Gram-Negative Rods Related to Animal Sources (Zoonotic Organisms)

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"Zoonoses" - Introduction

- Definition: Human diseases caused by organisms acquired from animals.
- Types: Bacterial, viral, fungal, parasitic.
- Transmission:
  - Direct from animal reservoir
  - Via vectors (mosquitoes, fleas, ticks).
- Medically important G-ve rods with animal reservoirs:
  - Brucella spp.
  - Francisella tularensis
  - Yersinia pestis
  - Pasteurella multocida

❖ Summary Table

Brucella species

- Disease: Brucellosis

- Animal source: Pigs, cattle, goats, sheep
- Transmission: Dairy products; contact with animal tissues
- Diagnosis: Serology or culture

Francisella tularensis

- Disease: Tularemia
- Animal source: Rabbits, deer, ticks
- Transmission: Contact with animal tissues; ticks
- Diagnosis: Serology

Yersinia pestis

- Disease: Plague
- Animal source: Rodents
- Transmission: Flea bite
- Diagnosis: Immunofluorescence or culture

Pasteurella multocida

- Disease: Cellulitis
- Animal source: Cats, dogs
- Transmission: Cat or dog bite
- Diagnosis: Wound culture

Bartonella henselae

- Diseases: Cat-scratch disease, Bacillary angiomatosis
- Animal source: Cats
- Transmission: Cat scratch or bite; bite of cat flea
- Diagnosis: Serology or Warthin-Starry silver stain of tissue

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➢ Brucella

Disease

- Brucellosis (Undulant Fever)

Important Properties

- Morphology:
    - Small Gram-negative rods
    - No capsule
- Species & Reservoirs:
    - *B. melitensis* → goats & sheep
    - *B. abortus* → cattle
    - *B. suis* → pigs

Pathogenesis & Epidemiology

- Entry:
    - Ingestion of contaminated milk products (esp. unpasteurized cheese)
    - Skin contact in occupational settings (farmers, abattoir workers, veterinarians).
- Spread & Localization:
    - Localizes in RES (lymph nodes, liver, spleen, bone marrow).
    - Inside macrophages: some killed, but survivors persist intracellularly, protected from antibody attack.
    - Granulomatous response: lymphocytes +

epithelioid giant cells → may form focal abscesses.

- Virulence factors:
  - Endotoxin (LPS) → role in pathogenesis
  - No exotoxins
- Epidemiology:
  - Worldwide disease
  - Rare in U.S. (due to milk pasteurization)
  - Imported cheese (Mexico, Mediterranean) = source of *B. melitensis*

Mini-Table: Brucella & Reservoirs

Species	Reservoir	Notes
B. melitensis	Goats, sheep	Most virulent, imported cheese
B. abortus	Cattle	Associated with abortion in cows
B. suis	Pigs	Causes chronic disease

Quick Explanation

Think of Brucella as a "stealth pathogen":

- It hides inside macrophages, avoiding antibodies.
- Your body tries to wall it off → granulomas.
- Clinical disease shows waves of fever (undulant).

Brucella – Clinical Aspects

Clinical Findings

- Incubation: 1–3 weeks
- Initial symptoms (nonspecific): fever, chills, fatigue, malaise, anorexia, weight loss
- Onset: acute or gradual
- Characteristic fever:
  - Undulant fever = intermittent, rising–falling pattern
  - Seen in minority of patients (but diagnostic clue!)
- Signs:
  - Lymphadenopathy

    - Hepatomegaly & splenomegaly
    - Pancytopenia (due to bone marrow involvement)

- Species differences:

    - *B. melitensis*: more severe, prolonged
    - *B. abortus*: self-limited

- Complications:

    - Osteomyelitis = most frequent

- Transmission: Person-to-person spread = rare

Laboratory Diagnosis

- Culture:

    - Needs enriched media + 10% CO_2 incubation
    - Gold standard, but slow/difficult

- Presumptive ID:

    - Slide agglutination test with Brucella antiserum

- Species ID:

    - Biochemical tests

- Serology:
    - Detect rise in antibody titer (paired sera)
    - If acute sample not available → ≥1:160 in convalescent sample = diagnostic

Treatment

- Choice regimen:
    - Tetracycline + Rifampin (combination to prevent relapse)
- Resistance: not significant

Prevention

- Public health:
    - Pasteurization of milk
    - Immunization of animals
    - Slaughter of infected animals
- No human vaccine

Quick Table: Clinical Snapshot

Feature	Key Point

Incubation	1–3 weeks
Classic sign	Undulant fever (minority)
Common signs	Lymphadenopathy, hepatosplenomegaly, pancytopenia
Severe species	*B. melitensis*
Complication	Osteomyelitis (most frequent)
Diagnosis	Culture (10% CO_2), serology ($\geq$1:160)
Treatment	Tetracycline + Rifampin
Prevention	Pasteurization, animal immunization

➢ Francisella tularensis

Disease

- Tularemia

Important Properties

- Morphology:

- Small, pleomorphic gram-negative rod
- Single serologic type

- Biotypes:

  - Type A → more virulent, U.S., rabbit-associated
  - Type B → less virulent, Europe, rodents & water sources

Pathogenesis & Epidemiology

- Animal hosts (enzootic):

  - Found in >100 wild species: rabbits, deer, rodents = most important
  - Present in every U.S. state (esp. Arkansas & Missouri)

- Vector transmission:

  - Ticks, mites, lice (esp. Dermacentor ticks)
  - Transovarian passage in ticks maintains reservoir

- Human infection (accidental, dead-end host):

  - Most common: tick bite
  - Others: handling infected animals (skin contact,

hide removal)
    - Rare: ingestion of meat → GI tularemia
    - Rare: inhalation → pneumonic tularemia
    - Rare: penetrating skin lesion (e.g., fish-hook in water)

- No person-to-person spread

- Main U.S. form: tick-borne tularemia from rabbit reservoir

Pathogenesis

- Entry: usually skin → ulcer at site of entry

- Spread: localizes in RES (lymph nodes, liver, spleen, BM)

- Host response: granulomas ± caseation necrosis & abscesses

- Toxins:

    - Endotoxin → major role in symptoms
    - No exotoxins

Quick Table: Francisella Key Points

Feature	Details

Disease	Tularemia
Biotype A	Virulent, U.S., rabbits
Biotype B	Less virulent, Europe, rodents/water
Transmission	Ticks (Dermacentor), mites, lice
Human entry	Tick bite (MC), handling animals, meat ingestion, inhalation, skin lesion in water
Pathology	Skin ulcer → RES localization → granulomas, caseation, abscess
Toxins	Endotoxin only (no exotoxins)
Person-to-person spread	Absent

Francisella tularensis – Clinical Aspects

Clinical Findings

- Presentation:

- Acute: sudden influenzalike illness
- Subacute: prolonged low-grade fever + adenopathy

- Most common form (~75%): Ulceroglandular tularemia
  - Ulcer at entry site
  - Painful, swollen regional lymph nodes

- Other forms (less common):
  - Glandular (lymphadenopathy without ulcer)
  - Oculoglandular (eye involvement)
  - Typhoidal (systemic, no obvious ulcer)
  - Gastrointestinal (from ingestion)
  - Pulmonary (from inhalation)

- Immunity: infection usually → lifelong immunity

Laboratory Diagnosis

- Culture: rarely done
  - Requires special cysteine-rich medium
  - Dangerous: risk of inhalation infection to lab workers

- Preferred methods:

- Agglutination test with acute & convalescent sera
- Fluorescent antibody staining (if available)

Treatment

- Drug of choice: Streptomycin
- Resistance: not significant

Prevention

- Avoid exposure:
  - Tick bites
  - Handling wild animals
- Vaccine:
  - Live attenuated bacterial vaccine (not commercial)
  - Used only for high-risk groups (e.g., fur trappers)
  - Available via U.S. Army Medical Research Command (Fort Detrick)
  - One of only two live bacterial vaccines for humans (other = BCG for TB)

Quick Table: Clinical Snapshot

Feature	Key Point
Common form	Ulceroglandular (ulcer + painful lymph nodes)
Other forms	Glandular, Oculoglandular, Typhoidal, GI, Pulmonary
Immunity	Lifelong
Diagnosis	Agglutination test, fluorescent Ab stain
Treatment	Streptomycin (DOC)
Vaccine	Live attenuated, experimental, not commercial

➢ Yersinia pestis (Plague)

Disease

- Cause: Plague ("Black Death")

- History: Pandemic in Middle Ages; still exists (US West + many countries)

- Other Yersinia species (less important here):

    - *Y. enterocolitica, Y. pseudotuberculosis* (GI pathogens, see Ch. 27)

Important Properties

- Morphology:

    - Small gram-negative rod
    - Bipolar staining → "safety pin" appearance

- Capsule:

    - Polysaccharide-protein complex
    - Present in fresh isolates; loss = ↓ virulence

- Virulence:

    - Extremely virulent; ID_{50} = 1-10 organisms

Pathogenesis & Epidemiology

- Reservoir & cycles:

    - Sylvatic (enzootic) cycle → wild rodents (e.g.,

prairie dogs in US), fleas transmit
    - Urban cycle → urban rats, rat fleas; worsens with poor sanitation (e.g., wartime)
    - Humans = accidental hosts (bitten by infected flea)

- Geography:
    - Endemic in rodents of Asia, Europe for millennia
    - Entered US early 1900s → now endemic in western US rodents
    - 99% of global cases in SE Asia

Key Flea Mechanism

1. Flea bites bacteremic rodent → ingests bacteria
2. Biofilm forms in flea's upper GI → blocks passage of blood
3. "Blocked flea" regurgitates organisms into bloodstream of next host (animal/human)

Spread in Humans

- Entry via flea bite → regional lymph nodes → buboes (swollen, tender nodes) → bubonic plague
- Can spread to:

- Blood → septicemia, abscesses, DIC, hemorrhages ("Black Death")
- Lungs → pneumonic plague (respiratory droplet spread → person-to-person)

Virulence Factors

1. F-1 capsular antigen → antiphagocytic

2. Endotoxin → DIC, shock, hemorrhages

3. Exotoxin (action unknown)

4. V & W antigens → intracellular survival (mechanism unclear)

5. Yops (Yersinia outer proteins) via type III secretion system:

   - Inhibit phagocytosis & cytokine production
   - YopJ = protease → blocks TNF signaling pathway → prevents host defense activation

Quick Table: Plague Types

Form of Plague	Source/Spread	Key Features

Bubonic	Flea bite	Buboes (painful, swollen LNs), fever, bacteremia
Septicemic	Secondary	High bacteremia, DIC, black skin hemorrhages
Pneumonic	Droplet spread	Rapid pneumonia, highly contagious, fatal

Yersinia pestis – Clinical Aspects

Clinical Findings

- Bubonic plague (most common)
    - Onset: sudden high fever, myalgia, prostration
    - Characteristic sign: buboes = painful, swollen, tender lymph nodes draining flea bite site
    - Complications: septic shock (endotoxin) + secondary pneumonia
- Pneumonic plague
    - Source: inhaled aerosol OR septic emboli to lungs
    - Features: severe pneumonia, highly contagious

    - Mortality: untreated = 100% fatal

- Fatality: untreated bubonic = ~50%, pneumonic = nearly 100%

Laboratory Diagnosis

- Best sample: blood or pus from bubo (⚠ aerosol risk!)

- Stains:

    - Giemsa or Wayson stain → "safety pin" bipolar rods (better than Gram stain)
    - Fluorescent antibody stain → confirm in tissues

- Serology: rise in antibody titer to envelope antigen (useful retrospectively)

Treatment

- First-line:

    - Streptomycin + tetracycline (e.g., doxycycline)
    - Streptomycin alone also effective
    - Levofloxacin can be used

- Key point:

- Start immediately, do not wait for culture (disease progresses rapidly)

- Surgery: Buboes usually not drained

Prevention

- Control measures:
  - Control urban rat populations
  - Prevent rat entry by ships/airplanes
  - Avoid flea bites & handling wild rodents

- Infected patients:
  - Strict isolation (quarantine) for 72 hrs after antibiotics
  - Close contacts: prophylactic tetracycline + monitor for fever
  - Mandatory reporting to public health authorities

- Vaccine:
  - Formalin-killed organisms → partial protection (bubonic only)
  - Used in military (e.g., Vietnam War)
  - Not recommended for travelers

➢ Pasteurella multocida

Disease

- Wound infections following cat and dog bites

Important Properties

- Morphology: short, encapsulated gram-negative rod
- Bipolar staining ("safety pin"-like, but less prominent than Yersinia)

Pathogenesis & Epidemiology

- Reservoir: normal oral flora of cats and dogs
- Transmission: animal bite
    - ~25% of animal bites become infected
    - Sutures = predisposing factor
- Polymicrobial infections:
    - Often mixed with facultative anaerobes (e.g., *Streptococcus*) & other anaerobes
- Virulence factors:

- Capsule → prevents phagocytosis
- Endotoxin → in cell wall
- No exotoxins

Clinical Findings

- Rapidly spreading cellulitis at bite site (incubation <24 hrs)
- Osteomyelitis possible (esp. cat bites → sharp teeth implant bacteria under periosteum)

Laboratory Diagnosis

- Culture of wound sample → identification of *P. multocida*

Treatment

- Drug of choice: Penicillin G
- Resistance: not significant

Prevention

- Post-bite prophylaxis: ampicillin (esp. for cat bites)
- Do not suture cat bite wounds

➢ Bartonella henselae

Disease

- Cat-scratch disease (CSD) → most common zoonotic disease in the US
- Bacillary angiomatosis → occurs mainly in immunocompromised patients

Important Properties

- Morphology: small, pleomorphic gram-negative rod
- Growth: fastidious → does not grow on routine blood agar; requires specialized media

Pathogenesis & Epidemiology

- Transmission:
  - Cat scratches or bites (esp. kittens)
  - Cat fleas may transmit from cat to human
  - Not transmitted via cat urine or feces
  - No significant person-to-person transmission
- Reservoir: oral flora of many cats
- Virulence: low

    - Disease is usually self-limited in immunocompetent individuals

- Bacillary angiomatosis in immunocompromised:

    - Likely due to endothelial infection → angiogenesis factor → endothelial proliferation

Clinical Features

- Cat-scratch disease (immunocompetent):

    - Regional lymphadenopathy near scratch/bite
    - Mild systemic symptoms: fever, malaise

- Bacillary angiomatosis (immunocompromised):

    - Red-purple vascular skin lesions
    - Can affect internal organs

Laboratory Diagnosis

- Culture: only on specialized media

- Serology or PCR often used for confirmation

Treatment

- Usually self-limited in healthy individuals
- Immunocompromised or severe cases:
    - Macrolides (e.g., azithromycin) or doxycycline

Bartonella henselae – Clinical Overview

Clinical Findings

1. Immunocompetent individuals → Cat-scratch disease (CSD)

- Symptoms: fever, tender enlarged lymph nodes (usually same side as scratch)
- Local sign: papule at scratch site may precede lymphadenopathy
- Course: prolonged but self-limiting
- Complications (rare): systemic disease → endocarditis, encephalitis

2. Immunocompromised individuals → Bacillary angiomatosis (BA)

- Features: raised, cherry-red vascular skin lesions (papular/nodular)

- Visceral involvement: liver, spleen (bacillary peliosis)
- Distinction: biopsy + Warthin-Starry silver stain → differentiate from Kaposi's sarcoma

Laboratory Diagnosis

- CSD: serology → antibodies against *B. henselae*
- Culture: possible on specialized media but slow (>5 days, rarely done)
- BA: pleomorphic rods in tissue biopsy using Warthin-Starry stain

Treatment

- CSD: usually self-limited
    - Severe lymphadenitis → azithromycin
- BA: doxycycline or erythromycin
- Resistance: not significant

Prevention

- No antibiotics prophylactically after cat scratch

- No vaccine available

➢ Exam Case Scnearios

1. Brucella (Brucellosis / Undulant Fever)

Case:

A 32-year-old farmer presents with intermittent fever, night sweats, fatigue, and weight loss for 3 weeks. On examination, he has hepatosplenomegaly and tender lymph nodes. He reports consuming unpasteurized goat cheese recently. Laboratory findings show pancytopenia.

Key Exam Clues:

- Occupational exposure / unpasteurized dairy
- Undulating fever
- Reticuloendothelial involvement

Most Likely Organism: *Brucella melitensis*

2. Francisella (Tularemia)

Case:

A 28-year-old hunter develops fever, chills, and painful swelling of axillary lymph nodes after handling a wild rabbit. A small ulcer is noted at the site of a scratch on his hand. He recalls being bitten by a tick during his hunting trip.

Key Exam Clues:

- Ulcer at entry site
- Regional lymphadenopathy (ulceroglandular type)
- Tick or rabbit exposure

Most Likely Organism: *Francisella tularensis*

3. Yersinia pestis (Plague)

Case:

A 40-year-old man from rural Western US presents with sudden high fever, myalgia, and malaise. He has a painful, swollen inguinal lymph node after being bitten by a flea on his prairie dog farm. Within 24 hours, he develops signs of septicemia.

Key Exam Clues:

- Buboes (painful lymphadenopathy)

- Rapid progression, systemic symptoms
- Flea bite exposure from rodents
- Safety-pin shaped bacteria (Giemsa/Wayson stain)

Most Likely Organism: *Yersinia pestis*

4. Pasteurella multocida

Case:

A 25-year-old woman presents with rapidly spreading cellulitis on her hand less than 24 hours after being bitten by her cat. The wound is red, swollen, and tender. She has no fever initially but complains of mild pain.

Key Exam Clues:

- Rapid onset <24h
- Associated with cat or dog bite
- Cellulitis, possibly osteomyelitis (cat bites)

  Most Likely Organism: *Pasteurella multocida*

5. Bartonella henselae

Case:

A 10-year-old boy develops fever and tender lymph nodes on the same side as a recent cat scratch on his forearm. There is a small papule at the scratch site. The child is otherwise healthy, and symptoms slowly resolve over weeks.

Alternate Case (Immunocompromised):

A 35-year-old patient with AIDS presents with cherry-red vascular skin lesions on the arms and back. Imaging shows liver lesions consistent with bacillary peliosis. He has a history of contact with cats.

Key Exam Clues:

- CSD: cat scratch, regional lymphadenopathy, papule
- BA: immunocompromised, vascular lesions, systemic involvement

Most Likely Organism: *Bartonella henselae*