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

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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)

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

Half life

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

Antibiotic serum concentration

AUC

Time above MIC

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

C_{max} (peak)

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

Time, hours
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
## Antibiotic Combinations

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC$_{24}$</th>
<th>P. aeruginosa (MIC)</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><strong>Total</strong></td>
<td><strong>254</strong></td>
<td></td>
<td></td>
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<tr>
<td>(Tob+Ceftaz)</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
$\text{AUC}_{24}=400$; $\text{AUIC}=\text{AUC}_{24}/\text{MIC}$

Ceftazidime

Cmax (peak)

Time, hours

MIC

AUIC=40

Peak:MIC=50, AUIC=200

Peak:MIC=100, AUIC=400

0  6  12  100  10  2  1
% remaining Culture positive

Time, Days of Treatment

- △ = Ceftazidime  AUIC < 125
- ▲ = Ceftazidime  AUIC > 125
- ⊘ = Cefmenoxime AUIC < 125
- ○ = Cefmenoxime 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
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

ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION

Version 1.0.0a

Copyright 1987–93, 1997–9, 2000-2001
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Buffalo NY

Developed by: Martin Adelman, PhD
and Jerome J Schentag, PharmD
Home Screen-Palm AUIC
AUIC Screening by Computer

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• 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
Type of Antibiotic Interventions

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