CHOLERA

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OBJECTIVES

At the end of this session each student will be able to:

1. Define cholera outbreak.
2. Describe the epidemiology of cholera.
3. Describe the cause of cholera.
4. Classify vibrio cholera.
5. Describe the pathophysiology of cholera.
6. Describe the clinical features of cholera.
7. Describe the differential diagnoses of cholera.
8. Describe the complications of cholera.
9. Investigate patients with cholera.
10. Treat patients with cholera.
11. Describe preventive measures for cholera.
12. Describe prognosis of cholera patients.

Background

- The term ‘cholera’ probably derived from the Greek word for the gutter of the roof, comparing an overflow of water following a rainstorm to that of the anus of an infected person.
- Cholera is a classical water-borne disease.

Definition

- Cholera outbreak should be suspected when a patient older than 5 years develops severe dehydration or die from acute, severe, watery diarrhoea or
- If there is a sudden increase in the daily number of patients with acute watery diarrhoea, especially patients who pass ‘rice-water’ stools typical of cholera.

Epidemiology

A. **Geographical:**

- Cholera has been rare in industrialized nations for the last 100 years.
- It is common in Indian subcontinent and sub-Saharan Africa.

B. **Age:**

- In non-endemic area, incidence of infection is similar in all age-groups.
- The exception is breastfed children, who are protected against severe disease because of less exposure and because of the antibodies to cholera they obtain in breast milk.

Epidemiology

C. **Host susceptibility factors:**

1. **Malnutrition.**
2. **Hypochlorhydria or achlorhydria of any cause:**
   - Helicobacter pylori.
   - Gastric surgery.
   - Vagotomy.
   - Use of H_2-receptor blockers for peptic ulcer disease e.g. cimetidine, ranitidine etc or proton pump inhibitors e.g. Omeprazole.

The presence of gastric acid in the stomach can quickly render an inoculum of vibrio cholerae non-infectious before it reaches the site of colonization in the small intestine.

Host susceptibility factors

3. **Blood group-O:**

- The role played by blood group-O is uncertain. The cause is unknown, but incidence of infection appears to be high in this population.

4. **Previous exposure and acquired immunity:**

- Rates are lower in areas where infection is endemic and if there are pre-existing vibriocidal antibodies from the previous encounters with the organisms, especially in adults.
- For the same reasons adults are symptomatic less frequently than children and secondary infections rarely occur or are mild.

Infection

- The risk of primary infection is facilitated by seasonal increase in the number of organism, possibly associated with changes in water temperature and algal blooms.
- **Hygiene:**

  Infection rates are highest in communities in which water, personal and community hygiene standards are low.

Transmission

- Transmission is normally through faecal-oral route by:

i. Drinking infected water.

ii. Eating uncooked or undercooked seafood.

iii. Eating food contaminated by flies or hands of carriers.

- Asymptomatic carriers:

They may have a role in transfer of disease in areas where the disease is not endemic.

Spread

- Infection spreads via the stool or vomitus of symptomatic patients or of the much larger number of subclinical cases.

Cholera pandemics in the world

1. First Pandemic, 1817-1823 involved middle east, the Indian Subcontinent and Zanzibar.
2. Second Pandemic, 1829-1851.
3. Third Pandemic, 1852-1859
4. Fourth Pandemic ,1863-1879
5. Fifth Pandemic, 1881-1896
6. Sixth Pandemic, 1899-1923
7. Seventh Pandemic, 1961 started on Suwalesi islands, Indonesia.

Cholera Epidemics in Tanzania Mainland

1. 1858-1859.
2. 1869-1870.
3. May to June, 1974 in Kyela Mbeya, 11 patients out of which 7 died.

   Stated to have been imported from Malawi.

Cholera Epidemics in Tanzania Mainland

4. 2nd October, 1977:

- Started in Twasalie Village, Rufiji District.
- Suspected to have been imported by a middle east merchant trading in “Mikoko” and “Mikandaa” coastal line timber in exchange for ornaments. His host died from cholera and attracted mourners from distant villages in Rufiji and else where in Tanzania.

Trend of the epidemics in Tanzania

Year	Cases	Deaths	%
1977	1,671	135	8.08
1978	13,300	1,076	8.09
1979	2,482	237	9.55
1980	5,169	504	9.75
1981	4,288	315	7.35

Cause

- Vibrio cholerae 01 and vibrio cholerae 0139.
- Vibrio cholerae are gram-negative, polar monotrichous, curved bacillus that ferments glucose, sucrose and mannitol.

Classification

- The species of vibrio choler has been classified according to carbohydrate determinant of its somatic O antigen.

Serotypes:

- Vibrio cholerae 01.
- Vibrio cholerae 0139.

Classification

Biotypes:

The 01 serogroup is divided into 2 biotypes:

- Classical.
- El Tor.

Each biotype has been subdivided into 2 serotypes:

- Inaba: It produces only A and C antigens.
- Ogawa: It produces the A and B antigens and a small amount of C.

NB: Hikojima, the third biotype, produces all three antigens but is rare and unstable.

Pathophysiology

- Cholera is a toxin mediated disease. Cholera toxin (CTX) is a potent protein enterotoxin elaborated by the organism in the small intestine.
- To reach the small intestine, the organism has to negotiate with normal defence mechanisms of the gastrointestinal tract.

Virulence factors for vibrio cholerae 01

1. Since the organism is not acid resistant, it depends on its large inoculum size to bypass gastric acidity.

- Infected water causes cholera when the infectious dose is between 10^{3-} 10^{6} bacteria.
- Infected food causes cholera when the infectious dose is between 10^{2-} 10^{4} bacteria.

Virulence factors for vibrio cholerae 01

The organism transcends the mucous layer of the small intestine by the following means:

2. Haemagglutinin or protease produced by vibrio cholerae:

- Cleaves the mucin and fibronectin.
- It also facilitates the spread and excretion of the vibrio cholerae within the intestine into the stool by detaching them from the intestinal walls.

Virulence factors for vibrio cholerae 01

3. Vibrio cholerae adhere to the intestinal wall by the fimbria, filamentous protein structures called toxin-coregulated pilus (TCP), extending from the cell wall and that attach vibrio cholerae to the receptors on the mucosa.
4. Bacterium’s motility helps to penetrate the mucus overlying the mucosa.

   With high concentration of vibrio cholerae closely attached to the mucosa, enterotoxin can be efficiently delivered directly to the mucosal cells.

Pathogenesis

- Once established, the organisms produce cholera toxin that consists of subunits A and B.
- The B-subunit is physiologically inactive but binds the toxin to the receptors in the small intestinal mucosa.
- Then, A-subunit is the transported into the cell where it transfers Adenosine Diphosphate (ADP) into Cyclic Adenosine Monophosphate (cAMP) and activate it.

Pathogenesis

- The activated Cyclic Adenosine Monophosphate:
  - Inhibits the absorptive sodium transport.
  - Activates the excretory chloride transport in the intestinal crypts cells. And
  - Inhibits the absorption of sodium chloride in the villus cells, eventually leading to an accumulation of sodium chloride in the intestinal lumen.

Pathogenesis

- The high osmolarity in the intestinal lumen is balanced by water secretion that eventually overwhelms the lumen absorptive capacity and leads to watery diarrhoea.
- Unless the wasted fluid and electrolytes are replaced adequately, shock (caused by profound dehydration) and acidosis (caused by loss of bicarbonates) follow.

History

- Incubation period is between 24-48 hours.
- Profuse watery diarrhoea is a hallmark of cholera.
- Stool contains food particles initially but later become watery with rice-like appearance.
- Abdominal cramps.
- Vomiting.

B. Examination

- **Dehydration:**

  Dehydration has been classified into 3 categories to facilitate treatment:

  1. Severe dehydration.
  2. Some dehydration.
  3. No dehydration.

Assessment of the patient with diarrhoea for dehydration

Condition	Eyes	Mouth and tongue	Skin pinch	Classification
Well and alert	Normal	Moist	Goes back immediately	**No dehydration**
Restless and irritable*	Sunken	Dry	Goes back slowly	If a patient has 2 or more signs including at least one* sign, **some dehydration is present.**

Assessment of the patient with diarrhoea for dehydration

Condition	Eyes	Mouth and tongue	Skin pinch	Classification
Lethargic (floppy) or unconscious*	Very sunken and dry	Very dry	Goes back very slowly	If a patient has 2 or more signs including at least one* sign, **severe dehydration is present.**

Dehydration

- Patients with severe dehydration approximately losses 10% of the total body weight.
- Patients with some dehydration losse 5-7.5% of the total body weight.

Other signs of dehydration

- Absent pulse.
- Tachycardia.
- Hypotension.
- Wrinkling hands (‘washer woman’s hands’).
- Absent or barely palpable peripheral pulses.
- Metabolic acidosis presenting with Kussmaul’s breathing and Hypercapnia .
- At first, patients are restless and extremely thirst, but as shock progresses, they become lethargic and may lose consciousness.

Differential diagnoses

A. Malaria.
B. Food poisoning.
B. Viral infections.
C. Bacterial infections.

Complications

1. Dehydration.
2. Renal failure.
3. **Hypoglycaemia.**
4. Paralytic ileus and abdominal distension.
5. **Miscarriage or premature delivery.**
6. Death.
7. **Electrolyte imbalance:**

A. **Hypokalaemia.**
B. **Acidosis**

Complications

8. Complications of therapy:

- Overhydration with parenteral fluids therapy.
- Pulmonary oedema.
- Hypocalcaemia.

Investigations

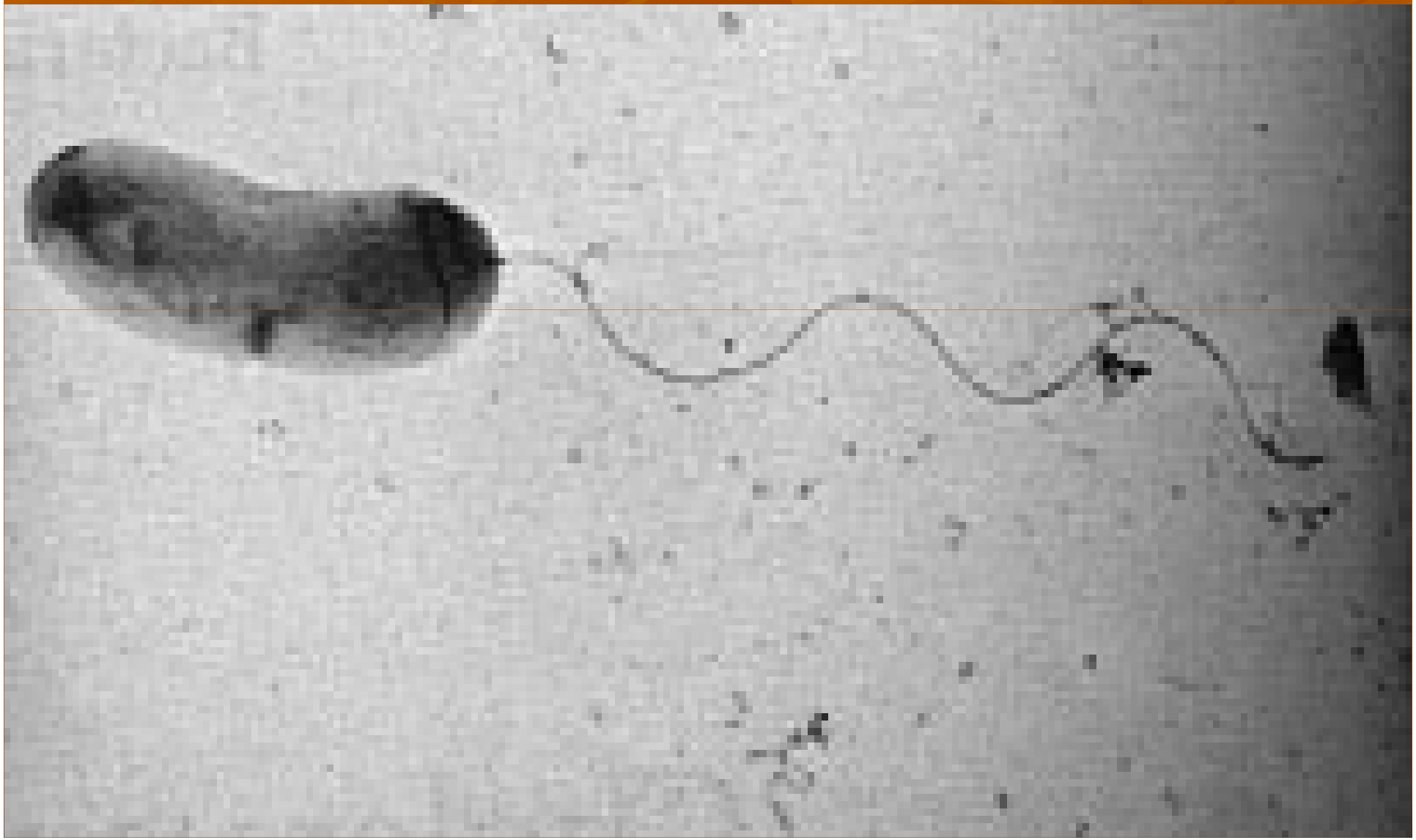
1. **Microscopic stool examination:**

A. **Direct:** Vibrio cholerae are gram-negative and curved (coma shaped) or straight bacillus.

B. **Dark-field of the wet mount of fresh stool:**

The organisms are mobile by means of a single flagellum. It can be confirmed by adding vibrio antisera, which results into cessation of motility of only the homologous organism.

Vibrio cholerae



Investigations

2. **Stool analysis:**

Stool contains few leucocytes and no erythrocytes.

3. **Haematological tests:**

A. **Haematocrit, serum specific gravity and serum protein:**

Are all elevated in dehydrated patients.

B. **Full blood picture:**

Shows neutrophil leucocytosis without a left shift when patients are first observed.

Investigations

4. **Stool culture:**

Routine differential media:

A. Triple sugar iron agar:

   Gives the non-pathogenic pattern of an acid (yellow) slant, because of fermentation of sucrose contained in the media.

B. Alkaline enrichment media:

- Peptone water (pH 8.5-9.0).
- Media containing bile salts e.g. thiosulphate–citrate bile-sucrose agar (pH 8.6). Sucrose fermenting vibrio cholerae grow as large, smooth, round yellow colonies that stand out against the blue-green agar.

Investigations

5. **Serum electrolytes:**

A. **Sodium:** Low (NR: 136-148 mmol/L).

B. **Potassium:**

Normal in acute phase of the illness (NR: 3.8-5.0 mmol/L). Later, hypokalaemia ensue.

C. **Bicarbonate:**

< 15 mmol/L in severely dehydrated patients and often is undetectable.

D. **Calcium and magnesium:**

Are high due to haemoconcentration.

Investigations

6. **Renal functional tests:**

- Blood urea nitrogen (BUN) and serum creatinine are elevated.
- The extent of their elevation is dependent on the degree and duration of dehydration.

Treatment

- The diagnosis of cholera is not mandatory before therapy.
- Steps in the management of a patient with suspected cholera are:

1. Assess the dehydration and classify the degree of dehydration as severe, some or no dehydration.
2. Rehydrate the patient and monitor frequently. Then, reassess hydration status.
3. Maintain hydration by replacing the ongoing fluid losses until diarrhoea stops.
4. Administer oral antibiotics to the patient with severe dehydration.
5. Feed the patient.

I. Severe dehydration

A. **Administer IV fluids immediately to replace fluid deficit:**

- Ringer lactate is the fluid of first choice or if not available, give isotonic sodium chloride solution.
- Amount of IV fluid: 100 ml/kg in 3 hours:
  - 30 ml/kg as rapidly as possible (within 30 minutes).
  - 70 ml/kg in the next 2 hours.
- If patient can drink, begin giving oral rehydration salt by mouth while the drip is being set up. If the patient cannot drink, give ORS by NGT.

I. Severe dehydration

B. **Monitor the patient very frequently:**

- After the initial 30 ml/kg has been administered, the radial pulse should be strong and blood pressure should be normal. If the pulse is not yet strong, continue to give IV fluid rapidly.
- Administer ORS solution 5 ml/kg/hr as soon the patient can drink, in addition to IV fluid.

I. Severe dehydration

c. **Reassess after 3 hours:**

- If signs of severe dehydration still exist, repeat the IV therapy already given.
- If signs of some dehydration are present, continue as indicated below for some dehydration.
- If no signs of dehydration of exist, maintain hydration by replacing ongoing fluid losses.

II. Some dehydration

- Give 75 ml/kg of ORS solution for the first 4 hours.
- If the patient passes watery stools or wants more ORS solution than indicated, give more.
- Discard the leftover solution after 24 hours.

II. Some dehydration

- Reassess the patient after 4 hours:
- If signs of severe dehydration have appeared (rare), Rehydrate for severe dehydration, as above.
- If some dehydration still present, repeat the procedures for some dehydration and start to offer food and other fluids.
- If no signs of dehydration are present, maintain hydration by replacing ongoing fluid losses.

III. No dehydration

- Give ORS packets to take at home, enough for 2 days (enough for 2000 mls/day).
- Demonstrate to the patient or caretaker how to prepare and give the solution.
- If diarrhoea stops, discharged patient should return for follow-up in 2 days.

III. No dehydration

- **Instruct the patient or the caretaker to return if any of the following signs develop:**
  - Increased number of watery stool.
  - Marked thirst.
  - Repeated vomiting.
  - Any signs indicating other problems e.g. fever or blood in stool.

Antibiotics

- Antimicrobial therapy for cholera is an adjunct to fluid therapy and is **not an essential therapeutic component.**
- The drug should be given when the patient is first seen and cholera is suspected before culture and susceptibility reports of the stool culture.
- It should not be given to asymptomatic contacts because of increased risk of developing resistance and not cost effective.

Antibiotics

- Azithromycin 1 g PO stat.
- Tetracycline 2 g PO stat.
- Doxycycline 300 mg PO stat.
- Ciprofloxacin 250 mg PO OD for 3 days or 1 g stat.
- Alternatively:
  - Ciprofloxacin 30 mg/kg PO stat (not to exceed 1 g/dose).
  - Ciprofloxacin 15 mg/kg PO bid for 3 days (not to exceed 1 g/dose).

Antibiotics

- Norfloxacin 400 mg PO bid for 3 days. Do not to exceed 800 mg/day.
- Erythromycin 40 mg/kg PO divided TID for 3 days.
- Co-trimoxazole 960 mg PO BID for 3 days.

Prevention

1. Early identification and case management.
2. Active surveillance and prompt reporting.
3. Water supply: Ensure a safe water supply (especially for municipal water system).
4. Improve sanitation and sewage disposal.
5. Making food safe for consumption by thorough cooking of high risk foods especially seafood and protecting it against flies.

Prevention

6. **Health education through mass media: Insisting on:**

- Importance of purifying water and cooking seafood.
- Washing hands after using the toilet and before food preparation.
- Recognition of the signs of cholera and location where treatment can be obtained to avoid delays in cases of illness.

Prevention

7. **Vaccines:**

A. **WC/rBS vaccine: (Dukoral)**

- The vaccine consists of killed whole cell vibrio cholerae 01 with purified recombinant B-subunit of cholera toxoid.
- The vaccine stimulates both antibacterial and antitoxic immunity.
- Efficacy: It confers 85-90% protection during 6 months in all age groups after administration of 2 doses, 1-6 week apart.

Prevention

7. **Vaccines:**

B. **Variant WC/rBS vaccine:**

- It contains no recombinant B-subunit. It is administered in 2 doses, 1 week apart.
- Efficacy: It confers 66% protection at 8 months in all age groups (licensed in Vietnam only).

C. **CVD103-HgR vaccine: (Orochol)**

- It contains attenuated live oral genetically modified vibrio cholerae 01 strain.
- Efficacy: Single dose confers high protection (95%) against vibrio cholera classical and 65% protection against vibrio cholerae El-Tor following a challenge given 3 months after administration.

Prognosis

- With effective intravenous fluids and oral rehydration, prognosis of cholera patients is good with mortality is less than 1% in patients with severe dehydration.
- In ineffective replacement of fluid and electrolytes or without treatment, the case fatality rate in severe disease is more than 50%. Most deaths occur during the first day.
- Mortality rates in Africa remain higher because of inadequate infrastructure, trained personnel and intravenous fluids.

Thank you for your attention

References

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