Gram Positive Rods Related to Enteric Tract

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"Enteric Gram-Positive Rods"

Introduction

- Medically important genera (5):
    1. Bacillus – spore-forming, aerobic
    2. Clostridium – spore-forming, anaerobic
- Morphological distinctions (Gram stain):
    - Bacillus & Clostridium: Long rods, deeply staining
    - Corynebacterium: Club-shaped, thin on one end
    - Listeria: V- or L-shaped rods
    - Gardnerella vaginalis: Short, gram-variable

Enteric Gram-Positive Rods of Medical Importance – Summary

1. Bacillus

- Anaerobic Growth: No
- Spore Formation: Yes
- Exotoxins Important in Pathogenesis: Yes

2. Clostridium

- Anaerobic Growth: Yes
- Spore Formation: Yes
- Exotoxins Important in Pathogenesis: Yes

⊙ Spore-Forming Gram-Positive Rods

❖ Bacillus

- Medically important species:

1. Bacillus anthracis
2. Bacillus cereus

Important Features of Pathogenesis by Bacillus Species – Summary

1. Bacillus anthracis

- Disease: Anthrax

- Transmission / Predisposing Factor:

1. Cutaneous anthrax → spores in soil enter a wound
2. Pulmonary anthrax → spores are inhaled into the lungs

- Action of Toxin: Exotoxin has three components:

  - Protective antigen: binds to cells
  - Edema factor: adenylate cyclase

- Lethal factor: protease that inhibits cell growth → cell death (necrosis)

- Prevention: Vaccine contains protective antigen as the immunogen

2. Bacillus cereus

- Disease: Food poisoning

- Transmission / Predisposing Factor: Spores germinate in reheated rice, then bacteria produce exotoxins which are ingested

- Action of Toxin: Two exotoxins (enterotoxins):

  1. Similar to cholera toxin → increases cyclic AMP
  2. Similar to staphylococcal enterotoxin → acts as a superantigen

➢ Bacillus anthracis

Disease

- Causes anthrax – primarily an animal disease, rare in humans.

- Forms in humans:

  1. Cutaneous – most common

2. Pulmonary (inhalation) – most severe

3. Gastrointestinal – from ingestion of contaminated meat

- Notable outbreak: 2001 U.S. postal anthrax outbreak → 18 cases, 5 deaths

Important Properties

- Morphology: Large gram-positive rod with square ends, often in chains

- Capsule: Antiphagocytic, composed of D-glutamate (unique; most bacterial capsules are polysaccharides)

- Motility: Nonmotile (distinct from other Bacillus species)

- Virulence factors:

  - Anthrax toxin: Encoded on one plasmid
  - Polyglutamate capsule: Encoded on a different plasmid

Quick Exam Tips / Mnemonics

- "Bacillus is Big & Bad" → Large rods, B-anthracis causes serious disease

- Remember: D-glutamate capsule = unique → antiphagocytic

- Forms of human anthrax: "C-P-G" → Cutaneous, Pulmonary, Gastrointestinal

Transmission

- Spores: Can persist in soil for years → highly resistant.

- Routes of human infection:

    1. Cutaneous (most common):

        - Entry through skin trauma
        - Contact with contaminated animal products: hides, bristles, wool

    2. Pulmonary (inhalation):

        - Spores inhaled → move rapidly to mediastinal lymph nodes → hemorrhagic mediastinitis
        - Not communicable person-to-person despite severity

3. Gastrointestinal:
    - Ingestion of contaminated meat

Pathogenesis

- Caused primarily by anthrax toxin (two exotoxins: edema factor and lethal factor)
- Toxin structure:
    - A–B subunit configuration:
        - B (binding) subunit: Protective antigen (PA) → mediates entry into host cell
        - A (active) subunit: Enzymatic activity
- Edema Factor (EF):
    - Adenylate cyclase → ↑ cAMP → fluid leakage into extracellular space → edema
    - Mechanism similar to cholera toxin
- Lethal Factor (LF):
    - Protease that cleaves phosphokinase in the MAPK pathway
    - Inhibits cell growth → contributes to tissue damage and shock

- Protective antigen: Antibody against PA protects against disease → target for vaccines

Clinical Findings

1. Cutaneous anthrax:
    - Painless ulcer → black eschar
    - Striking local edema
    - Lesion called malignant pustule
    - Untreated → bacteremia → death
2. Pulmonary (inhalation) anthrax ("wool-sorter's disease"):
    - Early: nonspecific respiratory symptoms (like influenza) → dry cough, substernal pressure
    - Rapid progression → hemorrhagic mediastinitis, bloody pleural effusions, septic shock, death
    - Lungs infected but classic pneumonia signs often absent
    - Chest X-ray: mediastinal widening → key diagnostic clue
    - Severe complications: hemorrhagic mediastinitis, hemorrhagic meningitis
3. Gastrointestinal anthrax:
    - Vomiting, abdominal pain, bloody diarrhea

Quick Exam Tips / Mnemonics

- Toxin mnemonic: "PA EF LF" → Protective antigen (entry), Edema factor (fluid), Lethal factor (cell death)

- Clinical pearl: Cutaneous → black eschar; Pulmonary → mediastinal widening; Gastrointestinal → bloody diarrhea

Laboratory Diagnosis

- Smears: Large gram-positive rods in chains; spores usually not seen in tissue smears (form only under nutrient-poor conditions).

- Culture:
    - Blood agar: Nonhemolytic colonies, characteristic flared "comet's tail" appearance

- Rapid diagnostics (bioterrorism scenarios):
    - PCR-based assays → detects bacterial DNA quickly
    - Direct fluorescent antibody test → detects antigens in lesion

- Serology: ELISA for antibodies → requires acute and convalescent sera; retrospective diagnosis

Treatment

- Drug of choice: Ciprofloxacin
- Alternative: Doxycycline
- Resistance: Clinically none reported

Prevention

- Post-exposure prophylaxis: Ciprofloxacin or doxycycline
- Vaccination: BioThrax (cell-free, protective antigen-based)
  - Weakly immunogenic → 6 doses over 18 months + annual boosters
- Immune globulin: Raxibacumab or Anthrasil → monoclonal antibody against protective antigen for high-risk individuals
- Environmental control: Incinerate animals that die from anthrax → prevents soil contamination

➢ Bacillus cereus

Disease

- Causes food poisoning

Transmission

- Spores on grains (e.g., rice) survive steaming/frying
- Spores germinate when rice is kept warm for hours (e.g., reheated fried rice)
- Portal of entry: Gastrointestinal tract

Pathogenesis

- Produces two enterotoxins:
    1. Emetic toxin: Mechanism similar to cholera toxin → ADP-ribosylation of G protein → ↑ cAMP in enterocytes → vomiting
    2. Diarrheal toxin: Mechanism similar to Staphylococcus aureus enterotoxin → acts as superantigen → watery diarrhea

Clinical Findings

1. Short incubation (≈4 h): Nausea, vomiting → resembles staphylococcal food poisoning

2. Long incubation (≈18 h): Watery, non-bloody diarrhea → resembles clostridial gastroenteritis

Laboratory Diagnosis

- Usually not performed

Treatment

- Symptomatic treatment only

Prevention

- Avoid keeping cooked rice warm for long periods

Quick Exam Tips / Mnemonics

- B. anthracis colonies: "Comet tail" → easy culture ID
- B. anthracis spores: Soil persistence → key in outbreaks & bioterrorism

❖ Clostridium (Spore-Forming Anaerobic Gram-Positive Rods)

Introduction

- Medically important species (4):

1. Clostridium tetani → tetanus
2. Clostridium botulinum → botulism
3. Clostridium perfringens → gas gangrene or food poisoning
4. Clostridium difficile → antibiotic-associated diarrhea / pseudomembranous colitis

- Characteristics:
  - Anaerobic
  - Spore-forming
  - Gram-positive rods
- Key Note: All clostridia are anaerobic, in contrast to Bacillus (aerobic).

Important Features of Pathogenesis by Enteric Clostridium Species – Summary

1. Clostridium botulinum

- Disease: Botulism
- Transmission / Predisposing Factor: Exotoxin in food is ingested

- Action of Toxin: Blocks release of acetylcholine
- Prevention: Proper canning; cook food

2. Clostridium perfringens

- Disease:
    1. Gas gangrene
    2. Food poisoning
- Transmission / Predisposing Factor:
    - Spores in soil enter wound (gas gangrene)
    - Exotoxin in food is ingested (food poisoning)
- Action of Toxin:
    - Lecithinase
    - Superantigen
- Prevention: Debride wounds; cook food

3. Clostridium difficile

- Disease: Pseudomembranous colitis

- Transmission / Predisposing Factor: Antibiotics suppress normal flora
- Action of Toxin: Cytotoxin damages colon mucosa
- Prevention: Appropriate use of antibiotics

➢ Clostridium botulinum

Disease

- Causes botulism

Transmission

- Spores: Widespread in soil → contaminate vegetables and meats
- Foodborne botulism:
    - Spores survive in improperly canned or vacuum-packed foods (anaerobic environment)
    - Toxin produced preformed in food → ingested
    - High-risk foods:
        1. Alkaline vegetables: green beans, peppers, mushrooms
        2. Smoked fish
- Prevention: Toxin is heat-labile → boiling for several

minutes inactivates it

Pathogenesis

- Toxin type: Botulinum toxin (polypeptide, encoded by lysogenic phage)

- Mechanism:

    1. Absorbed from gut → carried via blood to peripheral nerve synapses
    2. Blocks release of acetylcholine → flaccid paralysis
    3. Protease cleaves proteins involved in acetylcholine release

- Toxicity: Among the most toxic substances known (like tetanus toxin)

- Immunologic types: 8 types → A, B, E most common in humans

- Medical use:

    - Botox (toxin A): Cosmetic (wrinkle removal)
    - Treats spasmodic muscle disorders: torticollis, writer's cramp, blepharospasm

Quick Exam Tips / Mnemonics

- Tetanus vs Botulism:
    - Tetanus → spastic paralysis
    - Botulism → flaccid paralysis
- Transmission mnemonic: "Spoiled cans + smoked fish → botulism risk"
- Heat-labile toxin → cook food well to prevent

Clinical Findings

- Main features:
    - Descending paralysis → affects cranial nerves first
    - Symptoms: diplopia, ptosis, dysphagia, respiratory muscle failure
    - No fever
- Contrast with Guillain-Barré syndrome: Ascending paralysis
- Special forms:
    1. Wound botulism: Spores contaminate wound → toxin produced locally

2. Infant botulism: Organisms grow in gut → produce toxin

    - Transmission: honey containing spores
    - Symptoms: weakness/paralysis; respiratory support may be needed
    - Usually spontaneous recovery

- Epidemiology (U.S.): Infant botulism ≈ 50% of cases; wound botulism linked to skin-popping with black tar heroin

Laboratory Diagnosis

- Culture: Usually not done

- Toxin detection:

    - Mouse protection test: Clinical specimen injected into mice; death occurs unless antitoxin protection
    - Enzyme immunoassay (EIA): Detects toxin
    - PCR: Detects DNA encoding toxin

Treatment

- Antitoxin:

    - Heptavalent (A–G) preferred over trivalent (A, B,

E)
    - Infant botulism: Bivalent (A & B) human-derived antitoxin available
    - Note: Horse-derived antitoxin → risk of serum sickness

- Supportive care: Respiratory support is critical

Prevention

- Food safety:
    - Proper sterilization of canned and vacuum-packed foods
    - Adequate cooking to inactivate toxin
    - Discard swollen cans → gas produced by clostridial proteolytic enzymes

Quick Exam Tips / Mnemonics

- Descending paralysis mnemonic: "Botulinum Goes Down" → starts with cranial nerves, moves down
- Infant botulism: Honey = no!
- Wound botulism: Skin-popping addicts at risk
- Toxin heat-labile: Cook thoroughly → prevent disease

- Swollen cans: Classic exam clue for foodborne botulism

➢ Clostridium perfringens

Diseases

- Two main diseases:

  1. Gas gangrene (myonecrosis, necrotizing fasciitis)

  2. Food poisoning

Gas Gangrene (Myonecrosis)

Transmission

- Spores: Found in soil

- Vegetative cells: Part of normal flora of colon and vagina

- High-risk situations:

  - War wounds
  - Automobile/motorcycle accidents
  - Septic abortions (endometritis)

Pathogenesis

- Growth: Traumatized tissue, especially muscle

- Toxins and enzymes:

    - Alpha toxin (lecithinase): Damages cell membranes → hemolysis
    - Degradative enzymes: Produce gas in tissue (mainly hydrogen)

Clinical Findings

- Local signs:

    - Severe pain, edema, cellulitis, gangrene
    - Crepitus → gas in tissue (hydrogen)
    - Blood-tinged exudates, foul-smelling discharge in endometritis

- Systemic signs:

    - Hemolysis, jaundice, shock, high mortality

Other Histotoxic Clostridia

- C. histolyticum, C. septicum, C. novyi, C. sordellii
    - C. sordellii → toxic shock in postpartum/postabortion women

Quick Exam Tips / Mnemonics

- Mnemonic for gas gangrene features: "Painful, Puffy, Putrid, Pale"
    - Pain → severe pain at site
    - Puffy → edema
    - Putrid → foul discharge
    - Pale → hemolysis/jaundice
- Crepitus = gas in tissue → classic exam clue
- Alpha toxin = lecithinase → hemolysis
- Necrotizing fasciitis "flesh-eating" → also caused by S. pyogenes, MRSA

Laboratory Diagnosis – Gas Gangrene

- Smears: Large gram-positive rods
- Spores: Usually not seen (require nutrient deficiency)
- Culture: Anaerobic conditions → identified by:
    - Sugar fermentation reactions
    - Organic acid production
- Colony characteristics:
    - Double zone of hemolysis on blood agar

    - Precipitate on egg yolk agar → due to lecithinase

- Serology: Not useful

Treatment – Gas Gangrene

- Antibiotic: Penicillin G (drug of choice)
- Surgical: Wound debridement

Prevention – Gas Gangrene

- Cleanse and debride wounds
- Penicillin prophylaxis for high-risk wounds
- No vaccine available

C. perfringens – Food Poisoning

Transmission

- Spores in soil → contaminate food
- Heat-resistant spores survive cooking → germinate in reheated foods
- Common in meat dishes

Pathogenesis

- Normal flora in colon, not in small intestine

- Enterotoxin: Acts as superantigen → overstimulates immune response (stimulates T cells and cytokine release) → damages intestinal epithelium → increases secretion of fluid/electrolytes (increased intestinal secretion) → watery diarrhea

- Mode of action similar to Staphylococcus aureus enterotoxin

Clinical Findings

- Incubation: 8–16 hours

- Symptoms:
  - Watery diarrhea
  - Abdominal cramps
  - Little vomiting

- Duration: Resolves in ~24 hours

Laboratory Diagnosis

- Usually not performed

- No assay for toxin

- Large numbers of organisms may be isolated from uneaten food

Treatment

- Symptomatic care only
- No antibiotics needed

Prevention

- Proper cooking of food to kill spores
- No specific preventive measures

Quick Exam Tips / Mnemonics

- Gas gangrene: "Painful, Puffy, Putrid, Pale" → alpha toxin = lecithinase → hemolysis
- Food poisoning: "C. perfringens cooks fast food diarrhea" → reheated meats, watery diarrhea, short duration
- Lab clue: Double zone hemolysis + egg yolk precipitate → classic for gas gangrene

➢ Clostridium difficile

Disease

- Causes antibiotic-associated pseudomembranous colitis
- Most common nosocomial diarrhea
- Leading infectious cause of GI-associated deaths in the U.S.

Transmission

- Colonization:
  - ~3% of general population
  - Up to 30% of hospitalized patients
- Route: Fecal-oral
  - Transmission via spores or vegetative bacteria
- Majority of cases: Hospitalized patients
- Community-acquired: ~1/3 of cases
- Hands of hospital personnel: Major intermediary

Pathogenesis

- Trigger: Antibiotics suppress normal gut flora → C. difficile multiplies

- Toxins:
    - Exotoxin A & B → glucosyltransferases
    - They glucosylate Rho GTPases (small signaling proteins that regulate actin cytoskeleton) → depolymerization of actin → loss of cytoskeletal integrity, apoptosis, enterocyte death → mucosal damage → leads to pseudomembrane formation.
    - Exotoxin B → main mediator of symptoms (more cytotoxic)

- Predisposing factors:
    - Antibiotics: Clindamycin, 3rd-gen cephalosporins, ampicillin, fluoroquinolones
    - Other: Cancer chemotherapy, proton pump inhibitors

- Invasion: Rarely invades intestinal mucosa

Quick Exam Tips / Mnemonics

- Mnemonic for predisposing antibiotics: "CAF = Clindamycin, Ampicillin, Fluoroquinolones"

- Pathogenesis clue: Toxin B = bad (main culprit)

- Actin depolymerization → pseudomembranes → hallmark feature on colonoscopy

- Nosocomial diarrhea → think C. difficile

Clinical Findings

- Diarrhea: Usually watery, not bloody

- Pseudomembranes: Yellow-white plaques on colonic mucosa → visualized by sigmoidoscopy

- Stool: Neutrophils present in ~50% of cases

- Other symptoms: Fever, abdominal pain

- Severe complications:

    - Toxic megacolon → may require surgical resection
    - Recurrences: ~15–20%

- Hypervirulent strain (emerged 2005):

    - More severe disease
    - Higher recurrence rate
    - Less responsive to metronidazole
    - Quinolone-resistant

Laboratory Diagnosis

- Key principle: Detect toxins, not just the organism (colonization is common)

- Tests:

    1. Toxin detection (ELISA) → antibody-based detection of exotoxins A & B

    2. Gene detection (PCR/NAATs) → detects toxin-encoding genes

        - Higher sensitivity and specificity
        - Must interpret cautiously: positive result may indicate colonization, not disease

Treatment

- Discontinue the causative antibiotic

- Medications:

    - First-line: Oral metronidazole
    - Severe/life-threatening: Oral or rectal vancomycin (or both)
    - Relapse prevention / severe disease: Fidaxomicin
    - Monoclonal antibody: Bezlotoxumab (against exotoxin B)

- Surgical: Colectomy in life-threatening cases
- Supportive care: Fluid replacement
- Alternative therapy: Fecal microbiota transplantation → restores normal flora, very high cure rates

Prevention

- No vaccines or preventive drugs
- Antibiotic stewardship: Prescribe only when necessary
- Hospital infection control: Rigorous handwashing and hygiene
- Probiotics: Yeast (Saccharomyces) may help prevent infection

Quick Exam Tips / Mnemonics

- "CDI = Clostridium difficile infection" → nosocomial diarrhea, pseudomembranes
- Toxin B = Bad, main culprit

- Recurrence 15–20% → remember hypervirulent strain, quinolone resistance
- Diagnosis: Detect toxin, not just bacteria
- Treatment mnemonic: "Stop antibiotics, give Metro, Van for severe, Fida prevents relapse"
- Fecal transplant: "Replace bad bacteria with normal flora"

➢ Case Scenarios

1. Bacillus anthracis (Anthrax)

Case Scenario:

A 45-year-old wool factory worker presents with a painless ulcer on his right hand. The lesion has a black eschar surrounded by significant edema. He reports handling animal hides a few days ago. Fever is mild. Chest X-ray is normal.

Key Points:

- Organism: Bacillus anthracis
- Form: Cutaneous anthrax

- Transmission: Spores entering through skin trauma
- Exam clue: Black eschar + local edema
- Lab: Large gram-positive rods in chains; nonhemolytic colonies with "comet's tail" on blood agar
- Treatment: Ciprofloxacin or doxycycline

2. Bacillus cereus (Food Poisoning)

Case Scenario:

A 30-year-old man develops profuse watery diarrhea and abdominal cramps about 10 hours after eating leftover fried rice at a buffet. He had nausea but no vomiting. Symptoms resolve within 24 hours without antibiotics.

Key Points:

- Organism: Bacillus cereus
- Form: Diarrheal food poisoning
- Transmission: Heat-resistant spores germinate in reheated rice

- Lab: Usually not done; diagnosis is clinical
- Treatment: Symptomatic only

3. Clostridium botulinum (Botulism)

Case Scenario:

A 2-year-old infant presents with floppy posture, weak cry, poor feeding, and constipation. The parents report giving honey for the first time. No fever is present.

Key Points:

- Organism: Clostridium botulinum
- Form: Infant botulism
- Transmission: Ingestion of spores (honey) → germinate in infant gut → toxin production
- Pathogenesis: Toxin blocks acetylcholine release → flaccid paralysis
- Treatment: Supportive care, antitoxin if indicated
- Exam clue: Flaccid paralysis; descending weakness in adults

4. Clostridium perfringens (Gas Gangrene)

Case Scenario:

A 35-year-old man suffers a deep leg wound in a motorcycle accident. Within 24 hours, he develops severe pain, swelling, and foul-smelling discharge. On palpation, crepitus is felt. Laboratory shows large gram-positive rods with double zone of hemolysis on blood agar.

Key Points:

- Organism: Clostridium perfringens
- Form: Gas gangrene (myonecrosis)
- Pathogenesis: Alpha toxin (lecithinase) → hemolysis; gas production in tissue
- Treatment: Penicillin G + surgical debridement

5. Clostridium perfringens (Food Poisoning)

Case Scenario:

A 28-year-old woman develops watery diarrhea and abdominal cramps 12 hours after eating reheated meat

at a party. Vomiting is minimal, and symptoms resolve within 24 hours.

Key Points:

- Organism: Clostridium perfringens
- Form: Food poisoning
- Transmission: Heat-resistant spores in reheated meat
- Treatment: Symptomatic only

7. Clostridium difficile (Pseudomembranous Colitis)

Case Scenario:

A 70-year-old hospitalized patient on ceftriaxone for pneumonia develops watery diarrhea, abdominal pain, and fever. Sigmoidoscopy reveals yellow-white pseudomembranes. Laboratory confirms toxin B in stool.

Key Points:

- Organism: Clostridium difficile
- Pathogenesis: Antibiotic-induced dysbiosis → overgrowth → exotoxin A & B → cytoskeletal

damage

- Treatment: Stop causative antibiotic; oral metronidazole or vancomycin; fidaxomicin or fecal transplant for recurrences

- Prevention: Hand hygiene, antibiotic stewardship