Clinical Pharmacy and Optimization of Antibiotic Usage: How to Use what you have Learned in Pharmacokinetics and Pharmacodynamics of Antibiotics

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Presented at UCL on Thursday February 28th
Systems Approach to Antibiotics

• Value: Making sure every patient receives excellent care, every time..
• The Theoretical studies provide the means to do this
• We will talk about both theories and about putting them to work
$C_{\text{max}}$ (peak)

Antibiotic serum concentration

AUC

$\text{AUIC} = \frac{\text{AUC}_{24}}{\text{MIC}}$

Half life

$C_{\text{min}}$ (trough)

Time above MIC

Time
Antibiotic PK and PD attributes

• For antimicrobial effect:
  - $C_{\text{max}}$/MIC ratio should be $> 8$ to $10$
  - AUIC should be $> 125$
    (For rapid killing AUIC $> 250$)
• To minimize resistance development:
  - AUIC should be $> 100$
Antibiotics for Study in LRTI

• Concentration Dependent Actions
  – Fluoroquinolones
  – Aminoglycosides

• Concentration Independent Actions
  – Beta Lactams
  – Vancomycin
Tobramycin:
2 peaks of 6.0 in 24 hours
AUC$_{24}$=54

- Peak: MIC=3, AUIC=27
- Peak: MIC=6, AUIC=54
- Peak: MIC=12, AUIC=108
Aminoglycosides

• Low AUIC with typical dosing and levels
  – breakpoint MIC is 0.25 mcg/ml for AUIC of 125
• We say their activity is decreased
  – with the infection site pH below 6.0
  – at urine sites due to cations
  – with decreased PO₂
  – due to binding at the infection site
• Combination Therapy is necessary in most situations, because of a low AUIC
## Antibiotic Combinations

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt;</th>
<th>MIC P.aerug</th>
<th>AUIC&lt;sub&gt;24&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>54</td>
<td>1.0</td>
<td>54</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>400</td>
<td>2.0</td>
<td>200</td>
</tr>
<tr>
<td>Total (Tob+Ceftaz)</td>
<td></td>
<td></td>
<td>254</td>
</tr>
</tbody>
</table>
Ceftazidime 1000 mg BID:
Two SS pks of 100 in 24 hours
AUC$_{24}$=400; AUIC=AUC$_{24}$/MIC

$C_{max}$ (peak)

Ceftazidime serum concentration

<table>
<thead>
<tr>
<th>Time, hours</th>
<th>Peak:MIC</th>
<th>AUIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Peak:MIC=100, AUIC=400</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Peak:MIC=50, AUIC=200</td>
<td>100</td>
</tr>
</tbody>
</table>

AUC$_{24}$ = Area Under the Curve from 0 to 24 hours
AUIC = Area Under the Interaction Curve
Do Aminoglycosides protect against Resistance?

• Activity against the pre-existing sub-population that is resistant to the concomitant beta lactam?
• If so, then AUIC drives the action and additivity laws are served
• Protection only when the aminoglycosides contribute enough to bring total AUIC above 125….
Consequences of Under-dosing with Antibiotics

• Failure to Eradicate
• Long Eradication Time
• Resistance develops when AUIC is below 100
AUIC vs Resistance

Linkage between dosing and Antibiotic Resistance

- Marginal Organisms (MIC at the breakpoint) are the first organisms to express resistance
- Emergence by selective pressure occurs when dosing is lowered below MIC. Example: Ofloxacin resistant *Pseudomonas aeruginosa*
- Individual patients with foreign bodies and low doses are reservoirs for these resistant pathogens, once these conditions occur
Clinical Approaches

• Dose to Trough above MIC
• Increase doses for high MIC organisms and patients with high CCr
• When in doubt, combine antibiotics. When sure of isolates, refine regimens
• Gram Stain is the best monitoring tool
• Computer software to Estimate AUICs
Computerized Estimation of AUIC

- Selected patients who are now undertreated will benefit from the addition of a second antibiotic, or higher doses
  - Less resistance, fewer failures, shortened therapy
- Most cephalosporin doses will be lowered (elderly patients, low MIC organisms)
  - Cost Savings in the antibiotic budget
Use of AUIC in Patient Care

• 77 yoM, 70 in, 155 lb, with COPD, Lung Ca, and Diabetes, 7 days post-op LLL resection.
• Now with new S&S of LRTI, on a Ventilator
• Cefazolin for prophylaxis day 1, currently receiving no ABX. Serum creatinine is 1.2 mg/dl
• Cx taken, Ceftazidime 1.0 gm Q12hr is ordered.
• You were consulted for antibiotic management
Calculation of AUICs

- \( \text{DOSE}_{24} / \text{Clearance} = \text{AUC}_{24} \)
- Clearance = \( \text{CCr}(x) + \text{Clnr} \)
- Adjust AUC for 24 hr of Dosing if not already done
- MIC as Default or Exact value?
- \( \text{AUIC}_{24} = \text{AUC}_{24} / \text{MIC}_{18} \)
The A.U.I.C. Program for Antimicrobial Dosing

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Jerome J Schentag and Martin H Adelman
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Home Screen-Palm AUIC

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Begin

Info
Disclaimer
AUIC Screening by Computer

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  – Less resistance, fewer failures, shortened therapy

• Most cephalosporin doses will be lowered (elderly patients, low MIC organisms)
  – Cost Savings in the antibiotic budget

• Requires integrated computer datafiles
Computer Assisted Antibiotic Management

Pharmacy Orders
Census Admissions Financials
Micro/Lab Results
Clinical Database
Antibiotic Management
AUIC Calcs.
Cycling Protocols
Infection Control
Antibiotic Management and Infection Control

- Custom Reports for Specialists
- List of Target Organisms
- Antibiograms by unit or even by room, with ABX Use data
- Target Sites of Infection
- Resistance surveillance functions
Clinical Pharmacy Goals

• Implement AUIC dosing adjustment program for improvement of clinical outcomes. Raise doses for high MICs.

• Implement regimen refinement program to lower costs after first 3 days of Intravenousous therapy.
Type of Antibiotic Interventions

- Dosage Adjustment: 40%
- CPL Protocols: 11%
- Antibiotics D/C: 18%
- Change to oral: 17%
- Regimen Changes: 14%
Antibiotic Modifications

• By day 3 of treatment, most patients:
  – Have improved clinically
  – Have an Identified organism in cultures taken on day 1
  – Have organism eradication or inoculum reduction
  – Are taking oral diets and/or Medications