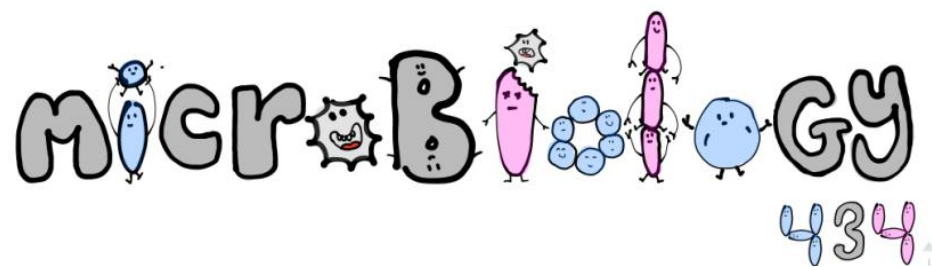


CHOLERA



General:

- A **life-threatening intestinal** infection
- Causes severe **secretory** diarrhea induced by **enterotoxin** secreted by *V. cholerae*
[non-invasive diarrheal disease → only produce toxin and doesn't invade the tissue]
- It has pathogenic & non-pathogenic strains
- **It can be identified by :**
 - **Genomic structure**
 - **Pathogenesis [MOA]**

Epidemiology:

- A major **epidemic** disease [وباء – مرض آلاف في وقت واحد]
- Common in India Sub-Saharan Africa, Southern Asia
- Very **rare** in industrialized countries
- Endemic in **poor sanitation** areas [India & Bangladesh] → **by O139**
- **7** Pandemics since 1817 first 6 [**classical**] – last one [**El tor**]
- 1993: **8th** pandemic in Bengal caused by **O139** type
- It is a leading cause of **Death** in Africa
- **Mortality rate:**
 - Causes 120,000 deaths/year worldwide
 - With prompt rehydration: <1%
 - Without treatment: 50%-60%

Serotypes:

- Has **over 150** identified serotypes **based on O antigens** & 206 serotypes **overall**
- only **O1 and O139** are **toxigenic** and cause Cholera disease

<u>O1 serotypes</u>	<u>O139 Serogroup</u>	<u>Non-O1, Non-O139 Serogroup</u>
<ul style="list-style-type: none">○ Have 2 categories:<ul style="list-style-type: none">▪ Classical: 1 case per 30-100 infections▪ El Tor: 1 case per 2-4 infections	<ul style="list-style-type: none">• In 1993, it emerged as a new serogroup and caused a epidemic in Bengladish• O139 organisms produce a polysaccharide capsule but do not produce O1 LPS or O1 antigen.• Toxigenic O139 cholera rose through the acquisition of a large block of genes encoding the O139 antigen by O1 El Tor.	<p>Most are CT (cholera toxin) negative and are not associated with epidemic disease.</p>

Profile of vibrio cholera:

- **Gram-negative** – **curved or coma** shaped rods - **Highly motile** by a single polar flagellum - Proliferate in **summers**
- Found in Brackish rivers & Costal waters :
 - Associate with **plankton and algae**
- Incubation Average is 1-3 days
- **Shorter incubation period in :** [range from hours to 5 days]
 - **High gastric pH** (from use of antacids)
 - Consumption of **high dosage of cholera**

Transmission:

- Grows in salt and fresh **water**
- **Strictly Human transmitted**
- Can survive and multiply in **brackish water** [may persist in **shellfish or plankton**]
- **Water-borne** illness caused by ingesting water/food contaminated by infecting copepods
- **Contamination of water could be due to:**
 - **Inadequate sewage treatment**
 - **Lack of water treatment**
 - **Improperly cooked shellfish**
- Transmitted by **fecal-oral** route
- Transmission by casual contact is **unlikely**

Pathogenesis:

- To establish disease, *V. cholerae* must be ingested in **contaminated food or water** and **survive passage** through the gastric barrier of the stomach.
- On **reaching the lumen** of the small intestine, the bacteria must **overcome** the clearing mechanism of the intestine (peristalsis), **penetrate** the mucous layer and establish contact with the epithelial cell layer.
- The biological activity of Cholera Toxin is dependent on **binding of the holotoxin B pentamer** to specific **receptors** on the eukaryotic cell.
- The B oligomer binds with **high affinity** exclusively to **GM1 ganglioside**.
- Enzymatically, **fragment A1 catalyzes** the transfer of the ADP-ribosyl moiety of NAD to a component of the adenylate cyclase system.
- The **A1 fragment** catalyzes the attachment of **ADP-Ribose (ADPR)** to the regulatory protein forming **Gs-ADPR** from which GTP cannot be hydrolyzed.
- Since GTP hydrolysis is the event that **inactivates** the **adenylate cyclase**, the enzyme **remains continually activated**
- Thus, the net effect of the toxin is to cause **cAMP** to be produced at an abnormally **high rate** which stimulates mucosal cells to pump **large amounts of Cl-** into the intestinal contents.
- H₂O, Na⁺ and other electrolytes **follow** due to the **osmotic and electrical** gradients caused by the loss of Cl⁻
- The **lost H₂O** and electrolytes in mucosal cells are **replaced from the blood**.
- Thus, the toxin-damaged cells become **pumps for water** and electrolytes causing the **diarrhea**, loss of electrolytes, and dehydration that are characteristic of cholera.

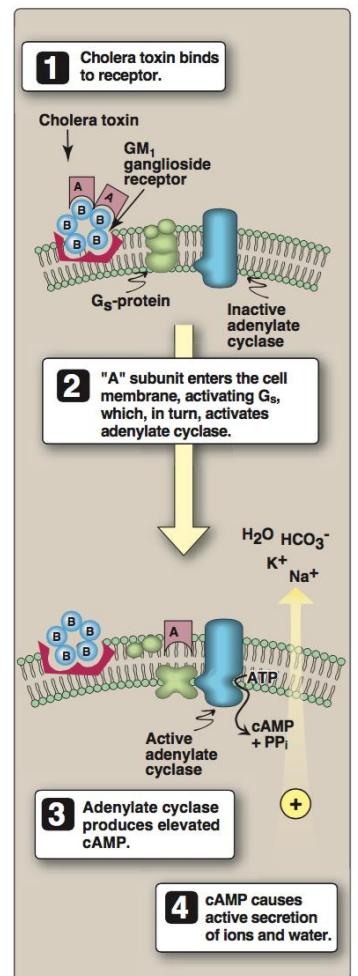


Figure 12.13
Action of cholera toxin. cAMP = cyclic adenosine monophosphate, PP_i = pyrophosphate.

How Does Cholera Toxin Work? [summarized version of the pathogenesis]

Inactivates GTPase function of G-protein coupled receptors in intestinal cells → G proteins stuck in "On" position → 100X increase in cAMP → activation of ion channels → Ions flow out and water follows

People who are most at risk:

- People with **low gastric acid**, more susceptible. (**children** more than adult).
- **O blood type** are at high risk than other blood group [O → B → A → AB]

Infectious Dose:

- 10^6 - 10^{11} colony forming units
- **Why such high dose ?**
 - It goes under a series of **changes** as it moves from the aquatic environment to the intestine [**Temp – Acidity**]
 - Stomach **acidity**
 - **Intestinal environment**
 - **Bile salts, organic acids, complement inhibit bacteria growth**
 - **Must penetrate mucous lining of intestinal epithelial cells**

Period of Communicability: the period where it can be transmitted to other people

- During **acute** stage
- A few days **after recovery**
- By end of week , **70%** of patients **non**-infectious
- By end of third week, **98%** **non**-infectious

Symptoms

1. Occur 2-3 days after consumption of contaminated food/water
2. Usually mild, or no symptoms at all [**75% asymptomatic – 20% mild disease – 2-5% severe**]
3. Vomiting
4. Cramps
5. **Watery** diarrhea (1L/hour)
6. Without treatment, death in [18 hours-several days] because of dehydration
7. **No fever—not invasive**

Visible Symptoms (Diagnostic symptoms):

Decreased **skin turgor**, **Sunken eyes-cheeks**, Almost **no urine production**, **Dry mucous membranes**, **Watery diarrhea** **consists of:**

- Fluid **without** RBC, proteins.
- **Electrolytes.**
- **Enormous numbers of vibrio cholera (10^7 vibrios/mL.)**

No clinical manifestations help distinguish cholera from other causes of severe diarrhea:

- **Enterotoxigenic e. coli.**
- **Viral gastroenteritis.**
- **Bacterial food poisoning.**

Cholera should be suspected when patients present with **watery diarrhea, severe dehydration**, Based on clinical presentation and confirmed by **isolation of vibrio cholera from stool**.

Cholera Gravis:

- More **severe symptoms**
- **Rapid loss of body fluids**
 - 6 liters/hour
 - 10^7 vibrios/mL
- Rapidly **lose** more than 10% of **bodyweight**
- Dehydration and shock
- **Death** within 12 hours or less
- Death can occur within 2-3 hour



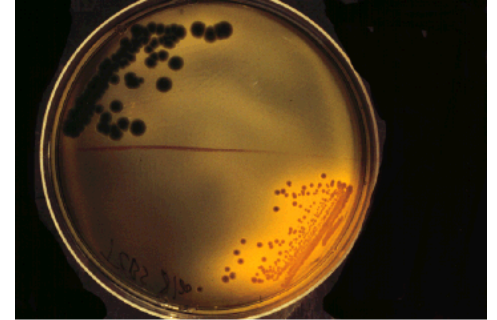
Consequences of Severe Dehydration:

- **Intravascular volume depletion.**
- Severe metabolic **acidosis.**
- **Hypokalemia.**
- Cardiac and renal **failure.**
- **Sunken eyes, decreased skin turgor.**
- Almost **no urine** production.



Laboratory Diagnosis:

- Visualization by dark field or phase microscopy
(**Look like “shooting stars”**) see picture
- Gram Stain (**Red**, curved rods of bacteria.)
- Isolate *V. cholerae* from patient’s stool
(Plate on Thiosulphate bile salt **sucrose agar** and **Yellow** colonies form.)



Vibrio species on TCBS agar Vibrio species can be selectively recovered from stool by culture on thiosulfate-citrate-bile salts-sucrose (TCBS) agar. On this medium, *V. parahaemolyticus* usually produces a green colony and *V. cholerae* a yellow colony (indicative of the fermentation of sucrose). Courtesy of Harriet Provine.

Prevention:

- **Disrupt fecal-oral** transmission.
- Water **Sanitation.**
- **Water treatment:**
 - **Disinfection:** **chlorine** added to kill remaining pathogens (only treatment given to water systems with groundwater sources)
 - **Storage:** put in **closed tank** or reservoir (clear well)
 - Allows **chlorine** to mix and disinfect all water.
 - **Distribution**

Prevention Efforts:

- **WHO: Global Task Force on Cholera Control**
 - **Reduce** mortality and morbidity
 - Provide aid for social and economic consequences of Cholera
- **CDC**
- **U.N.: GEMS/Water**
 - Global Water Quality **Monitoring** Project
 - Addresses global issues of water quality with monitoring stations on all continents.

Traveling precautions:

- Boil or treat water with chlorine or iodine
- No ice [we don’t know the source of the water]
- Cook everything
- Rule of thumb: “Boil it, cook it, peel it, or forget it.”
- Wash hands frequently

Treatment:

Even before identifying cause of disease, rehydration therapy must begin immediately because death can occur within hours

Oral rehydration	Intravenous rehydration	Antimicrobial therapy
<ul style="list-style-type: none"> – Reduces mortality rate from over 50% to less than 1%. – Recover within 3-6 days. – Should administer at least 1.5x amount of liquid lost in stools. – Use when less than 10% of bodyweight lost in dehydration. <p>Oral Rehydration Salts (ORS):</p> <ul style="list-style-type: none"> – Reduces mortality from over 50% to less than 1% – Packets of Oral Rehydration Salts <ul style="list-style-type: none"> ○ Distributed by WHO, UNICEF ○ Dissolve in 1 L water ○ NaCl, KCl, NaHCO₃, glucose 	<ul style="list-style-type: none"> – Used when patients have lost more than 10% bodyweight from dehydration. – Unable to drink due to vomiting. – Only treatment for severe dehydration. – Ringer’s Lactate <ul style="list-style-type: none"> ○ Commercial product ○ Has necessary concentrations of electrolytes – Alternative options <ul style="list-style-type: none"> ○ Saline ○ Sugar and water ○ Do not replace potassium, sodium, bicarbonate 	<ul style="list-style-type: none"> – Adjunct to oral rehydration. – Reduce fluid loss by half. – Reduce recovery time by half. <ul style="list-style-type: none"> ▪ 2-3 days instead of 4-6. <p>Tetracycline, Doxycycline.</p>

Vaccines:

- Need **localized mucosal** immune response
 - Oral Vaccine
- **Not recommended**
 - Travelers have **very low risk** of contracting disease: 1-2 cases per million international trips
 - **Not cost-effective** to administer vaccines in endemic regions
 - Brief and incomplete immunity
- **Two types approved for humans:**
 - Killed whole-cell
 - Live-attenuated

Killed Whole-cell Vaccines: <u>Disadvantages</u>	Live Attenuated Vaccines: <u>Disadvantages</u>
<ul style="list-style-type: none"> • 50% protection for 6 months to adults. • Gives less than 25% protection to children aged 2-5. • Need for multiple doses of nonliving antigens. 	<ul style="list-style-type: none"> • In children, protection rapidly declines after 6 months. • In adults, only receive 60% protection for 2 years. • Live vaccine induces mild cholera symptoms <ul style="list-style-type: none"> – Mild diarrhea, abdominal cramping.

Ideal Bioweapon:

- Ease of procurement.
- Simplicity of production in large quantities at minimal expense.
- Ease of dissemination with low technology.
- Silent dissemination.

MCQs:

1-Which of the following is not true regarding cholera:

- A) intestinal infection
- B) invasive diarrheal disease
- C) caused by V.cholera endotoxin
- D) major epidemic disease

2- a 32 year old male has traveled to Brazil for 3 months. During that period he went to a traditional see food restaurant after a while he noticed cramps and has developed severe diarrhea. When he went to the hospital he was diagnosed with cholera. What is the average period required to develop his symptoms.

- A) few hours -5 days
- B) 3-5 days
- C) 1-3 days
- D)1 week

3- which of the following is a characteristic feature of V.cholera:

- A) gram +ve
- B) ciliated
- C) proliferate in summers
- D) it has pathogenic and nonpathogenic strains.

4-what is the the most common way of transmission of V.cholera:

- A) contaminated food or water
- B) casual contact
- C) sexually
- D) inhalation

5- which of the following is at highest risk to be infected by V.cholera:

- A) pregnant women
- B) male
- C)AB blood type
- D) low gastric acidity

6-what is the action of cholera toxin on the intestinal cells:

- A) increase the flow out of electrolytes by activation of ion channels.
- B) decrease the absorption of water
- C) damage the wall of the intestines
- D) none

7- what is disadvantage of killed whole cell vaccines:

- A) the applied person may develop the symptoms
- B) requires multiple doses
- C) the protection in children rapidly declines after 6 months
- D) all

Answers: B - C - D - A - D - A - B

GOOD LUCK <3 ...

Hi, I'm V. cholerae.

I'm a Gram negative, oxidase positive fermenter bacteria.

Many of my strains cause cholera, a severe diarrhoeal illness.

I can be epidemic or pandemic and I love the developing world.

I have a high fatality in malnourished populations, where people get very dehydrated.



VIBRIO
CHOLERAЕ

To give you severe diarrhoea, my strains need to make the cholera toxin.

I have lots of strains!

Most of my strains that cause outbreaks are 'type-01' strains, but there are also 139 'non-type-01' strains.

You can classify me into Inaba, Ogawa and Hikojima serotypes if you want. Or you could classify me into classical and El Tor biotypes (you don't see my El Tor much anymore though).

حنان محمد عبدالمنعم

منيرة الدريهم

ندى العمري

سارة الجاسر