# Case 3 – *E.coli* O157:H7 Bacterial Pathogenesis

Catherine Gai

# Presentation Overview

**Encounter with *E.coli***

Geographical distribution

Location within the host & key bacterial characteristics

**Entry**

Entry & Adherence

Interactions with the host

**Multiplication & Spread**

Mechanisms of multiplication & spread after entry

Secondary sites of infection

**Damage to the host**

Direct damages to the host, signs & symptoms

Treatment recommendations

# Encounter: Sources of *E.coli*

## Sources of *E. coli* in food

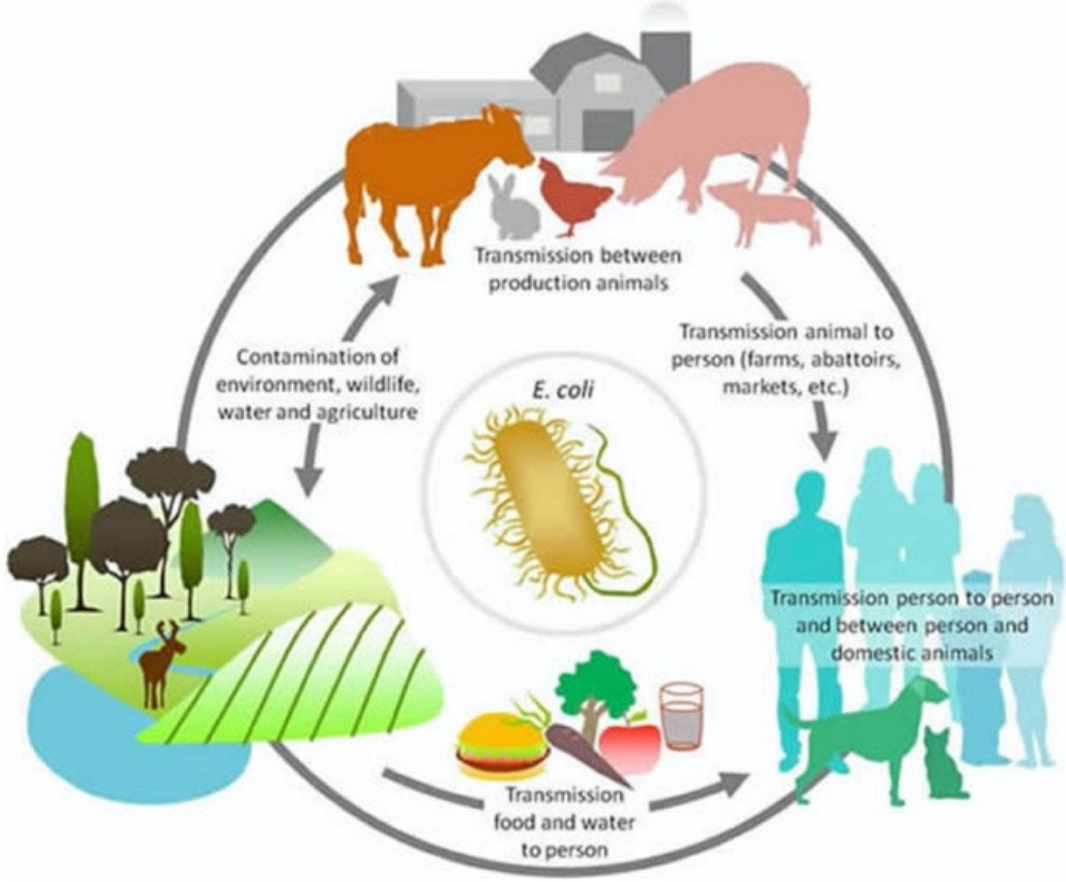
- Contaminated / raw meat, milk, fruit, vegetables

## Sources of *E. coli* in natural reservoir

- Ruminant animals on farms
  - In northwest U.S, cattles are commonly asymptomatic carriers
  - Other examples: sheep, pigs, horses, and dogs
- Farms, ponds, dams, wells, barns, contaminated water within lakes, pools, or various drinking sources

## Geographical distribution around the world

- More common in industrialized countries, compared to developing countries, for example
  - Canada (more common in western provinces)
  - United States (more common in northern states)
  - Europe
  - Japan




[1,2,4,5]

# Encounter: *E.coli* Within the Host

## How Ronnie may have been exposed to *E. coli* O157:H7

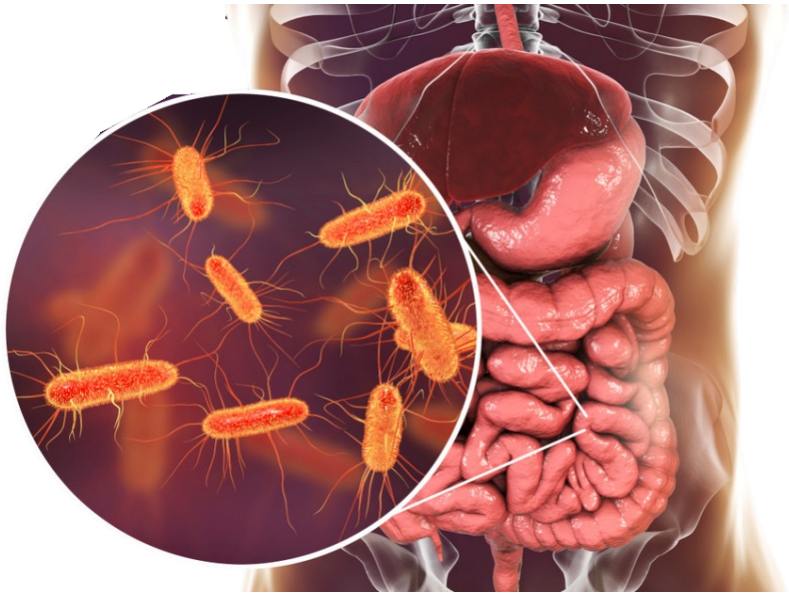
- Contaminated / undercooked burger meat from the barbecue

## *E. coli* O157:H7's location in the host

- *E. coli* resides within the intestinal cellular walls and gut of the host as a commensal or pathogenic bacteria

## *E. coli* colonization on the intestinal mucosa

- Attachment to intestinal epithelium layer
- Penetration of intestinal epithelium barrier



[1,2,4,5]

# Encounter: *E.coli* Characteristics

To be persistent in the host, *E. coli* O157:H7 can adapt to variations in different conditions due to these characteristics:

## Temperature

- Heat tolerance due to exopolysaccharide
- Ability to alter membrane lipid composition in response to heat stress

## Low pH due to stomach acid

- Acid tolerance due to exopolysaccharide
- Expression of acid resistance systems that remove protons

## Limited nutrient availability

- In nutrient deficient (starvation-survival) state
  - Increased activation of enzymes required for catabolizing available nutrients
  - Ability to reduce cell size to increase surface: volume ratio for more efficient nutrient uptake
  - Ability to increase toxin production to kill other cells to decrease competition
  - Use of multiple limiting sugars for growth

## Attachment to host structure

- Attachment to microvilli of intestinal epithelial cells through
  - Production of attaching and effacing (AE) lesions
  - Biofilm formation for better adherence

[2,5,7,10,13-21]

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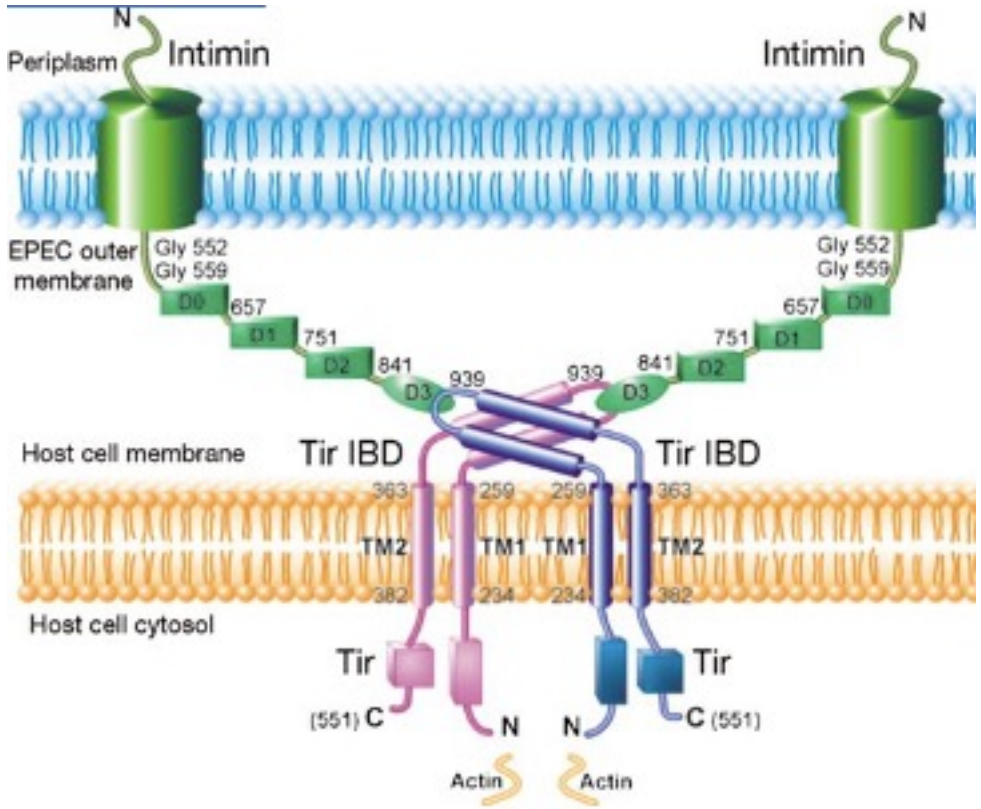
# *E.coli* Interaction with Host

## Entry

- Ingestion of contaminated meat
- Infection established in the intestine

## Adherence & colonization

- Attachment to the microvilli of the intestinal epithelial cells using intestinal cellular walls' fimbriae
  - Adherence to epithelial cells using Type 3-Secretion System
    - Tir injection into host cell membrane
      - Interaction with intimin on the *E.coli* surface
- Attachment leads to characteristic effacing lesions which flatten the microvilli of intestinal epithelial cells
  - Rearrangement of the cytoskeletal actin
    - Disrupts normal intestinal cell functioning
  - Shiga toxin productions disrupt protein synthesis in the epithelial cells
    - Causes sloughing off of the mucosa




[4-6]

# *E.coli* Interaction with Host

| Host Defense Mechanisms / Factors | *E.coli* Mechanisms / Characteristics |
|---|---|
| Stomach acid<br>• Barrier prior to *E.coli* colonization in the intestine | Protection against low pH<br>• Acid resistant systems that consume / remove protons to maintain internal pH<br>• Secretion of EPS neutralizes / buffers protons at the bacterium surface |
| Bile<br>• Stored in the gallbladder<br>• Released into the duodenum<br>• Causes oxidative stress & damages bacterial DNA<br>• Induces significant reduction in mRNA of genes that make up the locus of enterocyte effacement (LEE) pathogenicity island | Protections against bile<br>• Adaptations in membrane structures to reduce permeability; an abundance of efflux pumps to remove bile<br>• Example: arcA and arcB are genes that down-regulate ompF expression<br>  • ompF is a porin that allows for bile influx |

[1-3]

# *E.coli* Interaction with Host

| Host Defense Mechanisms / Factors | *E.coli* Mechanisms / Characteristics |
|---|---|
| Limited / variable oxygen level in the GI tract | *E. coli* is a facultative anaerobe<br>• Does not require oxygen<br>  • Instead uses fermentation or anaerobic respiration; however, it can grow in the presence of oxygen |
| Limited iron availability | *E.coli* can overcome the challenge of limited iron availability through other mechanisms<br>• Expression of heme uptake & transport proteins<br>  • Use of heme as source of iron<br>• Expression of siderophores |

[1-3]

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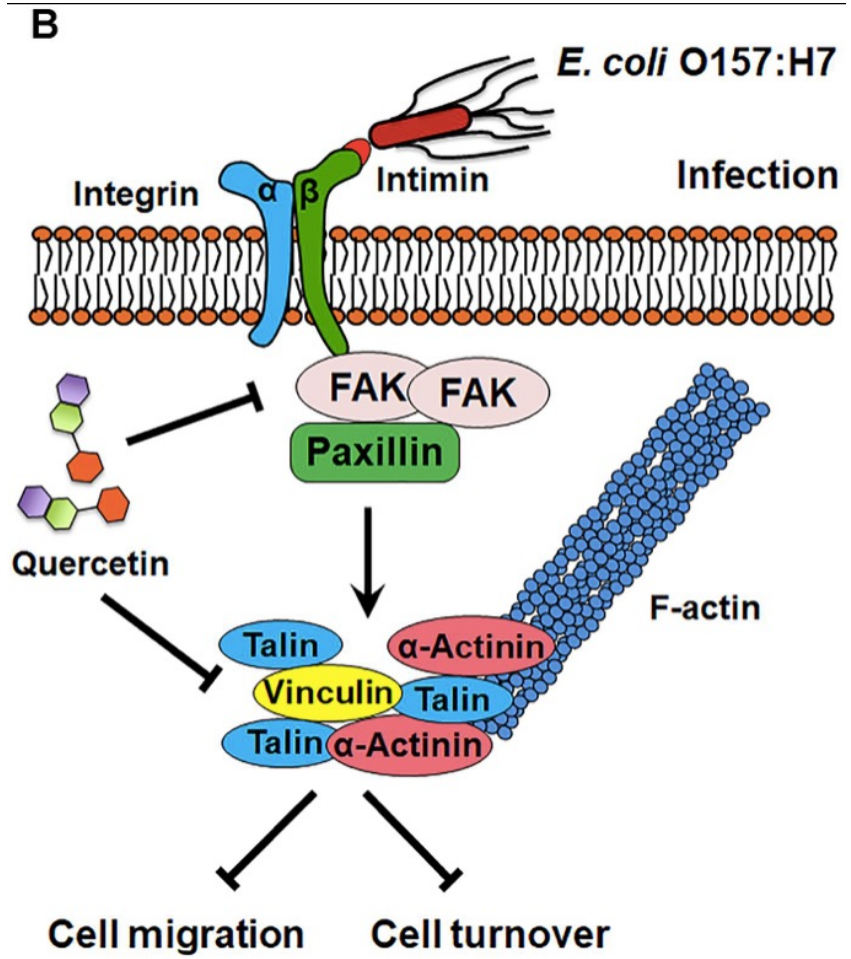
# Multiplication & Spread

*E.coli* actively invades the intestinal epithelial cells

Does not reproduce intracellularly

Instead, *E.coli* damage host cells through protein secretion or direct interactions

- Secretion of proteins that disrupt host cellular processes
- Allows for *E.coli* to evade host immune responses to better colonize the intestine
  - e.g., T3SS effectors that deliver bacterial proteins
  - e.g., OspG, a kinase that down-regulates host innate immune response
- Contributes to further illness

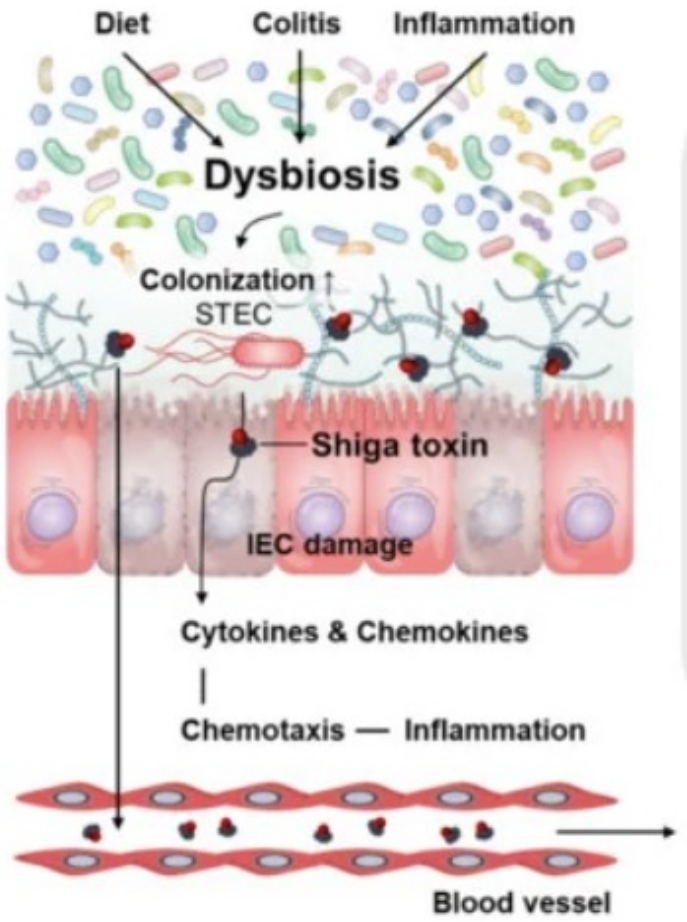



Example: *E. coli* O157:H7 colonization on host cell. Interaction with host integrin inhibits normal cellular processes

[1-3]

# Propagation - Shiga Toxin (Stx)

Shiga toxins can penetrate the intestinal epithelium with serious consequences




**Shiga toxin aids in cell binding**

- Stx1 and Stx2 bind enterocytes after adhesion

**Shiga toxins breach the intestinal epithelial barrier**

- Disrupts epithelial tight junctions
- Gains access to submucosa and spreads through the bloodstream

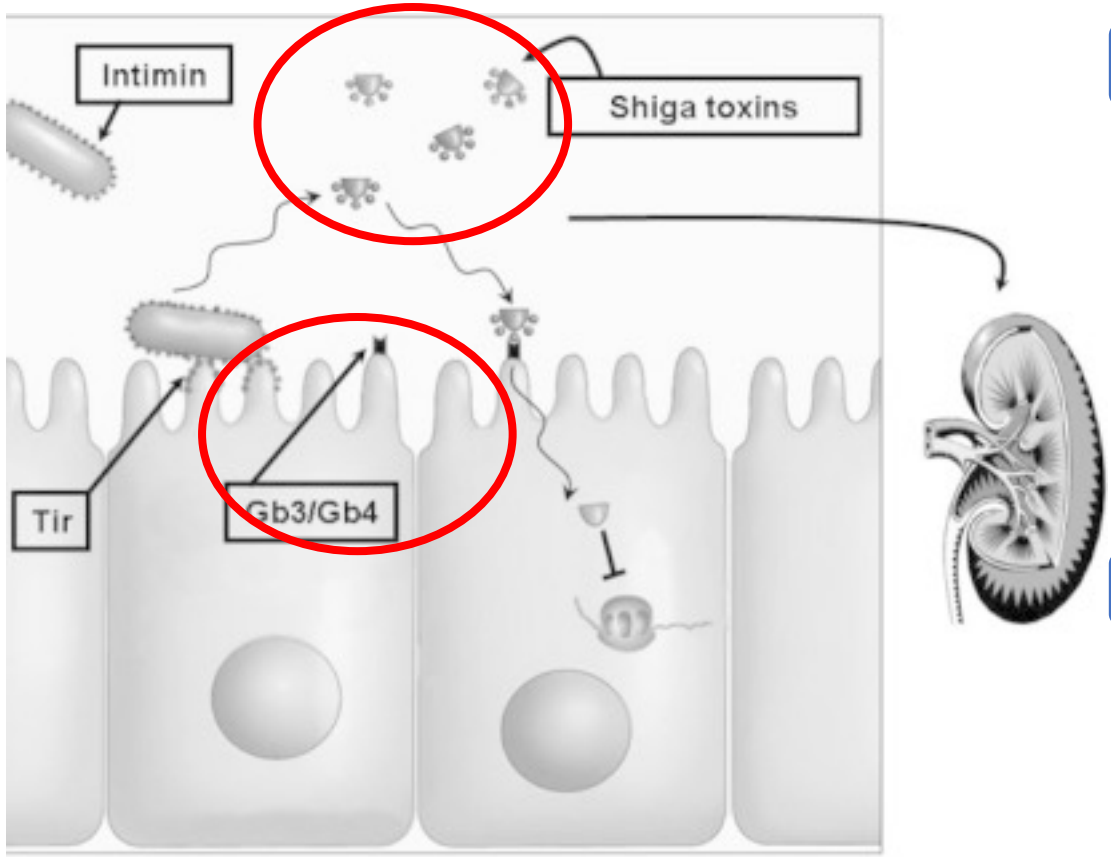
**Shiga toxin induces chemokine production**

- Chemokines activate the endothelium
- Chemokines induce PMN infiltration
  - Leads to increased toxin receptor expression
  - Causes injury to capillary endothelial cells due to breached barrier
  - Leads to activation and aggregation of platelets

[4,6,11,12,20]

# Secondary Sites of Infection

Shiga toxin dissemination through the bloodstream has systemic effects




**Secondary infections of major organs**

- Brain / Pancreas / Heart / Lung
- Kidneys
  - The kidney has many cell types with Stx receptors & high blood flow volume
    - E.g., glycolipid Gb3, a receptor for Stx
      - Gb3 is found in various glomerular cell types
      - E.g., mesengial cells, endothelial cells, podocytes

**Vasculitis due to chemokine production**

- Diffuse vasculitis injuries can cause organ failures

[17,20-22]

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# Direct & Induced Damages to Host – Stx

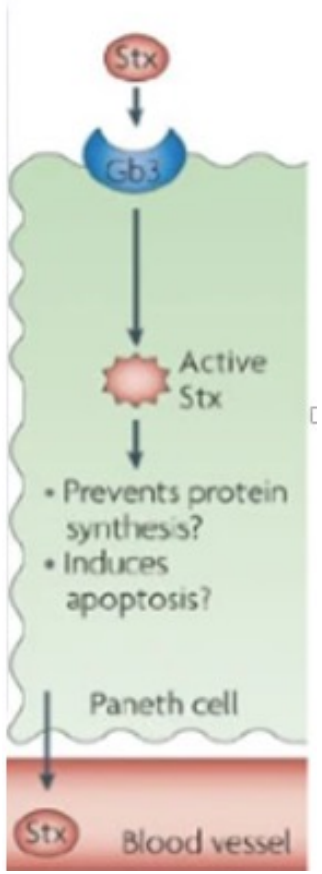
Stx enters enterocytes via endocytosis

**In the trans-Golgi network, Stx is cleaved into subunits which cleave RNA, which in turn**

- Inhibits protein translation
- Induces ER stress response & apoptosis
  - Leads to intestinal mucosa cell sloughing off – hemorrhagic diarrhea

**Endocytosis also induces chemokine synthesis from intestinal epithelial cells**

- IL-8, IL-1, TNF (pyrogens) enter organum vasculosum of the lamina terminalis (OVLT) and stimulate prostaglandin $E_2$ production
  - Increases temperature set point and initiates heat conservation – fever
- Inflammatory response also leads to abdominal pain / tenderness due to hemorrhagic vasculitis




[2-5]

# Other Direct & Induced Damages to Host

Toxin accumulation leads to multiple organ system failures through platelet aggregation, hemolysis, and microthrombi formation. For example:

- Hemolytic Uremic Syndrome (HUS) mostly develop in children, with the triad conditions of
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Acute renal failure
- Thrombotic thrombocytopenia purpura is a rare disorder that mostly develop in adults, characterized by
  - Formation of blood clots in small blood vessels throughout the body

Bacterial products – LPS

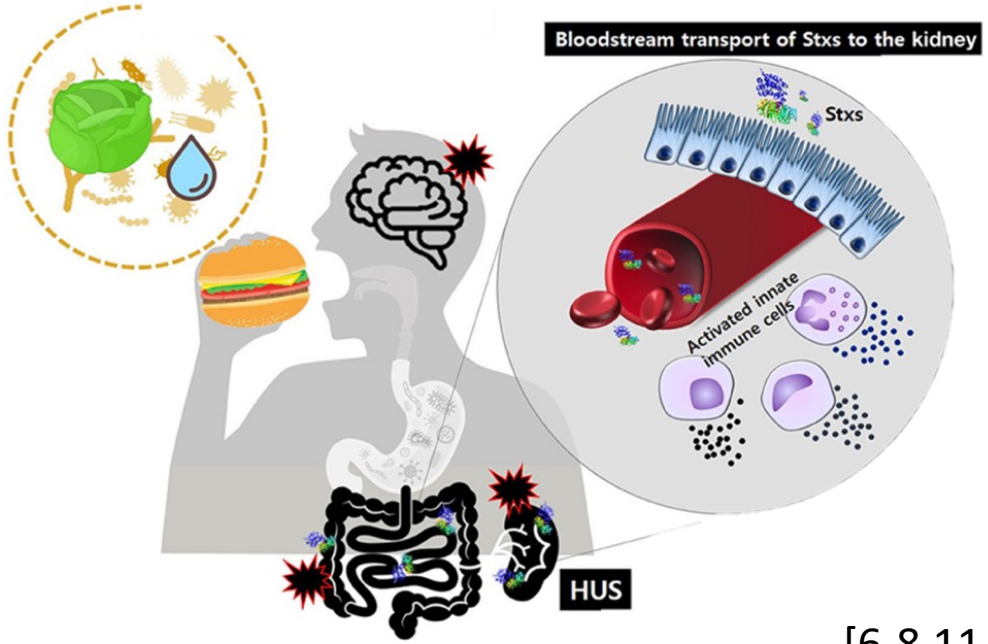
- Damages endothelial cells
- Activates platelet & coagulation cascade
- Induces TNF production
- Induces tissue-damaging enzyme production (e.g. elastase)

# Treatment

Rest + hydration

Antibiotics

- May enhance damage, therefore not recommended
  - May trigger lytic cycle of bacteriophages
    - Leads to large amount of toxin being released
  - May also lead to more severe conditions like HUS due to reduced bacterial motility and prolonged exposure to toxin
- Antibiotics usage is only recommended in cases of sepsis




[6-8,11,12,14]

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