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Acute Gastrointestinal Infections

Inflammatory Diarrhea- StEC and *Shigella*

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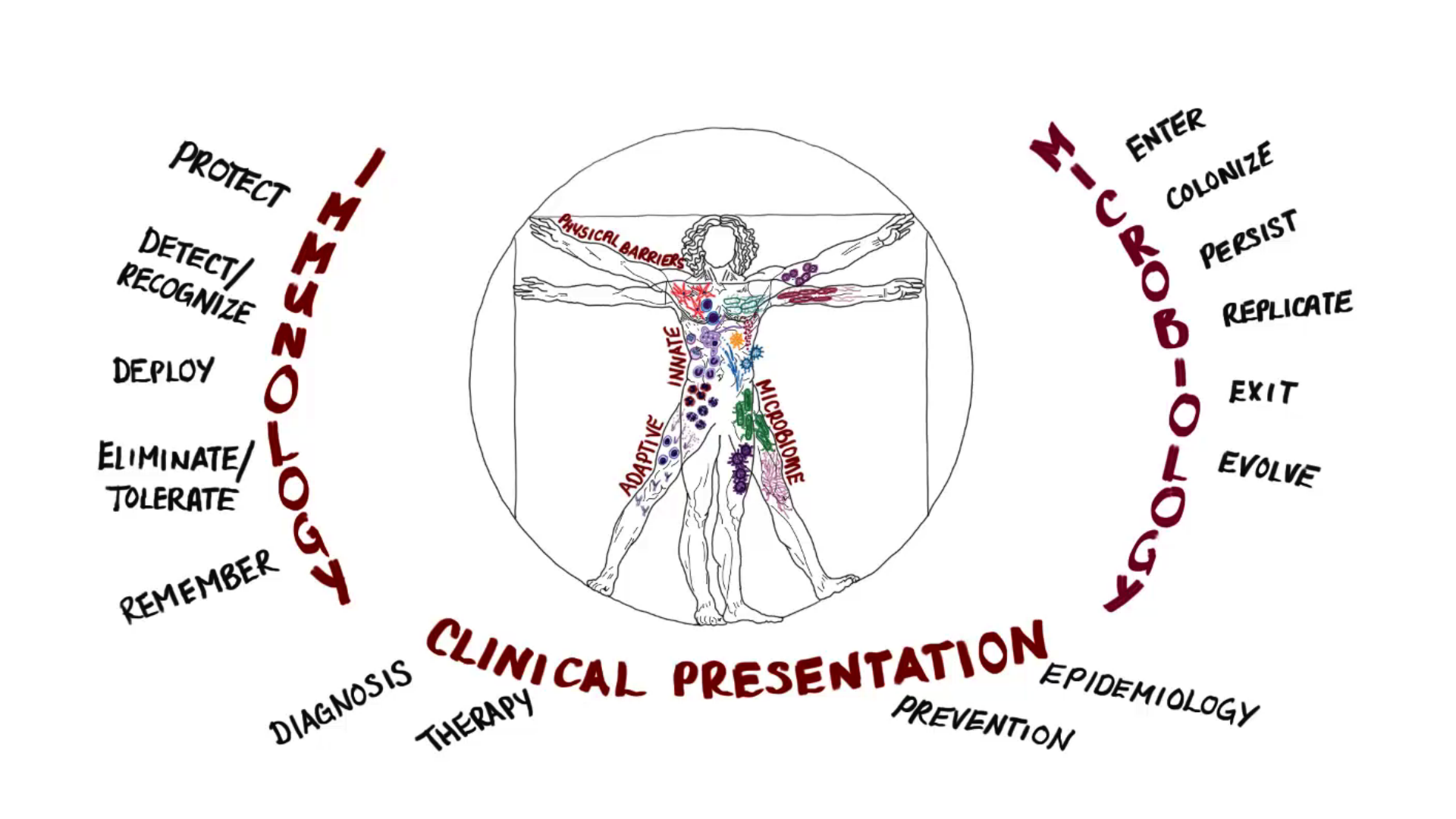
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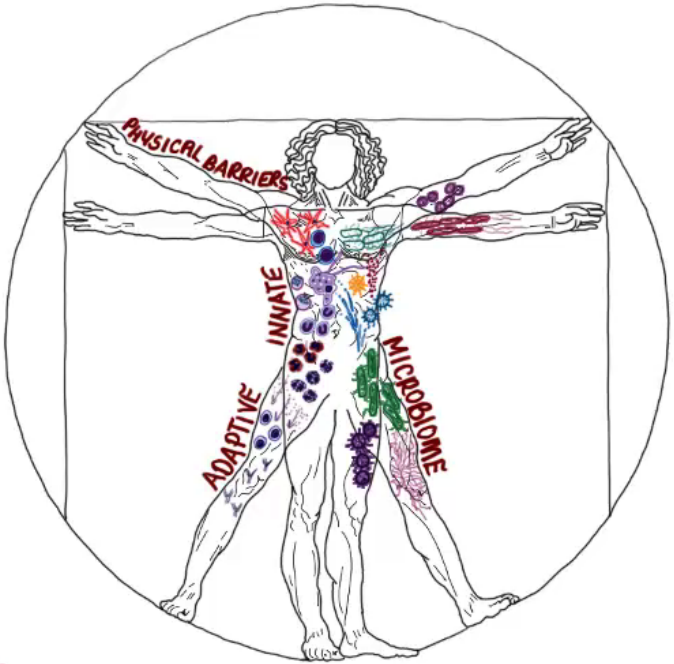

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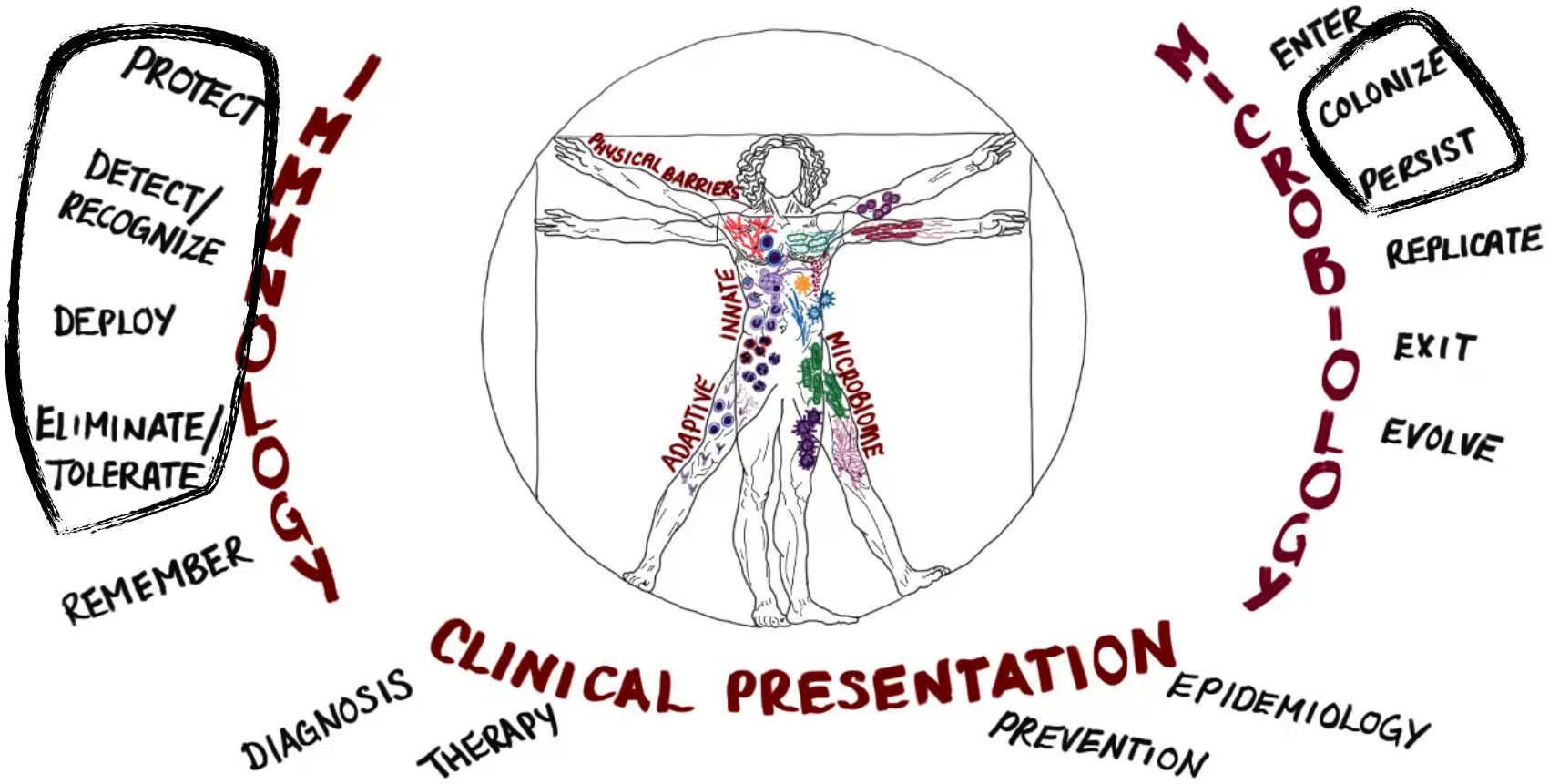
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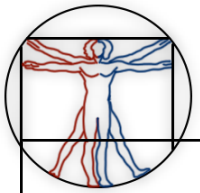
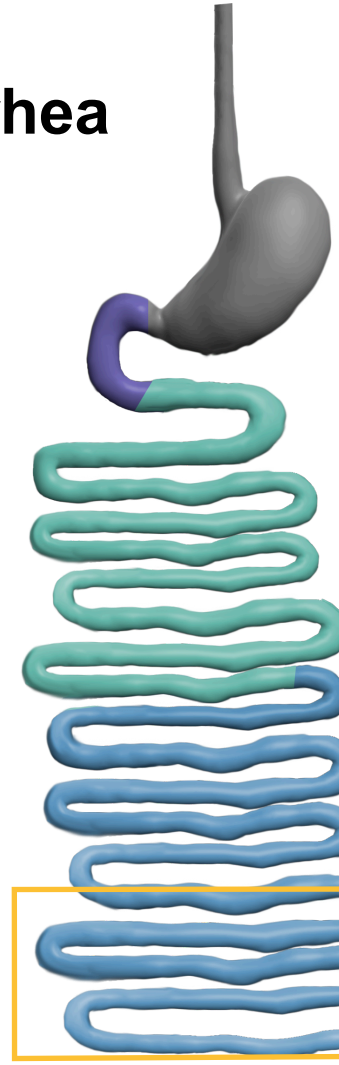
Learning Objectives

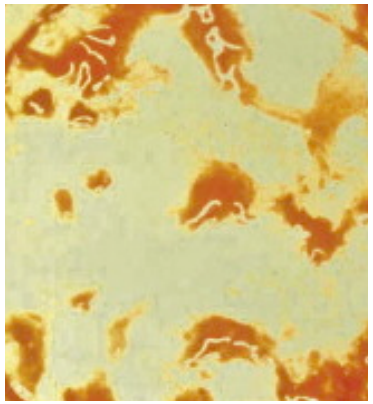
- Describe the clinical findings, epidemiology and pathogenesis of dysentery due to Shiga-toxigenic *E. coli* (StEC) and *Shigella*.

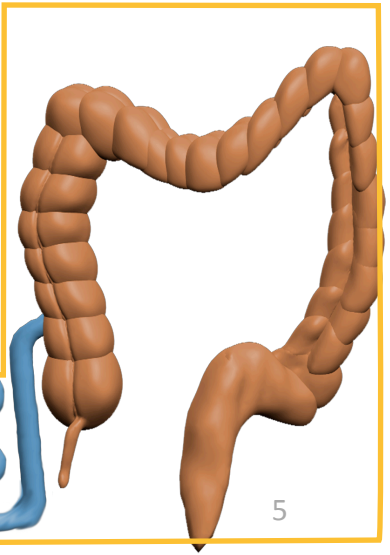


Inflammatory or Bloody Diarrhea

Clinical Features	Frequent small volume stools. May have streaks of blood, mucosy from pus. Pain on defecation (tenesmus), ileocolitis, colitis. Fever may be present.
Complications	Depend on etiology and host features- Hemolytic Uremic Syndrome, Bacteremia
Management	Consider stool cultures, antibiotics for some etiologies but may worsen others
Anatomical Location	Terminal ileum and colon
Pathogenesis	Damage to enterocytes with local inflammatory responses, direct invasion and cytotoxin damage- Locally invasive
Viruses	none in immunocompetent
Bacteria	**Shiga-toxigenic *E. coli* (StEC, EHEC)**, ***Shigella,*** EIEC, *Campylobacter jejuni, non-Typhi-Salmonella, Yersinia*
Protozoa	*Entamoeba histolytica*

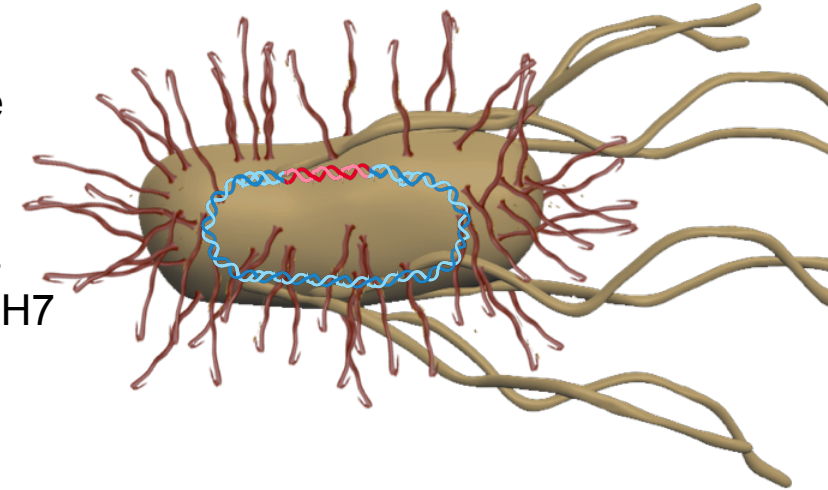






StEC- Shigatoxigenic *E. coli*

- StEC also known as EHEC- enterohemorrhagic *E. coli* causes bloody diarrhea that can be complicated by the hemolytic uremic syndrome (HUS) in 5-10%.
- There are many strains that can be distinguished with antibodies to the LPS (O-antigen) or to the flagellin (H-antigen). The most common strain in the U.S. is O157:H7
- **It is an animal form of EPEC that was infected by a bacteriophage that gave it the ability to produce a toxin- Shiga toxin**
- Like EPEC it has a T3SS that injects effectors into the cell to alter its adhesion- Attachment and effacement



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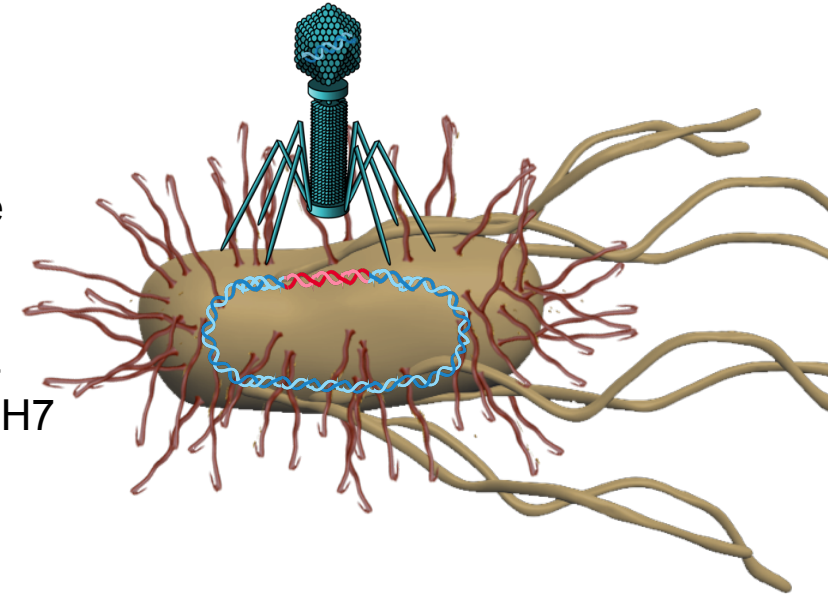

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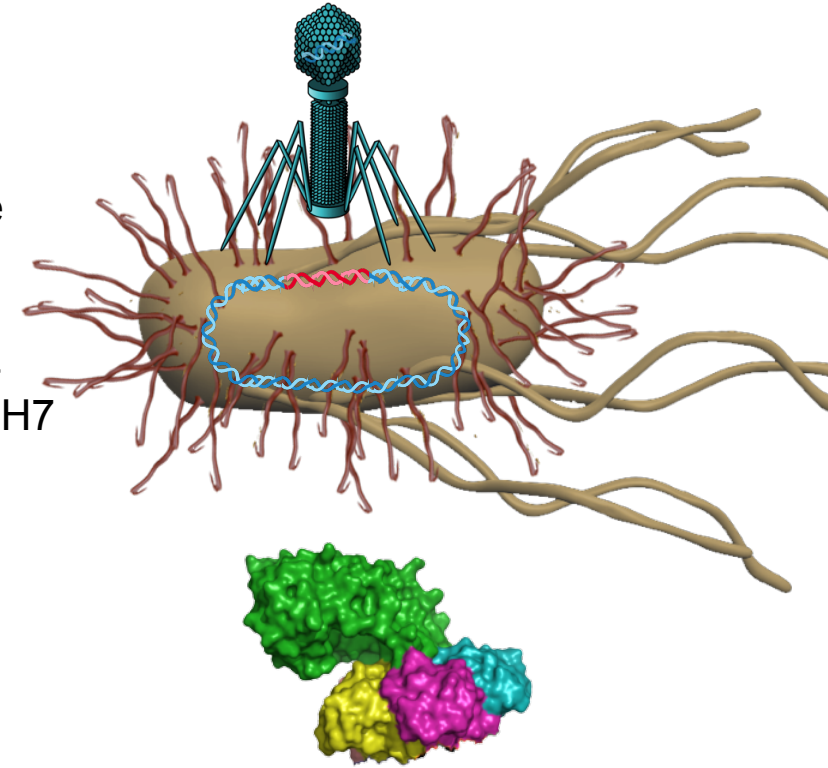
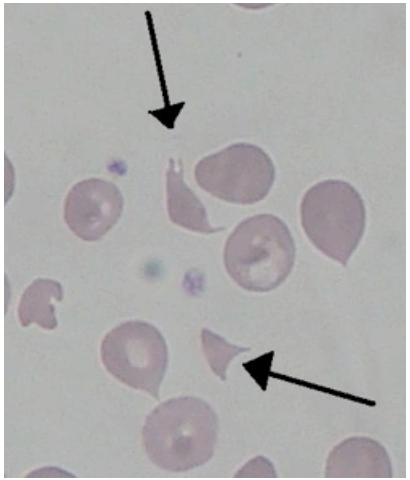


StEC Clinical Manifestations

- Igestion of contaminated food.
- Incubation period 2-5 days (range 1-9)
  - Watery diarrhea followed by bloody diarrhea.
- Symptoms subside and 5-10 days later 5-10% of people will develop HUS
  - Microangiopathic hemolytic anemia,
  - Thrombocytopenia,
  - Acute renal insufficiency or failure.
  - CNS involvement in some
- About half the patients with HUS require temporary dialysis.
- Even in the U.S., HUS carries 5-10% mortality



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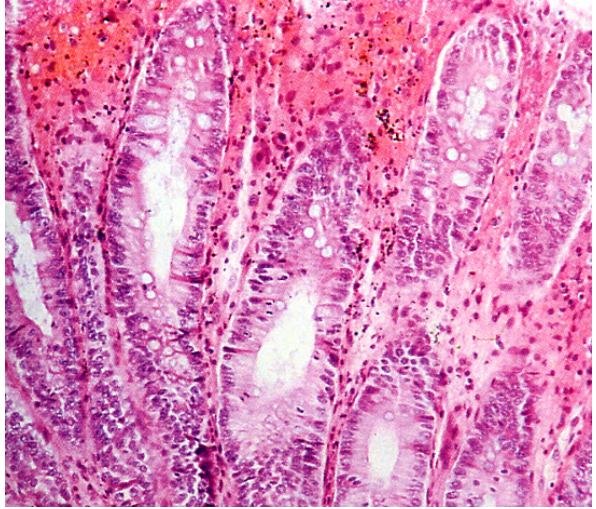

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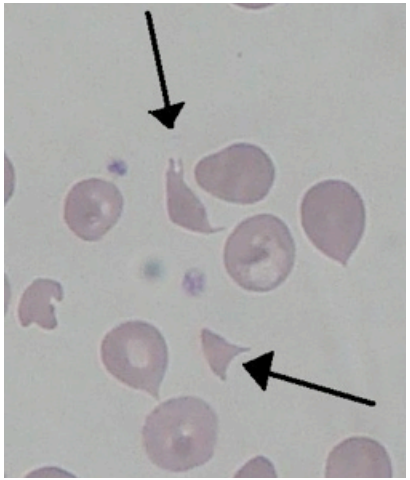

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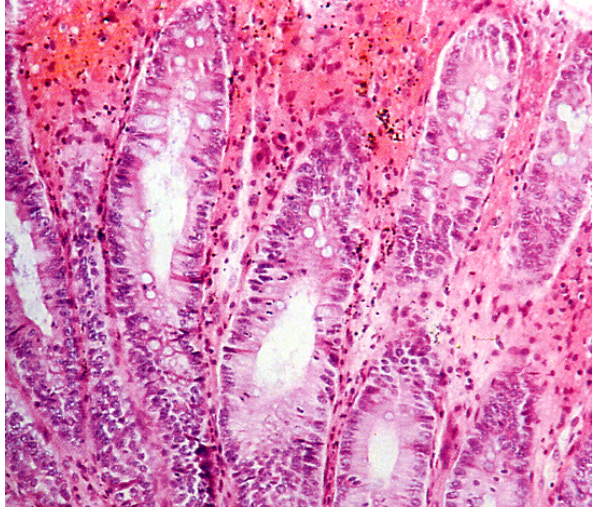
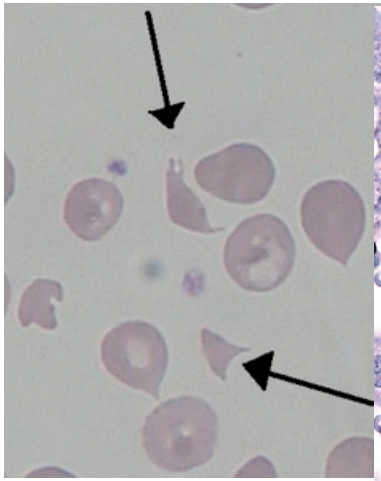
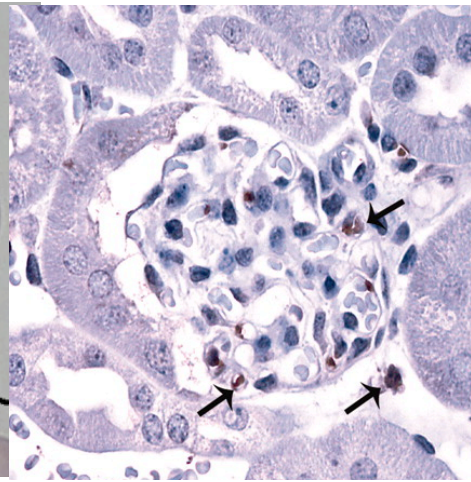
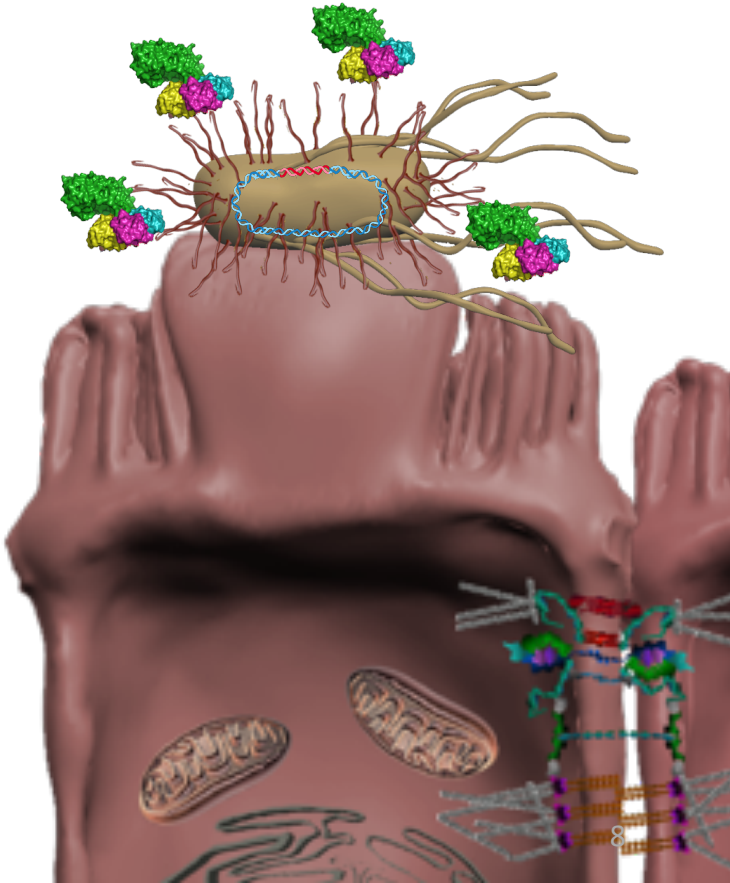






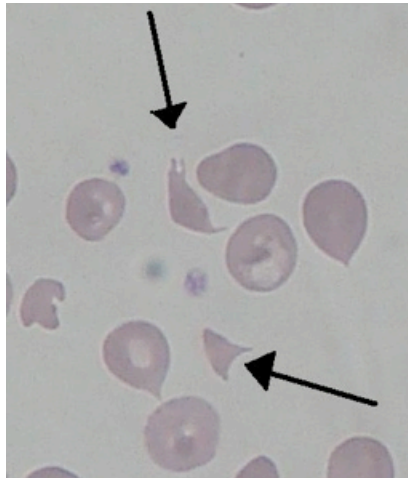
StEC pathogenesis

- After attachment and effacement, StEC produces Shiga toxins
- Shiga Toxin is an A-B toxin with 5 B subunits arranged in a ring around the A subunit
  - The B subunit binds the sugar decorated lipid, globotriosyl ceramide (Gb3) on the cell surface and initiates uptake.
    - susceptible cells include glomerular, colonic, and cerebral epithelial and microvascular endothelial cells, monocytes and platelets
  - The A subunit is an an enzyme that inactivates the ribosomes in the cytosol
    - Protein synthesis stops
    - intoxicated cells undergo apoptosis
    - proinflammatory cytokines (IL-8) and chemokines released



StEC pathogenesis

- Local blood vessels are affected
  - endothelial intoxication-
    - promotes platelet adhesion and vascular damage
  - Microthrombi lead to local ischemia
  - Bloody diarrhea
- Toxin can be distributed systemically
  - microthrombi and vascular damage cause shearing of red blood cells- i.e. hemolysis
  - Glomerular endothelial cells secrete multimers of VW Factor after toxin stimulation.
  - renal microthrombi lead to renal failure



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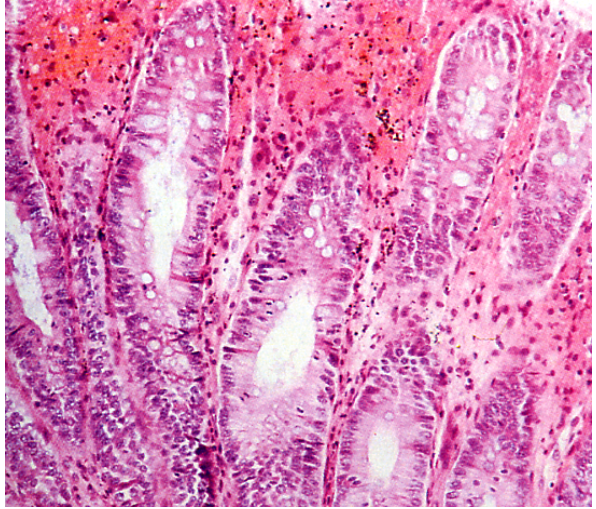

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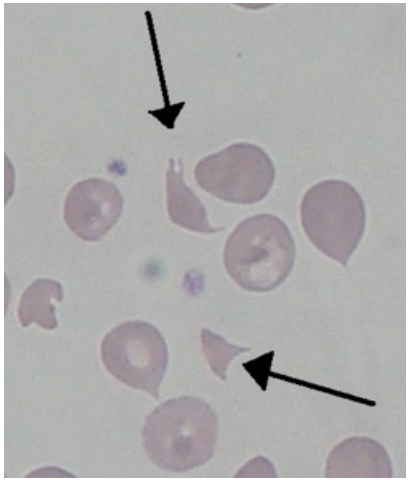

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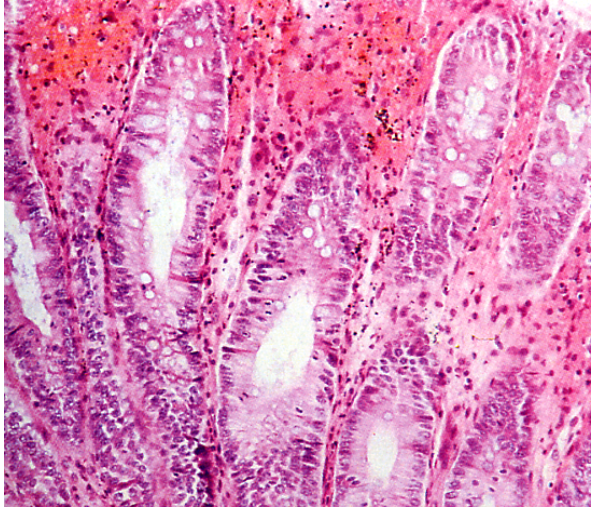
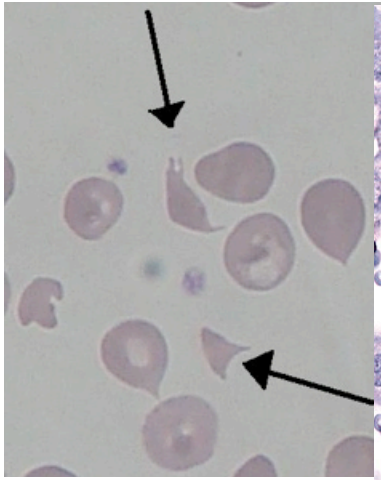
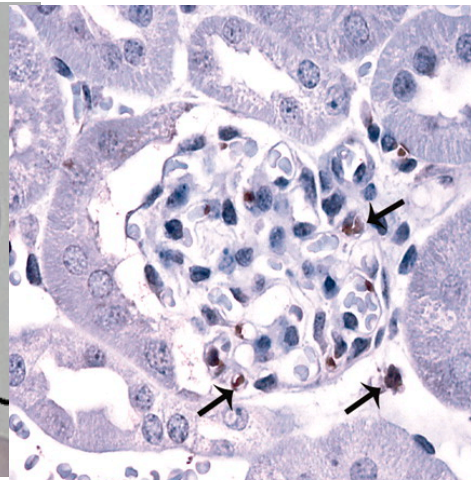
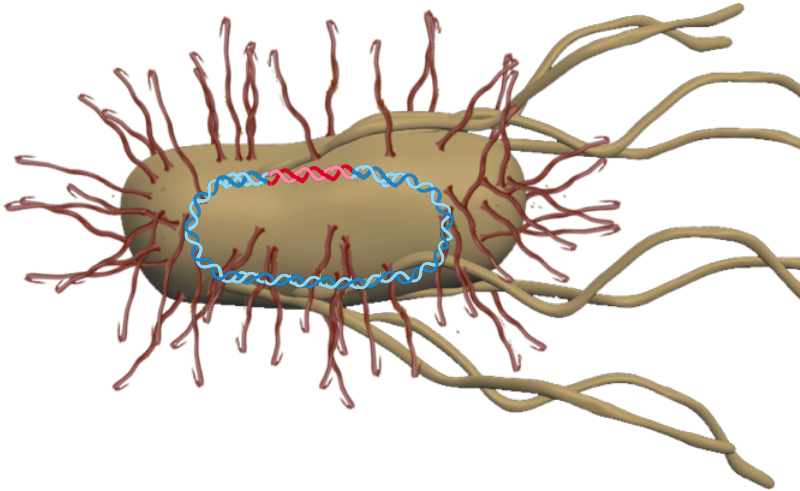


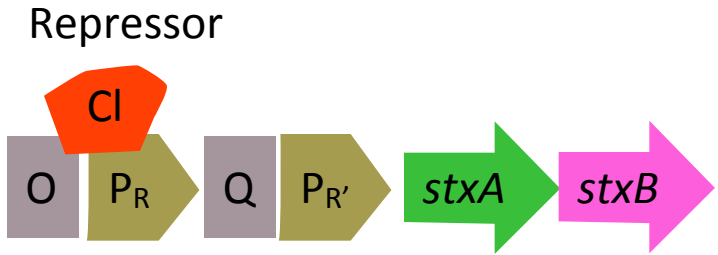




StEC Evolution & Treatment



- StEC acquired the Shiga-toxin genes through infection by a bacteriophage
  - Toxin genes are near other phage genes
- Toxin production and release increases when the bacteria are stressed-
  - induces bacteriophage lytic cycle
- Some antibiotics induce toxin production and release
- Antibiotic treatment increased rates of HUS in some studies



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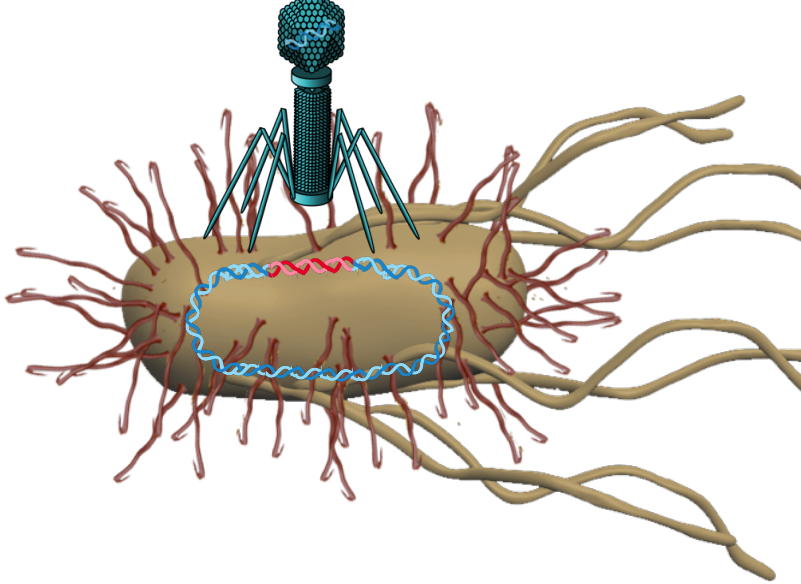

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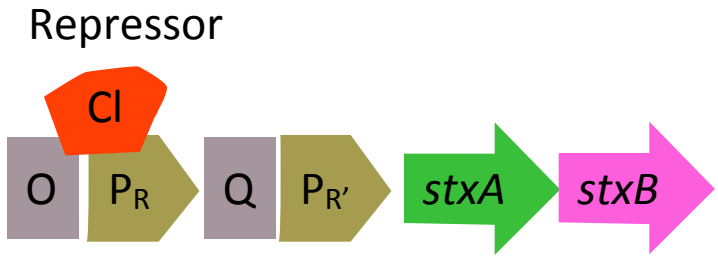

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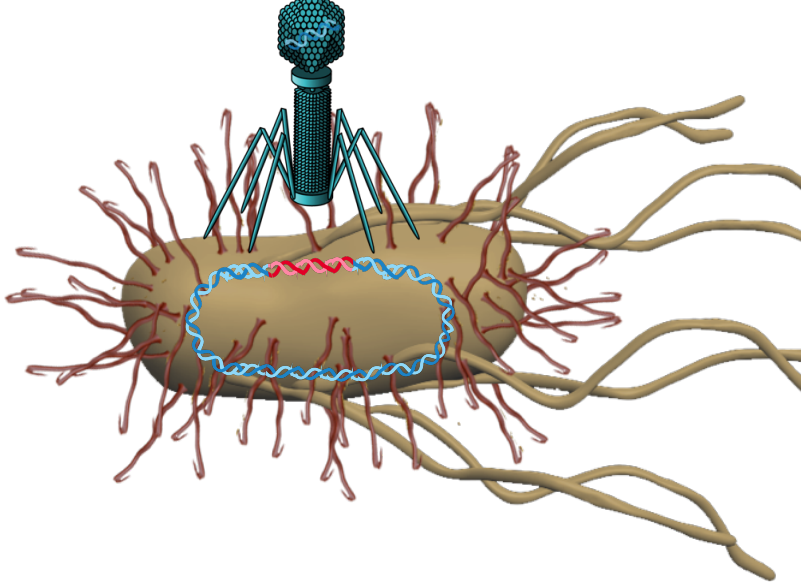

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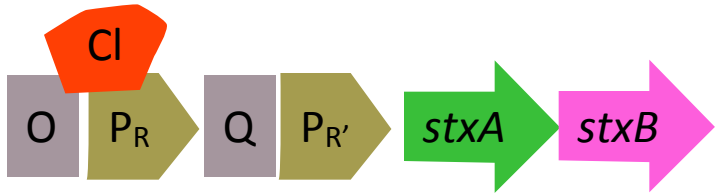
SOS!

Repressor



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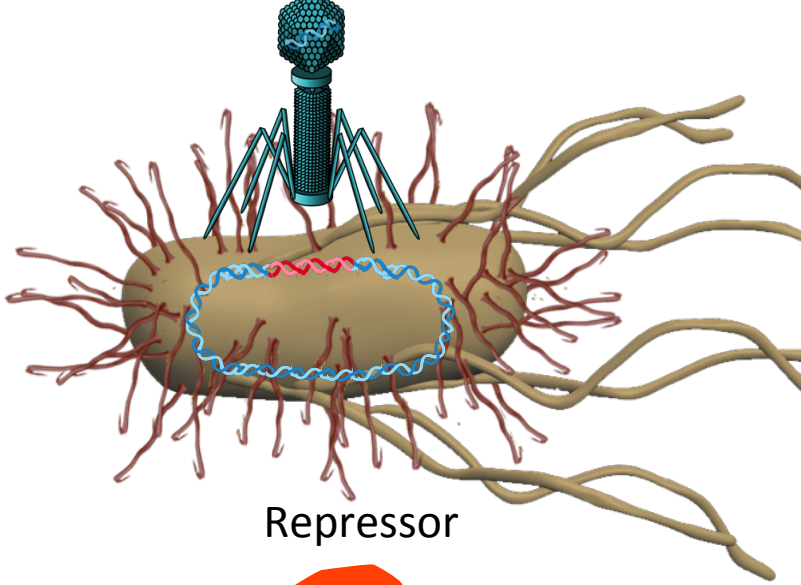

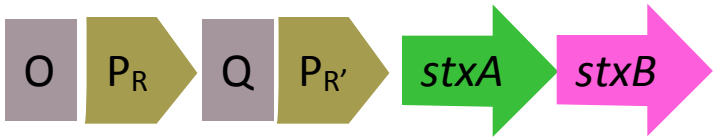

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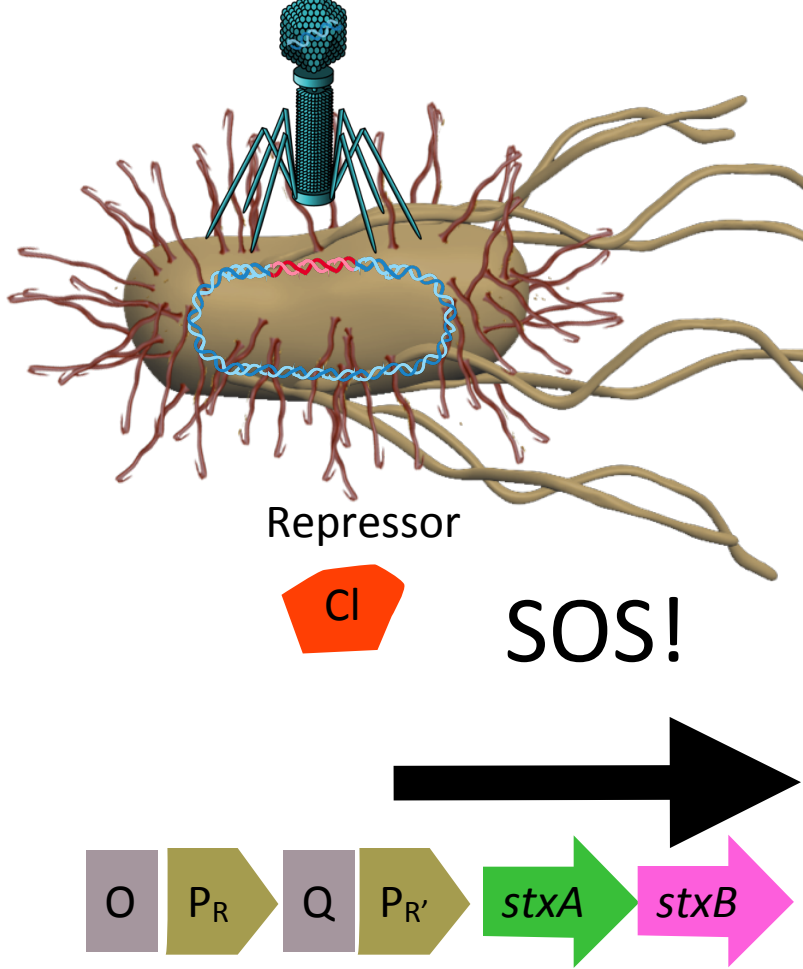

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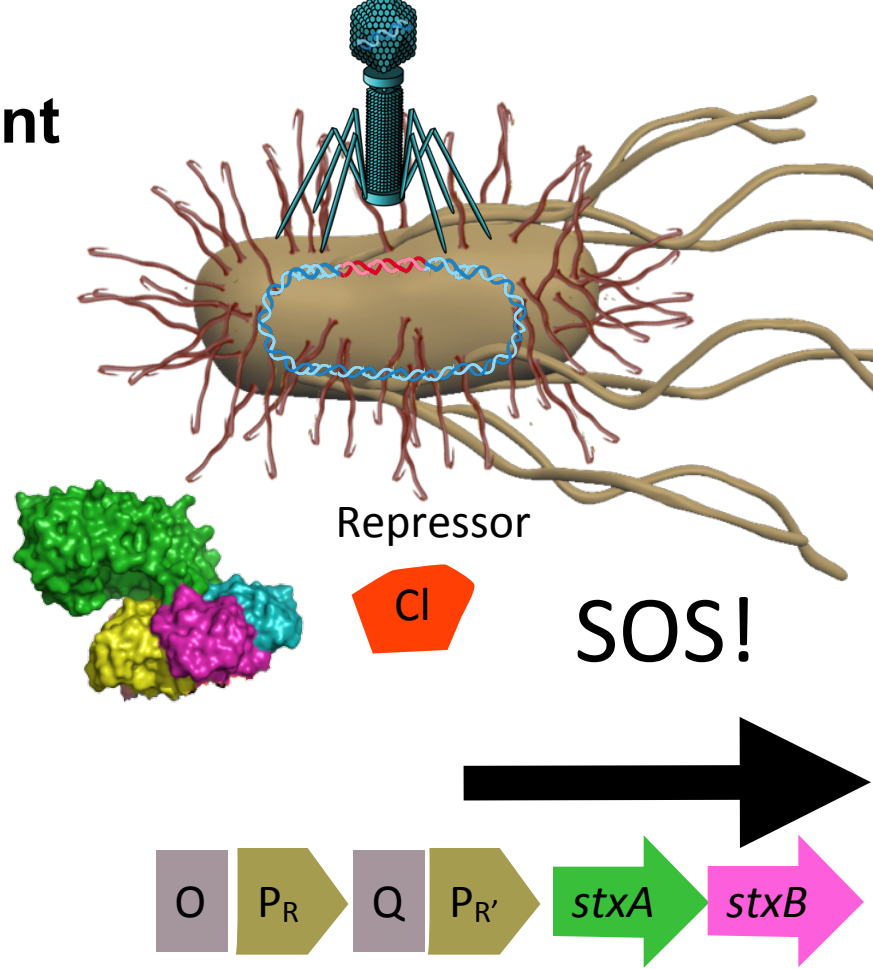

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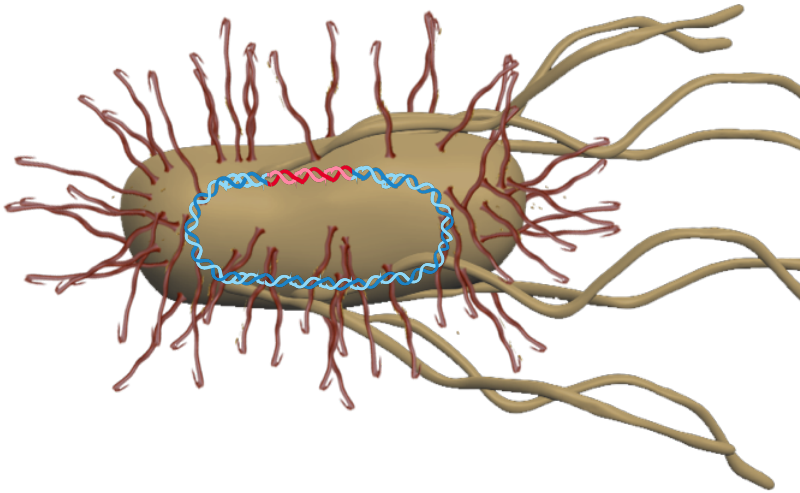

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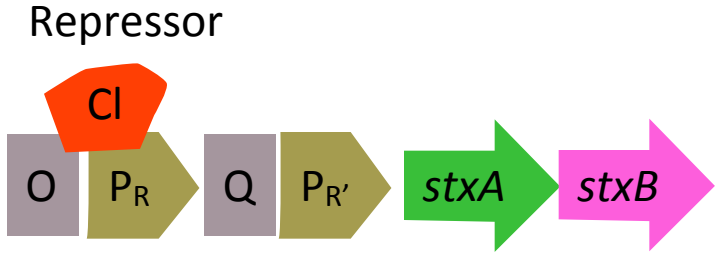
  - intravenous volume expansion
  - RBC and platelet transfusions
  - Dialysis
- New ideas being tested- but narrow therapeutic window
  - StEC vaccines
  - anti-toxin monoclonal antibodies
  - receptor mimics



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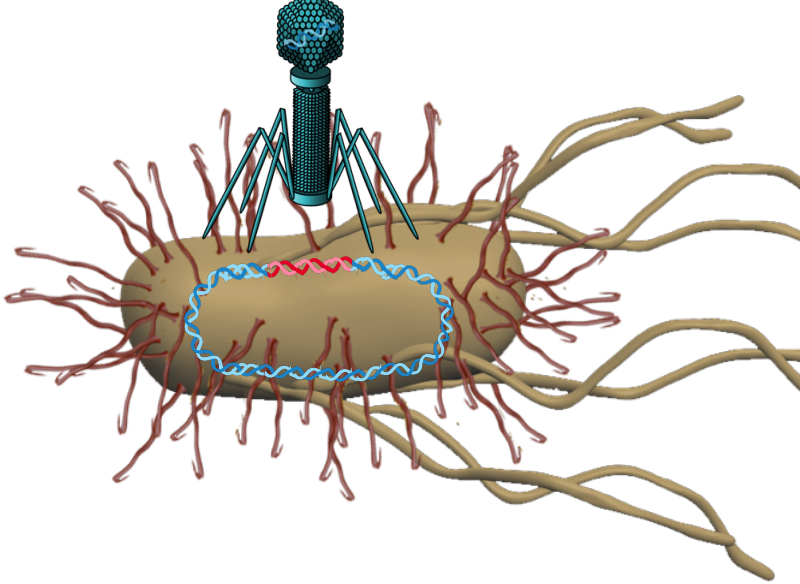

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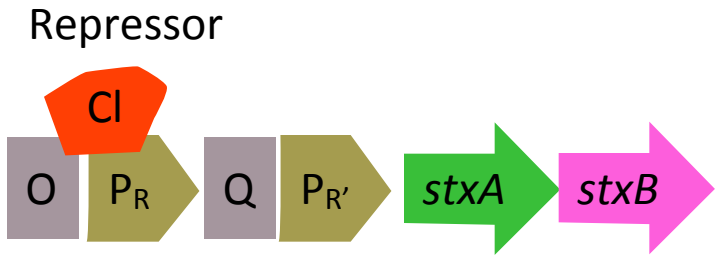

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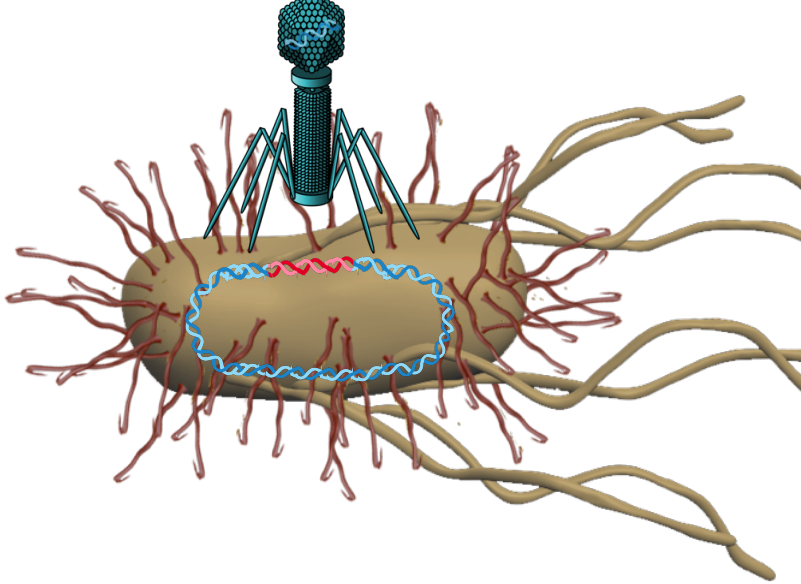

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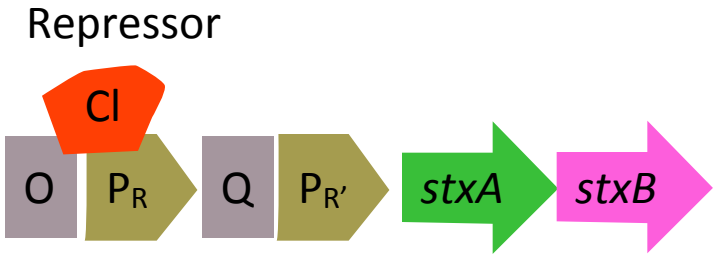

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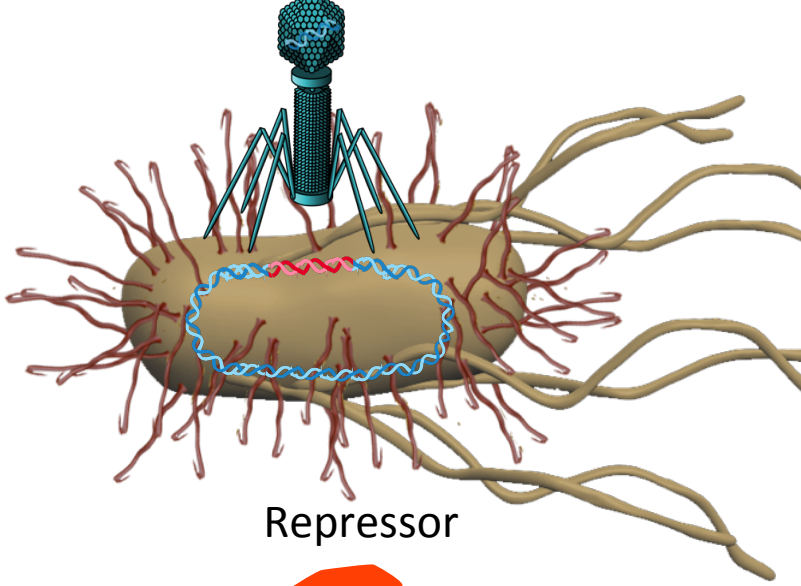

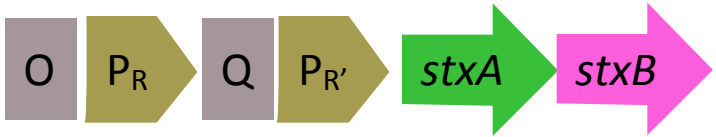

StEC Evolution & Treatment

- Treatment is thus supportive
  - intravenous volume expansion
  - RBC and platelet transfusions
  - Dialysis
- New ideas being tested- but narrow therapeutic window
  - StEC vaccines
  - anti-toxin monoclonal antibodies
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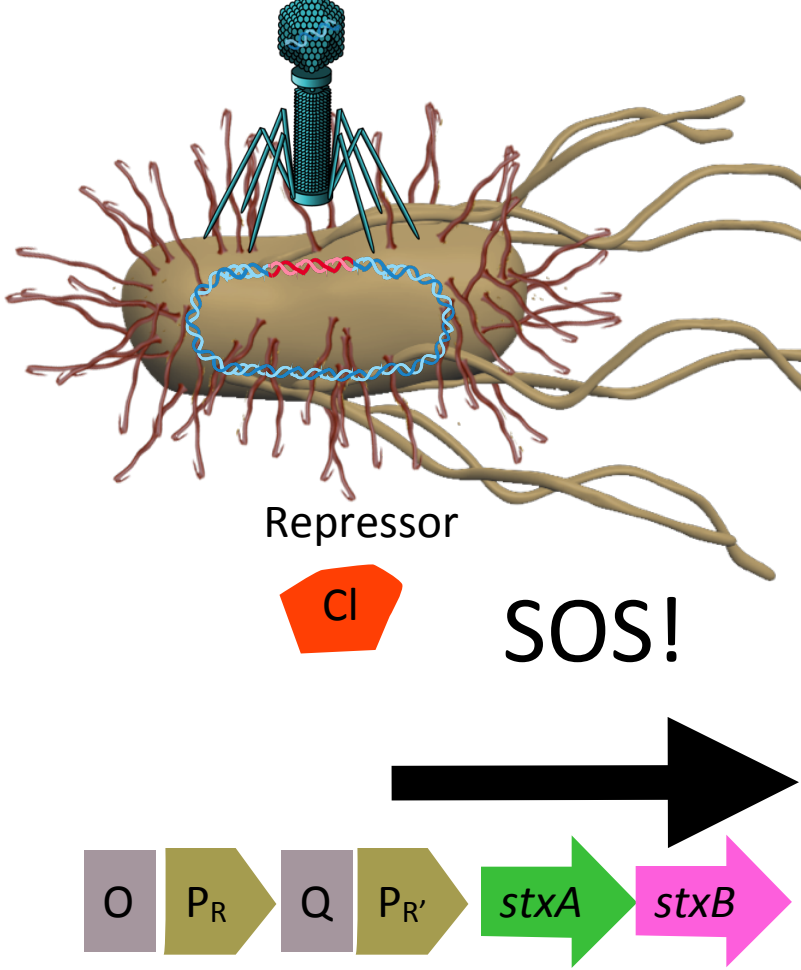

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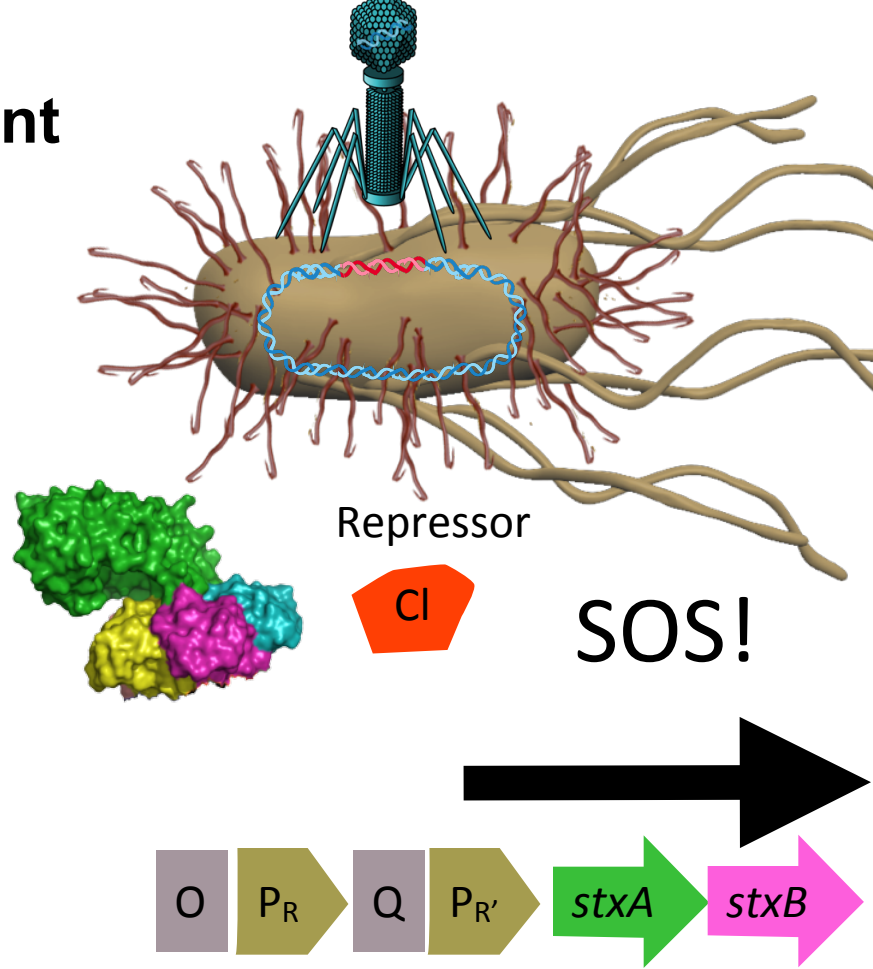
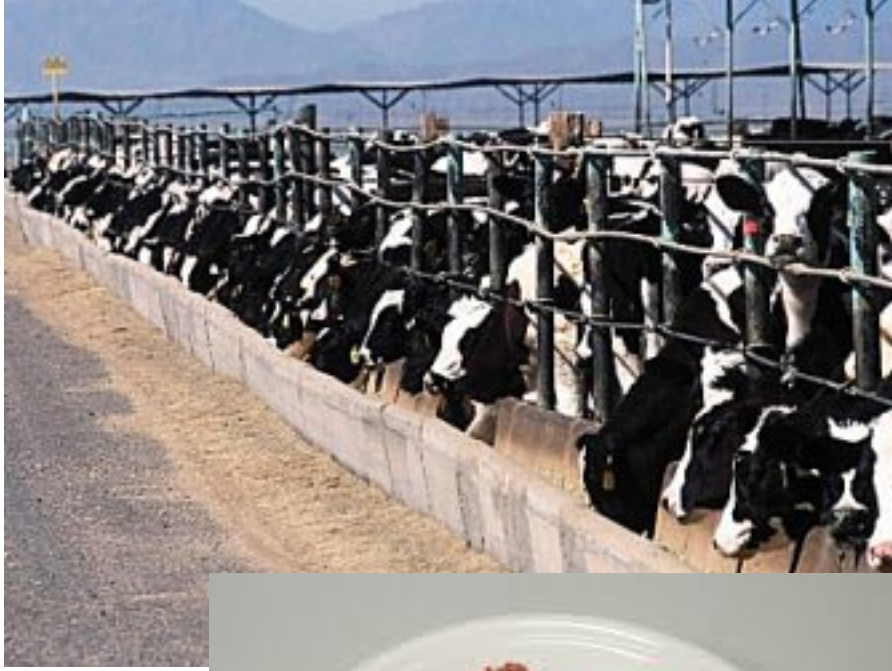


StEC Transmission

- The source of StEC is contaminated food.
- Zoonotic- commensals in animals
  - Healthy cattle
  - Not spread human to human like ETEC and EPEC
- Used to be called “hamburger disease” from consumption of contaminated undercooked meat
- Now leafy greens are the food most commonly associated with foodborne outbreaks
- U.S. Estimates: over one ton of animal manure per person per year.
- 40 times more than the amount of human waste

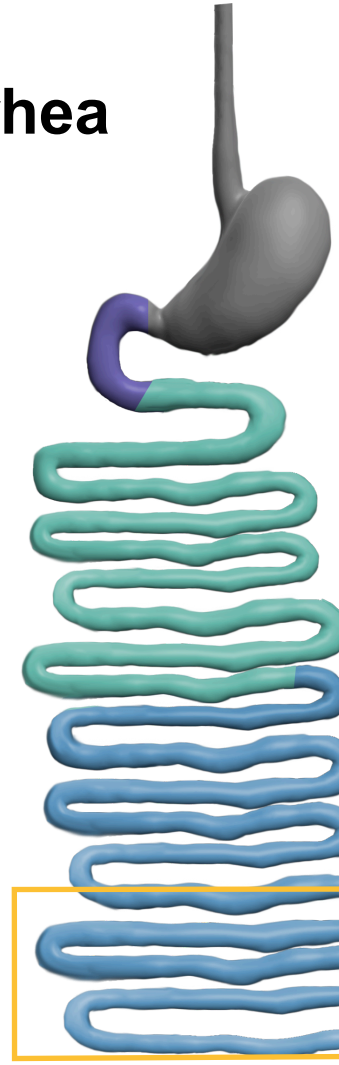


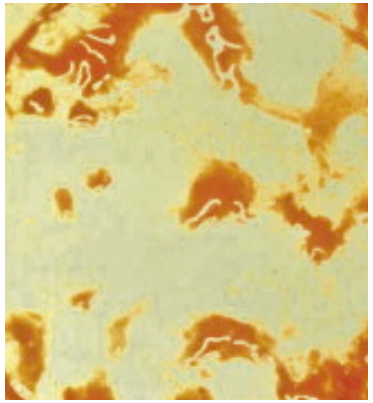
Emerging pathogens....

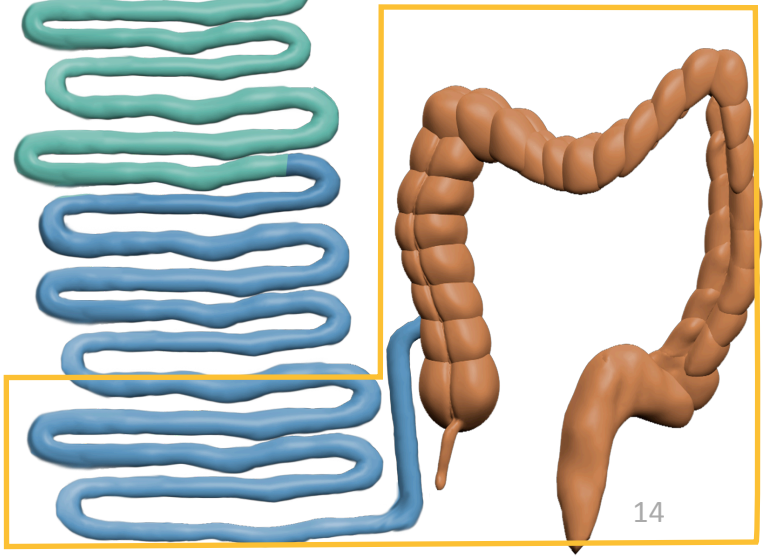
- In 2011 an foodborne outbreak of bloody diarrhea and HUS started in Germany and affected 4000 poople in several countries
- 25% developed HUS- worse than others
- New strain of StEC found to be an EAEC with Shiga toxin
- Source was Fenugreek Sprouts imported from Egypt into Germany- Health Foods

Inflammatory or Bloody Diarrhea

Clinical Features	Frequent small volume stools. May have streaks of blood, mucosy from pus. Pain on defecation (tenesmus), ileocolitis, colitis. Fever may be present.
Complications	Depend on etiology and host features- Hemolytic Uremic Syndrome, Bacteremia
Management	Consider stool cultures, antibiotics for some etiologies but may worsen others
Anatomical Location	Proximal Small Intestine
Pathogenesis	Damage to enterocytes with local inflammatory responses, direct invasion and cytotoxin damage- Locally invasive
Viruses	none in immunocompetent
Bacteria	***Shigella*, Shiga-toxigenic *E. coli* (EHEC, StEC)**, EIEC, *Campylobacter jejuni, non-Typhi-Salmonella, Yersinia*
Protozoa	*Entamoeba histolytica*





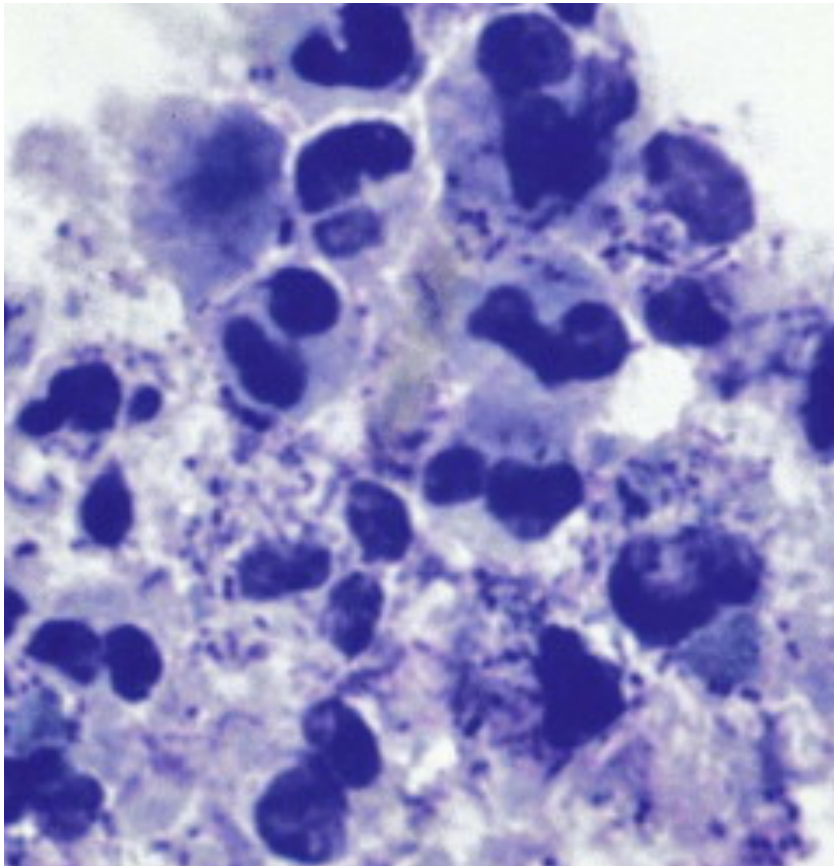


Shigella

- *Shigella* is a variant of *E. coli*
- Acquired a plasmid with virulence genes for invasion into epithelial cells and macrophages.
  - Can replicate intracellularly
- They only infect humans (primates)
- Fecal-oral transmission
- Very low infectious dose (10-100)
  - Food, feces, fingers, flies

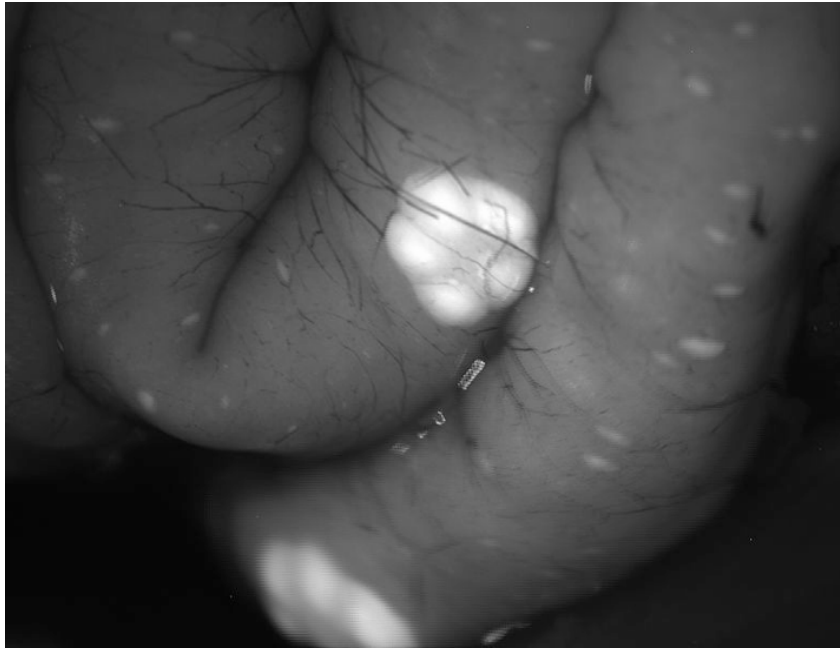
Shigellosis- dysentery

- Incubation period of 1- 7 days
- Fever, anorexia followed by abdominal cramping and watery diarrhea that becomes bloody with mucus and neutrophils in the stool
- Frequent, low volume stools (up to 50-100 per day) with a sense of urgency and pain on defecation (tenesmus)
- Treatment with antibiotics is recommended



Shigella pathogenesis

- Invade through M-cells in the terminal ileum and colon
- Like EPEC and StEC they have a T3SS which they use to inject cells
- T3SS effectors induce their uptake into the cells
- Intracellular *Shigella* escape into cytosol and use actin to move inside the cell
- Intracellular Shigella spread from cell to cell
- Infected cells secrete cytokines that cause inflammation



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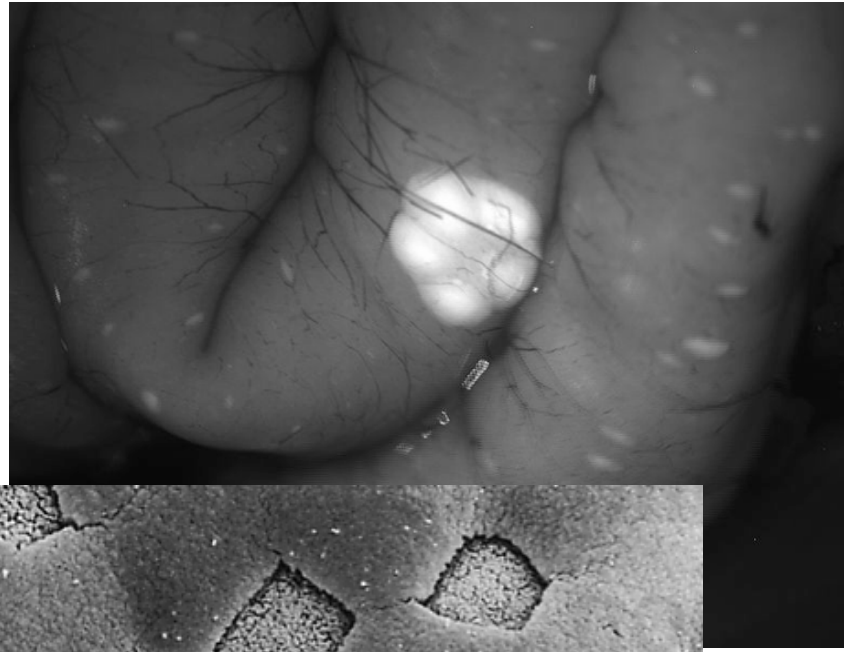

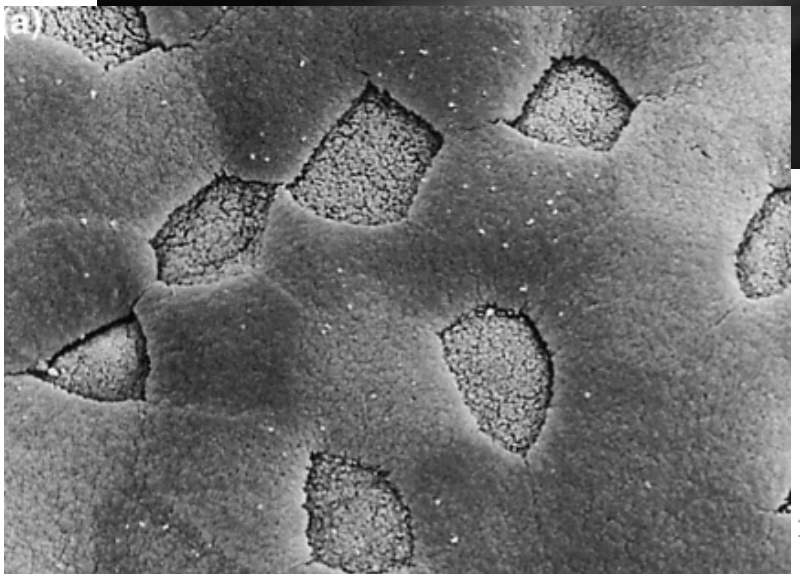

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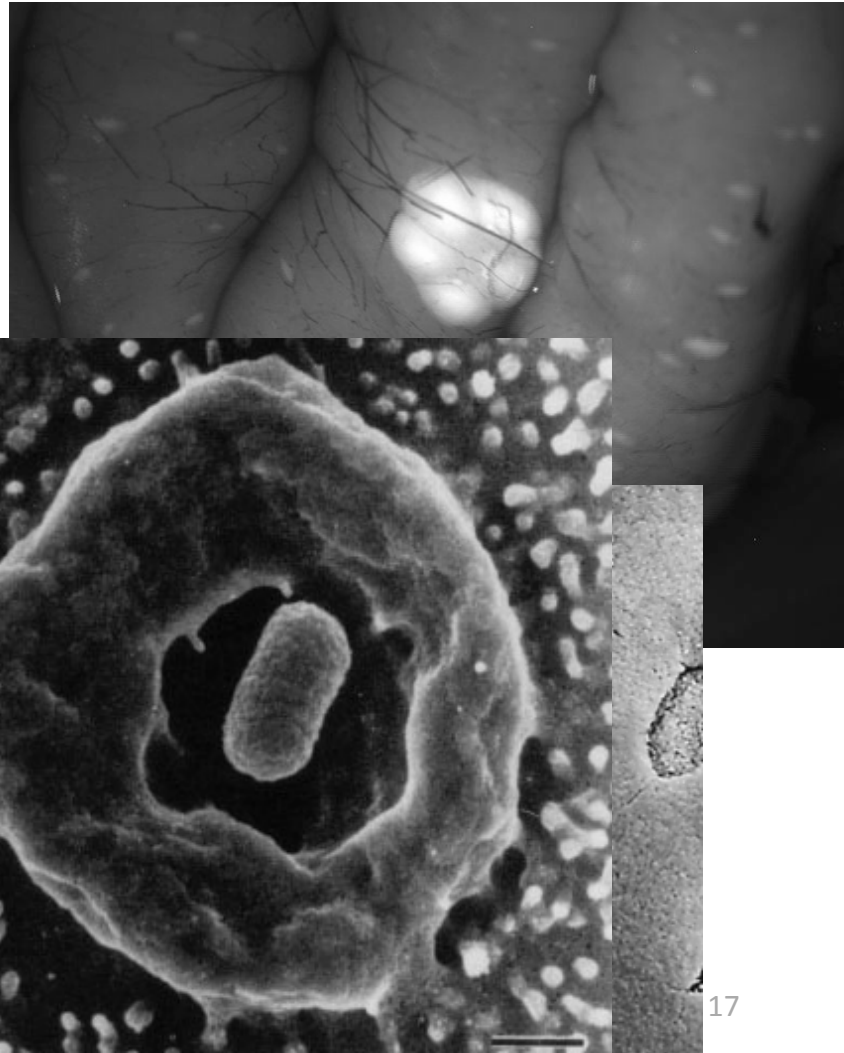

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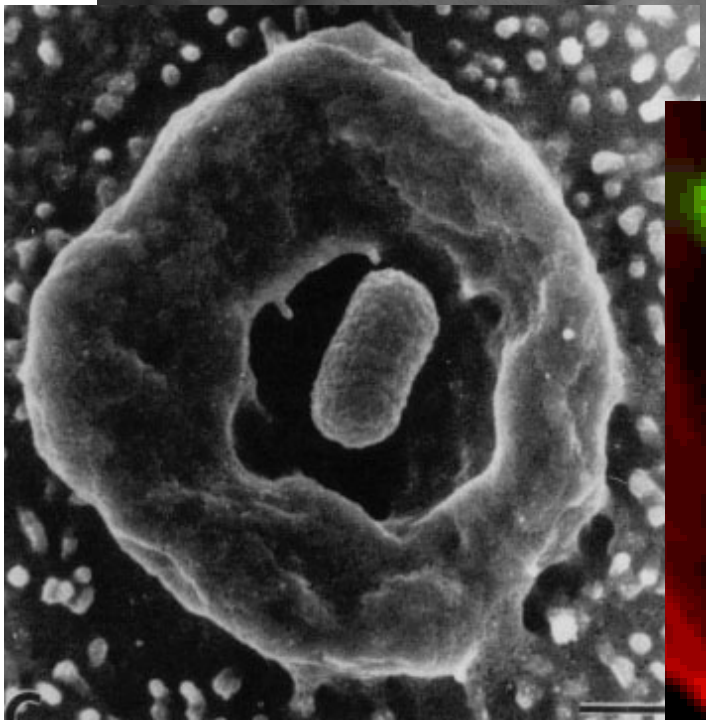

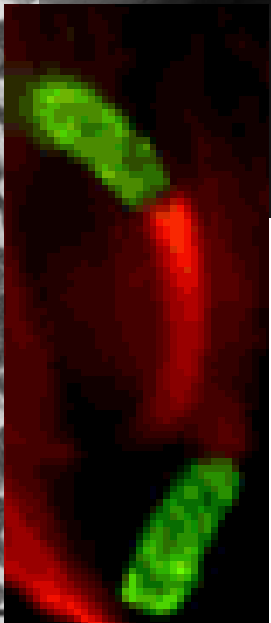

Credits: Inflammatory Diarrhea- StEC and Shigella

Slide 5: Dysenteric stool. Figure 18.6 Typical dysenteric stool is a small-volume mix of blood and pus. Such stools may be passed 30 or more times per day, often with increased pain (tenesmus). From: Shigellosis. Tropical Infectious Diseases: Principles, Pathogens and Practice. Keusch, Gerald T.; Salam, Mohammed A.; Kopecko, Dennis J. January 1, 2011. Pages 137-144. © 2011.
https://www.clinicalkey.com

Slide 7: Haemolytic microangiopathy
http://commons.wikimedia.org/wiki/File:Schizocyte_smear_2009-12-22.JPG

Slide 12: Concentrated Animal feeding operation.
http://commons.wikimedia.org/wiki/File:Confined-animal-feeding-operation.jpg

Hamburger meat
http://en.wikipedia.org/wiki/Ground_beef/

Slide 13: Fenugreek sprouts.
http://www.herbsarespecial.com.au/free-sprout-information/fenugreek.html

Slide 16: Fecal leukocytes taken from patient with diffuse colitis (methylene blue stain). In Bacillary Dysentery : Shigella and Enteroinvasive Escherichia coli in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. DuPont, Herbert L.. Published December 31, 2014. Volume 138, Issue 5. Pages 2569-2574.e1. © 2015. Copyright © 2014 Elsevier, Inc. All rights reserved.
https://www.clinicalkey.com

Slide 17: Peyer's patch (two large bright structures) in mouse guts. Transgenic mouse expressing MHCII-GFP protein, as seen by fluorescent stereomicroscope. MHC class II gene is expressed in antigen-presenting cells (APCs), such as B cells, dendritic cells and macrophages
http://commons.wikimedia.org/wiki/File:Peyer_patches_MHCII-GFP_mouse.jpg

Credits: Inflammatory Diarrhea- StEC and Shigella

Slide 17: M-cell and cell with actin membrane rearrangement being invaded by shigella courtesy of Stanley Falkow Shigella
http://commons.wikimedia.org/wiki/File:Peyer_patches_MHCII-GFP_mouse.jpg

Slide 18: Animation of Shigella invading the gut courtesy of Professor Chihiro Sasakawa University of Tokyo, Japan