Community Acquired Pneumonia (CAP) Update for 2003/2004

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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
- Now must be on watch for bioterrorism & SARS
- Diagnosis
  - Sputum gram stain & culture
    - <10 epithelial cells & > 25 PMN’s per field
    - Appropriate cultures of blood and CSF
  - Chest x-ray infiltrate
  - Fever, cough, SOB & pleuritic chest pain
**URTI & LRTI**

**Introduction**
- **CAP**
  - Annual incidence ~ 4.8 million cases
  - 1.4 million patients require hospitalization
  - Mortality 14%, 7th most common cause of death
  - Direct & indirect cost $23 billion / year
- **ABS**
  - Annual incidence ~ 30 million cases
  - Direct & indirect cost $2 billion / year
- **AECB (CB=airway disease of mucus hypersecretion)**
  - Chronic bronchitis defined as productive cough most days for 6 consecutive months for 2 years
  - Annual incidence ~20 million cases

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**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 vs 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?
**Nosocomial Pneumonias**

![Diagram of Nosocomial Pneumonias]

Early-onset pneumonia
- Staphylococcus pneumoniae (~5%)
- Haemophilus influenzae (<5%)

Late-onset pneumonia
- Pseudomonas aeruginosa (>60%)
- Acinetobacter baumannii (21.7%)
- Staphylococcus aureus (~20%)


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**Effect of Mechanical Ventilation and Prior Antibiotic Use on Development of Multiresistant Pathogens**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=72)</th>
<th>Group 3 (n=7)</th>
<th>Group 4 (n=6)</th>
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<tbody>
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<td>ART = yes</td>
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<td>4 (57.1)</td>
<td>4 (57.1)</td>
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<tr>
<td>P. aeruginosa</td>
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<td>4 (5.6)</td>
<td>0</td>
<td>4 (5.6)</td>
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<tr>
<td>A. baumannii</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>1 (1.4)</td>
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<td>E. coli</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MRSA</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
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<tr>
<td>Other bacteria</td>
<td>41 (100)</td>
<td>14 (19.4)</td>
<td>28 (87.5)</td>
<td>43 (14.4)</td>
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</table>

* p < 0.001 versus Group 4
† p < 0.001 versus Group 4


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**2. Steps to Prevent Antimicrobial Resistance in Hospitalized Adults**

1. Vaccinate
2. Get the catheters out
3. Target the pathogen
4. Access the experts
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not colonization
8. Know when to say "no" to vanco
9. Know when to say "no" to vanco
10. Stop treatment when infection is cured or unlikely

PREVENT INFECTION
DIAGNOSE AND TREAT INFECTION EFFECTIVELY
USE ANTIMICROBIALS WISELY
PREVENT TRANSMISSION
11. Isolate the pathogen
12. Break the chain of contagion

CDC. Drug Resistance / Healthcare Web

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**What's New From ICAAC 1999**

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3
CAP Treatment Guidelines

- American Thoracic Society
  - First published 1993
  - Revision published Am J Respir Crit Care Med 163:1738-1754, 2001
- Infectious Diseases Society of America
  - First published April 1998
  - Revision published CID 31:347-382, 2000
  - Revision published CID 37:1405-1433, 2003
- 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.

IDSA CAP Guidelines

Mandel, LA et al CID 37:1405-1433, 2003

- Initial treatment
  - Home vs hospital care & route of antibiotic therapy
    - Assess pre-existing conditions that compromise home care
    - Calculate PORT score
    - Clinical judgment
- Discharge Criteria (no more than one)
  - Temperature >37.8C, Pulse >100 bpm, Respiratory Rate >24/min, Systolic BP <90mm Hg, Oxygen Saturation < 90%, or Inability to maintain oral intake

PORT CAP 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
PORT Scoring System

<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>All Patient Mortality</th>
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<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%
Class 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

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*
  - *Mycoplasma*

### CAP – Viral & Fungal Pathogens

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Fungi</th>
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<tbody>
<tr>
<td>Influenza A</td>
<td><em>B. dermatitidis</em></td>
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<tr>
<td>RSV</td>
<td><em>H. capsulatum</em></td>
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<tr>
<td>Parainfluenza virus</td>
<td><em>C. immitis</em></td>
</tr>
<tr>
<td>Adenovirus</td>
<td><em>P. carinii</em></td>
</tr>
<tr>
<td>Hantavirus</td>
<td><em>C. neoformans</em></td>
</tr>
</tbody>
</table>

### CAP – Less Common Pathogens

- *N. meningitidis*
- *S. pyogenes*
- *M. tuberculosis*
- *Chlamydia psittaci*
- *Coxiella burnetii*
- *B. anthracis*
- *Y. pestis*
- *F. tularensis*
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

Smoking as a RTI Risk Factor

- Contributes to the bacterial colonization of the respiratory tract
  - Nonsmokers 0% colonization
  - Mild, Moderate, or Severe COPD results in 23%, 42%, & 58% colonization, respectively
    - Eur Resp J 13:343, 1999
- Reduces the efficiency of host defense mechanisms
  - Loss of cilia and increases IL-8
  - Causes hypersecretion of mucus gland
  - Increases number of goblet cells
  - Causes squamous cell metaplasia

CAP Risk Groups

- No Comorbidity
  - Mycoplasma, Chlamydia, *S. pneumoniae*
- Smoker
  - *S. pneumoniae, H. influenzae, & M. cattarhalis*
- Alcoholic
  - *S. pneumoniae, anaerobes, gram negatives*
- Epidemic
  - *Legionella*
- Animal/Bird Reservoir
  - Q-fever, psittacosis, tularemia
- Airway Obstruction
  - Anaerobes
HAP- Pathogens

- Usual
  - S. aureus
  - S. pneumoniae
  - Gram negatives
  - Anaerobes (aspiration)
  - Legionella
- Immunosuppressed
  - P. carinii
  - Aspergillus
  - CMV, HSV, VZV
  - Cryptococcus
  - Nocardia

Pneumococcal Sentinel Surveillance System
Definition of PCN-R. S. pneumoniae

- Sensitive
  - PCN MIC ≤ 0.06 mg/L
- Non-susceptible
  - PCN MIC = 0.12 to 1.0 mg/L
- Resistant
  - PCN MIC ≥ 2.0 mg/L
- Mechanism of resistance is alteration of penicillin binding proteins not the production beta-lactamase

*National Committee for Clinical Laboratory Standards

Comparison of Antimicrobial Resistance of S. pneumoniae, USA, 2001-2003

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>TRUST 5 2001</th>
<th>%R</th>
<th>TRUST 6 2002</th>
<th>%R</th>
<th>TRUST 7 2003</th>
<th>%R</th>
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<tr>
<td>Penicillin*</td>
<td>16.9</td>
<td></td>
<td>18.4</td>
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<td>17.4</td>
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<tr>
<td>Azithromycin</td>
<td>27.5</td>
<td></td>
<td>27.5</td>
<td></td>
<td>27.6</td>
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<tr>
<td>Trimeth/ sulfamethazine</td>
<td>28.1</td>
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<td>26.0</td>
<td></td>
<td>24.1</td>
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<tr>
<td>Ceftriaxone (nonmening)</td>
<td>1.6</td>
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<td>1.7</td>
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<td>1.5</td>
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<tr>
<td>Levofoxacin</td>
<td>0.78</td>
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<td>0.89</td>
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<td>0.96</td>
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<td>239</td>
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<td>226</td>
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</tr>
<tr>
<td>No. of isolates</td>
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<td></td>
<td>7671</td>
<td></td>
<td>4456</td>
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</table>

* Penicillin R = MIC > 2 mg/ml; NCCLS broth microdilution – centralized lab, Focus Technologies
Data on file, Ortho-McNeil Pharmaceutical, Inc.
What's New From ICAAC 1999

4,377 isolates, 226 labs.

**S. pneumoniae Antimicrobial Resistance**

**TRUST 7 (2002-2003)**

- **S. pneumoniae Penicillin Resistance** (Resistant, MIC ≥ 2 µg/mL)
- **S. pneumoniae Azithromycin Resistance** (Resistant, MIC ≥ 2 µg/mL)

**National Rates:**
- Azithromycin = 27.6% R
- Erythromycin = 27.9% R
- Penicillin = 17.4% R

- ≥ 20% R
- 12-19.9% R
- <12% R

**S. pneumoniae Antimicrobial Resistance TRUST 7 (2002-2003)**

- **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

**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
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
- Other Possible Antibiotic Options for PCN-R
  - Vancomycin, Linezolid, & Ketolides(not FDA approved)
- Heptavalent *S. pneumoniae* vaccine
  - Prevnar® -Wyeth-Lederle
- Pneumovax®

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*In vitro* Eradication of *S. pneumoniae*

*Growth Control (GC)*
- Ciprofloxacin 500 mg BID
- Gati 400mg QD; Moxi 400mg QD; Levo 500mg QD

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*Clinical Cure and Bacteriological Eradication of *S. pneumoniae* in CAP*

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Clinical Cure (%)</th>
<th><em>S. pneumoniae</em> Eradication (%)</th>
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<tbody>
<tr>
<td>Levofloxacin</td>
<td>87–94%</td>
<td>92–100%</td>
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<tr>
<td>Gatifloxacin</td>
<td>89–93%</td>
<td>95–100%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>89–94%</td>
<td>90–100%</td>
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</table>

CAP = Community-Acquired Pneumonia


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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

Selection of Antibiotic for URTI’s & LRTI’s

- Antibiotic Efficacy
  - Most studies powered for equivalence not superiority
- Safety of Agent
  - New agents may take ~2M cases to identify ADR’s
- Patient Convenience
  - Compliance
    - 1 vs 2 Tablets/Capsules per dose
    - QD vs BID, TID, or QID
    - 5 day vs 10-14 day
- Oral easier and less expensive than parenteral
  - Consider oral bioavailability
  - Focus on concentration at site of infection

IDSA CAP Guidelines
Mandel, LA et al CID 37:1405-1433, 2003

- Healthy & no previous antibiotic therapy
  - Macrolide or Doxycycline
- Healthy but has had previous antibiotic therapy
  - Fluoroquinolone (respiratory)
  - Advanced macrolide plus high dose amoxicillin
  - Advanced macrolide plus high dose amoxicillin/clavulanate
- Comorbidities present (COPD, CHF, Diabetes ect)
  - No previous antibiotics
  - Advanced macrolide or respiratory fluoroquinolone
- Previous antibiotics
  - Respiratory fluoroquinolone or advanced macrolide plus beta-lactam
What's New From ICAAC 1999

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

• 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
Mandel, LA et al CID 37:1405-1433, 2003

Suspected aspiration
• Clindamycin or amoxicillin/clavulanate

Inpatient no recent antibiotics
• Respiratory FQ or Advanced macrolide + beta-lactam
  • Cefotaxime, Ceftriaxone, Ampicillin/sulbactam, or Ertapenem

Inpatient recent antibiotic therapy
• Advanced macrolide + beta-lactam or Respiratory FQ

IDSA CAP Guidelines
Mandel, LA et al CID 37:1405-1433, 2003

ICU patient where P. aeruginosa is not an issue
• Respiratory FQ or Advanced macrolide + beta-lactam
  • Cefotaxime, Ceftriaxone, Ampicillin/sulbactam, or Ertapenem

ICU patient P. aeruginosa is a concern
• Antipseudomonal agent + Ciprofloxacin
  • Piperacillin/tazobactam, Ceftazidime, imipenem, or meropenem
• Antipseudomonal agent + Aminoglycoside + Respiratory FQ or macrolide
### ATS Treatment Guidelines

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

**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

**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 >125/min, BP <90 or >140 mm Hg, RR >30/min, pH < 7.35
- Hypert(>40C) or hypot(<35C) 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

Retail Charge for 10 day Supply
January 2004

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price</th>
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<tr>
<td>Cefaclor 500mg TID</td>
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<td>Cefixime 400mg QD</td>
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<td>Cefprozil 500mg BID</td>
<td>$167.99</td>
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<tr>
<td>Cefuroxime 500mg BID</td>
<td>$175.69</td>
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<tr>
<td>Cefdinir 300mg BID</td>
<td>$ 98.99</td>
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<tr>
<td>Amox/Clav 875/125mg BID</td>
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<tr>
<td>Amox/Clav 2000/125 BID</td>
<td>$ 67.39</td>
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<td>Clarithromycin 500mg BID</td>
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<tr>
<td>Telithromycin 800mg QD</td>
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<td>EES 400mg QID</td>
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<tr>
<td>PCE® 500mg BID</td>
<td>$56.99</td>
</tr>
<tr>
<td>TMP / SMX BID</td>
<td>$10.69 (generic)</td>
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<tr>
<td>Doxycycline 100 mg BID</td>
<td>$16.39</td>
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Retail Charge for 10 day Supply
January 2004

- Ciprofloxacin 750mg BID $125.39
- Cipro®
- Levofloxacin 500mg/750mg QD $106.99/$58.99
  - Levaquin®
- Moxifloxacin 400mg QD $100.69
  - Avelox®
- Gatifloxacin 400mg QD $96.99
  - Tequin®
- Ciprofloxacin 750mg BID $125.39
- Levofloxacin 500mg/750mg QD $106.99/$58.99
  - Levaquin®
- Moxifloxacin 400mg QD $100.69
  - Avelox®
- Gatifloxacin 400mg QD $96.99
  - Tequin®

Regions Hospital Cost/Day
January 2004

Parenteral Antibiotic Therapy:

- Ceftriaxone 1 Gm QD $20.74
- Ceftriaxone 2 Gm QD $41.24
- Erythromycin 500 mg QID $11.80
- Azithromycin 500 mg QD $21.74
  - Bioavailability 100% vs 40% orally
- Levofloxacin 500mg QD $15.62
- Levofloxacin 750mg QD $23.44

Antibiotic Overview

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<thead>
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<th>Pathogen</th>
<th>BL</th>
<th>MAC</th>
<th>FQ</th>
<th>DOX</th>
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<td>S. pneumoniae</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>PCN-R</td>
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<td>Macro-R</td>
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<td>+</td>
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<td>H. influenzae</td>
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<tr>
<td>M. catarrhalis</td>
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<td>0</td>
<td>+</td>
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- Antibiotic choice highly dependent on specific agent selected
- For S. pneumoniae with PCN MIC >2 mg/L, vancomycin, FQ, or ketolide probably best choice depending on circumstances
- Not yet FDA Approved
Looking Down the Road

- Presently, there is a lack of clinical failures with conventional therapy
- Unknown time frame for level of PCN-R to go from \( \leq 2 \text{ mg/L} \) to \( \geq 4 \text{ mg/L} \)
- Concern for increasing level of FQ-R *S. pneumoniae* because of FQ overuse & possible approval for pediatric use
- Increasing rate of vaccination for *S. pneumoniae*
  - Pneumovax & Heptavalent vaccine
- Safety concerns with new fluoroquinolones