Focus Session 16
Glycopeptide Revisited: PK & PD Properties

A-0178

Pharmacokinetics of Old and New Glycopeptides

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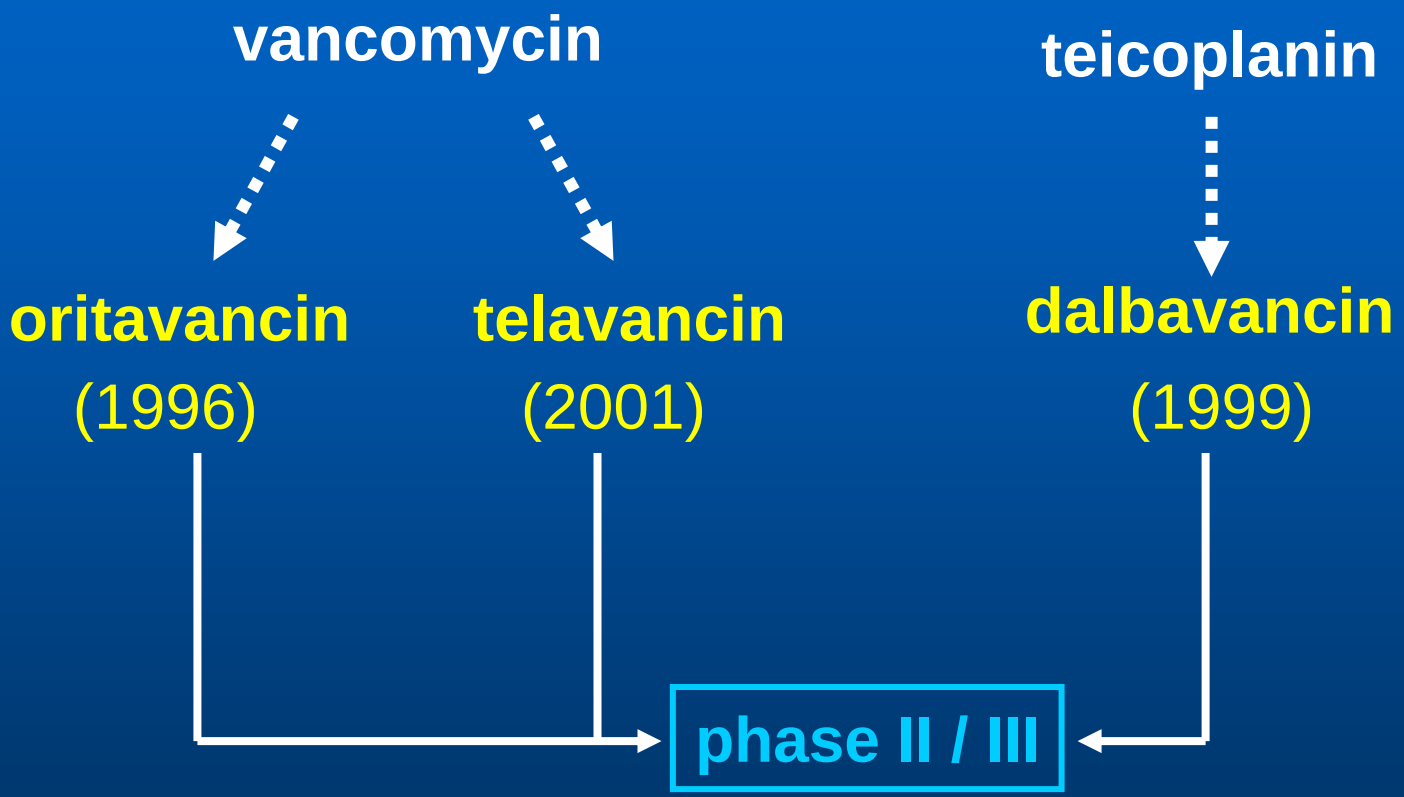
disclosure:
research grant from Theravance, Inc.

Glycopeptide story



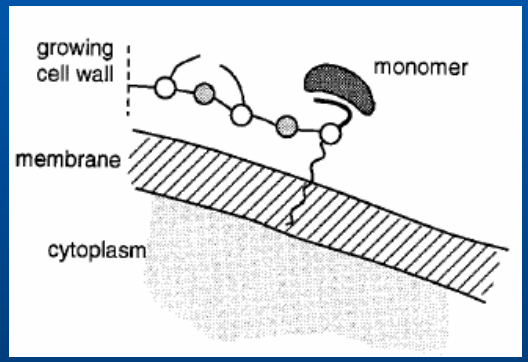
Van Bambeke (2004) Curr. Opin. Pharmacol. **4**:471-8

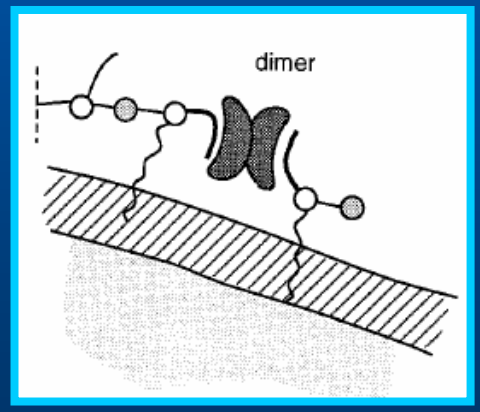
How to improve glycopeptide activity ?

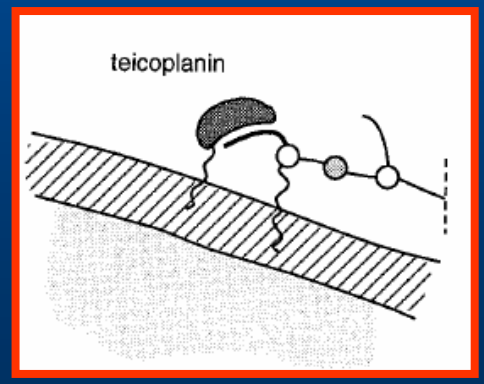
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 781–785 Vol. 39, No. 3
0066-4804/95/$04.00+0

Dimerization and Membrane Anchors in Extracellular Targeting of Vancomycin Group Antibiotics

DANIEL A. BEAUREGARD,[1] DUDLEY H. WILLIAMS,[1]* MICHAEL N. GWYNN,[2] AND DAVID J. C. KNOWLES[2]

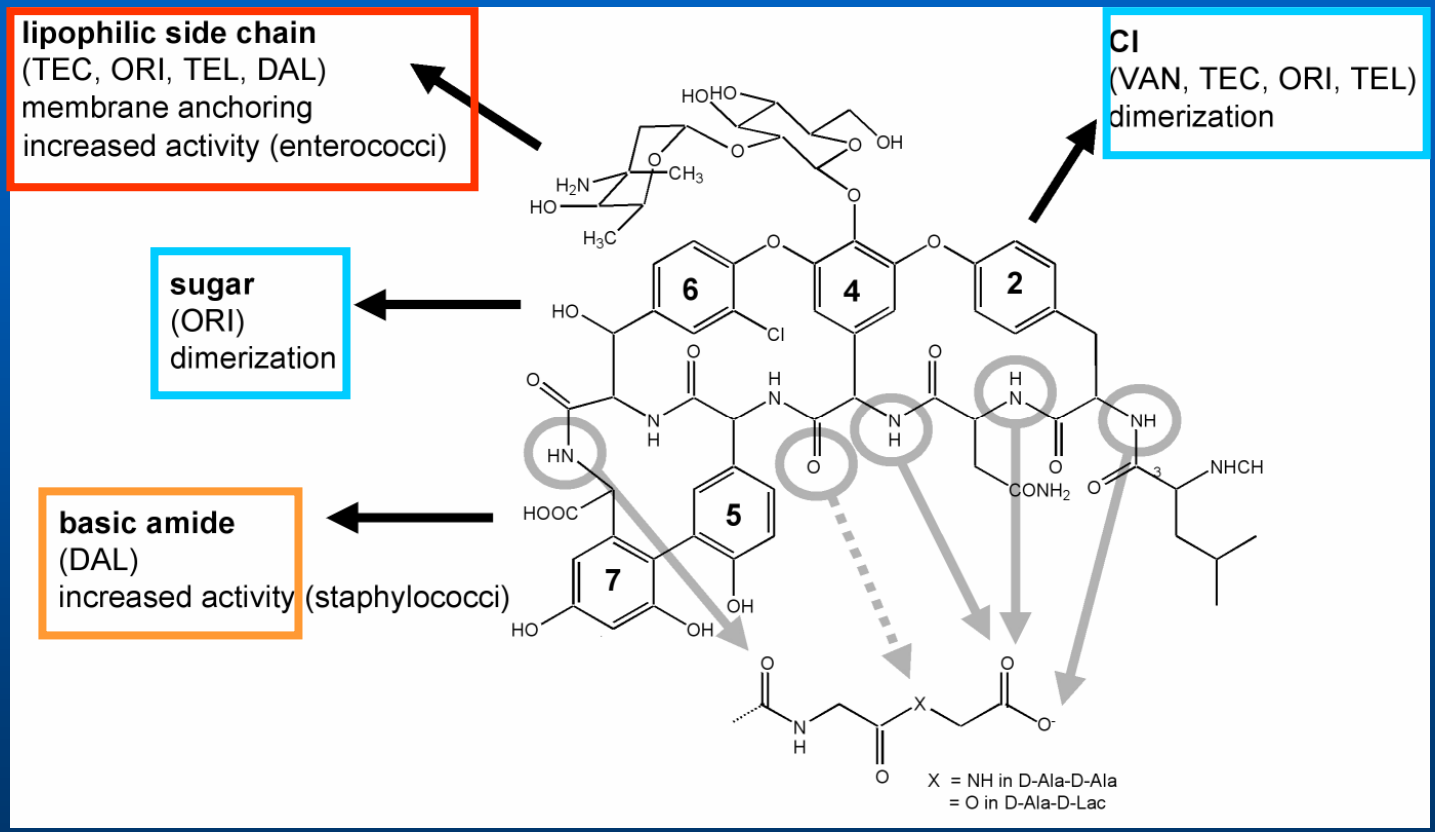






Design of new glycopeptides

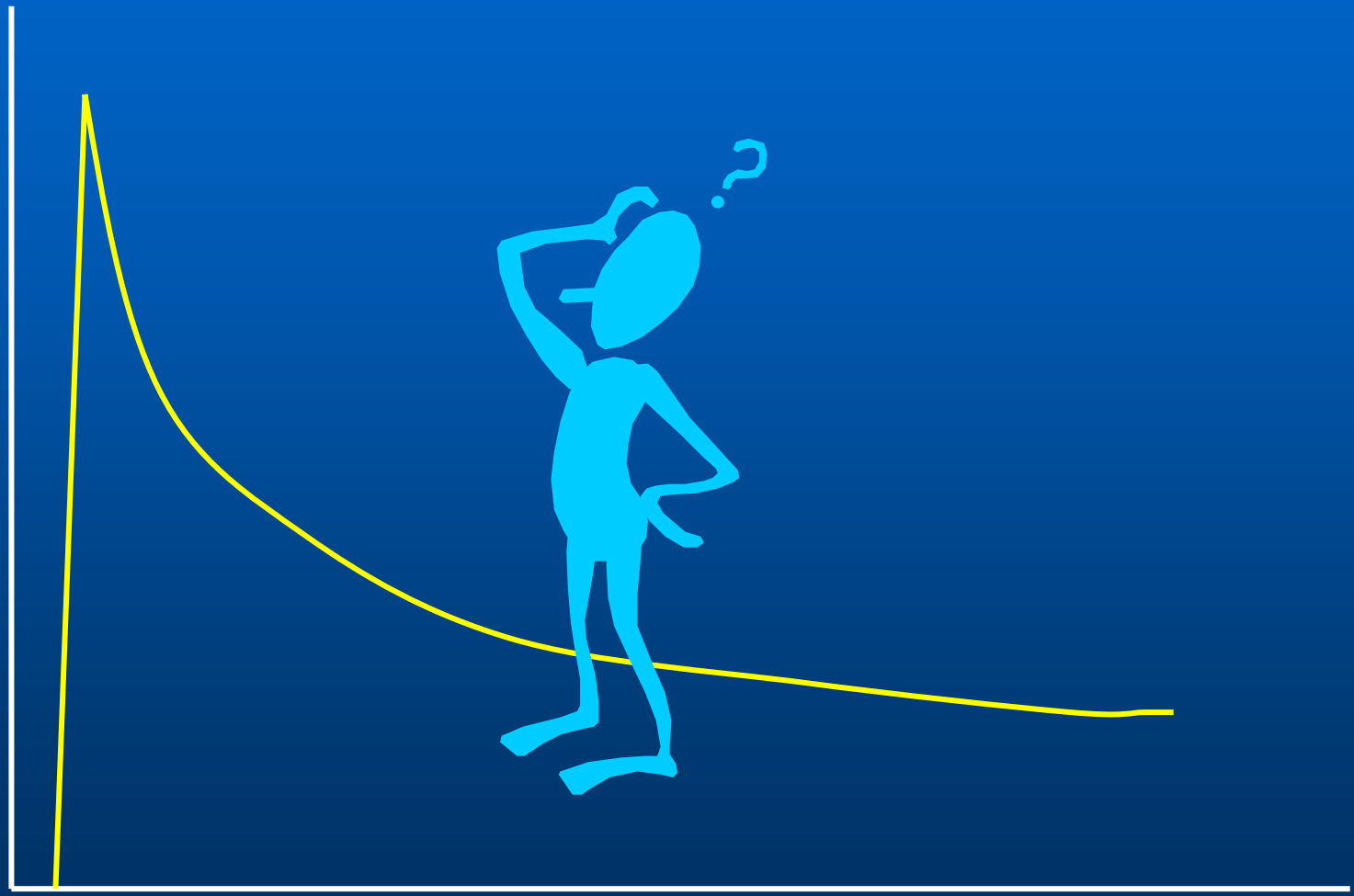
design aimed at improving activity



but chemical modifications also change PK profile …

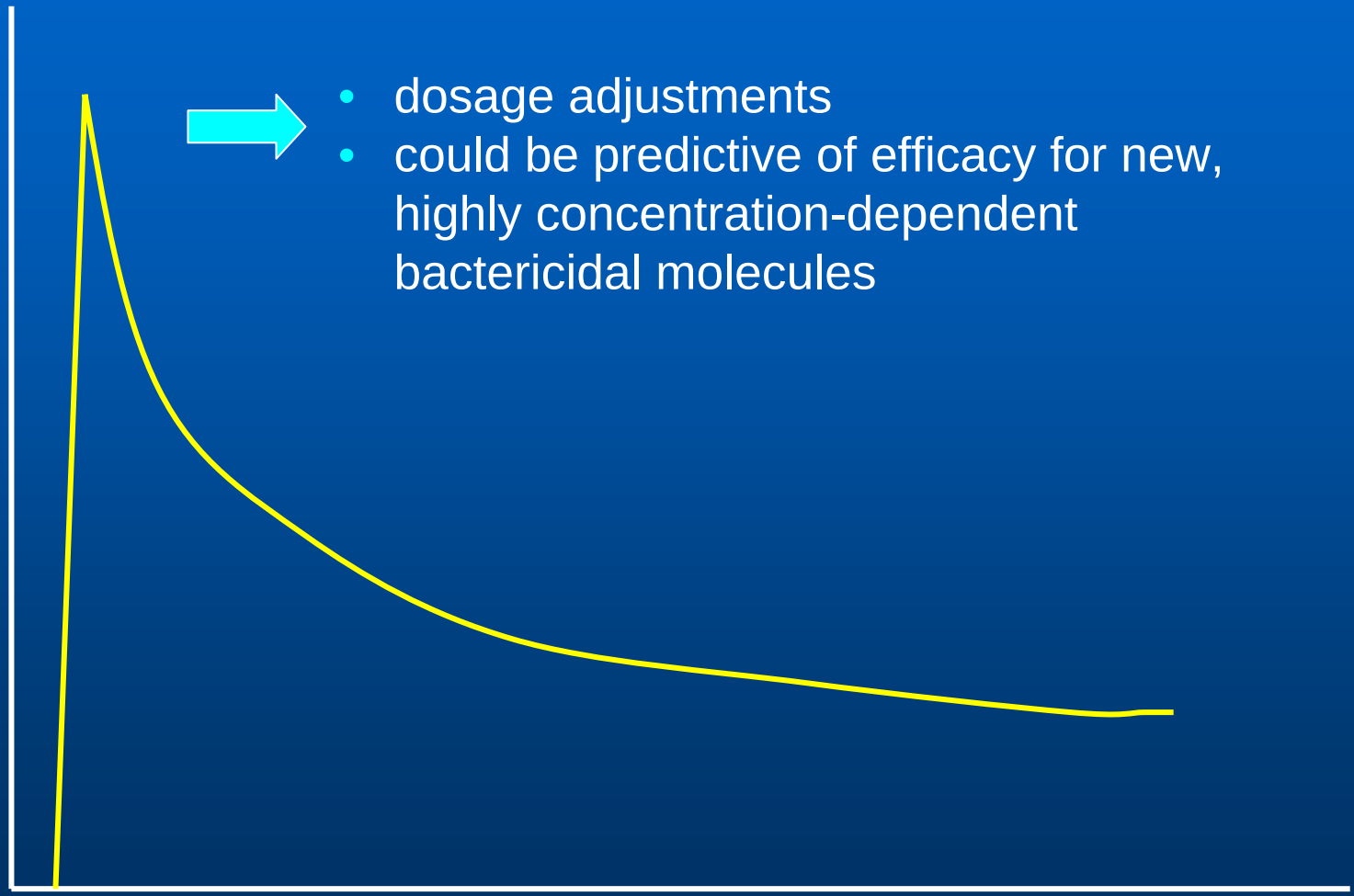
Van Bambeke (2004) Curr. Opin. Pharmacol. **4**:471-8

Which PK parameters are most important ?



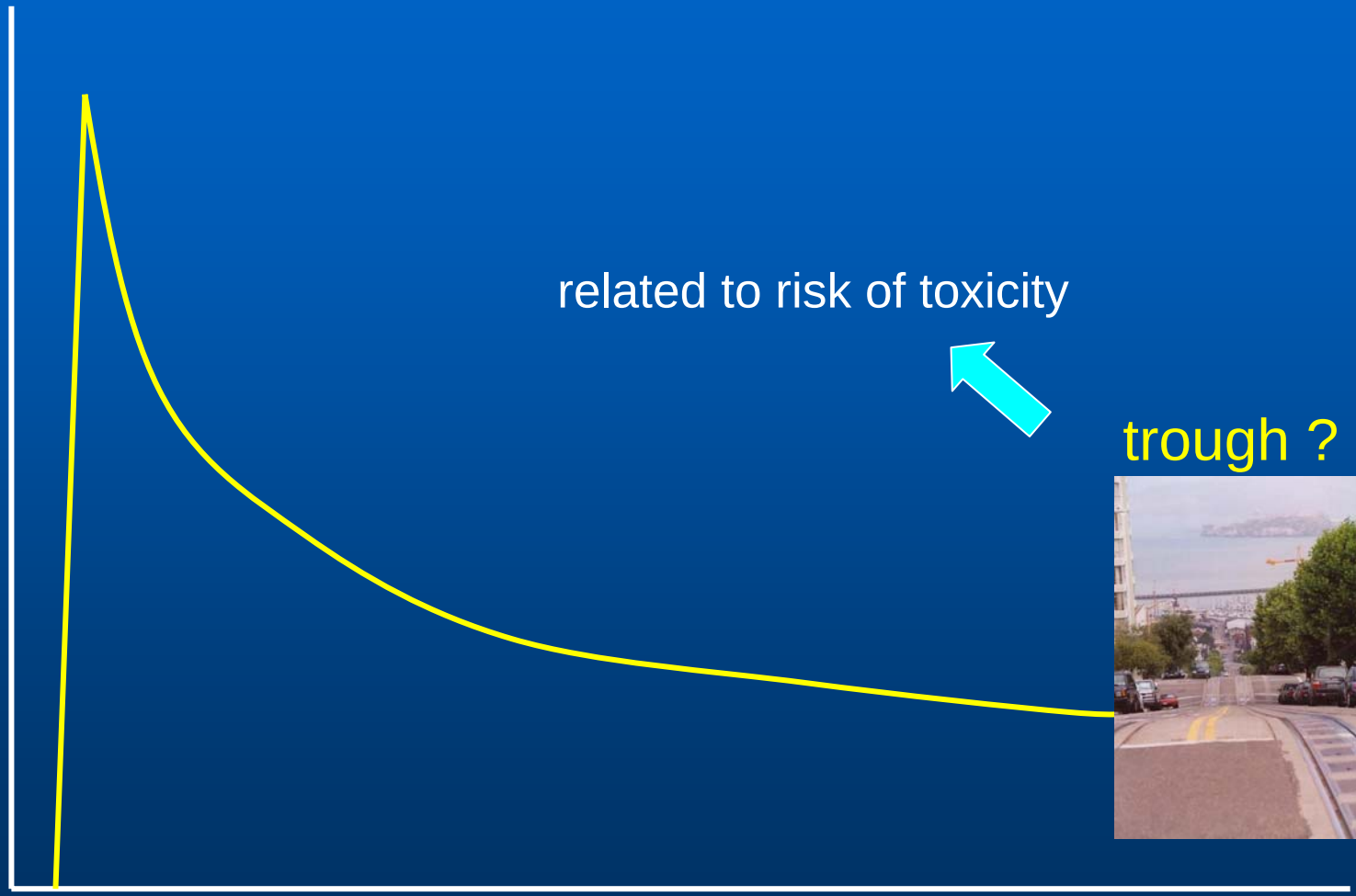
Which PK parameters are most important ?

peak ?

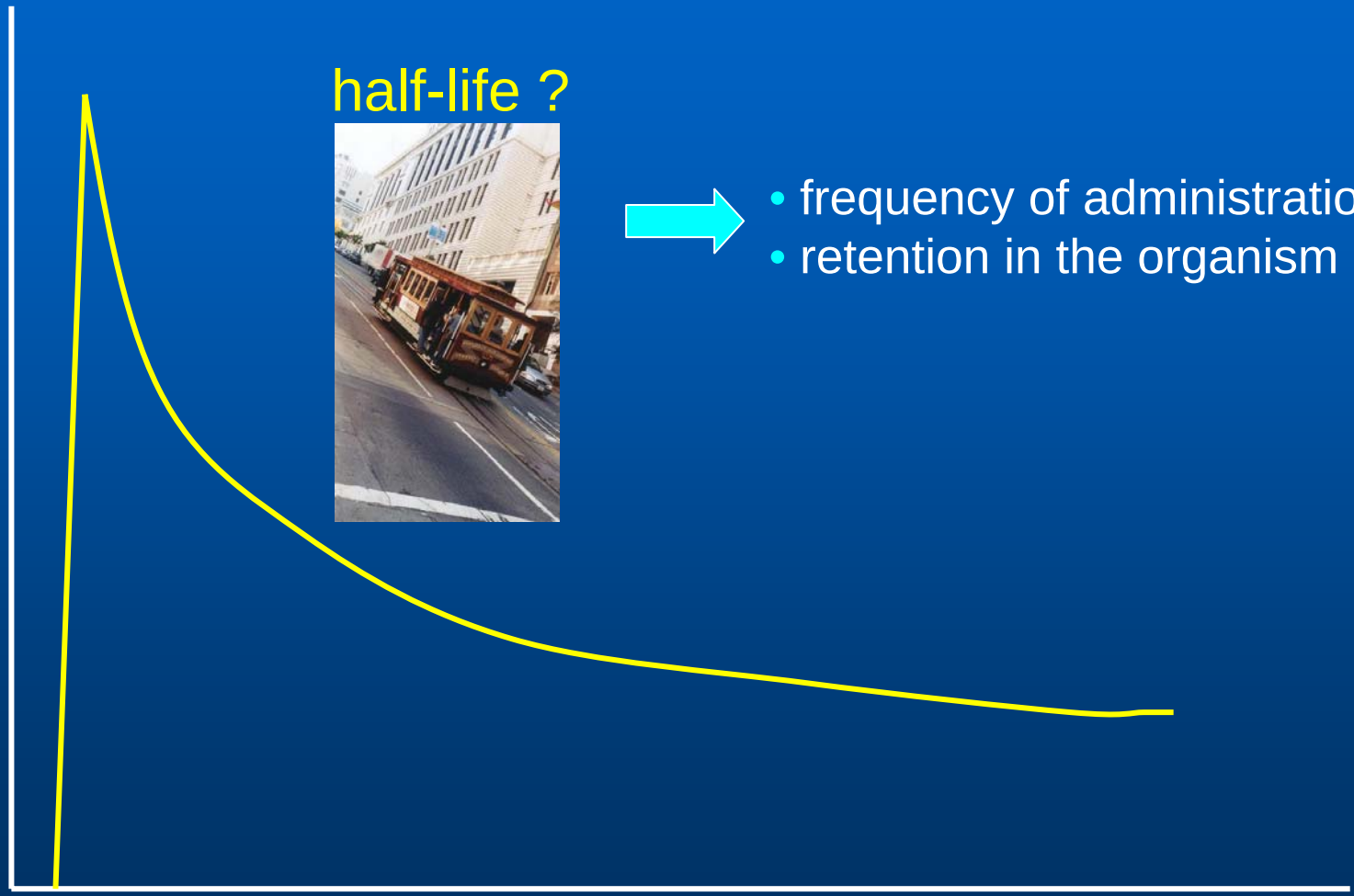


- dosage adjustments
- could be predictive of efficacy for new, highly concentration-dependent bactericidal molecules

Which PK parameters are most important ?



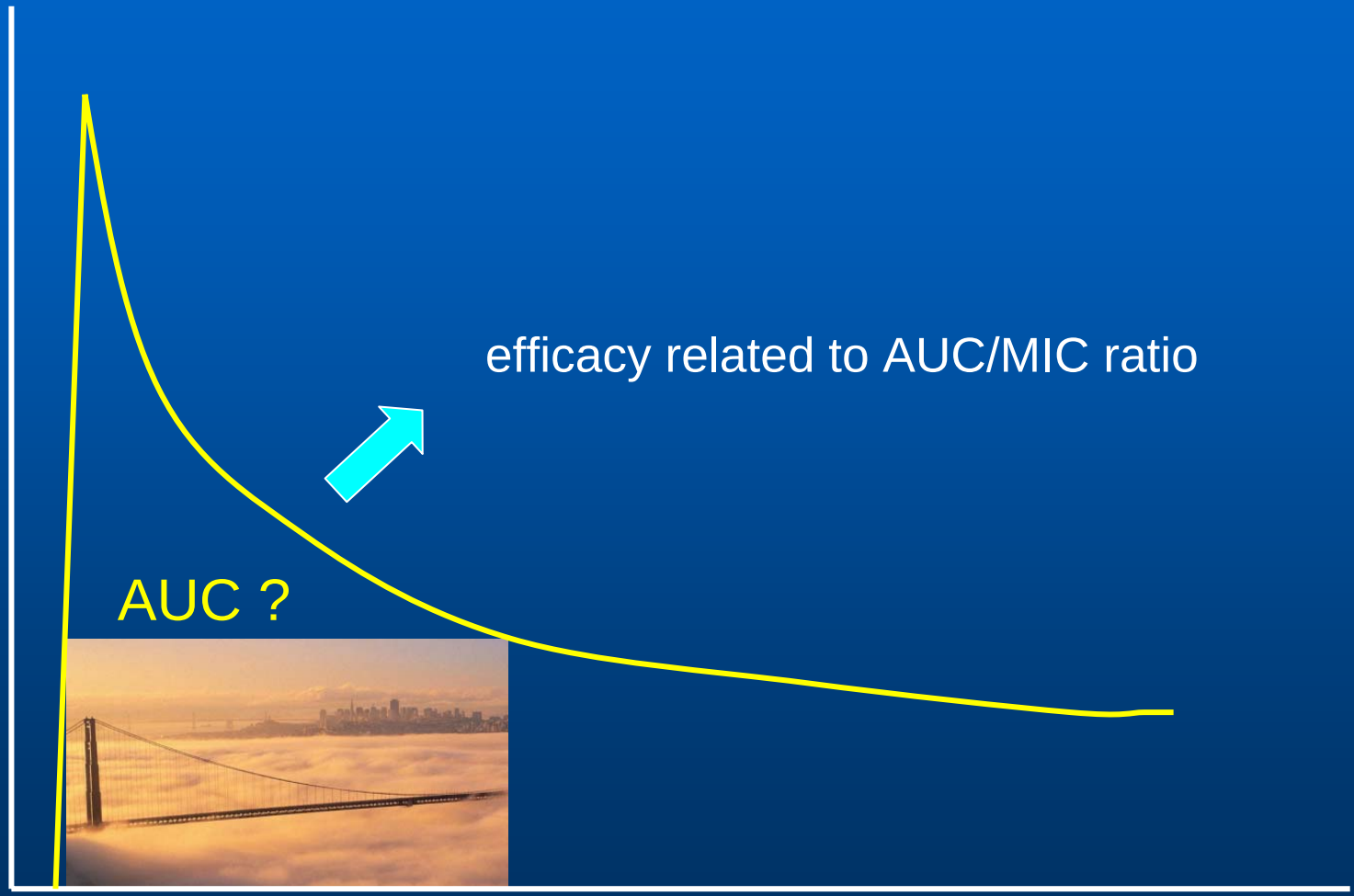
Which PK parameters are most important ?



half-life ?

- frequency of administration
- retention in the organism

Which PK parameters are most important ?



Which PK parameters are most important ?

protein binding ?

free fraction

- ~ active fraction ?
- able to distribute

Which PK parameters are most important ?

peak

half-life

protein binding

trough

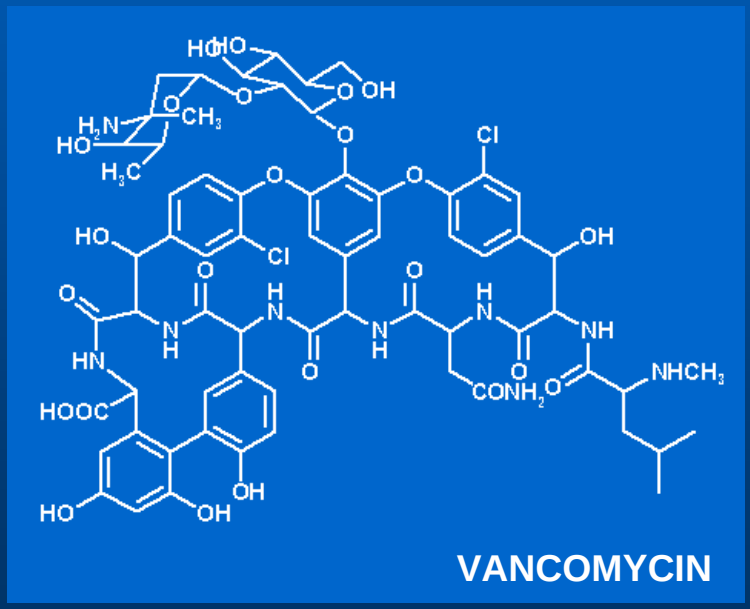
AUC

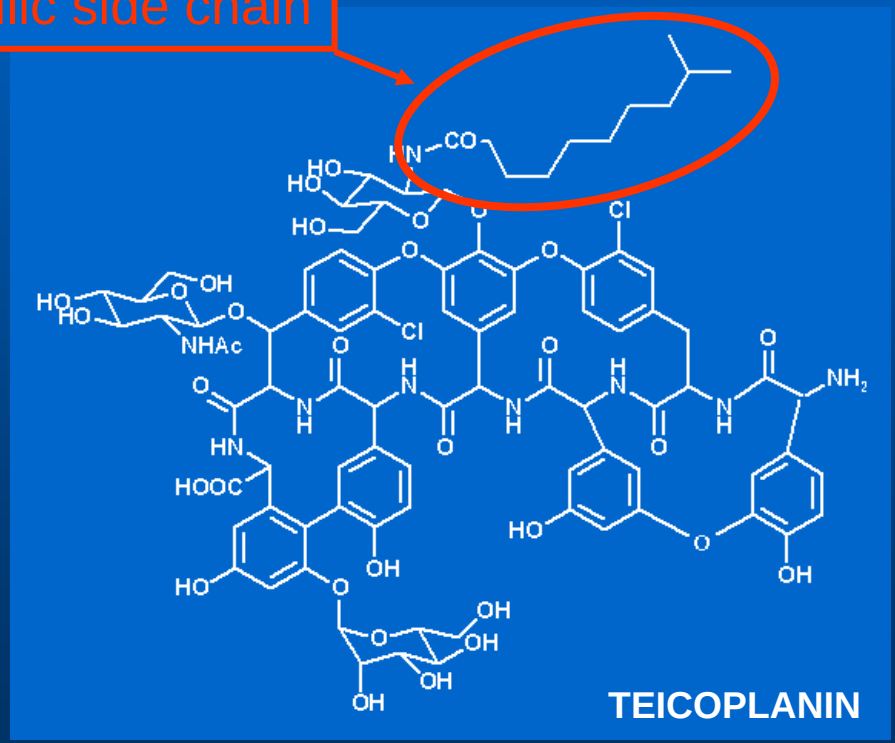
Let’s travel together …

vancomycin vs teicoplanin

↑ prot. binding

lipophilic side chain





vancomycin vs teicoplanin

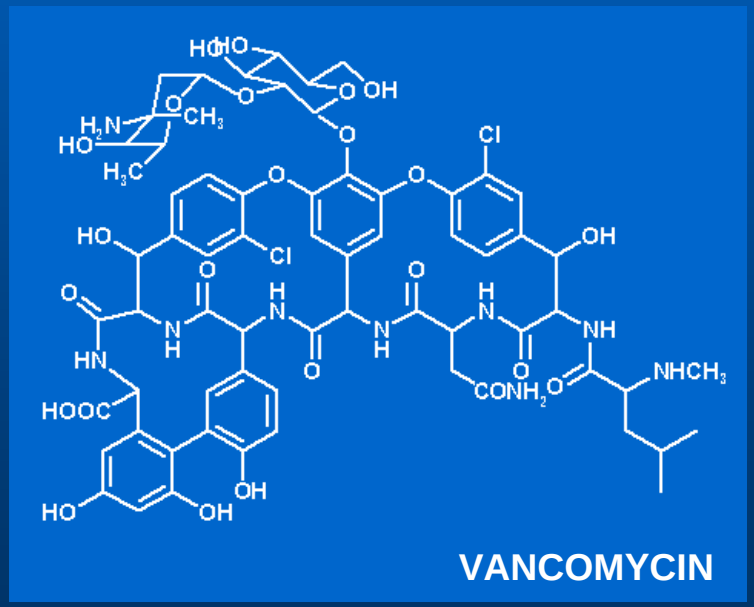
parameter	VAN	TEC
Dosage (mg/kg)	**15**	**6**
Cmax (mg/L)	**20-50**	**43**
Cmin (mg/L)	**5-12** (12 h)	**5** (24 h)
AUC (mg.h/L)	**260**	**600**
(%) prot. binding	**55**	**88-94**
T ½ (h)	**2-4** (β) **3-9** (γ)	**10** (β) **168** (γ)

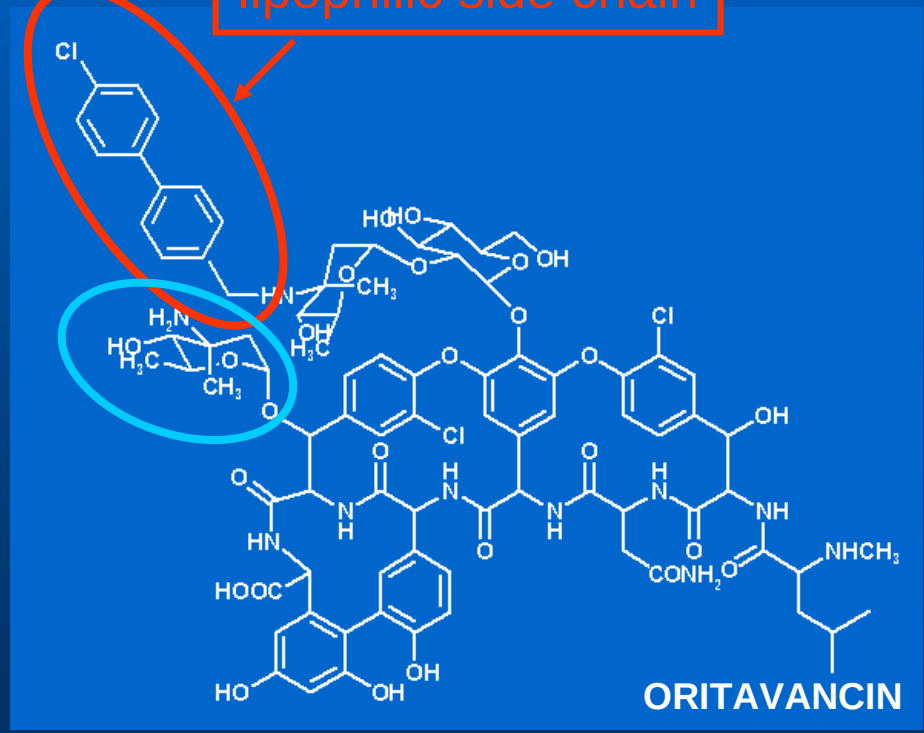
Harding & Sorgel (2000) J. Chemother. 12:15-20

vancomycin vs oritavancin

↑ prot. binding

lipophilic side chain





vancomycin vs oritavancin

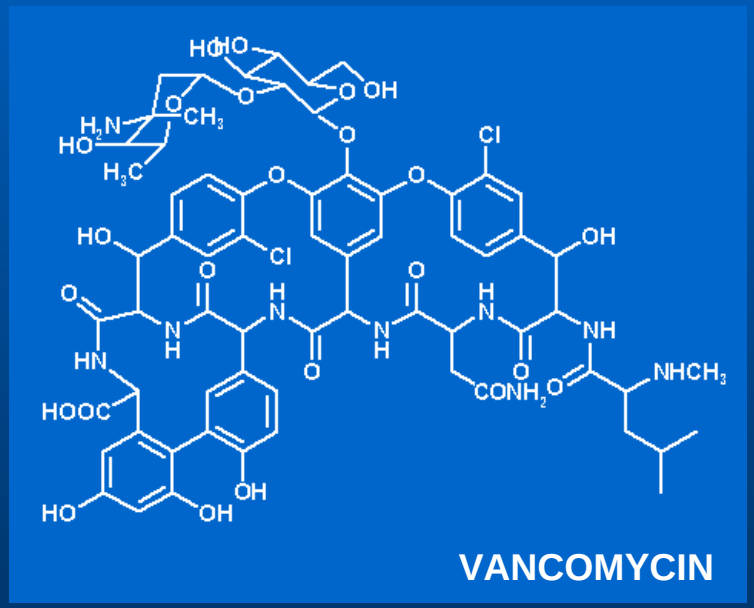
parameter	VAN	ORI
Dosage (mg/kg)	**15**	**3**
Cmax (mg/L)	**20-50**	**46**
Cmin (mg/L)	**5-12** (12 h)	**10** (24 h)
AUC (mg.h/L)	**260**	**457**
(%) prot. binding	**55**	**90**
T ½ (h)	**2-4** (β) **3-9** (γ)	**18** (β) **360** (γ)

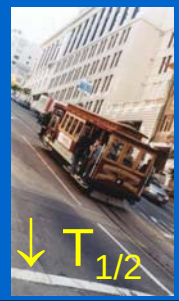
Fetterly *et al*. (2005) AAC **49**:148-52

vancomycin vs telavancin

↑ prot. binding

lipophilic side chain





polar substituant

vancomycin vs telavancin

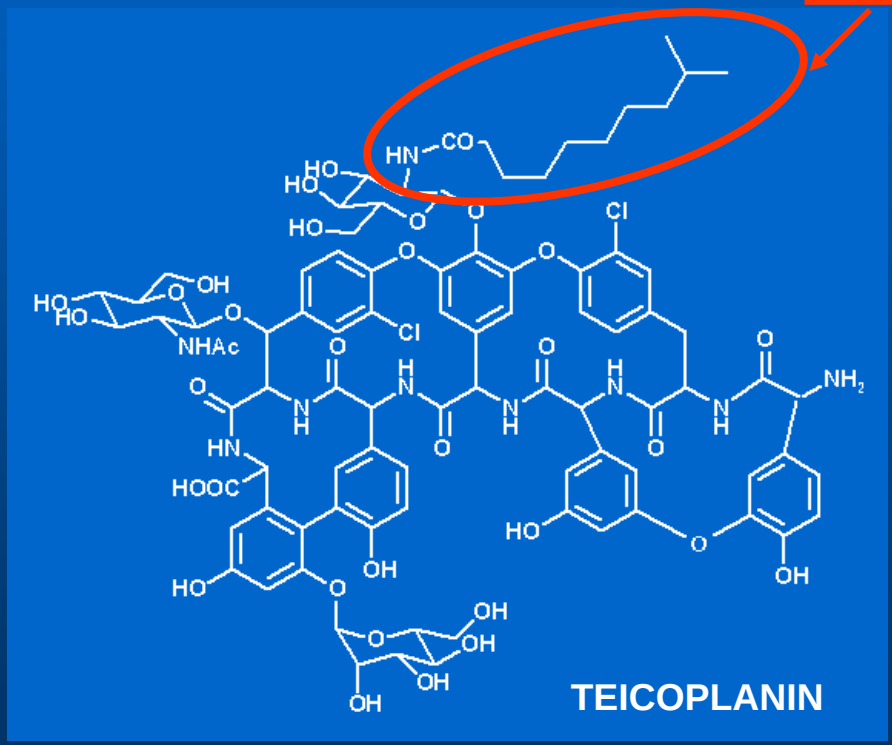
parameter	VAN	ORI	TLV
Dosage (mg/kg)	**15**	**3**	**7.5**
Cmax (mg/L)	**20-50**	**46**	**90**
Cmin (mg/L)	**5-12** (12 h)	**10** (24 h)	**~ 8** (24 h)
AUC (mg.h/L)	**260**	**457**	**668**
(%) prot. binding	**55**	**90**	**95**
T ½ (h)	**2-4** (β) **3-9** (γ)	**18** (β) **360** (γ)	**8** MRT ~10 h

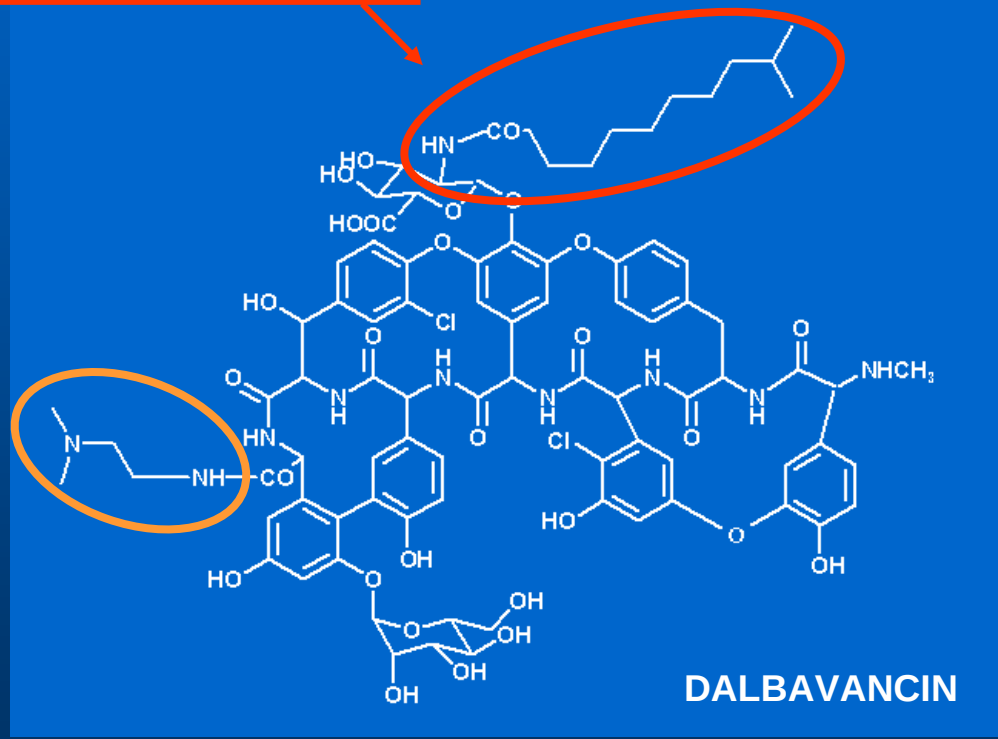
Hedge *et al*. (2004) AAC **48**:3043-50; Shaw *et al*. (2005) AAC **49**:195-201

teicoplanin vs dalbavancin

↑ prot. binding

lipophilic side chain





teicoplanin vs dalbavancin

parameter	TEC	DAL
Dosage (mg/kg)	**6**	**16**
Cmax (mg/L)	**43**	**312**
Cmin (mg/L)	**5** (24 h)	**40** (168 h)
AUC (mg.h/L)	**600**	**27100**
(%) prot. binding	**88-94**	**95**
T ½ (h)	**40** (β) **168** (γ)	**149-321**

call for

caution

…

Leighton *et al*. (2004) AAC **48**:940-5; Lin *et al*. (2006) Ann. Pharmac. **40**:449-60

Comparison of PK profiles in a PD perspective

parameter	VAN	ORI	TLV
Dosage (mg/kg)	15	3	7.5
Cmax (mg/L)	20-50	46	90
Free Cmax	10-23	5	5
AUC (mg.h/L)	260	457	668
Free AUC	50-120	46	34

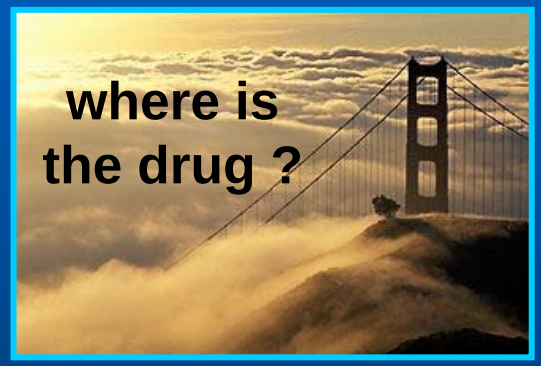
BUT

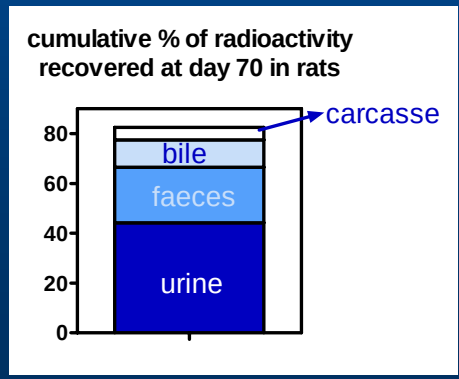
- PD profile more favorable because MIC lower
- prot. binding poorly affects activity *in vitro*

Comparison of PK profiles in a PD perspective

parameter	TEC	DAL
Dosage (mg/kg)	6	16
Cmax (mg/L)	43	312
Free Cmax	4	16
AUC (mg.h/L)	600	27100
Free AUC	60	1355

$$AUC = \frac{dose}{clearance}$$





Cavaleri *et al*. (2005) JAC **55S2**:31-5

Tissue distribution

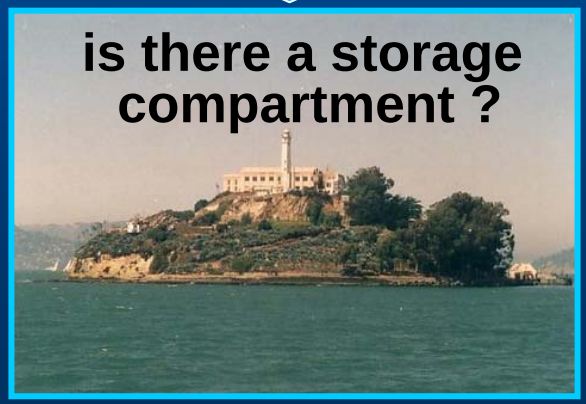
Fluid *	VAN	ORI	TLV	TEC	DAL
Blister		10 %	20 %	30 %	60 %
Epithelial Lining	20 %	26 %	10 %	20-50 %	
CerebroSpinal (inflam.)	1-37 %	3 % in rabbit		low	low

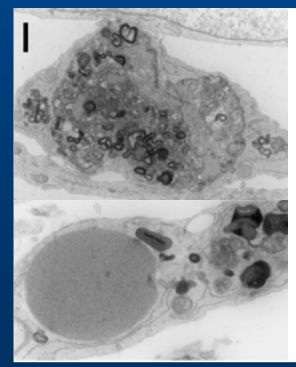
* C_{max} fluid /C_{max} serum ratio; AUC ratio higher if prolonged retention

macrophages *in vitro*	< 10 X	~ 300 X	~ 50 X	< 10 x	~ 25 X

Elimination routes

parameter	VAN	ORI	TLV	TEC	DAL
Urine	> 80 %	5 % day 7	60-70 % (24 h)	80 %	42% day 40
Faeces		< 1 %		3 %	50 % in rats
Metabolism	5-10 %	low	low	low	probable





mixed storage disorder in cultured cells …

Van Bambeke *et al*. (2005) AAC **49**:1695-700

Lessons from PK data

Administration scheme

	VAN	ORI	TLV	TEC	DAL
scheme	2 x / day or cont. inf.	1 x / day	1 x day	1 x / day	1 x / week
Reasons ?					
• $T_{1/2}$	short	long	intermed.	long	long
• cidal effect	slow	rapid	rapid	slow	slow
• trough	low	low	low	low	high

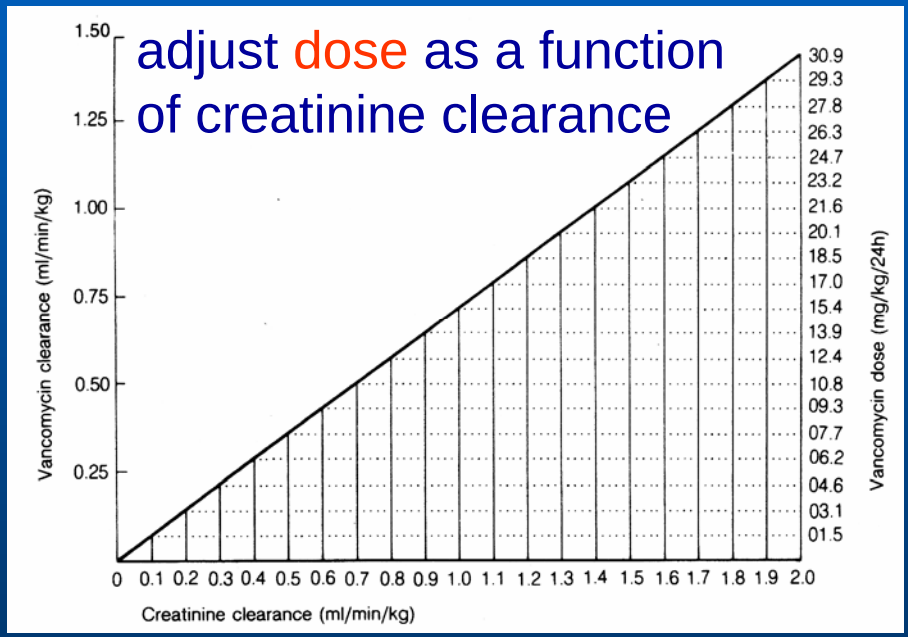
Lessons from PK data

Dose adjustments in case of organ failure

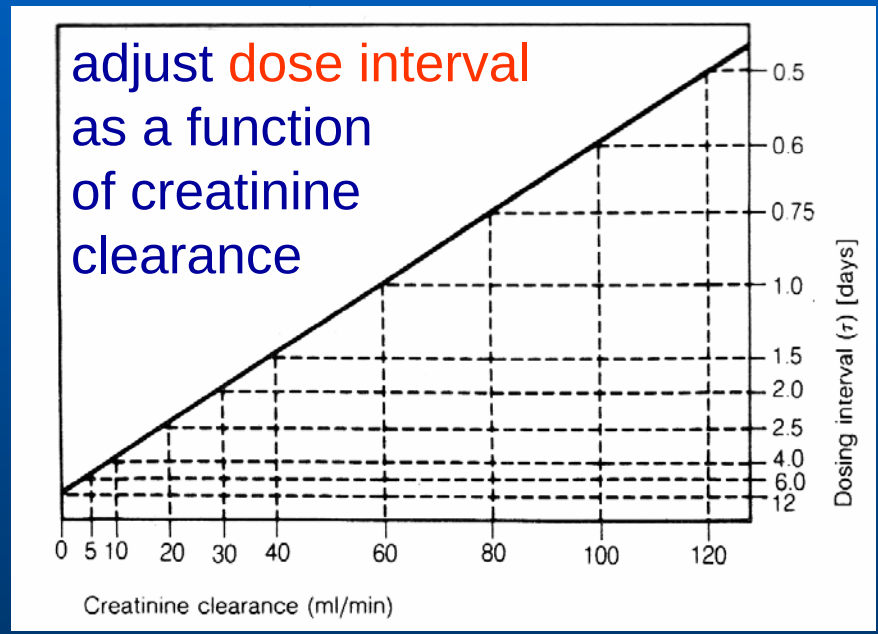
organ insufficiency	VAN	ORI	TLV	TEC	DAL
kidney	☑☑	?	☑	☑☑	☒
liver	☒	?	☒	☒	?

Lessons from PK data

Dose adjustments in case of organ failure



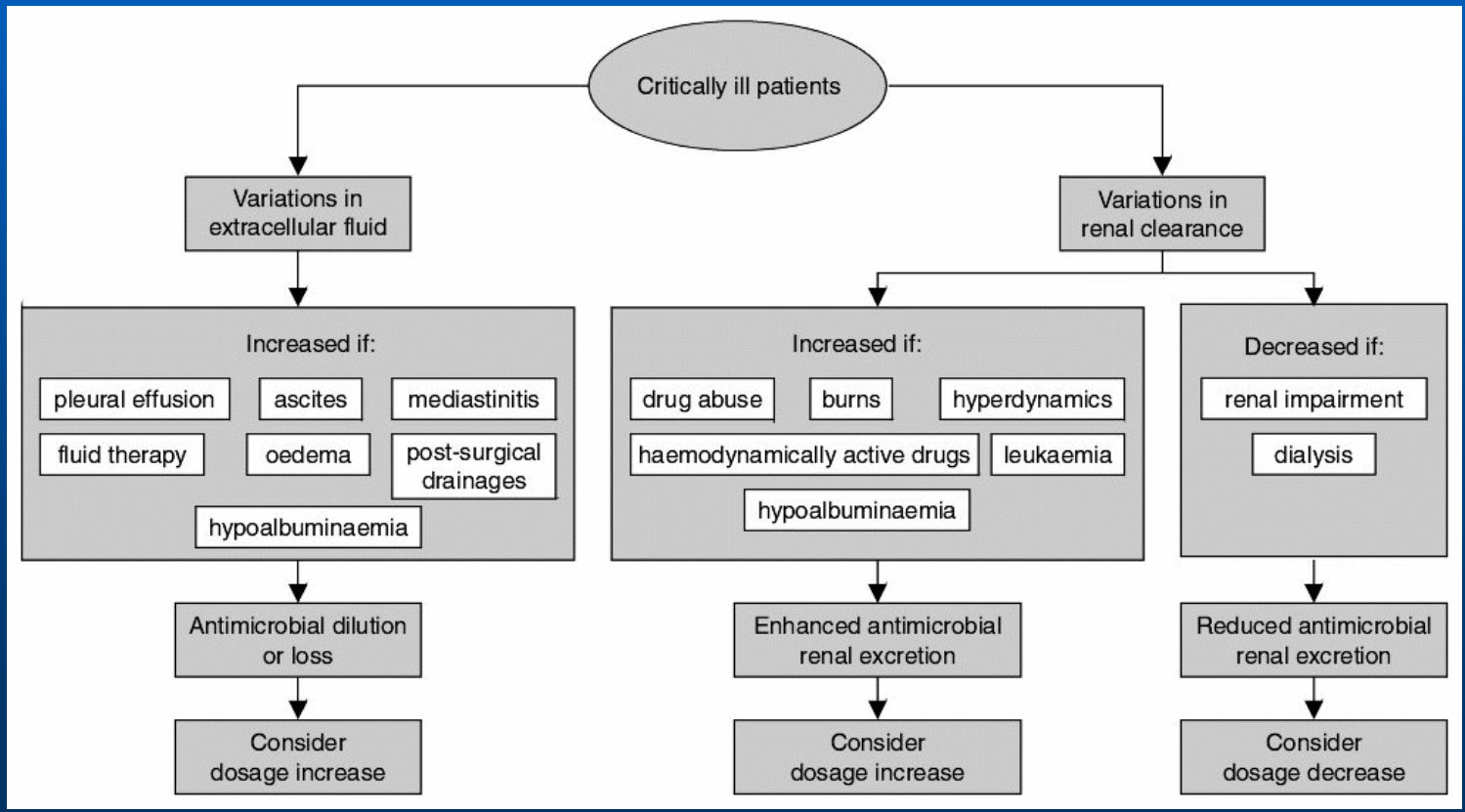
Moellering's nomogram
(Ann. Intern. Med. 1981 **94**: 343-6)



Matzke's nomogram
(AAC 1984 **25**: 433-7)

Does one size fit all ?

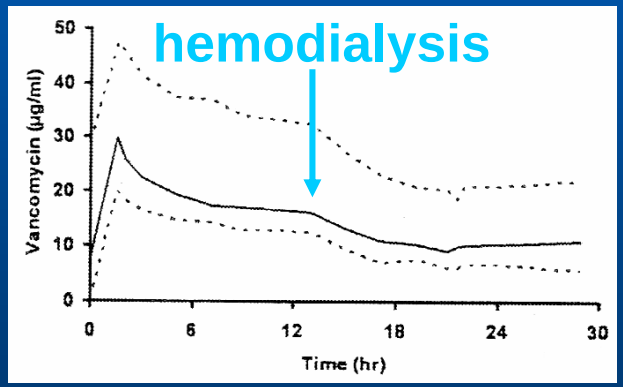
- intensive care : variation in extracellular fluid and renal clearance



Pea *et al*. (2005) Clin. Pharmacokinet **44**:1009-34

Does one size fit all ?

- dialysis : removal of the drug (high flux membranes)



➡ dose adjusted according to:

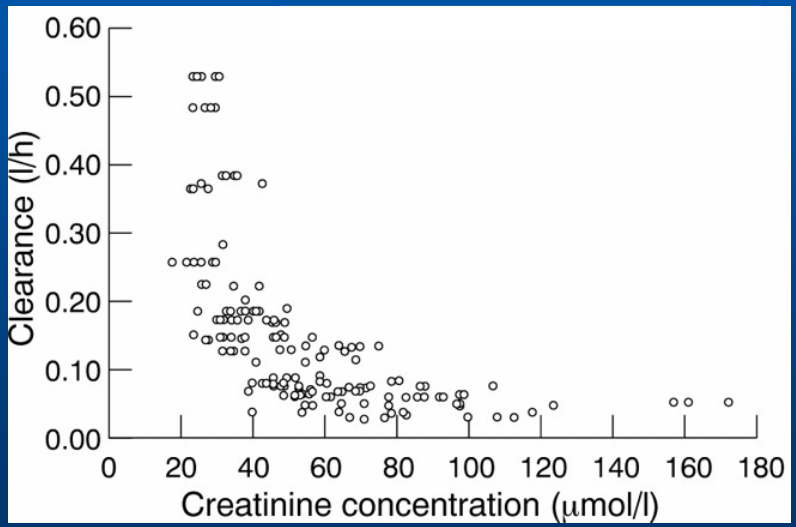
- trough level before intermittent dialysis
- plasma level at any time (continuous dialysis)
- 6 hours after the end of dialysis

Kielstein *et al*. (2006) Crit. Care Med. **34**:51-6

Launay-Vacher *et al.* (2002) Crit. Care **6**:313-6

Does one size fit all ?

- age: infants and children: extracellular volume and maturity of renal function
  - ↑ Vd
  - ↑ clearance



Vancomycin dose guidelines

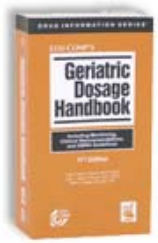
Serum creatinine concentration (μmol/l)	*Dose*	*Dose interval*
20–29	20 mg/kg	8 hours
30–39	20 mg/kg	12 hours
40–49	15 mg/kg	12 hours
50–59	12 mg/kg	12 hours
60–79	15 mg/kg	18 hours
80–100	15 mg/kg	24 hours
>100	15 mg/kg	check trough at 24 hours and dose according to measurements

➡ dose adjustment based on serum creatinine

Grimsley & Thomson. (1999) Arch. Dis. Child. Fetal Neonatal Ed. **81**:F221-7

Does one size fit all ?

- age: elderly patients: altered tissue distribution and renal function
  - ↑ Vd
  - ↓ clearance



dose (mg/kg/24 h) = (0.227 x Cl_{CR}) + 5.67

Dosing intervals of vancomycin as a function of CL_{CR}

CL_{CR} (ml/min per 70 kg)	Dosage interval (h)
>65	8
40–65	12
20–39	24
10–19	48

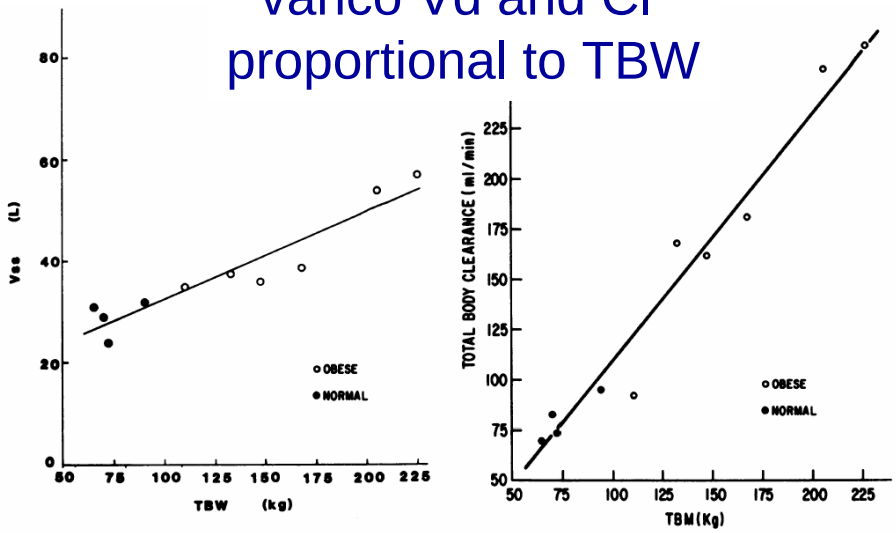
➡ adapt the dose and the interval as a function of Cl_{CR}

Rodvold *et al*. (1988) AAC **32**:848-52

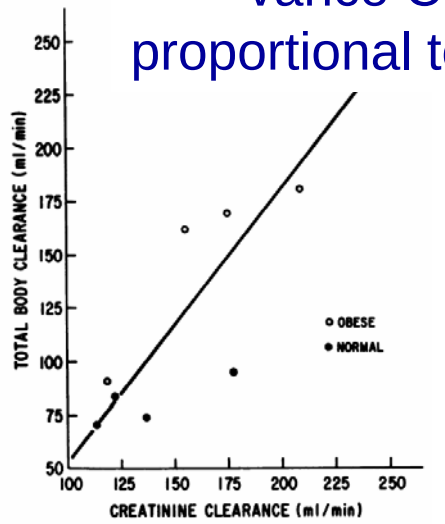
Does one size fit all ?

- obesity : altered tissue distribution and renal elimination
  - ↑ Vd (13-50 %)
  - ↑ clearance

vanco Vd and Cl proportional to TBW



vanco Cl proportional to Cl_{CR}



dose adjustment based on Total Body Weight and Cl_{CR}

Blouin *et al*. (1982) AAC **21**:575-80

Does one size fit all ?

- intensive care
- dialysis
- age
- obesity

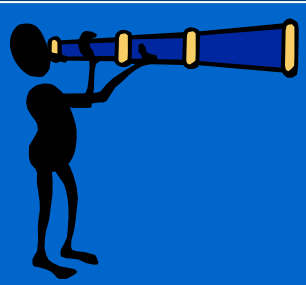
→ altered distribution and/or elimination

↓

dose individualisation

↓

Therapeutic Drug Monitoring

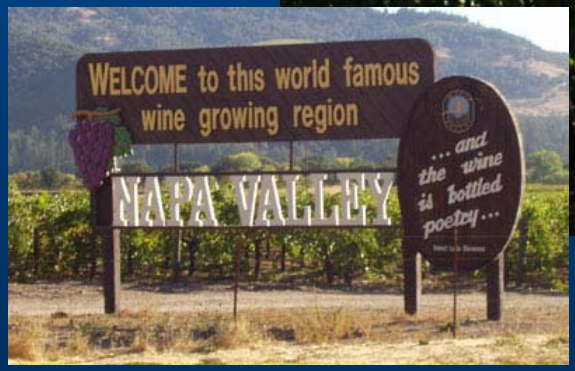


and for new molecules ?

no data so far …

but same concepts should be applicable

Best whishes for a fruitful use



of glycopeptides …