Pros and Cons of aminoglycosides

**Pros:**
- High potency
- Concentration-dependent killing
- Synergy with β-lactams
- Cheap

**Cons:**
- Perception of poor efficacy in some circumstances
- Nephrotoxicity
- Ototoxicity

Both efficacy and safety can be improved by appropriate dosing!
1. optimizing efficacy based on PK-PD
In vitro time-kill curves

Time and conc. – dependent killing

In vitro post-antibiotic effect

delay before regrowth

Amikacin versus Gram-Negative Bacilli: efficacy

Craig et al. IDSA, 2006.

Neutropenic mice were inoculated with $10^6$ CFU/thigh of either *P. aeruginosa* (MIC = 4 mg/L) or *S. marcescens* (MIC = 8 mg/L)

* Craig et al. IDSA, 2006.
## Animal PD model

### Amikacin versus Gram-Negative Bacilli: PK-PD attainment rate

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Dosing Regimen</th>
<th>PK-PD Target&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 mg/kg/day</td>
<td>AUC:MIC = 59</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>99.9</td>
<td>94.8</td>
</tr>
<tr>
<td>2</td>
<td>85.7</td>
<td>42.8</td>
</tr>
<tr>
<td>4</td>
<td>23.7</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

stasis and a 1 log CFU reduction

*Craig et al. IDSA, 2006.*
Concentration is important in patients also …

C_{\text{max}}/\text{MIC} > 8 !
in a TID treatment

Concentration is important in patients also ...

Gentamicin and *Pseudomonas* bacteriemia

Zelenitsky et al. JAC 2003; 52:668-674
What have we learned from models?

- Aminoglycosides have a concentration-dependent pattern of bactericidal activity and prolonged persistent effects both *in vitro* and *in vivo*.

- **PK-PD Goal** of dosing: **Maximize Concentrations!**

  - **Optimize peak (and AUC)**

  - **Once-a-day administration!**
Meta-analysis: Once-daily dosing has a lower risk of clinical failure

Favors once-a-day  Favors multiple dose

Risk ratio (log scale)

0.05  0.1  0.2  0.5  1  2  5  10  20

Estimate (95% confidence interval):

Klastersky et al 5  3.67 (1.16 to 11.6)
Hansen et al 14  0.20 (0.05 to 0.83)
Muijsken et al 15  1.46 (0.57 to 3.75)
Tuikens et al 16  1.00 (0.02 to 48.0)
Hollender et al 17  0.32 (0.01 to 7.74)
Mauracher et al 18  0.08 (0.00 to 1.36)
Sturm et al 19  0.20 (0.01 to 4.03)
De Vries et al 20  1.90 (0.49 to 7.33)
Nordstrom et al 7  0.70 (0.17 to 2.84)
Ter Braak et al 21  1.30 (0.55 to 3.11)
Giamarello et al 22  0.09 (0.01 to 1.57)
Marik et al 23  0.50 (0.33 to 0.75)
Van der Auwera et al 24  0.20 (0.01 to 4.00)
Vigno et al 25  2.84 (0.12 to 68.6)
Gonzalez et al 27  0.67 (0.28 to 1.61)
Maller et al 28  1.25 (0.69 to 2.65)
Prins et al 29  0.46 (0.13 to 1.72)
Rozdzinski et al 30  1.01 (0.55 to 1.87)
Vanhaeverbeek et al 31  1.05 (0.02 to 50.4)

All trials:
Mantel-Haenszel fixed effects model  0.76 (0.61 to 0.95)
DerSimonian and Laird random effects model  0.83 (0.57 to 1.21)

Barza et al, BMJ 1996; 312:338-344
Dosing once-a-day in practice

Peak/MIC > 8

1. adequate mode of administration
   - i.v. administration

2. calculate the peak you need
   - minimal peak = MIC x 8

3. calculate the dose you need
   - peak = dose / Vd
   - dose = peak x Vd
Finding the appropriate dose ...

increase the unit dose to get the appropriate peak!

- **MIC = 1 mg/L**: $C_{\text{max}} = 8 \text{ mg/L}$, 3 mg/kg
- **MIC = 2 mg/L**: $C_{\text{max}} = 16 \text{ mg/L}$, 6 mg/kg
- **MIC = 4 mg/L**: $C_{\text{max}} = 32 \text{ mg/L}$, 15 mg/kg

**Limit of G, T, N ??**

**Limit of A, I ??**
Setting up the limits of efficacy

Aminoglycosides 1st two rules of thumb...

anything with an MIC < 1 µg/ml will be treatable if in the indications...

efficacy may become a problem for MIC’s
• > 2 µg/ml for G, T, N ( up to 6 mg/kg )
• > 4 µg/ml for A, I ( up to 15 mg/kg )

PK / PD “safe” breakpoints for AG
• G, N, T : 2 µg / ml
• A / I : 4 µg / ml
Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides(^1)</td>
<td>MIC breakpoint (mg/L)</td>
</tr>
<tr>
<td></td>
<td>S ≤</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>2</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2</td>
</tr>
</tbody>
</table>

Notes
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.
Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

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<td>2</td>
</tr>
</tbody>
</table>

Notes
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of these agents. Aminoglycosides are given in combination with beta-lactam agents.

amikacin may be given at very high doses reasonably safely
Setting up the limits of efficacy

Aminoglycosides EUCAST breakpoints

**Pseudomonas spp.**

<table>
<thead>
<tr>
<th>Aminoglycosides¹</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>4</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

Notes:
Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

¹. Aminoglycoside breakpoints are based on once-daily administration of aminoglycosides are given in combination with beta-lactam agents.

This is to avoid splitting the wild type population in two.
EUCAST MIC distributions

Gentamicin / Pseudomonas aeruginosa
EUCAST MIC Distribution - Reference Database 2011-10-03

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

- MIC Epidemiological cut-off: WT ≤ 8 mg/L
- Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L

24384 observations (71 data sources)
2. Reducing toxicity based on PK-PD
The basis of the once-a-day schedule

- gentamicin enters proximal tubular cells by megalin- and acid phospholipids mediated pinocytosis and ends up in lysosomes
- a minor part escapes lysosomes either by membrane destabilization (our hypothesis) or by retrograde transport (Molitoris' hypothesis) to reach the cytososol and the mitochondria … where it induces apoptosis and other toxic disturbances…
- you could prevent toxicity either
  - by impairing the pinocytic uptake of aminoglycosides, or making an aminoglycoside that does not bind to megalin…
    ➔ block or avoid step one …
  - developing an that does not destabilize lysosomes and/or does not cause apoptosis …
    ➔ block step 2 and/or its consequences…
Making use of this knowledge to protect patients …

TABLE 2. Main approaches toward reduction of aminoglycoside nephrotoxicity*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Compound</th>
</tr>
</thead>
</table>

Mingeot & Tulkens, Antimicrob. Agents Chemother. 43:1003-1012, 1999
**TABLE 2. Main approaches toward reduction of aminoglycoside nephrotoxicity**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Decrease or prevention of drug accumulation by kidneys</td>
<td>Dextran sulfate (59)</td>
</tr>
<tr>
<td>Intracellular completion of aminoglycosides</td>
<td>Inositol hexasulfate (67)</td>
</tr>
<tr>
<td>Polymannan compounds</td>
<td></td>
</tr>
<tr>
<td>Acidic drugs</td>
<td></td>
</tr>
<tr>
<td>Piperacillin (44)</td>
<td></td>
</tr>
<tr>
<td>Latamoxef-mesalactam (68)</td>
<td></td>
</tr>
<tr>
<td>Fosfomycin (33, 54)</td>
<td></td>
</tr>
<tr>
<td>Pyridoxal-5'-phosphate (114)</td>
<td></td>
</tr>
<tr>
<td>Competition with or decrease in aminoglycoside binding to brush border</td>
<td></td>
</tr>
<tr>
<td>membrane</td>
<td></td>
</tr>
<tr>
<td>Raising the urine pH</td>
<td></td>
</tr>
<tr>
<td>Competitors</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ (diet supplementation [51] or vitamin D-induced hypercalcaemia [21])</td>
<td></td>
</tr>
<tr>
<td>Lysine (81)</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides (as their own competitors) (39)</td>
<td></td>
</tr>
<tr>
<td>Increase in exocytosis</td>
<td></td>
</tr>
<tr>
<td>II. Prevention or decrease of lysosomal phospholipase inhibition</td>
<td></td>
</tr>
<tr>
<td>Derivatives with lesser intrinsic binding</td>
<td></td>
</tr>
<tr>
<td>N-substitution</td>
<td></td>
</tr>
<tr>
<td>Other substitution</td>
<td></td>
</tr>
<tr>
<td>Fluorinated derivatives</td>
<td></td>
</tr>
<tr>
<td>Disaccharide aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Co-administration of agent preventing intralysosomal phospholipidosis</td>
<td></td>
</tr>
<tr>
<td>Intralysosomal sequestration of aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Increase of membrane negative charge</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>III. Protection against necrosis and other gross cellular alterations</td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td></td>
</tr>
<tr>
<td>IV. Protection against vascular and glomerular effects</td>
<td></td>
</tr>
<tr>
<td>Suppression of renin-angiotensin activation</td>
<td></td>
</tr>
<tr>
<td>Protection against Ca²⁺ influx</td>
<td></td>
</tr>
<tr>
<td>Undefined mechanism</td>
<td></td>
</tr>
<tr>
<td>V. Increase in kidney regeneration capabilities</td>
<td></td>
</tr>
<tr>
<td>Ursodiol</td>
<td></td>
</tr>
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<td>Antioxidant and multifactorial factors</td>
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</tr>
<tr>
<td>Antioxidant and multifactorial factors</td>
<td></td>
</tr>
</tbody>
</table>

---


A long list...
Aminoglycosides nephrotoxicity incidence is highly variable among patient populations

Patients with nephrotoxic reaction after treatment with gentamicin

- young volunteers
  - Smith et al., 1982

- random hospital population
  - Smith et al., 1980

- critically-ill patients
  - Plaut et al., 1979
High doses in animals cause renal necrosis, tubular dysfunction, and renal failure associated with regeneration.

Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day).
From Ref. 13.

Looking at the kidney with "plastic sections"
What does happen in the kidney proximal tubules?

gentamicin-treated: perfused kidney

gentamicin-treated: unperfused kidney
Gentamicin accumulates in lysosomes of proximal tubular cells

Schmitz et al., J. Biol. Chem. 277:618-622, 2002
Aminoglycoside entry in proximal tubular cells is via brush border binding...

- binding to
  - megalin
    (Moeströp et al., 1995)
  - acidic phospholipids
    (Humes et al, 1983)

Silverblatt & Kuehen, Kidney Intern., 1979
Mice deficient in megalin do not accumulate gentamicin in kidney

Schmitz et al., J. Biol. Chem. 277:618-622, 2002
Mechanism of uptake

1. binding to brush border
2. accumulation in lysosomes
Intralysosomal gentamicin binds to phospholipids and causes phospholipidosis

Tulkens, Am. J. Med. 80:105-114, 1986
A first global hypothesis ?...
Could lysosomal rupture cause apoptosis and necrosis?

Maldague et al., 1983

Servais et al., 2006
The current hypothesis…

- gentamicin enters proximal tubular cells by megalin- and acid phospholipids mediated pinocytosis and ends up in lysosomes.
- A minor part escapes lysosomes either by membrane destabilization (our hypothesis) or by retrograde transport (Molitoris' hypothesis) to reach the cytososol and the mitochondria … where it induces apoptosis and other toxic disturbances…

Reducing uptake by the kidney would result in reduced toxicity!

Once-a-day administration
Aminoglycoside toxicity is not linked to peak...
Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations ...

Giuliano et al., J. Pharm. Exp. Ther., 1986
Nephrotoxicity and schedule of administration … the first large scale clinical trial

- 141 predominantly elderly patients with severe bacterial infections.
- All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.

"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

And auditory alterations …

no. of patients [over 20 in each group] with lesions* and total no. of frequencies affected

<table>
<thead>
<tr>
<th></th>
<th>low tone (0.25-8 kHz)</th>
<th>high tone (10-18 kHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>amikacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q24h</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>q12h</td>
<td>0</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>netilmicin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q24h</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>q8h</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

* loss of 15dB or more over baseline (max. loss recorded: 30 dB)

Tulkens et al., 1989
Avoiding (or reducing) the toxicity

Aminoglycosides 3d rule of tumb...

give them once-a-day to reduce toxicity
• 1h peaks of 12-18 µg/ml for G, T, N
• 1h peaks of 20-30 µg/ml for A, I

Increase interval (⇒ 36h, ⇒ 48h)
in case of renal failure
before reducing the unit dose...

Once-daily dosing of aminoglycoside antibiotics

Fisman, DN; Beth Israel Deaconess Med Ctr; Div Infect Dis; Harvard Univ, Sch Publ Hlth, INFECTIOUS-DISEASE-CLINICS-OF-NORTH-AMERICA. JUN 2000
3. Monitoring
Monitoring recommendations for the once-a-day…: peak and trough values...

- **peak (1h post infusion)**
  - G, T, N : 18 - 24 mg/l
  - A, I : 25 - 50 mg/L

- **trough (before next dose)**
  - G, T, N : < 1 mg/L
  - A, I : < 2 mg/L

Monitoring is probably unnecessary for short duration therapies… except for efficacy…
Do not minimize the difficulties of a "good peak"

A "Clinical Pharmacy" study about the peak and through levels of amikacin in a Belgian University Hospital

eligible patients: 102
inclusion: 94 patients
111 treatments

vancomycin: 46
peak: 44

amikacin: 65
trough: 62

exclusions:
- 2 for inability to perform observation
- 6 for limited life expectancy

Ampe et al., in preparation
Do not minimize the difficulties of a "good peak"

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peak: 44

trough: 62

exclusions:
• 2 for inability to perform observation
• 6 for limited life expectancy

Ampe et al., in preparation
Points to consider for a "good peak"

1. the "time" of the real peak is highly dependent of your rate of infusion

Data for amikacin:
- **D** = 15 mg/kg
- **V_d** = 0.25 L/kg
- **ka** = variable
- **ke** = 0.346 h\(^{-1}\) (t\(_{1/2}\) = 2h)

Mathematical formula:

\[
C = \left(\frac{D}{V_d}\right) \times \frac{ka}{(ka-ke)} \times \left[ e^{-ke \times t} - e^{-ka \times t} \right]
\]

Graph showing the influence of rate of administration on the "1h peak" with different infusion rates.
Points to consider for a "good peak"

2. and the timing of the sample is even more critical

Data for amikacin:
D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} (t_{1/2} = 2h)

\[ C = \frac{D}{V_d} \times \frac{ka}{(ka - ke)} \times \left[ e^{-ke \times t} - e^{-ka \times t} \right] \]
The American Approach: Look for 8 h …

All that is less variable at 8 h!

**Data for amikacin:**
- \( D = 15 \text{ mg/kg} \)
- \( V_d = 0.25 \text{ L/kg} \)
- \( ka = \text{variable} \)
- \( ke = 0.346 \text{ h}^{-1} (t_{1/2} = 2\text{h}) \)

\[
C = \frac{D}{V_d} \frac{ka}{(ka-ke)} \left[ e^{-ke \times t} - e^{-ka \times t} \right]
\]

\( T_{1/2} \) in min = 5 to 30 min
The American Approach: Look for 8 h

Still some variation but will less influence the calculation….

Data for amikacin:
- \( D = 15 \text{ mg/kg} \)
- \( V_d = 0.25 \text{ L/kg} \)
- \( ka = \text{variable} \)
- \( ke = 0.346 \text{ h}^{-1} (t_{1/2} = 2\text{h}) \)

\[
C = \frac{D}{V_d} \times \frac{ka}{(ka-ke)} \times [e^{-ke \times t} - e^{-ka \times t}]
\]
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let us first see Vd

Data for amikacin:
\[ D = 15 \text{ mg/kg} \]
\[ V_d = \text{variable} \]
\[ ka = 2.772 \text{ h}^{-1} (t_{1/2} = 15 \text{ min}) \]
\[ ke = 0.346 \text{ h}^{-1} (t_{1/2} = 2\text{h}) \]
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let us first see Vd and zoom at 8h ...

you will detect easily an abnormal Vd
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let now see the elimination ($K_e$)

Data for amikacin:
- $D = 15 \text{ mg/kg}$
- $V_d = 0.25 \text{ L/kg}$
- $k_a = 2.772 \text{ h}^{-1}$ ($t_{1/2} = 15 \text{ min}$)
- $k_e = \text{variable}$
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination).

Let now see the elimination ($K_e$)

You do not even need to zoom!
The Hartford study (gentamicin)


Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

DAVID P. NICOLAU,1,2,3* COLLIN D. FREEMAN,1,3† PAUL P. BELLIVEAU,1,3‡ CHARLES H. NIGHTINGALE,3,4 JACK W. ROSS,2 AND RICHARD QUINTILIANI3,5

Department of Pharmacy,1 Office for Research4 and Department of Medicine,2 Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut 06102; School of Pharmacy, University of Connecticut, Storrs, Connecticut 062683; and School of Medicine, University of Connecticut, Farmington, Connecticut 060325

Received 11 April 1994/Returned for modification 2 October 1994/Accepted 8 January 1994
The Hartford study (gentamicin)

FIG. 2. Simulated concentration-versus-time profile of once-daily (7 mg/kg q24h) and conventional (1.5 mg/kg q8h) regimens for patients with normal renal function.

The Hartford study (gentamicin): recalculated for you …

**gentamicin**  
model of Nicolau et al. (1995)

\[ C = \frac{D}{V_d} \times ka / (ka-ke) \times [e^{-ke \times t} - e^{-ka \times t}] \]

- **D** = 7 mg/kg  
- **V_d** = 0.25 L/kg [Cl_{95}=0.22-0.29]  
- **ka** = 2.72  
- **ke** = 0.18 (t_{1/2} = 3.85 h)
The Hartford study (gentamicin)

FIG. 3. Simulated concentration-versus-time profile of once-daily 7- and 5-mg/kg regimens for patients with various CL\textsubscript{CR}s.

Take it easy: Hartford method
(Nicolau's nomogram for gentamicin)

Take it easy: Hartford method (Nicolau’s nomogram for gentamicin)

1. obtain a single random blood sample between 6 and 14 h after the start of the infusion
Take it easy: Hartford method
(Nicolau’s nomogram for gentamicin)

1. Obtain a single random blood sample between 6 and 14 h after the start of the infusion
2. Place value in nomogram
Take it easy: Hartford method (Nicolau’s nomogram for gentamicin)

1. Obtain a single random blood sample between 6 and 14 h after the start of the infusion

2. Place value in nomogram

3. Read interval corresponding to the zone of the nomogram
Take home message

• Maximize peak to increase efficacy and reduce toxicity
• Administer once-a-day
• Measure MIC and calculate the dose that is needed
• Reduce treatment duration as much as possible
• Do monitoring if
  - treatment > 5 days
  - special populations
  - risk factors
  - co-administration of other nephrotoxic drugs