Helicobacter pylori
Curved Gram-negative bacillus, urease production
Chronic gastritis, gastric and duodenal ulceration, gastric carcinoma

Pathogenesis
colonization of gastric mucosa, urease production, toxin production
Vacuolating cytotoxin – ion channel, immunosuppressive
Cag A - deranges tyrosine phosphorylation signalling, inflammation, proliferation
Non-inflammatory surface structures

Diagnosis
gastric urease activity – urease breath test; serology; fecal antigen; biopsy; histology; culture

Therapy – combination antibiotics, acid suppression

Epidemiology
fecal oral transmission, declining incidence,
association with gastric cancer
negative association (protection against) esophageal cancer

Vibrio cholerae
Gram-negative, highly motile curved bacillus
Cholera-producing strains limited to two serotypes, not found widely in environment
Non-cholera producing V. cholerae found in marine environments

Cholera
Profuse watery, non-inflammatory diarrhea, potentially severe and rapid dehydration

Pathogenesis of cholera
Colonization of small intestine, production of enterotoxin
Cholera toxin – AB toxin, A is ADP-ribosylating toxin, target is regulatory subunit of adenylate cyclase
Affected intestinal epithelial cells have high intracellular cAMP, causes secretion of electrolytes and fluid into intestine

Diagnosis
Culture and biochemicals

Therapy
Oral rehydration possible if glucose added to salts solution (activates glucose-sodium transporter on intestinal epithelial cells)

Prevention
Sanitation! Vaccines, not widely used

Epidemiology – fecal-oral transmission, fecal contamination of environment
Pandemic disease, high mortality in Africa
Haiti cholera epidemic
**Vibrio parahaemolyticus** (diarrhea associated with consumption of raw oysters)

**Campylobacter jejuni** – curved microaerophilic Gram negative bacillus
very common inflammatory diarrhea associated with consumption of improperly
prepared food, many animal sources. Rare complication is Guillain-Barré syndrome
(acute paralysis of extremities)

Enterobacteriaceae – family of facultative Gram negative bacilli, commensals and pathogens
found in the colons of humans and animals. Important enteric and opportunistic pathogens.

Enterohemorrhagic E. coli (O157:H7), bloody diarrhea, kidney disease associated with
uncooked food contaminated with cattle feces and fecal oral transmission

Shigella – bloody, highly inflammatory diarrhea, fecal-oral transmission

Salmonella enterica
very common inflammatory diarrhea associated with consumption of improperly
prepared food, many animal sources, risk of systemic disease in compromised patients
• **Helicobacter pylori**
  - Small, curved, Gram-negative bacillus, microaerophilic
  - Produce large amounts of urease
  \[ \text{REA} \rightarrow \text{CO}_2 + 2\text{NH}_3 \]

• **Diseases**
  - Acute upper gastrointestinal illness
    - Nausea, upper abdominal pain, burping
    - < 1 week duration
  - Chronic gastritis (all strains)
    - Usually asymptomatic!
  - Duodenal, gastric ulceration (some strains)
  - Gastric carcinoma, gastric lymphoma

• Production of vacuolating cytotoxin
  - Causes formation of vacuoles in tissue culture cells
  - Inserts ion channel in epithelial cell membrane
  - Secretion of urea into gastric lumen
  - Immunosuppressive effects on T lymphocytes

• Production of CagA
  - Protein injected directly into target epithelial cell by type IV secretion system
    - Binds tyrosine kinases, phosphatases
    - Deranges receptor tyrosine kinase signaling pathways
    - Activates proteins encoded by oncogenes
    - Actin skeleton rearrangement
    - Inflammation
    - Proliferation

• **H. pylori** establishes chronic inflammation by limiting its inflammatory potential
  - Non-inflammatory surface structures
    - LPS not recognized by TLR4
    - Flagella not recognized by TLR5

• **Diagnosis**
  - Demonstration of gastric urease activity
    - Urea breath test
    - Patient ingests radioactive urea, radioactive CO₂ exhaled if *H. pylori* present
  - Serology
  - Fecal antigen detection
  - Endoscopy and biopsy, histology and culture

• **Therapy**
  - Combination antibiotics combined with gastric acid suppression (acid inhibits antibiotic action)
  - Development of antibiotic resistance is a problem
**Helicobacter pylori**

- Epidemiology
  - Fecal-oral, familial transmission
  - Infection occurs at earlier age in developing world
  - Prevalence declining in developed countries
  - Gastric adenocarcinoma
    - 75% of gastric adenocarcinoma caused by H. pylori
    - 2nd leading cause of cancer deaths
    - Rates are declining due to decline in H. pylori colonization
    - H. pylori second only to smoking as a defined cause of cancer

- Beneficial effects of H. pylori, “I’m not all bad!”
  - H. pylori colonization is protective against gastro-esophageal reflux disease and esophageal cancer
  - Negative associations - these conditions associated with ABSENCE of H. pylori colonization (associations only, causation not established!)
    - asthma
    - inflammatory bowel diseases
    - obesity
    - gastric hormone ghrelin production inhibited by H. pylori infection
      - modest weight gain occurs after H. pylori eradication in Japanese population

**Vibrio cholerae**

- Gram negative, highly motile, curved bacilli, facultative
- Can tolerate higher salt concentrations than most normal flora
- Serogroups based on LPS antigens
  - Most serogroups found as natural inhabitants of marine environment
  - Only 2 virulent serogroups: O1, O139
    - Not found widely in environment, found in association with fecal contamination

**The Disease - Cholera**

- Acute onset of profuse watery diarrhea with little or no intestinal inflammation
  - Incubation period of 1-5 days
  - Rapid dehydration - fluid and electrolyte loss
    - Vomiting, decreased urine output, muscle cramps, loss of skin elasticity
    - Alert ⇒ Restless ⇒ Drowsy ⇒ Comatose
    - Acute renal failure
  - 10-30% mortality if untreated
  - <1% mortality with appropriate treatment
    - resolution in ~5 days

**Pathogenesis of cholera**

- Colonization of small intestine mediated by adhesive fimbriae
- Production of enterotoxin (toxin that induces fluid secretion from intestinal epithelium) - cholera toxin

**Cholera toxin**

- AB toxin –
  - B subunit binds toxin to intestinal epithelial cell
- A subunit is ADP-ribosyl transferase
  - NAD + protein ⇒ protein-ADPribose + nicotinamide
  - Target is GS regulator of adenylate cyclase
  - Intracellular cAMP concentration increases
    - Altered regulation of ion channels
- Genetics
  - Associated with lysogenic bacteriophage
• Diagnosis of cholera
  • Culture, biochemical tests
    • Selective media, e.g. thiosulfate citrate bile salts (TCBS)
  • Dark field microscopic examination of stool

• Therapy of cholera
  • Fluid and electrolyte replacement
    • Oral rehydration: glucose (or complex carbohydrates) + salts
    • Intravenous rehydration for extreme dehydration
  • Antibiotics shorten duration of disease
    • Doxycycline, TMP-SMX, fluoroquinolones

• Cholera Prevention
  • Oral killed whole cell (O1), recombinant B subunit vaccine (Dukoral)
  • Oral killed whole cell (O1, O139) (mORCVAX, Shanchol)
    • Shanchol produced in India under sponsorship of the Gates Foundation, $1-$2 per dose
  • Vaccine efficacy >50% protection lasting 2 years in endemic populations

• Epidemiology of cholera
  • Fecal-oral transmission via fecal contamination of environment
    • This discovery by John Snow in 1854, in London, was the beginning of the Sanitary Revolution
    • V. cholerae maintains a “hyperinfectious” state in environment for some hours after defecation
  • Pandemic disease
    • Current pandemic has extended into South and Central America
    • Since 1991, high endemicity has persisted in Africa, associated with high mortality

**Haiti Cholera Epidemic**

• There had NEVER before been a cholera epidemic documented in Haiti. “Although Port-au-Prince is the most disgusting city I have ever seen, it has never been visited by cholera.” Spenser St. John, British Charge d’Affairs to Haiti, 1886

• In 2009, only 6% of the population had access to clean drinking water.

• January 2010: major earthquake occurred: 200,000 killed, 2 million homeless, major shortages of food and clean water

• October 2010: beginning of the cholera epidemic

• November 2010: major flooding associated with hurricane Tomás

• At the peak of the epidemic in Dec. 2010, >4,000 new cases per day

**Origin of the Haiti Cholera Epidemic**

First cases occurred near a Nepalese military camp as part of the UN peacekeeping force established after the earthquake of January, 2010.

Rumors rapidly spread that the Nepalese had brought the epidemic strain, causing riots and violence against many UN activities including cholera treatment centers.

Epidemiological and molecular genetic studies have supported origin of the epidemic strain in Nepal.
Other Pathogenic Vibrios

Natural inhabitants of marine environments
Disease acquired by consumption of, or exposure to contaminated shellfish
These strains do NOT make cholera toxin

*Vibrio parahaemolyticus*
- Diarrhea (usually mild)
- Common in Puget Sound area

*Vibrio vulnificus*
- Wound infections
- Sepsis
- Gulf Coast states
- ~100 cases/year

Family Enterobacteriaceae

- Large family of facultative Gram-negative bacillus species
- Most are *normal flora* of the colon of humans and mammals
- Some important primary pathogens
  - *E. coli* (some strains)
  - *Salmonella enterica*
  - *Shigella*
- Commensal strains are important opportunistic pathogens

Campylobacter jejuni

- Curved, microaerophilic Gram-negative bacillus
- Enteric pathogen of *birds and mammals*
- *Food and animal contact*, fecal-oral human to human
- Inflammation of ileum and colon, *diarrhea, fever and abdominal pain*
- Complications are rare, include *Guillain Barré syndrome*
  - auto-immune neurological disease involving paralysis of extremities
  - Very common in U.S.

Enterohemorrhagic *E. coli* *E. coli* O157:H7

- Occasional commensal (?) of *cattle*
- Acquired through food, or fecal-oral from infected humans
- Differs from commensal strains in two important virulence factors
  - *Type three secretion system* directs "effector proteins" into epithelial cells
  - Disruption of cytoskeletal structure, *damage to epithelial surface*
- *Shiga toxin*
  - All toxin birds to endothelial cells (cells lining blood vessels)
  - Cleaves ribosomal RNA, stops protein synthesis
- Bacteria remain in colon, but *toxin mediated vascular damage* is intestinal and systemic
  - *Bloody diarrhea*
  - *Kidney damage* (Hemolytic uremic syndrome HUS)

Salmonella enterica

- Pathogenic species of humans, mammals, birds, and reptiles
- *Food, animal contact*, fecal oral human to human
- Invades epithelial cells of ileum and colon
- Replicates intracellularly in epithelial cells
- *Type three secretion system* directs effector proteins into cells
  - *Actin cytoskeletal structure disrupted, fluid secretion induced*
- *Inflammatory diarrhea, fever, abdominal pain*
- Bacterial usually limited to intestinal tissue
  - *Compromised patients at risk of bacteremia and disseminated infection*
- *Most common bacterial cause of diarrheal disease in U.S.*

Shigella species

- Pathogenic strains of *E. coli*, not really a separate genus
  - *Limited to humans, highly infectious*, efficient fecal-oral transmission
- *Type three secretion system* directs effector proteins into cells
  - Disrupts cytoskeletal organization
- Invades epithelial cells of colon
  - *Extensive replication intracellularly in epithelial cells*
  - *Extensive inflammation and tissue damage*
  - Bloody diarrhea with pus = *dysentery*
- In U.S. disease usually limited, except in elderly
- In developing world, significant mortality