Community-Acquired Pneumonia (CAP) - Outline

- Epidemiology
- Diagnosis
- Microbiology
- Risk stratification
- Treatment
- Prevention
Community-Acquired Pneumonia

- Talk will focus on adults

Epidemiology:
Acute Lower Respiratory Tract Infections

- In U.S., influenza and pneumonia 8th most common cause of death per the Centers for Disease Control and Prevention (moved up from 9th in 2010)
  - Most common cause of death from infectious disease
- Among those 85 and older, at least 1 in 20 hospitalized each year
Epidemiology:
Acute Lower Respiratory Tract Infections

- Inpatient mortality rate: may be influenced by coding
  - From 2003 – 2009, mortality rate for principal diagnosis pneumonia decreased from 5.8% to 4.2%
  - More patients coded with principal diagnosis sepsis or respiratory failure and secondary diagnosis pneumonia
    - Using all codes, little change in mortality rate
      
      Lindenauer et al, JAMA 2012;307:1405-13

- Outpatient mortality < 1%; about 80% of CAP treated in outpatient setting

Diagnosis

- Chest radiograph – needed in all cases?
  - Avoid over-treatment with antibiotics
  - Differentiate from other conditions
  - Specific etiology, e.g. tuberculosis
  - Co-existing conditions, such as lung mass or pleural effusion
  - Evaluate severity, e.g. multilobar

- Unfortunately, chest physical exam not sensitive or specific and significant variation between observers

Arch Intern Med 1999;159:1082-7
Microbiological Investigation

- **Sputum Gram stain and culture**
  - 30-40% patients cannot produce adequate sample
  - Most helpful if single organism in large numbers
  - Usually unnecessary in outpatients
  - Culture (if adequate specimen < 10 squamous cells/LPF; > 25 PMNs/LPF): antibiotic sensitivities
  - Limited utility after antibiotics for most common organisms

Microbiological Investigation - Inpatients

- **Blood cultures x 2 before antibiotics**
  - Blood cultures positive in 5 – 14% of hospitalized patients
  - Severe disease most important predictor
- **Consider evaluation for Legionella**
  - Urinary antigen test for *L. pneumophila* serogroup 1 (70%)
  - Culture with selective media
- **Pneumococcal urinary antigen test**
  - Simple, takes apx. 15 minutes
  - In adults, sensitivity 50-80%, specificity ~90% but specificity poor in children, possibly due to carriage
Microbiological Investigation - Inpatients

- Other studies as clinically indicated, e.g. influenza
- Multiplex PCR systems, e.g. BioFire
- Serology not typically used clinically but may be useful for public health
- Bronchoscopy perhaps for fulminant course, unresponsive to conventional therapy, or for specific pathogens (e.g. *Pneumocystis*)
Other diagnostics?

- Biomarkers - procalcitonin
  - Procalcitonin is produced in response to endotoxin and endogenous mediators released in the setting of bacterial infections
  - Rises in bacterial infections much more than, e.g., viral infections or inflammatory states
  - Rises and falls quickly
- Unfortunately, probably not sensitive / specific enough to rule out / rule in bacterial CAP in individual cases in most settings
  - May help limit duration of antibiotic exposure

BMC Medicine 2011;9:107

Etiology – historical data

- Clinical syndrome and CXR not reliably predictive
  - Streptococcus pneumoniae 20-60%
  - Haemophilus influenzae 3-10%
  - Mycoplasma pneumoniae up to 10%
  - Chlamydophila pneumoniae up to 10%
  - Legionella up to 10%
  - Enteric Gram negative rods up to 10%
  - Staphylococcus aureus up to 10%
  - Viruses up to 10%
  - No etiologic agent 20-70%
CAP Surveillance Study

- Adults hospitalized with CAP at 5 hospitals in Chicago and Nashville
- Extensive diagnostic testing done via culture, serology, antigen testing, and molecular diagnostics
- A pathogen was detected in only 38% of patients with specimens available
  - Viruses 62%
  - Bacteria 29%
  - Bacteria and virus 7%
  - Fungus or mycobacteria 2%

NEJM 2015;373:415-27

Typical vs. Atypical

**Typical**
- Visible on Gram stain, grows in routine culture
- Susceptible to beta lactams
- *S. pneumoniae, H. influenzae*

**Atypical**
- Not visible on Gram stain, special culture techniques
- Not treated with beta lactams
- *M. pneumoniae, C. pneumoniae, Legionella*
**S. pneumoniae**

- Risk factors

  - Extremes of age
  - Alcoholism
  - COPD and/or smoking
  - Nursing home residence
  - Influenza
  - Injection drug use
  - Airway obstruction
  - HIV infection

**Legionella**

- Think about with severe disease, high fever, hyponatremia, markedly elevated LDH, CNS abnormalities
- Fluoroquinolone or azithromycin drug of choice; usual rx 14-21 days
- Risk factors:
  - Older age
  - Smoking
  - Immune compromise, cell mediated
  - Travel
  - Renal disease
  - Liver disease
  - Diabetes
  - Malignancy
**Mycoplasma pneumoniae**

- Common cause respiratory infections in children/young adults
  - Pneumonia relatively uncommon
- Epidemics in close quarters
- May have sore throat, nausea, vomiting, hemolytic anemia, rash
- Treatment with doxycycline, macrolide, or fluoroquinolone
  - Rising rate of macrolide resistance – U.S. 8.2%; China 90%

*Pediatr Infect Dis J 2012;31:409-11*

**Risk Stratification**

- Outpatient vs. inpatient?
  - Cost
  - Patient satisfaction
  - Safety
Risk Stratification

- Outpatient vs. inpatient?
  - Pneumonia Patient Outcomes Research Team (PORT) study (Fine et al, NEJM 1997;336:243-250)
    - Prediction rule to identify low risk patients with CAP
    - Stratify into one of 5 classes
      - Class I: age ≤ 50, none of 5 co-morbid conditions, apx. normal VS, normal mental status
      - Class II-V: assigned via a point system

Risk Stratification

- Mortality < 1% for classes I, II
- Low risk patients hospitalized more than necessary
- Caveats:
  - Does not take into account social factors
Pneumonia Severity Index Calculator


Age and sex; resident of nursing home {yes/no}

Comorbid diseases {yes/no}: renal disease, liver disease, CHF, cerebrovascular disease, neoplasia

Physical exam {yes/no}: altered mental status, SBP < 90, temp < 35 or >=40, RR>=30, HR>=125

Labs/studies {yes/no}: pH<7.35, PO2<60 or Sat<90, Na<130, HCT<30, gluc>250, BUN>30, pleural eff

Patient #1

- 60 year-old man with diabetes presents with fever and dyspnea. Positive PORT items include HR=130, Na=129, glucose=300.

- Should this patient be hospitalized?

Please vote:
1. Yes
2. No
Pneumonia Severity Index Results

Class: IV
Score: 100

<table>
<thead>
<tr>
<th>Risk</th>
<th>Class</th>
<th>Score</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>I</td>
<td>&lt; 51</td>
<td>0.1%</td>
</tr>
<tr>
<td>Low</td>
<td>II</td>
<td>51 - 70</td>
<td>0.6%</td>
</tr>
<tr>
<td>Low</td>
<td>III</td>
<td>71 - 90</td>
<td>0.9%</td>
</tr>
<tr>
<td>Medium</td>
<td>IV</td>
<td>90 - 130</td>
<td>9.5%</td>
</tr>
<tr>
<td>High</td>
<td>V</td>
<td>&gt; 130</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

Hospitalization is recommended for class IV and V. Class III should be based on clinical judgment.

Patient #2

55 year-old woman with no other risk factors? Hospitalization? Please vote:

1. Yes
2. No

Class : II
Score : 45
Mortality : 0.1%
Patient #3

92 year-old man with no other risk factors?
Hospitalization? Please vote:

1. Yes
2. No

Class : IV
Score : 92
Mortality : 9.5%

Patient #4

20 year-old woman with SBP < 90 and a pleural effusion?

Hospitalization? Please vote:
1. Yes
2. No

Class : II
Score : 40
Mortality : 0.6%
Other Scoring Systems

- **CURB-65 (British Thoracic Society)**
  - Has only 5 variables, compared with 20 for Pneumonia Severity Index
- **Severe Community Acquired Pneumonia (SCAP)**
  - Has 8 variables
- **SMART-COP**
  - Used for predicting need for mechanical ventilation or vasopressors

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Clinical Infectious Diseases; March 1, 2007
Supplement 2
*Update in progress: projected spring 2018*
Is coverage of “atypical” organisms important?

- In Europe, amoxicillin commonly used as a single drug with data supporting a short course (3 days in responding patients)
  
  *el Moussaoui et al, BMJ 2006;332:1355 - 62*

- Some studies show no benefit of empirical atypical coverage on survival or clinical efficacy in hospitalized patients
  

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**Original Investigation**

**Association of Azithromycin With Mortality and Cardiovascular Events Among Older Patients Hospitalized With Pneumonia**

- V.A. retrospective, cohort study of patients 65 and older hospitalized with pneumonia 2002-2012
- 31,863 patients treated with azithromycin compared with 31,863 propensity matched patients with no exposure
- 90 day mortality significantly lower 17.4% vs. 22.3%, O.R. 0.73
- Myocardial infarct significantly higher 5.1% vs. 4.4%, O.R. 1.17

*JAMA 2014;311(21):2199-2208*
Cluster-randomized trial in 7 hospitals in the Netherlands with rotating strategies
Adults with CAP not requiring ICU
Beta-lactam alone (656 patients) vs. beta-lactam plus macrolide (739 patients) vs. fluoroquinolone alone (888 patients)
Primary outcome 90-day mortality: beta-lactam monotherapy non-inferior to other strategies
No difference in length of stay or complications

Outside the ICU...we love doxycycline
- Adult inpatients June 2005 – December 2010
- Compared those who received ceftriaxone + doxycycline to those who received ceftriaxone alone
- 2734 hospitalizations: 1668 no doxy, 1066 with doxy
- Outcome: CDI within 30 days of doxycycline receipt
- CDI incidence 8.11 / 10,000 patient days in those receiving ceftriaxone alone; 1.67 / 10,000 patient days in those who received ceftriaxone and doxycycline

_Doernberg et al, Clin Infect Dis 2012;55:615-20_
Empirical Treatment: IDSA/ATS Consensus Guidelines

Outpatient treatment
- Previously healthy, no antibiotics in 3 months
  - Macrolide (1st choice) or
  - Doxycycline
- Co-morbid conditions or antibiotics within 3 months (select a different class)
  - Respiratory fluoroquinolone: moxifloxacin, gemifloxacin, or levofloxacin (750 mg)
  - Beta-lactam (especially high dose amoxicillin) plus a macrolide (1st choice) or doxycycline

Empirical Treatment: IDSA/ATS Consensus Guidelines

Inpatient treatment, non-ICU
- Respiratory fluoroquinolone or
- Beta-lactam (cefotaxime, ceftriaxone, ampicillin; consider ertapenem) plus a macrolide (1st choice) or doxycycline
Empirical Treatment: 
IDSA/ATS Consensus Guidelines

Inpatient treatment, ICU

- Beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus
- Azithromycin or a respiratory fluoroquinolone

➢ For penicillin allergy: respiratory fluoroquinolone + aztreonam

Empirical Treatment: 
IDSA/ATS Consensus Guidelines

For suspected *Pseudomonas aeruginosa*:

- Antipneumococcal, antipseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg) Or
- The above beta-lactam plus an aminoglycoside and either azithromycin or a respiratory fluoroquinolone
  ➢ For penicillin allergy: substitute aztreonam for the beta-lactam

Suspect with structural lung disease (e.g. bronchiectasis), frequent steroid use, prior antibiotic therapy
Empirical Treatment: IDSA/ATS Consensus Guidelines

Inpatient therapy, concern for community methicillin-resistant *Staphylococcus aureus* (MRSA):

- Add vancomycin or linezolid to regimen you would select otherwise

*Consider for patients admitted to the ICU – obtain Gram strain of respiratory specimen (sputum or tracheal aspirate)*

What about steroids?

- Randomized, double blind trial in Switzerland
- 785 adult inpatients received 50 mg prednisone daily x 7 days or placebo
- Primary outcome clinical stability: 3.0 days prednisone vs. 4.4 days placebo, p<.0001
- Time to hospital discharge 6 days prednisone vs. 7 days placebo, p=.01
- No difference complications except slightly higher in-hospital hyperglycemia with prednisone
Questions re study

- 2911 patients assessed to randomize 802
- Why was length of stay so long?
  - 4% prednisone and 6% placebo admitted to ICU
  - Death from any cause 4% prednisone and 3% placebo

What about steroids?

- Multicenter, double-blind, RCT at 3 hospitals in Spain
- Adults with severe CAP (75% in ICU)
- Methylprednisolone 0.5 mg/kg q 12h x 5 days (n=61) vs. placebo (n=59)
  - Recruited 2004 – 2012
- Primary outcome: treatment failure (composite) 13% vs. 31%, P=.02
  - Mortality 10% vs. 15%, P=.37

JAMA 2015;313(7):677-86
What about steroids?

• Systematic review and meta-analysis of steroids for patients hospitalized with CAP
• Included 13 RCTs with 2005 patients total
  • Both studies on previous slides included
• Outcomes:
  • Possible 2.8% reduction in mortality
  • 5% reduction mechanical ventilation
  • 1 day decrease hospital stay
  • 3.5% increase in hyperglycemia requiring treatment
  
  Ann Intern Med 2015;163(7):519-28

What about steroids?

• At least 2 multicenter trials in progress with data expected 2018-2019
  • ESCAPE: patients with severe CAP, VA hospitals, methylprednisolone
    • Recruitment completed
  • CAPE_COD: patients with severe CAP, French hospitals, hydrocortisone
    • Recruitment in progress
  
  https://clinicaltrials.gov/
Length of Therapy

- 7 – 10 days has been standard for most patients but probably not necessary
  - Shorter course with azithromycin or high dose levofloxacin
  - Meta-analysis that patients with mild to moderate disease can be treated with 7 days or less

*Li et al. Am J Med. 2007;120(9):783-90*

Switch to Oral Therapy

- Reduces costs, shortens length of stay, may reduce complications
- As soon as improving clinically, able to take POs, GI tract functioning
  - Usually within 3 days; no need to observe in hospital
- Narrow spectrum agent if organism identified (usually *S. pneumoniae*)
- Empirical therapy: macrolide, doxycycline, antipneumococcal fluoroquinolone, or combination therapy
Prevention

There are steps patients and providers can take....

- Vaccination
  - Influenza vaccine
  - Pneumococcal vaccines

- Smoking cessation
  - Smoking, with or without COPD, is a significant risk factor
HAP and VAP...

But, what happened to healthcare-associated pneumonia (HCAP)?
The HCAP Gap

Clin Infect Dis 2009;49(12):1868-74

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

• The concept of HCAP has been removed – why?
  • Increasing evidence that most patients with HCAP are not at high risk for resistant pathogens
  • Other features besides exposure to the healthcare system may be important
  • May be covered by new CAP guidelines
Practical tips for HCAP

- Most patients with “HCAP” can be treated like CAP
- Consider expanded initial therapy if
  - Severely ill
  - History of resistant organism or other risk factors such as extensive antibiotic exposure
- Knowledge of local flora/resistance patterns is helpful
- If using expanded therapy, prioritize microbiologic diagnosis
  - De-escalate based on results

2016 guidelines: take home points for both HAP and VAP

- Perform microbiologic testing – preferred over empirical therapy
  - Obtain non-invasively – expectorated, induced sputum, endotracheal aspirate
  - BAL, mini-BAL, protected-brush specimens not recommended
- Not recommended for decision to initiate therapy
  - Procalcitonin
  - C-reactive protein
  - CPIS score
- Most patients should be treated for 7 days
2016 guidelines: initial treatment of HAP (based on very low quality evidence)

- Use local pathogen and antibiotic resistance data
- Cover MRSA in selected patient
  - Prior IV antibiotics within 90 days
  - > 20 of S. aureus isolates on unit are MRSA
  - High risk of mortality
- Cover *Pseudomonas aeruginosa*
  - Double coverage of *P. aeruginosa* with risk factors
    - Prior IV antibiotics within 90 days
    - High risk for mortality

2016 guidelines: initial treatment of HAP (based on very low quality evidence)

- Not at high risk of mortality and no risk factors increasing likelihood of MRSA (cover MSSA and *P. aeruginosa*)
  - One of the following:
    - Piperacillin-tazobactam 4.5 g IV q 6h
    - Cefepime 2 g IV q 8h
    - Levofoxacin 750 mg IV daily
    - Imipenem 500 mg IV q 6h
    - Meropenem 1 g IV q 8h
2016 guidelines: initial treatment of HAP (based on very low quality evidence)

- Not at high risk of mortality but increased risk of MRSA:
  - Piperacillin-tazobactam 4.5 g IV q 6h
  - Cefepime 2 g IV q 8h
  - Levofloxacin 750 mg IV daily
  - Imipenem 500 mg IV q 6h
  - Meropenem 1 g IV q 8h
  - Aztreonam 2 g IV q 8h
  PLUS
  - Vancomycin 15 mg/kg IV q 8h-12h (goal trough 15 – 20) OR
  - Linezolid 600 mg IV q 12h

2016 guidelines: initial treatment of HAP (based on very low quality evidence)

- High risk of mortality or IV antibiotics with 90 days:
  - Antipsuedomonal beta lactam: piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, imipenem, meropenem
    PLUS
  - A second antipseudomonal antibiotic: levofloxacin, ciprofloxacin, amikacin, gentamicin, tobramycin
    PLUS
  - Vancomycin or linezolid
2016 guidelines: initial treatment of VAP (based on very low quality evidence)

- Use local pathogen and antibiotic resistance data
- Do not treat ventilator-associated tracheobronchitis with antibiotics
- Cover *S. aureus*, *P. aeruginosa*, and other Gram-negative bacilli in all empirical regimens
  - Cover MRSA with vancomycin or linezolid when > 10 – 20% of *S. aureus* isolates in unit are MRSA
- Use two antipseudomonal antibiotics if
  - Prior IV antibiotic use within 90 days
  - Septic shock
  - ARDS preceding VAP
  - 5 or more days of hospitalization preceding VAP
  - > 10% of Gram negative isolates resistant to planned monotherapy
  - Susceptibility rates unknown

ZSFG HAP and VAP antibiotic guideline: initial therapy

- Mild HAP: ceftriaxone or ertapenem or levofloxacin
- Severe HAP (e.g. high O2 requirement, cavitary disease): vancomycin plus cefepime or piperacillin/tazobactam
- VAP, intubated ≤ 5 days without complications (e.g. multifocal or cavitary disease): ceftriaxone or ertapenem or levofloxacin
- VAP, intubated > 5 days or complicated: vancomycin plus cefepime or piperacillin/tazobactam