MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

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University of New Mexico Hospitals
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OBJECTIVES

• Pharmacists: By the end of this presentation you should be able to...
  • Describe common etiologies of community-acquired pneumonia
  • Recall the most important bacterial etiologies and those unique to New Mexico
  • Create antibacterial regimens specific to your patients
  • Understand the current paradigm regarding durations of therapy
• Pharmacy Techs: By the end of this presentation you should be able to...
  • Describe the common etiologies of community-acquired pneumonia
  • Identify patients for whom vaccinations should be offered
  • Understand the role duration of therapy plays in community-acquired pneumonia
  • Understand the importance of obtaining accurate patient allergy history and previous medications

COMMUNITY-ACQUIRED PNEUMONIA (CAP) GUIDELINES

ECOLOGY OF RESPIRATORY MICROBIOME

POSITIVE FEEDBACK LOOP OF ABRUPT PNEUMONIA

- Microbial Growth
- Nutrient Abundance
- Intra-alveolar Edema
- Endo/epithelial Injury
- Inflammation


REVIEW

- Pathogenesis:
  - Conventional: Pathogens are aspirated or inhaled as small, aerosolized droplets
  - Emerging: Ecology, homeostasis, and dysbiosis of lung microbiome

- Bacterial infection of alveoli induces:
  - Edema that spreads to other alveoli
  - Infiltration by PMNs and RBCs, followed by macrophages

- Predisposing factors:
  - Viral infections: damage cilia
  - Smoking: damages bronchial epithelia and impairs ciliary function
  - Cold and dry weather: dries mucous membranes and increases person-to-person spread of infection
  - Age: immunosenescence and sarcopenia


DISTRIBUTION OF PNEUMONIA BY AGE AND ITS IMPACT ON MORTALITY

- Distribution of Pneumonia by Age and Region (%)

- CAP by Age and Associated Mortality

- Mortality Number of Cases

- Low (0-1) 8%
- Intermediate (2-9) 12%
- High (>9) 20%


ETIOLOGY

- CDC Etiology of Pneumonia in the Community (EPIC) study
  - Multi-center, prospective surveillance study of hospitalized adults with CAP
  - Jan 2010 - July 2012
  - Across hospitals in Chicago, IL (3) and Nashville, TN (2)
  - Aggressive diagnostics within 72 hr of admission
  - Excluded patients:
    - Hospitalized within 28 days if immunocompetent or 90 days if immunocompromised
    - Patients with tracheostomy, percutaneous gastrostomy tube, CF, SOT/HSCT
    - Neutropenic patients with malignancies
    - AIDS
  - 2259 patients included with clinical pneumonia

- Only 38% had an identified pathogen
- 22% had viral pathogen only
- 11% had bacterial pathogen
- 3% had some combination of viral/bacterial
- Most common pathogens:
  - Influenza (14)
  - Rhinovirus (12)
  - Streptococcus pneumoniae (6)

Adapted from Jain S et al. NEJM 2015;373:415-427

EPIC STUDY, CONT

- Only 38% had an identified pathogen
- 22% had viral pathogen only
- 11% had bacterial pathogen
- 3% had some combination of viral/bacterial
- Most common pathogens:
  - Influenza (14)
  - Rhinovirus (12)
  - Streptococcus pneumoniae (6)


SEVERITY OF ILLNESS SCORING

- CURB-65 Score
  - Confusion: Glasgow Coma <8
  - Urea ≥19mg/dL
  - Respiratory Rate ≥30 breaths/min
  - Blood Pressure Systolic <90 or DBP <60mm Hg
  - Age ≥65 years of age

- Core-62 Score
  - 0: Low
  - 1: Intermediate
  - 2: High

- Treatment Setting
  - Likely Outpatient
  - Likely Inpatient
  - Inpatient's ICU

MACROLIDE RESISTANCE IN PNEUMOCOCCUS BY REGION


WHAT ABOUT DOXYCYCLINE MONOTHERAPY?

• 1179 Strep pneumo isolates from the U.S. from 2010 and 2014
  • Doxycycline resistance in 23.6%
  • Only 7.9% resistant to ceftriaxone (non-meningeal)
• 1878 Strep pneumo isolates from the U.S. from 2013
  • Intravenous resistance 24.3%
  • Penicillin (parenteral, non-meningeal) resistance in 0.9% (9.1% non-susceptible)
**GUIDELINES FOR OUTPATIENT CAP SINCE 2007**

<table>
<thead>
<tr>
<th>SEPAR (Spain)</th>
<th>MICE (United Kingdom)</th>
<th>Chinese Thoracic Society, Chinese Medical Association</th>
<th>South African Thoracic Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>Amoxicillin</td>
<td>Amoxicillin/Clavulanate (PCN allergy)</td>
<td>Amoxicillin/Clavulanate (PCN allergy)</td>
</tr>
<tr>
<td>Oil + Macrolide</td>
<td>OR Macrolide</td>
<td>OR Macrolide</td>
<td>OR Macrolide</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>1.10(0.7)/200%</td>
<td>2. 1.0(0.7)/200%</td>
<td>3. 1.0(0.7)/200%</td>
</tr>
<tr>
<td>2. 1.0(0.7)/200%</td>
<td>3. 1.0(0.7)/200%</td>
<td>4. Fluoroquinolone</td>
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</tr>
<tr>
<td>5. Macrolide</td>
<td>6. (poison-resistance cases only)</td>
<td>7. 8. 1.0(0.7)/200%</td>
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<tr>
<td>Young adult w/o underlying disease:</td>
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**WHAT ABOUT PO BETA-LACTAMS?**

- Amoxicillin/clavulanate
- B-lactam/β-lactamase inhibitor comb
- Fluoroquinolone
- Cefuroxime (500mg)
- Ceftriaxone (500mg)
- Cephalosporin (200mg)
- Doxycycline (200mg)
- Clindamycin (200mg)
- Clavulanate

**CAP-START**

- Multi-center, cluster randomized, cross-over trial of hospitalized, non-ICU CAP in the Netherlands
- Assessed noninferiority (13% margin) of B-lactam monotherapy vs fluoroquinolone or β-lactam/macrolide
- 2583 patients enrolled, median CURB/65/12
- Recall 0-1 may be managed outpatient!
- Most common pathogens: S. pneumoniae (41%), H. influenzae (9%), and atypicals (2%)
- 90 d mortality 9.8% of all patients
- No difference in 90 d mortality

Postma DF et al. NEJM 2015;372:214

**BETA-LACTAM MONOTHERAPY VS BETA-LACTAM-MACROLIDE COMBINATION TREATMENT**

- Multicenter, randomized trial in 6 hospitals across Switzerland
- Noninferiority (18% margin) of B-lactam against B-lactam macrolide combo for clinical stability at 1 d
  - HH 100 beats/min
  - SBP 90mm Hg
  - T<100°C
  - RR<24 breath/min
  - O2>90% on room air
- Allowed for addition of macrolide if Legionella identified

Garin et al. AMA Intern Med. 2014;184:190

**BETA-LACTAM VS BETA-LACTAM + MACROLIDE**

- 580 patients
- 31% and 34% having CURB-65
- 31% had an identified pathogen (S. pneumoniae-15%)
- 90 d mortality 8.2 vs 6.9% (p=0.54)
- Failure to reach clinical stability at 7 d of 41.2 vs 33.6% (p=0.07)
- +1 sided 95% CI 1.3%
- 2-sided 95% CI 0.8 to 1.6%
- 30 d readmission 7.9 vs 3.1% (p=0.001)

*Results displayed as OR with 95% CI.*

Garin et al. AMA Intern Med. 2014;184:190
MACROLIDE VS DOXY IN COMBINATION WITH BETA-LACTAM FOR CAP

- Retrospective evaluation of 855 patients with CAP in Australia

<table>
<thead>
<tr>
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<th>Overall (n=855)</th>
<th>Typical PNA</th>
<th>Atypical PNA</th>
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<tr>
<td></td>
<td>BLA (n=257)</td>
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<td>BLA (n=187)</td>
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<td>CAP Fever Rate</td>
<td>13 (13.3%)</td>
<td>37 (13.9%)</td>
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<td>Blood Stream Infection</td>
<td>2 (1.7%)</td>
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<td>C-reactive Protein</td>
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<td>19 (27.0%)</td>
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<td>Event Determination</td>
<td>26 (14.9%)</td>
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<td>12 (19.7%)</td>
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<tr>
<td>Mortality Rate</td>
<td>5 (2.8%)</td>
<td>13 (6.3%)</td>
<td>5 (3.3%)</td>
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<tr>
<td>Days to Stability (d)</td>
<td>2 (1.1%)</td>
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<td>LOS (d)</td>
<td>5 (0.7)</td>
<td>6 (0.7)</td>
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<tr>
<td>Early Deterioration</td>
<td>1 (5.8%)</td>
<td>13 (46.2%)</td>
<td>2 (15.6%)</td>
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<tr>
<td>30d Mortality</td>
<td>93 (52.2%)</td>
<td>375 (55.1%)</td>
<td>20 (62.5%)</td>
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<td>Required Intubation</td>
<td>2 (1.1%)</td>
<td>92 (13.5%)</td>
<td>1 (3.1%)</td>
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<td>Days to Stabilize</td>
<td>2 (0.6)</td>
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CAP PSI ≥ 4

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CLOSTRIDIODES DIFFICILE AND TETRACYCLINE USE

- Inpatients to San Francisco General Hospital evaluated addition of doxy to ceftriaxone (CRO) for CAP
- 1066 patients CRO+D vs 1668 CRO from 2005-2010
- Excluded if had CDI within previous 30d or within 48h of hospitalization
- 43 patients with CDI
  - 5 in CRO+D vs 38 in control
  - Univariate HR 0.67 (95%CI: 0.48-0.96)
  - Multivariate HR 0.73  (95%CI: 0.56-0.96)
  - Compared with CRO+azithromycin HR 0.15 (95%CI: 0.03-0.77)
  - Doxy may decrease CDI burden, but not enough data in ICU


CONSIDERATIONS FOR THE LAND OF ENCHANTMENT

WHAT ABOUT LEGIONELLA PNEUMOPHILA?

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of Strains Inhibited at Indicated Concentrations (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVX</td>
<td>0.008 0.016 0.032 0.064 0.125 0.25 0.5 1 2 4 8</td>
</tr>
<tr>
<td>MOX</td>
<td>2 5 9 14 28 56 105 210 420 840 1680</td>
</tr>
<tr>
<td>CIP</td>
<td>5 9 14 28 56 105 210 420 840 1680</td>
</tr>
<tr>
<td>RIF</td>
<td>11 49 90 180 360 720 1440 2880 5760 11520</td>
</tr>
<tr>
<td>AZM</td>
<td>4 10 43 26 4 13*</td>
</tr>
<tr>
<td>CLS</td>
<td>1 3 40 30 26*</td>
</tr>
<tr>
<td>DOXY</td>
<td>53 52 13 2 0*</td>
</tr>
</tbody>
</table>

*Tentative EUCAST breakpoints
Adapted from Koshkolda T, Luck C. / Antimicrob Chemother 2018;73:S41-S42
ONE LAST WORD ON LEGIONELLA PNEUMOPHILIA

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Rifampin+Azithromycin</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Minocycline+Azithromycin</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Rifampin+Minocycline</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Ceftazidime+Azithromycin</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Levofloxacin+Minocycline, ASIR, or Rif</td>
<td>No interaction</td>
</tr>
<tr>
<td>Azith+Rif+Minocycline</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Ceftazidime+Doxycycline</td>
<td>Synergistic</td>
</tr>
</tbody>
</table>

*Ceftazidime does not concentrate well intracellularly.
Chiaraviglio L, Kirby JE. AAC 2015; 59(12):7517-7529

How do you feel about the current status of healthcare-associated pneumonia (HCAP)?

- It may be gone from HAP/VAP, but it lives on in my institution
- It’s finally gone, everyone’s on board, and I’m thrilled
- I miss it, we don’t use enough

CAP 2018: THE NEW HOME FOR HCAP?

- What was healthcare-associated pneumonia (HCAP)?
  - Hospitalized ≥2 d in previous 90 d
  - Nursing home/LTAC resident
  - IV antibiotics/chemotherapy/home wound care in previous 30 d
  - Hospital or hemodialysis clinic
  - Numerous meta-analyses found increase in antibiotic use with no consistent increase in MDR microbes identified

- 2016 HAP/VAP Guidelines
  - “…it was thought that [HCAP] could be included in the upcoming CAP guidelines because patients frequently present from the community…”

DURATIONS OF ANTIMICROBIAL THERAPY FOR CAP

- Multicenter, noninferiority randomized trial across 4 hospitals in Spain
- 312 patients with moderate-severe CAP treated with investigator chosen antibiotics
- 5 d therapy with discontinuation of treatment if Temp ≤37.8ºC and ≤1 sign of instability (n=162) vs 10 d (n=150)
- Clinical success at 10 d: 56.3 vs 48.6% (p=0.18)
- Clinical success at 30 d: 91.9 vs 88.6% (p=0.33)

Uranga A et al. JAMA Intern Med 2016;176 (9):1257-65

THE IMPACT OF IMPROVED VACCINATION

<table>
<thead>
<tr>
<th>Region</th>
<th>0-14 yr</th>
<th>15-24 yr</th>
<th>25-59 yr</th>
<th>≥60 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORTH AMERICA</td>
<td>35%</td>
<td>25%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>SOUTH AMERICA</td>
<td>30%</td>
<td>30%</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>EUROPE</td>
<td>40%</td>
<td>45%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>WORLD</td>
<td>35%</td>
<td>25%</td>
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<td>20%</td>
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</table>

- All adults ≥65 y: PPSV23 followed by PCV13 after ≥1
- CDC research in 2016 found glaring deficits:
  - Only 43% of beneficiaries had at least one dose of PPSV23
  - Only 32% PCV13
  - Only 18% had both
- PPSV23 for patients with chronic heart disease, chronic lung disease, EtOH abuse, cigarette smoking
- Always refer to ACIP recommendations!

Need for Pneumococcal Vaccination

MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

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