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
Antibiotic PK and PD attributes

- For antimicrobial effect:
  - $\frac{C_{\text{max}}}{\text{MIC}}$ 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
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 PO$_2$
  – due to binding at the infection site
• Combination Therapy is necessary in most situations, because of a low AUIC

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC$_{24}$</th>
<th>P.aerug</th>
<th>AUIC$_{24}$</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>254</td>
<td></td>
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</tbody>
</table>
Ceftazidime serum concentration

\[ C_{\text{max}} \] (peak)

Ceftazidime 1000 mg BID: Two SS pks of 100 in 24 hours

\[ \text{AUC}_{24} = 400; \ AUIC = \frac{\text{AUC}_{24}}{\text{MIC}} \]

- Peak: MIC = 50, AUIC = 200
- Peak: MIC = 100, AUIC = 400

**% remaining Culture positive**

**Time, Hours**

\[ 0 \quad 6 \quad 12 \]

**Time, Days of Treatment**

\[ 0 \quad 7 \quad 14 \quad 21 \]

- ▲ = Ceftazidime \( \text{AUIC} < 125 \)
- ▲ = Ceftazidime \( \text{AUIC} > 125 \)
- ○ = Cefmenoxime \( \text{AUIC} < 125 \)
- --- = Cefmenoxime \( \text{AUIC} > 125 \)
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
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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Home Screen-Palm AUIC

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Info
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Begin
AUIC Screening by Computer

- Selected patients who are now under-treated will benefit from the addition of a second antibiotic, or from the use of 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
- 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 Intravenous therapy
**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