Objectives

- Define from a clinical perspective what is meant by the term single daily dosing of aminoglycosides.
- Differentiate between single daily dosing (SDD) and a conventional strategy for administering aminoglycosides.
- Provide the rationale used by the Hartford group in designing their 7 mg/kg/day SDD therapeutic recommendation.
- Identify what is currently believed to be the appropriate pharmacodynamic outcome predictor for aminoglycosides and an appropriate range of values for this parameter. Also identify any clinical shortcomings in how these data have been applied to SDD dosing strategies.
- Define the concept of the aminoglycoside free interval and how the PAE concept applies to extending aminoglycoside dosing intervals.
- Outline what is meant by adaptive resistance and how this concept applies to SDD aminoglycoside dosing strategies.
- Provide 3 situations where a SDD strategy for aminoglycosides might not be appropriate.

Aminoglycosides

- Goal of therapy
  - Dose is sufficient to kill suspected pathogen
  - Dose has low probability of adverse drug reaction
  - SDD
    - Dose and definition of what constitutes SDD has been a moving target in the literature
      - Dose for gentamicin and tobramycin ranges from 3 to 7 mg/kg/day
      - The "Daily" dose depending on method and renal function ranges from Q 12, 24, 36, to 48 H
SDD Rationale

- Maximize the effect of concentration dependent killing
  - Optimize Peak : MIC ratio
    - Increases the rate of bacterial kill
    - Aminoglycosides may be concentration dependent killers of Gram-negative but data unclear for staphylococci, streptococci, enterococci, and mycobacterium
  - May extend PAE
- Create a drug free interval that overcomes adaptive resistance and limits drug accumulation & related toxicity
  - Exact magnitude of this interval is unknown

Aminoglycoside Transport

Blood & Tissue Equilibrium

<table>
<thead>
<tr>
<th>Blood Compartment</th>
<th>Tissue Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturable</td>
<td>Cp</td>
</tr>
<tr>
<td>Cp</td>
<td>Ct</td>
</tr>
</tbody>
</table>

Aminoglycoside Transport

<table>
<thead>
<tr>
<th>Gram Negative Pathogen</th>
<th>Passive Transport</th>
<th>Energy Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
<td>Time</td>
<td>Frame</td>
</tr>
<tr>
<td>Concentration</td>
<td>2 Hours</td>
<td>Rapid Kill</td>
</tr>
<tr>
<td>Dependent</td>
<td>2 to 4 Hours</td>
<td>Slow Kill</td>
</tr>
<tr>
<td>Concentration</td>
<td>Independent</td>
<td></td>
</tr>
</tbody>
</table>

Diagram of Aminoglycoside Transport:

- Blood and tissue equilibrium
- Saturable concentration (Cp) and tissue concentration (Ct)
- Diagram showing blood and tissue compartments with arrows indicating transport
- Table showing effects and time frames for rapid and slow kill
Single Daily Dosing of Aminoglycosides

- Moore et. al. JID 155:93
- Maximal response seen as Peak/hr post : MIC ratio ~ 10
- Majority patients studied had urosepsis
- Patients not necessarily individualized to targeted peak & troughs for > 72 hr
- These data serve as foundation for 10 X MIC SDD rationale

Aminoglycosides

- Clinical studies & meta analysis to date compare SDD vs conventional multiple daily dose (MDD)
  - Virtually all studies underpowered to show difference in efficacy or toxicity
  - No clear trend evident other than SDD ~ MDD
- SDD attempts to produce high peaks in all patients for every infection
- SDD does not address the diversity in patient pharmacokinetic parameters
- No studies have attempted to optimize the Peak/MIC ratio on SDD

Bacterial Concentration Kill Curve & Concentration Dependent Killing

- Bacterial Infection Burden
  - $10^7$ CFU/ml or Grm

<table>
<thead>
<tr>
<th>CFU/ml</th>
<th>SDD 7mg/Kg</th>
<th>Cpx =20-25 mg/L</th>
<th>MDD 15mg/Kg</th>
<th>Cpx =6-8 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC = 2 mg/L</td>
<td>MIC = 0.5 mg/L</td>
<td>MIC = 0.5 mg/L</td>
<td>MIC = 0.5 mg/L</td>
</tr>
</tbody>
</table>
Therapeutic Goal for SDD?

- Conflicting or Complimenting Goals
  - A Cp-max gentamicin concentration 20 mg/L in all patients?
  - A Cp-max : MIC ratio ≥ 10 in all patients?

Hartford Program Rationale

- Based on worst case scenario P. aeruginosa gentamicin MIC = 2mg/L
- To produce Cpx = 20 mg/L requires dose of 7 mg/Kg/day (based on 1 compartment model)
- Had the investigators used the same rationale but:
  - Substituted tobramycin for gentamicin
  - For P. aeruginosa, tobramycin MIC ≥ 1 tube dilution lower
  - Recommended dose would be < 3.5 vs 7

Distribution Phase with SDD

- Demczar et al Abstract 103 36th ICAAC 1996

- Was the appropriate pharmacokinetic model used to construct the nomogram?
- In 7 mg/Kg the appropriate dose?
Hartford Program

Rather than *P. aeruginosa*, patient likely to have:

+ No bacterial pathogen
+ Gram positive pathogen
+ Gram negative pathogen with MIC ≤ 0.5 mg/L
+ If serum peak = 20 mg/L, peak/MIC ratio ≥ 40
+ Concentrations & ratios higher or lower in other sites
+ Suspect that most physicians capable of identifying situations where probability of *P. aeruginosa* is high.

**Gentamicin or Tobramycin**

Steady State Cpx & Cpn's on 7 mg/Kg

<table>
<thead>
<tr>
<th>T1/2 (hr)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd (L/Kg)</td>
<td>0.1</td>
<td>59/0</td>
<td>65/1</td>
<td>70/5</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>29/0</td>
<td>33/&lt;1</td>
<td>35/2</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>20/0</td>
<td>22/&lt;1</td>
<td>23/2</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>15/0</td>
<td>16/&lt;1</td>
<td>17/1</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>10/&lt;1</td>
<td>12/&lt;1</td>
<td>15/</td>
</tr>
</tbody>
</table>

*Once T1/2 ≥ 4 hrs essentially no drug free interval*


Zaske, DE et al AAC 21:407, 1982

**7 mg/Kg/day Peak / MIC Ratio**

Pathogen MIC = 0.5 mg/L

<table>
<thead>
<tr>
<th>T1/2 (hr)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd (L/Kg)</td>
<td>0.1</td>
<td>118</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>58</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>40</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>30</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>20</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

7 mg/Kg/day Peak / MIC Ratio
Pathogen MIC = 4 mg/L

<table>
<thead>
<tr>
<th>Vd (L/Kg)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>15</td>
<td>16</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>0.2</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>11</td>
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<tr>
<td>0.3</td>
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</tr>
<tr>
<td>0.6</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>


Single Daily Dose Therapy Case
Gram Negative Pneumonia
- Pathogen MIC = 2 mg/L
  - Peak = 20 mg/L
  - Conc (lung) ≤ 10 mg/L
    - Assume 30 to 50% Alveolar penetration
  - Peak : MIC Ratio = 10
  - Conc (lung) : MIC ratio ≤ 5

Single Daily Dose Therapy Case
Urosepsis
- Gram negative MIC ≤ 0.5 mg/L
  - Peak = 7 mg/L
  - Conc (urinary tract) = Very High
  - Peak : MIC Ratio ≥ 14
  - Conc (urinary tract) : MIC ratio = Huge
### SDD Serum Sampling Policies

<table>
<thead>
<tr>
<th>Option</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No levels:</td>
<td>Potential liability</td>
</tr>
<tr>
<td>One Level 6-8 hrs post:</td>
<td>Provides no PK data</td>
</tr>
<tr>
<td>High:</td>
<td>$&gt;\text{t}_{1/2}$, $&lt;\text{Vd}$, RN error</td>
</tr>
<tr>
<td>Low:</td>
<td>$&lt;\text{t}_{1/2}$, $&gt;\text{Vd}$, RN error</td>
</tr>
<tr>
<td>Trough/Peak:</td>
<td>Cps = 0-9mg/L</td>
</tr>
<tr>
<td>PK Study:</td>
<td>Can be done with 2 levels &amp; provides PK data</td>
</tr>
</tbody>
</table>

### Confounding Variables in SDD Studies
- Mixed patient populations
- Patients with no documented pathogen or a variety of pathogens and infections examined collectively
- MDD group likely optimized (Peak/MIC ratio) in many infections
- Include different aminoglycosides & doses
- Different institutions and standard of care
- Different inclusion criteria
- Different definitions of toxicity
- Difficult to tease out the importance of the aminoglycoside dosing method in this background

### Single Daily Dosing of Aminoglycosides Contraindications?
- SDD Relative Contraindications:
  - Long-term therapy (Endocarditis or Osteomyelitis)
  - Half-life $>4$ Hours
  - Elderly
  - Patients with compromised renal function
  - Adjacent Therapy
  - $S$. aureus $\beta$-lactamase
  - Bacterial pathogens MIC $>2$ mg/L
  - Mycobacterial infections
  - Bacterial pneumonia with pathogens having high MIC
  - Most urinary tract infections
  - Pregnancy
Other Issues with SDD

- Lot to lot manufacturing variability which is exaggerated by SDD
  - Does 1cc = 40 mg of gentamicin or tobramycin?
- Previous issues with endotoxin like reactions which is also exaggerated with SDD
- Nephrotoxicity and Ototoxicity are still very real issues that have not gone away with SDD
- Appropriate monitoring
  - Especially with home therapy
  - Long term therapy

Is SDD better than MDD or Pharmacokinetic Method?

- Question will likely go unanswered:
  - Aminoglycosides used less frequently vs fluoroquinolones
  - Aminoglycosides are used for shorter duration of time
  - Aminoglycosides are generic drugs and industry unlikely to sponsor trials with sufficient power to detect differences in dosing method

Is SDD better than MDD or Pharmacokinetic Method?

- Question will likely go unanswered:
  - Clinicians less likely to publish their experiences with aminoglycosides today as opposed to past
  - Difficult to identify the role dosing methods play in background of medical/surgical care, other antibiotics, and the presence of aminoglycosides in both study arms
  - If SDD really makes a difference in efficacy &/or toxicity, the data should be showing a clear trend
Single Daily Dosing (SDD) of Aminoglycosides

Conclusions
- SDD not for every infection, pathogen, or patient
- SDD has not eliminated aminoglycoside ADR's
- Still must have therapeutic goal based on pathogen susceptibility and location of infection
- Pharmacokinetics remains a useful tool to