Community Acquired Pneumonia (CAP)
Update for 2001/2002

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University of Minnesota
URTI & LRTI Objectives
John C. Rotschafer, Pharm. D.

- Participants will be able to identify the mechanism of resistance associated with PCN-R *S. pneumoniae* and AMP-R *H. influenzae* and *M. catarrhalis*.
- Participants will be able to state the prevalence of PCN-R *S. pneumoniae* and AMP-R *H. influenzae* both in the community and nationally.
- Participants will be able to identify the 3 major organizations that will be offering treatment guidelines for CAP.
- Participants will be able to identify an appropriate first line antibiotic regimen for an outpatient, general in-patient, and an ICU patient with CAP.
- Participants will be able to identify the potential advantage of heptavalent pneumococcal vaccine over the current commercial preparation.
- Participants will be able to provide general data regarding the cost of standard antibiotic regimens to treat CAP.
Pneumonia

- Many different types
  - Community acquired (CAP)
  - Hospital acquired (HAP)
    - Ventilator (VAP)
  - Aspiration

- Diagnosis
  - Sputum gram stain & culture
    - <10 epithelial cells & > 25 PMN’s per field
    - Appropriate cultures of blood and CSF
  - Chest x-ray infiltrate
  - Fever, elevated WBC, SOB & pleuritic chest pain
**URTI & LRTI**

- **Introduction**
  - **CAP**
    - Annual incidence ~ 4 million cases
    - Mortality 14%
    - Direct & indirect cost $23 billion / year
  - **ABS**
    - Annual incidence ~ 30 million cases
    - Direct & indirect cost $2 billion / year
  - **AECB**
    - Annual incidence ~ 20 million cases
Question

Factors that help distinguish CAP from HAP or nosocomial pneumonia include all of the following except:

A. Prior antibiotic therapy
B. Intubation
C. Extended hospitalization
D. Underlying respiratory disease
E. All of the above are risk factors for HAP
Directed antibiotic therapy for pneumonia is possible approximately what percent of the time?

A. 90%
B. 75%
C. 50%
D. 30%
E. 10%
Community Acquired Pneumonia - CAP

- Hospital cases represent the tip of the iceberg
  - Diagnosis in office setting confounded
    - +Gram Stain
    - +Culture (positive ~50% of the time) & antibiotic sensitivity
    - +X-ray
  - Differential Diagnosis
    - Bronchitis vs Pneumonia +Bacteremia
    - Viral vs Bacterial
      - Estimated ~50% of antibiotic Rx’s unnecessary
  - How should patients be treated?
    - Oral vs Parenteral
  - In what setting should patients be treated?
CAP Treatment Guidelines

- **American Thoracic Society**
  - First published 1993
  - Revision published Am J Respir Crit Care Med 163:1730-1754, 2001

- **Infectious Diseases Society of America**
  - First published April 1998
  - Revision published CID 31:347-382, 2000

- **Center for Disease Control**
  - Arch Intern Med 160:1399-1408, 2000
  - Promote macrolides, doxycycline, or beta-lactams
  - Fluoroquinolones suggested if: 1) Failed previous Tx, 2) Allergy to alternative antibiotics, & 3) PCN MIC > 4mg/L
CAP Patient Scoring System

- Scoring system incorporates
  - Patient age
  - Location
  - Coexisting Illness
  - Physical Findings
  - Laboratory Findings
  - Radiographic Findings

- Difficult to use in clinical setting
  - Point values vary for different parameters
  - May not have all of the required data
  - Cumbersome addition
# CAP Patient Scoring System


<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>All Patient Mortality</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>N/A</td>
<td>0.1%</td>
</tr>
<tr>
<td>II</td>
<td>≤70</td>
<td>0.6%</td>
</tr>
<tr>
<td>III</td>
<td>71-90</td>
<td>0.9%</td>
</tr>
<tr>
<td>IV</td>
<td>91-130</td>
<td>9.3%</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
<td>27%</td>
</tr>
</tbody>
</table>

Class I, II, & III mortality < 1%

Can likely be treated as outpatients with oral antibiotic
ATS CAP 2001 Classification Scheme

- **Group I** (1993 - outpatient <60 yrs no co-morbidity)
  - Outpatient CAP
  - No CHF or COPD
  - No risk factors for other resistant pathogens

- **Group II** (1993 – outpatient with co-morbidity&/or >60yrs)
  - Outpatient CAP
  - History of CHF & /or COPD
  - Risk factors for resistant pathogens may or may not be present

Am J Respir Crit Care Med 163:1730-1754, 2001
ATS CAP 2001 Classification Scheme

- **Group III** (1993 – hospitalized with CAP)
  - Inpatient but does not require ICU setting
    - No CHF or COPD and/or resistant bacteria risk factors
    - CHF and/or COPD plus possible risk factors for resistance and may be nursing home patient

- **Group IV** (1993 – hospitalized with severe CAP)
  - ICU patient
    - No risk for *P. aeruginosa*
    - At risk for *P. aeruginosa*

*Am J Respir Crit Care Med 163:1730-1754, 2001*
CAP Pathogens

- **Typical**
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*

- **Atypical**
  - *C. pneumoniae*
  - *L. pneumophila*
  - *Mycosplasma*
ATS Pathogen Risk Factors

Am J Respir Crit Care Med 163:1730-1754, 2001

- **PCN-NS/R *S. pneumoniae***
  - > 65 years
  - Multiple co-morbidities
  - Alcoholism
  - Exposure to children in day care
  - Immunosuppressed
  - Use of beta-lactam within last 90 days

- **P. aeruginosa**
  - Use of broad spectrum antibiotic for > 1 week in last month
  - Structural lung disease
  - Steroid use
  - Malnutrition

- **Gram Negatives**
  - Nursing home resident
  - Cardiopulmonary disease
  - Multiple co-morbidities
  - History of recent antibiotic therapy
Thanks to PENICILLIN
...He Will Come Home!
Pneumococcal Sentinel Surveillance System
Definition of PCN-R *S. pneumoniae*

- **Sensitive**
  - PCN MIC $\leq 0.06$ mg/L

- **Non-susceptible**
  - PCN MIC $= 0.12$ to $1.0$ mg/L

- **Resistant**
  - PCN MIC $\geq 2.0$ mg/L
  - Mechanism of resistance is an alteration of penicillin binding proteins (PBP)
Resistance in Respiratory Pathogens
Staples, A., Thornsberry, C. et al ICAAC Abst 1221, 2000

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>USA Resistance</th>
<th>Germany Resistance</th>
<th>Korea Resistance</th>
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</thead>
<tbody>
<tr>
<td>H. influenzae</td>
<td>~35% AMP-R</td>
<td>17% AMP-R</td>
<td>88% AMP-R</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>94% AMP-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>35% PCN-NS/R</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>PCN-NS / PCN-R %</th>
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<tbody>
<tr>
<td>Tmp/Smx</td>
<td>32 / 87%</td>
</tr>
<tr>
<td>Azithro</td>
<td>29 / 66%</td>
</tr>
<tr>
<td>Ceftriax</td>
<td>4 / 22%</td>
</tr>
<tr>
<td>Clari</td>
<td>31 / 76%</td>
</tr>
<tr>
<td>Cefur</td>
<td>99.9 / 99.9%</td>
</tr>
<tr>
<td>Levo</td>
<td>1.3 / 2.6%</td>
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</table>
TRUST Studies 1999-2001: Comparison of Antimicrobial Resistance of *S. pneumoniae*

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>% R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin (MIC ≥ 2µg/mL)</td>
<td>14.7</td>
<td>16.0</td>
<td>16.9</td>
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<tr>
<td>Azithromycin</td>
<td>22.7</td>
<td>23.4</td>
<td>27.5</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>3.4</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Levofloxacinc</td>
<td>0.6</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>No. of institutions</td>
<td>96</td>
<td>238</td>
<td>240</td>
</tr>
<tr>
<td>No. of isolates</td>
<td>4,296</td>
<td>9,499</td>
<td>6,362</td>
</tr>
</tbody>
</table>

**S. pneumoniae**

**Penicillin Resistance**
(Resistant, MIC ≥ 2 µg/mL)

**Azithromycin Resistance**
(Resistant, MIC ≥ 2 µg/mL)

**National Rate:**
Penicillin=17% R

**National Rates:**
Azithromycin=28% R
Clarithromycin=28% R
Erythromycin=28% R

*6,362 isolates, 240 labs.
Lab report vs Clinical Outcome Disconnect

- In-vitro susceptibility does not seem to correlate with clinical outcome in LRTI
  - Clinical failures with conventional antibiotics & resistant pathogens are rare for RTI’s
  - Phenomena poorly studied
    - Cultures & susceptibility studies rarely done
  - Question as to the timeframe where PCN & multiply antibiotic resistant strains will become an issue
Macrolide Resistant *S. pneumoniae*

- **Three Types**
  - **Ribosomal resistance (erm ~30% of strains)**
    - Alters the binding of macrolide to the 50S ribosome
    - Conveys resistance to all macrolides
  - **Efflux pump (mef ~70% of strains)**
    - Macrolide pumped out of bacteria
    - Resistance is macrolide dependent
  - **23S r RNA or ribosomal protein mutations, only 20 strains reported** ([AAC 44:3395-3401, 2000](#))

- **Testing is problematic**
  - **Erythromycin used as class disk**
  - **Quick check erythromycin vs clindamycin susceptibility**
    - Many labs do not report clindamycin result
PCN-R *S. pneumoniae* Therapeutic Options

- **New Quinolones (URTI & LRTI agents)**
  - Levofloxacin *(Ortho)* 500 / 750mg PO/IV QD
  - Moxifloxacin-Avelox® *(Bayer)* 400mg PO/IV QD
  - Gatifloxacin-Tequin® *(BMS)* 400mg PO/IV QD
  - Gemifloxacin-Factive® *(SKB)* 320mg PO QD

- **Other Possible Antibiotic Options for PCN-R**
  - Vancomycin, Linezolid, & Ketolides

- **Heptavalent *S. pneumoniae* vaccine**
  - Prevnar® - Wyeth-Lederle

- **Pneumovax®**
Fluoroquinolone *S. pneumoniae* MIC-90

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>MIC-90 (mg/L)</th>
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<tbody>
<tr>
<td>Levofloxacin</td>
<td>1-2</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>Clinafloxacin</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>Sitafl oxacin</td>
<td>0.06-0.12</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>0.015</td>
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Assorted Abstracts ICAAC 2000
## Fluoroquinolone Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cp-x mg/L</th>
<th>PB %</th>
<th>t1/2 Hr</th>
<th>f %</th>
<th>F %</th>
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<tr>
<td>Ciprofloxacin</td>
<td>3.5</td>
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<td>Levofloxacin</td>
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<td>&lt;30</td>
<td>8.0</td>
<td>90</td>
<td>90</td>
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<td>Sparfloxacin</td>
<td>1.1</td>
<td>45</td>
<td>16-30</td>
<td>10</td>
<td>90</td>
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<tr>
<td>Grepafloxacin</td>
<td>1.5</td>
<td>50</td>
<td>12</td>
<td>&lt;10</td>
<td>70</td>
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<tr>
<td>Trovaflouxacin</td>
<td>1-4</td>
<td>70</td>
<td>10-12</td>
<td>&lt;10</td>
<td>90</td>
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<tr>
<td>Moxifloxacin</td>
<td>3.3-4.5</td>
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<td>10-12</td>
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<td>90</td>
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<tr>
<td>Gatifloxacin</td>
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<tr>
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<td>1.6</td>
<td>60</td>
<td>8.0</td>
<td>36</td>
<td>71</td>
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**Fluoroquinolone Serum AUC / MIC Ratios**

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC-24* (mg•hr/L)</th>
<th>MIC (mg/L)</th>
<th>2.0</th>
<th>1.0</th>
<th>0.5</th>
<th>0.25</th>
<th>0.125</th>
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<tr>
<td>Ciprofloxacin</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>80</td>
<td>160</td>
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<tr>
<td>Levofloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
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<tr>
<td>Moxifloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
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<tr>
<td>Gatifloxacin</td>
<td>51</td>
<td>25</td>
<td>51</td>
<td>102</td>
<td>204</td>
<td>408</td>
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<tr>
<td>Gemifloxacin+</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>64</td>
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</table>

+ Gemifloxacin AUC / MIC ratio for *S. pneumoniae* = 8 / 0.015 = 533

- AUC likely higher in real patients vs human volunteers
- Correct values for extent of protein binding
Fluoroquinolone Resistant Respiratory Pathogens

- **S. pneumoniae**
    - 0% FQ-R in 1993 to 1.7% in 1997/1998
  - **Hong Kong** (Ho, P.L. AAC 43:1310-1313, 1999)
    - PCN-R (MIC>0.06)  69.1%
    - Cipro-R (MIC>2)  12.1%  Clonal Problem
    - Levo-R (MIC>2)  5.5%
    - Trova-R (MIC>1)  2.2%

- **H. influenzae & M. catarrhalis**
  (Biedenbach, D.J. Diagn Micro & Infect Dis 36:255-259, 2000)
  - 4 FQ-R *H. influenzae* (Sentry Data 1997-1999)
  - 1 FQ-R *M. catarrhalis*
Effect of Single Mutations on Fluoroquinolone MICs by Selecting Fluoroquinolone Mutants of *S. pneumoniae*

<table>
<thead>
<tr>
<th>DNA gyrase</th>
<th>Topo IV</th>
<th>MIC (µg/mL)</th>
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<tbody>
<tr>
<td><strong>gyrA</strong></td>
<td><strong>parC</strong></td>
<td></td>
</tr>
<tr>
<td>Ser81</td>
<td>Ser79</td>
<td>Asp83</td>
</tr>
<tr>
<td>Phe</td>
<td>---</td>
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</tr>
<tr>
<td>Tyr</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>---</td>
<td>Tyr</td>
<td>---</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>Asn</td>
</tr>
</tbody>
</table>

Ciprofloxacin and levofloxacin select for single Topo IV mutants
Sparfloxacin and gatifloxacin select for single DNA gyrase mutants

Heptavalent Pneumococcal Vaccine
Kaiser Permanente Trial
Abstract 1398, ICAAC, San Francisco, 1999

- Wyeth-Lederle Heptavalent CRM 197 given to infants 2,4,6,& 12-15 months
- 37,000 children randomly assigned pneumococcal or meningococcal vaccine
  - Double Blind Trial
- October/95-July/98 vaccine efficacy 100%
  - Highly effective in preventing invasive disease & pneumonia
  - Significant impact on otitis media

Lieu,TA et al JAMA 283:1460,2000
Prevnar® (Wyeth Lederle Vaccines)

Advisory Committee on Immunization Practices
MMWR (October 6, 2000) 49 (RR-9) recommends vaccination for:

- All children 2-23 months
- Children 24-59 months at risk of pneumococcal disease
- All Native-American, Alaskan-Native, & African-American children < 5 yrs
- Administered at 2, 4, 6, & 12-15 months

Cost driven recommendation (WSJ February 17, 2000)

- 20,000 children @ $232/child = $4.6M
Selection of Antibiotic for URTI’s & LRTI’s

- **Antibiotic Efficacy**
  - Most studies powered for equivalence

- **Safety of Agent**

- **Patient Convenience**
  - Compliance
    - QD vs other
    - 5 day vs 10-14 day
    - Oral easier and less expensive than parenteral
      - Consider oral bioavailability
      - Focus on concentration at site of infection
Outpatient Empiric Selection

- Macrolide
- Fluoroquinolone (expanded spectrum)
- Doxycycline
Group I
- Clarithromycin or Azithromycin or Doxycycline

Group II
- Oral
  - Cefpodoxime, Cefuroxime, HD Amoxicillin, or Augmentin plus macrolide or doxycycline
  - Antipneumococcal fluoroquinolone
- Parenteral
  - Ceftriaxone followed by oral cefpodoxime
IDSA CAP Guidelines

- General Medical Ward
  - Cefotaxime or Ceftriaxone plus Macrolide
  - Fluoroquinolone alone

- Performance Indicators
  - Blood cultures prior to antibiotic therapy
  - Antibiotics within 8 hours of hospitalization
Empiric Selection for Intensive Care

- Cefotaxime or
- Ceftriaxone or
- Ampicillin/sulbactam or
- Piperacillin/tazobactam
- Fluoroquinolone or Macrolide
Group III

- **Subgroup A** (No risk factors)
  - IV Azithromycin alone
  - Doxycycline plus beta-lactam
  - Antipneumococcal fluoroquinolone

- **Subgroup B** (CHF &/or COPD &/or antibiotic risk)
  - Cefotaxime, Ceftriaxone, Unasyn, or high dose Ampicillin plus IV or PO Macrolide or Doxycycline
  - Antipneumococcal fluoroquinolone
ATS Treatment Guidelines
Am J Respir Crit Care Med 163:1730-1754, 2001

- Group IV
  - Subgroup A (No *P. aeruginosa* risk)
    - Cefotaxime or Ceftriaxone plus Azithromycin or Fluoroquinolone
  - Subgroup B (*P. aeruginosa* risk)
    - Cefepime, imipenem, meropenem, or Zosyn plus Ciprofloxacin or Aminoglycoside
    - PLUS
    - Azithromycin or nonpseudomonal fluoroquinolone
Factors Contributing to Increased Morbidity &/or Mortality

- **Symptoms**
  - HR $\geq 125$/min, BP $< 90$ or/ $< 60$ mm Hg , RR $\geq 30$/min, pH $< 7.35$
  - Hyper($\geq 40^\circ C$) or hypo($< 35^\circ C$) thermic

- **Factors**
  - Advanced age and state of consciousness
  - CHF
  - COPD / Bronchiectasis
  - Cancer
  - Diabetes
  - Chronic renal and/or hepatic disease
  - Alcoholism
  - Cerebral vascular disease
  - Malnutrition
  - Hospitalized within last year
  - Splenectomy
Parenteral to Oral Conversion for CAP Patients

Four Criteria for IV to PO Conversion

- Improvement in cough and dyspnea
- Afebrile on two occasions spaced by eight hours
- WBC returning toward normal
- Functional GI tract with evidence patient able to take fluids, food, and/or medications

Am J Respir Crit Care Med 163:1730-1754, 2001
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Cycle</th>
<th>Cost</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor 500mg TID</td>
<td></td>
<td>$73.39</td>
<td>Ceclor ®</td>
</tr>
<tr>
<td>Loracarbef 400mg BID</td>
<td></td>
<td>$124.39</td>
<td>Lorabid ®</td>
</tr>
<tr>
<td>Cefpodoxime 200mg BID</td>
<td></td>
<td>$90.39</td>
<td>Vantin ®</td>
</tr>
<tr>
<td>Cefixime 400mg QD</td>
<td></td>
<td>$85.69</td>
<td>Suprax ®</td>
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<td>Cefprozil 500mg BID</td>
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<tr>
<td>Cefuroxime 500mg BID</td>
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<td>Cefdinir 300mg BID</td>
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<td>$93.99</td>
<td>Omnicef</td>
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<tr>
<td>Amox/Clav 875/125mg BID</td>
<td></td>
<td>$118.39</td>
<td>Augmentin®</td>
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Retail Charge for 10 day Supply
March 2002

- Clarithromycin 500mg BID  $86.99
- Clarithromycin XL  $54.69
  - Biaxin ®
- Azithromycin Z-Pack  $45.69
  - Zithromax ®
- EES 400mg QID  $19.99
- PCE® 500mg BID  $54.69
- TMP / SMX  BID  $ 6.69 (generic)
- Doxycycline 100 mg BID  $12.69
Retail Charge for 10 day Supply
March 2002

- Ciprofloxacin 750mg BID $110.39
  - Cipro®
- Levofloxacin 500mg QD $107.39
  - Levaquin ®
- Moxifloxacin 400mg QD $51.39 (5d) / $96.99
  - Avelox ®
- Gatifloxacin 400mg QD $82.39
  - Tequin ®
Regions Hospital Cost/Day
October 2001

Parenteral Antibiotic Therapy:

- Ceftriaxone 1 Gm QD $20.79
- Ceftriaxone 2 Gm QD $41.32
- Erythromycin 500 mg QID $9.40
- Azithromycin 500 mg QD $19.75
  - Bioavailability 100% vs 40% orally
- Levofloxacin 500mg QD $16.00
Antibiotic Overview

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>BL</th>
<th>MAC</th>
<th>FQ</th>
<th>DOX</th>
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<tbody>
<tr>
<td>S. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCN-R</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atypicals</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- Antibiotic choice highly dependent on specific agent selected
- For S. pneumoniae with PCN MIC >2 mg/L, vancomycin or FQ probably best choice depending on circumstances
Looking Down the Road

- Presently, there is a lack of clinical failures with conventional therapy
- Should NCCLS redefine PCN-R *S. pneumoniae* ???
  - 35% resistance going to ~ 12-14% in U.S.A.
- Unknown time frame for level of PCN-R to go from < 2 mg/L to ≥ 4 mg/L
- Increasing rate of vaccination for *S. pneumoniae*
  - Pneumovax & Heptavalent vaccine
- Increasing rate of FQ-R *S. pneumoniae* & others
- Safety concerns with new fluoroquinolones