GI

MICROBIOLOGY

 # 5

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VIBRIOS, CAMPYLOBACTERS, HELICOBACTER.

❖ **Overview:**

▪ **These species are gram-negative rods that are all widely distributed in nature,** they are considered as contaminants of water.

▪ **Vibrio cholerae produces an enterotoxin that causes cholera, a profuse watery diarrhea that can rapidly lead to dehydration and death (cholera caused by vibrio cholera is the most dramatic diarrhea in humans, patients effected with cholera loss about on 1 liter of their fluids in each hour -nearly 20-30 liter a day-).**

▪ **Campylobacter jejuni and campylobacter coli are the most common bacterial causes of enteritis and gastroenteritis in humans. Less commonly, Aeromonas and, rarely, Plesiomonas have been associated with diarrheal disease in humans.**

▪ **Helicobacter pylori has been associated with gastritis, duodenal ulcer** disease, adenocarcinoma of the stomach and MALT lymphoma.

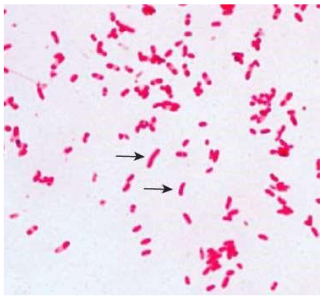
THE VIBRIEOS

▪ **Vibrios are among the most common bacteria in surface waters worldwide.** some vibrieos are halotolerant -can withstand in water that contain salinity. However, some species that are halophilic prefer to present in salinity and multiply there. The ability of vibrieos to withstand salinity and NaCl is used to differentiate between them and other aqueous bacteria (Aeromonas and Plesiomonas).

▪ **V.Cholerae serogroups O1 and O139 cause cholera in humans, and other vibrios may cause soft tissue infections, sepsis or enteritis.**

▪ **Other important Vibrio species (non-O1 and non-O139) are primarily associated with gastroenteritis include: V parahaemolyticus the most common cause of Seafoodborne (raw fish or shellfish) gastroenteritis in Asia, and V vulnificus (oysters), a cause of severe sepsis in patients with cirrhosis and primary wound infection (Vulnificus is Latin for "wound maker.") and V alginolyticus occasionally causes eye, ear, and wound infections.**

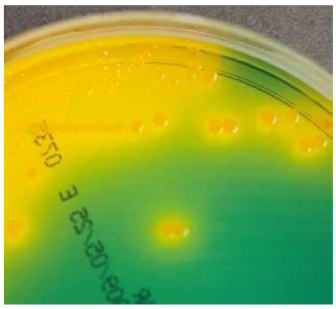
▪ **Vibrio cause a number of important infectious syndromes. Classic among them is cholera, a devastating diarrheal disease caused by Vibrio cholerae** (mainly by O1 serotype) **that has been responsible for seven global pandemics and much suffering over the past two centuries and remains a significant public health concern in the developing world today.**



▪ **The epidemiology of cholera closely parallels the recognition of V cholerae transmission in water and the development of sanitary water systems.**

▪ **V cholerae is a comma-shaped, curved rod 2–4 µm long. It is actively motile by means of a polar flagellum in one of their sides (they permit H antigen). On prolonged cultivation, vibrios may become straight rods that resemble the gram-negative enteric bacteria.**

▪ **Characteristically, vibrios grow at a very high pH (8.5–9.5) and are rapidly killed by acid.**



▪ **V cholerae produces convex, smooth, round colonies that are opaque and granular in transmitted light.**

▪ **V cholera grows well on thiosulfate-citrate-bile sucrose (TCBS) agar, a selective media for vibrios, on which it produces yellow colonies with yellow hallow diffusion around each colony (sucrose fermented) that are readily visible against the dark green background of the agar.**

▪ **A positive oxidase test result is a key step in the preliminary identification of V cholerae and other vibrios.**

▪ **Vibrio species are susceptible to be killed with O/129 compound (2,4-diamino6,7diisopropylpteridine phosphate), which differentiates them from Aeromonas species, which are resistant to O/129.**

▪ **Most Vibrio species are halotolerant, and NaCl often stimulates their growth. Some vibrios are halophilic, requiring the presence of NaCl to grow.**

❖ Antigenic Structure and Biologic Classification:

▪ **Many vibrios share a single heat-labile flagellar H antigen** (recall that V.cholera are motile). **Antibodies to the H antigen are probably not involved in the protection of susceptible hosts.**

▪ **V cholerae has O lipopolysaccharides (O antigen) that confer serologic specificity. There are at least 206 O antigen groups.**

▪ **V cholerae strains of O group 1 and O group 139** have the ability to elaborate cholera toxin accordingly **causing the classic cholera. occasionally, non-O1/non-O139 V cholerae causes cholera-like disease** (gastroenteritis).

▪ V cholera O1 dese not have a capsule while O139 has.

▪ **Antibodies to the O antigens tend to protect laboratory animals against infections with V cholerae.**

▪ **Two biotypes of V. cholerae O1: classical and El Tor, are distinguished. Each biotype is further subdivided into two serotypes, termed Inaba and Ogawa.**

❖ Vibreio cholerae enterotoxin:

▪ **Cholera toxin, a potent protein enterotoxin elaborated by the organism in the small intestine with a molecular weight (MW) of about 84,000, consisting of subunits A** for activating **(MW,28,000) and B** for binding**.**

▪ **The genes for V cholerae enterotoxin are on the bacterial chromosome.**

▪ **Ganglioside GM1 serves as the mucosal receptor for subunit B, which promotes entry of subunit A into the cell. Activation of subunit A1 yields increased levels of intracellular cyclic adenosine monophosphate (cAMP)** through the activation of adenylate Cyclase **and results in prolonged hypersecretion of water and electrolytes** to the intestinal lumen and prevention of reabsorption which result a perfusing diarrhea which is the most dramatic diarrhea that effect humans.

❖ Pathogenesis:

▪ Under natural conditions, V cholerae is pathogenic only for humans. A person with normal gastric acidity may have to ingest as many as 1010 or more V cholerae to become infected when the vehicle is water because the organisms are susceptible to acid (recall that V cholerae is sensitive to acids, so antiacids increase the chance of cholerae).

▪ When the vehicle is food, as few as 102–104 organisms are necessary because of the buffering capacity of food (food neutralize the acidity of the stomach).

▪ In addition to O antigen and H antigen **V.Cholerea also have The toxin-coregulated pilus (TCP) , so named because its synthesis is regulated in parallel with that of cholera toxin→ is essential for V. cholerae to survive and multiply in (colonize) the small intestine** accordingly producing toxins.

▪ The organisms do not reach the bloodstream but remain within the intestinal tract.

▪ Virulent V cholerae organisms attach to the microvilli of the brush border of epithelial cells. There they multiply and liberate cholera toxin and perhaps mucinases and endotoxin.

❖ Clinical findings:

▪ The burden of disease is often greatest during "cholera seasons" associated with high temperatures, heavy rainfall, and flooding, but cholera can occur year-round.

▪ About 50% of infections with classic V cholerae are asymptomatic, as are about 75% of infections with the El Tor biotype.

▪ The incubation period is 12 hours–3 days for persons who develop symptoms, depending largely on the size of the inoculum ingested.

▪ There is a sudden onset of nausea and vomiting and profuse diarrhea with abdominal cramps. Stools, which resemble "rice water," contain mucus, epithelial cells, and large numbers of vibrios with grey appearance.

▪ There is rapid loss of fluid and electrolytes, which leads to profound dehydration, circulatory collapse, and anuria. The mortality rate without treatment is between 25% and 50%.

▪ The diagnosis of a full blown case of cholera presents no problem in the presence of an epidemic. However, sporadic or mild cases are not readily differentiated from other diarrheal diseases. The El Tor biotype tends to cause milder disease than the classic biotype.

❖ Diagnostic Laboratory Tests:

▪ Specimens: Specimens for culture consist of mucus flecks from stools on TCBS agar (yellow colonies on green background).

▪ Smears: Dark-field or phase contrast microscopy may show the rapidly motile vibrios.

▪ Culture: Growth is rapid in peptone agar, on blood agar with a pH near 9.0, or on TCBS agar, and typical colonies can be picked in 18 hours only vibrieos can withstand alkalinity while normal intestinal flora cannot.

▪ D. Specific Tests: V cholerae organisms are further identified by slide agglutination tests using anti-O group 1 or group 139 antisera and by biochemical reaction patterns.

❖ Treatment:

▪ The most important part of therapy consists of water and electrolyte replacement to correct the severe dehydration and salt depletion.

▪ Many antimicrobial agents are effective against V cholerae, but these play a secondary role in patient management. Oral tetracycline and doxycycline tend to reduce stool output in cholera and shorten the period of excretion of vibrios.

▪ In some endemic areas, tetracycline resistance of V cholerae has emerged; the genes are carried by transmissible plasmids. In children and pregnant women, alternatives to the tetracyclines include erythromycin and furazolidine.

❖ Prevention:

▪ Provision of safe water and of facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household can significantly reduce the incidence of cholera.

▪ **Currently, two oral killed cholera vaccines have been prequalified by the WHO and are available internationally:**

1)WC-rBS (Dukoral.; Crucell, Stockholm, Sweden) contains several biotypes and serotypes of V. cholerae O1 supplemented with recombinant cholera toxin B subunit.

2)BivWC (Shanchol™; Shantha Biotechnics–Sanofi Pasteur, Mumbai, India) contains several biotypes and serotypes of V. cholerae O1 and V. cholerae O139 without supplemental cholera toxin B subunit.

Both of them are not effective in preventing epidemics and pandemics (not given for the whole populations), but these vaccines are recommended for high exposed individuals eg: travelling from a developing to a developed country.

▪ When the disease is confirmed health authorities must be notified immediately

CAMPYLOBACTER

▪ **Campylobacters are motile, non-spore-forming, curved, gram-negative rods.**

▪ **Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and many household pets (including birds, dogs, and cats)** and the shed it in their secretions.

▪ **Campylobacters cause both diarrheal** (intestinal) **and systemic diseases** (extraintestinal) **and are among the most widespread causes of infection in the world.**

▪ **The classification of bacteria within the family Campylobacteriaceae has changed frequently. Some species previously classified as campylobacters have been reclassified in the genus Helicobacter. The genus Arcobacter has been created.** (Helicobacter and campylobacter: intestine While Helicobacter pylori: stomach)

▪ **Campylobacter jejuni is the prototype organism in the group and is a very common cause of diarrhea in humans.**

▪ **The human pathogens fall into two major groups: those that primarily cause diarrheal disease** (mainly C.jejuni and C.coli) **and those that cause extraintestinal infection.**

Note: C.jejuni and C.coli are not clinically distinguishable.

▪ **Campylobacter fetus has two subspecies, fetus and venerealis. C fetus subspecies fetus is an opportunistic pathogen that causes systemic infections in immunocompromised patients** (HIV infections, cancer patients, glucocortisteroid and immunosuppressants, organ transplantations). **It may occasionally cause diarrhea.**

▪ **Campylobacter upsaliensis, Campylobacter lari, Campylobacter hyointestinalis, Campylobacter fetus, Arcobacter butzleri, Arcobacter cryaerophilus, Helicobacter cinaedi, and Helicobacter fennelliae** (intestinal helicobacters not gastric).

❖ Campylobacter jejuni and campylobacter coli:

▪ **C jejuni and Campylobacter coli have emerged as common human pathogens, causing mainly enteritis and occasionally systemic infection.**

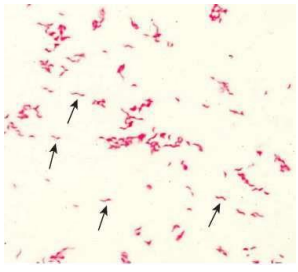
▪ **C jejuni and C coli cause infections that are clinically indistinguishable, and laboratories generally do not differentiate between the two species.**

▪ **Between 5% and 10% of infections reported to be caused by C jejuni are probably caused by C coli. These bacteria are at least as common as salmonellae and shigellae as a cause of diarrhea especially in the developed world.**

❖ Campylobacter jejuni:

▪ **gram-negative rods with comma, S, or "gull wing" shapes. They are motile, with a single polar flagellum, and do not form spores.**

▪ **Selective media are needed (microaerophilic conditions), and incubation must be in an atmosphere with reduced O_2 (5% O_2) with added CO_2 (10% CO_2).etures**



Note: Helicobacter pylori Also grow in microaerophilic conditions same as C. jujeni. The difference between them that C.jejeni are thermophilic and favor to grow under high temperatures.

▪ Incubation of primary plates for isolation of C jejuni should be at 42°C. Although C jejuni grows well at 36– 37°C, incubation at 42°C prevents growth of most of the other bacteria present in feces, thus simplifying the identification of C jejuni. Several selective media are in widespread use.

❖ Pathogenesis:

• The infection is acquired by the oral route from food, drink, or contact with infected animals or animal products, especially poultry.

• C jejuni is susceptible to gastric acid, and ingestion of about 104 organisms is usually necessary to produce infection.

• C.jejeuni use various of virulence factors in their pathogenesis such as: motility of certain strains and their capacity to adhere to host tissues are the two main virulence factors that play a primary role in their pathogenesis. However, the classic enterotoxins and cytotoxins (cytolethal distending toxin, or CDT) play a secondary substantial role in tissue injury or disease production.

• The organisms multiply in the small intestine, invade the epithelium, and produce inflammation that results in the appearance of red and white blood cells in the stools (bloody diarrhea). **Occasionally the bloodstream is invaded. Localized tissue invasion coupled with the toxic activity appears to be responsible for the enteritis.**

❖ Clinical findings:

▪ A prodrome of fever, headache, myalgia, and/or malaise often occurs 12–48 h before the onset of diarrheal symptoms. profuse diarrhea that may be grossly bloody (patients start having watery diarrhea then they progress a bloody diarrhea due to the invasion of campylobacter to the intestinal epithelial cells causing the symptom of bloody diarrhea).

▪ Most cases resolve without antimicrobial therapy; however, in about 5–10% of patients, symptoms may recur as Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, arthritis, peritonitis, cellulitis, and septic abortion Hepatitis, interstitial nephritis. All these complications are rare, except in immunocompromised hosts.

▪ Usually the illness is self-limited to a period of 5–8 days, but occasionally it continues longer.

• Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection

▪ Patients may develop (post infection sequelae) such as the hemolytic-uremic syndrome (hus syndrome) , heat syndrome or Reye's syndrome (conjunctivitis, arthritis and urethritis).

▪ Certain serotypes of C jejuni have been associated with post-diarrheal GuillainBarré syndrome, a form of ascending paralytic disease. Reactive arthritis and Reiter's syndrome may also follow acute campylobacter diarrhea

For knowledge:

A **sequela** (UK: /sɪˈkwiːlə/,[1] US: /sɪˈkwɛlə/;[2][3] usually used in the plural, **sequelae** /-iː/) is a pathological condition resulting from a disease, injury, therapy, or other trauma. Derived from the Latin word, meaning "sequel", it is used in the medical field to mean a complication or condition following a prior illness or disease.[4]

Heat Exhaustion. Heat exhaustion is the body's response to an excessive loss of the water and salt, usually through excessive sweating. Workers most prone to heat exhaustion are those that are elderly, have high blood pressure, and those working in a hot environment.

❖ Diagnostic laboratory tests:

▪ **Specimens** (gram negative comma shaped bacilli)**: Diarrheal stool is the usual specimen .C.jejuni, C.fetus and other campylobacters may occasionally be recovered from blood cultures usually from immunocompromised or elderly patients.**

▪ B.Smears: Gram-stained smears of stool may show the typical "gullwing"–shaped rods. Darkfield or phase contrast microscopy may show the typical darting and instant motility of the organisms.

▪ C.culture: Culture on the selective media under microaerophilic and thermophilic conditions (Skirrow's, Butzler's, Blaser's, Campy-BAP and Preston media) is the definitive test to diagnose C jejuni and C Coli .If another species of Campylobacter is suspected, medium without a cephalosporin should be used and incubated at 36–37° C.

❖ **Treatment:**

▪ Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses.

▪ Even among patients presenting for medical attention with Campylobacter enteritis, not all clearly benefit from specific antimicrobial therapy. Indications for therapy include high fever, bloody diarrhea, severe diarrhea, persistence for >1 week, and worsening of symptoms. A 5- to 7-day course of erythromycin is the regimen of choice.

▪ An alternative regimen for adults is ciprofloxacin or another fluoroquinolone for 5–7 days.

▪ For systemic infections, treatment with gentamicin or imipenem or chloramphenicol should be started empirically, but susceptibility testing should then be performed.

HELICOBACTER BYLORI

• H pylori is a spiral-shaped gram-negative rod.

• It has multiple flagella at one pole and is actively motile.

• The organism has several acid-resistance mechanisms, most notably a highly expressed urease that catalyzes urea hydrolysis to produce buffering ammonia therefore, acting as buffering agent in the stomach, consequently can survive there. **H. pylori is microaerophilic (i.e., requires low levels of oxygen) is oxidase positive and catalase positive is slow-growing, and requires complex growth media in vitro** accordingly their culture is very difficult and not common in hospitals for diagnostic reasons.

• H pylori is associated with antral gastritis, duodenal (peptic) ulcer disease, gastric ulcers (80% of gastric ulcers and 80% of duodenal ulcers are mainly caused by H.pylori) , gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphomas. It may be one initial precipitant of pernicious anemia and also may predispose some patients to iron deficiency through occult blood loss and/or hypochlorhydria and reduced iron absorption.

❖ Epidemiology:

▪ Helicobacter pylori colonizes the stomach in ~50% of the world's human population, essentially for life unless eradicated by antibiotic treatment.

Note: There are differences between people and the way they respond to infection due several factors. There are people who have colonization and haven't infection and there is people who have the colonization and the infection but they haven't the disease while others have the colonization, infection and the disease all of that depends on infection-illness ratio.

▪ Humans are the only important reservoir of H. pylori.

▪ The rout of transmission for H.pylori is feco-oral , but there is no accurate evidence to ensure the rout of transmit for H.pylori. One of the evidences that supports that → **Children may acquire the organism from their parents (most often the primary caregiver) or from other children.**

▪ Most H. pylori–colonized persons do not develop clinical sequelae. That some persons develop overt disease whereas others do not is related to a combination of factors: bacterial strain differences (cag-positive , type IV secretion system, the vacuolating cytotoxin VacA), host susceptibility to disease, and environmental factors (the interleukin 1 gene polymorphisms, and smoking)

❖ Pathogenesis:

• H pylori is found deep in the mucous layer near the epithelial surface where physiologic pH is present.

• H pylori is quite motile, even in mucus, and is able to find its way to the epithelial surface. H pylori overlies gastric-type but not intestinal- type epithelial cells.

• H pylori also produces a protease that modifies the gastric mucus and further reduces the ability of acid to diffuse through the mucus.

• H pylori produces potent urease activity, which yields production of ammonia and further buffering of acid.

•H. pylori colonization induces chronic superficial gastritis, a tissue response in the stomach that includes infiltration of the mucosa by both mononuclear and polymorphonuclear cells

• The mechanisms by which H pylori causes mucosal inflammation and damage are not well defined but probably involve both bacterial and host factors. The bacteria invade the epithelial cell surface to a limited degree. Toxins and lipopolysaccharide may damage the mucosal cells, and the ammonia produced by the urease activity may also directly damage the cells.

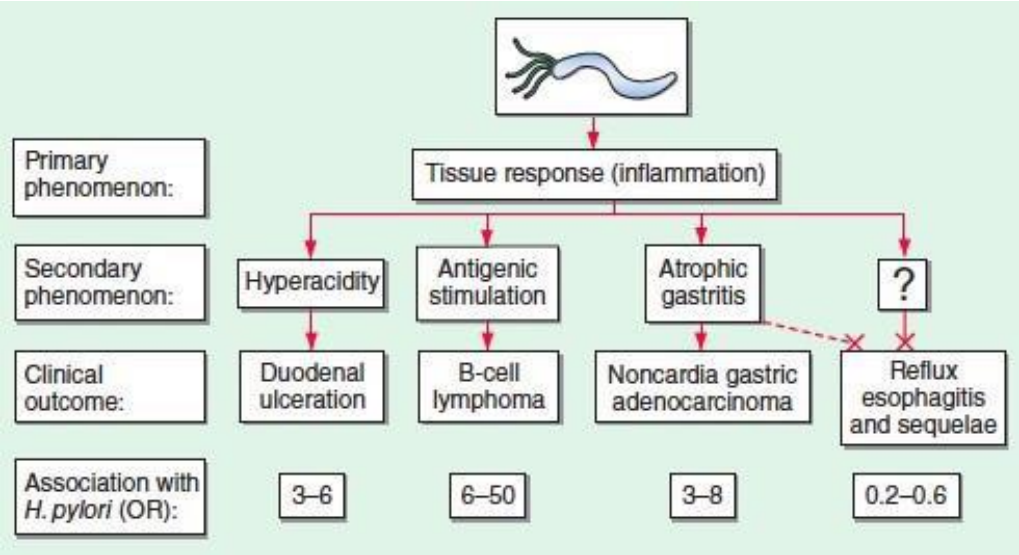
• Polymorphonuclear and mononuclear cell infiltrates are seen within the epithelium and lamina propria. Vacuoles within cells are often pronounced. Destruction of the epithelium is common, and glandular atrophy may occur. H pylori thus is a major risk factor for gastric cancer.

❖ Clinical findings:

• most cases are asymptomatic and H.pylori infections can be acute or chronic. **Acute infection can yield an upper gastrointestinal illness with nausea and gastric pain; vomiting fever and gastroesophageal reflux may also be present . The acute symptoms may last for less than 1 week or as long as 2 weeks**

• After colonization, the H pylori infection persists for years and perhaps decades or even a lifetime. About 90% of patients with duodenal ulcers and 50–80% of those with gastric ulcers have H pylori infection. Recent studies confirm that H pylori also is a risk factor for gastric carcinoma and lymphoma.

❖ Relationships between colonization with Helicobacter pylori and diseases of the upper gastrointestinal tract:



Statistically there is something called odd ratio or OR; this ratio is used to measure the exposure to risk factors and the outcome for the disease. If this ratio is greater than 1 the susceptibility for disease increase when humans are affected by a certain risk factor. However, if OR is less than 1 means the patient is protected from disease. Observe the picture above.

❖ Diagnostic laboratory tests:

➢ Smears:

• The diagnosis of gastritis and H pylori infection can be made histologically. A gastroscopy procedure with biopsy is required. Routine stains demonstrate gastritis, and Giemsa or special silver stains can show curved or spiral-shaped organisms.

➢ Culture:

• Culture is performed when patients are not responding to treatment, and there is a need to assess susceptibility patterns (culturing H.pylori is very difficult thus it is not a routine diagnostic test in hospitals).

➢ Special Tests:

• Rapid tests to detect urease activity in vitro are widely used for presumptive identification of H pylori in specimens. A gastric specimens is put in a jar with a specific dye if H.pylori are present , urease enzyme is active so they will split urea and there will be a discoloration in that jar due to changes in acidity.

• In vivo tests for urease activity can be done also. In urea breath tests,13C-or14C- labeled urea is ingested by the patient. If H pylori is present, the urease activity generates labeled CO_2 that can be detected in the patient's exhaled breath.

• Detection of H pylori antigen in stool specimens is appropriate as a test of cure for patients with known H pylori infection who have been treated.

❖ Treatment:

• Triple therapy with metronidazole and either bismuth subsalicylate or bismuth subcitrate plus either amoxicillin or tetracycline for 14 days eradicates H pylori infection in 70–95% of patients.

• An acid-suppressing agent given for 4 o 6 weeks enhances ulcer healing. Proton pump inhibitors (PPIs) directly inhibit H pylori and appear to be potent urease inhibitors.

• The preferred initial therapy is 7–10 days of a PPI plus amoxicillin and clarithromycin or a quadruple regimen of a PPI metronidazole, tetracycline, and bismuth for 10 days

- Bismuth is not available in Jordan-.

THANK YOU

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