Enterobacteriaceae
Gram Negative Rod

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Enterobacteriaceae

• The largest, most heterogeneous collection of medically important gram-negative rods
• >40 genera and 150 species
• Fewer than 20 species are responsible for more than 95% of the infections
• Ubiquitous organisms, found worldwide in soil, water, and vegetation
• part of the normal intestinal flora
• 30% to 35% of all septicemias, more than 70% of urinary tract infections (UTIs), and many intestinal infections
• Become pathogenic when they acquire virulence factor
• Can originate from an animal or from a human carrier, or through the endogenous spread of organisms
• Either nonmotile or motile with peritrichous flagella
• All except Klebsiella, Shigella and Yersinia are motile
• Do not form spores
• Facultative anaerobes
• Have simple nutritional requirements
**Enterobacteriaceae**

- Ferment **glucose**, reduce nitrate
- Catalase positive and oxidase negative
- The ability to ferment lactose *Escherichia, Klebsiella, Enterobacter, Citrobacter, Shigella sonni*, and *Serratia* spp
- Do not ferment lactose *Proteus, Salmonella, Shigella*, and *Yersinia* spp.
- Some have prominent capsules
Lactose fermentation on MacConkey agar
Common Medically Important Enterobacteriaceae

- *Citrobacter freundii, Citrobacter koseri*
- *Enterobacter aerogenes, Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella pneumoniae, Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus mirabilis, Proteus vulgaris*
- *Salmonella enterica*
- *Serratia marcescens*
- *Shigella sonnei, Shigella flexneri*
- *Yersinia pestis, Yersinia enterocolitica, Yersinia pseudotuberculosis*
Based on clinical infections produced, Enterobacteriaceae members are divided into two categories:

1. Opportunistic pathogens – normally part of the usual intestinal flora that may produce infection outside the intestine

2. Primary intestinal pathogens (fecal - oral), *salmonella*, *shigella*, and *yersinia sp*
• Serologic classification
  - O polysaccharides (LPS)
  - Capsular K antigens (type-specific polysaccharides)
  - Flagellar H proteins
Escherichia coli

- The most common gram-negative rods isolated from patients with **Sepsis**
- Responsible for causing more than 80% of all community-acquired UTIs
- **Gastroenteritis** in developing countries
- Most infections are **Endogenous**
Escherichia coli

**Diseases**

- **Bacteremia** (most commonly isolated gram-negative rod)
- **Urinary tract infection** (most common cause of bacterial UTIs); limited to bladder (cystitis) or can spread to kidneys (pyelonephritis) or prostate (prostatitis)
- At least five different pathogenic groups cause **Gastroenteritis** (EPEC, ETEC, EHEC, EIEC, EAEC); most cause diseases in developing countries, although **EHEC** is an important cause of **hemorrhagic colitis (HC)** and **hemolytic uremic syndrome (HUS)**
- **Neonatal meningitis** (usually with strains carrying the K1 capsular antigen)
- **Intraabdominal infections** (associated with intestinal perforation)
Incidence of Enterobacteriaceae associated with bacteremia

- 45% Escherichia
- 22% Klebsiella
- 20% Enterobacter
- 4% Proteus
- 4% Serratia
- 2% Citrobacter
- 3% Other
**Escherichia coli Associated with Gastroenteritis**

- **ETEC**: Traveler's diarrhea; infant diarrhea in developing countries
- Watery diarrhea, vomiting, cramps, nausea, low-grade fever
- Plasmid-mediated, heat-stable (ST) and/or heat-labile (LT) enterotoxins that stimulate hypersecretion of fluids and electrolytes
**Escherichia coli**

**EPEC**: Infant diarrhea in underdeveloped countries; watery diarrhea and vomiting, nonbloody stools.

After attachment, there is loss of microvilli (effacement)

- Person to person spread
- Disruption of normal microvillus
- Nonfimbrial adhesin, no LT or ST
- Moderately invasive
Escherichia coli

- **EAEC**: Infant diarrhea in underdeveloped countries; traveler's diarrhea, persistent or chronic diarrhea
  - Plasmid-mediated aggregative adherence of rods
  - Enteroaggregative heat stable toxin (EAST)
Escherichia coli

- **EHEC**: Initial watery diarrhea, followed by grossly bloody diarrhea (hemorrhagic colitis) with abdominal cramps; may progress to hemolytic uremic syndrome (HUS)
  - Mediated by cytotoxic Shiga toxins, which disrupt protein synthesis (lesions)
  - Destruction of intestinal microvillus resulting in decreased absorption
**Escherichia coli**

**EIEC**: fever, cramping, watery diarrhea; may progress to dysentery with scant, bloody stools, fever, severe inflammation.

Plasmid-mediated invasion and destruction of epithelial cells
**Escherichia coli-UTI**

- Colon → Contaminate Urethra → ascending to the bladder and may migrate to kidney or prostate
- UTIs: adhesins (primarily P pili) and hemolysin

**Escherichia coli-Neonatal Meningitis**

- E.coli and group B - Streptococci major CNS pathogens
- K1 capsular antigen
- Commonly present in the GIS

**Escherichia coli-Septicemia**

- May be originated from UT or GIS
- Mortality is high
Salmonella

- *Salmonella enterica* and *Salmonella bongori*
- *S. enterica* is subdivided into six subspecies, *S. enterica subsp. enterica*
- the two species have been subdivided into more than 2500 unique serotypes
- *S. enterica subspecies enterica serotype Typhimurium* or *S. typhimurium*
Media used

- Enrichment broth: Tetrathionat, selenit broth
- Selective media: MacConkey, SS agar, Hektoen Enteric Agar, Bismuth sulfide agar
Salmonella

- 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 activity
Salmonella-Diseases

- *Salmonella paratyphi* A (serogroup A)
- *Salmonella paratyphi* B (serogroup B)
- *Salmonella choleraesuis* (serogroup C1)
- *Salmonella typhi* (serogroup D).

These spp. are associated with **Enteric fever(Typhoid)**

- Most infections are acquired by eating contaminated food products
- Direct fecal-oral spread in children.
- Strict human pathogens.
- Individuals at risk for infection include those who
  1. eat improperly cooked poultry or eggs
  2. patients with reduced gastric acid levels
  3. immunocompromised patients
The ingested Salmonellae reach the SI, from which they enter the lymphatics and then the BS. They are carried by the blood to many organs, including the intestine.

The organisms multiply in intestinal lymphoid tissue and are excreted in stools.

After an incubation period of 10–14 days, fever, malaise, headache, constipation, bradycardia, and myalgia occur.

The fever rises to a high plateau, and the spleen and liver become enlarged.
Faeco-oral transmission

7-14 days incubation period

Adhesion to mucosa
Invasion of epithelial cells

In the submucosa encounters:
• dendritic cells
• enterocytes
• macrophages

Peyer's patches

Mesenterial lymph nodes

Reticulo-endothelial system

Blood stream

Severe complications:
• toxic encephalopathy with myocarditis and haemodynamic shock
• necrosis of Peyer's patches with peritonitis and sepsis

Secondary infection:
• Bone-marrow
• Liver
• Spleen
• Gallbladder - chronic reservoir -

Re-infection via bile excretion
Bacteremia with focal lesions
this is associated commonly with
*S. choleraesuis*
after oral infection, there is early invasion of the bloodstream (with possible focal lesions in lungs, bones, meninges, and so on).

Intestinal manifestations are often absent.
Enterocolitis

- This is the most common manifestation of salmonella infection.

  - *Salmonella typhimurium*
  - *Salmonella enteritidis* are prominent

- Eight to 48 hours after ingestion of salmonellae, there is nausea, headache, vomiting, and profuse diarrhea, with few leukocytes in the stools.

- Inflammatory lesions of the small and large intestine are present.

- Bacteremia is rare (2–4%) except in immunodeficient persons.
Diagnosis

- Culture
- Stool, urine, blood
- Selective media
- Typhoid fever 1. week blood culture
  - ≥3. week stool culture
- Widal test for Typhoid fever
  - Anti-O Ab
  - Anti-H Ab
  - Anti-Vi Ab (Long term carriers)
Therapy

• Replacement
• Quinolones, ampicillin, Co-trimoxazole
• Cephalosporin 1., 2. Gen and aminoglycosides are ineffective
• Oral attenuate and Vi parenteral vaccines available
Shigella

- *S. dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*
- *S. sonnei* is the most common cause of shigellosis in the industrial world
- *S. flexneri* is the most common cause in developing countries
- They are very much like *Escherichia*
- Nonmotile, Noncapsulated, H₂S negative
• Shigella $\rightarrow 10^3$ ID
• C.jejuni $\rightarrow 10^2$-$10^6$
• Salmonella Typhi $\rightarrow 10^3$
• E.coli $\rightarrow 10^8$
• V.cholerae $\rightarrow 10^{10}$ with water
  $10^2$-$4$ with food
Shigella-Pathogenesis

• Endotoxin, invasion, and intracellular replication

• 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
Shigella-Epidemiology

- After a short incubation period (1–2 days), there is a sudden onset of abdominal pain, fever, and watery diarrhea.
- The diarrhea has been attributed to an exotoxin acting in the small intestine.
- Humans are only reservoir for these bacteria.
- Disease spread person to person by **fecal-oral route**
- Relatively few organisms can produce disease (highly infectious)
- Disease occurs worldwide with no seasonal incidence
Activation of NF-κB caused by IL-1β and intracellular NLR activation

Disruption of epithelial permeability barrier by PMNs

Massive invasion of epithelium

Cell-to-cell spread

Shigella

M cell

Epithelial cell

IcsA

Type III secretion

Macrophages

IpaB

IpaC

IpaA

Caspase-I activation by IpaB
- Bacterial survival
- Initiation of inflammation


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Shigella-Treatment, Prevention, and Control

• Empiric therapy can be initiated with a fluoroquinolone or trimethoprim-sulfamethoxazole.
• Appropriate infection control measures should be instituted to prevent spread of the organism.
Yersinia

- 11 species
  - *Y. Pestis*
  - *Yersinia enterocolitica*
  - *Yersinia pseudotuberculosis*
- *Y. pestis* is covered with a capsule-like antigen (F1)
- Some species (e.g., *Y. enterocolitica*) can grow at cold temperatures.
Yersinia

- *Y. pestis* systemic disease (Plague) with a high mortality
- The ability of this organism to be transmitted by aerosol and the severity and high mortality of pneumonic plague make *y. pestis* a potential biological weapon.
- *Yersinia pseudotuberculosis* (*TB like disease in animals*) and *Yersinia enterocolitica*, causes of human diarrheal diseases
- Capsule on *Y. pestis* is antiphagocytic
- *Yersinia with genes for adherence*, pYV(plasmid Yersinia virulence- live parasitically), The virulent Yersinia produce V and W antigens(antiphagocytic) *cytotoxic activity (Toxin)*, *inhibition of phagocytic migration*, *and inhibition of platelet aggregation*, Siderophore.
Yersinia

- **Y. pestis** a zoonotic infection with humans the accidental host; natural reservoirs include rats, squirrels, rabbits, and domestic animals

- Disease is spread by
  1. flea bites
  2. direct contact with infected tissues
  3. person to person by inhalation of infectious aerosols from a patient with pulmonary disease
  4. spread through exposure to contaminated food products (**Y. enterocolitica**)
  5. **Y. enterocolitica** (bull’s eye appearance with a red center)
Yersinia

- Safety pin shape (miss diagnosed as spore forming bacteria) showed bipolarity.
- Y. pestis causes Bubonic plague (most common) and Pneumonic plague, both having a high mortality rate.
- Y. Enterocolitica cause gastroenteritis (acute watery diarrhea or chronic diarrhea).
- Enteric disease in children may manifest as enlarge mesenteric lymph nodes and mimic acute appendicitis.
When a flea feeds on a rodent infected with *Y. pestis*, the ingested organisms multiply in the gut of the flea and, helped by the coagulase, block its proventriculus so that no food can pass through.

*Yersinia* has Coagulase activity at 20°C–28°C, the temperature of the flea and fibrinolytic activity at 35°C–37°C, the temperature of the host.

Subsequently, the “blocked” and hungry flea bites, and the aspirated blood, contaminated with *Y. pestis* from the flea, is regurgitated into the bite wound. The inoculated organisms may be phagocytosed by PMN and macrophages.
Bubonic plague is a serious, life-threatening disease, which is transmitted to humans when they are bit by an infected rat flea and causes death quickly. There are more than 100 species of fleas that have been reported to naturally be infected with the plague. *Y. pestis* is mostly found in rats but have also been found in other wild animals.
The pathogens reach the **lymphatics**, and an intense hemorrhagic inflammation develops in the enlarged lymph nodes, which may undergo necrosis. **ENLARGED, TENDER NODES (BUBOES) IN THE NECK, GROIN, OR AXILLAE IS BUBONIC PLAQUE.**

*Y. pestis* organisms often reach the **bloodstream** and become widely disseminated. Hemorrhagic and necrotic lesions may develop in all organs; meningitis, pneumonia, and pleuropericarditis are prominent features. Primary **PNEUMONIC PLAGUE** results from inhalation of infective droplets and it is characterized by hemorrhagic consolidation, sepsis, and death.
Bubonic and Pneumonic Plague

**Bubonic Plague**
1. Entry – bite of infected rat flea
2. Spread
   - Lymphatic and systemic
3. Disease
   - Buboes
   - (black hemorrhagic lymph nodes)
   - Pneumonia
   - Internal organ hemorrhage
4. Exit (highly contagious)

**Pneumonic Plague**
1. Entry
2. Disease
   - Pneumonia
   - (usually 100% mortality)
3. Exit (highly contagious)
**Klebsiella**

- **K. Pneumoniae**
- **Klebsiella oxytoca**
- *K pneumoniae* is present in the **Respiratory tract and feces** of about **5%** of normal individuals.
- It causes a small proportion (~1%) of bacterial pneumonias.
- *K. pneumonia* can produce **extensive hemorrhagic necrotizing consolidation of the lung**.
- It produces **UTI** and **bacteremia** with focal lesions in debilitated patients.
- **Klebsiella species rank among the top ten bacterial pathogens responsible for hospital-acquired infections.**
Proteus

- They are found in **urinary tract infections** and produce bacteremia, pneumonia, and **focal lesions** in debilitated patients or those receiving contaminated intravenous infusions.

- *P. mirabilis* causes **UTI**

- *Proteus vulgaris* and *M. morganii* are important nosocomial pathogens.

- The rapid motility of *Proteus*(Swarming) may contribute to its invasion of the urinary tract.
ENTEROBACTER, CITROBACTER, MORGANELLA, SERRATIA

- *Citrobacter koseri* has a predilection for causing UTI, meningitis and brain abscesses in neonates.
- *Serratia* (usually non-pigmented) causes pneumonia, bacteremia, and endocarditis, especially in narcotics addicts and hospitalized patients.
- Only about 10% of the isolates form the red pigment (prodigiosin) that has long characterized *S. marcescens*.
- Resistance is a particularly serious problem with *Enterobacter species*. These organisms cause a broad range of hospital-acquired infections such as pneumonia, UTI, and wound and device infections.