Chlamydophila pneumoniae
Respiratory Tract Syndrome

Charles W. Stratton, M.D.
Associate Professor of Medicine and Pathology
Vanderbilt University School of Medicine
Nashville, Tennessee
**Chlamydophila pneumoniae**

- *Chlamydia* are unique microorganisms
- Placed in their own order with two families
  - *Chlamydia* and *Chlamydophila*
- Characterized by distinct life forms
  - Extracellular infectious form (elementary body)
  - Intracellular replicating form (reticulate body)
  - Intracellular cryptic form (cryptic body)
- Considered energy parasites (steal ATP)
- *C. pneumoniae* first described in 1986
Chlamydophila pneumoniae

- Airborne pathogen (infectious elementary body)
- Initially infects epithelial cells in respiratory tract
- Able to survive phagocytosis by macrophages
- Appears to cause persistent respiratory tract infection
- Able to disseminate in monocytes via blood stream
- Typically infects endothelial cells and monocytes
- Able to infect many other types of cells
- Immune response causes additional tissue damage
Chlamydophila pneumoniae
Respiratory Tract Syndrome

• Begins with mild sore throat and hoarseness over several days
  – Low grade fever if any - often afebrile
  – Feels well otherwise - continues to work

• Postnasal discharge occurs next
  – No facial/tooth pain - sinuses not tender

• Upper respiratory symptoms generally last for one week, but may recur later
Chlamydophila pneumoniae
Respiratory Tract Syndrome

- After one week, upper respiratory tract symptoms fade and are replaced by a dry cough that is worse at night
  - Usually afebrile
  - Feels well - continues to work
- Dry cough for a week, then cough becomes productive, but only in the morning
  - Greenish bronchial plugs
- Cough is now accompanied by malaise/fatigue
*Chlamydophila pneumoniae*

Respiratory Tract Syndrome

- Untreated, this syndrome may last up to two months
- Upper respiratory tract symptoms may recur during this time
- After this infection has resolved, patients typically will have at least two or three more similar episodes in their lifetime, and may have several each year
Chlamydophila pneumoniae
Respiratory Tract Syndrome

• Most oral antibiotics will provide symptomatic relief while the patient is on therapy
• However, symptoms usually recur within days to a week after the antibiotic is stopped
• There are two reasons for this recurrence
  – Most antibiotics only inhibit C. pneumoniae
  – The unique chlamydial life cycle can cause relapse
Chlamydia pneumoniae is an intracellular bacterial parasite of eukaryotic cells. The organism has a unique biphasic development cycle with distinct morphological and functional forms. This development growth cycle alternates between intracellular life forms of which two are currently recognized; 1) an intracellular life form which can exist as a metabolically-active, replicating organism known as the reticulate body (RB) or as a persistent, nonreplicating organism known as the cryptic body (CB), and 2) an extracellular life form that is an infectious, metabolically-inactive form known as the elementary body (EB).
*Chlamydia pneumoniae*

Respiratory Tract Infection

- Role of Telithromycin in treating chlamydial respiratory tract infections
  - FDA approved for chlamydial respiratory infections
  - Only chlamydicidal agent available
  - Eradication demonstrated in murine model
  - Prevents dissemination in murine model
Telithromycin Structure

Antimicrobial activity via 23S domain II

Acid stability

Sugar

- Changed metabolism
- Acid stability
- Induction of resistance
Macrolide Binding Sites and Resistance
The Pathogenesis of *Chlamydophila pneumoniae*

- Elementary body (EB)
  - Only chlamydial form that is infectious
  - Spore-like means for spreading infection
  - Metabolically inert
  - Rugged cell wall having disulfide bonds
  - Surrounded by glycocalyx
  - Attaches to host cells via heparin molecules
  - Internalized and becomes reticulate body
The Pathogenesis of *Chlamydophila pneumoniae*

- Reticulate body (RB)
  - Obligate intracellular form
  - Fragile cell wall with “spikes”
  - Has type III secretion apparatus
  - Metabolically active
  - Requires host cell energy for replication
  - Replicates within inclusion body
  - Able to condense back to elementary body
The Pathogenesis of
*Chlamydophila pneumoniae*

- Cryptic body (CB)
  - Least understood chlamydial form
  - Commonly found in mononuclear cells
  - Possibly a stringent response
  - Metabolically active as per messenger RNA
  - Does not replicate and form inclusions
  - May shift to EB or RB forms
  - Relatively resistant to antichlamydial agents
Chlamydophila pneumoniae

• Human cells infected by *C. pneumoniae*
  – Epithelial cells
  – Endothelial cells
  – Smooth muscle cells
  – Myosites
  – Monocytes/Macrophages/Leukocytes
  – Lymphocytes (B-cells and T-cells)
  – Astrocytes, glial cells, and microglial cells
Chlamydophila pneumoniae

- Effect of *Chlamydophila* infection on host cells
  - *Chlamydophila* replication followed by cell death
  - Impaired host cell function and signaling
  - Host cell production of nitric oxide
  - Host cell production of growth factors
  - Host cell production of cytokines
  - Host cell production of chemokines
  - Inhibition of host cell apoptosis
The Pathogenesis of *Chlamydophila pneumoniae*

- Examples of immune modulators produced by host cells after infection with *Chlamydia*
  - TNF
  - IL-1
  - IL-6
  - IL-8
  - IL-11
  - IL-12
The Pathogenesis of *Chlamydophila pneumoniae*

- Examples of growth factors produced by host cells after chlamydial infection
  - Heparin-binding epidermal growth factor
  - Epidermal growth factor
  - Vascular endothelial growth factor
  - Fibroblast growth factor
  - Connective tissue growth factor
  - Transforming growth factor
Chlamydophila pneumoniae

- *Chlamydophila* and Apoptosis
  - Activation of NF-kB can inhibit apoptosis
  - Activation of COX2 can inhibit apoptosis
  - Members of the caspase family of cysteine proteases transmit the apoptotic signal
  - *C. pneumoniae* appears to synthesize a protein that blocks caspase 3 activation and release of mitochondrial cytochrome *c*, thus inhibiting apoptosis
The Pathogenesis of *Chlamydophila pneumoniae*

- Role of chlamydial heat shock protein 60
  - *Chlamydophila* produce Hsp60
  - Hsp60 interacts with Toll-like receptors
  - TLRs activate nuclear factor (NF)-kB and mitogen-activated protein kinases (MAPKS)
  - NF-kB and MAPKS regulate the expression of proinflammatory cytokines and other mediators of innate immune responses
The Pathogenesis of *Chlamydophila pneumoniae*

- Chlamydial diseases are characterized by intense and chronic inflammation that is elicited and maintained by reinfection or persistent infection.
- Such diseases have been thought to be mediated by antigen-dependent delayed-type hypersensitivity or autoimmunity.
The Pathogenesis of *Chlamydophila pneumoniae*

- *Chlamydophila*-infected non-immune mammalian cells are known to produce proinflammatory chemokines, cytokines, growth factors, and other cellular modulators.
- These modulators are now thought to be sufficient to account for chronic and intense inflammation.
The Pathogenesis of *Chlamydophila pneumoniae*

- Diseases in which *C. pneumoniae* may play a role include:
  - Atherosclerosis
  - Asthma
  - Alzheimer’s Dementia
  - Multiple Sclerosis
  - Pyoderma Gangrenosum
  - Interstitial Cystitis