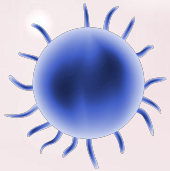
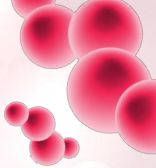


THANK YOU!