True Pathogens of the Enterobacteriaceae: Salmonella, Shigella & Yersinia
Anatomy of Digestive Tract

- Digestive tract is a “tube” (from mouth to anus); technically “outside” of the body
  - **Lumen** = space within tubular or hollow organ such as an artery, vein, or intestine
  - **Intestinal lumen** = the inside of the intestine
- **Mesentery** = membrane attaching organ (e.g., intestine) to body wall; often has lymphoid tissue
- Food is moved down tract via **peristalsis**
- Entire length of digestive tract epithelium is covered by mucosal membrane (**mucosa**) with mucus that is secreted from specialized glands
- Surface area of intestine increased by presence of **villi** (finger-like projections) and **microvilli** that absorb nutrients and other products of digestion
**Anatomy of Digestive Tract (cont.)**

- Mouth, pharynx, esophagus & esophageal sphincter
- Stomach and pyloric valve (sphincter)
- **Small intestine** (about 23 feet in length)
  - **Duodenum** (~10” in length) (bile & pancreatic ducts carry digestive juices secreted by gall bladder, liver & pancreas)
  - **Jejunum** (~8 feet in length)
  - **Ileum** (final 3/5 of length) and **ileocecal valve**
    - Absorbs bile salts & nutrients, including vitamin B12
- **Large intestine**
  - **Cecum** (caecum) (blind pouch where appendix also enters)
  - **Colon** (ascending, transverse, descending, sigmoid)
  - **Rectum** and **anus** (with internal and external sphincters)
General Characteristics of Salmonella

- **Coliform** bacilli (enteric rods)
- Motile gram-negative facultative anaerobes
- Non-lactose fermenting
- Resistant to bile salts
- $\text{H}_2\text{S}$ producing
Classification and Taxonomy of Salmonella (Confused)

Old: Serotyping & biochemical assays used to name individual species within genus (e.g., Salmonella enteritidis, S. choleraesuis, S. typhi)

- Over 2400 O-serotypes (referred to as species) (Kauffman-White antigenic schema)
- Bioserotyping (e.g., S. typhimurium)

New: DNA homology shows only two species Salmonella enterica (six subspecies) and S. bongori

- Most pathogens in S. enterica ssp. enterica
Epidemiology of Salmonella Infection

DISEASE/BACTERIAL FACTORS
Enteritis, septicemia, enteric fever, asymptomatic carriage
Animals are main reservoir of human disease except for bacteria responsible for typhoid and paratyphoid fevers
Numerous virulence factors

TRANSMISSION
Ingestion of contaminated food products (especially poultry, eggs, dairy products)
Direct fecal-oral spread in children

WHO IS AT RISK?
Anyone consuming foods contaminated with large numbers of Salmonella, particularly children younger than 1 year old, elderly, patients with reduced gastric acids, and patients with AIDS
S. typhi: foreign travelers or individuals exposed to carriers

GEOGRAPHY/SEASON
Worldwide
More common in warm months

MODES OF CONTROL
Symptomatic treatment rather than antibiotics
Proper preparation and refrigeration of foods
Improved hygiene
Annual Reported Incidence of Salmonella Infection (excluding typhoid fever)
Clinical Syndromes of Salmonella

Salmonellosis = Generic term for disease

Clinical Syndromes

- **Enteritis** (acute gastroenteritis)
- **Enteric fever** (prototype is *typhoid fever* and less severe paratyphoid fever)
- **Septicemia** (particularly *S. choleraesuis, S. typhi, and S. paratyphi*)
- **Asymptomatic carriage** (gall bladder is the reservoir for *Salmonella typhi*)
Enteritis

- Most common form of salmonellosis with major foodborne outbreaks and sporadic disease
- High infectious dose \((10^8 \text{ CFU})\)
- Poultry, eggs, etc. are sources of infection
- 6-48h incubation period
- Nausea, vomiting, nonbloody diarrhea, fever, cramps, myalgia and headache common
- \textit{S. enteritidis} bioserotypes (e.g., \textit{S. typhimurium})
Pathogenesis of Salmonella

Enteritis (cont.)

Virulence attributable to:

- Invasiveness
- Intracellular survival & multiplication
- Endotoxin
- Exotoxins: Effects in host have not been identified
  - Several *Salmonella* serotypes produce enterotoxins similar to both the heat-labile (LT) and heat-stable enterotoxins (ST), but their effect has not been identified
  - A distinct cytotoxin is also produced and may be involved in invasion and cell destruction
Pathogenesis of Salmonella (cont.)

Invasiveness in Enteritis (cont.)

- Penetrate mucus, adhere to and invade into epithelial layer (enterocytes) of terminal small intestine and further into subepithelial tissue.
- Bacterial cells are internalized in endocytic vacuoles (intracellular) and the organisms multiply.
- PMN’s confine infection to gastrointestinal (GI) tract, but organisms may spread hematogenously (through blood, i.e., septicemia) to other body sites.
- Inflammatory response mediates release of prostaglandins, stimulating cAMP and active fluid secretion with loose diarrheal stools; epithelial destruction occurs during late stage of disease.
Clinical Progression of Salmonella Enteritis

Lamina propria = thin membrane between epithelium & basement layer

Hyperplasia = abnormal increase in # of normal cells

Hypertrophy = abnormal increase in normal tissue/organ size

Prostaglandins = potent mediators of diverse set of physiologic processes
S. typhi causes typhoid fever

S. paratyphi A, B (S. schottmuelleri) and C (S. hirschfeldii) cause milder form of enteric fever

Infectious dose = 10^6 CFU

Fecal-oral route of transmission

- Person-to-person spread by chronic carrier
- Fecally-contaminated food or water

10-14 day incubation period

Initially signs of sepsis/bacteremia with sustained fever (delirium) for > one week before abdominal pain and gastrointestinal symptoms
Pathogenesis of Salmonella (cont.)

Enteric Fevers (cont.)

Virulence attributable to:

- **Invasiveness**
  - Pass through intestinal epithelial cells in ileocecal region, infect the regional lymphatic system, invade the bloodstream, and infect other parts of the reticuloendothelial system
  - Organisms are **phagocytosed** by macrophages and monocytes, **but survive, multiply** and are **transported** to the liver, spleen, and bone marrow where they **continue to replicate**
  - **Second week:** organisms **reenter bloodstream** and cause **prolonged bacteremia**; biliary tree and other organs are infected; gradually increasing **sustained fever** likely from endotoxemia
  - **Second to third week:** bacteria colonize **gallbladder, reinf ect intestinal tract** with **diarrheal symptoms** and possible necrosis of the Peyer's patches
Liver, spleen, bone marrow

(10-14 days)

Gastrointestinal Symptoms

Clinical Progression of Enteric Fever
(Typhoid fever)

Salmonella typhi

Ingestion

S. typhi passes through and between epithelial cells lining the ileocecal area

Remains viable after engulfment by macrophage

Intraluminal multiplication

Mononuclear cell response

Intracellular multiplication continues in the cells of reticuloendothelial system (RES)

Liver, spleen, bone marrow

Clinical signs of sepsis

(10-14 days)

Hyperplastic changes in mesenteric lymphoid tissue

Necrosis
Hemorrhage
Perforation of intestinal wall

Reenters bowel (liver to gall bladder to intestine) found in stool specimens

Gastrointestinal Symptoms

Lumen (intraluminal); ileocecal area = see above - Anatomy of Digestive Tract

RES = sum total of strongly phagocytic cells; primarily found in lymph nodes, blood, liver, spleen and bone marrow

Hyperplastic changes = see hyperplasia above - Clinical Progression of Enteritis
**Microbial Defenses Against Host Immunological Clearance**

**ENCAPSULATION** and **ANTIGENIC MIMICRY, MASKING** or **SHIFT**

**CAPSULE, GLYCOCALYX** or **SLIME LAYER**
- Polysachharide capsules *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, etc.
- Polypeptide capsule of *Bacillus anthracis*

**EVASION** or **INCAPACITATION** of **PHAGOCYTOSIS** and/or **IMMUNE CLEARANCE**

**PHAGOCYTOSIS INHIBITORS**: mechanisms enabling an invading microorganism to resist being engulfed, ingested, and or lysed by phagocytes/ phagolysosomes

**RESISTANCE** to **HUMORAL FACTORS**

**RESISTANCE** to **CELLULAR FACTORS**

See Chpt. 19
<table>
<thead>
<tr>
<th>METHOD</th>
<th>EXAMPLE</th>
</tr>
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<tbody>
<tr>
<td>Inhibition of phagolysosome infusion</td>
<td>Legionella species, Mycobacterium tuberculosis, Chlamydia species</td>
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<tr>
<td>Resistance to lysosomal enzymes</td>
<td>Salmonella typhimurium, Coxiella species</td>
</tr>
<tr>
<td></td>
<td>Ehrlichia species, Mycobacterium leprae, Leishmania species</td>
</tr>
<tr>
<td></td>
<td>Salmonella typhi</td>
</tr>
<tr>
<td>Adaptation to cytoplasmic replication</td>
<td>Listeria species, Francisella species, Rickettsia species</td>
</tr>
</tbody>
</table>
Septicemia

- Can be caused by all species, but more commonly associated with *S. choleraesuis*, *S. paratyphi*, *S. typhi*, and *S. dublin*

- Old, young and immunocompromised (e.g., AIDS patients) at increased risk
Asymptomatic Carriage

- Chronic carriage in 1-5% of cases following S. typhi or S. paratyphi infection
- Gall bladder usually the reservoir
- Chronic carriage with other Salmonella spp. occurs in <<1% of cases and does not play a role in human disease transmission
Treatment, Prevention and Control of Salmonella Infections

Enteritis:

- Antibiotics not recommended for enteritis because prolong duration
- Control by proper preparation of poultry & eggs

Enteric fever:

- Antibiotics to avoid carrier state
- Identify & treat carriers of S. typhi & S. paratyphi
- Vaccination can reduce risk of disease for travellers in endemic areas
General Characteristics of Shigella

- **Coliform** bacilli (enteric rods)
- Nonmotile gram-negative facultative anaerobes
- Four species
  - *Shigella sonnei* (most common in industrial world)
  - *Shigella flexneri* (most common in developing countries)
  - *Shigella boydii*
  - *Shigella dysenteriae*
- Non-lactose fermenting
- Resistant to bile salts
Epidemiology and Clinical Syndromes of Shigella

Shigellosis = Generic term for disease

- Low infectious dose ($10^2$-$10^4$ CFU)
- Humans are only reservoir
- Transmission by fecal-oral route
- Incubation period = 1-3 days
- Watery diarrhea with fever; changing to dysentery
- Major cause of bacillary dysentery (severe 2nd stage) in pediatric age group (1-10 yrs) via fecal-oral route
- Outbreaks in daycare centers, nurseries, institutions
- Estimated 15% of pediatric diarrhea in U.S.
- Leading cause of infant diarrhea and mortality (death) in developing countries
DEFINITIONS

- **Enterotoxin** = an exotoxin with enteric activity, i.e., affects the intestinal tract.

- **Dysentery** = inflammation of intestines (especially the colon (colitis) of the large intestine) with accompanying severe abdominal cramps, tenesmus (straining to defecate), and frequent, low-volume stools containing blood, mucus, and fecal leukocytes (PMN’s).

- **Bacillary dysentery** = dysentery caused by bacterial infection with invasion of host cells/tissues and/or production of exotoxins.
Epidemiology
of Shigella
Infection

DISEASE/BACTERIAL FACTORS
Shigellosis
Numerous virulence factors (see Box 24-1)

TRANSMISSION
Person to person; primarily fecal-oral by contaminated hands
Consumption of contaminated food or water less important

WHO IS AT RISK?
Anyone exposed to carrier, particularly young children or those in day-care centers, nurseries, custodial institutions
Male homosexuals
Communities with poor sanitation and hygiene

GEOGRAPHY/SEASON
Worldwide
No seasonal incidence

MODES OF CONTROL
Antibiotic therapy used to decrease number of organisms and duration of carriage in symptomatic patients (thus reducing person-to-person spread)
Infection control procedures: hand washing, disposal of soiled linens
Pathogenesis of Shigella Shigellosis

Two-stage disease:

➢ Early stage:
  • Watery diarrhea attributed to the enterotoxic activity of Shiga toxin following ingestion and noninvasive colonization, multiplication, and production of enterotoxin in the small intestine
  • Fever attributed to neurotoxic activity of toxin

➢ Second stage:
  • Adherence to and tissue invasion of large intestine with typical symptoms of dysentery
  • Cytotoxic activity of Shiga toxin increases severity
Pathogenesis and Virulence Factors (cont.)

Virulence attributable to:

- **Invasiveness**
  - Attachment (adherence) and *internalization* with complex genetic control
  - Large multi-gene virulence plasmid regulated by multiple chromosomal genes

- **Exotoxin** (Shiga toxin)

- Intracellular survival & multiplication
Penetrate through mucosal surface of colon (colonic mucosa) and invade and multiply in the colonic epithelium but do not typically invade beyond the epithelium into the lamina propria (thin layer of fibrous connective tissue immediately beneath the surface epithelium of mucous membranes).

Preferentially attach to and invade into M cells in Peyer’s patches (lymphoid tissue, i.e., lymphatic system) of small intestine.
M cells typically transport foreign antigens from the intestine to underlying macrophages, but *Shigella* can lyse the phagocytic vacuole (phagosome) and replicate in the cytoplasm.

- **Note**: This contrasts with *Salmonella* which multiplies in the phagocytic vacuole.

- **Actin filaments** propel the bacteria through the cytoplasm and into adjacent epithelial cells with cell-to-cell passage, thereby effectively avoiding antibody-mediated humoral immunity (similar to *Listeria monocytogenes*).
Methods That Circumvent Phagocytic Killing

<table>
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<tr>
<th>Method</th>
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<tr>
<td>Adaptation to cytoplasmic replication</td>
<td>Listeria species, Francisella species, Rickettsia species, Shigella spp.</td>
</tr>
</tbody>
</table>

See Chpt. 19
Characteristics of Shiga Toxin

- Enterotoxic, neurotoxic and cytotoxic
- Encoded by chromosomal genes
- Two domain (A-5B) structure
- Similar to the Shiga-like toxin of enterohemorrhagic *E. coli* (EHEC)
  - **NOTE:** except that Shiga-like toxin is encoded by lysogenic bacteriophage
Shiga Toxin Effects in Shigellosis

Enterotoxic Effect:

- Adheres to small intestine receptors
- Blocks absorption (uptake) of electrolytes, glucose, and amino acids from the intestinal lumen

Note: This contrasts with the effects of cholera toxin (Vibrio cholerae) and labile toxin (LT) of enterotoxigenic E. coli (ETEC) which act by blocking absorption of $\text{Na}^+$, but also cause hypersecretion of water and ions of $\text{Cl}^-$, $\text{K}^+$ (low potassium = hypokalemia), and $\text{HCO}_3^-$ (loss of bicarbonate buffering capacity leads to metabolic acidosis) out of the intestine and into the lumen
Pathogenesis and Virulence Factors (cont.)

Shiga Toxin Effects in Shigellosis (cont.)

Cytotoxic Effect:
- B subunit of Shiga toxin binds host cell glycolipid
- A domain is internalized via receptor-mediated endocytosis (coated pits)
- Causes irreversible inactivation of the 60S ribosomal subunit, thereby causing:
  - Inhibition of protein synthesis
  - Cell death
  - Microvasculature damage to the intestine
  - Hemorrhage (blood & fecal leukocytes in stool)

Neurotoxic Effect: Fever, abdominal cramping are considered signs of neurotoxicity
<table>
<thead>
<tr>
<th>TOXIN</th>
<th>ORGANISM</th>
<th>GENETIC CONTROL</th>
<th>SUBUNIT STRUCTURE</th>
<th>TARGET CELL RECEPTOR</th>
<th>BIOLOGICAL EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax toxins</td>
<td>Bacillus anthracis</td>
<td>Plasmid</td>
<td>Three separate proteins (EF, LF, PA)</td>
<td>Unknown, probably glycoprotein</td>
<td>EF + PA: increase in target-cell cAMP level, localized edema; LF + PA: death of target cells and experimental animals</td>
</tr>
<tr>
<td>Bordetella adenylate cyclase toxin</td>
<td>Bordetella species</td>
<td>Chromosomal</td>
<td>A-B</td>
<td>Unknown, probably glycolipid</td>
<td>Increase in target cell cAMP level, modified cell function or cell death</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>C. botulinum</td>
<td>Phage</td>
<td>A-B</td>
<td>Possibly ganglioside (GD₁₆)</td>
<td>Decrease in peripheral, presynaptic acetylcholine release, flaccid paralysis</td>
</tr>
<tr>
<td>Cholera toxin</td>
<td>V. cholerae</td>
<td>Chromosomal</td>
<td>A-5B</td>
<td>Ganglioside (GM₁)</td>
<td>Activation of adenylate cyclase, increase in cAMP level, secretory diarrhea</td>
</tr>
<tr>
<td>Diphtheria toxin</td>
<td>C. diphtheriae</td>
<td>Phage</td>
<td>A-B</td>
<td>Probably glycoprotein</td>
<td>Inhibition of protein synthesis, cell death</td>
</tr>
<tr>
<td>Heat-labile enterotoxins</td>
<td>E. coli</td>
<td>Plasmid</td>
<td>Similar or identical to cholera toxin</td>
<td></td>
<td>Block of signal transduction mediated by target G proteins</td>
</tr>
<tr>
<td>Pertussis toxin</td>
<td>B. pertussis</td>
<td>Chromosomal</td>
<td>A-5B</td>
<td>Unknown, probably glycoprotein</td>
<td>Similar or identical to diphtheria toxin</td>
</tr>
<tr>
<td>Pseudomonas exotoxin A</td>
<td>P. aeruginosa</td>
<td>Chromosomal</td>
<td>A-B</td>
<td>Unknown, but different from diphtheria toxin</td>
<td>Inhibition of protein synthesis, cell death</td>
</tr>
<tr>
<td>Shiga toxin</td>
<td>Shigella dysenteriae</td>
<td>Chromosomal</td>
<td>A-5B</td>
<td>Glycoprotein or glycolipid</td>
<td>Similar or identical to diphtheria toxin</td>
</tr>
<tr>
<td>Shiga-like toxins</td>
<td>Shigella species,</td>
<td>Phage</td>
<td>Similar or identical to Shiga toxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus toxin</td>
<td>C. tetani</td>
<td>Plasmid</td>
<td>A-B</td>
<td>Ganglioside (GT₁) and/or GD₁₆</td>
<td>Decrease in neurotransmitter release from inhibitory neurons, spastic paralysis</td>
</tr>
</tbody>
</table>

**Heparin-binding epidermal growth factor on heart & nerve surfaces**
Yersinia pestis

Clinical Forms of Plague (a.k.a., Black Death):

- **Bubonic plague** with swollen and painful axillary (arm pit) & inguinal (groin) lymph nodes (buboes)
  - Transmitted from mammalian reservoirs by flea (arthropod) bites or contact with contaminated animal tissues
- **Pneumonic plaque**
  - Person-to-person spread

Yersinia enterocolitica

- Enterocolitis
- Transfusion-related septicemia
Epidemiology and History of Plague

- Zoonotic infection; Humans are accidental hosts
- Outbreaks are cyclical corresponding to rodent reservoir and arthropod vector populations
- Plague recorded more than 2000 years ago
- Three pandemics
  - 1st 542AD; 100million dead in 60 years; from N.Africa
  - 2nd 14th century; Black Death; 25million dead in Europe alone (>1/4 of entire population); from central Asia; disease became endemic in urban rat population and smaller epidemics occurred through 17th century
  - 3rd ended in 1990s; Burma to China (1894) & Hong Kong to other continents including N. America via rat-infected ships; 20million dead in India alone; foci of infection firmly established in wild rodents in rural areas
- Folk stories & nursery rhymes: Pied Piper of Hamelin (Ring Around the Rosie is “urban myth”??)
Epidemiology of Yersinia Infection

DISEASE/BACTERIAL FACTORS
- *Y. pestis*: plague
- *Y. enterocolitica*: enterocolitis, transfusion-related septicemia
- *Y. pseudotuberculosis*: enterocolitis
- *Y. pestis*: present in animal reservoir, fleas
- Other *Yersinia*: present in domestic animals (GI tract) and contaminated food products
- Numerous virulence factors (see Box 24-1)

TRANSMISSION
- *Y. pestis*: spread from mammalian reservoir (rats, prairie dogs, dogs, mice, rabbits) via fleas or contact with contaminated animal tissues
- Other *Yersinia*: ingestion of contaminated food products, infusion of contaminated blood products

WHO IS AT RISK?
- *Y. pestis*: communities with endemic plague and exposure to infected animals
- *Y. enterocolitica*: individuals eating contaminated food, recipients of contaminated blood products

GEOGRAPHY/SEASON
- *Y. pestis*: primarily Asia and Africa
- *Y. pestis* disease is cyclical, as reservoir population increases/decreases
- Other *Yersinia*: infections worldwide but primarily in cold climates

MODES OF CONTROL
- *Y. pestis*: control of rodent vector and improved hygiene vaccination, chemoprophylaxis
- *Y. enterocolitica*: proper food preparation
Epidemiological Cycles of Plague

- **Sylvatic (wild) Cycle of Plague**
  - Reservoir (foci) = wild rodents (prairie dogs, rabbits, mice, dogs)
  - Vector = wild rodent flea

- **Urban (domestic) Cycle of Plague**
  - Reservoir = domestic (urban) black rat
    - Over 8 million in NYC = human population
  - Vector = oriental rat flea (*Xenopsylla cheopis*)

- **Human Cycle of Plague**
  - Bubonic plague acquired from contact with either sylvatic or urban reservoirs or arthropod vector bite and further transmitted in human population by spread of pneumonic plague
Epidemiological Cycles of Plague

**SYLVATIC CYCLE**

- Wild Rodent → Direct contact → Bubonic plague

**DOMESTIC CYCLE** (Urban Cycle)

- Domestic Rodent → Direct contact → Oriental rat flea → Infective flea
- Oriental rat flea → Infective flea

**PATHWAYS**

- usual
- occasional
- rare or theoretical

**Human cycle**

- Human → Secondary plague pneumonia
- Pneumonic plague epidemic

**Note**

Overwintering reservoir mechanism
Annual Incidence of Plague in U.S.
Annual Incidence of Plague in U.S.
Arthropod-Borne Transmission of Plague

- Fleas required for perpetuation of plague vary greatly in vector efficiency and host range
- Organisms ingested during blood meal from bacteremic host
- Coagulase of flea may cause fibrin clot of organism in stomach which fixes to spines of proventriculus (throat parts of flea)
- Organisms multiply causing blockage
- Flea regurgitates infectious material into new host during subsequent attempts at blood meal
- Flea remains hungry & feeds more aggressively
- Sudden eradication of rats could lead to outbreak
Yersinia

Summary

Table

Physiology and Structure

Gram-negative bacilli.
- Facultative anaerobe.
- Fermenter.
- Oxidase-negative.
- Outer membrane makes the organisms susceptible to drying.
- Lipopolysaccharide consists of somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin).
- *Y. pestis* is covered with a protein capsule.
- Some species (e.g., *Y. enterocolitica*) can grow at cold temperatures (e.g., can grow to high numbers in contaminated, refrigerated food or blood products).

Virulence

Refer to Box 29–2.
- Capsule on *Y. pestis* is antiphagocytic.
- *Y. pestis* is also resistant to serum killing.
- *Yersinia* with genes for adherence, cytotoxic activity, inhibition of phagocytic migration and engulfment, and inhibition of platelet aggregation.

Epidemiology

*Y. pestis* is a zoonotic infection with humans the accidental host. Natural reservoirs include rats, squirrels, rabbits, and domestic animals. Disease is spread by flea bites or direct contact with infected tissues or person-to-person by inhalation of infectious aerosols from a patient with pulmonary disease.
**Yersinia**

**Summary**

**Table (cont.)**

**Diseases**
- Y. pestis causes bubonic plague (most common) and pulmonary plague, both having a high mortality rate.
- Other Yersinia species cause gastroenteritis (acute watery diarrhea or chronic diarrhea) and transfusion-related sepsis.

**Colonization with other Yersinia species can occur.**

**Other Yersinia infections are spread through exposure to contaminated food products or blood products (Y. enterocolitica).**

**Prevention and Control**
- Plague is controlled by reduction of the rodent population and vaccination of individuals at risk.
- Other Yersinia infections are controlled by the proper preparation of food products.

**Treatment**
- Y. pestis infections are treated with streptomycin, tetracyclines, chloramphenicol, or trimethoprim/sulfamethoxazole.
- Enteric infections with other Yersinia species are usually self-limited. If antibiotic therapy is indicated, most organisms are susceptible to broad-spectrum cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, and trimethoprim/sulfamethoxazole can be administered as alternative therapy.

**Diagnosis**
- Organisms grow on most culture media; prolonged storage at 4°C can selectively enhance isolation.
- Enteric disease in children may manifest as enlarged mesenteric lymph nodes and mimic acute appendicitis.
REVIEW
See Handouts
Salmonella

Summary

Table

**Physiology and Structure**
- Gram-negative bacilli.
- Facultative anaerobe.
- Fermenter.
- Oxidase-negative.
- Outer membrane makes the organisms susceptible to drying.
- Lipopolysaccharide consists of outer somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin).
- More than 2400 O serotypes (commonly referred to as individual *Salmonella* species).

**Virulence**
- Refer to Box 29–2.
  - Tolerant to acids in phagocytic vesicles.
  - Can survive in macrophages and spread from the intestine to other body sites (particularly true of *S. typhi*).
  - Endotoxin.

**Epidemiology**
- Most infections are acquired by eating contaminated food products (poultry, eggs, and dairy products the most common sources of infection).
  - Direct fecal-oral spread in children.
- *S. typhi* and *S. paratyphi* are strict human pathogens (no alternative reservoir); these infections are passed person to person; asymptomatic long-term colonization occurs commonly.
- Individuals at risk for infection include those who eat improperly cooked poultry or eggs, patients with reduced gastric acid levels, and immunocompromised patients (especially patients with acquired immunodeficiency syndrome).
Infections occur worldwide, particularly in the warm months of the year.

Diseases
Asymptomatic colonization (primarily with \textit{S. typhi} and \textit{S. paratyphi}).

Enteric fever (also called typhoid fever [\textit{S. typhi}] or paratyphoid fever [\textit{S. paratyphi}]).

Enteritis characterized by fever, nausea, vomiting, bloody or nonbloody diarrhea, and abdominal cramps.

Bacteremia (most commonly seen with \textit{S. typhi}, \textit{S. paratyphi}, \textit{S. choleraesuis}, and \textit{S. enteritidis}).

Diagnosis
Isolation from stool specimens requires use of selective media.

Treatment, Prevention, and Control
Antibiotic treatment not recommended for enteritis because the duration of disease may be prolonged.

Infections with \textit{S. typhi} and \textit{S. paratyphi} or disseminated infections with other organisms should be treated with an effective antibiotic (selected by in vitro susceptibility tests); fluoroquinolones (e.g., ciprofloxacin), chloramphenicol, trimethoprim/sulfamethoxazole, or a broad-spectrum cephalosporin can be used.

Most infections can be controlled by proper preparation of poultry and eggs (completely cooked) and avoidance of contamination of other foods with uncooked poultry products.

Carriers of \textit{S. typhi} and \textit{S. paratyphi} should be identified and treated.

Vaccination against \textit{S. typhi} can reduce the risk of disease for travelers into endemic areas.
Clinical Syndromes of Salmonella

Salmonellosis = Generic term for disease

Clinical Syndromes

- Enteritis (acute gastroenteritis)
- Enteric fever (prototype is typhoid fever and less severe paratyphoid fever)
- Septicemia (particularly S. choleraesuis, S. typhi, and S. paratyphi)
- Asymptomatic carriage (gall bladder is the reservoir for Salmonella typhi)
Epidemiology and Clinical Syndromes of Salmonella (cont.)

Enteritis

- Most common form of salmonellosis with major foodborne outbreaks and sporadic disease
- High infectious dose ($10^8$ CFU)
- Poultry, eggs, etc. are sources of infection
- 6-48h incubation period
- Nausea, vomiting, nonbloody diarrhea, fever, cramps, myalgia and headache common
- *S. enteritidis* bioserotypes (e.g., *S. typhimurium*)
**Pathogenesis of Salmonella**

**Enteritis** (cont.)

**Virulence attributable to:**

- Invasiveness
- Intracellular survival & multiplication
- Endotoxin
- Exotoxins: Effects in host have not been identified
  - Several *Salmonella* serotypes produce enterotoxins similar to both the heat-labile (LT) and heat-stable enterotoxins (ST), but their effect has not been identified
  - A distinct cytotoxin is also produced and may be involved in invasion and cell destruction
Clinical Progression of Salmonella Enteritis

Lamina propria = thin membrane between epithelium & basement layer

Hyperplasia = abnormal increase in # of normal cells

Hypertrophy = abnormal increase in normal tissue/organ size

Prostaglandins = potent mediators of diverse set of physiologic processes

- Lamina propria
- Ingestion
- Absorbed to epithelial cells in terminal portion of small intestine
- Bacteria penetrate cells and migrate to lamina propria layer of ileocecal region
- Multiply in lymphoid follicles. Reticuloendothelial hyperplasia and hypertrophy
- Inflammatory response also mediates release of prostaglandins
- Stimulates cAMP and active fluid secretion
- Loose diarrheal stools
- Polymorphonuclear leukocytes mount and confine infection to gastrointestinal tract
**Clinical Progression of Enteric Fever**

*(Typhoid fever)*

- **Ingestion**: Salmonella typhi enters through and between epithelial cells lining the ileocecal area.
- **Remains viable after engulfment by macrophage**: Intraluminal multiplication continues in the cells of reticuloendothelial system (RES).
  - Liver, spleen, bone marrow
- **Mononuclear cell response**: Hyperplastic changes in mesenteric lymphoid tissue.
  - Liver to gall bladder to intestine, found in stool specimens
  - Clinical signs of sepsis
- **Necrosis**, Hemorrhage, Perforation of intestinal wall
- **Reenters bowel**: Lumen (intraluminal); ileocecal area
- **Gastrointestinal Symptoms**

**RES** = sum total of strongly phagocytic cells; primarily found in lymph nodes, blood, liver, spleen, and bone marrow

**Hyperplastic changes** = see hyperplasia above - *Clinical Progression of Enteritis*
Shigella

Summary

Table

Physiology and Structure

Gram-negative bacilli.
Facultative anaerobe.
Fermenter.
Oxidase-negative.
Outer membrane makes the organisms susceptible to drying.
Lipopolysaccharide consists of somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin).

Four species recognized: *S. sonnei* responsible for most infections in developed countries, *S. flexneri* for infections in developing countries, and *S. dysenteriae* for the most severe infections. *S. boydii* is not commonly isolated.

Virulence

Refer to Box 29–2.
Endotoxin and genes for adherence, invasion, and intracellular replication.
Permeability barrier of outer membrane.
Exotoxin (Shiga toxin) is produced by *S. dysenteriae*; disrupts protein synthesis and produces endothelial damage.
Hemolytic colitis (HC) and hemolytic uremic syndrome (HUS) associated with *Shigella*.

Epidemiology

Humans are only reservoir for these bacteria.
Disease spread person-to-person by fecal-oral route.
Patients at highest risk for disease are young children in daycare centers, nurseries, and custodial institutions; siblings and parents of these children; male homosexuals.
Shigella Summary Table (cont.)

Relatively few organisms can produce disease (highly infectious).

Disease is worldwide with no seasonal incidence (consistent with person-to-person spread involving a low inoculum).

Diseases
Gastroenteritis (shigellosis).
Most common form is an initial watery diarrhea progressing within 1 to 2 days to abdominal cramps and tenesmus (with or without bloody stools).
Asymptomatic carriage develops in a small number of patients (reservoir for future infections).
A severe form of disease is caused by *S. dysenteriae* (bacterial dysentery).

Diagnosis
Isolation from stool specimens requires use of selective media.

Treatment, Prevention, and Control
Antibiotic therapy shortens the course of symptomatic disease and fecal shedding.
Treatment should be guided by in vitro susceptibility tests.
Empiric therapy can be initiated with a fluoroquinolone or trimethoprim/sulfamethoxazole.
Appropriate infection control measures should be instituted to prevent spread of the organism, including hand washing and proper disposal of soiled linens.
Epidemiology and Clinical Syndromes of Shigella

Shigellosis = Generic term for disease

- Low infectious dose (10^2-10^4 CFU)
- Humans are only reservoir
- Transmission by fecal-oral route
- Incubation period = 1-3 days
- Watery diarrhea with fever; changing to dysentery
- Major cause of bacillary dysentery (severe 2nd stage) in pediatric age group (1-10 yrs) via fecal-oral route
- Outbreaks in daycare centers, nurseries, institutions
- Estimated 15% of pediatric diarrhea in U.S.
- Leading cause of infant diarrhea and mortality (death) in developing countries
DEFINITIONS

- **Enterotoxin** = an exotoxin with enteric activity, i.e., affects the intestinal tract

- **Dysentery** = inflammation of intestines (especially the colon (colitis) of the large intestine) with accompanying severe abdominal cramps, tenesmus (straining to defecate), and frequent, low-volume stools containing blood, mucus, and fecal leukocytes (PMN’s)

- **Bacillary dysentery** = dysentery caused by bacterial infection with invasion of host cells/tissues and/or production of exotoxins
Two-stage disease:

- **Early stage:**
  - Watery diarrhea attributed to the enterotoxic activity of Shiga toxin following ingestion and noninvasive colonization, multiplication, and production of enterotoxin in the small intestine.
  - Fever attributed to neurotoxic activity of toxin.

- **Second stage:**
  - Adherence to and tissue invasion of large intestine with typical symptoms of dysentery.
  - Cytotoxic activity of Shiga toxin increases severity.
Pathogenesis and Virulence Factors (cont.)

Virulence attributable to:

- Invasiveness
  - Attachment (adherence) and internalization with complex genetic control
  - Large multi-gene virulence plasmid regulated by multiple chromosomal genes

- Exotoxin (Shiga toxin)

- Intracellular survival & multiplication
Pathogenesis and Virulence Factors (cont.)

Characteristics of Shiga Toxin

- Enterotoxic, neurotoxic and cytotoxic
- Encoded by chromosomal genes
- Two domain (A-5B) structure
- Similar to the Shiga-like toxin of enterohemorrhagic *E. coli* (EHEC)

- **NOTE:** except that Shiga-like toxin is encoded by lysogenic bacteriophage
Yersinia

Summary

Table

Physiology and Structure
Gram-negative bacilli.
Facultative anaerobe.
Fermenter.
Oxidase-negative.
Outer membrane makes the organisms susceptible to drying.
Lipopolysaccharide consists of somatic O polysaccharide, core polysaccharide (common antigen), and lipid A (endotoxin).

*Y. pestis* is covered with a protein capsule.

Some species (e.g., *Y. enterocolitica*) can grow at cold temperatures (e.g., can grow to high numbers in contaminated, refrigerated food or blood products).

Virulence

Refer to Box 29–2.

Capsule on *Y. pestis* is antiphagocytic.

*Y. pestis* is also resistant to serum killing.

*Yersinia* with genes for adherence, cytotoxic activity, inhibition of phagocytic migration and engulfment, and inhibition of platelet aggregation.

Epidemiology

*Y. pestis* is a zoonotic infection with humans the accidental host. Natural reservoirs include rats, squirrels, rabbits, and domestic animals. Disease is spread by flea bites or direct contact with infected tissues or person-to-person by inhalation of infectious aerosols from a patient with pulmonary disease.
Other *Yersinia* infections are spread through exposure to contaminated food products or blood products (*Y. enterocolitica*).

Colonization with other *Yersinia* species can occur.

### Diseases

*Y. pestis* causes bubonic plague (most common) and pulmonary plague, both having a high mortality rate.

Other *Yersinia* species cause gastroenteritis (acute watery diarrhea or chronic diarrhea) and transfusion-related sepsis. Enteric disease in children may manifest as enlarge mesenteric lymph nodes and mimic acute appendicitis.

### Diagnosis

Organisms grow on most culture media; prolonged storage at 4°C can selectively enhance isolation.

### Treatment, Prevention, and Control

*Y. pestis* infections are treated with streptomycin; tetracyclines, chloramphenicol, or trimethoprim/sulfamethoxazole can be administered as alternative therapy.

Enteric infections with other *Yersinia* species are usually self-limited. If antibiotic therapy is indicated, most organisms are susceptible to broad-spectrum cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, and trimethoprim/sulfamethoxazole.

Plague is controlled by reduction of the rodent population and vaccination of individuals at risk.

Other *Yersinia* infections are controlled by the proper preparation of food products.
Summary of Yersinia Infections

**Yersinia pestis**

Clinical Forms of Plague (a.k.a., Black Death):

- **Bubonic plague** with swollen and painful **axillary** (arm pit) & **inguinal** (groin) lymph nodes (buboes)
  - Transmitted from mammalian reservoirs by flea (arthropod) bites or contact with contaminated animal tissues
- **Pneumonic plague**
  - Person-to-person spread

**Yersinia enterocolitica**

- Enterocolitis
- Transfusion-related septicemia
Epidemiology and History of Plague

- Zoonotic infection; Humans are accidental hosts
- Outbreaks are cyclical corresponding to rodent reservoir and arthropod vector populations
- Plague recorded more than 2000 years ago
- Three pandemics
  - 1st 542AD; 100 million dead in 60 years; from N. Africa
  - 2nd 14th century; Black Death; 25 million dead in Europe alone (>1/4 of entire population); from central Asia; disease became endemic in urban rat population and smaller epidemics occurred through 17th century
  - 3rd ended in 1990s; Burma to China (1894) & Hong Kong to other continents including N. America via rat-infected ships; 20 million dead in India alone; foci of infection firmly established in wild rodents in rural areas
- Folk stories & nursery rhymes: Pied Piper of Hamelin (Ring Around the Rosie is “urban myth”??)
Epidemiological Cycles of Plague

- **Sylvatic (wild) Cycle of Plague**
  - Reservoir (foci) = wild rodents (prairie dogs, rabbits, mice, dogs)
  - Vector = wild rodent flea

- **Urban (domestic) Cycle of Plague**
  - Reservoir = domestic (urban) black rat
    - Over 8 million in NYC = human population
  - Vector = oriental rat flea (*Xenopsylla cheopis*)

- **Human Cycle of Plague**
  - Bubonic plague acquired from contact with either sylvatic or urban reservoirs or arthropod vector bite and further transmitted in human population by spread of pneumonic plague
Epidemiological Cycles of Plague

**SYLVATIC CYCLE**

- Wild Rodent
- Winter dormancy
- Contaminated Flea
- Infective Flea
- Hibernation

*Overwintering reservoir mechanism*

**PATHWAYS**

- usual
- occasional
- rare or theoretical

**DOMESTIC CYCLE**

- Domestic Rodent
- Infective Flea
- Domestic Cycle (Urban Cycle)

**HUMAN CYCLE**

- Secondary plague pneumonia
- Pneumonic plague epidemic

2 Types of human disease:
- 1. Bubonic plague
- 2. Human cycle