Campylobacter & Helicobacter

rRNA Superfamily VI of Class Proteobacteria

General Characteristics Common to Superfamily

- Gram-negative
- **Helical** (spiral or curved) morphology; Tend to be pleomorphic
- Characteristics that **facilitate penetration and colonization of mucosal environments** (e.g., motile by polar flagella; corkscrew shape)
- **Microaerophilic** atmospheric requirements
- Become **coccoid** when exposed to oxygen or upon prolonged culture
- **Neither ferment nor oxidize carbohydrates**

History of Campylobacter

- First isolated as *Vibrio fetus* in 1909 from spontaneous abortions in livestock
- ***Campylobacter enteritis*** was not recognized until the mid-1970s when selective isolation media were developed for culturing campylobacters from human feces
- **Most common form of acute infectious diarrhea in developed countries**; Higher incidence than *Salmonella* & *Shigella* combined
- In the U.S., >2 million cases annually, an annual incidence close to the 1.1% observed in the United Kingdom; Estimated 200-700 deaths

Morphology & Physiology of Campylobacter

- **Small**, thin (0.2 - 0.5 um X 0.5 - 5.0 um), **helical** (spiral or curved) cells with typical gram-negative cell wall; "Gull-winged" appearance
  - Tendency to form coccoid & elongated forms on prolonged culture or when exposed to O_2
- Distinctive rapid **darting motility**
  - Long sheathed polar flagellum at one (**polar**) or both (**bipolar**) ends of the cell
  - Motility slows quickly in wet mount preparation
- **Microaerophilic** & **capnophilic** $5\%O_2, 10\%CO_2, 85\%N_2$
- **Thermophilic** (42-43C) (except *C. fetus*)
  - Body temperature of natural avian reservoir
- May become **nonculturable** in nature

Campylobacter Species Associated with Human Disease

Species	Reservoir Host	Human Disease	Frequency
C. jejuni	Poultry, pigs, bulls, dogs, cats, birds, minks, rabbits, insects	Gastroenteritis, septicemia, meningitis, spontaneous abortion, proctitis, Guillain-Barré syndrome	Common
C. jejuni subsp. *doylei*	Humans	Gastroenteritis, gastritis, septicemia	Uncommon
C. coli	Pigs, poultry, bulls, sheep, birds	Gastroenteritis, septicemia, gastroenteritis, spontaneous abortion, meningitis	Uncommon
C. upsaliensis	Dogs, cats	Gastroenteritis, septicemia, abscesses	Uncommon
C. fetus	Cattle, sheep	Septicemia, gastroenteritis, spontaneous abortion, meningitis	Uncommon
C. fetus subsp. *venerealis*	Cattle	Septicemia	Uncommon
C. hyointestinalis	Pigs, cattle, hamsters, deer	Gastroenteritis	Rare
C. concisus	Humans	Periodontal disease, gastroenteritis	Rare
C. sputorum subsp. *sputorum*	Humans, cattle, pigs	Abscesses, gastroenteritis	Rare
C. curvus	Humans	Periodontal disease, gastroenteritis	Rare
C. rectus	Humans	Periodontal disease	Rare
C. showae	Humans	Periodontal disease	Rare
C. lari	Poultry, birds, dogs, cats, monkeys, horses, seals	Gastroenteritis, septicemia	Rare

Guillain-Barre Syndrome (GBS)

- Low incidence potential **sequela**
- Reactive, self-limited, autoimmune disease
- *Campylobacter jejuni* most frequent antecedent pathogen
- Immune response to specific O-antigens **cross-reacts with ganglioside** surface components of peripheral nerves (**molecular or antigenic mimicry**)
  - Acute inflammatory demyelinating neuropathy (85% of cases) from cross reaction with **Schwann-cells** or **myelin**
  - Acute axonal forms of GBS (15% of cases) from molecular mimicry of axonal membrane

Epidemiology of Campylobacteriosis

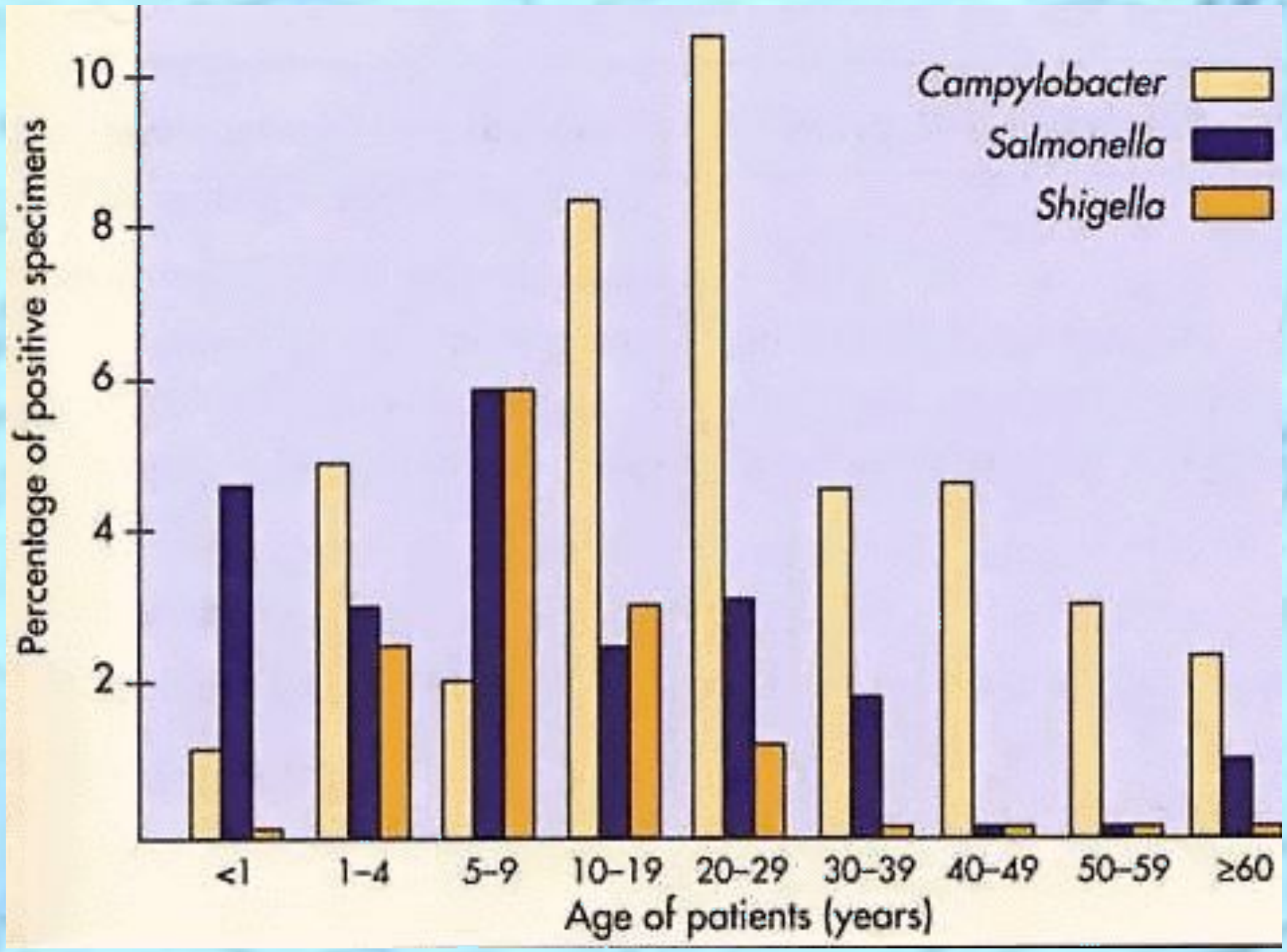
- **Zoonotic** infections in many animals particularly **avian** (bird) **reservoirs**
- Spontaneous abortions in cattle, sheep, and swine, but generally asymptomatic carriage in animal reservoir
- Humans acquire via **ingestion of contaminated food** (particularly **poultry**), unpasteurized milk, or improperly treated water
- **Infectious dose** is reduced by foods that neutralize gastric acidity, e.g., milk. Fecal-oral transmission also occurs

Epidemiology of Campylobacteriosis (cont.)

- **Contaminated poultry** accounts for more than half of the camylobacteriosis cases in **developed countries** but different epidemiological picture in developing countries
- **In U.S.** and **developed countries**: Peak incidence in children below one year of age and young adults (15-24 years old)
- **In developing countries** where campylobacters are hyperendemic: Symptomatic disease occurs in young children and persistent, asymptomatic carriage in adults

Epidemiology of Campylobacteriosis (cont.)

- **Sporadic infections** in humans far outnumber those affected in point-source outbreaks
- Sporadic cases peak in the summer in temperate climates with a secondary peak in the late fall seen in the U.S.
- Globally, ***C. jejuni* subsp. *jejuni*** accounts for more than 80% of all *Campylobacter* enteriti
- *C. coli* accounts for only 2-5% of the total cases in the U.S.; *C. coli* accounts for a higher percentage of cases in developing countries


Campylobacter
Salmonella
Shigella
Percentage of positive specimens
10
8
6
4
2
<1
1–4
5–9
10–19
20–29
30–39
40–49
50–59
≥60
Age of patients (years)

Pathogenesis & Immunity

- **Infectious dose and host immunity** determine whether gastroenteric disease develops
  - Some people infected with as few as 500 organisms while others need >10^6 CFU
- Pathogenesis not fully characterized
  - No good animal model
  - Damage (ulcerated, edematous and bloody) to the **mucosal surfaces** of the jejunum, ileum, colon
  - Inflammatory process consistent with **invasion** of the organisms into the intestinal tissue; M-cell (Peyer's patches) uptake and presentation of antigen to underlying lymphatic system
- Non-motile & adhesin-lacking strains are **avirulent**

Putative Virulence Factors

Cellular components:

- Endotoxin
- Flagellum: Motility
- Adhesins: Mediate attachment to mucosa
- Invasins
- GBS is associated with *C. jejuni* serogroup O19
- **S-layer** protein “microcapsule” in ***C. fetus***:

Extracellular components:

- Enterotoxins
- Cytopathic toxins

Laboratory Identification

Specimen Collection and Processing:

- Feces refrigerated & examined within few hours
- Rectal swabs in semisolid transport medium
- Blood drawn for *C. fetus*
- Care to avoid oxygen exposure
- Selective isolation by filtration of stool specimen
- Enrichment broth & selective media
- Filtration: pass through 0.45 µm filters

Microscopy:

- Gull-wing appearance in gram stain
- **Darting motility** in fresh stool (rarely done in clinical lab)
- Fecal leukocytes are commonly present

Identification:

- Growth at 25º, 37º, or 42-43ºC
- **Hippurate hydrolysis** (*C. jejuni* is positive)
- Susceptibility to **nalidixic acid & cephalothin**

Laboratory Identification (cont.)

Characteristics	C. jejuni	C. coli	C. upsaliensis	C. fetus	H. pylori	H. cinaedi	H. fennelliae
Oxidase	+	+	+	+	+	+	+
Catalase	+	+	−/W	+	+	+	+
Nitrate reduction	+	+	+	+	−	+	−
Urease	−	−	−	−	+	−	−
Hydrolysis of:							
Hippurate	+	−	−	−	−	−	−
Indoxyl acetate	+	+	+	−	−	−	+
Growth at:							
25°C	−	−	−	+	−	−	−
37°C	+	+	+	+	+	+	+
42°C	+	+	+	−	−	−	−
Growth in 1% glycine	+	+	V	+	−	+	+
Susceptibility to:							
Nalidixic acid	S	S	S	V	R	S	S
Cephalothin	R	R	S	S	S	I	S

Treatment, Prevention & Control

- **Gastroenteritis:**
  - Self-limiting; Replace fluids and electrolytes
  - Antibiotic treatment can shorten the excretion period; **Erythromycin** is **drug of choice** for severe or complicated enteritis & bacteremia; Fluroquinolones are highly active (e.g., ciprofloxacin was becoming drug of choice) but **fluoroquinolone resistance** has developed rapidly since the mid-1980s apparently related to unrestricted use and the use of enrofloxacin in poultry
  - **Azithromycin** was effective in recent human clinical trials
  - Control should be directed at domestic animal reservoirs and interrupting transmission to humans
- **Guillain-Barre Syndrome (GBS)**
  - Favorable prognosis with optimal supportive care
  - Intensive-care unit for 33% of cases

History & Taxonomy of Helicobacter

- Family not yet named (17 species by rRNA sequencing)
- First observed in 1983 as *Campylobacter*-like organisms (formerly *Campylobacter pyloridis*) in the stomachs of patients with **type B gastritis**
- Nomenclature of *Helicobacter* was first established in 1989, but only three species are currently considered to be human pathogens

Important Human Pathogens:

- *Helicobacter pylori* (human; no animal reservoir)
- *H. cinaedi* (male homosexuals; rodents)
- *H. fenneliae* (male homosexuals; rodents)

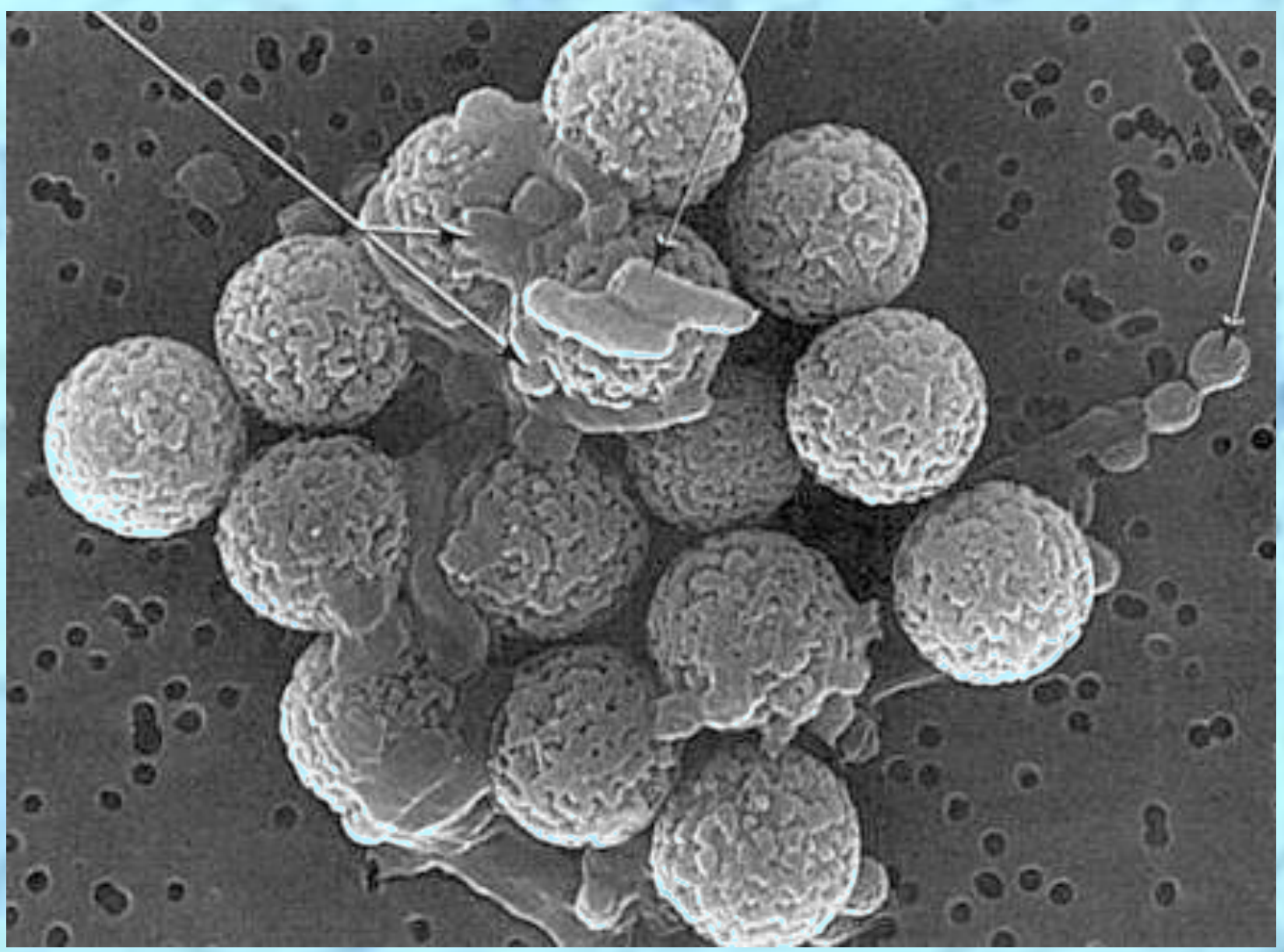
General Characteristics of *Helicobacter*

- ***Helicobacter pylori*** is major human pathogen associated **with gastric antral epithelium** in patients with active **chronic gastritis**
- Stomach of many animal species also colonized
- **Urease** (gastric strains only), **mucinase, and catalase positive** highly motile microorganisms
- **Other Helicobacters: *H. cinnaedi* and *H. fenneliae***
  - Colonize human intestinal tract
  - Isolated from homosexual men with proctitis, proctocolitis, enteritis, and bacteremia and are often transmitted through sexual practices

Morphology & Physiology of Helicobacter

- Gram-negative; **Helical** (spiral or curved) (0.5-1.0 um X 2.5-5.0 um); Blunted/rounded ends in gastric biopsy specimens; Cells become rod-like and coccoid on prolonged culture
- Produce **urease**, **mucinase**, and **catalase**
- *H. pylori* tuft (**lophotrichous**) of 4-6 sheathed flagella (30um X 2.5nm) attached at one pole
- Single polar flagellum on *H. fennellae* & *H. cinaedi*
- Smooth cell wall with unusual fatty acids

Helicobacter on Paramagnetic Beads



Helicobacter Species Associated with Human Disease

Species	Reservoir Host	Human Disease	Frequency
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H. cinaedi	Humans, hamsters	Gastroenteritis, septicemia, proctocolitis, cellulitis	Uncommon
H. fennelliae	Humans	Gastroenteritis, septicemia, proctocolitis	Uncommon
H. canis	Dogs	Gastroenteritis	Rare
H. pullorum	Poultry	Gastroenteritis	Rare
H. rappini	Humans, sheep, mice	Gastroenteritis	Rare
H. canadensis	Humans	Gastroenteritis	Rare

Epidemiology of Helicobacter Infections

- **Family Clusters**
- **Orally** transmitted **person-to-person (?)**

Worldwide:

- ~ 20% below the age of 40 years are infected
- 50% above the age of 60 years are infected
- *H. pylori* is uncommon in young children

Epidemiology of Helicobacter Infections (cont.)

Developed Countries:

- **United States**: 30% of total population infected
  - Of those, ~1% per year develop duodenal ulcer
  - ~1/3 eventually have peptic ulcer disease(PUD)
- 70% **gastric ulcer cases** colonized with *H. pylori*
- Low socioeconomic status predicts *H. pylori* infection

Developing Countries:

- Hyperendemic
- About 10% acquisition rate per year for children between 2 and 8 years of age
- Most adults infected but no disease
  - Protective immunity from multiple childhood infections

Pathogenesis of Helicobacter Infections

- **Colonize mucosal lining of stomach & duodenum** in man & animals
  - Adherent to gastric surface epithelium or pit epithelial cells deep within the mucosal crypts adjacent to gastric mucosal cells
  - Mucosa protects the stomach wall from its own gastric milleu of digestive enzymes and hydrochloric acid
  - Mucosa also protects *Helicobacter* from immune response
- Most gastric a**denocarcinomas** and **lymphomas** are concurrent with or preceded by an infection with *H. pylori*

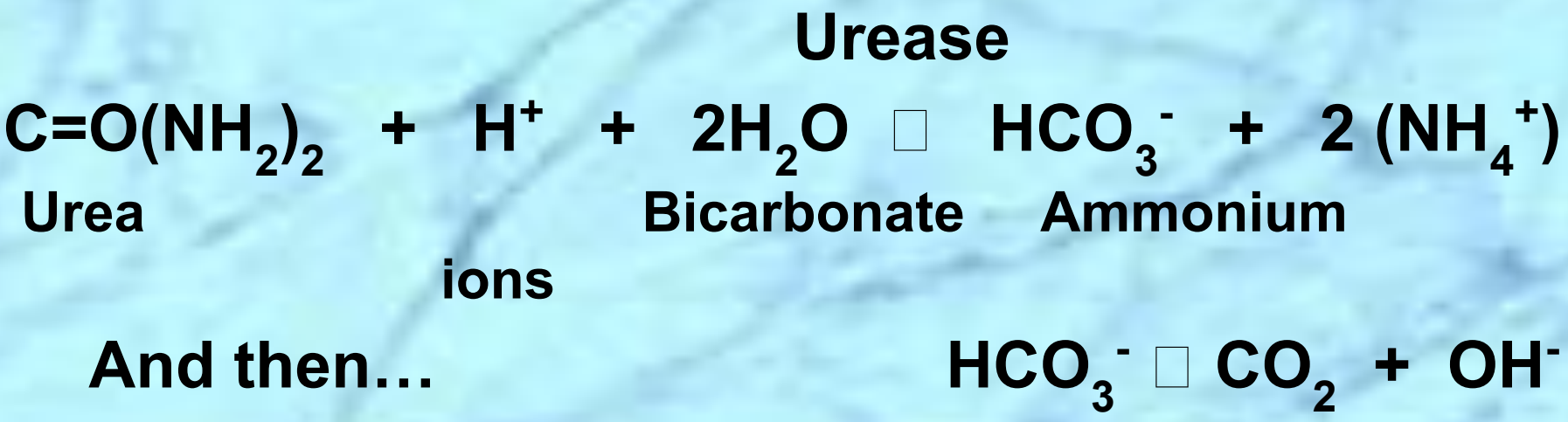
Virulence Factors of Helicobacter

Virulence Factors	Function
Urease	Neutralizes gastric acids; stimulates monocytes and neutrophil chemotaxis; stimulates production of inflammatory cytokines
Heat shock protein (HspB)	Enhances expression of urease
Acid-inhibitory protein	Induces hypochlorhydria during acute infection by blocking acid secretion from parietal cells
Flagella	Allow penetration into gastric mucous layer and protection from acid environment
Adhesins	Mediate binding to host cells; examples of adhesins are hemagglutinins, sialic acid–binding adhesin, Lewis blood group adhesin
Mucinase	Disrupts gastric mucus
Phospholipases	Disrupt gastric mucus
Superoxide dismutase	Prevents phagocytic killing by neutralizing oxygen metabolites
Catalase	Prevents phagocytic killing by neutralizing peroxides
Vacuolating cytotoxin	Induces vacuolation in epithelial cells; stimulates neutrophil migration into mucosa
Poorly defined factors	*H. pylori:* Stimulates interleukin-8 secretion by gastric epithelial cells, which recruits and activates neutrophils Stimulates gastric mucosal cells to produce platelet-activating factor (PAF), which stimulates gastric acid secretion Induces nitric oxide synthase in gastric epithelial cells, which mediates tissue injury Induces death of gastric epithelial cells

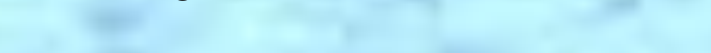
Virulence Factors of Helicobacter

- **Multiple polar, sheathed flagella**
  - Corkscrew motility enables penetration into viscous environment (mucus)
- **Adhesins:** Hemagglutinins; Sialic acid binding adhesin; Lewis blood group adhesin
- **Mucinase**: Degrades gastric mucus; Localized tissue damage
- **Urease** converts urea (abundant in saliva and gastric juices) into bicarbonate (to CO_2) and ammonia
  - Neutralize the local acid environment
  - Localized tissue damage
- Acid-inhibitory protein

Urea Hydrolysis



And then…



Virulence Factors of Helicobacter (cont.)

Tissue damage:

- **Vacuolating cytotoxin:** Epithelial cell damage
- **Invasin(s)(??):** Poorly defined (e.g., hemolysins; phospholipases; alcohol dehydrogenase)

Protection from phagocytosis & intracellular killing:

- Superoxide dismutase
- Catalase

Laboratory Identification

- Recovered from or detected in endoscopic antral gastric biopsy material; Multiple biopsies are taken
- Many different transport media
- Culture media containing **whole or lysed blood**
- **Microaerophilic**
- **Grow well at 37oC**, but not at 25 nor 42oC
- Like *Campylobacter*, does not use carbohydrates, neither fermentatively nor oxidatively

Treatment, Prevention & Control

Triple Chemotherapy (synergism):

- Proton pump inhibitor (e.g., omeprazole = Prilosec(R))
- One or more antibiotics (e.g., clarithromycin; amoxicillin; metronidazole)
- Bismuth compound

Inadequate treatment results in recurrence of symptoms

REVIEW

Campylobacter & Helicobacter Superfamily

General Characteristics Common to Superfamily

- Gram-negative
- **Helical** (spiral or curved) morphology; Tend to be pleomorphic
- Characteristics that **facilitate penetration and colonization of mucosal environments** (e.g., motile by polar flagella; corkscrew shape)
- **Microaerophilic** atmospheric requirements
- Become **coccoid** when exposed to oxygen or upon prolonged culture
- **Neither ferment nor oxidize carbohydrates**

REVIEW

Campylobacter Review

History of Campylobacter

- First isolated as *Vibrio fetus* in 1909 from spontaneous abortions in livestock
- ***Campylobacter enteritis*** was not recognized until the mid-1970s when selective isolation media were developed for culturing campylobacters from human feces
- **Most common form of acute infectious diarrhea in developed countries**; Higher incidence than ***Salmonella* & *Shigella* combined**
- In the U.S., >2 million cases annually, an annual incidence close to the 1.1% observed in the United Kingdom; Estimated 200-700 deaths

REVIEW

Diseases

Refer to Table 31–1.

Acute enteritis with diarrhea, malaise, fever, and abdominal pain. Most infections are self-limited but can persist for a week or more.

C. fetus is associated with septicemia and is disseminated to multiple organs.

Diagnosis

Microscopy is insensitive.

Culture requires use of specialized media incubated with reduced oxygen, increased carbon dioxide, and (for thermophilic species) elevated temperatures; slow grower requiring incubation for 2 days or more.

Nonfermenter.

Treatment, Prevention, and Control

For gastroenteritis, infection is self-limited and is managed by fluid and electrolyte replacement.

Severe gastroenteritis and septicemia are treated with erythromycin (drug of choice), tetracyclines, quinolones.

Gastroenteritis is prevented by proper preparation of food and consumption of pasteurized milk; prevention of contaminated water supplies also controls infection.

Physiology and Structure

Thin, curved gram-negative bacilli; too thin to be seen in most clinical specimens by brightfield microscopy.

Virulence

Factors that regulate adhesion, motility, and invasion into intestinal mucosa are poorly defined for *C. jejuni*, *C. upsaliensis*, and *C. coli*.

S protein in *C. fetus* inhibits C3b binding and subsequent complement-mediated phagocytosis and killing (i.e., resistant to serum killing).

Guillain-Barré syndrome believed to be an autoimmune disease due to antigenic cross-reactivity between oligosaccharides in bacterial capsule and glycosphingolipids on surface of neural tissues.

Epidemiology

Zoonotic infection; improperly prepared poultry is a common source of human infections.

Infections acquired by ingestion of contaminated food, unpasteurized milk, or contaminated water.

Person-to-person spread is unusual.

Infectious dose is high unless the gastric acids are neutralized or absent.

Worldwide distribution, with enteric infections most commonly seen in warm months.

Morphology & Physiology of Campylobacter

- **Small**, thin (0.2 - 0.5 um X 0.5 - 5.0 um), **helical** (spiral or curved) cells with typical gram-negative cell wall; "Gull-winged" appearance
  - Tendency to form coccoid & elongated forms on prolonged culture or when exposed to O_2
- Distinctive rapid **darting motility**
  - Long sheathed polar flagellum at one (**polar**) or both (**bipolar**) ends of the cell
  - Motility slows quickly in wet mount preparation
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REVIEW

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REVIEW

Guillain-Barre Syndrome (GBS)

- Low incidence potential **sequela**
- Reactive, self-limited, autoimmune disease
- *Campylobacter jejuni* most frequent antecedent pathogen
- Immune response to specific O-antigens **cross-reacts with ganglioside** surface components of peripheral nerves (**molecular or antigenic mimicry**)
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  - Acute axonal forms of GBS (15% of cases) from molecular mimicry of axonal membrane

REVIEW

Epidemiology of Campylobacteriosis

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- Spontaneous abortions in cattle, sheep, and swine, but generally asymptomatic carriage in animal reservoir
- Humans acquire via **ingestion of contaminated food** (particularly **poultry**), unpasteurized milk, or improperly treated water
- **Infectious dose** is reduced by foods that neutralize gastric acidity, e.g., milk. Fecal-oral transmission also occurs

REVIEW

Epidemiology of Campylobacteriosis (cont.)

- **Contaminated poultry** accounts for more than half of the camylobacteriosis cases in **developed countries** but different epidemiological picture in developing countries
- **In U.S.** and **developed countries**: Peak incidence in children below one year of age and young adults (15-24 years old)
- **In developing countries** where campylobacters are hyperendemic: Symptomatic disease occurs in young children and persistent, asymptomatic carriage in adults

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Epidemiology of Campylobacteriosis (cont.)

- **Sporadic infections** in humans far outnumber those affected in point-source outbreaks
- Sporadic cases peak in the summer in temperate climates with a secondary peak in the late fall seen in the U.S.
- Globally, ***C. jejuni* subsp. *jejuni*** accounts for more than 80% of all *Campylobacter* enteriti
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Helicobacter Review

History & Taxonomy of Helicobacter

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- First observed in 1983 as *Campylobacter*-like organisms (formerly *Campylobacter pyloridis*) in the stomachs of patients with **type B gastritis**
- Nomenclature of *Helicobacter* was first established in 1989, but only three species are currently considered to be human pathogens

Important Human Pathogens:

- *Helicobacter pylori* (human; no animal reservoir)
- *H. cinaedi* (male homosexuals; rodents)
- *H. fenneliae* (male homosexuals; rodents)

REVIEW

General Characteristics of *Helicobacter*

- ***Helicobacter pylori*** is major human pathogen associated **with gastric antral epithelium** in patients with active **chronic gastritis**
- Stomach of many animal species also colonized
- **Urease** (gastric strains only), **mucinase, and catalase positive** highly motile microorganisms
- **Other Helicobacters: *H. cinnaedi* and *H. fenneliae***
  - Colonize human intestinal tract
  - Isolated from homosexual men with proctitis, proctocolitis, enteritis, and bacteremia and are often transmitted through sexual practices

REVIEW

Physiology and Structure

Curved gram-negative bacilli.

Urease production at very high levels is typical of gastric helicobacters (e.g., *H. pylori*) and uncommon in intestinal helicobacters (important diagnostic test for *H. pylori*).

Virulence

Refer to Table 31–4.

Epidemiology

Infections are common, particularly in people in a low socioeconomic class or in developing nations.

Humans are the primary reservoir.

Person-to-person spread is important (typically fecal-oral).

An animal reservoir has not been identified.

Ubiquitous and worldwide with no seasonal incidence of disease.

REVIEW

Diseases

Refer to Table 31–3.

Diagnosis

Microscopy—histologic examination of biopsy specimens is sensitive and specific.

Culture requires incubation in microaerophilic conditions; growth is slow.

Serology useful for demonstrating exposure to *H. pylori*.

Treatment, Prevention, and Control

Multiple regimens have been evaluated for treatment of *H. pylori* infections. Therapy with tetracycline, metronidazole, bismuth, and omeprazole for 2 weeks has had a high success rate.

Prophylactic treatment of colonized individuals has not been useful and potentially has adverse effects, such as predisposing patients to adenocarcinomas of the lower esophagus.

Human vaccines are not currently available.

Morphology & Physiology of Helicobacter

- Gram-negative; **Helical** (spiral or curved) (0.5-1.0 um X 2.5-5.0 um); Blunted/rounded ends in gastric biopsy specimens; Cells become rod-like and coccoid on prolonged culture
- Produce **urease**, **mucinase**, and **catalase**
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H. canis	Dogs	Gastroenteritis	Rare
H. pullorum	Poultry	Gastroenteritis	Rare
H. rappini	Humans, sheep, mice	Gastroenteritis	Rare
H. canadensis	Humans	Gastroenteritis	Rare

REVIEW

Epidemiology of Helicobacter Infections

- **Family Clusters**
- **Orally** transmitted **person-to-person**
- ~ 20% below the age of 40 years are infected
- 50% above the age of 60 years are infected
- *H. pylori* is uncommon in young children

REVIEW

Epidemiology of Helicobacter Infections (cont.)

Developed Countries:

- **United States**: 30% of total population infected
  - Of those, ~1% per year develop duodenal ulcer
  - ~1/3 eventually have peptic ulcer disease(PUD)
- 70% **gastric ulcer cases** colonized with *H. pylori*
- Low socioeconomic status predicts *H. pylori* infection

Developing Countries:

- Hyperendemic
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- Most adults infected but no disease
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Pathogenesis of Helicobacter Infections

- **Colonize mucosal lining of stomach & duodenum** in man & animals
  - Adherent to gastric surface epithelium or pit epithelial cells deep within the mucosal crypts adjacent to gastric mucosal cells
  - Mucosa protects the stomach wall from its own gastric milleu of digestive enzymes and hydrochloric acid
  - Mucosa also protects *Helicobacter* from immune response
- Most gastric a**denocarcinomas** and **lymphomas** are concurrent with or preceded by an infection with *H. pylori*

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REVIEW

Treatment, Prevention & Control

Triple Chemotherapy (synergism):

- Proton pump inhibitor (e.g., omeprazole = Prilosec(R))
- One or more antibiotics (e.g., clarithromycin; amoxicillin; metronidazole)
- Bismuth compound

Inadequate treatment results in recurrence of symptoms