Atypical Pneumonia

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Objectives

- Describe the major clinical and epidemiological characteristics that differentiate atypical from typical pneumonia
- Identify the major microbiological characteristics of Legionella, Mycoplasma and Chlamydophila
- List key diagnostic tests and the performance characteristics of the assays

Causative Agents of Acute Pneumonia—Bacteria

Common
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Haemophilus influenzae*
- Mixed anaerobic bacteria (aspiration)
  - *Bacteroides* spp.
  - *Fusobacterium* spp.
  - *Peptostreptococcus* spp.
  - *Peptococcus* spp.
  - *Prevotella* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Enterobacter* spp.
  - *Serratia* spp.
  - *Pseudomonas aeruginosa*
- *Legionella* spp. (including *L. pneumophila* and *L. micdadei*)

Uncommon
- *Acinetobacter* var. *anitratus*
- *Actinomyces* and *Arachnia* spp.
- *Bacillus* spp.
- *Moraxella catarrhalis*
- *Campylobacter fetus*
- *Eikenella corrodens*
- *Francisella tularensis*
- *Neisseria meningitidis*
- *Nocardia* spp.
- *Pasteurella multocida*
- *Proteus* spp.
- *Pseudomonas pseudomallei*
- *Salmonella* spp.
- *Enterococcus faecalis*
- *Streptococcus pyogenes*

Causative Agents of Acute Pneumonia—Viruses

Children

Common
- Respiratory syncytial virus
- Parainfluenza virus types 1, 2, 3
- Influenza A virus

Uncommon
- Adenovirus types 1, 2, 3, 5
- Influenza B virus
- Rhinovirus
- Coxsackievirus
- Echovirus
- Measles virus
- Hantavirus

Adults

Common
- Influenza A virus
- Influenza B virus
- Respiratory syncytial virus
- Human metapneumovirus
- Adenovirus types 4 and 7 (in military recruits)

Uncommon
- Rhinovirus
- Enteroviruses
- Echovirus
- Coxsackievirus
- Epstein-Barr virus
- Cytomegalovirus
- Varicella-zoster virus
- Parainfluenza virus
- Measles virus
- Herpes simplex virus
- Hantavirus
- Human herpesvirus 6
- Coronavirus (SARS)

Causative Agents of Acute Pneumonia—Other Agents

Rickettsia
- *Coxiella burnetii*
- *Rickettsia rickettsiae*

Mycoplasma *and* Chlamydia
- *Mycoplasma pneumoniae*
- *Chlamydophila psittaci*
- *Chlamydia trachomatis*
- *Chlamydophila pneumoniae* (TWAR)

Mycobacteria
- *Mycobacterium tuberculosis*
- *Nontuberculous* Mycobacteria

Atypical pneumonia syndrome

- Mild respiratory illness followed by pneumonia with dyspnea and cough without sputum production
  - M. pneumoniae
  - C. pneumoniae
  - Legionella
  - Respiratory viruses

Incidence

- Pneumonia accounts for only 4 – 6% of visits to primary care physicians for complaints of cough
- Prevalence varies with age of the patient population and comorbid conditions
- Clinical findings
  - Cough, sputum production, dyspnea, fever
  - Fatigue, sweats, headache, nausea, myalgia
- Frequency of atypical pneumonia varies depending on the means of diagnosis

Mycoplasma pneumoniae

- Accounts for 1 – 20% of cases of community acquired pneumonia, with the highest percentages noted in ambulatory patients
  - Majority of cases in < 40 year olds
    - Most likely in children >5, adolescents, and young adults
  - Accounts for <1 – 5% in older population and more likely to lead to hospitalization
- Occurs throughout the year

Mycoplasma pneumoniae (cont.)

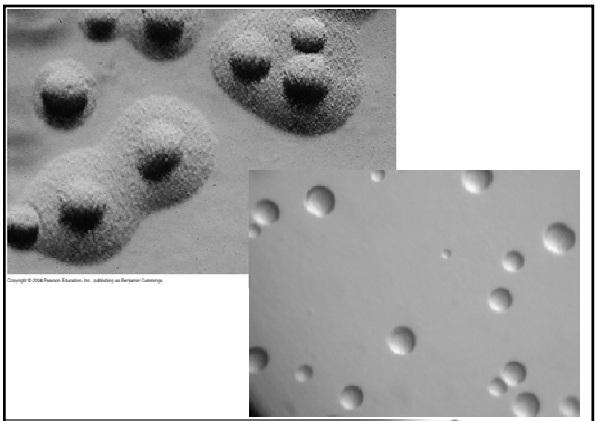
- Course prolonged
  - 10 days symptoms before seeking medical care
  - Progression from upper to lower respiratory tract
  - Radiographs demonstrate pulmonary involvement more extensive than physical findings would suggest
    - Unilateral or bilateral patchy infiltrates in lower lobes
- Extrapulmonary manifestations

Organism

- Prior to 1960's thought to be a virus
- Short rod shaped organism without a cell wall
  - Not visible on gram stain
  - Not affected by beta-lactam antibiotics
- Long doubling time, so culture is slow process

Detection

- Culture
  - Slow
  - Specialized media
  - Commercially available kits
  - Identification based on colony, glucose fermentation, slow growth and specimen source
  - The organism can persist for variable lengths of time following acute infection



Detection (cont.)

- Serologic testing
  - Cold agglutinins
  - Antibody to lipid and protein antigens develops after about one week, peaks 3 to 6 weeks and gradually declines
  - IgG and IgM
    - Adults may elaborate only an IgG response
    - IgM can persist for several months
    - Best use is with acute and convalescent samples

Detection (cont.)

- Commercially available kits
  - IFA (Zeus)
  - EIA
    - IgG and IgM separately and combined
    - Elisa - Zeus, Remel (Sensitivity 35%, Specificity 96%)
    - Membrane based
      - » Meridian – IgM only
        - » Poor sensitivity (48%) when used a single sample, Specificity 79%
      - » Remel – IgG and IgM combined
  - Use a variety of antigens
  - Limitations for diagnosis of acute infections
  - Positives seen in healthy blood donors
  - Requires acute and convalescent testing

JCM, 2005; 43:2277

Detection (cont.)

- Nucleic acid amplification
  - No commercially available kit
  - Analyte-specific reagents
    - Nanogen, Focus, Cepheid,
    - Sensitivity 98%, 88%, 83%, respectively
  - Available as reference test
  - Recommended method
  - Debate over best specimen to use, nasopharyngeal or throat swab

JCM, 2009; 47:2269

Chlamydophila pneumoniae

- Accounts for 6 – 20% of cases of community acquired pneumonia
  - Uncommon in < 5 year olds
  - Serologic evidence of infection in 50% of adults
  - Important in >65 year old population
- Co-infection with S. pneumoniae may occur frequently
- Asymptomatic infections may also occur

Chlamydophila pneumoniae (cont.)

- Occurs throughout the year
- Course prolonged
  - Cough – days to weeks prior
  - Sore throat and hoarseness
  - Slow progression from upper to lower respiratory tract

Organism

- Obligate intracellular bacterial pathogen
- Gram negative envelope without peptidoglycan
- Unique developmental cycle

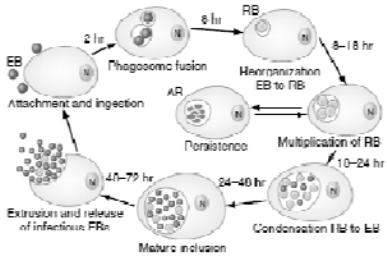
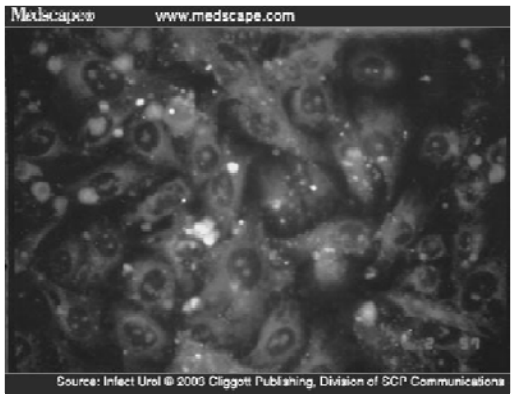


Figure 182-1 **Life cycle of Chlamydiae in epithelial cells.** EB, elementary body; N, nucleus; RB, reticulate body. (Modified from Hammerschlag MR, Kohlhoff SA, Darville T: Chlamydia pneumoniae and Chlamydia trachomatis. In Plotkin SA, Orenstein PM, Smith JE, Brogdon KA, editors: Post Infectious Sequelae and Long Term Consequences of Infectious Diseases, Washington, DC, 2008, American Society for Microbiology.)

Mandell, Douglas and Bennett Principles and Practice of Infectious Disease, 7th ed.

Detection

- Culture
  - Slow
  - Cell culture of NP, BAL, throat to Hep-2 cells for 72 hours
  - Identification based on immunofluorescence staining



Detection (cont.)

- Serologic testing
  - No commercially available FDA approved assay for C. pneumoniae
    - There are commercially available FDA approved assays for Chlamydia sp., not specified
  - Poor correlation between culture or NAAT and serology
  - MicroImmunofluorescence, Elisa
  - Insensitive, Inadequate

Detection (cont.)

- Nucleic acid amplification
  - No commercially available kit
  - Numerous in-house developed assays
  - Most assays have only analytical validation – no clinical data
  - Available as reference test
  - Recommended method
  - Nasopharyngeal, throat swab, BAL

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Legionella sp.

- Important cause of community acquired pneumonia
  - Accounts for 2 – 8 % of those hospitalized
  - Incubation period 2 -10 days
- May require intensive care
- Sporadic and Epidemic forms
  - 65 – 75% not associated with epidemics
  - Occurs throughout the year, increased incidence during summer months
- Uncommon in children

Legionaires Disease

- First recognized in 1976
- Initiated by inhalation of the organism from aerosolized water contaminated with the organism
- Phagocytosed by macrophages, grow intracellularly, kill the macrophage and are released into the lung
- Systemic disease related to production of cytokines
- Immune control is mediated by cellular immune system, although antibodies do develop

Legionaires Disease (cont.)

- Acute pneumonia similar to pneumococcal pneumonia
- Fever, myalgia, cough, elevated liver-associated enzymes
- May have prodrome of headache, myalgia and fever
- Fatality rate of 12%, if not promptly treated

Legionaires Disease (cont.)

- Risk factors predispose to disease
  - Immunosuppression
  - Smoking
  - Well water
  - Travel outside the home
  - Chronic heart or lung disease
  - Anti-tumor necrosis factor therapy for autoimmune diseases

Pontiac Fever

- Identified by employing serologic tests for Legionella
- May be caused by inhalation of the organism from aerosolized water contaminated with the organism
- May be inhalation of endotoxin
- Short duration, self-limited febrile illness
  - No pneumonia
  - Recover 3- 5 days

Organism

- Gram negative bacillus
  - Require L-cysteine for growth
  - Enhanced by iron
  - Utilizes amino acids as energy source
- Can be grown on artificial media
  - Activated charcoal inactivates toxic lipids and other components
- 52 validly published named species
  - L. pneumophila, L. micdadei, L. longbeachae and L. dumoffii most important clinically

Organism (cont.)

- L. pneumophila responsible for 90% of cases of Legionnaires Disease
  - 16 different serogroups and 3 recognized subspecies
  - Serogroup 1 constitutes 80 – 90% of clinical isolates
    - The Pontiac subtype of serogroup 1 is responsible for 50% of sporadic disease
  - Most L. pneumophila strains found in environment are unusual causes of LD
    - These are intracellular parasites of free-living amoeba

Detection

- Direct exam
  - Gram stain
    - Small coccobacillus
    - Very difficult to see
      - 0.1% basic fuschin instead of safranin improves visibility
  - Immunofluorescence stain
    - Requires precise methodology and microscopic expertise
    - Insensitive
    - Nonspecific
    - No longer recommended for use

Detection (cont.)

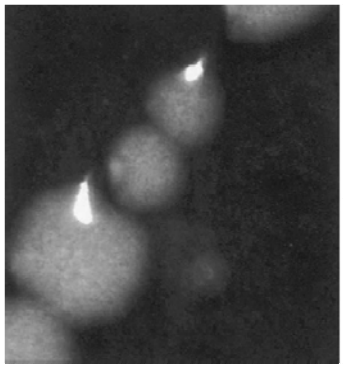
- Antigen Detection
  - Immunochromatographic card assay or EIA
    - Commercially available FDA approved
    - Performed on urine
    - Detect L. pneumophila serogroup 1
    - Sensitivity varies depending on disease severity, subgroup and serogroup, length of illness
    - 99 – 99.9% Specificity

Detection (cont.)

- Culture
  - Respiratory tract specimens, pleural fluid, blood, extrapulmonary tissue
  - Diluted 1:10 to reduce inhibition by serum and tissue factors
  - Decontaminate by dilution in low-pH buffer to reduce contaminating microbiota
  - Use selective and non-selective media
    - BCYEα
    - BCYEα with antibiotics
  - Incubate 35 C 2 – 5% CO_2 for up to 5 days (most grow within 1-3 days)
  - Examine with dissecting microscope

Detection (cont.)

- Identification
  - Confirm L-cysteine requirement, examine for fluorescence, type or identify by sequencing
  - Identify using immunofluorescence assay
    - Outer membrane protein of L. pneumophila
  - Morphologically consistent organisms with L-cysteine requirement can be called presumptive Legionella wthout serotyping



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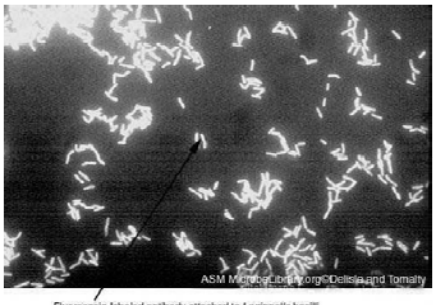

Fluorescein labeled antibody attached to *Legionella* bacilli

Detection (cont.)

- Serologic testing
  - Indirect immunofluorescence
    - Total antibodies, not just IgG
    - IgM persists
  - Seroconversion can take weeks to months with only 50% at 2 weeks, 80% at 4 weeks
  - Only 75% of culture proven LD will seroconvert at all
  - Insensitive and nonspecific unless acute and convalescent specimens are tested

Detection (cont.)

- Nucleic acid amplification
  - One commercially available FDA approved kit
    - BD ProbeTec, 2004
  - Numerous in-house developed assays
  - Most assays have only analytical validation – little clinical data
  - Available as reference test
  - Nasopharyngeal, throat swab, BAL

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Contact Information

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