Clinical Pharmacokinetics

Aminoglycoside Pharmacokinetics

Ronald A. Herman

University of Iowa Hospitals & Clinics
Department of Pharmaceutical Care

The University of Iowa College of Pharmacy
REAL WORLD | REAL EXCELLENCE | REAL IMPACT

Objectives

- Describe the pharmacological properties and clinical indications of aminoglycosides.
- Describe the absorption, distribution and elimination of aminoglycosides.

Objectives

- Describe the therapeutic window for aminoglycoside concentrations and explain pharmacodynamic considerations for interpreting a given concentration.
- List criteria for when conventional and pulse dosing of aminoglycosides is appropriate.

Objectives

- Recommend appropriate sampling times and monitoring parameters for a given patient's demographic characteristics and clinical setting.
- Given a patient's demographic characteristics without concentration-time data, calculate the appropriate initial dosage regimen.

Objectives

- Given a patient's demographic characteristics and aminoglycoside concentration-time data, calculate a dosage regimen to achieve a desired peak and trough concentration.
- Recommend an appropriate initial extended interval dosing regimen and explain how to adjust extended interval therapy.

Aminoglycosides

(*Chapter 14, pp 299-300*)

- Semisynthetic Antibiotic
- Mechanism of Action
  - Concentration dependent killing by interfering with cell wall synthesis.
- Spectrum of Activity
  - Fairly broad spectrum of activity with some gram +, but mostly gram – activity.

Basic Pharmacokinetics

- **L** iberation
- **A** bsorption
- **D** istribution
- **M** etabolism
- **E** limination
- **T** herapeutic Drug Monitoring

Liberation and Absorption

(Chapter 14, p 286)

- No special release dosage forms available

- Oral Absorption

- Parenteral Absorption
  - Good IM absorption
  - Peak 30-120 min

Distribution

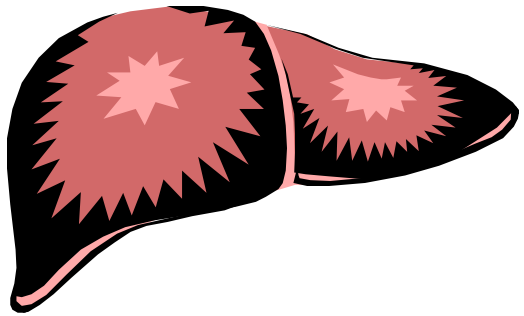
(*Chapter 14, pp 287*)

- **Fairly rapid, but measurable distribution**
- **Protein binding is low (< 10%)**
- **Approximates extracellular fluid distribution**
- **Poor lipid solubility**
  - **Distribution into adipose tissue**
  - **Penetration into the CSF**

Metabolism

- 85-95 % is excreted unchanged.

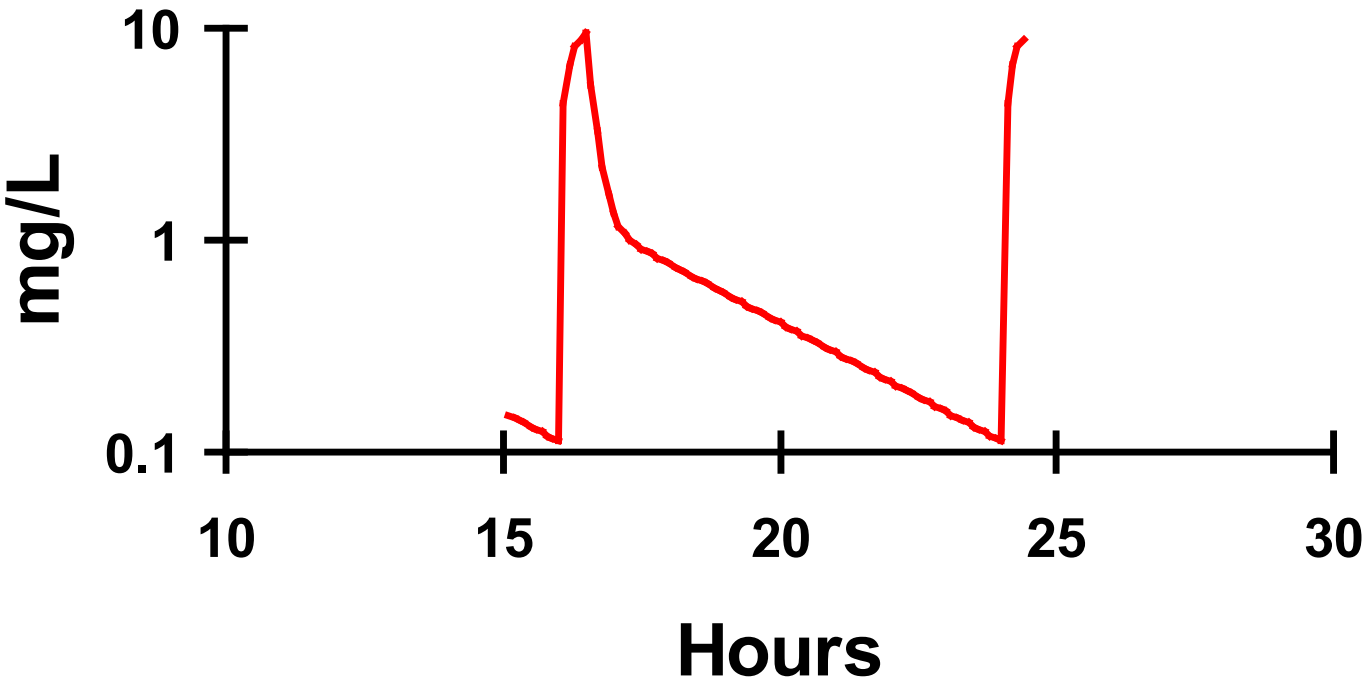
Gyselynck et al, *J Infect Dis* 1971,S70-6.



Elimination

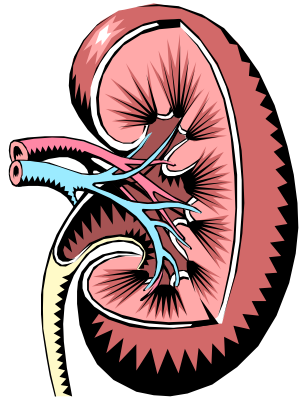
(*Chapter 14, pp 289-292*)

Tri-exponential Disposition



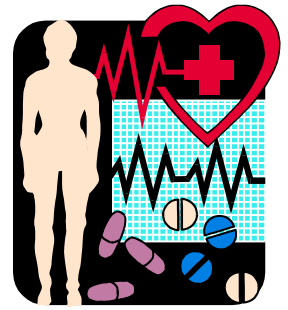
Distribution and Elimination

- **Volume of Distribution**
  - Normal subject — V_{ss} = 0.2–0.25 L/Kg
  - Dehydrated subject — V_{ss} = 0.15 L/Kg
  - Overhydrated subject — V_{ss} = 0.30 L/Kg
- **Elimination Half-Lives**
  - α = 5 minutes
  - β = 2-4 hours
  - γ = 100 hours



Pharmacodynamic Characteristics

(Chapter 16, pp 342-347)



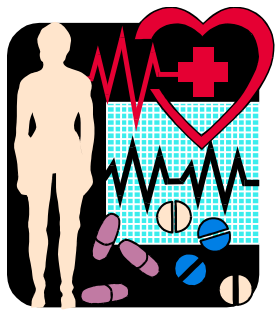
Concentration Effect Relationship

Concentration Dependent Activity:

- The rate and/or extent of antibacterial activity is improved as the concentration of the drug increases at the site of action.
- The parameters which describe this are the peak:MIC ratio and the AUC:MIC ratio.
- Maximum effect is noted when the concentrations are 8 – 20 times the MIC.

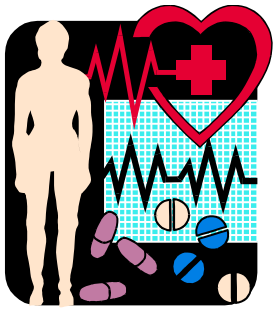
Pharmacodynamic Characteristics

- **Concentration Effect Relationship**
  - **Non-concentration Dependent Activity:**
    - The rate and/or extent of kill are not improved once the concentration exceeds 2-4 times the MIC. **e.g. Vancomycin**



    - Activity is most closely associated with the duration of exposure.
    - Thus the time the concentration is above the MIC is most important.

Pharmacodynamic Characteristics



❁ Post-Antibiotic Effect (PAE)

- ✵ It is the persistent inhibitory effect of the antibiotic following its removal.
  - ➢ Could be due to non-lethal cellular damage.
  - ➢ Residual drug binding to the target site.
- ✵ Can be dosed at intervals longer than half-life would suggest.

Toxicity Considerations

(*Chapter 14, pp 293-298*)

- **Nephrotoxicity**
  - **Generally reversible**
  - **Thought to be due to prolonged elevation of trough > 2 mg/L**
- **Ototoxicity**
  - **Often it is not reversible**
  - **May be due to elevated peaks, but data is unclear.**

Target Concentrations

Traditional Dosing

(Chapter 14, p 306)

	Peak (mg/L)	Trough (mg/L)
Gentamicin	6-10	1
Tobramycin	6-10	1
Amikacin	20-30	10

Dosing Interval is generally every 8 to 24 hours.

Target Concentrations

(Chapter 14, pp 304-305)

☸ Extended Interval (Once Daily) Approach

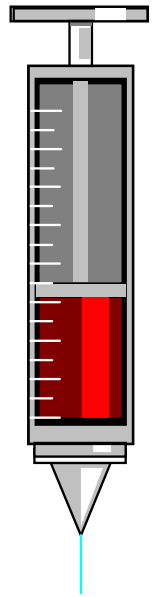
✵ Dose to optimize peak:MIC ratio

Target is approximately
10:1 to 20:1

Dosing Interval is generally every 24 hours.

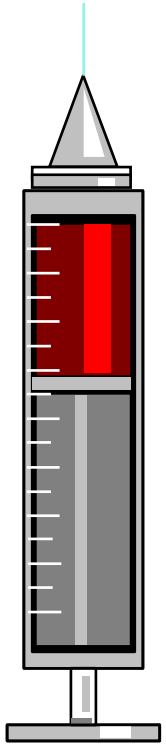
Blood Level Determinations

- **Multiple Dosing:**
  - When you reach steady state.
  - When distribution is complete.
- **Extended Interval Regimen**
  - Single level, 6-14 hours after the first dose.



Optimum Sampling Times

- **Aminoglycosides (MD)**
  - **Trough within 30 minutes of a scheduled dose.**
  - **Infusion – 30 minutes for traditional dosing.**
  - **Peak 30 minutes after the infusion stops.**



Extended Interval Dosing

- **Initial Dose**
  - **5-7 mg/Kg (for adults)**
  - **Children – based on age**
- **Initial Interval**
  - **Based on CrCl estimate (for adults)**
- **Dosage Adjustment**
  - **Measure single level 6-14 hours after the initial dose.**
  - **Adjust interval according to the nomogram.**

Nicolau: *Antibmicrob Agents Chemother* 1995

Hartford Hospital EID
Once-Daily Aminoglycoside (ODA)

CrCl (ml/min)	Adult Initial Dosing
> 60	7 mg/kg every 24 h
40–59	7 mg/kg every 36 h
20–39	7 mg/kg every 48 h
< 20	7 mg/kg, then follow serial levels *

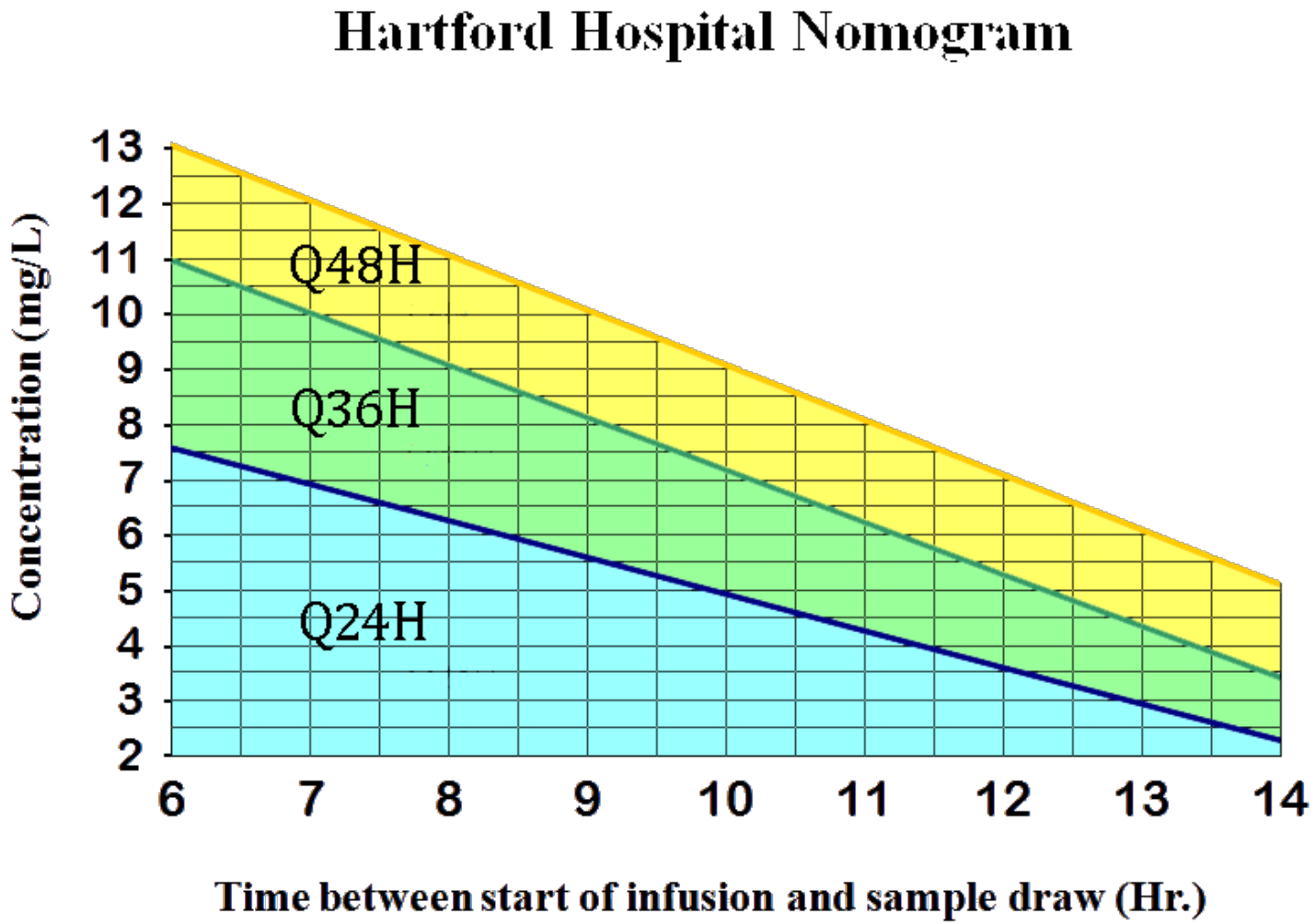
* Some say just use conventional dosing.

Hartford Hospital EID
Once-Daily Aminoglycoside (ODA)

Age	Pediatric Initial Dosing
3 mo. – 2 yr	9.5 mg/kg every 24 h
2 yr – 8 yr	8.5 mg/kg every 24 h
> 8 yr	7.0 mg/kg every 24 h

McDade EJ, Wagner JL, Moffett BS, Palazzi DL. Once-daily gentamicin dosing in pediatric patients without cystic fibrosis. *Pharmacotherapy* 2010;30(3):248-53.

Hartford Hospital Nomogram EID



Predicting Steady Levels

- Target concentrations.
- Volume of distribution.
- Rate of elimination.

Prospectively

- **Population Pharmacokinetic Estimates**

Gentamicin

$$K_e = 0.015 + (0.00285 \times CrCl)$$

Tobramycin

$$K_e = 0.010 + (0.0031 \times CrCl)$$

Amikacin

$$K_e = 0.010 + (0.0024 \times CrCl)$$

$$CrCl = \frac{(140 - Age) \cdot CrClWt}{72 \cdot SrCr}(0.85 + Sex \cdot 0.15)$$

Cockcroft & Gault:
Nephron 1976;6:31-41.

Prospectively (K_e)

- If the patient is < IBW
  - use CrClWt = ActBW.
- If the patient is > IBW and BMI < 25 Kg/m^2
  - use CrClWt = IBW
- If the patient has a BMI ≥ 25 Kg/m^2
  - Use CrClWt = AdjWT
  - = IBW + 0.4*(ActBW – IBW)

Volume of Distribution

Aminoglycosides

Normal hydration: $V_f = 0.225$ L/Kg

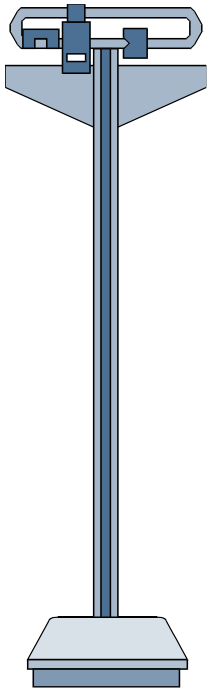
Overhydration: $V_f = 0.30$ L/Kg

Dehydration: $V_f = 0.15$ L/Kg

Use an adjusted body weight (DWT)

If ABW > 30% over IBW – otherwise use ABW for DWT

Dosing Weight



IBW (males) =

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females) =

45.5 Kg + 2.3 Kg/inch over 5 feet

If ABW is > 30% over IBW, then

DWT = (ABW - IBW)(0.4) + IBW

Sawchuk - Zaske Approach to Dosage Adjustment

1. Calculate the elimination rate constant.

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln C_{pk} - \ln C_{tr}}{t_{tr} - t_{pk}} = \frac{\ln\left(C_{pk}/C_{tr}\right)}{\tau - t_{inf} - t_{pi}}$$

2. Calculate C_o (t_{pk} = elapsed time from start of infusion)

$$C_0 = \frac{C_{pk}}{e^{-k_e(t_{pk} - t_{inf})}}$$

Sawchuk - Zaske Approach to Dosage Adjustment

3. Calculate the half-life.

$$t_{1/2} = \frac{\ln 2}{k_e}$$

4. Calculate the volume of distribution.

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{inf}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{inf}})}$$

Sawchuk - Zaske Approach to Dosage Adjustment

5. Calculate the dosing interval.

$$\tau = \frac{\ln\left(C_{Max,desired} / C_{Min,desired}\right)}{k_e} + t_{inf}$$

- Practical
- Estimate

6. Calculate the new infusion rate.

$$R_0 = C_{Max,desired} \cdot k_e \cdot V_{ss} \cdot \frac{\left(1 - e^{-k_e \tau}\right)}{\left(1 - e^{-k_e t_{inf}}\right)}$$

Target Peak (7 mg/L)

Sawchuk - Zaske Approach to Dosage Adjustment

7. Calculate the new peak.

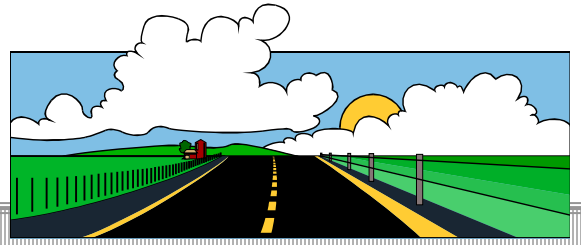
$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \cdot \frac{\left(1 - e^{-k_e t_{inf}}\right)}{\left(1 - e^{-k_e \tau}\right)}$$

8. Calculate the new trough.

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e \left(\tau - t_{inf}\right)}$$

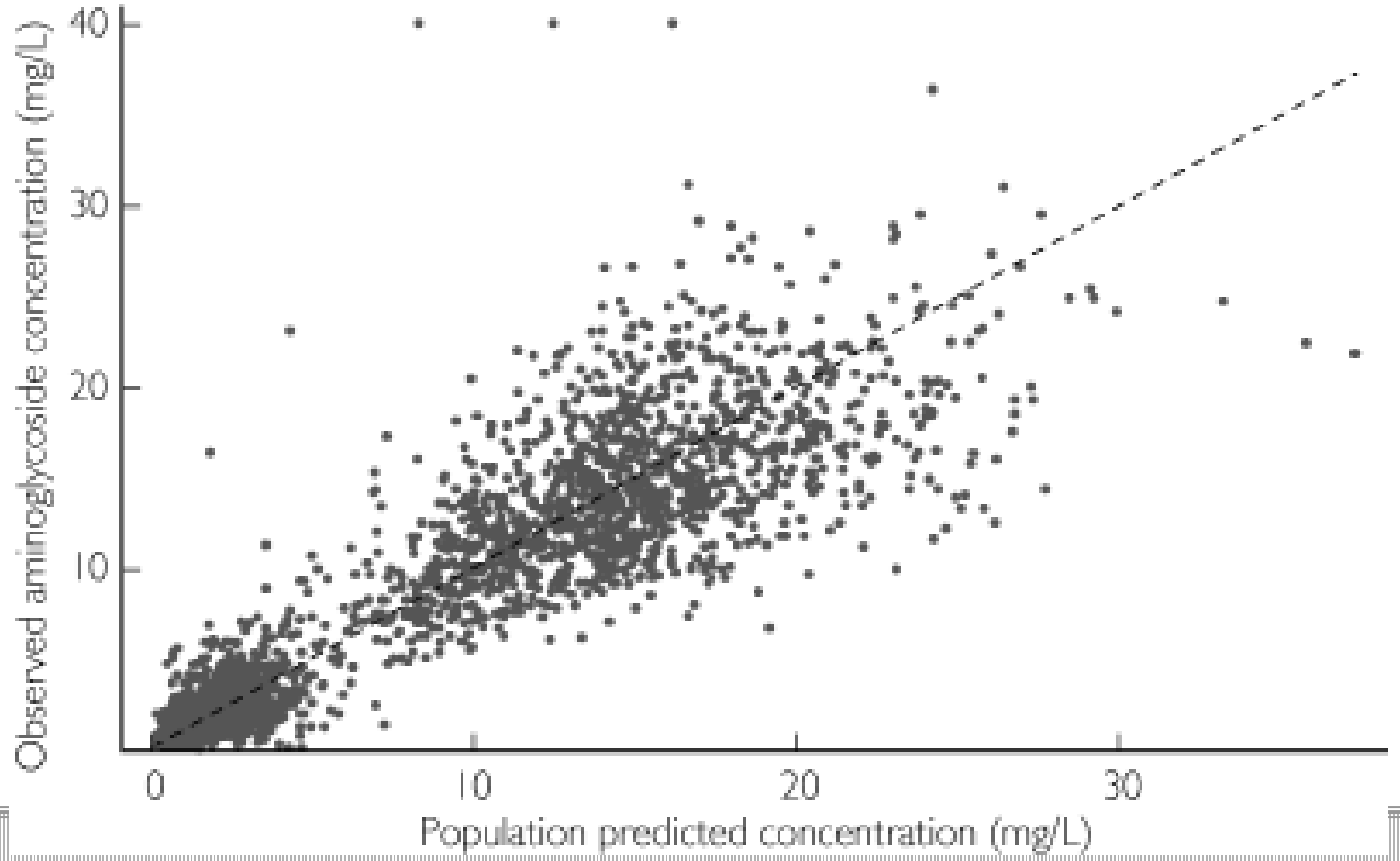
Summary

- Current evidence suggests that EID has some significant therapeutic and economic advantages.
- There are some circumstances where careful monitoring using traditional approaches is still preferred.



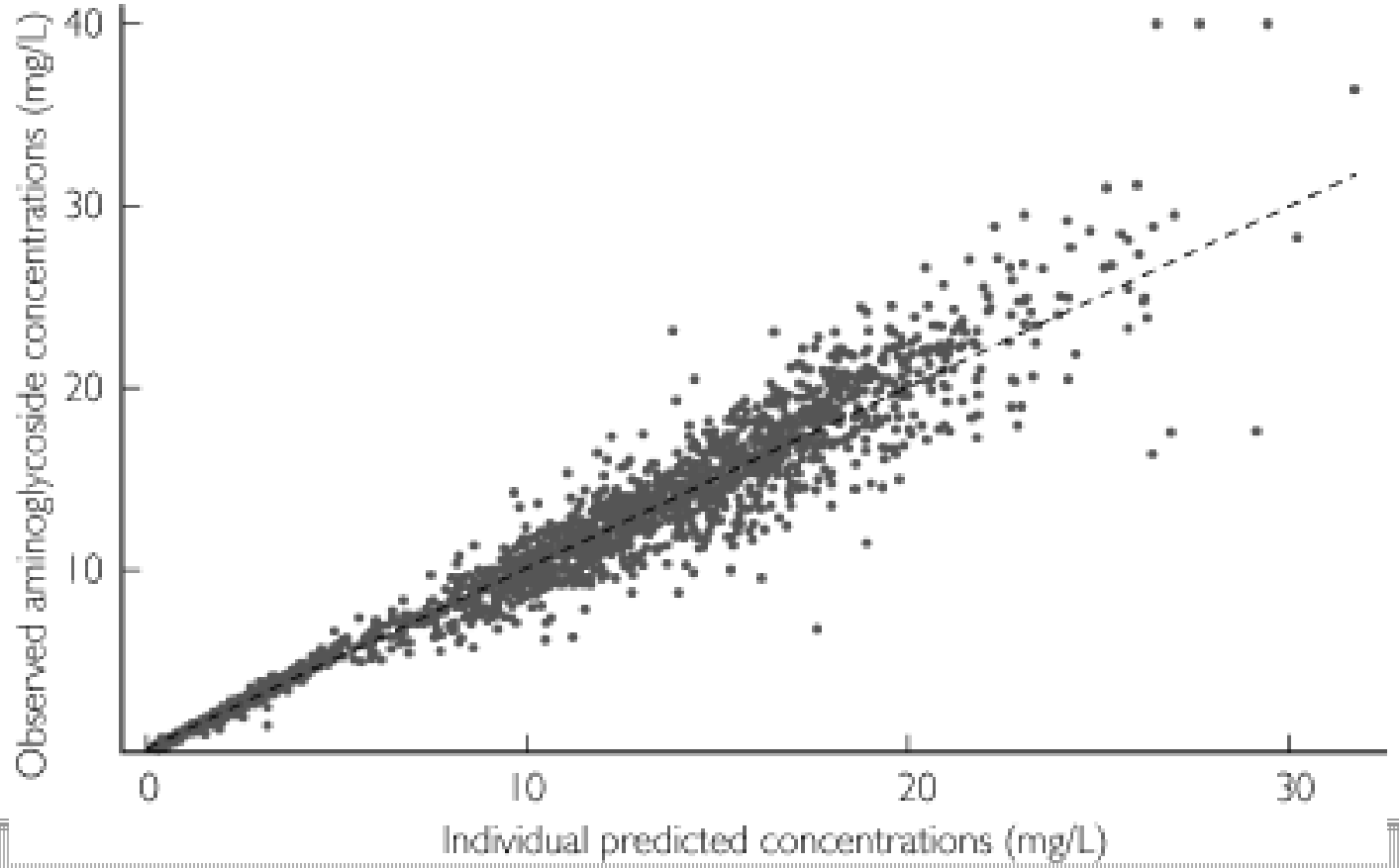
Population predicted concentrations *vs.* observed concentrations.

Matthews et. al. *Br J Clin Pharmacol* 58(1):8-19.



Individual predicted concentrations *vs.* observed concentrations.

Matthews et. al. *Br J Clin Pharmacol* 58(1):8-19.



Cases

Case 6: SW is a 45 YO 180cm male with a *Pseudomonas* pneumonia. His weight is 195 lb. and his serum creatinine is 0.9 mg/dl. Blood pressure, heart rate, skin turgor and vascular filling of neck veins indicate that SW is normally hydrated. What dose (mg) of gentamicin would you recommend for initiation of therapy and what dosing interval would you recommend?

Case 7: If we went with the 140 mg Q8H and the levels came back at 3.3 mg/L at 9:15 am and 0.4 mg/L at 07:50 am and the dose was scheduled to be given at 8:00 am, what recommendation would you make?

Case 8: You have a 64 YO WF who will have abdominal surgery and the physician wants to initiate EID Gentamicin. The patient weighs 79 Kg and is 5'2" and has a SrCr of 1.3. What should be her EID? Then following the initial EID of gentamicin, the patient has a gentamicin level drawn 10.5 hours after the infusion was started. The level came back at 6.5 mg/L. What should be the new EID regimen of gentamicin for the patient based on the Hartford nomogram?