GSK-Chair of Infectious Diseases
(Chaire GSK de Maladies Infectieuses / GSK-Leerstoel in Infectieziekten)
a joint academic activity of the
Université catholique de Louvain **and the** *Katholieke Universiteit Leuven*

How to Adapt Antibiotic Treatments for Elderly and Other Populations

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Applied PK/PD 4 Text: Chapters on Aminoglycosides and Dual Individualization

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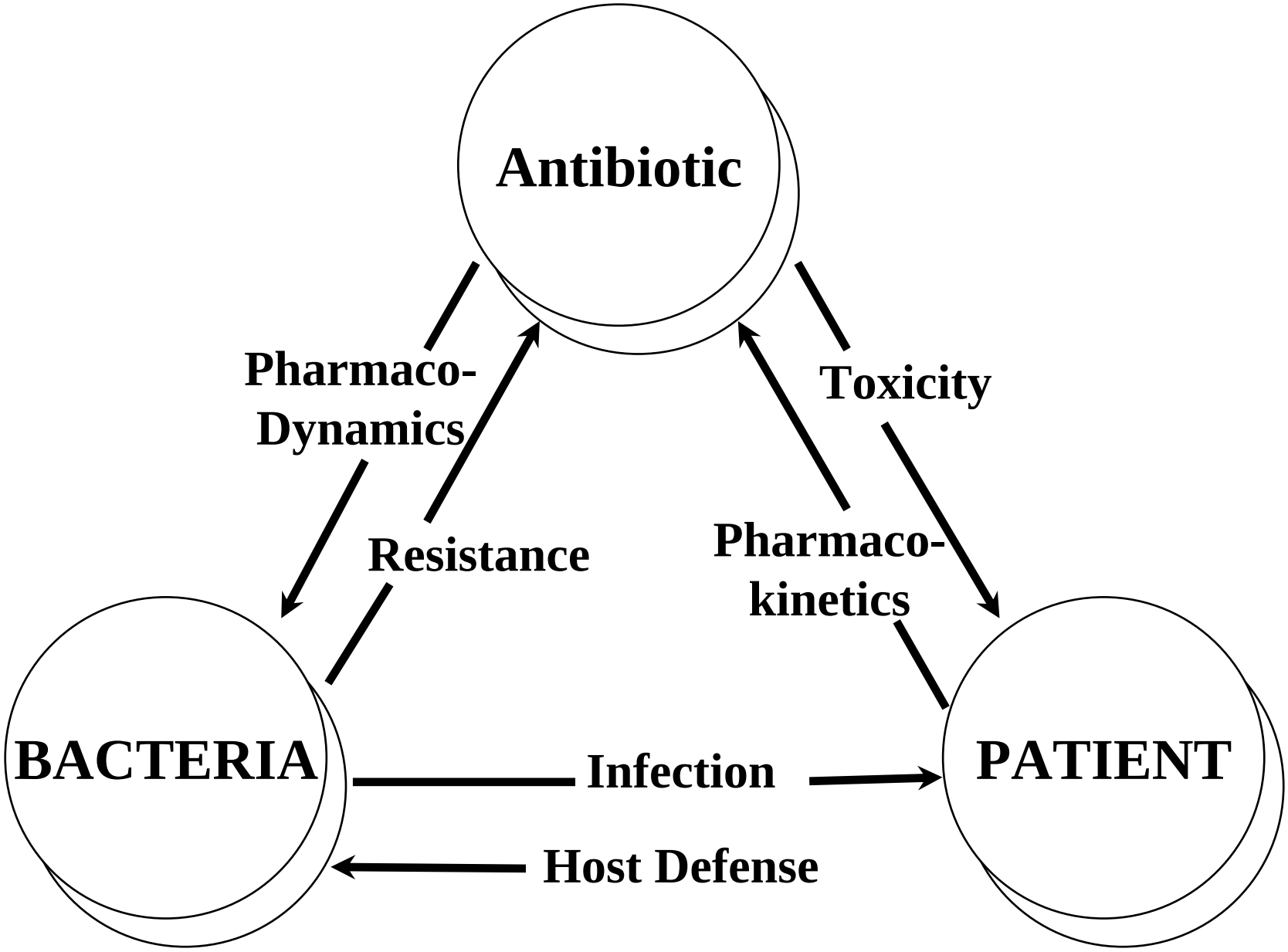
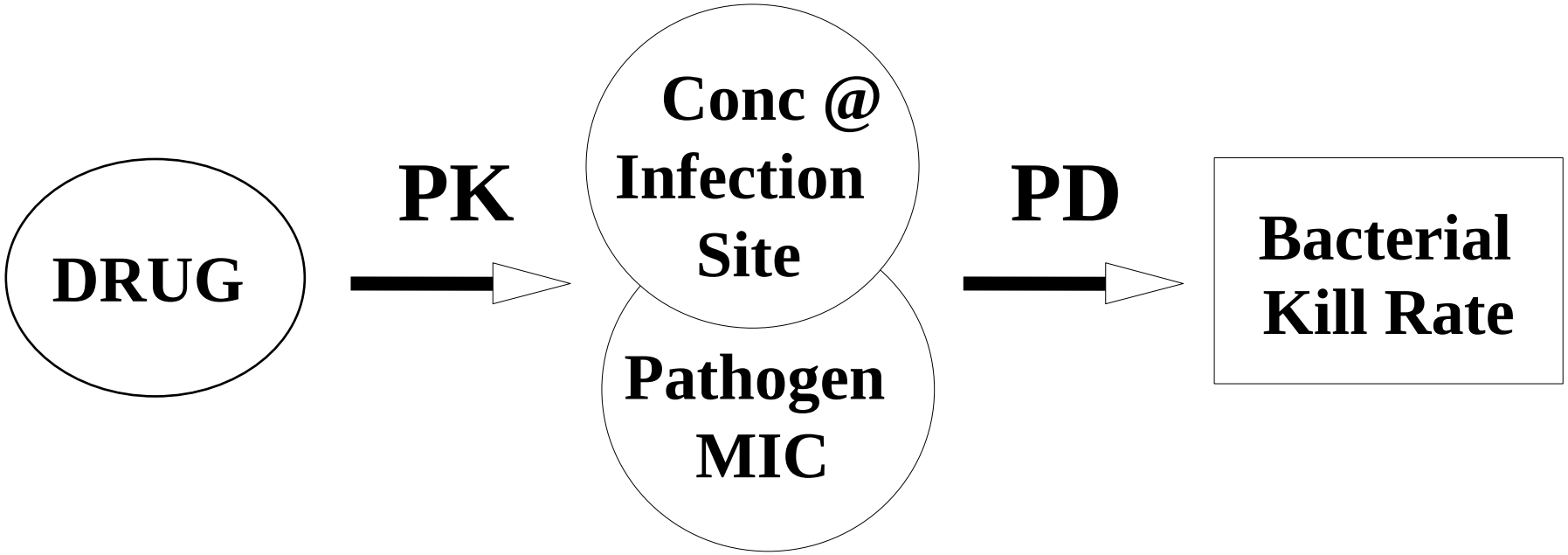
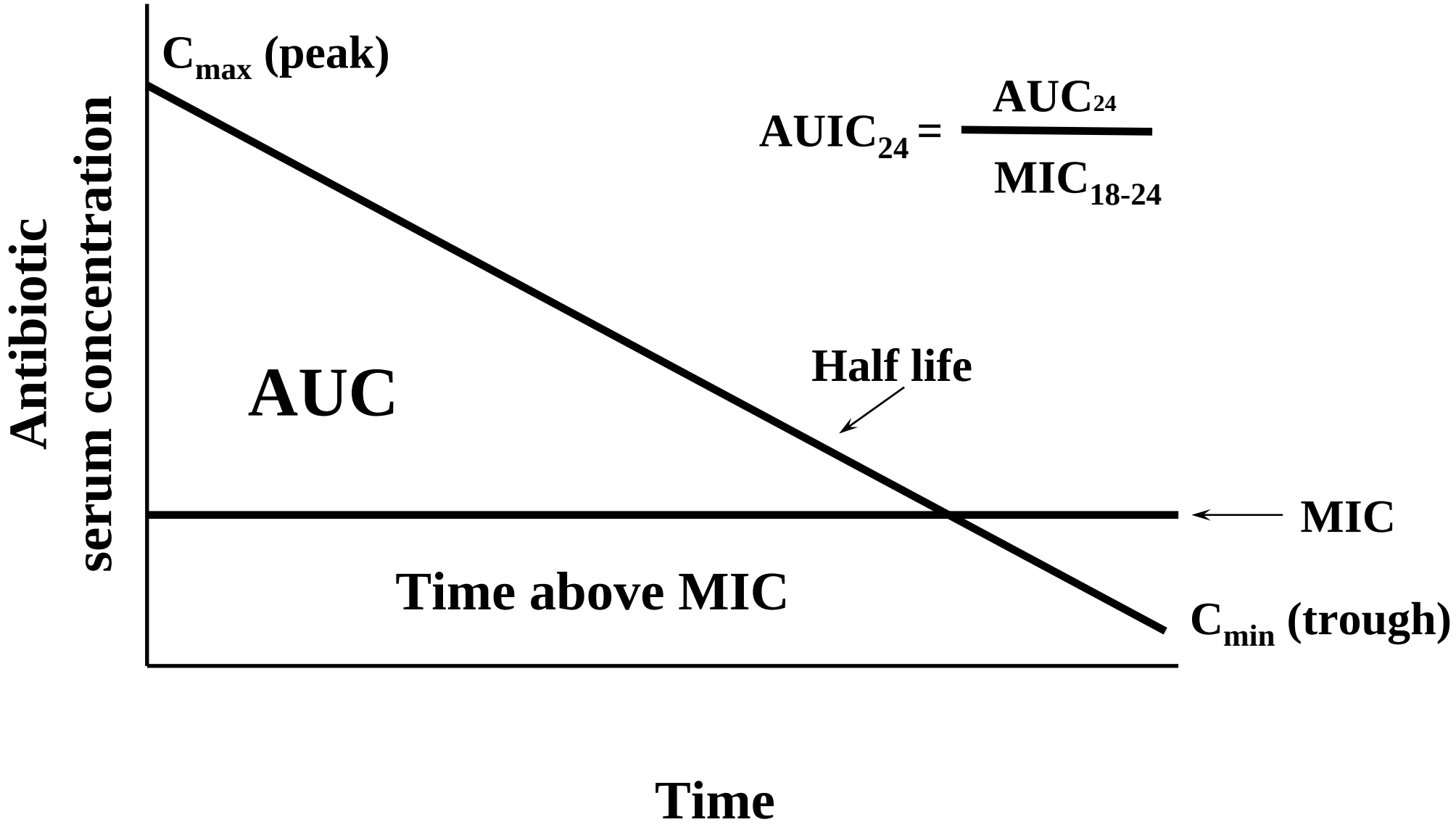
Presented at UCL on Thursday February 28th


Antibiotic
Pharmaco-
Dynamics
Resistance
Toxicity
Pharmaco-
kinetics
BACTERIA
Infection
PATIENT
Host Defense

Optimizing Antimicrobial Therapy




Antibiotic serum concentration
C_{max} (peak)
$AUIC_{24} = \frac{AUC_{24}}{MIC_{18\text{-}24}}$
AUC
Half life
MIC
Time above MIC
C_{min} (trough)
Time

Defined and Optimal PK and PD attributes

- For antimicrobial effect:
  - C_{max}/MIC ratio should be > 8 to 10
  - AUC/MIC ratio for ‘static effect > 30
  - AUC/MIC ratio for ‘cidal should be > 125
  - AUC/MIC ratio should be > 250 for rapid killing of organisms with conc. dependent
- To minimize resistance development:

  -AUC/MIC ratio should be >100

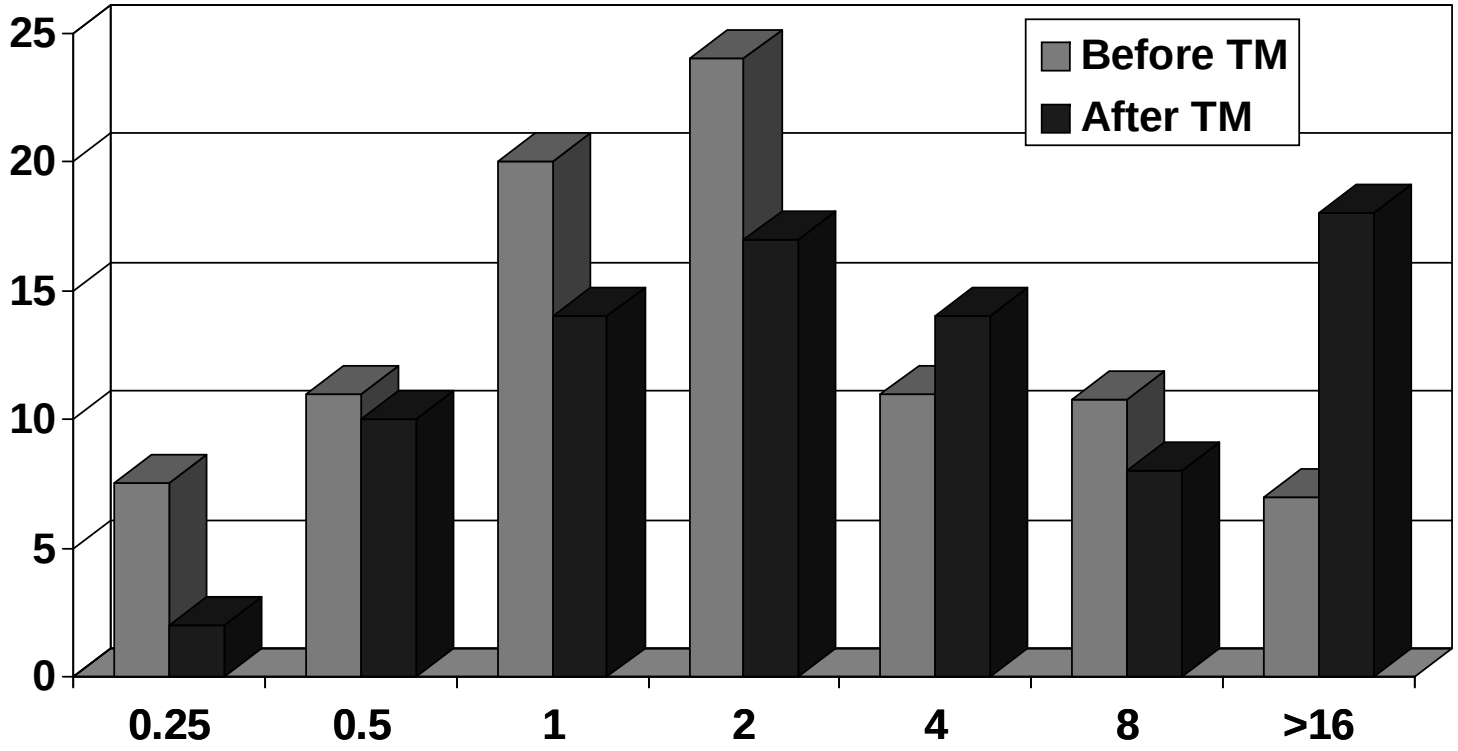
TARGETED OUTCOMES

- Clinical
  - abatement of infection
    - Overall Cure vs Time to symptom Resolution
- Microbiological
  - eradication of the causative organism(s) at EOT
  - Time to eradication
- PK/PD
  - Time to clinical cure vs time to organism eradication

Aminoglycoside Antibiotics

- Gentamicin
- Tobramycin
- Amikacin
- Netilmicin
- Kanamycin
- Streptomycin

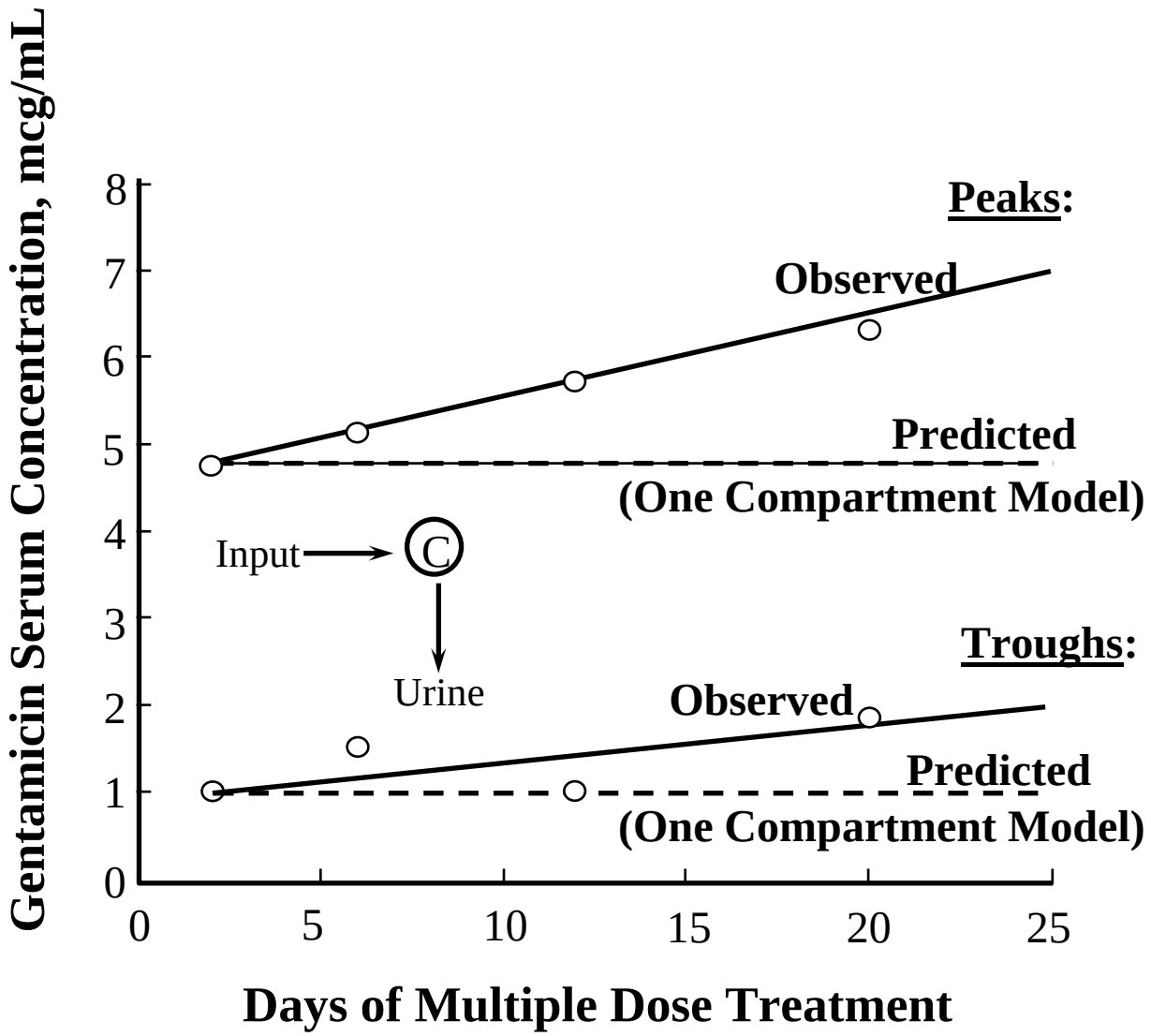
Tobramycin vs Pseudomonas

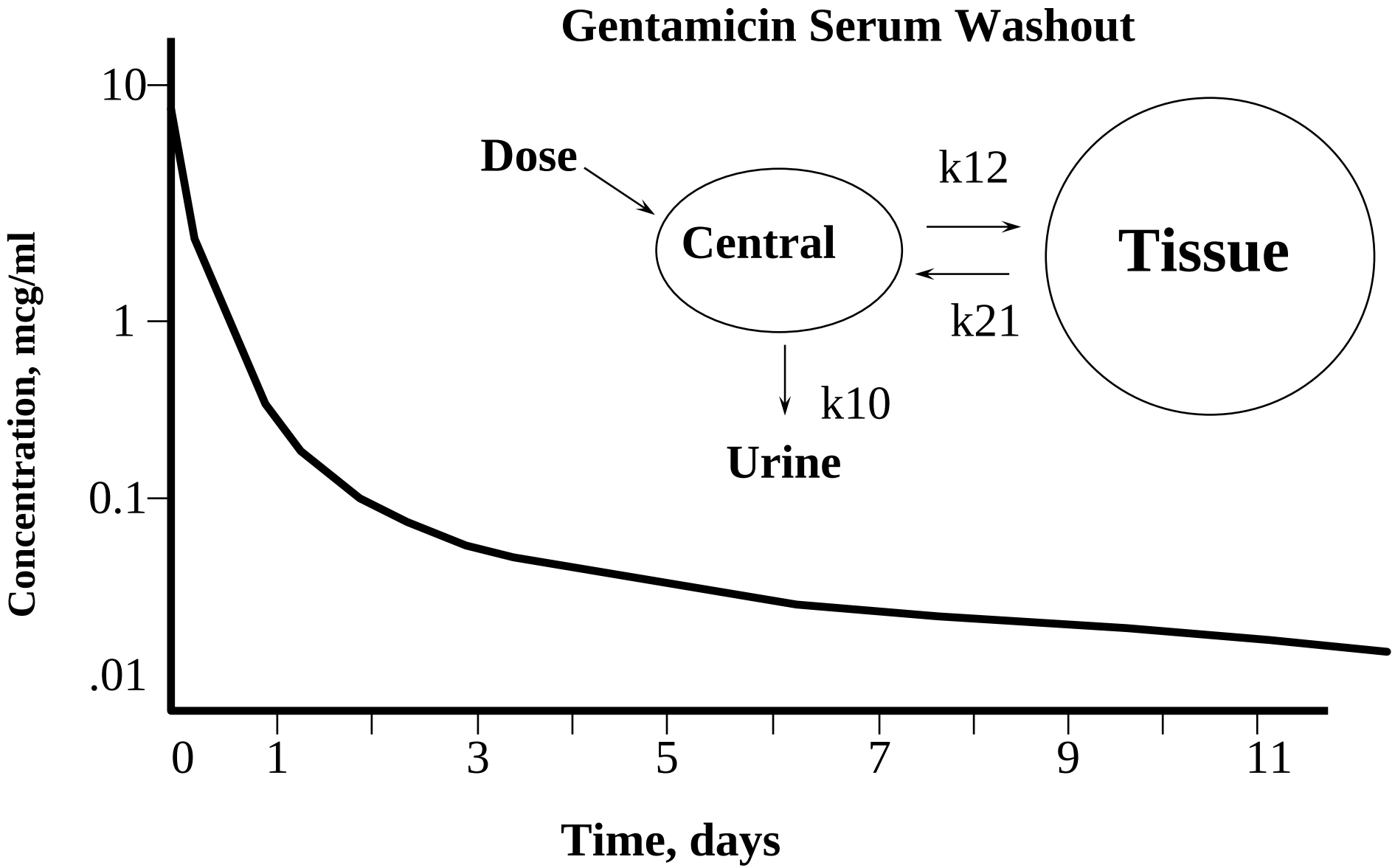


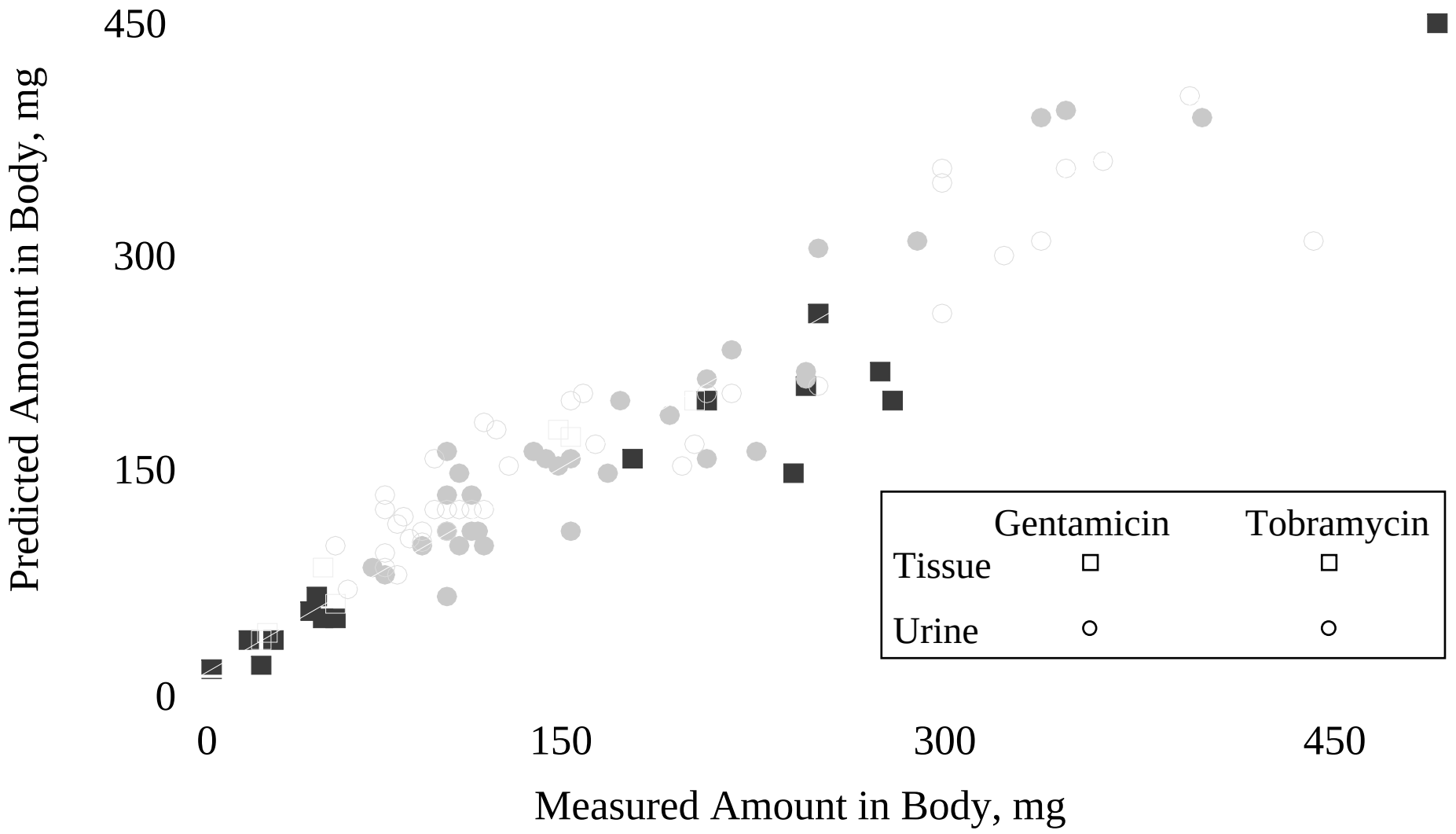
NEJM 340; 23-29, 1999

Aminoglycoside Pharmacokinetics

- Removed by Glomerular Filtration
- No metabolism and minor biliary excretion
- Serum half life is about 2 hrs
  - Only 60-80% of dose found in the urine in the first 24 hrs after the dose
  - Can recover aminoglycosides from urine up to 200 hrs after last dose


Gentamicin Serum Concentration, mcg/mL
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
Days of Multiple Dose Treatment
Peaks:
Observed
Predicted
(One Compartment Model)
Input
C
Urine
Troughs:
Observed
Predicted
(One Compartment Model)


Gentamicin Serum Washout
10
1
0.1
.01
Concentration, mcg/ml
Dose
Central
k12
k21
Tissue
k10
Urine
0
1
3
5
7
9
11
Time, days


Predicted Amount in Body, mg
450
300
150
0
0
150
300
450
Measured Amount in Body, mg
Gentamicin
Tobramycin
Tissue
Urine

Aminoglycoside Accumulation and Disposition

- **Two-compartment model for tissue accumulation**
- **Pharmacokinetic factors in nephrotoxicity**
- **Pharmacodynamics of nephrotoxicity**
  - **Comparisons between aminoglycosides (clinical and pharmacokinetic)**

Methods

- 201 patients given 267 courses of gentamicin or tobramycin
- 240 courses evaluable
  - 120 gentamicin, 120 tobramycin
- Older adults in intensive care units:
  - Age
  - Diseases
  - Renal function
  - Dosing

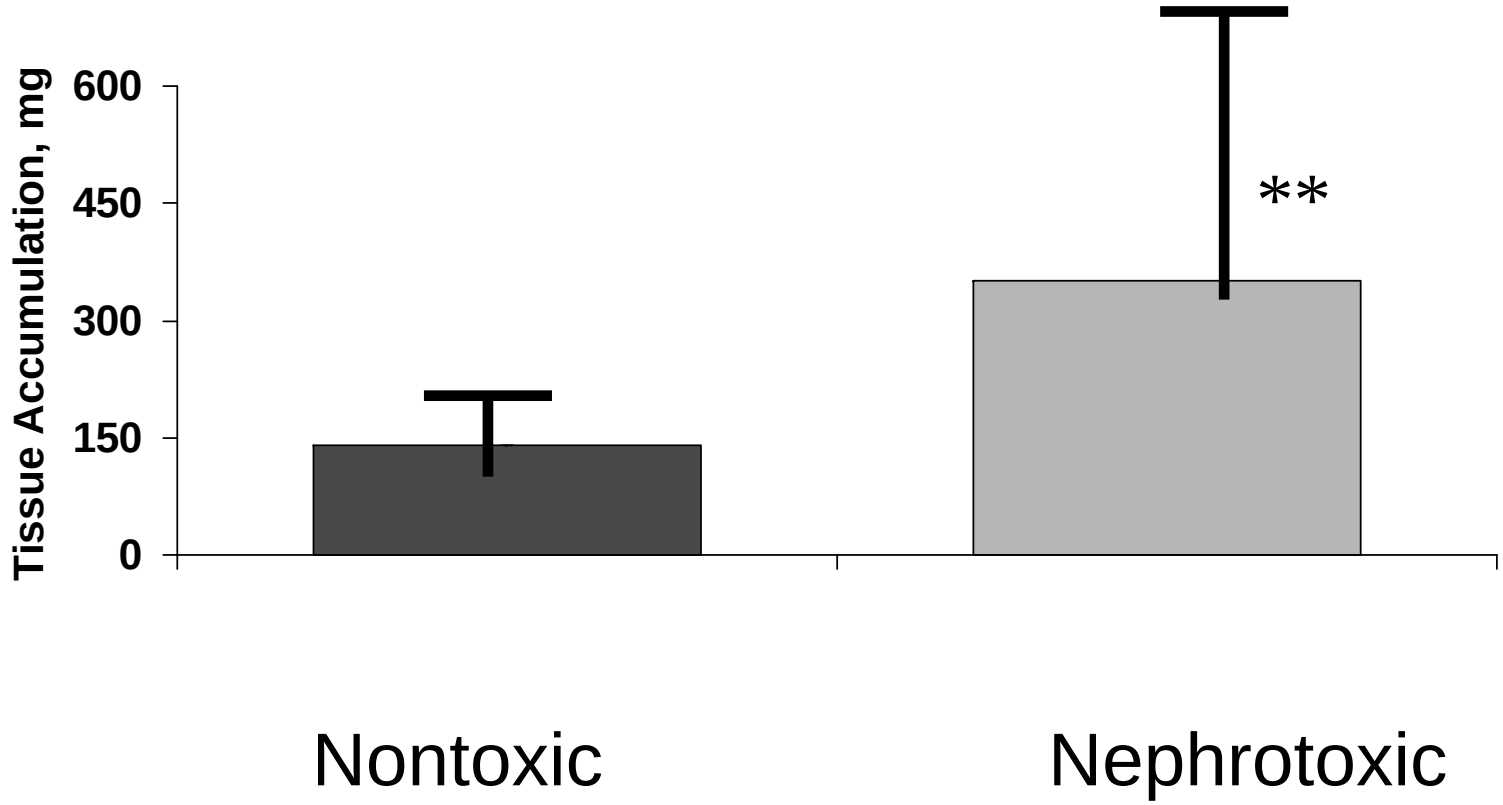
Nontoxic (199) and Nephrotoxic (41) Patients Did Not Differ Statistically In:

- Age (67)
- Sex (60% M)
- Weight (70 kg)
- Baseline C_{cr} (55 ml/min)
- Positive blood cultures
- Concurrent cephalosporin (36%)
- Peaks (5.4 μg/mL)
- Troughs (1.6 μg/mL)
- Duration (10 days)
- Dosage changes (1.1)
- Concurrent diuretics (58%)

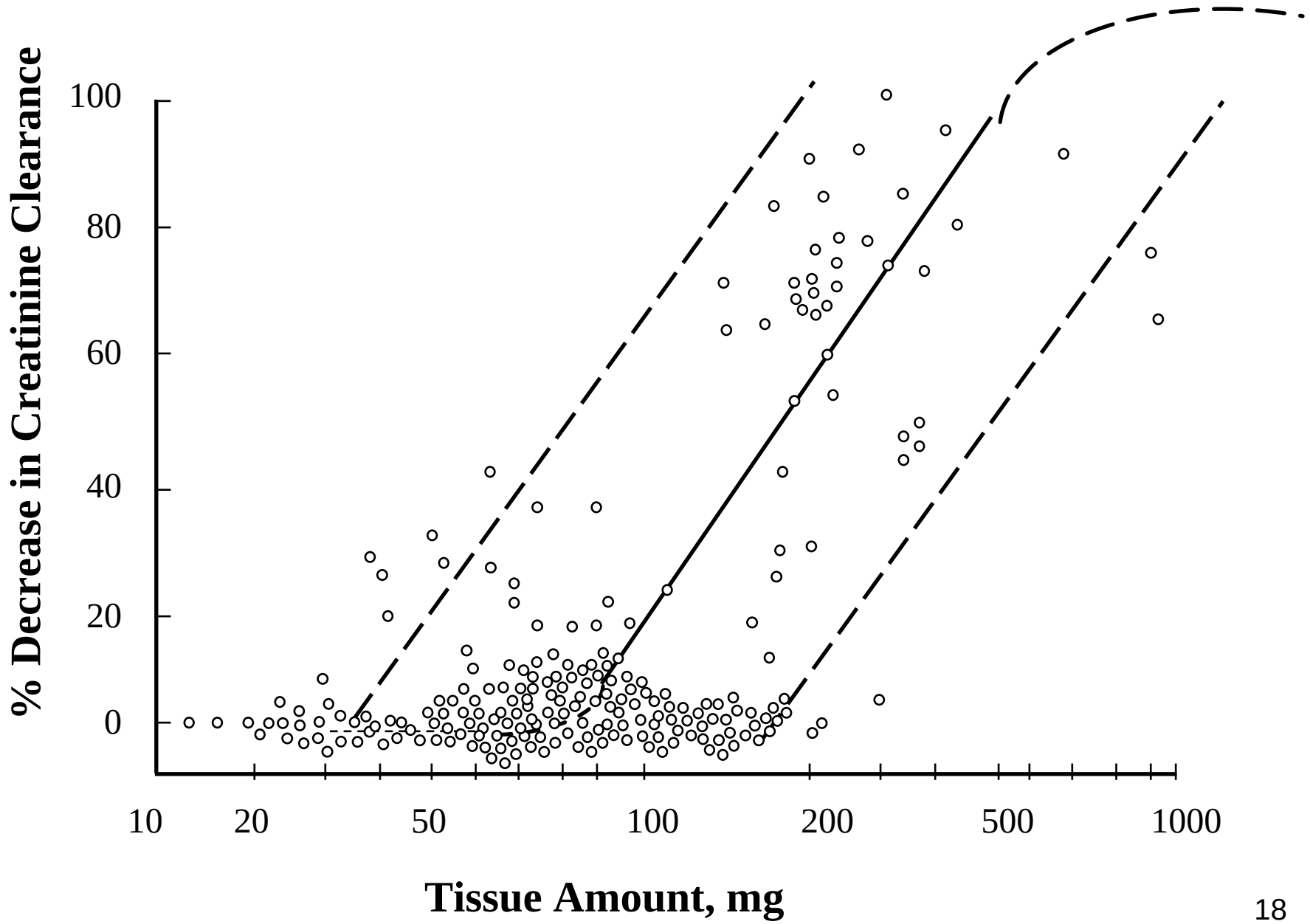
Schentag AAC 21:721-726, 1982.

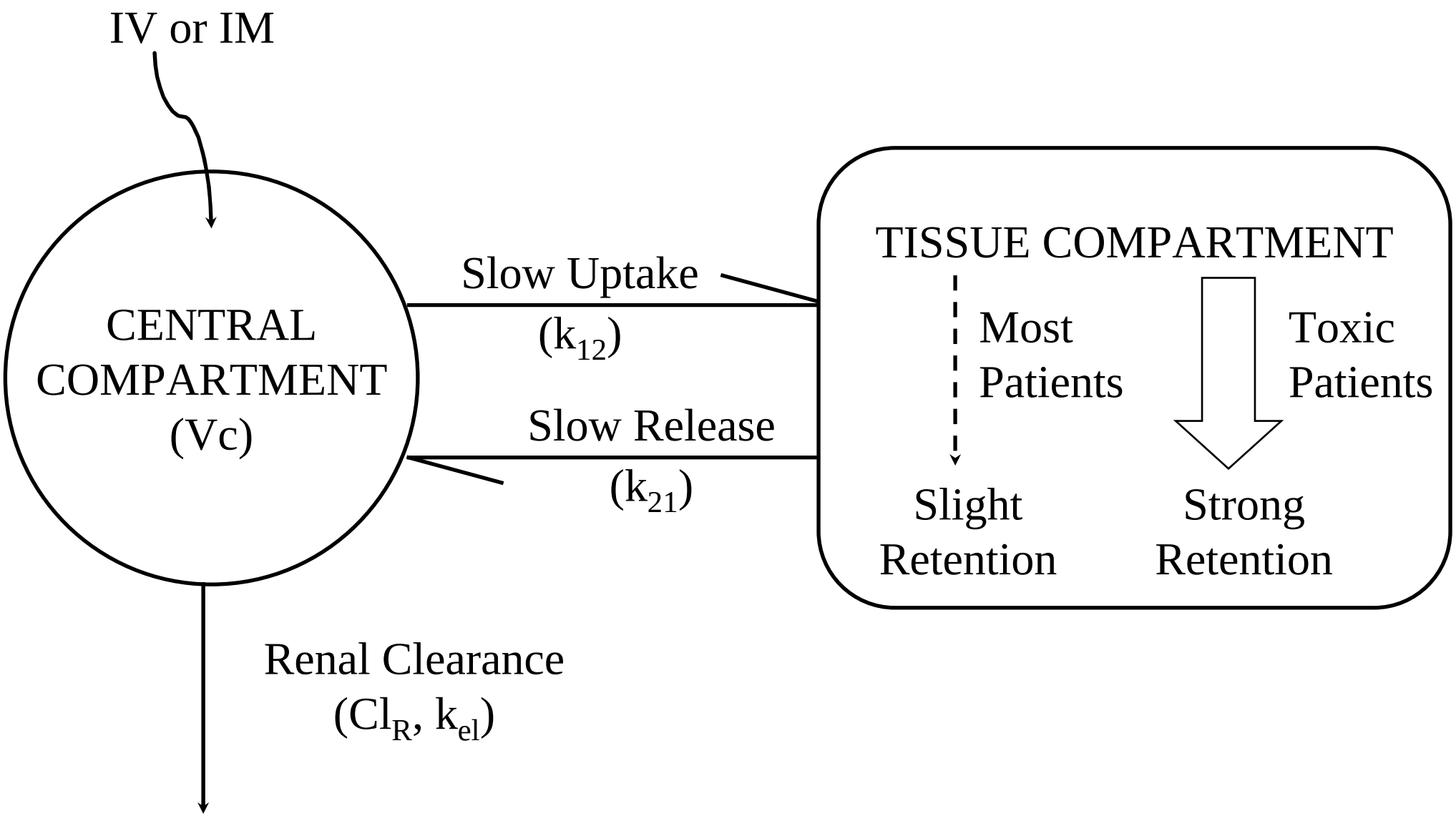
Comparative Tissue accumulation and Toxicity

- **Since aminoglycosides accumulate in all patients who receive them, we compared the rate and extent of tissue accumulation between nontoxic and nephrotoxic patients who were clinically similar.**
- **We sought to determine if abnormally high serum and tissue accumulation was present before renal function changes were detectable.**



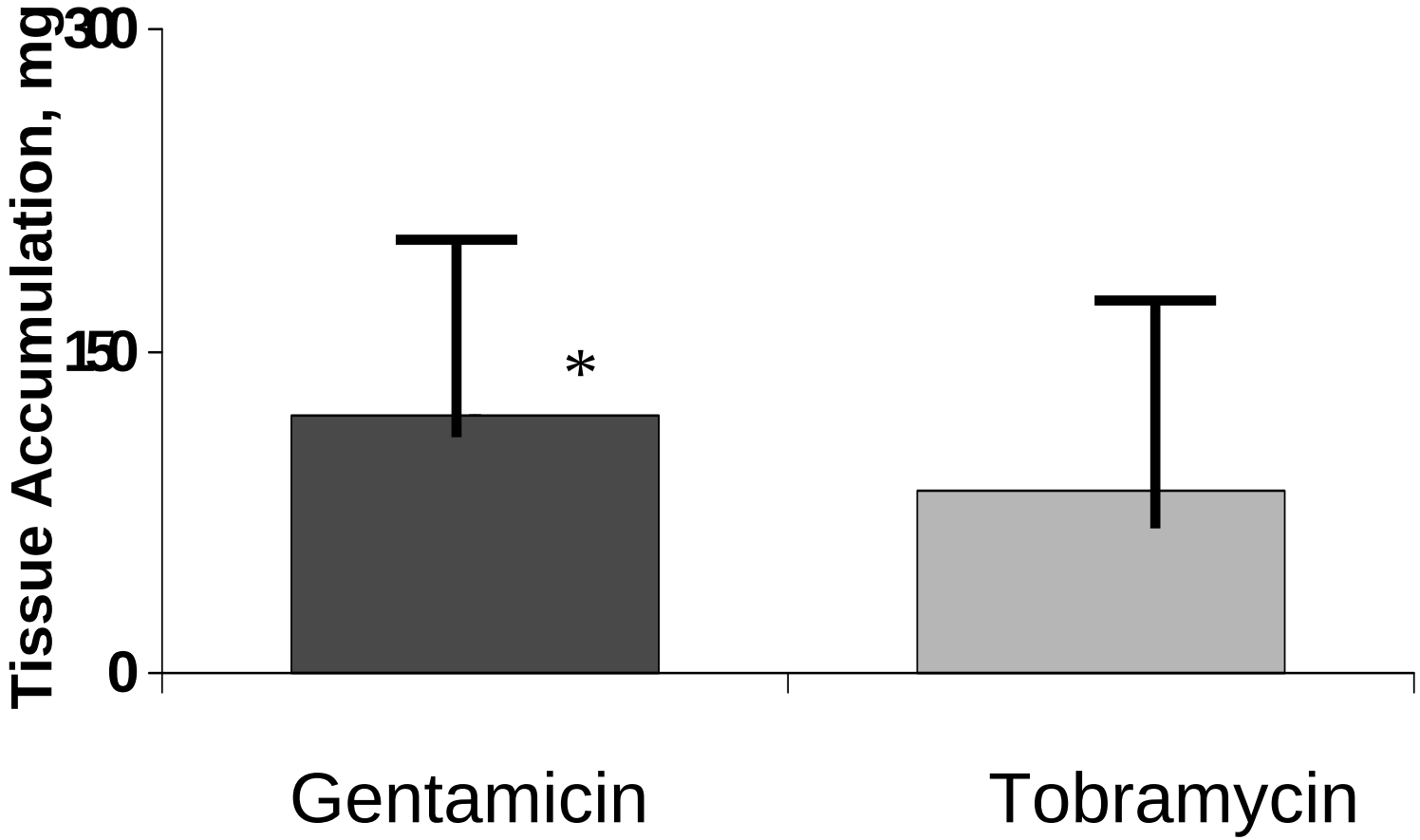
Schentag: AAC 21:721-726, 1982.


% Decrease in Creatinine Clearance
100
80
60
40
20
0
10
20
50
100
200
500
1000
Tissue Amount, mg


IV or IM
CENTRAL
COMPARTMENT
(Vc)
Slow Uptake
(k_{12})
Slow Release
(k_{21})
TISSUE COMPARTMENT
Most
Patients
Toxic
Patients
Slight
Retention
Strong
Retention
Renal Clearance
(Cl_R, k_{el})

Patients Given Gentamicin (120) and Tobramycin (120) Did Not Differ Statistically in the Following:

- Age
- Sex
- Weight
- Creatinine clearance
- Site of infection
- Underlying disease
- Severity of disease
- Cephalosporins
- Diuretics
- Total dose
- Peaks and troughs
- Duration of treatment
- Mortality
- Positive blood cultures



Schentag JJ: AAC 19:859-866, 1981.

Comparative Aminoglycoside Nephrotoxicity

Parameter	All Gentamicin N=120	All Tobramycin N=120
Nephrotoxic (Pharmacokinetic criteria)	24%	10%**

***p < 0.01*

Schentag JJ: AAC 19:859-866, 1981.

Nephrotoxicity-Hopkins 1979

Toxicity	GM	TM	p-value
Nephro	19/72 (26%)	9/74 (12%)	0.025
Ototox	5/47	5/44	NS

NEJM 302: 1106-1109, 1979

Health Care Costs of Aminoglycoside Nephrotoxicity

- Even mild renal damage complicates the critically ill patient, adding days in hospital, and increasing the need for supportive technology
- Each patient requiring hemodialysis adds $15,000 per month to hospital bill
- Although small studies do not show differences, the better and the larger trials show gentamicin about 2 fold more nephrotoxic than tobramycin

Health Care Costs of Aminoglycoside Nephrotoxicity

- It costs as much to dose, monitor and treat the complication of aminoglycosides, as the drugs themselves
- Cost savings of generic gentamicin (50 cents vs $1.00) are off-set by:
  - A greater need for monitoring tests (Cr, levels, UA)
  - A greater need for highly trained personnel to adjust doses and monitor
  - An approximately 2x greater risk of nephrotoxic reactions

Even After Individualization

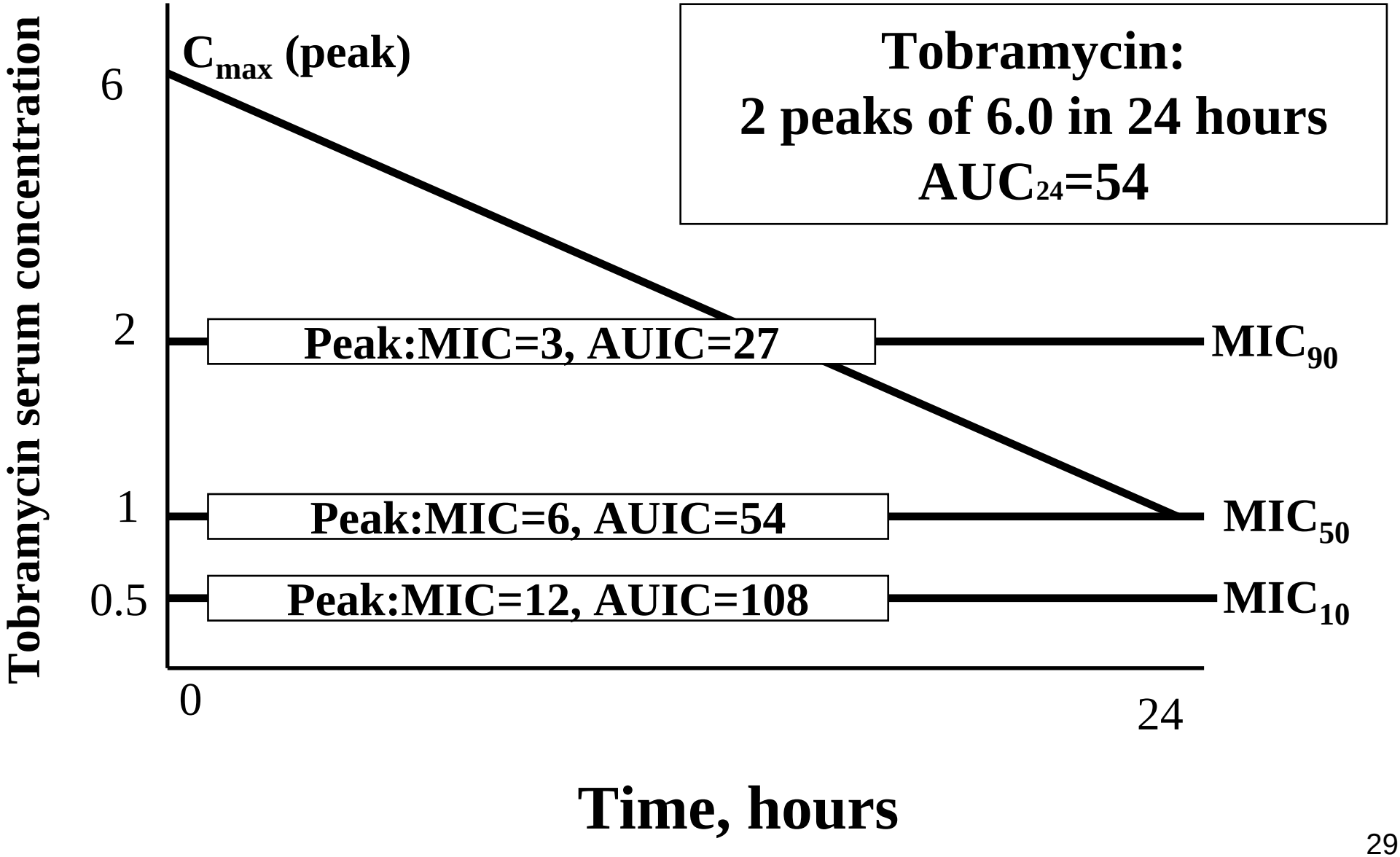
- Not every blood level curve stays where you started
- Toxicity may still occur due to factors beyond the blood level
- All of these factors are worse with Gentamicin than Tobramycin

Recommendations – PK/PD and otherwise..

- Dose all patients based on their calculated creatinine clearance-Regardless of OD vs BID
- Monitor those who are at highest risk for nephrotoxicity with frequent blood levels and frequent serum creatinine measurements
- Shorten Courses to < 7 days
- Use tobramycin first and hold gentamicin in reserve – Twice as active, half as nephrotoxic, and cochlear ototoxic vs. vestibular

Aminoglycoside Serum Concentration Measurements

- Nephrotoxicity
  - Trough concentrations > 2.0 mcg/mL
  - UNPREDICTABLE once concentrations are in range.
  - Cause/effect not clearly established
- Ototoxicity
  - No relationship to blood levels established, probably duration related
- Efficacy
  - Predictive PK/PD parameters:
    - Peak/MIC, AUC/MIC (AUIC)

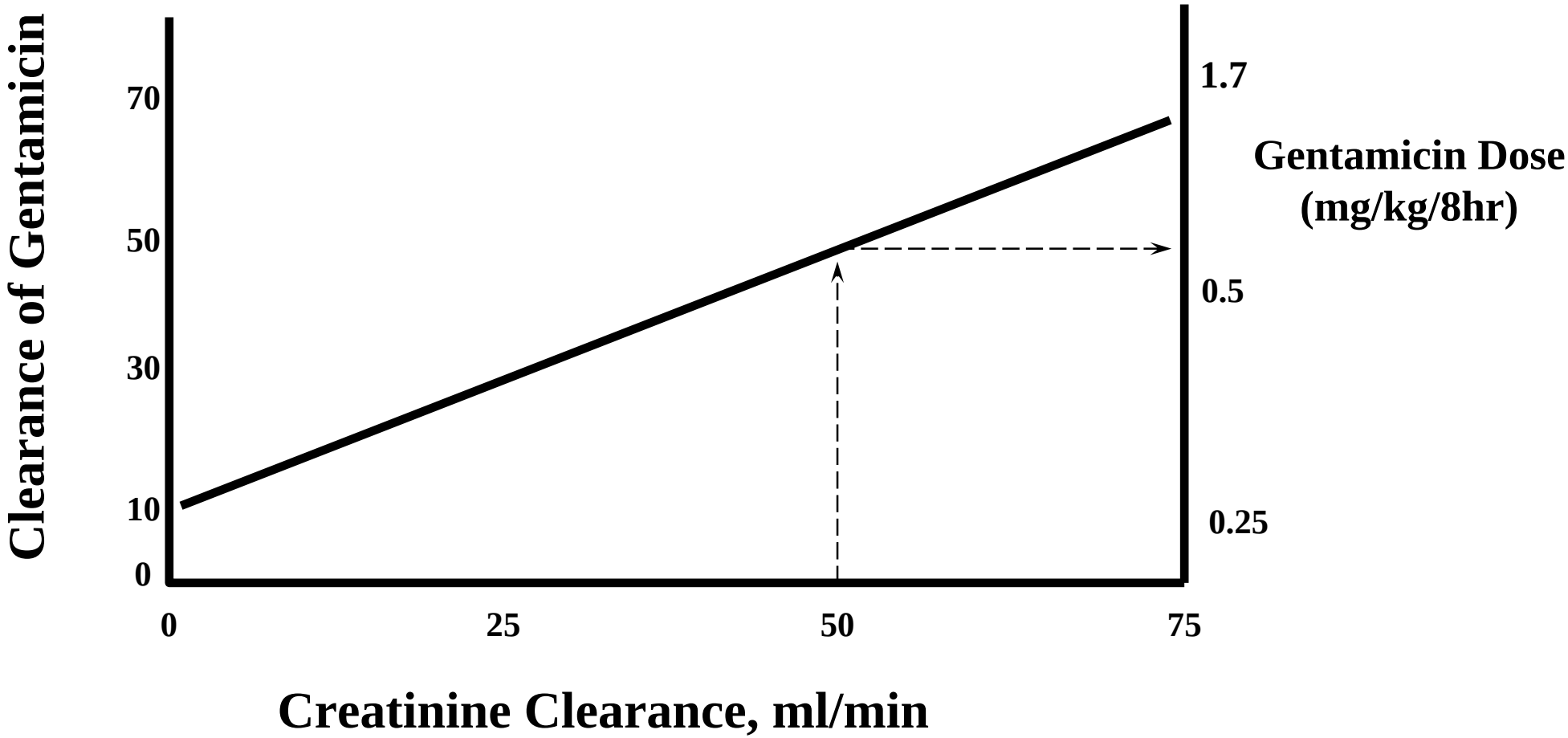

Tobramycin serum concentration
C_{max} (peak)
6
2
1
0.5
0
24
Tobramycin:
2 peaks of 6.0 in 24 hours
AUC_{24}=54
Peak:MIC=3, AUIC=27
Peak:MIC=6, AUIC=54
Peak:MIC=12, AUIC=108
MIC_{90}
MIC_{50}
MIC_{10}
Time, hours

Efficacy in Bacteremia

Initial C_{max}	***Outcome:***	
	Died	Survived
< 5.0 mcg/ml	20.9%	79.1%
> 5.1 mcg/ml	2.4%	97.6%

Moore, Am J Med 77: 657-662, 1984

Chan Nomogram



Efficacy vs C_{max}: Hopkins Studies

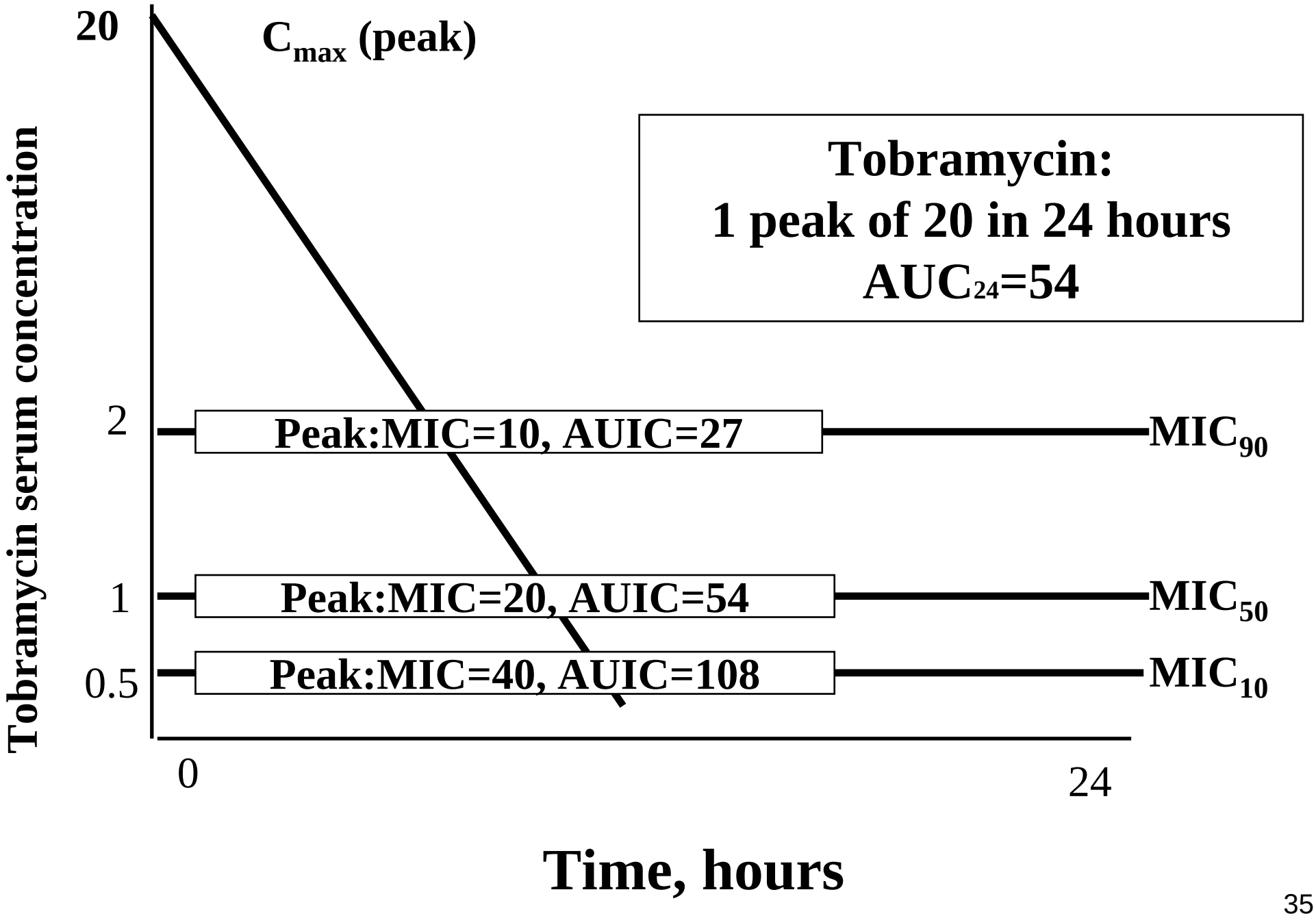
- Studies used 2 mg/kg dosing for patients every 8 hours, infused over 30 min
- In renal insufficiency, the dose was lowered, but the q. 8 hr dosing interval was retained (Dosing via Chan Nomogram)
  - This means that the data used to justify once daily dosing were derived from studies of q 8hr regimens of gentamicin and tobramycin.....

Once Daily dosing?

- The entire 24 hour regimen of 5-7 mg/kg/day is given once daily.
- In vitro data favors peak to MIC as a predictor of efficacy
- Supported by the known mechanisms of aminoglycoside action on bacteria
- Supported by animal model data of safety
- Supported for cost and convenience reasons

Single daily dosing

- Will this solve the problem of low peak to MIC ratios for the aminoglycosides?
- Will this solve the problem of low AUICs for the aminoglycosides?
- Certainly will not increase Time > MIC for these agents


20
C_{max} (peak)
Tobramycin:
1 peak of 20 in 24 hours
AUC_{24}=54
2
Peak:MIC=10, AUIC=27
MIC_{90}
1
Peak:MIC=20, AUIC=54
MIC_{50}
0.5
Peak:MIC=40, AUIC=108
MIC_{10}
Tobramycin serum concentration
0
24
Time, hours

Detroit Study- OD vs TID

Parameter	OD	TID
Age	44.9	46.2
S_{CR}	0.84	0.89
C_{MAX}	14.6	7.6
AUC_{24}/MIC	56.5	52.3
Cure + Imp %	94.4	88

McKinnon and Rybak, ICAAC 1996

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 and used in most situations, because there is insufficient activity for these antibiotics to function as single agents.**

Antibiotic Combinations

Compound	**AUC_{24}**	**MIC P.aerug**	**$AUIC_{24}$**
Tobramycin	54	1.0	54
Ceftazidime	400	2.0	200
Total (Tob+Ceftaz)			254

Aminoglycosides in Combination regimens

- Add about 25-30% of the activity needed to generate an effective regimen
- Eradicate sub-populations that would otherwise be selected by the concomitant beta lactam, lowering the overall risk of resistance
- If an AMG/BL regimen is failing:
  - Adjust the dose of the Beta Lactam….
  - Adjust the dose of the Aminoglycoside….
  - Once daily dosing for a higher peak?

Efficacy vs C_{max}: Hopkins Studies

- Peaks were obtained 30 minutes after a 30 minute infusion.
  - This means that they are post-distributional
- A variety of infections were studied, but about 60% of these patients were UTIs.
- Few LRTIs were treated (~16% of the patient population), but greater numbers of these failed.
- Remember, there was no effective concomitant antibiotic in 1979.

Why focus on AUC and AUIC?

- All of these PK parameters change in parallel with each other, as the dose changes in relationship to the patient's clearance
- None of the data used to justify once daily use is based on optimized peaks
- Whenever you raise the dose, you increase the peak, but also the AUC

Single daily dosing

- Will this solve the problem of low peak to MIC ratios for the aminoglycosides?
- Will this solve the problem of low AUICs for the aminoglycosides?
- Will this solve the problem of Ototoxicity?
- Will this solve the problem of Nephrotoxicity?

Nephrotoxicity: Detroit

	OD	*TID*	*p-value*
# Eval pts	187 (94%)	95 (95%)	
Nephrotox	14 (7.5%)	14(15%)	0.05
chg in S_{CR}	0.36	0.57	0.15
Concomitant Vancomycin in N-Tox	35.7%	64.3%	0.13

Why focus AMGs on AUC?

- At the same average dose, AUCs remain constant with changes of interval.
- Unfortunately, peaks change.
- When Dosing, it is most useful to determine an AUC for patients dose and clearance;
  - This assures a safe AUC of 50-60 per 24 hours, regardless of the shape of the curve;
  - Then the interval can be either once daily or divided using q 24, q12 or q8hr increments

Why Focus AMGs on AUC?

- AUC correlates to total dose over time.
- AUC is the best overall safety measure
- AUC is independent of the shape of the curve
- AUC/MIC is a parameter predictive of clinical and microbiological outcome in the available q. 8hr studies
  - even with the varied times that levels were drawn.

Use of AUIC in Patient Care-Case 06

- **56 yoM, 68 in, 190 lb, with COPD, early Diabetes, with perforated diverticulum.**
- **Abdominal X-Ray has free air**
- **Currently receiving no antibiotics. Serum creatinine is 1.2 mg/dl on admission to ER**
- **Gentamicin 400 mg Q24 hr is ordered along with Unasyn (ampicillin-sulbactam) for anaerobes**
- **You were consulted for antibiotic management**
  - Should you allow this regimen to be used?

Calculation of AUICs

- DOSE/Clearance=AUC
- Clearance = CCr(x) +Cl_{nr}
- Adjust AUC for 24 hr of Dosing
- MIC as Default or Exact value?
- $AUIC_{24}$=AUC_{24}/MIC

The A.U.I.C. Program for Antimicrobial Dosing

ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION
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Version 1.0.0a

Developed by: Martin H. Adelman, PhD
and Jerome J. Schentag, PharmD

INDICATIONS FOR AMINOGYCOSIDE Concentrations, in conventional therapy

- Not routinely performed
  - Uncomplicated UTI
  - Synergy dosing
- Routinely performed, therapy > 72 hours
  - Changing renal function
  - Underlying renal impairment (incl. elderly)
  - Septic or immunosuppressed patients
  - Altered pharmacokinetics
  - Not responding to therapy or have suspected AG-related toxicity, but therapy to continue

Aminoglycoside Serum concentrations

- Efficacy
  - Predictive PK/PD parameters:
    - Peak/MIC, AUC/MIC
- Ototoxicity
  - No relationship to blood levels established
  - No clinical risk factors identified
  - probably duration related
- Nephrotoxicity
  - Trough concentrations > 2 mcg/mL; AUC>80 mcg x hr/ml
  - UNPREDICTABLE once concentrations are in range.
  - Cause/effect not clearly established

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