PNEUMONIA
Therapeutics/PHMPR-732
John A. Bosso, Pharm.D.

Pneumonia: Epidemiology

- Most common infectious cause of death in USA
- ~ 4 million cases per year
- Occurs throughout the year
  - Prevalence from various etiologies varies from season to season
- Affects all age groups
  - Most severe in infants, elderly, chronically ill

Host Defenses of the Respiratory Tract

- Anatomical
  - Gag reflex
  - Cough reflex
  - Aerodynamic turbulence/filtration
  - Humidification
  - Mucus blanket
  - Ciliary movement
  - Alveolar surfactant

- Immune Function
  - Alveolar macrophages
  - Chemotactic response of phagocytic cells
  - Secretory IgA
  - Secretory IgG
  - Complement

Pneumonia: Pathogenesis

- Microorganisms gain access to the lungs
  - Aspiration of oropharyngeal contents
  - Inhalation
  - Blood-borne

- Factors promoting aspiration
  - Altered sensorium, neuromuscular disease, viral pulmonary infections, alcohol, narcotics

- Organisms normally cleared with intact immune system/defenses
Pneumonia: Pathogenesis

Impairment of host defense → Colonization of upper respiratory tract ↓ Aspiration of oropharyngeal secretions → Pulmonary infection

Pneumonia: Etiology

- Varies with age group and comorbidities
- Bacterial
  - Community-, Nursing Home-, vs Hospital-acquired
- Viral
  - Account for most pneumonias in pediatric age group
- N.B.: causative pathogen identified in only 40-60% of cases


Pathogens Associated with CAP

- **S. pneumoniae** is the primary bacterial cause of respiratory infections
- Atypical Pathogens: 23%
  - 16%
  - 40%
  - 10%
  - 7%
  - 20%
  - 1%

- □ **S. pneumoniae**
- □ **M. catarrhalis**
- □ **H. influenzae**
- □ Legionella spp.
- □ **M. pneumoniae**
- □ **C. pneumoniae**
- □ Others

Etiology: “Typical” Pathogens

- **S. pneumoniae**: accounts for as many as 60-70% of all cases of CAP in which a pathogen is identified
  - Particularly common in elderly, those with chronic comorbid conditions, immunocompromise
- **S. aureus**: seen in either CAP or HAP
- **Group B streptococci**
Etiology: “Typical” Pathogens

- *H. influenzae*: esp. with chronic cardio-pulmonary diseases
- *M. catarrhalis*: esp. with immuno-compromise and hospitalization
- Gram-negative bacilli
  - *K. pneumoniae*
  - *E. coli*
  - *Proteus* spp
  - *Enterobacter* spp

Etiology: “Atypical” Pathogens

- *Mycoplasma pneumoniae*:
  - accounts for ~20% of all CAP
  - Esp. in outpatients with milder infections
  - Peak incidence in adolescents & young adults
- *Chlamydia pneumoniae*:
  - ~5-15% of all CAP
- *Legionella pneumophila*
  - ≤ 15% of all CAP

Etiology: Anaerobic Pathogens

- Most likely seen in those predisposed to aspiration or with bronchogenic carcinoma
- Gram-positive anaerobes
  - *Peptostreptococcus* spp. & *Peptococcus* spp.
- Gram-negative anaerobes
  - *Bacteroides* spp. & *Fusobacterium*

Etiology: Viruses

- Account for most cases in children and many cases in adults
  - Influenza and adenovirus especially common in adults
  - RSV, parainfluenza, and adenovirus predominate in infants and young children
Patient Characteristics Related to Specific Pathogens

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td><em>S. pneumoniae</em>, anaerobes, gram-negative bacilli</td>
</tr>
<tr>
<td>COPD/smoker</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>M. catarrhalis</em>, Legionella spp.</td>
</tr>
<tr>
<td>Nursing home residency</td>
<td><em>S. pneumoniae</em>, gram-negative bacilli, <em>H. influenzae</em>, <em>S. aureus</em>, anaerobes, <em>C. pneumoniae</em></td>
</tr>
<tr>
<td>HIV infection</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>M. tuberculosis</em>, <em>P. carinii</em></td>
</tr>
<tr>
<td>Structural lung disease</td>
<td><em>P. aeruginosa</em>, <em>Pseudomonas spp.</em>, <em>S. aureus</em></td>
</tr>
</tbody>
</table>

Adapted from Bartlett et al, 1998.

Signs & Symptoms of Pneumonia

- Generally similar regardless of etiology
- Onset is abrupt or sometimes subacute
- Fever, chills, dyspnea, productive cough most common
- Sputum production (sometimes hemoptysis)
- Tachypnea, tachycardia, retractions, grunting respirations, decreased or abnormal breath sounds

Signs & Symptoms of “Atypical” Pneumonia

- Begins with nonspecific constitutional symptoms which increase over 2-4 days
- Non-productive cough is prominent
- Non-pulmonary symptoms
  - Nausea, vomiting, diarrhea, myalgias

Diagnosis of Pneumonia

- Physical exam and history
- Chest x-ray
- Gram’s stain of sputum
- Other laboratory tests
  - Blood cultures
  - CBC with WBC differential
  - Blood gases
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PHMPR-732
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Use of a Sputum Gram’s Stain

- Variable specificity and sensitivity
- May allow pathogen-directed therapy
- Validates adequacy of specimen for culture
- Adequate specimens difficult to obtain

Other Diagnostic Testing for Pneumonia

**Outpatients**
- Assess illness severity
- Sputum Gram’s stain?
- Consider sputum culture

**Inpatients**
- Sputum Gram’s stain/culture?
- CBC with differential
- Serum chemistries
- Renal and liver function
- Blood gases or oximetry
- Blood cultures

Adapted from Bartlett et al, 1998.

Diagnosis: Chest Radiograph

Diagnosis: Gram’s Stain of Sputum
Community-Acquired Pneumonia (CAP) Epidemiology

- Sixth leading cause of death
- Leading cause of death due to infectious disease
- More than 3 million cases of CAP per year
- 500-600,000 hospitalizations per year
- 45-90,000 deaths per year
- Cost: $21 billion (2000)

Factors Predisposing to CAP & Increased Risk of Morbidity & Mortality

- Advanced age
- Chronic pulmonary disease
- Neurologic disorders
- Congestive heart failure
- Chronic liver disease
- Chronic renal disease
- Neoplastic diseases
- Diabetes mellitus
- Immunosuppression
- Neutropenia
- Cigarette smoking
- Alcoholism

Bacterial Etiology of CAP: In General

<table>
<thead>
<tr>
<th>Organism</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>15–60</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>3–10</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>1–2</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3–5</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>3–10</td>
</tr>
<tr>
<td>&quot;Atypical agents&quot;</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>1–30</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>5–30</td>
</tr>
<tr>
<td>Legionella</td>
<td>2–8</td>
</tr>
<tr>
<td>Viruses</td>
<td>2–15</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>6–10</td>
</tr>
<tr>
<td>Other considerations</td>
<td></td>
</tr>
<tr>
<td>(TB, PCP, Q Fever, Fungi...)</td>
<td></td>
</tr>
<tr>
<td>No diagnosis</td>
<td>30–60</td>
</tr>
</tbody>
</table>

Bacterial Etiology of CAP: by Age & Co-morbidity

- No Comorbidity
  - <60 Years Old: S. pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae
  - >60 Years Old: S. pneumoniae, H. influenzae, K. pneumoniae, S. aureus

- Comorbidity and/or
  - <60 Years Old: Others: Legionella pneumophila, Streptococcus aureus, Klebsiella pneumoniae (and other gram-negative bacilli), Moraxella catarrhalis
  - >60 Years Old: Others: S. aureus, L. pneumophila

References:
Ohio Pneumonia Study

Age-specific rates of hospital admission for community-acquired pneumonia due to S. pneumoniae, Legionella, M. pneumoniae or C. pneumoniae. Rates for infection with each organism are calculated based on criteria for definite diagnosis. Rates of infection with Legionella, M. pneumoniae, and C. pneumoniae are adjusted for incomplete testing.


Bacterial Etiology of CAP: by Patient Type/Location

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of Cases</th>
<th>Mortality Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>4432</td>
<td>12.3%</td>
</tr>
<tr>
<td>Legionella spp.</td>
<td>272</td>
<td>14.7%</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>507</td>
<td>1.4%</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>41</td>
<td>9.8%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>833</td>
<td>7.4%</td>
</tr>
<tr>
<td>Other</td>
<td>781</td>
<td>0–61.1%*</td>
</tr>
<tr>
<td>Total</td>
<td>6866</td>
<td></td>
</tr>
</tbody>
</table>

* Mortality rate depends on pathogen. Mortality for P. aeruginosa was 41.1%, but that organism was isolated in only 16 cases; mortality for C. psittaci was 0, and that organism was isolated in 32 cases.

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PHMPR-732
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Prognostic Factors Associated With Mortality in Patients With CAP

- Age and male gender
- Alcoholism
- Diabetes mellitus
- Renal failure
- Neurologic and neoplastic disease
- Bacteremia
- Hypotension
- Hypothermia
- Leukopenia \( \leq 10 \times 10^9/L \)
- Multilobar pulmonary infiltrate
- Tachypnea


CAP Management Issues

- Diagnosis of community-acquired pneumonia
  (Need chest x-ray?). Other diagnostic testing.
- Site of care: inpatient vs outpatient
- Therapy: empiric vs pathogen-directed
  - Causative pathogen frequently not found
  - Treatment predominantly empiric
  - Pneumococcal and atypical coverage important
  - Increasing antibiotic resistance

CAP Management Issues (continued)

- Importance of initial therapy (timing & selection)
- Switch therapy
- Evaluation of nonresponding patient
- Quality indicators

**Pneumonia: Hospitalization or Outpatient Care?**

- Degree of hypoxemia
- Underlying medical conditions
- Ability to take oral medications
- Reliability of patient adherence
- Availability of home care
- Availability of outpatient follow-up


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**Considerations for Admission to the ICU**

- Respiratory distress/high work of breathing
- PaO$_2$/FiO$_2$ ratio <250 mmHg
- Need for mechanical ventilation
- Shock
- Need for vasopressors
- Urine output <20 mL/h or acute renal failure


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**Site of Care: IDSA (2000)**

- Significant impact on
  - Extent of laboratory evaluation
  - Antimicrobial therapy
  - Cost
- Prediction rule by Fine et al.$^1$ endorsed (CTS, IDSA)
  - Based on derivation and validation studies
  - Two-step process based on mortality risks
  - Validated by controlled studies$^2,3$


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**Pneumonia Severity of Illness Scoring System (PSI) Prediction Rule**

(also referred to as Fine or PORT rule)

Patients with Community-Acquired Pneumonia

1. Over age 50
2. History of cancer, CHF, CVA, renal or liver disease

Altered mental status: pulse ≥ 125;
respiratory rate ≥ 30; systolic BP < 90 mm Hg;
temperature < 30°C or ≥ 40°C

No Assign patient to Risk Class I

Step 2 Prediction Rule

**Demographic factors**
- Age: Male Age in years
- Female Age (years) –10
- Nursing home resident +10

**Comorbid medical conditions**
- Neoplastic disease (active < 1 year) +30
- Liver disease +20
- Congestive heart failure +10
- Cerebrovascular disease +10
- Renal disease +10

Step 2 (continued)

**Physical-examination findings**
- Altered mental status +20
- Respiration rate ≥ 30/minute +20
- Systolic blood pressure < 90 mm Hg +20
- 35°C < temperature ≥ 40°C +15
- Pulse ≥ 125/minute +10

Step 2 (continued)

**Laboratory and radiographic findings**
- Arterial pH < 7.35 +30
- BUN ≥ 30, sodium < 130 mmol/L +20
- Glucose ≥ 250 +10
- Hematocrit < 30% +10
- Partial pressure of arterial oxygen < 60 +10
- Pleural effusion +10

Risk Class, PSI Score, Mortality and Site for Care

| Risk Class | PSI points | % Mortality | Recommend-
ed care site |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Low</td>
<td>-</td>
<td>0.1</td>
<td>outpatient</td>
</tr>
<tr>
<td>II. Low</td>
<td>≤ 70</td>
<td>0.6</td>
<td>outpatient</td>
</tr>
<tr>
<td>III. Low</td>
<td>71 - 90</td>
<td>2.8</td>
<td>outpatient or brief inpatient</td>
</tr>
<tr>
<td>IV. Moderate</td>
<td>91 - 130</td>
<td>8.2</td>
<td>inpatient</td>
</tr>
<tr>
<td>V. High</td>
<td>&gt; 130</td>
<td>27.0</td>
<td>inpatient</td>
</tr>
</tbody>
</table>

Limitations of the Prediction Rule

- Overemphasis on age
- Does not account for continuing patient evaluation and improvement
- Not prospectively studied or compared with physician judgment
- Thresholds but not continuous variables are used for abnormal findings (e.g., respiratory rate ≥30/min)

Pneumonia Outcome Based on Initial Antibiotics

- Retrospective review of 13,000 elderly hospitalized Medicare patients with CAP
- Adjusted for baseline differences in illness severity and processes of care by Cox proportional hazards models
- Comparison to third-generation nonpseudomonal cephalosporin alone as reference


Rules and Policies

Well, they are really more like... guidelines.

But, what about the pirates’ code?

Treatment of Community-acquired Pneumonia

Importance of Initial Therapy
Overall Outcomes
(Hazards ratios)

- Lowest 30-day mortality when analyzed by initial antibiotic regimen (8 hours)
  - Third-generation cephalosporin alone (ref. gp.; 1.0)
  - Second-generation cephalosporin + macrolide (0.71)
  - Non-Pseudomonas third-generation cephalosporin + macrolide (0.74)
  - Fluoroquinolone alone (0.64)

- Highest mortality with
  - β-Lactam/β-lactamase inhibitor + macrolide (1.77)
  - Aminoglycoside + any other (1.21)


Treatment of Community-acquired Pneumonia
Guidelines

Community-Acquired Pneumonia: Guidelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidelines</th>
</tr>
</thead>
</table>
| 1993 | British Thoracic Society (BTS)  
Canadian Thoracic Society (CTS)  
American Thoracic Society (ATS) |
| 1998 | Infectious Diseases Society of America (IDSA)  
European Respiratory Society (ERS) |
| 2000 | IDSA, CTS  
Drug Resistant Streptococcus pneumoniae Therapy Working Group (DRSPTWG)  
Japanese Respiratory Society (JRS) |
| 2001 | ATS*  
IDSA AT* |
| 2003 | IDSA* |
| 2007 | IDSA/ATS* |

*Infections, such as those caused by methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and Pseudomonas aeruginosa.  
†Leflunomide, etanercept, golimumab, or another tumor necrosis factor blocker with enhanced activity vs. S. pneumoniae.  
‡Amoxicillin or amoxicillin/clavulanic acid.  
§Amoxicillin or amoxicillin/clavulanic acid.  
*Azithromycin or clarithromycin.

2003 IDSA Treatment Guidelines for Community-Acquired Pneumonia: Outpatient

- Previously healthy
  - No recent abx tx: macrolide or doxycycline
  - Recent abx tx: FQ† or macrolide§ + amox or amox/clav

- Comorbidities (COPD, diabetes, CHF etc)
  - No recent abx tx: macrolide§ or FQ†
  - Recent abx tx: FQ† or macrolide§ + β-lactam

- Suspected aspiration with infection
  - Amox/clav or clindamycin

- Influenza with bacterial superinfection
  - β-lactam or FQ†
2007 IDSA/ATS Treatment Guidelines for Community-Acquired Pneumonia: Outpatient

- Previously healthy
  - And, no risk factors for DRSP infection
  - macrolide or doxycycline
- Comorbidities (COPD, diabetes, CHF etc)
  - FQ† or β-lactam (amox/clav) plus a macrolide
- Regions with >25% of infections with high-level macrolide resistance (MIC≥15 µg/ml)
  - FQ‡, β-lactam

*Risk for Drug-Resistant S. pneumoniae (DRSP)
- Recent antimicrobial use
- Recent hospitalization
- Association with daycare
- HIV
- Age, immunosuppression

Critical Pathways or Guidelines for Treatment of CAP: Do they work?

**Critical Pathways for CAP**

**PURPOSE**
Provide standardization of treatment and setting for care based upon risk factors by:

*Using current literature and guidelines*

*Identifying best processes*

*Providing a mechanism for continuous improvement in these processes*
Critical Pathways
How well do they work?

- Study of 1743 patients at 19 hospitals in Canada (CAPITAL study)
- Objective to determine if use of critical pathway improves efficiency of tx without compromising well-being of patients
- Hospitals were randomly assigned tx regimen
  - Critical pathway or conventional treatment
- Outcome measures: QOL at 6 weeks, resource utilization (# bed days per patient)


Critical Pathways
How well do they work?

- Critical pathway utilized:
  - Diagnosis of pneumonia in ER
  - Severity score assigned
  - Patients treated as OP or hospitalized
    - OP tx consisted of 10 days oral quinolone
    - IP tx started with IV quinolone with specific criteria for switch to oral tx and discharge with oral therapy


CAPITAL Study Design

19 Canadian Hospitals (1743 patients)

Randomization
(Stratified by teaching or community hospital)

Critical Pathway
Conventional Management


CAPITAL Study Conclusions

- Use of the Critical Pathway resulted in
  - Significantly reduced hospital resource use (4.4 vs 6.1 BDPM*, P=0.01)
  - No adverse effect on patient well-being or other clinical parameters including
    - Mortality, ICU admissions, re-admissions, community-acquired pneumonia complications, or health-related quality of life
  - Reduced admission rates
    - Proportion of low-risk patients admitted, 31% vs 49% (P=0.01)

*Number of bed days per patient managed.
CAPITAL Study Conclusions

continued

• Use of the Critical Pathway resulted in
  – Reduced number of antibiotic classes used
    • Proportion of patients treated with a single antibiotic, 27% vs 64%, (P=0.01)
  – Reduced number of days of IV therapy
    • 4.6 days vs 6.3 days (P=0.01)
  – Reduced overall costs
    • Potential savings of $1,700 per patient treated

Switching from Intravenous to Oral Therapy in the Treatment of CAP


Why Switch to Oral Therapy?

• Increasing pressure to shorten duration of hospitalization
• Switch to oral therapy after short course of parenteral therapy facilitates discharge
• Advantages of oral therapy
  – lower acquisition cost
  – convenience
  – minimal expertise and time for administration
  – avoidance of infusion-related complications (e.g., phlebitis)
  – few ancillary materials

IV/PO Switch Therapy

– Recommended when patients are stable
  • Ramirez criteria
    – Improved cough, decreased shortness of breath
    – White blood cell count normalizing
    – Decreased temperature
    – Able to take PO
  • IDSA criteria
    – Stable/improving clinically
    – Hemodynamically stable
    – Able to ingest orally
– Use of highly bioavailable agents recommended
**750-mg, Short-Course Levofloxacin for CAP**

- Multicenter, randomized, double-blind, noninferiority study
- Comparison of 500-mg levofloxacin QD x 10 days vs 750-mg levofloxacin QD x 5 days
- Patients stratified according to Pneumonia Severity Index (PSI)
  - Stratum I: PSI >70 but ≤130: Patients treated as inpatients for at least 24 hours
  - Stratum II: PSI ≥70: Patients treated as inpatients or outpatients

**Non-pharmacologic Treatment**

- Hydration
- Antipyresis
- Supplemental O₂ (humidified)
- Bronchodilators
- Pulmonary Physiotherapy

**Treatment of CAP**

- Time to initial response & duration of tx:
  - Some improvement is expected within 48-72 hr
    - Delayed resolution with increasing age multiple underlying illnesses, & increasing severity of infection
  - Usual duration of tx: 7 - 10 days
    - Longer (14 days) with organisms causing necrosis (e.g., *S. aureus, K. pneumoniae*) or atypical pathogens
    - *L. pneumophila*: 21 days
Therapeutic Monitoring

- Resolution of signs and symptoms

Hospitalized patients:
- Vital signs
- CBC (WBC)
- O₂ saturation
- Chest x-ray
- Arterial Blood Gases

Management of Failure

- Consider cause
  - Resistant pathogen (typical or unusual organism)
  - Complication (metastatic infection, empyema, obstruction)
  - Superinfection
  - Noninfectious cause

- Evaluation
  - CT scan
  - Bronchoscopy
  - Biopsy

When to Change to Oral Antibiotics

- Patient started on IV antibiotics
- Patient demonstrating clinical improvement
- Patient able to take oral medications
- Taking other po medications
- Functioning GI

CAP: Treatment Failures

- 444 patients admitted for CAP (Spain)
- 49 (11%) failed to respond within 72 hours
  - 30 had nonresponding pneumonia
  - 19 had progressive pneumonia

- Causes of failure:
  - 34-Infections
    - Pathogens: S. pneumoniae (6), GNB (5), Legionella (1); Resistance (6)
    - Empyema:6; Aspiration:7
  - 9-Noninfectious
    - Malignancy:3; Interstitial Lung Disease (BOOP):3; Heart Disease:2; Foreign Body:1
  - 8-Nondiagnostic

BOOP (bronchiolitis obliterans organizing pneumonia)
Processes of Care and Outcome

<table>
<thead>
<tr>
<th>Process</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient vs Inpatient</td>
<td>Increased resolution(^1)</td>
</tr>
<tr>
<td>Early antimicrobials (&lt;8h)</td>
<td>Decreased 30d mortality(^2)</td>
</tr>
<tr>
<td>Blood cultures within 24h</td>
<td>Decreased 30d mortality(^2)</td>
</tr>
<tr>
<td>(O_2) assessment</td>
<td>Increased 30d mortality(^3)</td>
</tr>
<tr>
<td>Appropriate antimicrobials</td>
<td>Decreased 30d mortality(^3,4)</td>
</tr>
<tr>
<td>Early IV to PO switch</td>
<td>Decreased LOS/Cost(^5)</td>
</tr>
<tr>
<td>Critical pathway</td>
<td>Decreased LOS/Cost(^6)</td>
</tr>
</tbody>
</table>

\(^3\) Gordon et al. Chest. 1996

Influenza

- Influenza virus subdivided into 3 types:
  - A: causes severe & widespread epidemics & pandemics (most prevalent)
    - Subtypes classified based on antigenic differences in 2 surface glycoproteins (hemagglutinin; H1-15 and neuraminidase; N1-9)
  - B: causes regional and widespread epidemics
  - C: causes sporadic outbreaks of mild disease
- Mortality in USA estimated at 36,000 per year

\(\text{MMWR. 2005;54(RR-8):1-40. See also: http://www.cdc.gov/flu}\)

Influenza - Epidemiology

- Worldwide, ~20% of children and 5% of adults develop symptomatic flu yearly
- Course of illness is affected by the patient’s:
  - Age
  - Degree of pre-existing immunity
  - Properties of the virus
  - Smoking
  - Co-morbidities

Influenza A Virus

- Hemagglutinin (H)–16 subtypes (attachment, penetration)
- Neuraminidase (NA)–9 subtypes (release)
- 8 viral genes (assembly, replication)
- M2 protein (penetration)
Antigenic Drift & Shift

- Virus has ability to genetically change its antigenic structure
  - Which is why we don’t develop immunity
- Antigenic composition includes 16 hemagglutinin and 9 neuraminidase subtypes
- Accumulation of mutations to surface proteins: ANTIGENIC DRIFT
- Substantial change in surface antigens: ANTIGENIC SHIFT
  - Human populations has no previous exposure → Pandemic

Influenzal Pneumonia

Primary Influenza Viral Pneumonia vs. Secondary Bacterial Pneumonia

Primary Influenza Viral Pneumonia

- Occurs predominantly in persons with cardiovascular disease (esp. rheumatic heart disease with mitral stenosis) and pulmonary disorders
- Clinically, typical flu symptoms followed quickly with sx of pneumonia progressing to ARDS
- Mortality is high

Secondary Bacterial Pneumonia

- Occurs especially in elderly and/or those with chronic pulmonary, cardiac and metabolic disease
- Clinically, typical course of influenza followed by improvement (4-14 d) then return of symptoms of pneumonia
- Predominant organisms:
  - *S. pneumoniae, H. influenzae*
Antiviral Therapies for Influenza

Neuraminidase (NA)
- NA Inhibitors
  - Oseltamivir
  - Zanamivir
- Matrix protein (M2)
  - M2 Inhibitors
    - Amantadine
    - Rimantadine

Matrix protein (M2)

Approved Antiviral Agents for Influenza Treatment and Prophylaxis

<table>
<thead>
<tr>
<th>Protein target</th>
<th>Amantadine*</th>
<th>Rimantadine*</th>
<th>Zanamivir</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>A only</td>
<td>A only</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Therapy</td>
<td>Adults and children of &lt; 1 year</td>
<td>Adults only</td>
<td>Adults and children of &lt; 5 years</td>
<td>Adults and children of &lt; 1 year</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Yes</td>
<td>Yes</td>
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<td>Adults only</td>
<td>Adults and children of &lt; 5 years</td>
<td>Adults and children of &lt; 1 year</td>
</tr>
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</table>

Approved Antiviral Agents for Influenza Treatment and Prophylaxis

<table>
<thead>
<tr>
<th>Protein target</th>
<th>Amantadine*</th>
<th>Rimantadine*</th>
<th>Zanamivir</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>A only</td>
<td>A only</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Therapy</td>
<td>Adults and children of &lt; 1 year</td>
<td>Adults only</td>
<td>Adults and children of &lt; 5 years</td>
<td>Adults and children of &lt; 1 year</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapy</td>
<td>Adults and children of &lt; 1 year</td>
<td>Adults only</td>
<td>Adults and children of &lt; 5 years</td>
<td>Adults and children of &lt; 1 year</td>
</tr>
</tbody>
</table>

Prevention of CAP

- Smoking cessation
- Preventative vaccines
  - S. pneumoniae
    - Vaccines
  - Influenza
    - Vaccines
    - Antiviral drugs

Reference:

Kyaw MA. NEJM 2006;354:1455-63
Trivalent Inactivated and Live Attenuated Influenza Virus Vaccines

<table>
<thead>
<tr>
<th>Category</th>
<th>Trivalent Inactivated (TIV)</th>
<th>Live Attenuated Influenza Virus (LAIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration &amp; immune response</td>
<td>IM → Serum antibodies</td>
<td>Intranasal → Mucosal immunity</td>
</tr>
<tr>
<td>Formulation</td>
<td>Inactivated</td>
<td>Live attenuated</td>
</tr>
<tr>
<td>Safety (side effects)</td>
<td>Sore arm</td>
<td>Coryza</td>
</tr>
<tr>
<td>Growth medium</td>
<td>Chick embryos</td>
<td>Chick cells</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigerated</td>
<td>Frozen</td>
</tr>
<tr>
<td>Indication</td>
<td>≥6 m (healthy &amp; HR)</td>
<td>5–49 y (healthy)</td>
</tr>
</tbody>
</table>

Vaccination Recommendations 2007-08
Advisory Committee on Immunization Practices (ACIP)

- Persons at high risk for influenza-related complications and severe disease, including
- Those aged 18-49 years with high risk (of complications) conditions
- Children aged 6–59 months
- Pregnant women
- Persons aged ≥50 years
- Persons who live with or care for persons at high risk, including
- Health care workers
- Anyone who doesn’t want to get the flu or transmit it to others

Vaccine Coverage
(Adults ≥ 65 years)
Vaccine Coverage in Adults
2005-06

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<tr>
<td>West</td>
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<td>78.0%</td>
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<td>82.0%</td>
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</tbody>
</table>

Vaccination of Hospitalized Patients

IDSA recommends that patients hospitalized for CAP that are candidates for influenza and pneumococcal vaccines receive vaccinations prior to discharge (C-III).


Nosocomial Pneumonia Epidemiology

- 300,000 cases/year
- 20-30,000 deaths/year
- Estimated $2 billion in excess costs related to hospitalization/year
Risk Factors for HAP

- Severe illness
- Advanced age
- Prolonged hospitalization
- Coma
- Malnutrition
- Hypotension
- Metabolic acidosis

- Cigarette smoking
- Alcoholism
- Major organ dysfunction
- Nasogastric tubes
- Endotracheal tubes
- Enteral feeding
- Certain drugs

Drugs Increasing Risk of HAP

- Sedatives
- Steroids
- Immunosuppressive agents
- Antacids
- $\mathrm{H}_2$-receptor antagonists
- Prior antibiotic exposure
  - Infection with resistant organisms

Mean Mortality Rates in Patients With CAP, HCAP, HAP, and VAP

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>HCAP</th>
<th>HAP</th>
<th>VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality Rate (%) patients</td>
<td>10.0</td>
<td>19.8</td>
<td>18.8</td>
<td>29.3</td>
</tr>
</tbody>
</table>


Etiology: early onset HAP

- $S.\ pneumoniae$
- $H.\ influenzae$
- $S.\ aureus$
- Gram-negative bacilli
  - $E.\ coli$
  - Proteus spp
  - Klebsiella spp
  - Serratia marcescens
  - Enterobacter spp
  - $P.\ aeruginosa$
Etiology: late onset HAP

- Similar organisms but more likely to include:
  - \( P. \) aeruginosa
  - Acinetobacter \( \text{spp} \)
  - Stenotrophomonas maltophilia
  - MRSA

Antimicrobial Resistance in Nosocomial Infections

Gram-Negative Pathogens


Gram-Positive Pathogens


Clinical Presentation of HAP

- Similar symptoms to CAP
- Signs and symptoms may be masked by comorbid illnesses
Diagnosis of HAP (based on 5 criteria)

1. Unexplained new or worsening fever
2. New or unexplained increased WBC
3. Change in quantity or quality of sputum
4. Worsening respiratory function
   - RR, oximetry, PFTs
5. New or worsening infiltrates on CXR

Additional Diagnostic Tests for HAP

- Chest x-rays
- Gram’s stain and culture of
  - Sputum (deep expectorated)
  - Endotracheal aspirate (mechanically ventilated patients)
- Blood cultures

Prognosis with Nosocomial Pneumonia

- Mortality rate: 38 - 52%
- Mortality rate in critically ill patients with severe complications: >70%
  - e.g., ARDS

Risk Factors for Increased Risk of Increased Mortality in HAP

- Bacteremia
- Dysfunction of other organs
- Severe underlying diseases
- Transfer from another ICU
- Late onset pneumonia with resistant pathogens
- Inappropriate initial antibiotics
Impact on Inadequate Initial Therapy on Outcome in VAP

- 132 patients with VAP
  - Mortality with adequate initial tx: 38%
  - Mortality with inadequate initial tx: 91%
  - Mortality with no tx: 60%
- Immunocompromise and inadequate initial tx independent risk factors for mortality


Impact on Inadequate Initial Therapy on Outcome in VAP

Treatment of Nosocomial Pneumonia

- Time to initial response & duration of tx:
  - Some improvement is expected within 48-72 hr
  - Delayed resolution with increasing age multiple underlying illnesses, & increasing severity of infection
  - Usual duration of tx: 14 days
- Longer with severe infections with difficult to treat organisms (e.g., P. aeruginosa) or complicated by abscesses

Empiric Antibiotic Therapy for HAP

HAP, VAP or HCAP Suspected

Late onset (≥ 5 d) or risk factors for Multidrug Resistant Pathogens

NO

Limited Spectrum Antibiotic Therapy

YES

Broad Spectrum Antibiotic Therapy for MDR Pathogens


“Limited Spectrum” Empiric Therapy

- Ceftriaxone or
- Levofloxacin, moxifloxacin, or ciprofloxacin or
- Ampicillin/sulbactam or
- Ertapenem

“Broad Spectrum” Empiric Therapy

- Cefepime or ceftazidime or
- Imipenem or meropenem or
- Piperacillin/tazobactam
  **PLUS**
- Ciprofloxacin or levofloxacin or
- Aminoglycoside

  *Plus, if MRSA a consideration*

- Linezolid or vancomycin


Other Pharmacotherapeutic Issues and Considerations

Duration of Antibiotic Treatment

- Prospective, randomized, multicenter trial
- Comparing the outcome of therapy with a short (8 d) or a long (15 d) course of antibiotic in patients
  - with microbiologically proven VAP (bronchoscopic BAL PSB or CombiCath)
  - receiving appropriate initial empirical treatment
  - double blind until day 8
- Major end-points (day 28):
  - mortality
  - recurrence of pulmonary infection
  - antibiotic use

Chastre J, Wolff M, Fagon JY; ATS 2003

Duration of Antibiotic Treatment

- 401 patients: 197 “short” vs 201 “long”
- Mortality: 18.8 vs 17.2% (NS)
- Pulmonary infection recurrence: 28.9 vs 26.0% (NS)
- Antibiotic use: number of antibiotic-free days, 13.1±7.4 vs 8.7±5.2 days (p<0.0001)
- No differences with regard to the number of ventilator-free days, the number of organ failure-free days, the duration of ICU stay, and mortality at day 60
- Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence: 42.1 vs 62.3%, p=0.04)
Rationale for Combination Therapy

- Broad spectrum of activity
- Synergistic activity
- Delay or prevent emergence of resistance
- N.B. not proven more effective than mono-therapy but strongly recommended with:
  - Nosocomial pneumonia with mechanical ventilation of > 7 days duration, presence of empyema or bacteremia, use of broad-spectrum antibiotics within previous 2 weeks, and/or profound neutropenia

Add Vancomycin?

- Institutional rate of MRSA?
  - yes, if rate is >20%
- Other agents in the empiric regimen
  - Many other β-lactams are adequate for MSSA
    - Pip/tazo, cefepime, imipenem, meropenem

Non-pharmacologic Treatment

- Mechanical ventilation
- Supplemental O₂
- Hydration
- Nutritional support
- Antipyretics
- Bronchodilators (for bronchospasm)
- Ipratropium (to dry respiratory secretions)
- Chest physiotherapy

Dealing with Therapeutic Failure

- r/o nosocomial sinusitis
- Expand antibacterial spectrum
  - Cover MRSA, anaerobes, other Gram-negatives
- Add antiviral agents?
- Add antifungal agents?
Therapeutic Monitoring

- Signs & symptoms of infection
- Vital signs
- Hemodynamic status
  - Mental status, urine output, etc
- CBC (WBC count and diff.)
- $O_2$ saturation, ABG’s
- Chest x-ray

Prevention of Nosocomial Pneumonia

- Infection control procedures
  - Handwashing
  - Isolation (patients with resistant organisms)
- Maintenance/restoration of good pulmonary mechanics
  - Ambulation, incentive spirometers, etc
- Avoidance of drugs increasing gastric pH
- ± selective digestive decontamination

Example Case-1

GC is a 62 year old white female who was well up until 24 hours prior to presentation. Past medical history is positive for type II diabetes mellitus and hypertension (well controlled with glyburide and enalapril, respectively). She presents to the outpatient department with complaints of fever and difficulty breathing. On physical exam, she is noted to be in moderate respiratory distress with a respiratory rate of 33 bpm, mild perioral cyanosis, and a temperature of 40.1°C. Chest auscultation reveals decreased breath sounds over the right lower lobe. Laboratory test results: WBC 19,000/mm$^3$ with a left shift, sputum contains many WBCs and Gram-positive cocci in chains, and oxygen saturation of 90% on room air. A presumptive diagnosis of community-acquired pneumonia is made.

1. What is the most likely bacterial etiology for this patient’s pneumonia?
2. Where should this patient’s treatment be initiated?

Example Case-1 (continued)

GC is a 62 year old white female who was well up until 24 hours prior to presentation. Past medical history is positive for type II diabetes mellitus and hypertension (well controlled with glyburide and enalapril, respectively). She presents to the outpatient department with complaints of fever and difficulty breathing. On physical exam, she is noted to be in moderate respiratory distress with a respiratory rate of 33 bpm, mild perioral cyanosis, and a temperature of 40.1°C. Chest auscultation reveals decreased breath sounds over the right lower lobe. Laboratory test results: WBC 19,000/mm$^3$ with a left shift, sputum contains many WBCs and Gram-positive cocci in chains, and oxygen saturation of 90% on room air. A presumptive diagnosis of community-acquired pneumonia is made.

3. What initial antibiotic therapy would you recommend?
4. What are the appropriate monitoring parameters in this case?
5. How would you determine whether this patient is a candidate for switch therapy?