Implications of Bacterial Resistance on Antibiotic Selection

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Overview

- **Bacterial resistance**
  - Gram positive & Gram negative bacterial resistance is increasing
  - Pathogens often resistant to multiple antibiotics
    - Reduced susceptibility to conventional antibiotics
    - New gram positive agents are limited & expensive
    - Virtually nothing on the horizon for resistant gram negatives
  - Complicates medical management & clinical outcome
    - Morbidity & Mortality
  - Increases the cost of care
    - LOS, supportive measures & antibiotics/drugs
  - Function of antibiotic pressure
  - Wide based societal problem
What would “the mind” do in regards to ???

- Antibiotic Resistance
- Appropriate antibiotic use
- Appropriate use of infection control practices

Minnesota’s Mr. Right
# Bacterial Resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic transport to site</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug must be taken into cell</td>
<td>Influx/Efflux</td>
</tr>
<tr>
<td>Drug must remain viable</td>
<td>Enzyme/Environment</td>
</tr>
<tr>
<td>Drug binds to target</td>
<td>Target alteration</td>
</tr>
<tr>
<td>Drug attack metabolic process</td>
<td>Bypasses effect using antidote</td>
</tr>
</tbody>
</table>

- Bacteria can rapidly replace the former generation
- Bacteria naturally mutate or acquire resistance (plasmids)
- Mechanisms of resistance are not mutually exclusive
The Antibiotics We Use

- Overt and Covert Use of Antibiotics
  - Hospital vs. Nursing Home vs. Day Care vs. Community
    - Prophylaxis
    - Therapeutic
    - Inappropriate
  - Passed Down the Food Chain (Animal Feed)
  - Antibiotics are part of our daily living (Triclosan)
- Overuse, misuse, and/or underdosing of antibiotic can precipitate bacterial resistance
- Direct and Collateral Damage
  - Ceftazidime – ESBL
  - Cephalosporins, Vancomycin, Anaerobic Agents - VRE
**Antibiotic Selection & Dosing**

*Right drug, dose, interval, and duration*

- **Level of prescribing sophistication:**
  - Known or suspected site of infection
  - Known or suspected bacteria
  - Known or likely antibiotic susceptibility
  - Level of understanding regarding antibiotic mechanism of action &/or resistance
  - Knowledge of antibiotic pharmacokinetic & pharmacodynamic principles
  - Understanding of evidenced based disease state literature

- **Bacterial resistance drives antibiotic selection but antibiotic selection also drives bacterial resistance**
### Influences that Increase Antibiotic Prescribing

**July 1998 Survey of all primary care MD’s in Massachusetts**

**APUA Newsletter Vol 19 2001**

- 499 usable responses out of ~6,000 questionnaires (8%)
  - 93% agreed that physicians over prescribe antibiotics

<table>
<thead>
<tr>
<th>Factor</th>
<th>% MD’s Factor influenced Rx</th>
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<tbody>
<tr>
<td>Purulent Discharge</td>
<td>64%</td>
</tr>
<tr>
<td>Dx Uncertainty</td>
<td>62%</td>
</tr>
<tr>
<td>Patient request</td>
<td>59%</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>48%</td>
</tr>
<tr>
<td>Fever</td>
<td>47%</td>
</tr>
<tr>
<td>Tx Uncertainty</td>
<td>36%</td>
</tr>
<tr>
<td>Payer Policy-formulary</td>
<td>28%</td>
</tr>
<tr>
<td>Time Pressure</td>
<td>26%</td>
</tr>
<tr>
<td>?Return visit cost</td>
<td>20%</td>
</tr>
<tr>
<td>Litigation concern</td>
<td>19%</td>
</tr>
<tr>
<td>Payer policy-QA</td>
<td>13%</td>
</tr>
<tr>
<td>Drug promotion</td>
<td>7%</td>
</tr>
<tr>
<td>Resistance concern</td>
<td>5%</td>
</tr>
<tr>
<td>Cost</td>
<td>2%</td>
</tr>
</tbody>
</table>
Ceftazidime Induced ESBL with Gram Negative Bacteria
Rice, LB Pharmacother 19: 120S-128S, 1999

- Overuse &/or underdosing of ceftazidime may precipitate an ESBL (TEM or SHV) problem with Klebsiella or Enterobacter
- Piperacillin/tazobactam substituted for ceftazidime but Amp-C like enzymes or overproduction of ESBL can inactivate tazobactam
- Treatment of these organisms with imipenem or fluoroquinolones may precipitate multi-resistant A. baumannii
Antibiotic Use and Resistance

Rice et al. CID 1996
## Resistant *A. baumannii* in ICU

Weingarten, CM Pharmacother 19:1080-1085, 1999

<table>
<thead>
<tr>
<th></th>
<th>Infected</th>
<th>Match</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51 yrs</td>
<td>50 yrs</td>
<td>NS</td>
</tr>
<tr>
<td>Apache II</td>
<td>16</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>34%</td>
<td>18%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LOS</td>
<td>51 days</td>
<td>19 days</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phar cost</td>
<td>$19K</td>
<td>$3K</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hosp cost</td>
<td>$128K</td>
<td>$31K</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Vancomycin Prescribing Patterns

- Retrospective study May 1993-April 1994
  - Preliminary guidelines published Federal Regis May 1994
  - N = 135 patients
- Appropriate or inappropriate usage defined using CDC criteria
- 83/135 (61%) of vancomycin usage was inappropriate
- Question whether U.S. hospitals doing an adequate job controlling usage

Johnson SV et al. Pharmacotherapy 1995
Wide Overuse of Antibiotic Cited in Study
WSJ (September 4, 1997)

- 7,147 medicare patients in 131 hospitals studied in 1995
- 63% of vancomycin orders did not follow CDC guidelines
- No difference in comparing large urban teaching centers to small rural hospitals
- Beth Israel-Deaconess - fliers & lectures did not alter prescribing behavior
Is Vancomycin Bigger, Better, & More Powerful?

**Karchmer Editorial**

**Data suggests**
- Vancomycin kills bacteria at a slower rate
- Higher mortality with vancomycin treated patients
  - Gonzalez: CID 29:1171, 1999
- Clox/gent significantly better than Vanco or Teico/gent in short course therapy of right side endocarditis
  - Fortun: CID 33:120-125, 2001
- Vancomycin is an independent risk factor for the development of gram negative bacteremia

Independent risk factor for VRE
Resistance in Respiratory Pathogens

Staples, A., Thornsberry, C. et al ICAAC Abst 1221, 2000

USA ~35%
Germany 5.3%
Korea 88%

- H. influenzae 17% AMP-R
- M. catarrhalis 94% AMP-R
- S. pneumoniae 35% PCN-NS/R

PCN-NS / PCN-R %
- Tmp/Smx 32 / 87%
- Azithro 29 / 66%
- Ceftriax 4 / 22%
- Clari 31 / 76%
- Cefur 99.9/ 99.9%
- Levo 1.3 / 2.6%
Retrospective 1995-1997 study of US 5,837 adults pneumococcal pneumonia or bacteremia

- 3,452 Pen-S, 377 Pen-NS, and 364 Pen-R

- Pen-R (MIC ≥ 4) 5.5 x RR death after day 2, 7.1 x RR death after day 4.

- Cefotaxime-R (MIC ≥ 2) 4.3 x RR death after day 2, 5.9 x RR death after day 4.
PCN-R *S. pneumoniae*
Therapeutic Options

- The 20% resistance threshold for change
- New quinolones (URTI & LRTI agents)
  - Levofloxacin—Levaquin® (OMP) 500/750 mg PO QD
  - Moxifloxacin—Avelox® (Bayer) 400 mg PO/IV QD
  - Gatifloxacin—Tequin® (BMS) 400 mg PO/IV QD
  - Gemifloxacin—Factive® (SKB) 320 mg PO QD—?
- Other possible antibiotic options
  - Vancomycin, linezolid, & ketolides
- Pneumovax ®
- Heptavalent *S pneumoniae* (Prevnar ®) vaccine
Increased Efficacy for Advanced Generation Fluoroquinolones in Community Acquired Pneumonia
Metge et al ICAAC 2000

• Inpatient: FQ vs. Ceftriaxone and Macrolide
  – 5 additional clinical successes/100 pts Tx with FQ’s
  – Reduced cost with FQ’s

• Outpatient: FQ vs. New Generation Macrolide
  – 3 additional clinical successes/100 pts Tx with FQ’s
  – Reduced cost with FQ’s
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
Preventing Bacterial Resistance: Underdosing

- Examined relationship between bacterial resistance, kinetics, & MIC in 4 LRTI trials
- N=107 patients, 128 pathogens, & 5 antibiotic regimens
- 32/128 (25%) initially susceptible pathogens developed resistance during therapy
- AUC/MIC ratio < 100 risk factor for developing resistance during therapy
- Underdosing would appear to be a significant risk factor for the development of resistance
Cost of Nosocomial Infections
Roberts, R SHEA 2001

- Retrospective cohort study of patients at Cook County with hospital acquired infections (HAI-CDC criteria)
  - Randomly selected patients from 1998 discharge database with >5 ICD-9 diagnoses
  - Severity of illness measured using Apache III scores
  - Costs calculated from hospital perspective
- 193 (164 medical & 29 surgical) patients (41/193 with HAI)
  - Medicine average cost of hospitalization with HAI $24,762 vs. $6,202 without
  - Surgical average cost of hospitalization with HAI $52,422 vs. $20,823 without
  - Confounding variable analysis showed suspected HAI added $13,236 (SE $3,146) & documented HAI added $18,223 (SE $2,225)
Combating Bacterial Resistance
McGowan, J. SHEA 2001

- Development of new antimicrobials & vaccines
- Validation of laboratory diagnostic methods
  - 67% of 416 labs using an acceptable method to detect VISA
  - 17% of 416 labs using an acceptable method to detect ESBL’s
- Infection control
- Benchmarking bacterial resistance and antibiotic use against yourself and others
- Formal training programs in bacterial resistance
- Restricting & rotating antibiotic use
- Practice guidelines
- Use multiple tactics & monitor impact of steps taken
- Monitor all healthcare settings
## Strategy

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Vaccination</td>
<td>Rapid &amp; Accurate Pathogen ID</td>
</tr>
<tr>
<td>Infection Control</td>
<td>Infection Control</td>
</tr>
<tr>
<td>Formulary Selection</td>
<td>Pharmacokinetic &amp;/or Pharmacodynamic dosing</td>
</tr>
<tr>
<td>Education</td>
<td>Practice Guidelines</td>
</tr>
<tr>
<td>Antibiotic Rotation</td>
<td>New Agents</td>
</tr>
<tr>
<td>Antibiotic Program</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotic Control Program Induced Pseudo-outbreak of Infections
Calfee, D.P. Abstract # 19 IDSA 2000 New Orleans

- Number of nosocomial infections rose after introduction of antibiotic control program
- No specific pathogen identified
- Patient acuity index unchanged
- Mortality rate actually decreased
- Physicians changed diagnostic and prescribing practices to comply with antibiotic program
  - “Squeezing the balloon” syndrome
Pharmacodynamic Outcome Parameters

AUC / MIC = 100 / 0.5 = 200

Cpmax / MIC = 10 / 0.5 = 20

T > MIC approx 24 hrs

AUC = 100 mg h / L
Dosing Strategies for Concentration Dependent Killer

- Use larger doses less frequently
  - Optimize the PD parameter
- Use CD agents first to quickly reduce bacterial burden then suppress regrowth with concentration independent agent
- Try to use agents of different chemical classes with different mechanisms of action
- Probably do not want to use two concentration dependent agents together
Dosing Strategies for Concentration Independent Antimicrobial Agents

- Select agent with long half-life, low protein binding, and large Vd
- More frequent dosage administration
- Continuous infusion of antibiotic
- Repository antibiotic dosage forms
- Block excretion (probenecid)
- Select product with active metabolite
- Select class product with lowest MIC
Proposed Pharmacodynamic Outcome Parameters

- **Gram negatives**
  - Fluoroquinolone AUC/MIC ratio ≥ 125
  - Aminoglycosides Cp-max / MIC ratio ≥ 10

- **S. pneumoniae**
  - Fluoroquinolone AUC/MIC ratio ≥ 30
  - Penicillin T>MIC ≥ 40% of dosage interval

- **Anaerobes**
  - Fluoroquinolone AUC/MIC ratio ≥ 50
# Fluoroquinolone Serum AUC / MIC Ratios

<table>
<thead>
<tr>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>192</td>
<td>384</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>51</td>
<td>25</td>
<td>51</td>
<td>102</td>
<td>204</td>
<td>408</td>
</tr>
<tr>
<td>Gemifloxacin+</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
</tbody>
</table>

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

*AUC likely higher in patients vs. human volunteers? correct AUC for %PB*
New Antibiotics & Antibiotics on the Horizon

- Quinupristin / Dalfopristin (Synercid®)
- Gatifloxacin (Tequin®)
- Moxifloxacin (Avelox®)
- Linezolid (Zyvox®)
- Ertapenem (Invanz®)
- Oritavancin (LY 333328)
- Daptomycin (Cidecin®)
- Ketolides (Telithromycin & ABT 773)
- Glycylcyclines (Tigecycline-GAR 936)
Conclusions

Goal:

- Promote appropriate use of antibiotics
- Consider the potential of new antibiotic to induce bacterial resistance in formulary evaluations
- Promote appropriate pharmacokinetic & pharmacodynamic concepts when dosing antibiotics
- Develop programs to monitor use of antibiotics & resistance within the hospital & benchmark data
- Communicate data among colleagues
- While not primary function can help promote appropriate and aggressive use of infection control measures
Stuart Smalley Closing Thoughts

- **Remember:**
  - Every time you use an antibiotic, you are conducting your own experiment in Darwinian theory!
  - Wash your hands, there are some bad bugs out there!