Campylobacter

Helicobacter

Arcobacter

History

● 1906: John McFadyean
  - sheep abortions caused by “Vibrio”
● 1919: Smith and Taylor
  - reported the vibrionic abortion in cattle
  - named it “Vibrio fetus”
● 1931: Jones et al.
  - isolated a “vibrio” from cattle
  - named it “Vibrio jejuni”
● 1963: Sebald and Veron
  - named the genus “Campylobacter”

● Formerly in the genus Vibrio
  ➔ Still called “vibriosis” by many
General

- Gram-negative
- Short, curved (comma shaped), spiral or S forms → May turn coccoid in old cultures
- Oxidase +
- Urease negative
cf. Helicobacter – mostly urease positive
- Microaerophilic (3% - 15% O₂)
- Capnophilic (requires CO₂)
- Slow growing (2 – 6 days)

How different from Vibrio?

- Glucose fermentation
  - Vibrio: Glucose (+)
  - Campylobacter: Glucose (−)
    (lack of phosphofructokinase)
How different from Vibrio?

- Vibrio
  - Monotrichous flagella
  - Examples: V. parahaemolyticus, V. alginolyticus, V. harveyi, V. vulnificus, V. anguillarum, V. fischeri, V. cholerae

- Campylobacter
  - Amphitrichous flagella
  - C. jejuni

Campylobacter & Diseases

- Animals
  - Reproductive Diseases
- Humans
  - Gastrointestinal Diseases
Campylobacter-associated abortion

C. fetus subsp. venerealis

- **Habitat:** obligate parasite of the genitalia of ♀ & ♂ cattle
- **Disease:** early embryonic death & occasionally abortions in cattle
- **Pathogenesis**
  - Colonize the prepuce of bulls
    - Transmitted venereally
    - Localizes in the anterior vagina and cervix
      - then invade the uterus and oviducts (ascending infection)
    - Infertility and occasional abortions
  - Develop IgG in the uterus: clear the organism from here & IgA in the vagina but lasts shortly
  - Venereally transmitted to other bulls
- **Vaccination:** bacterins (killed-vaccines) are successful
**C. fetus subsp. venerealis**

- **Diagnosis**
  - Culture: possible but difficult
  - Direct exam of fetal membranes: best with a darkfield microscopy

- Bovine genital campylobacteriosis is “a statutory disease” ([http://www.oie.int/eng/normes/mcode/code2003/a_00057.htm](http://www.oie.int/eng/normes/mcode/code2003/a_00057.htm)) → important for the purpose of international trade of breeding bulls, embryos and the artificial insemination industry

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**C. fetus subsp. fetus**

- **Habitat:** Intestinal tract and reproductive tract of sheep and cattle
- **Transmission:** via “ingestion” (not venereally)

- **Disease**
  - Colonize host’s intestines → a transient bacteremia → spread to the placentas of pregnant animals → placentitis and abortions
  - Cause of abortion in sheep and occasionally cattle
    But does not cause infertility

- **Treatment**
  - Susceptible to some antibiotics (tetracycline)
  - Probably best to try controlling with vaccination

Vib Shield® Plus L5 (Norvatis)
**C. fetus infections in humans**

- A uncommon human pathogen, but its infection is fatal
- Nearly all human infections are due to "*C. fetus spp. fetus*" rather than *C. fetus* spp. *venerealis*

**Oral ingestion**

- **Intestinal colonization**
  - Normal hosts
  - Transient or no Systemic bacteremia
  - Immunocompromised hosts
  - Sustained bacteremia meningitis and abortion

- **Diarrhea**

**C. fetus: S-layer**

- S-layer (Surface layer)
  - Located external to bacterial outer membrane
  - Consisting of proteins

- Possessed by two *Campylobacter* species: *C. fetus* & *C. rectus*

- Roles in pathogenesis
  - Resistance to serum
  - Resistance to phagocytosis
  - Important for colonization and the translocation to the placenta

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C. fetus: S-layer

- Complex DNA inversion
- Continual changes in antigenic types of S-layer
- “Avoid or delay antibody response”

Overview of C. fetus

<table>
<thead>
<tr>
<th>Species</th>
<th>Host(s)</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. fetus ssp. venerealis</td>
<td>Cattle</td>
<td>Bovine genital campylobacteriosis, infertility, early embryonic death,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occasional abortions</td>
</tr>
<tr>
<td>C. fetus ssp. fetus</td>
<td>Sheep, Cattle</td>
<td>Ovine genital campylobacteriosis, abortions, sporadic abortions</td>
</tr>
<tr>
<td></td>
<td>Humans</td>
<td>Sporadic infections mainly in immunocompromised people</td>
</tr>
</tbody>
</table>
**Story of C. fetus**

- **C. fetus ssp. fetus**
  - Oral ingestion
  - Fecal-oral
  - Ovine genital campylobacteriosis - abortion

- **C. fetus ssp. venerealis**
  - Venereal transmission
  - Bovine genital campylobacteriosis
  - Infertility
  - Occasional abortion

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**C. jejuni and C. coli**

- **Habitat:** Intestinal tract of various wild and domestic animals including *poultry*, cattle, pigs, cats, and dogs
- **Transmission:** Oral ingestion
- **Disease**
  - **Humans**
    - Enteritis: “*C. jejuni*” is major (92~95%)
    - *C. jejuni* ssp. *jejuni*
      - *C. jejuni* ssp. *doylei*: often isolated from human clinical samples
      - A major cause of human gastroenteritis worldwide
        - annually 0.6 M (Canada) and 400-500 M (worldwide)
    - A primary cause of Guillain-Barré syndrome
  - **Animals**
    - Often found in fecal samples from dogs and cats with diarrhea
    - Sheep abortion in the US
- **Treatment:** Susceptible to some antibiotics (macrolides)
Human infection by C. jejuni

Guillain-Barré syndrome

- An acute autoimmune disease causing muscular paralysis
- A quarter of GB patients are associated with certain serotypes of C. jejuni
- GBS destroys myelin sheath covering the peripheral nerves
  → Disable the nerves from transmitting signals to muscles
Guillain-Barré syndrome

- Molecular similarity between *C. jejuni* LOS and human ganglioside

![Diagram showing molecular similarity between *C. jejuni* LOS and human ganglioside](TRENDS in Microbiology)

Ovine abortion by *C. jejuni*

- *C. fetus* was the major cause of ovine abortion
- Ovine abortion caused by *C. jejuni* is increasing
- An identical single clone has been isolated, causing sheep abortions in several states in the US
- Tet resistant

![Genetic analysis of *C. jejuni* strains](Orhan et al. (2008) J. Clin. Microbiol.)
Other Campylobacter species

- **C. consisus**
  - implicated in human gastrointestinal diseases

- **C. upsaliensis**
  - isolated from feces of dogs and cats with diarrhea
  - associated with human enteric disease

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Reservoir and Disease

<table>
<thead>
<tr>
<th>Species</th>
<th>Host &amp; Disease</th>
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<tbody>
<tr>
<td><em>C. jejuni</em></td>
<td>Chicken, cattle, turkey, pigs, dogs, wild birds</td>
</tr>
<tr>
<td><em>C. coli</em></td>
<td>Turkey, pigs, chicken, cattle, cats</td>
</tr>
<tr>
<td></td>
<td>→ Enteritis in humans</td>
</tr>
<tr>
<td></td>
<td>→ Often found in fecal samples from dogs and cats with diarrhea</td>
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<tr>
<td><em>C. upsaliensis</em></td>
<td>Isolated from feces of dogs and cats with diarrhea</td>
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<tr>
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<td>→ Enteritis in humans, cats, and dogs</td>
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</tbody>
</table>
## Phenotype Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C. fetus</th>
<th>ssp. fetus</th>
<th>ssp. venerealis</th>
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<th>C. coli</th>
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<tr>
<td>Catalase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urease</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nitrate reductase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H₂S from TSI</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>H₂S from Pb acetate strip</td>
<td>V</td>
<td>V</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Growth at 25°C</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Growth at 42°C</td>
<td>(+)</td>
<td>(-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Growth in 1% glycine</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Growth in 3.5% NaCl</td>
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<td>-</td>
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</tr>
<tr>
<td>Nitrate reductase</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Nitrate reductase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Hippurate test

- **Important test to identify** *Campylobacter* infecting humans (*C. jejuni*)
- Hippurate – (hippuricase) → glycine + benzoic acid

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**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C. fetus</th>
<th>C. jejuni</th>
<th>C. coli</th>
<th>C. fetus</th>
<th>C. jejuni</th>
<th>C. coli</th>
<th>C. fetus</th>
<th>C. jejuni</th>
<th>C. coli</th>
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<tr>
<td>Catalase</td>
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<td>+</td>
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<tr>
<td>Urease</td>
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<tr>
<td>Hippurate hydrolysis</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Sulfate reduction</td>
<td>+</td>
<td>M</td>
<td>F + M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
</tr>
<tr>
<td>Nitrate reduction</td>
<td>M + F + M</td>
<td>F + M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
</tr>
<tr>
<td>H₂S/TSI</td>
<td>M + F + M</td>
<td>F + M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
</tr>
<tr>
<td>25°C</td>
<td>M + M + F</td>
<td>M + F</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
</tr>
<tr>
<td>42°C</td>
<td>M + M + F</td>
<td>M + F</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
<td>+ M</td>
</tr>
<tr>
<td>1% glycine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Symbols: +, 95–100% strains positive; -, 0–1% strains positive; V, test result varies between defined infraeuroppeic tons (see text for details); F, 14–50% strains positive; M, 66–80% strains positive. All data are based on reactions obtained by using recommended standardized procedures (On and Holmes 1991, 1992, 1995).
**General**

- Gram-negative
- Formerly named "*Campylobacter pylori*" ⬅️ "*C. pyloridis*"
- Microaerophilic
- Morphology
  - In tissue: helical and curved rod
  - In culture: rod or rounded form
    - As culture gets old, forms coccoid shapes
- Motile via 2 to 6 unipolar flagella
Discovery

- Marshall and Warren, 1982
  - Described a spiral or curved bacilli in 60% of biopsy specimens (histology, microscopic)
  - Microaerophilic, Gram-negative, Campylobacter-like

- In order to verify the virulent nature (to fulfill Koch’s Postulates)
  Warren drank the culture!
  ➔ Developed acute gastritis ➔ proved gastritis is caused by infection

Robin Warren              Barry Marshall

Helicobacter Species & Disease

- High level of organ specificity ➔ subdivide into two lineages
  1) Gastric Helicobacter species
  2) Enterohepatic (nongastric) Helicobacter species
- Disease: Gastritis, gastric cancer, hepatic cancer

<table>
<thead>
<tr>
<th>Table 1. Gastric Helicobacter taxa.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxon</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td><em>H. acinonychis</em></td>
</tr>
<tr>
<td><em>H. bizzozeronii</em></td>
</tr>
<tr>
<td><em>H. felis</em></td>
</tr>
<tr>
<td><em>H. mustelae</em></td>
</tr>
<tr>
<td><em>H. nemestrina</em>&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
</tr>
<tr>
<td><em>H. salomonis</em></td>
</tr>
</tbody>
</table>

Abbreviations: ATCC, American Type Culture Collection; <sup>T</sup>, type strain; and CCUG, Culture Collection, University of Göteborg, Dept. of Clinical Bacteriology, Göteborg, Sweden.

*H. nemestrina* has now been classified as a junior heterotypic synonym of *H. pylori* (see text; Suerbaum et al., 2002).

Prokaryotes (2006)
**Helicobacter Species & Disease**

Table 2. Enterohepatic Helicobacter taxa.

<table>
<thead>
<tr>
<th>Taxon</th>
<th>Natural host</th>
<th>Strain</th>
<th>GenBank 16S rRNA accession no.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. aurati</em></td>
<td>Hamster</td>
<td>ATCC BAA-17</td>
<td>AF297868</td>
<td>Patterson et al., 2000</td>
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<tr>
<td><em>H. bilis</em></td>
<td>Mice, dog, and human</td>
<td>ATCC 51630T</td>
<td>U18766</td>
<td>Fox et al., 1995</td>
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<tr>
<td><em>H. canadensis</em></td>
<td>Human</td>
<td>ATCC 700968T</td>
<td>AF262037</td>
<td>Fox et al., 2000</td>
</tr>
<tr>
<td><em>H. canis</em></td>
<td>Dog, human</td>
<td>ATCC 51401T</td>
<td>L13464</td>
<td>Stanley et al., 1993</td>
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<tr>
<td><em>H. cholecystus</em></td>
<td>Hamster</td>
<td>ATCC 700242T</td>
<td>U46129</td>
<td>Franklin et al., 1996</td>
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<tr>
<td><em>H. cinedi</em></td>
<td>Human, hamster, and rhesus monkey</td>
<td>CCUG 18818T</td>
<td>M88150</td>
<td>Totten et al., 1985</td>
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<tr>
<td><em>H. fennelliae</em></td>
<td>Human</td>
<td>ATCC 35684T</td>
<td>M88154</td>
<td>Vandenbroucke et al., 1991</td>
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<tr>
<td><em>H. ganmani</em></td>
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<td><em>H. hepaticus</em></td>
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<td><em>H. mesocricetorum</em></td>
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<td><em>H. muriendanum</em></td>
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<td><em>H. pomentis</em></td>
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<td>Stanley et al., 1994</td>
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<td><em>H. rodentium</em></td>
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<td>U96296</td>
<td>Shen et al., 1997</td>
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<td><em>H. trogontum</em></td>
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<td>U65103</td>
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<td><em>H. typhlonius</em></td>
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<td>MU9617T</td>
<td>AF061104</td>
<td>Fox et al., 1999</td>
</tr>
</tbody>
</table>

Abbreviations: Please refer to footnote in Table 1.

Prokaryotes (2006)

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**Selected Helicobacter Species**

**Gastric Helicobacter spp.**

- **H. pylori**: Human, primate, Gastritis, peptic ulcer disease, gastric adenocarcinoma,
- **H. felis**: Cat, dog, mouse, Gastritis in natural host; may cause peptic ulcers or gastric adenocarcinoma in mouse
- **H. mustelae**: Ferret, Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma
- **H. acinonychis**: Cheetah, tiger, Gastritis, peptic ulcer disease, other big cats
- **H. heilmannii**: Human, dog, cat, monkey, cheetah, rat, Gastritis, dyspeptic symptoms, MALT lymphoma

**Enterohepatic Helicobacter spp.**

- **H. hepaticus**: Mouse, other rodents, Hepatitis, hepatocellular carcinoma
**H. pylori**

- **Habitat:** unknown, perhaps carried by humans
- **Disease**
  - 50% of world’s population infected
  - Acute or chronic gastritis
  - 90-95% of people with duodenal ulcers
  - 70-90% with gastric ulcers infected with *H. pylori*
  - Gastric cancer (classified as a “carcinogen”)
- **Pathogenesis**
  - Survive in the deeper layers of mucous
  - Virulence factors: Urease, CagA, VacA
- **Treatment:** antibiotic cocktails
  - metronidazole, amoxicillin, tetracycline or clarithromycin in combination with a proton pump inhibitor or bismuth
Detection

- **Bacterial Culture**
  - Brucella or Columbia agar supplemented with antibiotics (Trimethoprim, Vancomycin, Polymyxin B)

- **Biopsy**
  - Isolation or observance of bacteria in endoscopy biopsy specimens
  - Invasive, false negatives (stomach is huge)

- **Urea Breath Test**
  - Uses $^{13}$C or $^{14}$C to test for urease enzyme
    
    \[
    (\text{NH}_2)_2\text{C}^\text{O} + \text{H}_2\text{O} \rightarrow \text{NH}_3 + \text{C}^\text{O}_2
    \]
  - Non-invasive

Campylobacter
Helicobacter
Arcobacter
General

- Gram-negative, curved to spiral shaped
- Optimal growth under microaerobic
  - “Aerotolerant” \(\rightarrow\) Grows “aerobically
- Growth at 15-30 °C, not at 4 °C
- Difference from *Campylobacter*

<table>
<thead>
<tr>
<th></th>
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<th>Campylobacter</th>
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<tr>
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<td>Microaerophilic</td>
</tr>
<tr>
<td>Optimal Growth Temperature</td>
<td>Low (25-30 °C)</td>
<td>High (30-42 °C)</td>
</tr>
</tbody>
</table>

General

- Energy is obtained from amino acids and TCA cycle intermediates, not carbohydrates
- Various habitats:
  - The reproductive organs
  - Aborted fetuses of various animals
  - Intestinal tract of animals and humans
- *A. cryaerophilus*
  - Abortion in swine, cattle, horses, sheep, and dogs
- *A. butzleri & A. skirrowii*
  - Diarrhea, nausea, vomiting and fever in humans