Viral Infection
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Pulmonary Infections with Respiratory Viruses

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Objectives:
To learn:
- The common causes of viral LRTI
- Some basic facts about viral infection
- The common imaging appearances of viral LRTI

Significance:
Viral pneumonias account for 9-29% of all community-acquired pneumonias requiring hospitalization in adults*.

Lim WS. Thorax 2001; 56:296-301.
Marston BJ. Arch Intern Med 1997; 157:1709-1718.

Viral Structure:
- Simple, ingenious organism
- Uses host reproductive machinery to replicate itself
- Payload
  - RNA or DNA genome
  - Enzymes to initiate viral replication
- Delivery system
  - Protective protein coat (capsid) + lipid membrane
  - Virus encoded binding proteins

Virus-Cell Interactions
- Attachment
  - Viral proteins bind cell surface molecules
- Penetration and disassembly
  - Endocytosis of enveloped viruses
- Genome replication
  - RNA - cell ribosomes or viral RNA polymerase
  - DNA - entry into nucleus
- Cell death (apoptosis)
  - Cell defense vs. viral spread
  - Viral genome - reduce apoptosis - spread
  - DNA viruses - block apoptosis - latency

Viral Causes
Lower Resp Tract Infections
Community Acquired

Influenza
RSV
Adenovirus
Parainfluenza
Metapneumovirus
Other
Coronavirus
Rhinovirus
Varicella

Mechanism:
- Inspired respiratory droplets

Influenza
Figure 162-1
RSV
Figure 155-2
Adenovirus
Figure 139-2
Parainfluenza
Metapneumovirus
Other
Coronavirus
Rhinovirus
Varicella
Viral Causes
Lower Resp Tract Infections
Opportunistic Viruses

- ONLY Herpes group
  - Simplex I & II (HSV)
  - Cytomegalovirus (CMV)
  - Varicella Zoster (VZV)

- Mechanism
  - Latency (nerve cell/s, lymphocytes)
  - T cell immune suppression
  - Reactivation
  - Viremia - lung involvement

CMV EM?

Herpes simplex EM?

Community Acquired Viruses:
Clinical Manifestations

- All cause "flu-like" symptoms
- Heralded by upper tract infection
  - Fever, coryza
- Lower tract disease
  - Cough, dyspnea, sputum production
  - Tracheobronchitis
  - Bronchiolitis
  - Pneumonia
- Duration can be prolonged
  - 7-21 days

Imaging Features:
Community Acquired Viral Infection

- PENN study (CAV LRTI)
- Definition of Disease
  - Positive viral PCR of NP swab or BAL
  - Lower resp tract symptoms
    - New onset dyspnea, cough or sputum production
- Exclusions
  - Concomitant bacterial pneumonia
  - Pre-existing diffuse lung disease
- Control Group
  - Individual with negative PCR assay
  - Lower resp tract symptoms

Imaging Features:
Computed Tomography

- Population
  - 97 index cases
  - 267 negative controls
- Virus
  - Influenza 56 (58%)
  - RSV 24 (25%)
  - Adenovirus 11 (11%)
  - Parainfluenza 6 (6%)

Imaging Features:
Computed Tomography

- All CAVI similar appearance
- 3 broad patterns of appearance
- No imaging findings/Normal ~ 1/3
  - Imaging insensitive for CAVI
- Tracheobronchitis/bronchiolitis pattern ~ 1/3
- Multifocal pneumonia pattern ~ 1/4
  - Often confused with aspiration pneumonia
- Variable appearance ~ 1/20

Imaging Features:
Normal CT

- Clinical history of severe symptoms/normal CT

Image of Normal
Imaging Features:
Bronchitis/Bronchiolitis Pattern

- Tree-in-Bud
- Br wall thick

41M HIV+ 1 mo cough, dyspnea, night sweats
RSV bronchiolitis

Imaging Features:
Bronchitis/Bronchiolitis Pattern

- Tree-in-Bud
- Br wall thick

41 man fever, cough, dyspnea
RSV bronchiolitis

Imaging Features:
Multifocal Pneumonia Pattern

- Multifocal GGO
- Multifocal consolidation

21 pregnant W fever, cough, myalgias
Influenza A

Imaging Features:
Diffuse Pneumonia Pattern

- Diffuse GGO
- Diffuse consolidation

Image of Diffuse GGO Pneumonia

Imaging Features:
Focal Pneumonia Pattern

Image of Focal Pneumonia

- Clinical history

Imaging Features:
Comparison with Controls

<table>
<thead>
<tr>
<th>Infection Pattern</th>
<th>Viral LRTI</th>
<th>Non-Viral LRTI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/No Acute Disease</td>
<td>34 (35%)</td>
<td>90 (34%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Bronchitis/ Bronchiolitis</td>
<td>32 (33%)</td>
<td>27 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Focal Pneumonia</td>
<td>6 (6%)</td>
<td>30 (11%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Multifocal Pneumonia</td>
<td>23 (24%)</td>
<td>76 (28%)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- Bronchiolitis pattern: 80-85% specificity CAVI
- Pneumonia pattern: non specific
Imaging Features:
Subgroup Analysis

- Individual viruses tend to have a typical appearance
- RSV
  - Bronchiolitis pattern
- Adenovirus
  - Pneumonia pattern
- Influenza
  - Normal CT

* unpublished data

Other Community Acquired LRTI:
The Lesson of SARS

- Coronavirus epidemic
  - Novel virus
  - Increased prevalence severe disease (pneumonia)
- Occasionally other respiratory viruses will produce “Flue-like” disease
- Sporadic - epidemic - pandemic

Radiograph of SARS

Community Acquired LRTI:
Chest Radiographs?

- Insensitive for disease
  - Influenza: normal exam in ~
- Pneumonia
  - Usually detected
  - Multifocal - diffuse consolidation
- Bronchiolitis
  - Faint bronchial wall thickening (“peribronchial cuffing”) 
  - Small fuzzy nodules
  - difficult to detect
  - Underdiagnosis/overdiagnosis

Radiograph of viral bronchiolitis

Radiograph of SARS

RSV bronchiolitis
Viral Lower Respiratory Infections: Conclusions

- Community acquired
  - 4 common causes: influenza, RSV, adenovirus, parainfluenza
  - Occasionally others: metapneumovirus, coronavirus (SARS), 1-2 VZV
  - Inhalation of infected droplets

- Opportunistic
  - Ability to remain dormant
  - Herpes group viruses: CMV, HSV 1, HSV 2, VZV
  - Reactivation - Viremia - Pneumonia

Imaging Features: Do Opportunistic Viruses Look Different?

- CMV and HSV
  - reactivation
  - viremia
  - pneumonia

- Diffuse GGO more common appearance?
  - Literature references that this is typical appearance

Imaging Features: CMV

Viral Lower Respiratory Infections: Conclusions

- 3 Imaging Patterns of community acquired viral infection
  - No Imaging findings/ Normal exam
  - Imaging insensitive for viral LTRI

- Bronchitis/bronchiolitis
  - Bronchial wall thickening, Tree-in-bud
  - Specific sign of viral infection in appropriate clinical setting

- Pneumonia
  - Multifocal GGO/consolidation
  - Diffuse GGO/consolidation rare
  - Non-specific finding often confused with aspiration

- Different appearance of opportunistic infections?
  - Diffuse GGO
    - Different mechanism of spread - viremia
Influenza: Seasonal Flue and the New H1N1 Virus
• If time will talk specifically about influenza and new epidemic

Influenza: Viral Structure
• 3 strains (A, B, C)
  • Only A can cause pandemics
  • C does not cause human respiratory infection
• Single stranded, - sense, RNA genome
• Enveloped virus
  • 2 primary surface spikes
    • Hemagglutinin (HA)
    • Neuraminidase (NA)

Influenza: Epidemiology
• Seasonality:
  • Temperate: winter peak - summer trough
  • Tropical: year round low level disease
• At risk populations
  • Infants
  • Elderly
  • 3rd trimester pregnancy (rel T cell immunosuppression)
  • Immunosuppressed (HIV, organ Tx)

Influenza: Spread
• Epidemic
  • Outbreak confined to one location
  • Modification of existing virus (Antigenic drift)
    • Partial immunity in population
    • Attack rates 10-20%
    • Single winter peak
• Pandemic
  • Outbreak that spreads rapidly across the world
  • Emergence of a new virus (Antigenic drift)
    • No immunity in population
    • Attack rates increased
    • Infection out of season
    • Multiple waves of disease

Influenza: Antigenic Shift and Human Pandemics
• Large diverse avian reservoir of Influenza A
• No significant transfer avian influenza to humans
• Isolated from human influenza
• Progressive drift away from human strains
• Antigenic Shift theories
  • Intermediate Host: Pigs
    • Can be infected with both human and avian influenza A
    • Gene rearrangement during coinfection or evolution avian virus in pig
    • New strain capable of infecting humans
  • Direct Transmission
    • Avian strain mutates capability to infect humans
• With antigenic Shift: Human Pandemic
Influenza: Pathogenesis

- Infectious aerosols (cough, sneeze)
- Infect columnar epithelial cells and PML’s
  - Epithelial cells:
    - Diffuse inflammation of trachea and bronchi
    - Viral replication cell apoptosis
    - PML’s: Diminished chemotaxis, phagocytosis
- Viral shedding
  - Infect adjacent cells
  - Spread to other hosts
- Illness severity α quantity viral shedding

Influenza: Host Response

- Systemic Antibodies (IgM, IgG)
  - To HA and NA receptors M and NP proteins
  - Protects against re-infection with homologue/similar strain
- Mucosal Antibodies (IgA, IgG)
  - Protects against re-infection with homologue/similar strain
  - More important than systemic antibodies?
- Cellular response (cytotoxic T-cells)
  - Primary means of clearing infection

Influenza: Infection

- Influenza B milder than Influenza A?
- Systemic effects (Rhinitis, run - 8 days)
  - Fever, chills, HA, myalgias, malaise, anorexia, coryza
  - Predominance of systemic effects distinguish Influenza from other viral RTIs
- Pulmonary Involvement (~10%)
  - Tracheobronchitis (several days into infection)
  - Pneumonia
    - Primary viral
    - Secondary bacterial
      - Initial improvement/recrudescence of Fever, cough
      - Strep pneumonia, H. Influenzae, Staf. Aureus
  - Croup
  - Exacerbation COPD