**Legionella pneumophila**

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**Objectives:** After participating in class and reviewing the handout, you should be able to discuss the following:

1. Morphological and growth characteristics of *L. pneumophila*.
2. The *L. pneumophila* natural history (ecology) and its relations to epidemiology and transmission of the bacterium.
3. Mode of transmission and susceptibility to infection.
4. The intracellular life cycle of *L. pneumophila* within alveolar macrophages and protozoa.
5. Compare and contrast Legionnaire's pneumonia to that of pneumococci.
7. Diagnosis, treatment, and prevention of Legionnaire's pneumonia.

*Legionella pneumophila:* 3rd or 4th most frequent cause of Community acquired pneumonia in US:  
Legionnaire's Disease (LD) or Legionnaire's pneumonia.  
A milder form of legionellosis is Pontiac Fever.

**Properties of Legionella**

-- Gram-negative; stains poorly with Gram stain.
-- Fastidious; routinely cultured on buffered charcoal extract agar supplemented with \( \alpha \)-ketoglutarate, cysteine, and iron (BCYE-\( \alpha \)).  
-- Sensitive to pH; use 4.9
-- Grows relatively slowly: requires 2 to 5 days.
-- Can grow at temperatures as high as 46°C and can resist much higher temperatures.
-- 46 recognized species. But *L. pneumophila* causes >90% LD in US.
  -- 16 serogroups of *L. pneumophila*, but 80% LD due to serogroup-1.
  -- The most common other species are *L. micdadei* and *L. bozemanii*.  
  -- Growth inhibited by culture media; must add charcoal.
Ecology

-- Ubiquitous in fresh water, soil, even marine surface waters.
-- *L. pneumophila* grows in protozoa and causes lysis, releasing the bacteria.
-- Colonizes in biofilms in nature and in building water systems.
  -- Warm stagnant water permits build-up of biofilm that resists cleaning methods.

Transmission

-- People are infected by aerosols containing free bacteria or bacteria within protozoa.
-- No person-to-person spread.

Epidemiology

-- Opportunistic pathogen.
  
  **High risk groups:** immunocompromised and immunosuppressed:
  elderly, smokers, people with chronic lung or heart disease; people receiving corticosteroids; people with chronic kidney disease, diabetes, alcoholism.

-- In the hospitalized: solid organ or BM transplant surgery, Hairy Cell leukemia, head and neck surgery, intubation or mechanical ventilation.

Middle-age is a risk; possibility of exposure to heavily contaminated aerosol.

-- Responsible for 2-15% of pneumonias that cause hospitalization.
-- Majority of cases are isolated ("sporadic"). 10-20% are in outbreaks. 23% are nosocomial.

Intracellular life cycle of * Legionella pneumophila*

-- Facultative intracellular pathogen. In nature, replicates within protozoa; in humans, grows intracellularly in macrophages and epithelial cells.

-- Bacteria bind receptors on macrophage or epithelial cell and trigger engulfment.

-- **Dot/Icm** contact-dependent secretion system inhibits the fusion of phagosome with lysosomes, and the phagosome does not acidify.

-- The phagosome recruits ER vesicles by a process that requires Dot/Icm function.
-- An ER-like vacuole studded with ribosomes is created by *Legionella*, and the bacteria grow within this organelle.

-- Another secretion mechanism secretes proteins necessary for intracellular growth of the bacteria.

-- *L. pneumophila* virulence is growth-phase dependent. The bacteria detect nutrition:
  -- Abundant nutrition promotes exponential growth and low infectivity.

"replicative form"
-- Starvation in stationary phase causes gene expression for enhanced fitness.
-- Starvation induces a pore-forming toxin that lyses cell and releases bacteria.

Pathology

-- Intracellular replication within monocytes and macrophages in the alveolar spaces is the hallmark of LD.
-- Cytokines released by infected macrophages promote inflammation.
-- Infiltrate visible on chest X-ray; high ratio of mononuclear phagocytes to PMNs.
-- X-ray pattern is not unique to LD; multifocal and initially nodular but may become confluent and lobar; Involvement of alveoli and distal bronchioles.
-- Extensive necrosis of alveolar epithelial lining and lysis of inflammatory cells may be due to pore-forming activity and may amplify inflammatory response.
-- In immunocompromised people, microabscesses may form and coalesce (cavitation)

Clinical Features of Legionnaire's Pneumonia

-- Incubation period is 2 to 10 d after exposure. & Coughing begins at 3 days
-- Non-productive cough.
-- Watery diarrhea can occur
-- Mental confusion, disorientation, loss of memory that seem out of proportion to the seriousness of the fever.

But general picture of LD is similar to pneumonia from other causes, such as pneumococcal.
-- Mortality is 10-15%. Can be very high in nosocomial outbreaks.

Immune response

-- Cell-mediated (Th1) immunity required to resolve the infection
-- IFN\(_{\gamma}\) inhibits intracellular growth; TNF\(\alpha\) and IFN\(_{\gamma}\) contribute to bacterial clearance.
-- Antibody appears to limit replication in the lung.

Microbiologic Diagnosis

-- Gram stain not work well.
-- Direct fluorescent antibody staining of sputum is useful.
-- Legionella soluble antigen in urine only detects serogroup 1.
-- Paired acute and convalescent serum samples
-- PCR detection is promising.
-- Culture is 100% specific and allows speciation and typing. -> COLD STANDARD
-- Often have to treat on suspicion.
Chlamydia pneumoniae

-- Infects endothelial cells, smooth muscle cells, monocytes/macrophages.

Epidemiology

-- Discovered as respir. pathogen in 1983
-- Initially called TWAR. This terminology not accepted anymore.

-- Causes both upper and lower RTI:
  -- Majority of disease is asymptomatic or mild URTI: pharyngitis.
  -- The most recognized diseases are lower RTI: bronchitis, pneumonia.
  -- 10% of community acquired pneumonia; 5% of bronchitis.

-- Infections most common in school-aged children. By age 20, 50% of population has antibodies against C.p.; 75% among elderly. Reinfections are common.

-- Most of the pneumonia is in the elderly; less common in people under 20 y.o.
-- Infections occur year-around.
-- Transmission person-to-person through respiratory droplets.
-- Incubation period is long: 10-21 days usually (case-to-case interval averages 30 d).
-- Not clear how long an infected person is contagious: thought long (weeks).

Clinical manifestations

-- No unique set of symptoms or signs. Resembles mycoplasma pneumonia, etc.
-- Gradual onset is typical.
  -- First: upper respiratory symptoms, esp. pharyngitis, often with hoarsness, and usually fever.
  -- These s/s may regress, then bronchitis or pneumonia can appear in several days to 3 weeks.
  -- Gradual onset of cough with little or no fever. Rhonchi and rales even in mild disease.
  -- Sinusitis can accompany either the initial URTI or the later LRTI.
  -- Overall relatively mild disease: "walking pneumonia".
-- Chest X-ray usually shows a single interstitial lesion; in severe cases there can be more than one and extensive bilateral disease. "Wispy, patchy pattern"
-- Recovery is slow: several weeks or months despite appropriate therapy.

Proposed sequelae

-- C. pneumoniae infection proposed to be associated with atherosclerotic vascular disease. Not proven yet.
  \*upreg of adhesion molecules \* all to vasc. walls
  \* art. \* upreg \* ↑ LDL \* ↑ foam cells
Also proposed connection between *C. pneumoniae* infection and Alzheimer's disease, asthma, and reactive arthritis. Not proven yet.

**Diagnosis and treatment**

- Special laboratories can diagnose it by serology, but this is not routinely done.
- Diagnosis is usually made based on clinical symptoms.
- Doxycycline or tetracycline, erythromycin are effective. Macrolides have fewer adverse reactions; Quinolones.
  Drugs have to penetrate cells and work on Gm- bacteria.

**Chlamydia psittaci**

- Name from Greek *Psittakos* = parrot. Disease in humans is called psittacosis, also known as parrot fever and ornithosis.

**Transmission**

- Transmitted to humans from birds with avian chlamydiosis. Is a zoonosis = an animal disease that can be transmitted to humans.
  - The birds can have overt disease or be asymptomatic carriers.
  - EBs are shed in feces and nasal discharges. Ebs can survive in dried feces for months. People inhale particles containing EBs.

- All birds are susceptible, but pet birds and poultry (turkeys and ducks) most frequently involved in transmission to people.
  Person-to-person transmission rare but can occur by aerosol or venereal spread.

**Epidemiology**

- Bird owners, pet shop employees, veterinarians, poultry processors.
- 100-200 cases/yr.

**Disease**

- Incubation period 1 to 4 weeks; usually ca. 10 d.
- Unapparent illness to systemic illness with severe pneumonia. Fever (up to 103-105°F), chills, headache, muscle aches, and a dry cough.
  - Sometimes: pulse not elevated despite fever; splenomegaly; erythematous, blanching, maculopapular rash.

*This + pneumonia is tip off*