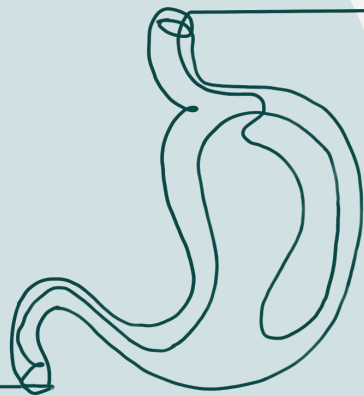


Cholera

Microbiology



An interesting story about cholera

Editing File

Summary

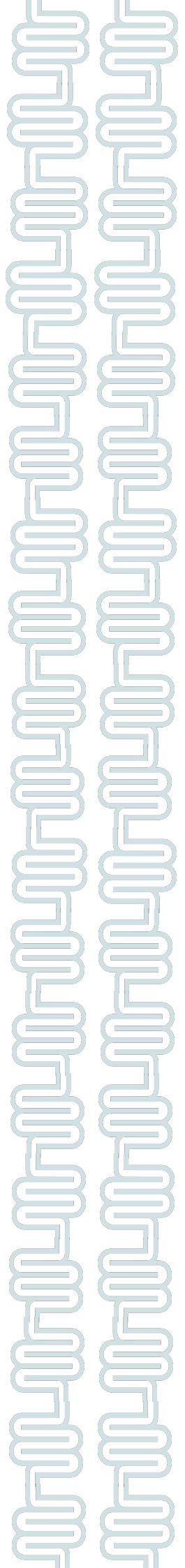
Color index

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| ● Girls' slides | ● Boys' slides |
| ● Main content | ● Extra |
| ● Important | ● Drs' notes |



Objectives:

- Know the epidemiology of cholera and history of cholera
- Know the microbiological characteristic of cholera
- Describe the pathogenesis of cholera
- Describe the clinical features of cholera
- Describe the methods laboratory diagnosis
- Know the management of cholera and control of outbreak



Cholera

A **waterborne** life threatening **diarrheal disease**

Etiology

- Vibrio Cholerae
- **Comma shaped Gram -ve rods**
(oxidase positive)

Epidemiology

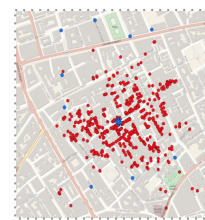
- Found in **salt and fresh water**.
- leads to outbreak and epidemic.

Characteristics

- Has many serotypes based on O-antigen
- **O 1 and O 139.**
- **Produce a non-invasive enterotoxin.**
- Can be prevented by good sanitation system.

Discovery

- John Snow discovered an outbreak in London 1854.
- It was related to broad street pump sewage contamination.
- 'Removal of the pump handle' end of the outbreak



John Snow



Jon Snow

Epidemiology

Dr: Just know that it has different serotypes O1 and O139.

V. cholera O1 and O139 serogroup organisms are the causes of epidemic cholera.

O1 (from 1817 till now):

- Classical: 1 case per 30-100 infections
- El Tor: 1 case per 2-4 infections (Seventh pandemic)

O139 (recently in 1992 in Asia only):

- Contained in India, Bangladesh.

- o Seven major outbreaks.
- o Majority in India, Sub-Saharan Africa, Southern Asia. Usually due to problems with infrastructure. (Poor access to clean water)
- o Endemic in > 50 countries.
- o Each year 3-5 millions cases result in 100,000 deaths.

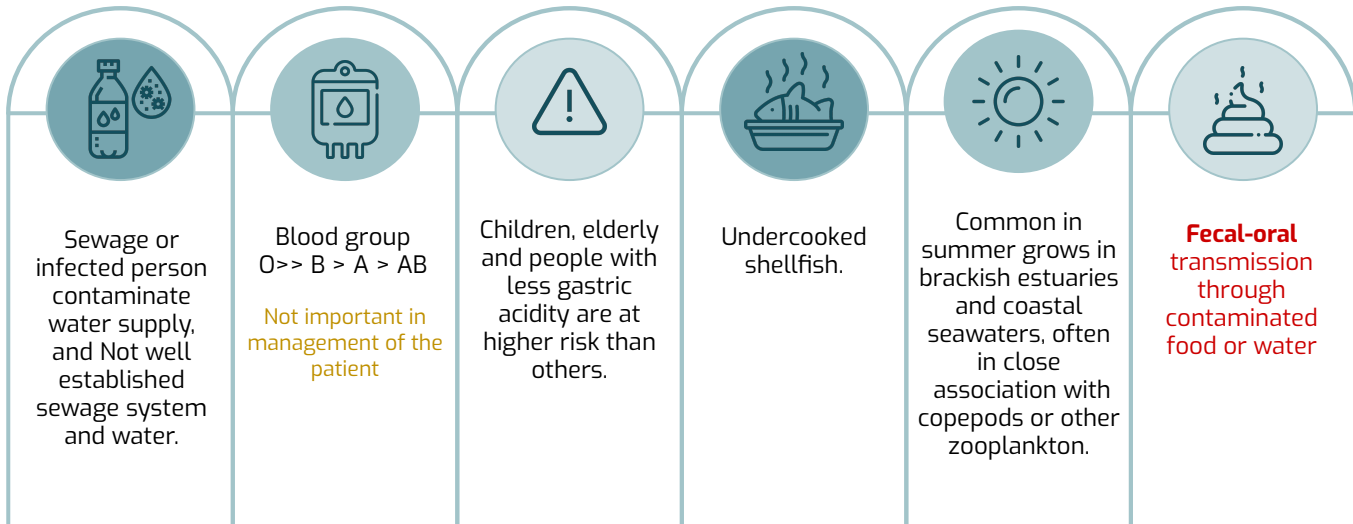
Infectivity



- o **Period of infectivity during acute stage till recovery (end one to three weeks)**
- o **Infected person can produce up to 20 L of 10^9 CFU/ml/day**⁽¹⁾
- o **Has high infectious dose NOT like Shigella (shigella only 200 CFU)**
- o **Infectious dose 10^6 - 10^{11} colony-forming units.**
Due to harsh environment of the intestine i.e. temperature and stomach acidity, Bile salts and organic acids in the intestine (small amount can't survive)

⁽¹⁾ Colony - Forming Unit

Transmission



Clinical Manifestation




Ranges from a few hours to 5 days (range 1-3 days)

- Depending on gastric acidity and initial infectious dose.
If patient is taking antiacids, he will get the infection quickly (because if the gastric acidity is low you are not able to destroy the bacteria)
- Majority have mild, or no symptoms at all

- 75% asymptomatic
- 20% mild disease
- 2-5% severe **Mainly pediatrics**

Pathogenesis

Pathogenesis

Toxin AB Toxin	<ul style="list-style-type: none"> Vibrio cholerae uses toxin-coregulated pili (TCP) to colonize the human intestine. Cholera results from secretory diarrhea caused by the actions of cholera toxin (CT) on intestinal epithelial cells. CT is an adenosine diphosphate – ribosylating enzyme that leads to chloride, sodium, and water loss from intestinal epithelial cells 	
Mechanism Toxin binds and affects cAMP → affects the channel responsible for electrolyte movement → electrolytes pass to lumen → dehydration and diarrhea	<ol style="list-style-type: none"> Cholera toxin binds to Monosialoganglioside (GM1) which is a glycosphingolipid on the surface of epithelial cells. The toxin must undergo cleavage of the active, A1 component (CTA1), which goes on to constitutively activate the Gs protein Nicotinamide adenine dinucleotide (NAD), mediated by CTA1 becomes Adenosine diphosphate (ADP)-ribose & binds to G protein G protein regulates adenylyl (adenylate) cyclase activity (AC). Elevation in the intracellular cyclic adenosine monophosphate (cAMP) concentration. When the concentration of cAMP increases water and electrolyte shift from the cell to the intestinal lumen, This results in extremely watery diarrhea accompanied by electrolyte imbalances 	
	Mild disease	Cholera gravis <small>Severe form</small>
Symptoms	<p> Vomiting.</p> <p> Cramps.</p> <p> Watery diarrhea⁽¹⁾ (1L/hour): with flecks of white mucus NOT pus! (rice watery stool) very characteristic (especially if patient is coming from area with poor infrastructure) & a fishy/foul odor.</p> <p> ↓ Ca++ and K can lead to ileus, muscle pain, spasm, & even tetany.</p>	<p>More severe symptoms due to Rapid loss of body fluids:</p> <p> Rapidly lose more than 10% of body weight.</p> <p> Dehydration and shock. <small>The most common cause of death</small></p> <p> Sunken eyes,⁽²⁾ and ↓ skin turgor⁽³⁾ (tenting), cold and clammy.</p> <p> Anuric & lactic acidosis (Kussmaul breathing).⁽⁴⁾</p> <p> Hypoglycemia → seizure or comma.</p> <p> Cardiac and Renal failure.</p> <p> Aspiration pneumonia. <small>when patient is dehydrated he might lose consciousness. When he vomits in this state, the risk of aspiration pneumonia increases.</small></p>
Water Loss	1 liter/hour.	6 liters/hour (10 ⁷⁻⁹ vibrios CFU/mL).
Mortality	Death occurred in (18 hours - several days) if not treated due to dehydration. loss of fluid & electrolytes	<ul style="list-style-type: none"> Death within 2-12 hours or less. Mortality 50-60% without treatment. Mortality <1% with rehydration.

⁽¹⁾ Watery diarrhea with viral infections and Bloody diarrhea with bacterial infection

⁽²⁾ جحوظ العين، لأن السوائل تثبت العين في مكانها

⁽³⁾ is the skin's elasticity. It is the ability of skin to change shape and return to normal ، الجلد يبصير جاف و يابس بسبب فقد السوائل

⁽⁴⁾ Is a deep breathing pattern associated with severe metabolic acidosis

Diagnosis

Diagnosis

Dr: just remember the color of colonies (yellow) and Gram stain (Gram negative comma shaped bacilli)

Suspect in severe diarrhea with dehydration.

Other non-invasive bacterial, ETEC and viral gastroenteritis might have similar presentation.

Complete history and physical examination.

Insert central line for IV fluid, collect blood for basic routine tests (chemistry and hematology).

Send stool for smear and culture on special media.

Culture not routinely performed, you have to request it

Dark field microscopy (motile shooting stars) this bacteria is motile (has flagella), and it moves very quickly like shooting stars

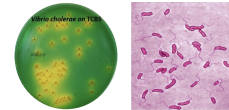
Gram stain : curve Gram Negative bacilli

Culture on thiosulfate citrate bile sucrose (TCBS)^[1] agar-**yellow colonies** this media is special for *Vibrio cholerae* (other bacteria cannot grow, and if it grows, it will not produce yellow colonies appearance)

Recovery of organisms can be enhanced by enrichment of stool in alkaline peptone water (60-100%)

Diagnosis / Microbiology

Vibrio cholerae is highly **motile, Gram-negative, curved or comma-shaped rods/bacilli** with a single polar flagellum.



Dr: No need to memorize the classification (just know that there are serotypes O1 and O139

Biotype O 1 antigen	Serotype	Antigen	O 139 serogroup appeared in Bangladesh 1992	Non-O1, Non-O139 Serogroup
Classical	Ogawa	A,B	Has polysaccharide capsule but does not have O1 antigen	Most are CT (cholera toxin) negative and are not associated with epidemic disease.
	Inaba	A,C		
	Hikojima	A,B,C		
El Tor	Ogawa	A,B		
	Inaba	A,C		
	Hikojima	A,B,C		

^[1] no need to remember it (just know that it needs special media)

Treatment

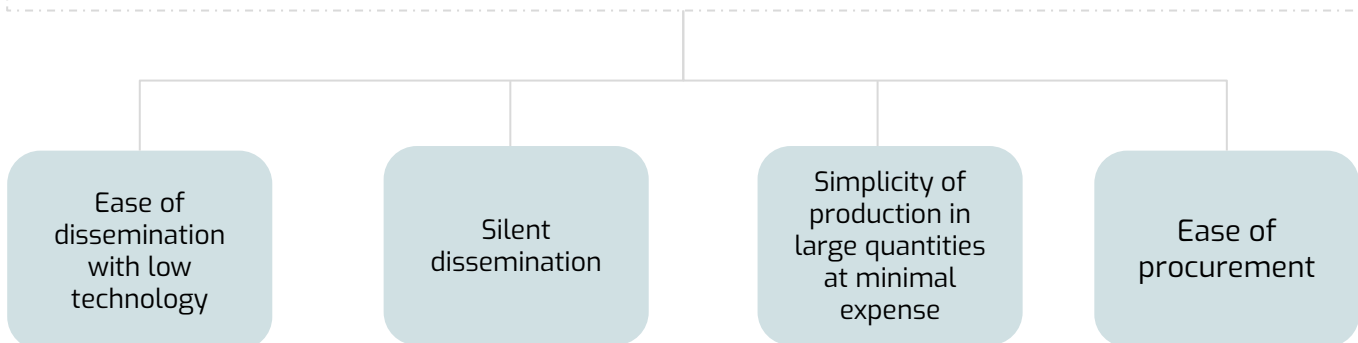
★ Remember: **BOTH Fluid + Antibiotics**

Rehydration and antimicrobial therapy.

Rehydration	Antibiotics Choice depends on condition & age of patient.
<ul style="list-style-type: none"> - Rehydration should be started immediately before confirming the diagnosis - Either oral rehydration if the patient can tolerate it (not vomiting) or start IV rehydration. - Decrease mortality from 50% to 1 % - Give 1.5 time the amount lost. - Start when 10% of total body weight lost. - Patients recovered within 3-6 days. - Oral Rehydration Salt (ORS) by WHO and UNICEF one pack in 1 liter contain NaCl, KCl, NaHCO₃, glucose - IV use either Ringer's lactate, Saline or Sugar and water 	<ul style="list-style-type: none"> - Reduce the recovery time to 2-3 days - Decrease infectivity - Azithromycin single-dose is often the preferred therapy especially in children, - or Ciprofloxacin Dr:contraindicated in patients under 18 and pregnancy - or Tetracycline contraindicated in children under age 8 and pregnancy , Doxycycline

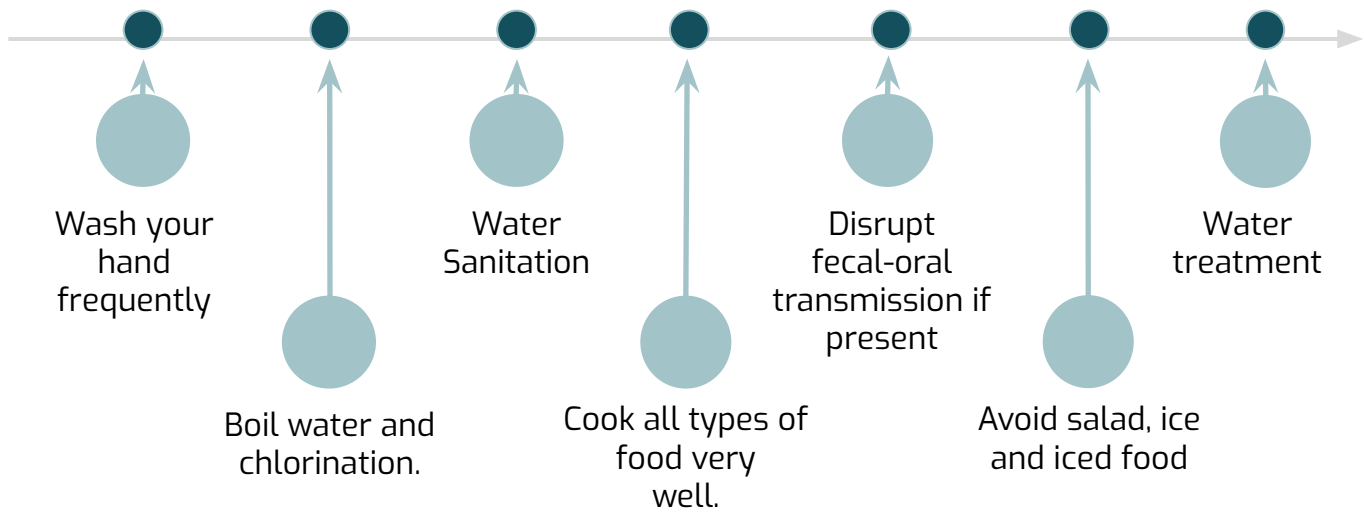
Bioterrorism

Can be a bioterrorism agents:



Prevention

Prevention



Vaccines are not used unless it is indicated for special situation (poor infrastructure, outbreak, or people who work in something related to sewage).

	Killed Whole-cell Vaccines	Live Attenuated Vaccines
Adult	50% protection for 6 months	60% protection for 2 years
children aged 2-5	< 25% protection	protection rapidly declines after 6 months
Doses	Multiple doses	-
Side effects	-	Mild diarrhea, abdominal cramping

International 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

Dr. Ali

- *Vibrio cholerae* is mostly acquired by fecal-oral route (Outbreak of *Vibrio cholerae* is by water contamination with sewage water usually due to problems with infrastructure. (Poor access to clean water). We do not see it very often, but if we did, it will be an international interest.
- ★ **Important:** morphology is Gram negative bacilli (most enteropathogenic bacteria are gram negative bacilli, but cholera has a unique characteristic which is that it is **comma shaped/curved**).
- When compared to shigella, *vibrio cholerae* needs a much higher dose to cause the infection. (One must drink a very large amount of contaminated water in order for him to get the infection). Whereas in shigella, small amount is enough to cause the disease.
- Usually, this organism gets killed by GIT flora and stomach acidity (that is why a high infectious dose is needed). For this reason, **people with low gastric acidity or those on antacids are more in risk** of getting this infection.
- Pathogenesis:
 - Cytotoxin: damages cells
 - **Enterotoxin (responsible for diarrhea):** affects/disturbs electrolyte → leads to passage of large amounts of fluid to lumen of intestine → diarrhea → patient gets dehydrated very quickly (within hours) → might lead to death if not treated especially in people who live in areas with short access to medical care.
- Exact mechanism of the enterotoxin: it binds and affects cAMP → affects the channel responsible for electrolyte movement → electrolytes pass to lumen → dehydration and diarrhea.
- Patients need to be given IV fluids because they will probably vomit the water they drink.
- ★ Patients mainly present with **watery diarrhea with flecks of white mucus (rice watery stool)** which is very characteristic (especially if the patient is coming from area with poor infrastructure).
- ★ Dr: just remember the color of colonies (**yellow**) and Gram stain (**Gram negative comma shaped bacilli**)
- *Vibrio cholerae* is motile (has flagella), and it moves very quickly like shooting stars under dark field microscopy.
- No need to memorize the classification (**just know that there are serotypes O1 and O139**)
- Treatment is medical and supportive. First of all, giving fluid and rehydrating the patient is essential (IV fluid if the patient is vomiting). Also, **electrolyte replacement** should be given. **Antibiotics** must be given not only to treat the patient, but also to stop the outbreak.
- ★ **Antibiotics + Fluid** لو جاكم سؤال لازم تذكرون كل الاتنين
- Not all enteropathogenic bacteria is treated. However, shigella, *vibrio cholerae*, and salmonella typhi must be treated (fluid + antibiotics).
- Vaccines are not used unless it is indicated for special situation (poor infrastructure, outbreak, or people who work in something related to sewage).

Dr. Fawzia

- From all O antigens. O1 and O139 are the ones that can cause epidemics.
- Characteristically, it affects small intestine (that is why it interferes with water reabsorption).
- Cholera is not a zoonotic disease, and it has nothing to do with animals (source of infection is human feces).
- The organism itself is not involved directly in causing the toxin itself. However, the toxin is the one responsible for causing the diarrhea.
- Cause of death in case of cholera is the hypotensive shock caused by the severe dehydration.
- The first line of management of cholera is giving IV fluid.
- Vaccine is not really effective.

Quiz

MCQ

Q1: Which of the following is NOT correct about cholera?

- A- Gram -ve bacilli
- B- Has a single polar flagellum
- C- produce not invasive enterotoxin
- D- Low infectious dose

Q2: A 13 year-old came with his parents suffering from severe diarrhea and dehydration caused by an outbreak of V.cholera what's your management goal

- A- Fluid rehydration
- B- Antibiotics therapy
- C- Antidiarrheal Therapy
- D- fluid rehydration + antibiotics therapy

Q3: Which blood type that is more susceptible to cholera more than the other?

- A- Blood type A
- B- Blood type B
- C- Blood type AB
- D- Blood type O

Q4: Which of the following is not true about cholera?

- A- Gram negative
- B- Highly motile
- C- Curved or comma shaped rods
- D- has multiple flagella

Q5: what other differential diagnosis that have the same clinical presentation as cholera?

- A- viral gastroenteritis
- B- esophagitis
- C- peptic ulcer
- D- GERD

Q6: a 30 years old female came to the ER with severe diarrhea and dehydration, bacterial culture revealed a highly motile gram negative bacilli with a single polar flagellum, which one of the following antibiotics is used to treat this patient?

- A- penicillin
- B- ciprofloxacin
- C- Amphotericin B
- D- vancomycin

Answers: Q1:D | Q2:D | Q3:D | Q4:D | Q5:A | Q6:B

SAQ

Case: A group of villagers came to the clinic complaining of muscle cramps, dehydration and watery diarrhea they described it as a watery stool with flecks of white mucus (rice water stool) in further investigation they have been diagnosed with Cholera caused by a contaminated water supply **IMPORTANT male's DR**

Q1: Describe the Gram Stain

A: curved or comma Gram Negative bacilli

Q2: what's the clinical presentation

A: mainly dehydration and watery diarrhea

Q3: What do you see under Dark-Field microscopy

A: motile shooting stars microbes

Q4: Describe the culture in TCBS media

A: yellow colonies

Q5: What's the infectious dose of this organism

A: 10^6 - 10^{11} very high

Q6: What's the management

A: fluid rehydration and antibiotic therapy

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