Vibrio cholerae, other Vibrio, Campylobacter, and Helicobacter

Vibrio cholerae causes cholera.

Microbiology: Gram-negative curved rods
   Highly motile
   Oxidase positive

Epidemiology:
   Acquired via ingestion of contaminated water or food (poor sanitation).
   Infective dose: large ($10^8$), due to susceptibility to acid in stomach. (People on antacids
   or with low stomach acid may succumb with doses of $10^7$ or lower.)
   May survive in marine environments in a semi-dormant state or as a fellow traveler with
   zooplankton or phytoplankton.
   No significant carrier state, but stools from active cases contain many infectious bacteria.

Not all V. cholerae isolates cause disease; many serogroups are not pathogenic.
Nonpathogenic strains can become pathogenic due to horizontal transfer of virulence
genes carried by bacteriophage or on pathogenicity islands.
Serogroup 01 has caused most epidemics. But recently, a new serogroup important:
   O139. Outbreaks by nonO1/nonO139 serogroups can also occur. This year (2004)
   outbreaks in Africa have been major. Most epidemic started in India

Biotype names: e.g., El Tor. El Tor is a subdivision of 01, and has caused much of the
epidemic of 20th century. Is a slight biochemical variant of 01.

Virulence factors:

Flagella/motility: bacteria swim to mucosal surface. Motility is required for successful
   colonization of the intestines.
Pili: mediate adherence. The major adherence pilus type is called Tcp, for toxin co-regulated
   pilus. Encoded by pathogenicity island, VPI-1.

   Must adhere to epith
   + expr. w/ toxin => once inside human host, will get expr.
Cholera toxin (CT): The major diarrheagenic toxin of *V. cholerae.*

CT is encoded by a bacteriophage, called CTXΦ.

CT consists of 5 B (binding) subunits and 1 A (active) subunit.

A is nicked to produce an active A1 fragment; A1 and A2 are linked by a disulfide bond.

B recognizes and binds to ganglioside GM1, after which the entire toxin is taken up into the cell.

The toxin traffics in a retrograde fashion to the ER; A1 exits and finds its way to the basolateral membrane where its substrate, Gt, is located.

CT activity: A1 catalyzes the ADP-ribosylation of Gt0, a subunit of the GTP-hydrolyzing protein that participates in the regulation of adenylate cyclase. This modification inhibits deactivation of the α-subunit, leading to 100-fold increases in intracellular cAMP levels. As a consequence, protein kinases including protein kinase A are activated, which then phosphorylate and activate the apical chloride channel. Chloride ion is secreted, sodium ion absorption is inhibited and water loss follows.

A1 ribosylates Gt, alpha, activating adenyl cyclase.

Intracellular cAMP levels rise dramatically.

cAMP activates protein kinase A which phosphorylates several substrates including the apical chloride channel.
Treatment: Fluid and electrolyte replacement. Antibiotics may be used to shorten duration of symptoms and magnitude of fluid loss (e.g., erythromycin, ciprofloxacin, doxycycline).

Vaccines: The world would definitely benefit from a safe, long-lasting vaccine to cholera. Current options:
1. Orochol—a single oral dose vaccine of live, attenuated V. cholerae. It is only for high-risk travelers.
2. Dukoral—two doses of a killed whole cell vaccine supplemented with purified CT B subunit. They do not provide good long-term immunity. And, they are not licensed in the USA.

*Vibrio vulnificus:*

*V. vulnificus* causes septicemia and wound infections. — of swimming in area w/ back s w/ wound.

Microbiology: Halophilic (requires about 1% NaCl for growth).

Epidemiology: Found in sea water. Acquired through the ingestion of contaminated shellfish, particularly raw oysters, clams, and shrimp. Or, trauma followed by exposure to marine environment.

Seasonal: most cases are acquired during warm-weather months.

US incidence: about 50 cases/year. Mostly near the gulf-coast.

(In Kentucky: Not common, but are cases. Individuals who eat raw oysters in Kentucky or people who arrive here before symptoms start.)

Virulence factors: Polysaccharide capsule. → assists in evasion of immune system.

- invades mucosal surface
- Proteases.
- Phospholipases.

Disease: The bacterium invades the intestinal mucosa and develops into a life-threatening septicemia.

Mortality at 50%-Most often people with liver disease or iron-overload disease, alcoholics, or immunocompromised patients. (People with liver disease should be warned about the dangers of eating raw oysters.) –Tx must be immediate!

Clinical manifestations of septicemia: rapid onset of fever, nausea, chills, prostration, hypotension, and death in 24 hours.
Campylobacter jejuni

Causes gastroenteritis; 2 to 3 million cases/year in USA. **Major US Pathogen!**

Microbiology: gram-negative curved rod, **mobile**
- Microaerophilic
- Can't grow aerobically or anaerobically
- Requires special selective medium

Several closely related species are also pathogenic: C. coli, C. fetus, C. lari

Epidemiology: Colonizes the gastrointestinal tract of a variety of animals (cattle, sheep, birds)
- Uncooked chicken is the primary source; also raw milk and contaminated water
- Person-to-person transmission is rare
- Sporadic outbreaks

Two pronounced age peaks: <1 year, 15-44 yrs
- Males more often affected (this is not explained)
- Seasonal: Incidence peaks in summer months

Virulence Factors:
- Motility and adherence—these are required for colonization
- Invasion—C. jejuni is somewhat invasive; overall contribution to disease is not yet established
- Toxin—cytolethal distending toxin (CDT). CDT is made by all C. jejuni strains.
  - Causes DNA damage, resulting in cell cycle block and cell death.
  - Again, role in disease is not established: may be epithelial cell destruction, may be immunosuppressive (kills T cells).

Disease: After ingestion, the intestines are colonized. Incubation period of 1 to 7 days (mean of 3 days, which is longer than most other intestinal infections).

Symptoms variable, include:
- Abdominal pain (can be intense)
- Watery diarrhea (and in USA usually progresses in 1-2 days) to bloody diarrhea
- Many leukocytes in stools
- Can be nausea and vomiting
- May be fever
- Lasts 5-10 days

**TABLE 1** Clinical features of *Campylobacter* enteritis derived from surveys of community outbreaks in which 50 or more people were affected and analyzed

<table>
<thead>
<tr>
<th>Symptom*</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/median</td>
</tr>
<tr>
<td>Fever (25)</td>
<td>50/52</td>
</tr>
<tr>
<td>Diarrhea (26)</td>
<td>84/85</td>
</tr>
<tr>
<td>Headache (21)</td>
<td>41/47</td>
</tr>
<tr>
<td>Abdominal pain (26)</td>
<td>79/80</td>
</tr>
<tr>
<td>Myalgia (5)</td>
<td>42/37</td>
</tr>
<tr>
<td>Vomiting (20)</td>
<td>15/11</td>
</tr>
<tr>
<td>Blood in feces (7)</td>
<td>15/13</td>
</tr>
</tbody>
</table>

* Compiled from references 52, 68, 71, 75, 93, 98, 102, 105, 138, 139, 148, 149, 152, 166, 167, 172, 175, and 180.
* Numbers in parentheses are the number of outbreaks from which data were obtained.
An inflammatory enteritis, lesions seen in jejunum, ileum, and colon.

Can be mistaken for Crohn's disease, acute ulcerative colitis, or acute appendicitis.

Autoimmune sequel: 30-40% of Guillain-Barré cases in USA—most freq. cause of GB
An autoimmune-mediated disorder of the peripheral nervous system. Flaccid paralysis.
After 2 to 3 weeks there is partial or complete recovery.
Mortality: 2-3% in developed countries.

Based on similarities of C. jejuni LOS to gangliosides.

Diagnosis: gram-negative curved rod in stools, follow with culture confirmation
(C. jejuni requires special media and incubation conditions)

Treatment: healthy individuals will spontaneously recover; systemic or immunocompromised patients need antibiotics, fluid and electrolyte replacement

C. fetus

Causes a gastroenteritis that may become systemic, particulary in immunocompromised individuals.

Disease: Symptoms similar to C. jejuni, but more serious if systemic.

Key virulence factor: serum resistance from surface protein.

Diagnosis: if suspect systemic, culture from blood.

Treatment: antibiotics (Campylobacters are generally resistant to penicillins, cephalosporins, and trimethoprim-sulfamethoxazole); use aminoglycosides, erythromycin, etc.

Helicobacter pylori discovered 1983

Causes gastric ulcers and predisposes to stomach cancer.

Microbiology: Gram-negative, curved-to-spiral rod
Microaerophlic.
Produces a powerful urease.
Epidemiology: More common in older people in USA.* not in children in the US  → rest of the world get it sooner

50% of the world population may be infected (varies by country).

Source? Ingested. Likely, fecal-oral or contaminated water.

Causes 90% of gastritis, gastric and duodenal ulcers.
Seems to predispose to gastric adenocarcinoma and gastric lymphoma.
But, humans may have *H. pylori* in stomach without having ulcers.

Virulence Factors:

Urease—converts urea to ammonia and CO₂; role?
- very powerful
- facilitates colonization w/ buffering

Adhesins: BabA—binds Lewis blood group B antigen
- often on surface of stomach
Adherence, in vitro, causes cytoskeletal rearrangements, and stimulates IL-8 production.

CagA—Many of these changes are a result of the contact-dependent secretion of CagA into eukaryotic cells. Effacement of microvilli follows; cup/pedastal formation, and phosphorylation of CagA by Src kinases. Phosphorylated CagA then initiates signaling events which affect spreading, migration and adhesion of epithelial cells, and slows apoptosis. CagA is encoded on a pathogenicity island, along with the secretion system.

VacA—cytotoxin (vacuolating toxin). VacA has several affects including cell damage, immune suppression, and pore formation. VacA is somewhat polymorphic. VacA is not encoded on the pathogenicity island.

LPS—may mimic Lewis x and Lewis y antigens
- delays immune detection

Two types of strains—called Type I and Type II

Type 1: The majority of clinical isolates from gastrodeudenal ulcers or adenocarcinoma are type 1 strains. (Produce CagA and VacA)
- more pathogenic have CagA

Type II: These strains do not produce CagA.

However, this classification is somewhat old. Truer picture is that *H. pylori* is very mutable; within one host, the population is heterogeneous.
Symptoms: may include nausea, anorexia, vomiting, epigastric pain, belching. Again, often asymptomatic.

Diagnosis: Endoscopy; biopsy and culture. Microaerobic w/ selective medium

Rapid, noninvasive, tests: antibody detection, urea "breath" test.

Treatment: antibiotics, regimen has evolved substantially in recent years. Currently: 10 days to 2 weeks of one or two antibiotics such as amoxicillin, tetracycline, metronidazole, or clarithromycin plus an acid suppressing agent (e.g., a proton pump inhibitor).

Vaccine: numerous researchers are working to develop a vaccine; trials have not been successful.

\* esp. bic quiescent infant