Legionellosis

Andrew Lee

Bacteria Pathogenesis

Legionellosis is caused by Legionella bacteria

https://www.condair.co.uk/knowledge-hub/legionnaires-disease-humidifiers-what-you-need-to-know

Most common Legionella strain: *Legionella pneumophilia (1)*

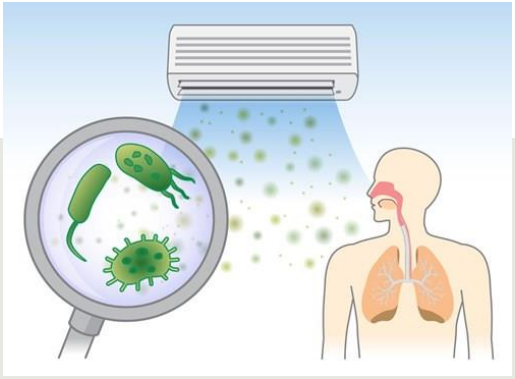
Characteristics:

- Gram-negative rods (shape can change to coccoid or filamentous depending on environment)(2)
- Survival temperature: 0-60 °C (Optimal: ~35 °C) (3)

Location: aquatic environments (2)

- Natural: lakes, ground water, soil, rivers
- Anthropogenic: water fountains, plumbing systems, air humidifiers, hot tubs

Legionella affects human lungs



https://www.hawaiipacifichealth.org/healthier-hawaii/news/legionnaires-disease-what-you-need-to-know/

Transmission: inhaling/consumption of contaminated water droplets into lungs (4)

Symptoms: respiratory symptoms (eg. fever, cough, shortness of breath, and pneumonia) (5)

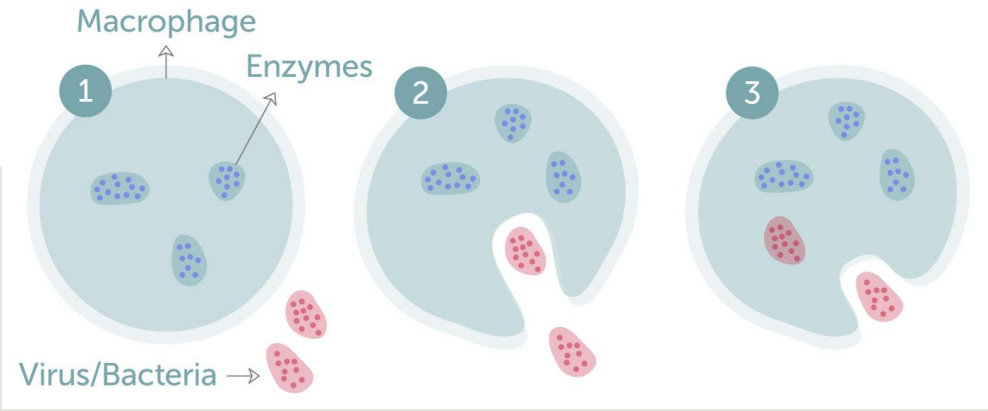
Infection life cycle mostly localized in alveolar macrophages in lungs (5)

This case: patient had recent asthma flare-up and used corticosteroid medication – compromised immune system, more susceptible to infection (6)

Characteristics that contribute to success in Legionella

- Type 4 secretion system and over 300 effector proteins: block phagosome maturation and lysosome fusion (5)
  - Bacteria don't need to move around in body to avoid degradation (so stay in alveolar macrophages in lungs)
- Quorum sensing (Lqs) system, transcription factor (LvbR), twin-arginine translocation system (Tat): allow biofilm formation (7)
  - Helps survival in aquatic systems
  - Biofilms: high resistance to antibiotics, metabolically active, and express virulence genes (8)
- Able to resist unfavorable environments
  - Starvation and environmental stress induce Legionella to transition from a metabolically active, replicating form to a motile, stress-resistant, transmissible form (9)

Legionella entry into host



https://www.lumacyte.com/the-cyte-blog/2018/3/20/macrophages-the-first-responder

1. Inhaled into lungs
2. Penetrates host epithelium using bacterial peptidylprolyl cis-trans isomerase (PPIase) **Mip** (1)
3. Attaches to alveolar macrophages using its **flagella, pili**, and other proteins (10)
4. Binds complement receptors on alveolar macrophages to trigger engulfment (11)
5. Entry through receptor-mediated phagocytosis or coiling phagocytosis
   - Mediated by the host protein phosphatidylinositol 3 **(PI-3)-kinase** (1)

Other bacteria and host components improtant for entry

Bacteria

- Major outer membrane protein (**MOMP**) binds complement components C3 and C3bi (12)
- type 4 secretion system (**T4SS**) help entry and allow effectors to manipulate host cell processes (5)
  - eg. membrane transport systems, inhibiting host cell apoptosis, modulating host cell signaling pathways
- Proteins **EnhC, LpnE, RtxA, LvhB2, and HtpB** help entry (13, 14)

Host

- Binding of **C3 and C3bi** to complement receptors **CR1 and CR3** on alveolar macrophages help initiate phagocytosis (12)

Legionella intracellular survival

Legionella-containing vacuole (LCV) is important for evading host defense (15)

LCV formation and propagation (15)

- Legionella effectors regulate host small GTPases for LCV biogenesis
- Vacuolar ATPases pump H+ into LCV for acidification (16)
- T4SS blocks phagolysosomal fusion in LCVs to instead form ribosome-studded phagosomes, LCV recruits endoplasmic reticulum (ER) derived vesicles remodeling and resemble rough ER (17)
  - ER derived vesicles are rich in lipids and proteins such as Rab1, Rab2, and Rab6
- Ultimately creates a replication permissive compartment for Legionella (1)

Legionella replication

Obtain nutrients from ER for amino acids (main carbon source and mitochondria) (18)

Replication relies on host amino acid transporter solute carriers and the phagolysosomal transporter A (PhtA) (9)

Increase amino acid availability by

- Ubiquinate host proteins: Legionella proteins mimic ubiquitin ligases to catalyze protein degradation to release amino acids (19)
- Inhibit host translation
- Modulate autophagy

Other Legionella proteins for nutrient accumulation: chymotrypsin-like enzyme, caseinase, gelatinase, serum protein degrading protease, aminopeptidase, phosphatase, lipase, deoxyribonuclease, ribonuclease, cellulase, and starch hydrolysis enzymes (20)

Legionella induces cell lysis and escapes from cell

- Cytotoxicity and host cell lysis in response to nutrient depletion (21)
- Legionella changes from replicative to transmissive/virulent form (9)
  - Replicating Legionella: rod-shaped, slender, non-motile, wavy cell wall, and don't express motility or cytotoxicity-related genes
  - Virulent Legionella: rod-shaped, stubby ends containing poly-3-hydroxybutyrate (PHB), smooth thick cell wall, and express transmissivity-related genes
- Legionella T4SS protein intracellular multiplication T (Icm-T): induces pore formation, leading to cell lysis (9)

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