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 Chlamydia
• 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.
- 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
- Nocardia meningitidis
- Nocardia spp.
- Pasteurella multocida
- Proteus spp.
- Pseudomonas pseudomallei
- Salmoneella spp.
- Enterococcus faecalis
- Streptococcus pyogenes

Causative Agents of Acute Pneumonia—Viruses

Children

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

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
- Echovirus
- Coxsackievirus
- Epstein-Barr virus
- Lamda virus
- 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
- Chlamydia pneumoniae (TWAR)
- Chlamydia trachomata
- Mycobacterium tuberculosis

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.)**

- 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

**Chlamydia 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

**Chlamydia 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
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

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
**Legionnaires 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

**Legionnaires 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

**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 90% 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% CO₂ 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 without serotyping
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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