Latest issues in PK/PD of vancomycin

Stefaan J. Vandecasteele, MD, PhD

Dept. Nephrology and Infectious Diseases

AZ Sint-Jan Brugge, Belgium

Independence Maroc

?

Hungarian revolution against Sovjet

Marriage Grace Kelly of Monaco

Suez crisis

Beginning of Cuban revolution

Independence Maroc

Marriage Grace Kelly of Monaco

Hungarian revolution against Sovjet

Suez crisis

1956

Beginning of Cuban revolution

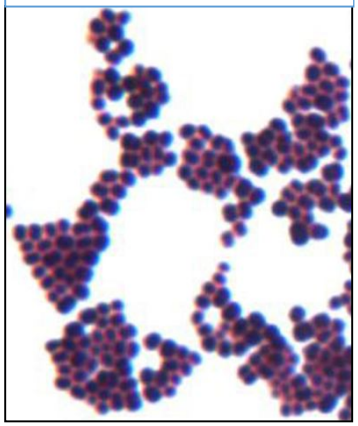
- **Pharmacokinetics (PK):**
  = all the way the body manipulates the drugs
  1. Absorption
  2. Distribution
  3. Metabolism
  4. Elimination
- **Pharmacodynamics (PD):**
  = biochemical and physiological effects of a drug and its mechanism of action
- **PK/PD of vancomycin:**
  = the quantitative relation between pharmacokinetic parameters and microbiological parameters used to predict the effect

Can optimization of vancomycin dosing improve outcome (mortality and morbidity) ?

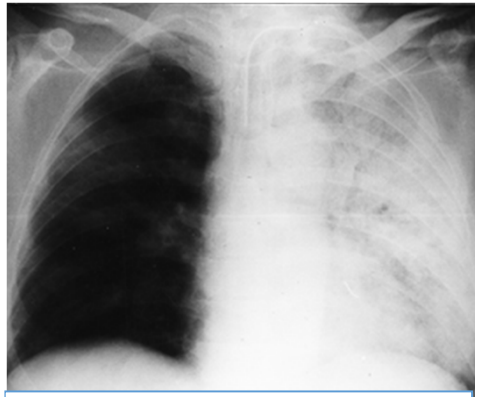
HOST

+

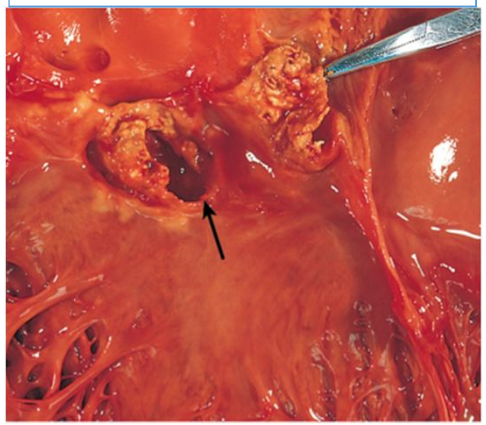
BACTERIA

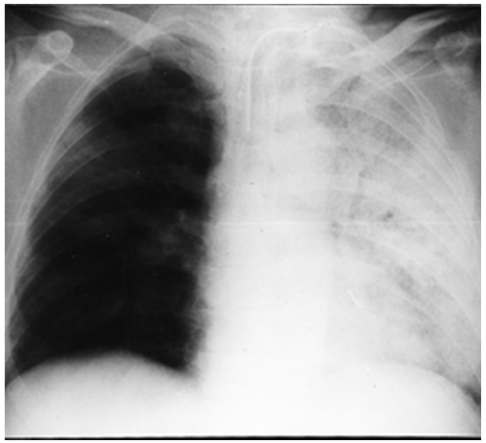


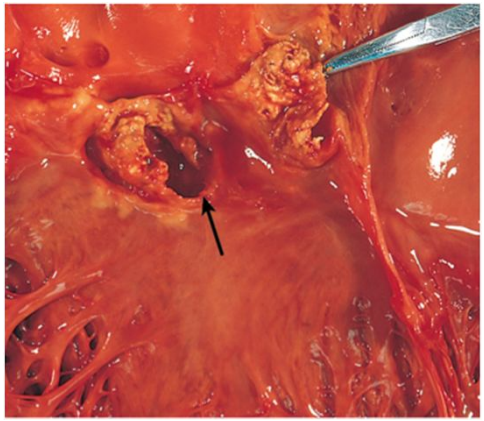
=



INFECTION



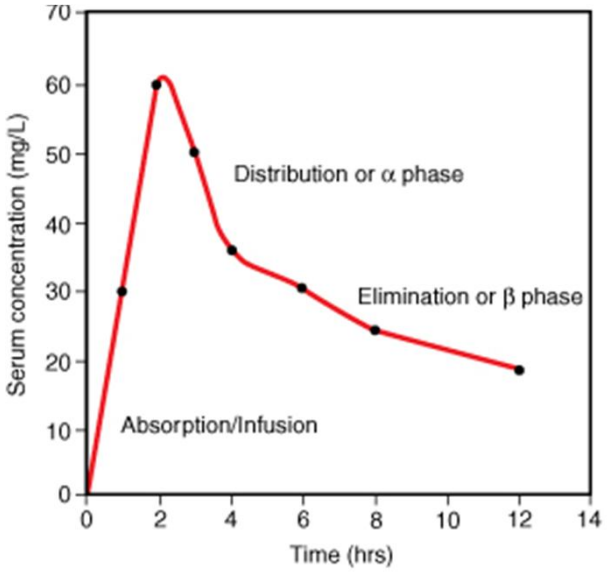




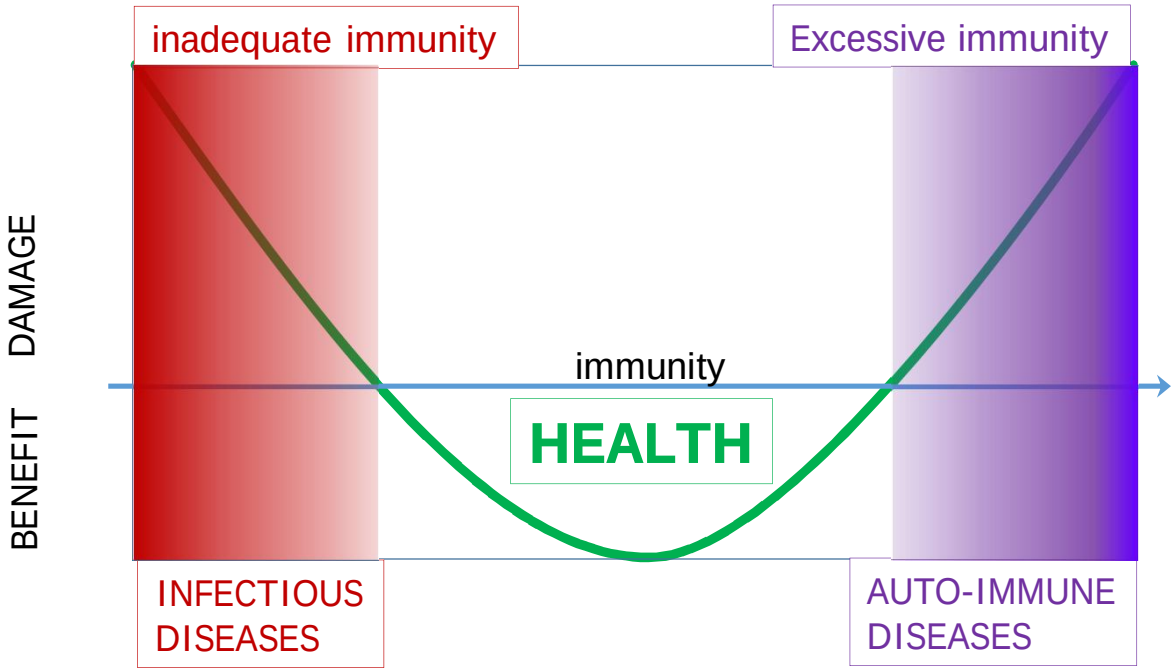
INFECTION + **ANTIBIOTIC** = **CURED HOST**

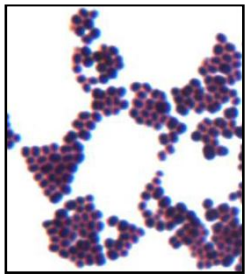
HOST FACTORS

PK of AB



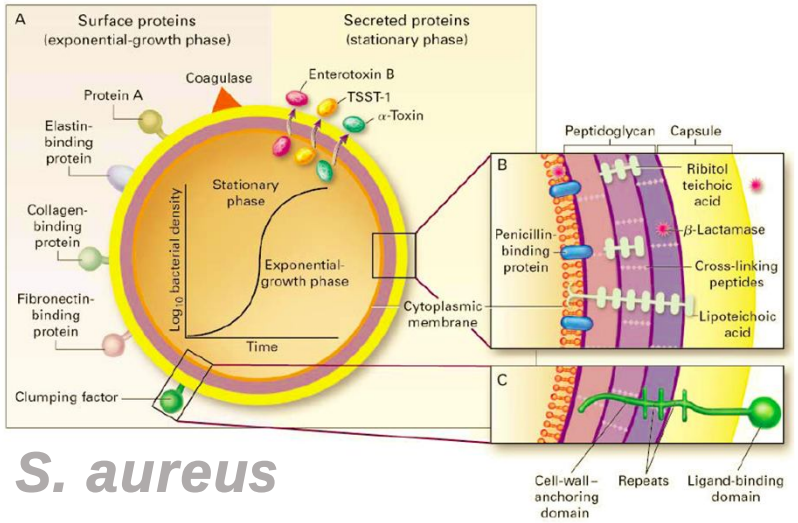
Immune system





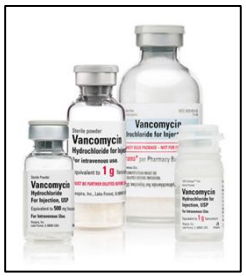
BACTERIAL FACTORS

Virulence factors



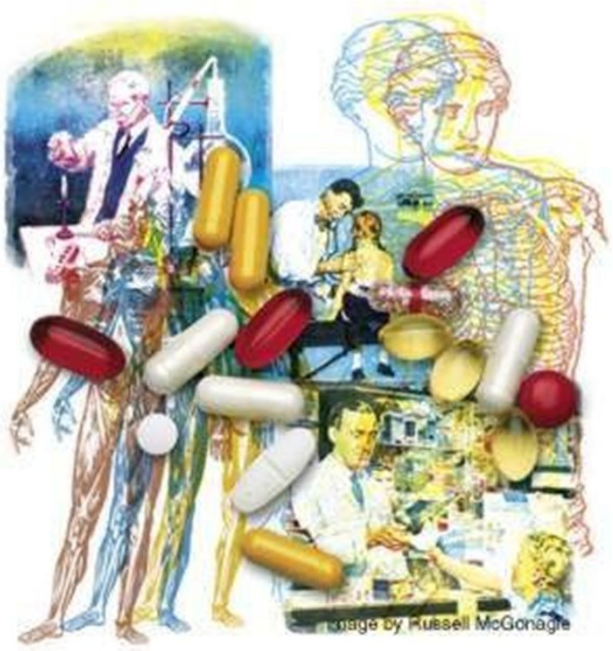
S. aureus

Susceptibility: MIC

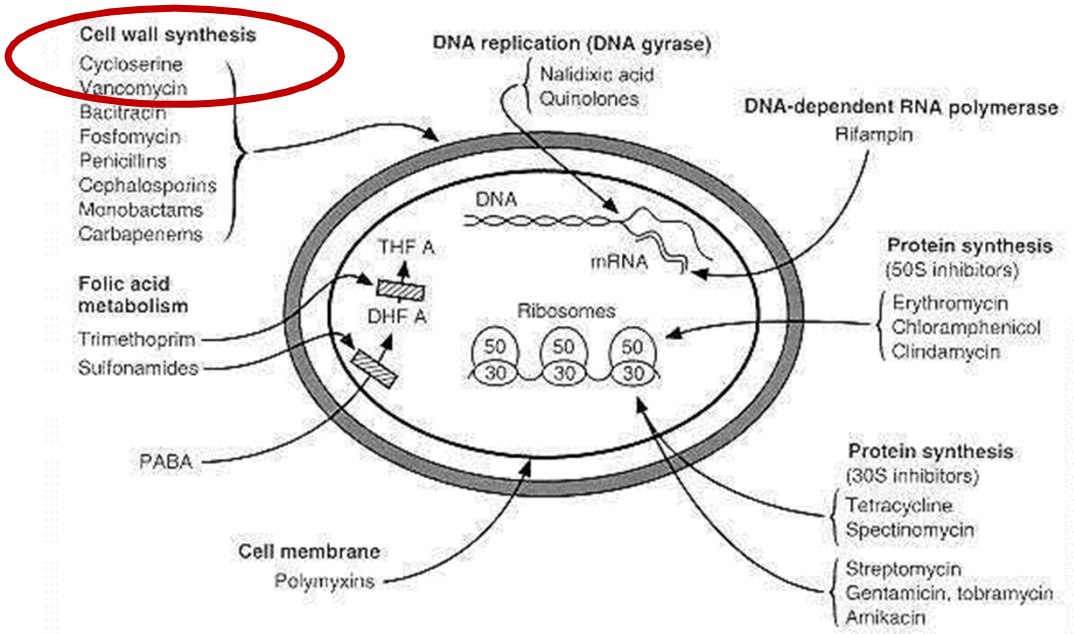


ANTIBIOTIC FACTORS

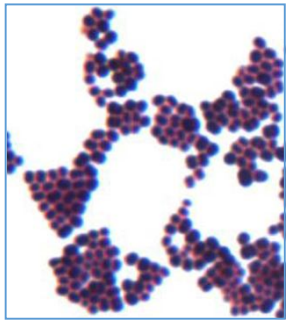
PD of AB

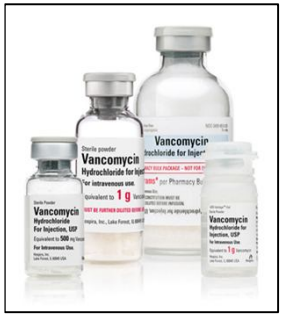


Mechanism of action

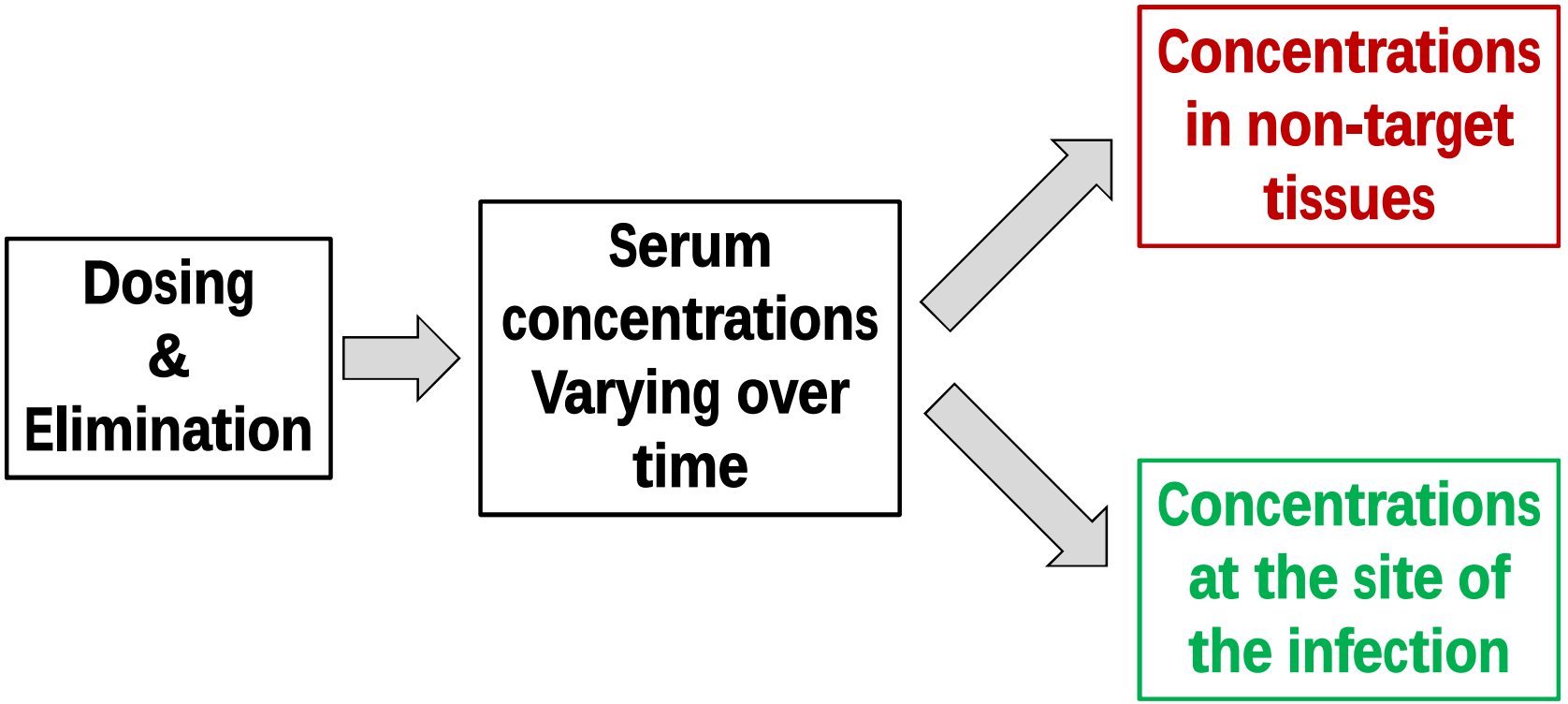


PK/PD

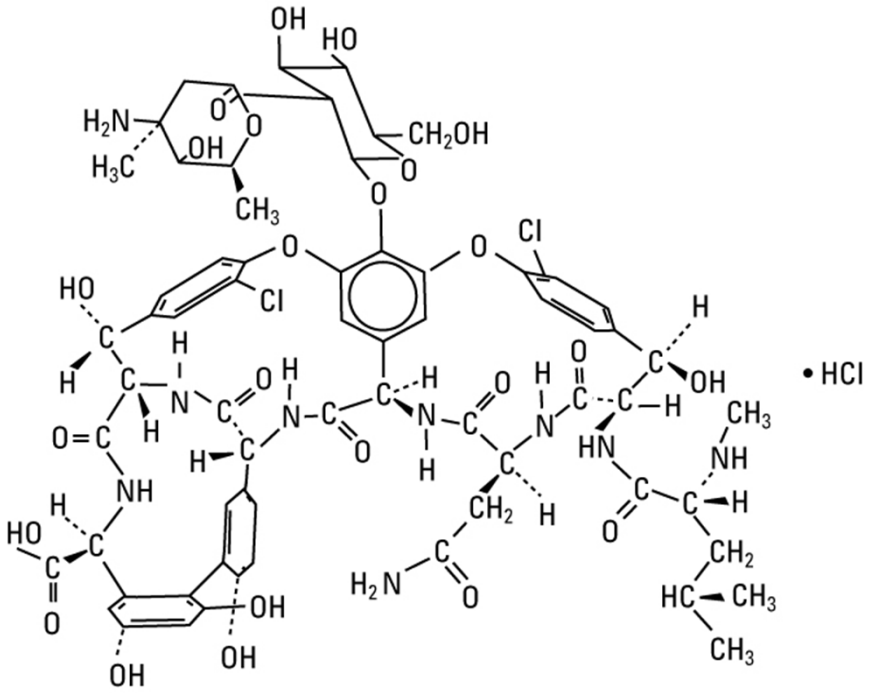




1. Pharmacokinetics of vancomycin (PK)



Dosing & Elimination



- Large molecule, only suitable for IV use (IM = too painful)

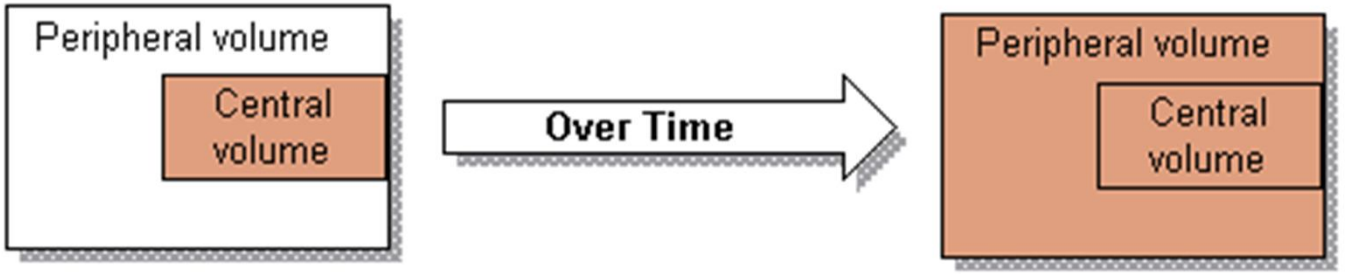
Matzke, Clin Pharmacology, 1986, 11, 257-82
Vandecasteele, JAC, 2013, 68, 743-748

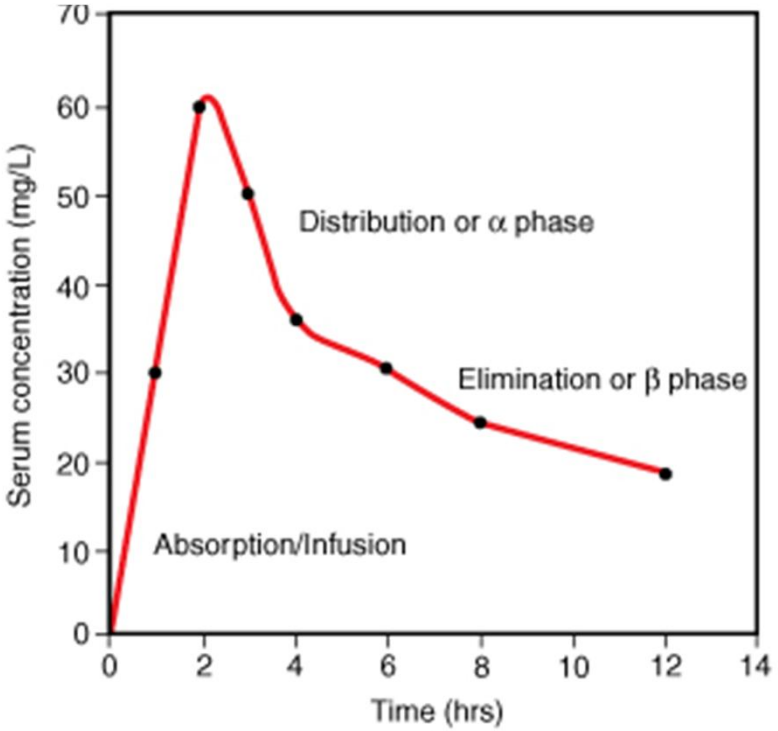
- <u>New data:</u>
  - Considerable oral absorption.
  - 85 pt C.diff, 117 samples
  - 68,2 % > 0,05 µg/ml
  - 17,6 % > 2,50 µg/ml
  - Risk: dose and duration
    Severe CID/ICU stay
    Renal failure

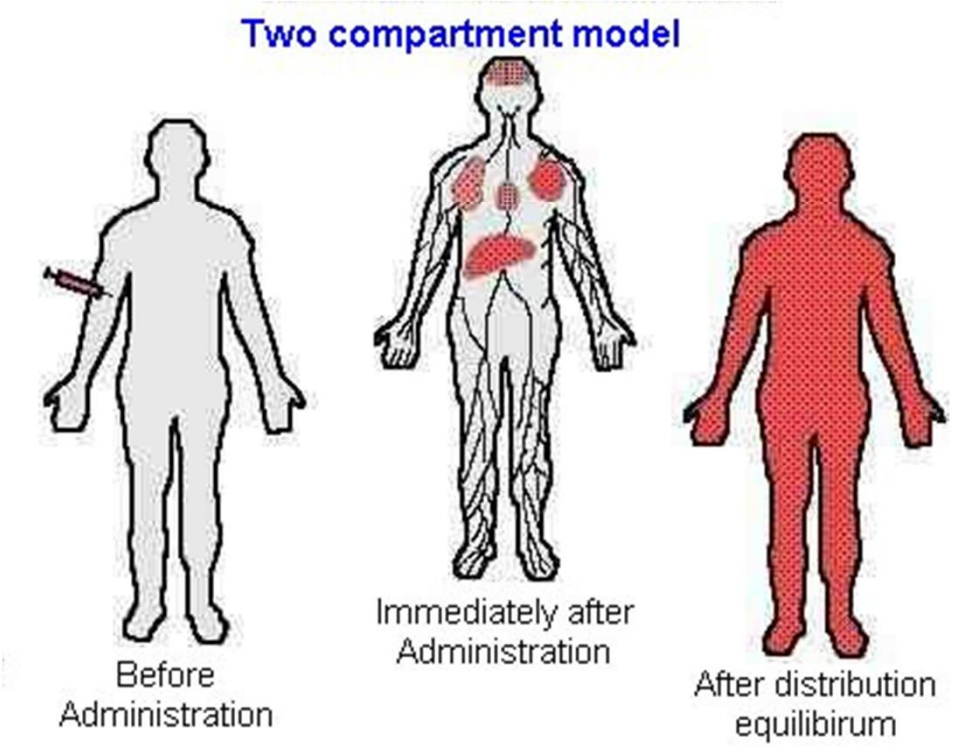
Petit, Pharmacotherapy, 2015, 35, 2, 119-126

Geraci, Proc Staff Meet Mayo Clin, 1956, 31, 564-582
Griffith, Antibiot Annu, 1956, 3, 619-622

Dosing & Elimination







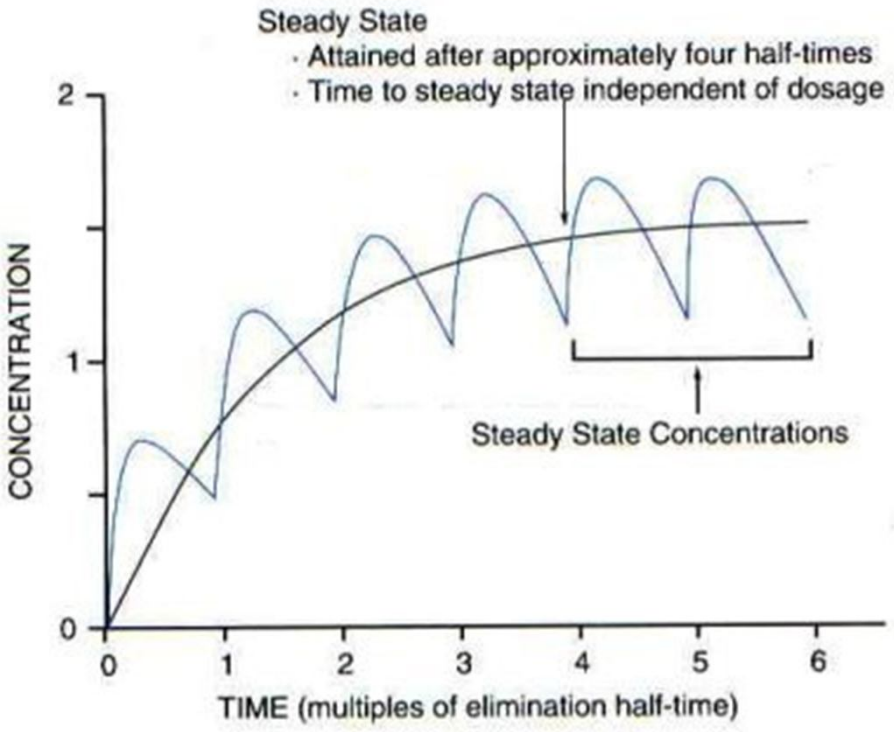
1 - 2 - 3 compartiment model

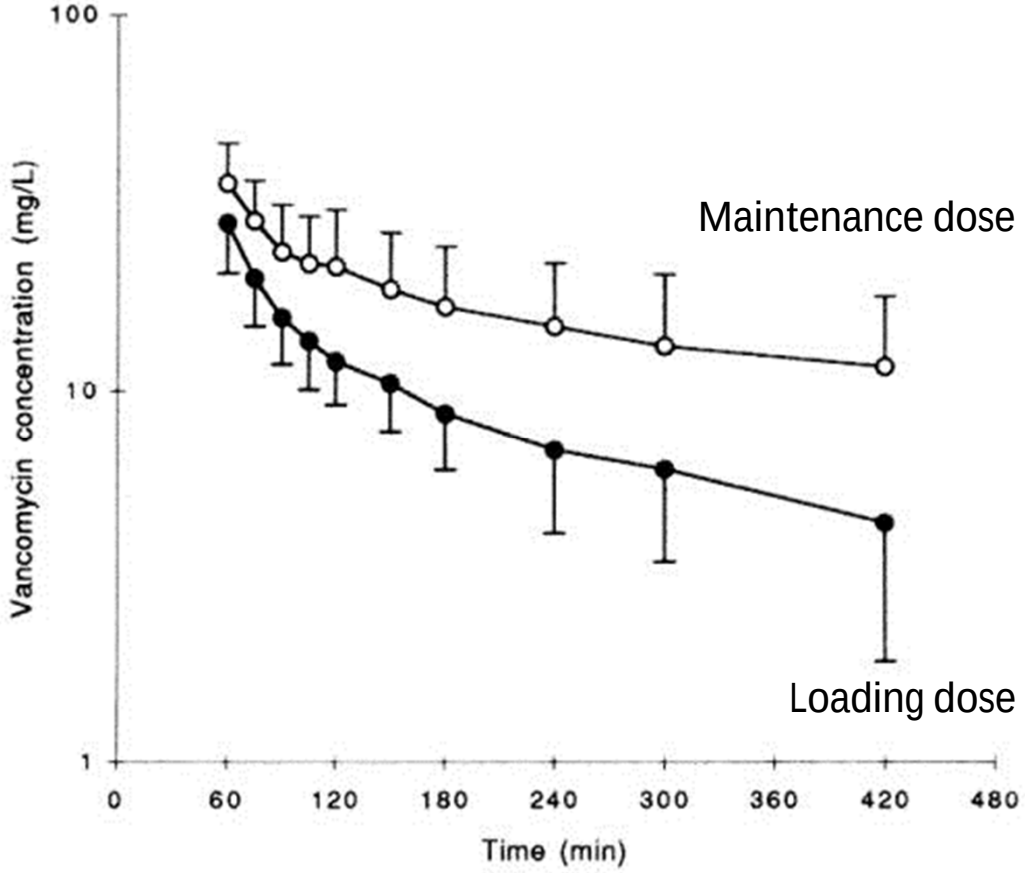
Matzke, Clin Pharmacology, 1986, 11, 257-82

Dosing
&
Elimination

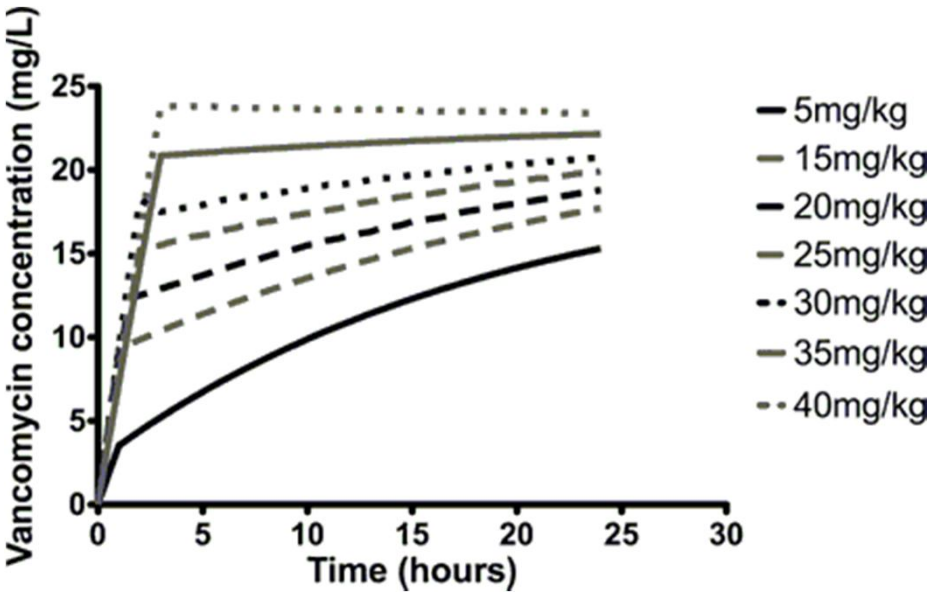
- **Steady state** → **5 x $T_{1/2}$**

Matzke, Clin Pharmacology, 1986, 11, 257-82
Polard, Ther Drug Monit, 1999, 21, 395-403





Dosing
&
Elimination



- Need for **loading dose**:

15 – 35 mg/kg

2015 systematic review:

- ✓Faster target (15 – 20 µg/ml) attainment in adults
- ✓No good data in children
- ✓No data on clinical and microbiological outcome

Readon, Ann Pharmacology, 2015, Eprint

Roberts, AAC, 2011, 55, 2704-2709

Dosing
&
Elimination

- **Infusion rate:**

  Maximum 15 mg/min

Red man (neck) syndrome:

- ✓Cardiac depression and hypotension
- ✓Diffuse redness

~ vancomycin induced histamine release

Garrelis, NEJM, 1985, 312, 245

Newfield, Ann Int Med, 1979, 91, 581

Rybak, Am J Health Syst Pharm, 2009, 66, 82-98

Dosing & Elimination

95 % renal (glomerular filtration): ↓ with ↓CL_{Cr}
5 % non-renal metabolism: ↑ with ↓Cl_{Cr}
(vancomycin degradation products)

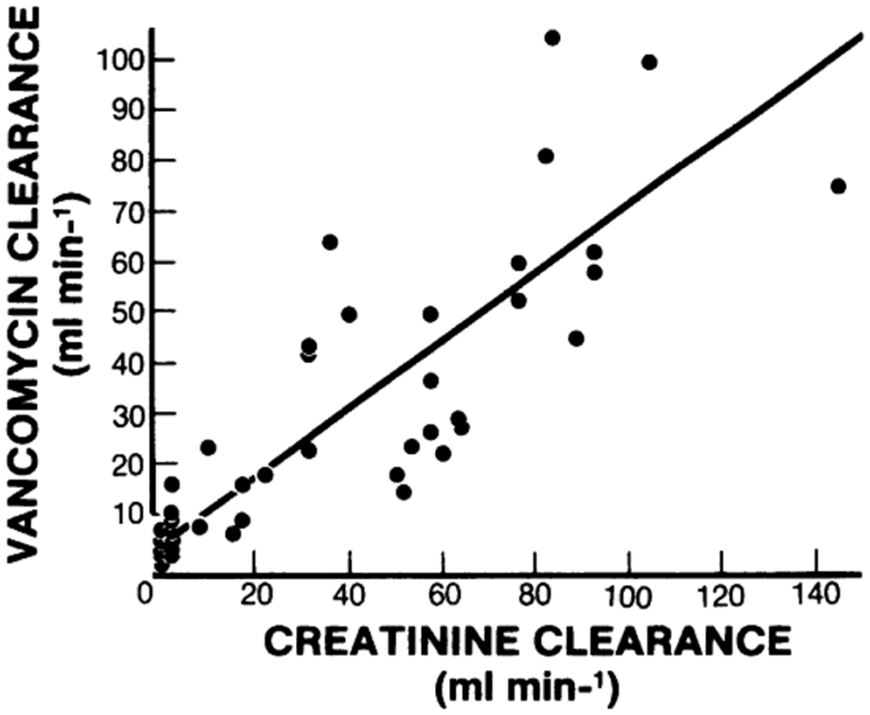


FIG. 3. Vancomycin clearance versus CL_{CR} ($r = 0.8807$; $y = 0.689\,x + 3.66$; $n = 75$).

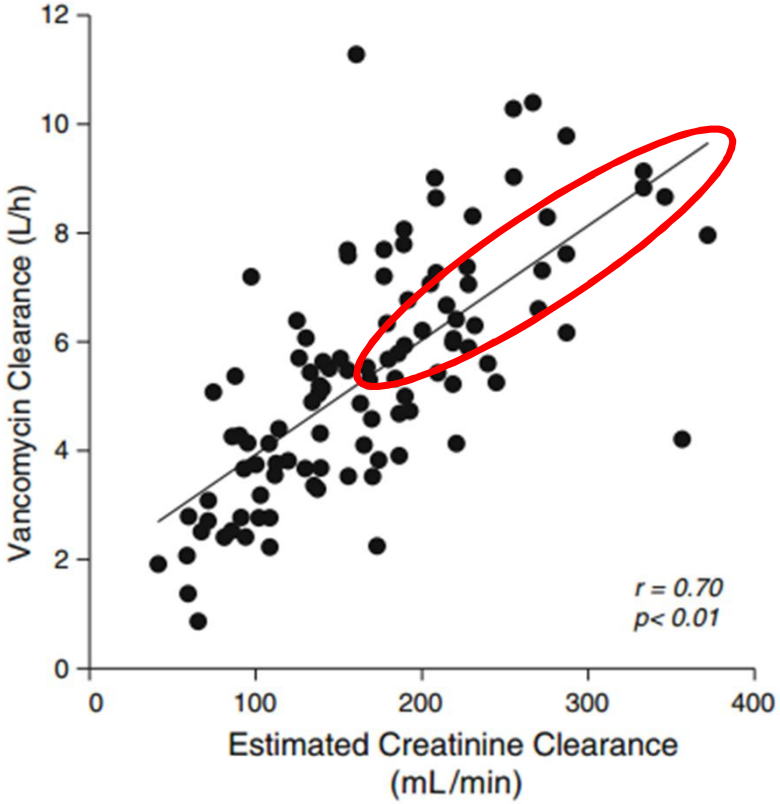
Linear correlation CL_{Cr} and Cl_{Van}

1 study 1984, 56 ptn, among them 30 with CL_{CR} < 10 ml/min (C & G)

Matzke, AAC, 1984, 25, 433-437
Kitzes-Cohen, 2000, Ther Drug Monitoring, 22, 661-667

Dosing & Elimination

- **Linear correlation CL_{Cr} and Cl_{Van}**



Also in hyper-filtration:

➢ICU, sepsis and SIRS

Shimanato, Int Care Med, 2013, 1247-1251
Lin Wu, Ther Drug Mont, 2015, Eprint
Phharm, J Med Assoc Thai, 2014, 97, 11, 1209-1219
Roberts, AAC, 2011, 55, 2704-2709
Matzke, AAC, 1984, 25, 433-437

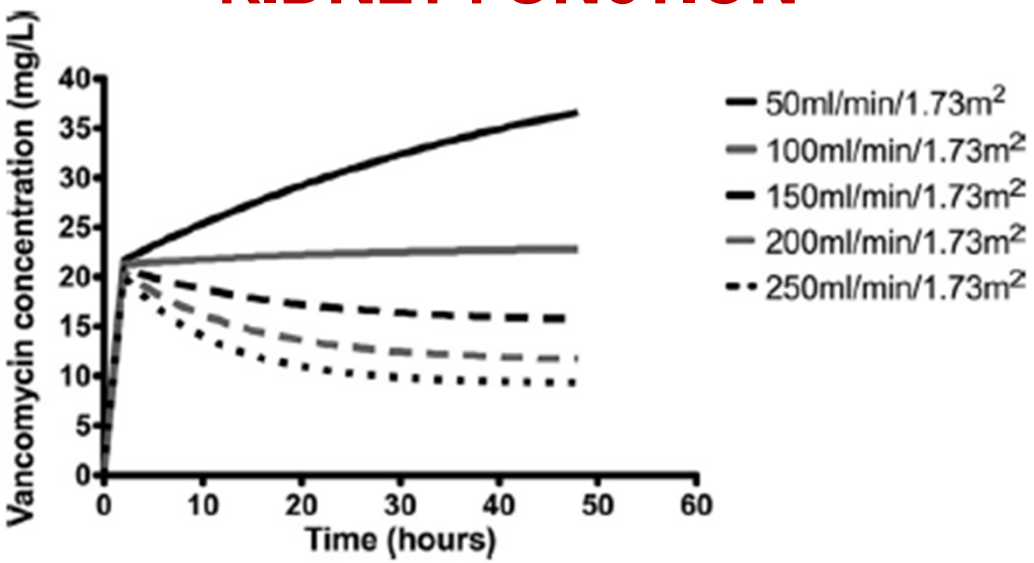
➢Obesity

Adane, Pharmacotherapy, 2015, 35, 127-139
Hall, Am J Med, 2008, 121, 515-518
Matzke, AAC, 1984, 25, 433-437

Dosing & Elimination

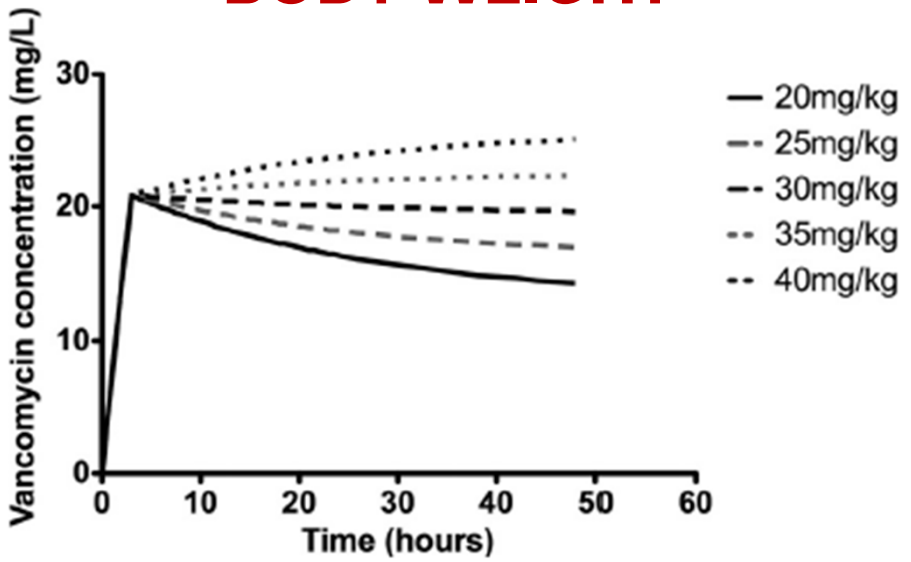
Need to adapt maintenance dose to

KIDNEY FUNCTION



Effect **Cl_{Cr}** (loading dose 35 mg/kg Maintenance dose 35 mg/kg)

BODY WEIGHT

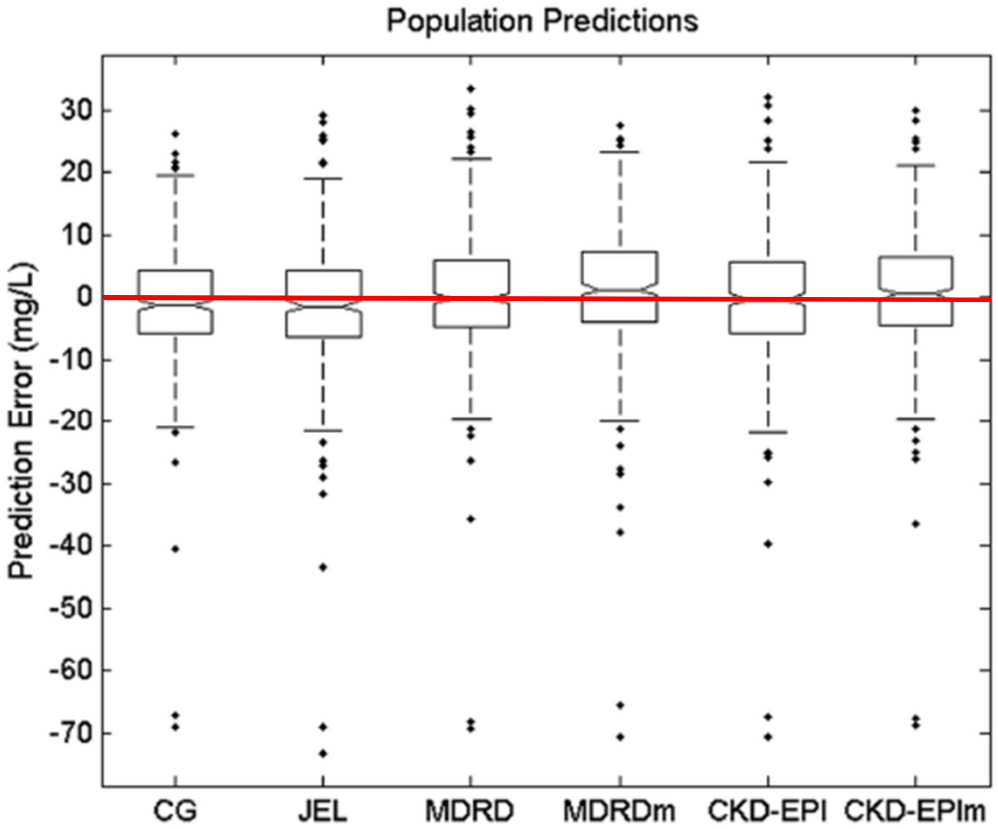


Effect **body weight** Cl (loading dose 35 mg/kg; Cl_{Cr} Cl 100 ml/min/1,73m^2)

Roberts, AAC, 2011, 55, 2704-2709

Dosing & Elimination

Need to adapt dose to kidney function body weight



Prediction vancomycin clearance according to method of estimation of Cl_{Cr} used

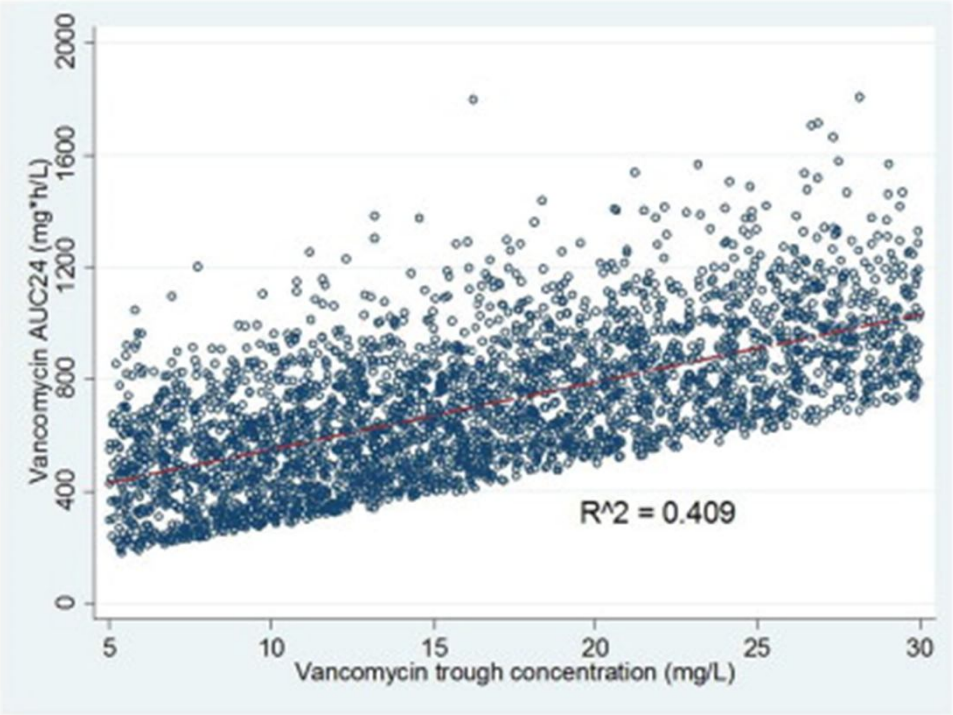
- 78 elderly
- 25-75 percentile
- Significant different (p=0,0071)

Clatard, AAC, 2015, Eprint

Dosing & Elimination

• Correlation Trough – AUC_{24}

Ryback Am Jhealth Syst Pharm 2009, 66, 82-98



Poor correlation, with up to 23 % underestimation AUC

- 3 historical data sets, 47 patients, *"richly sampled"*
- Various modelling
- Good correlation full AUC and trough (r=0,97)

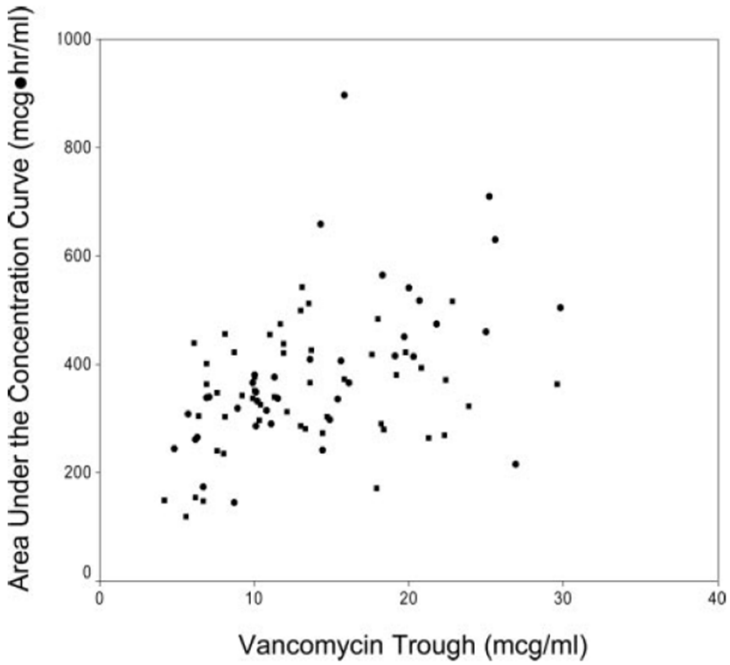
Neely, AAC, 2014, 58, 309-316.
Neely, Adv Drug Deliv Rev, 2014, 77, 50-57,

Dosing & Elimination

• Correlation Trough – AUC_{24}

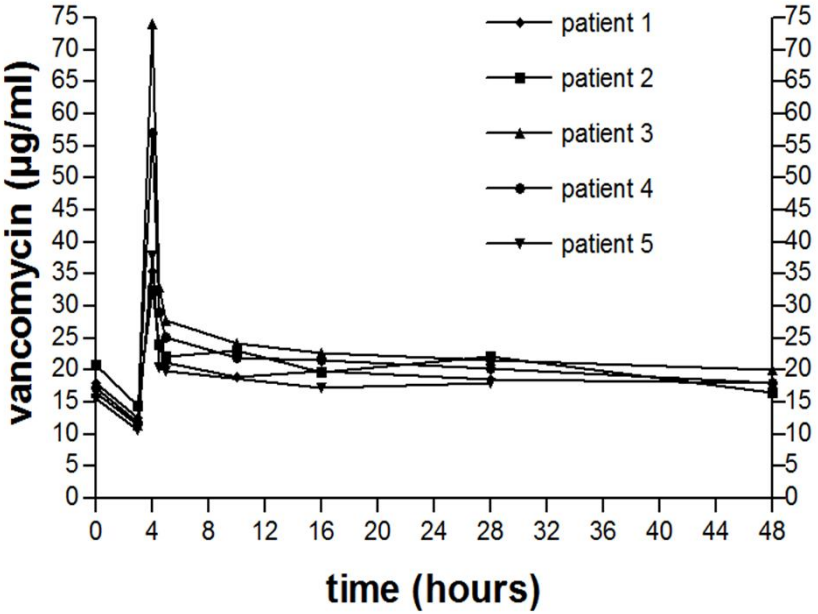
Ryback Am Jhealth Syst Pharm 2009, 66, 82-98

Good correlation



r^2=0.44; P<0.01

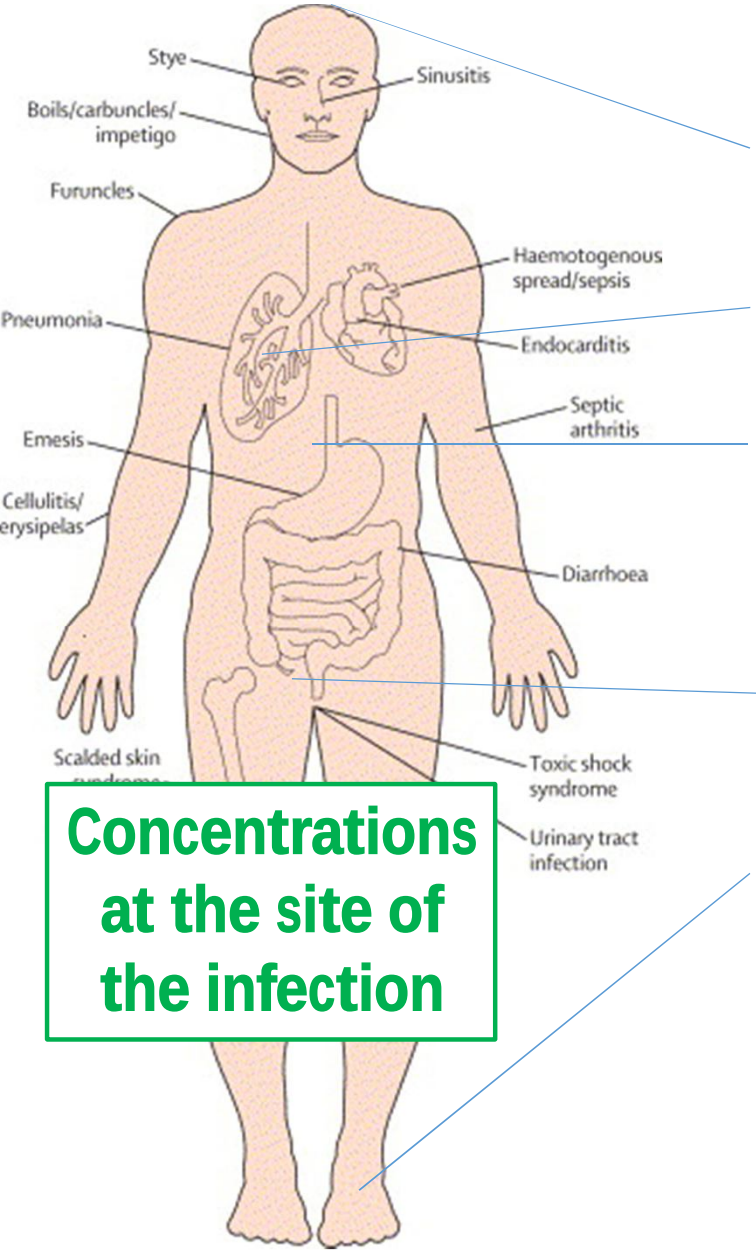
Jeffres, Chest, 2006;130: 947-55



r^2=0.97, p=0.016

Trough 16,6 - 20,9 µg/mL; 24h AUC/MIC 455 – 541

Vandecasteele, CID, 2011;53:124-9



Concentrations at the site of the infection

Poor tissue penetration

- **Brain** ~ 10 % (0-48 %)

Lutsar, CID, 1998, 27, 1117-1129

- **Lung** fluid: < 10 % serum

Georges, EJCMID, 1997, 16, 385-388

- **Bone** and **skin** ~ 20 %

  Fat < 10 %

Kitzes-Cohen, 2000, Ther Drug Monitor, 22, 661-667

- **Intracellular**: “no activity”

Valou, 2015, 59, 2029-2036

- **Diabetic foot** “under target”

Hamada, 2015, JAC, Eprint

CAVE: methodological issues with interpretation tissue concentrations

Mouton, 2008, JAC, 61, 235-237

Dosing & Elimination

	Normal renal function		Renal failure
Oral absorption		Very low	
α-Distribution phase		30–60 min	
Half-life (hours)	6–12		9.1 (CrCl > 60) 32.3 (60 > CrCl > 10) 146.7 (10 > CrCl)
Renal clearance		3.66+(0.689 × CrCl) ml/min	
Extrarenal clearance (%)	5–8.5		Unknown
Dialysance (%)		89.6–93.4	
Protein binding (%)	50–55		20
Tissue penetration		Variable, but generally low	
Volume of distribution	0.4–1 l/kg		0.72–0.9 l/kg
PK/PD parameter		AUC/MIC	
Drug monitoring		Trough levels (target 15–20 μg/ml)	
Post-antibiotic effect		0.2–2 h (in *S. aureus*)	

Matzke, Clin Pharmacology, 1986, 11, 257-82
Vandecasteele, JAC, 2013, 68, 743-748

Dosing & Elimination

Evidence based

1. IV administration, complex PK
2. Variable, often poor, tissue penetration
3. Red men: 15 mg/min IV
4. Loading dose:
   → More rapidly target attainment
   →Body weight based (30-35 mg/kg ?)
5. Maintenance dose:
   → Body weight and Cl_{Cr} based
6. Drug monitoring: Trough ~ AUC_{24}

Dosing & Elimination

Unresolved issues

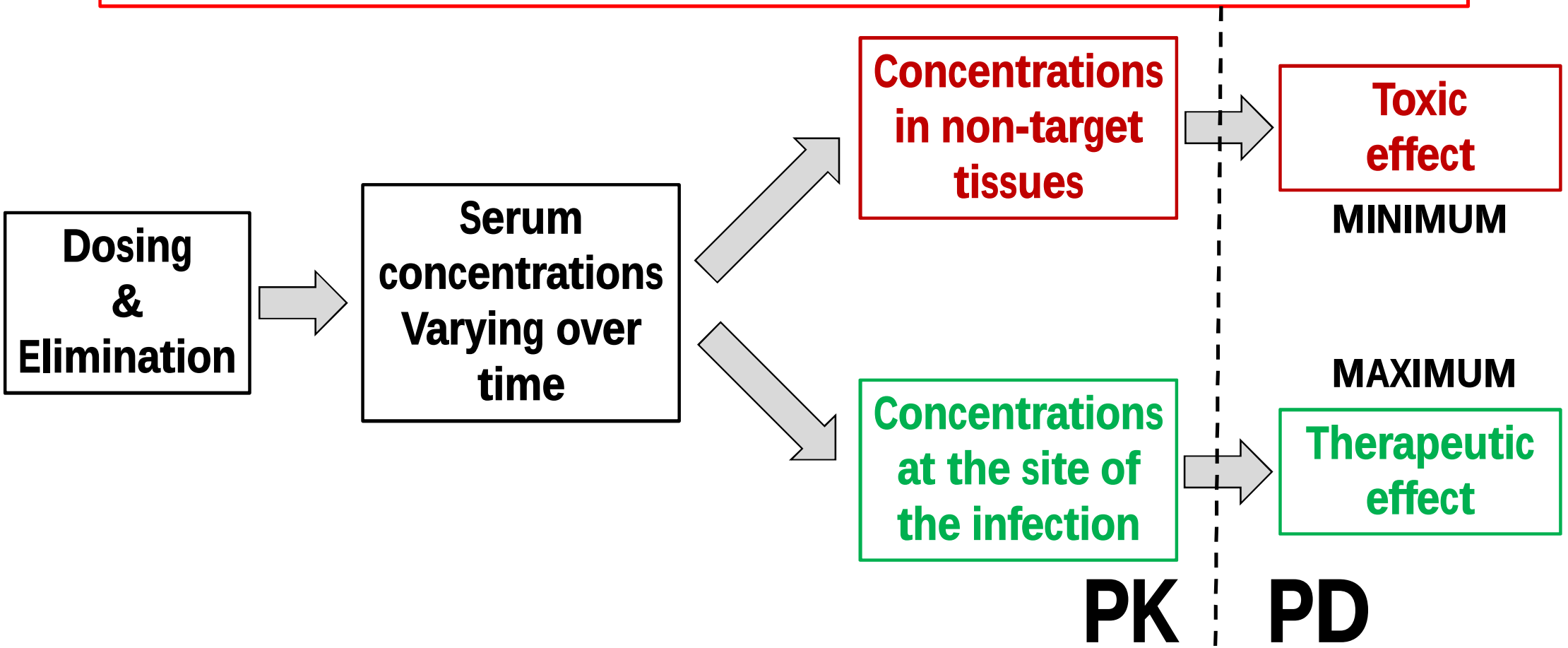
1. Total or free vancomycin concentrations ?
2. Best method to measure vancomycin concentrations

Oyaert, Clinica Chimica Acta, 2015, 441, 63-70

3. Extend of non-renal elimination?
4. Loading dose? How much?
5. Exact influence of renal failure on dosing?
6. How to estimate renal function?
7. Correlation AUC_{24} and through levels
8. What maintenance dose?
9. …

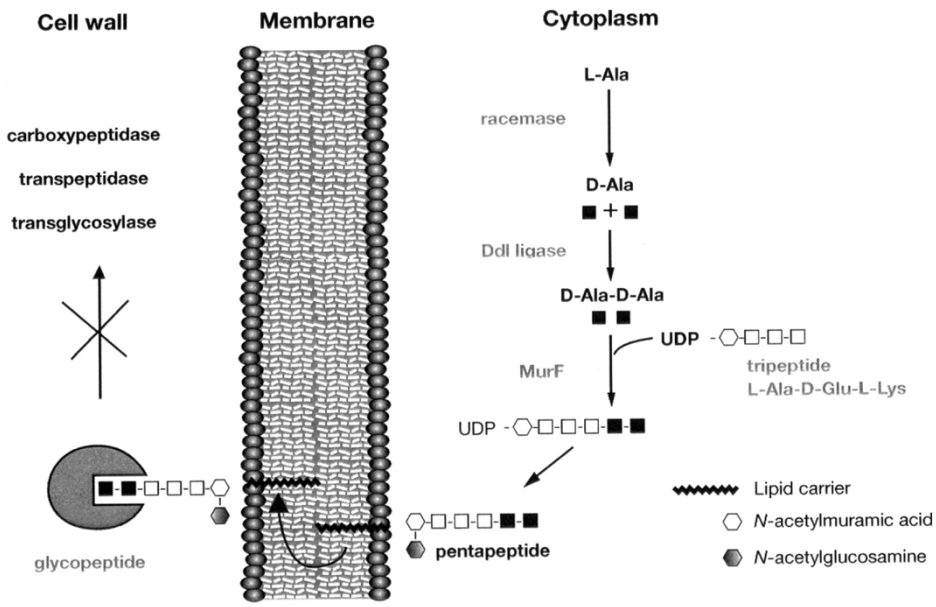
GUESS

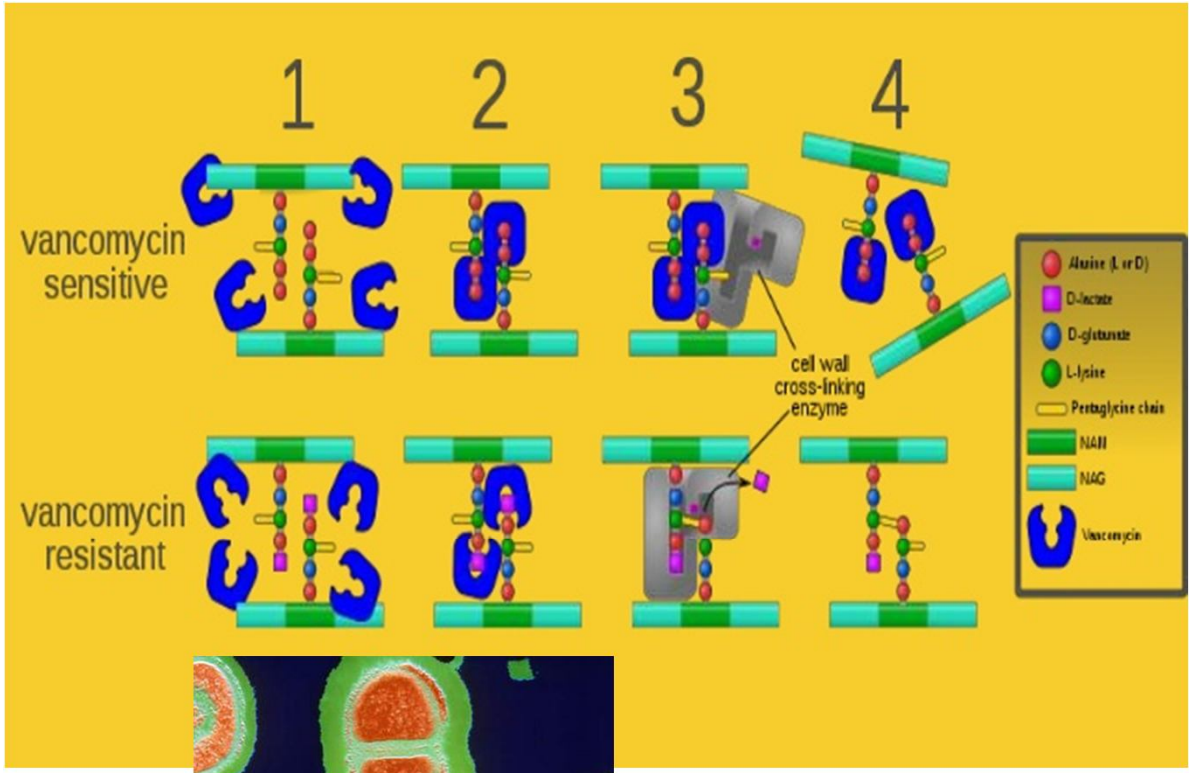
2. Pharmacodynamics of vancomycin (PK)

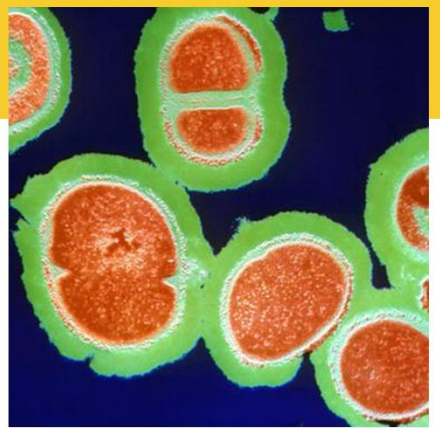


Therapeutic effect

S. aureus





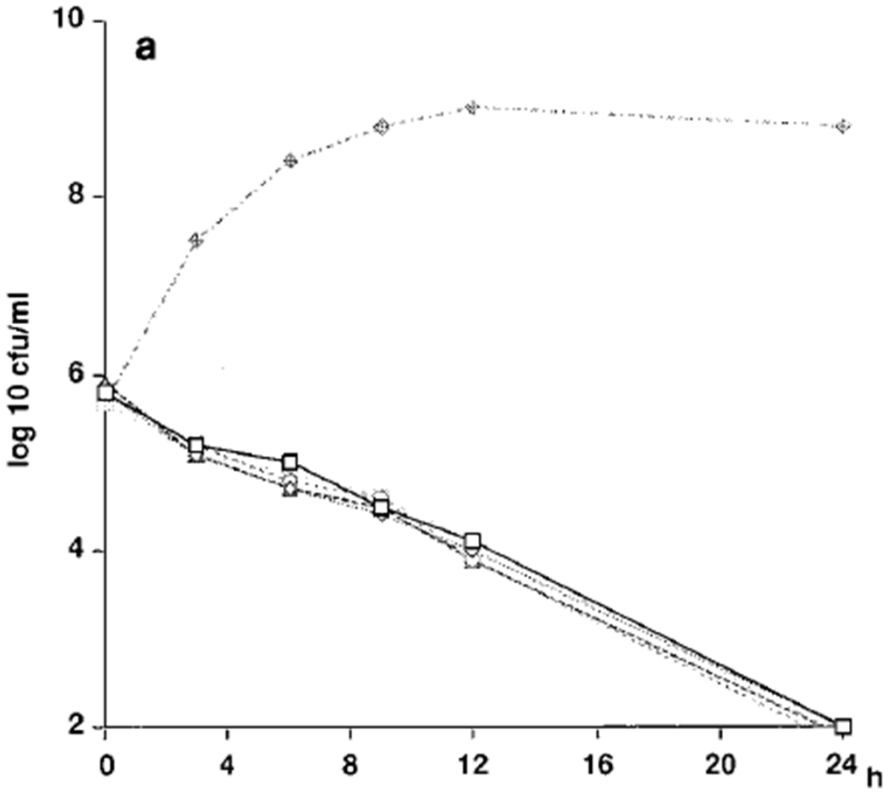


Osmotic cytolysis may take up to 32 hours

Couvalin, 2006, CID, 42, S25-S34

Therapeutic effect

S. aureus



- Killing curve = for 2, 4, 8, 16 and 64 x MIC (Inoculum 10^5 *S. aureus*)
- Higher concentrations → long PAE

→ **Time dependent killing**

Lowdin AAC, 1998, 42, 2739-2744

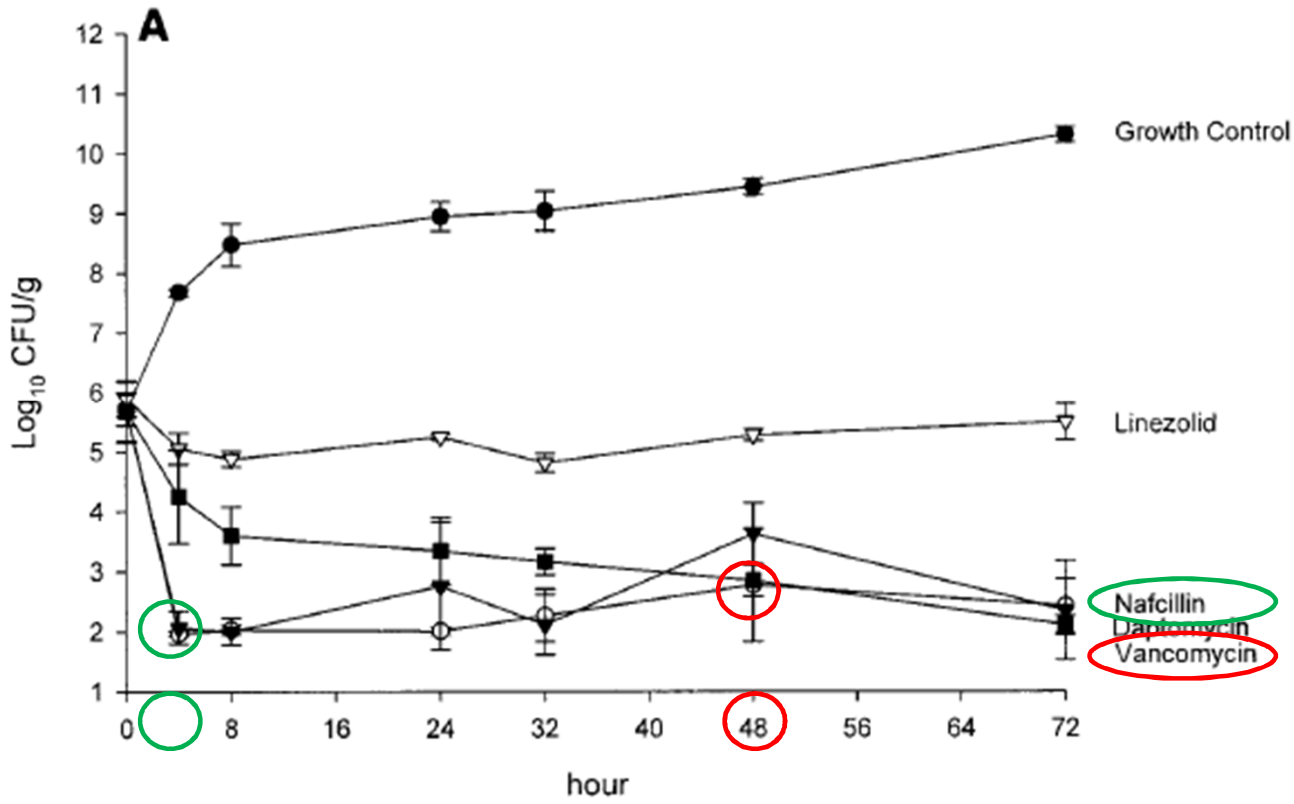
Foreign bodies: no killing

- MBC > 256 times MIC

Chuard, JID, 1991, 163, 1369-1373

Therapeutic effect

Slow killing effect vancomycin:

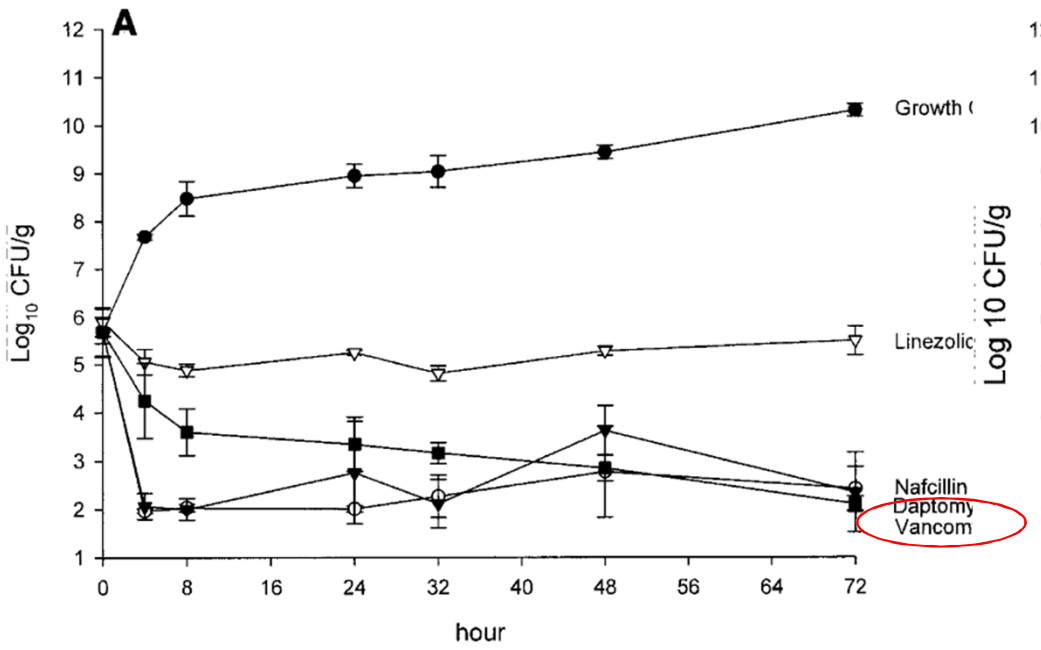


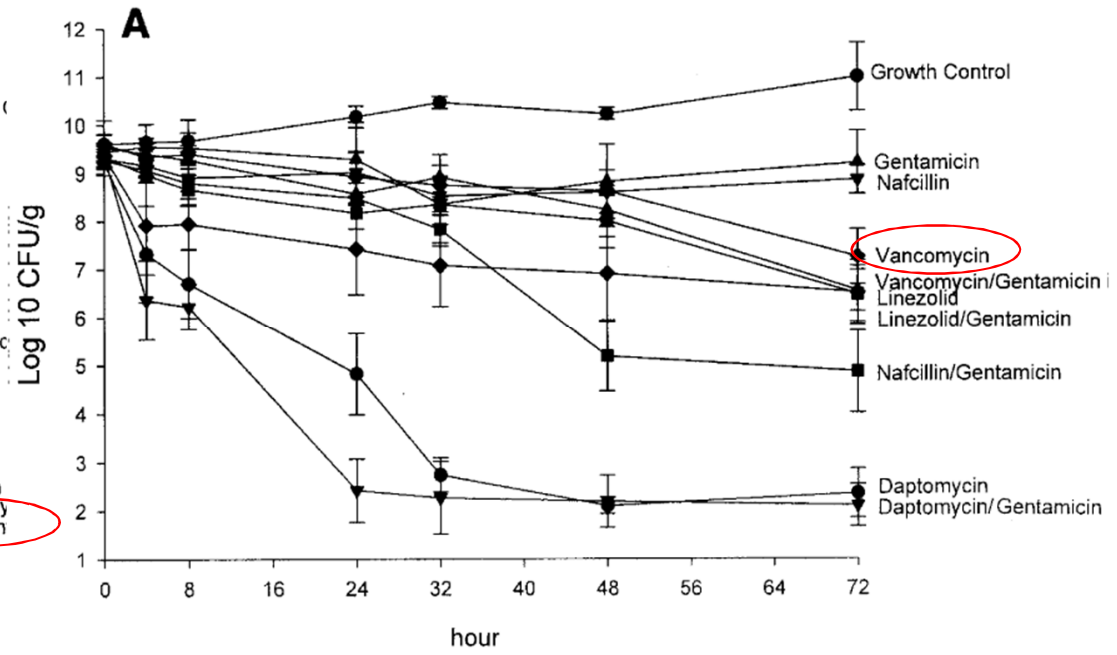
- Nafcillin and daptomycin: bactericidal activity after 4 hours
- Vancomycin: bactericidal activity after 48 hours

Laplanta, AAC, 2004, 48, 4665-4672.

Therapeutic effect

The inoculum effect of vancomycin:





$5x10^5$

↓ 3 log/48 hour

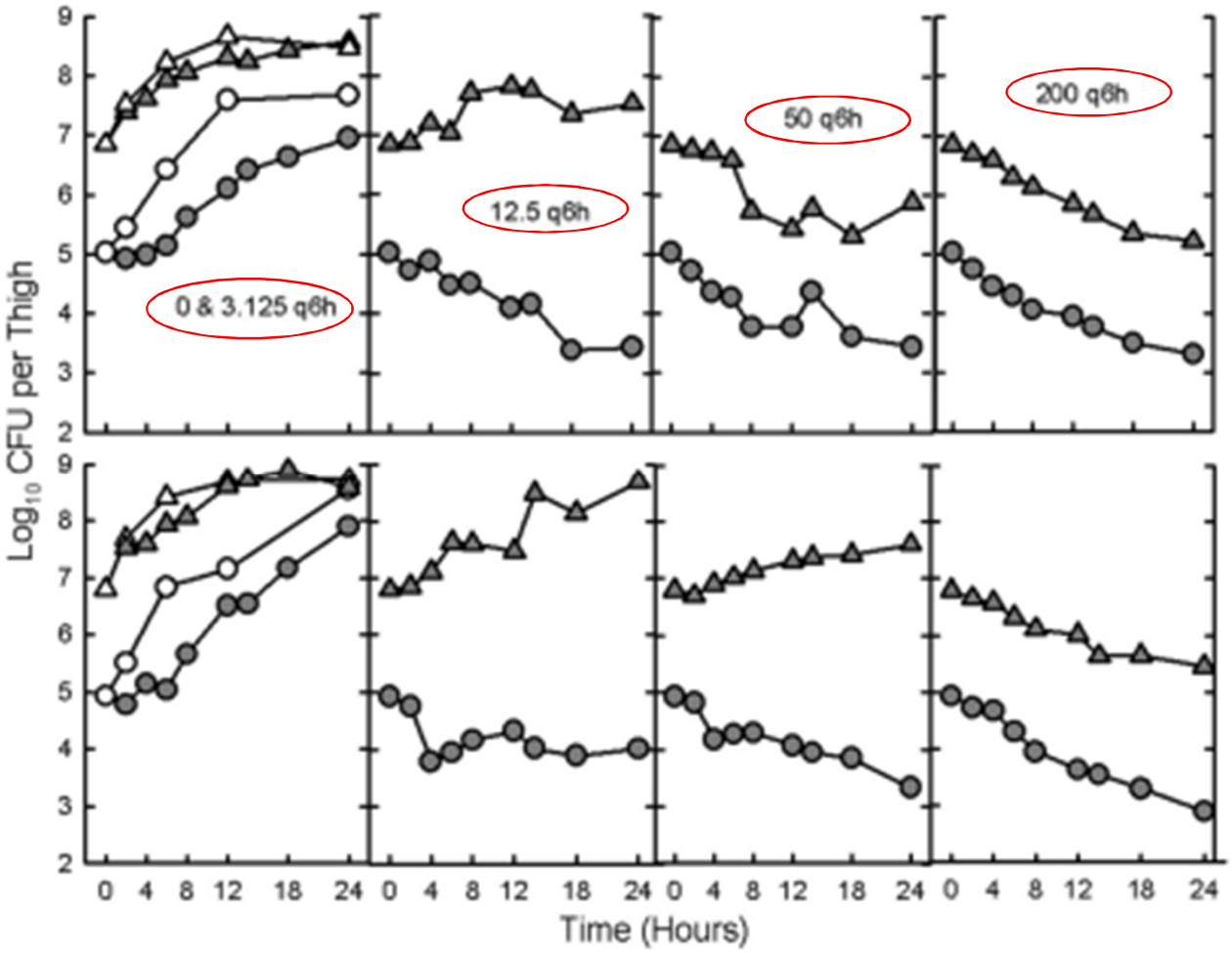
$5x10^9$

↓ < 1 log/48 hour

Laplanta, AAC, 2004, 48, 4665-4672.

Therapeutic effect

The inoculum effect of vancomycin:

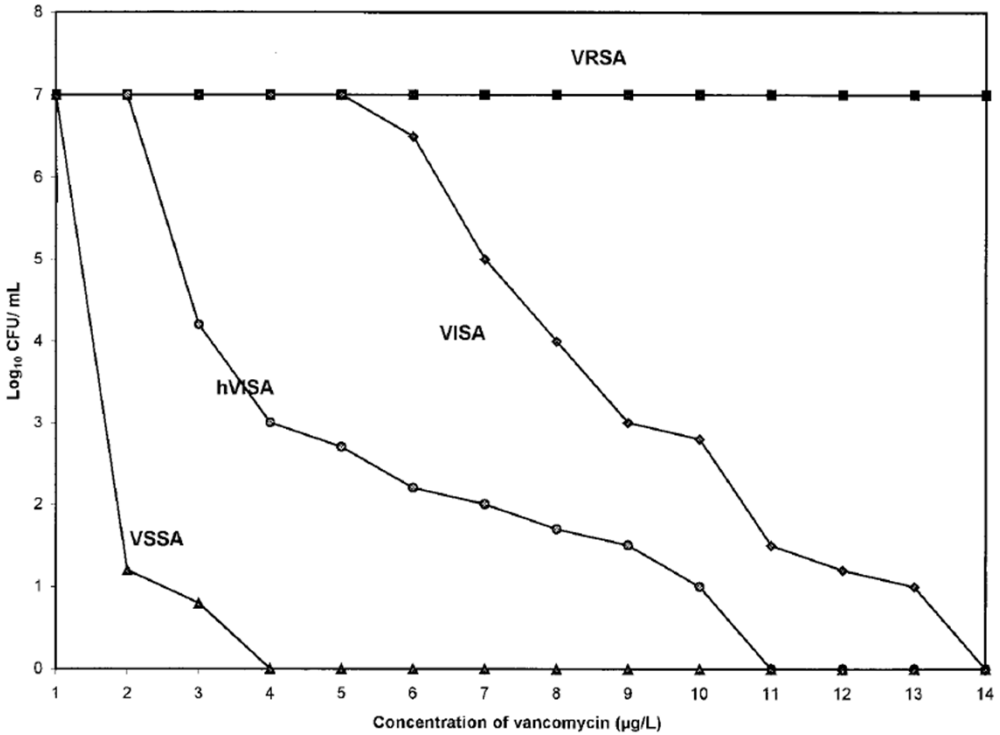


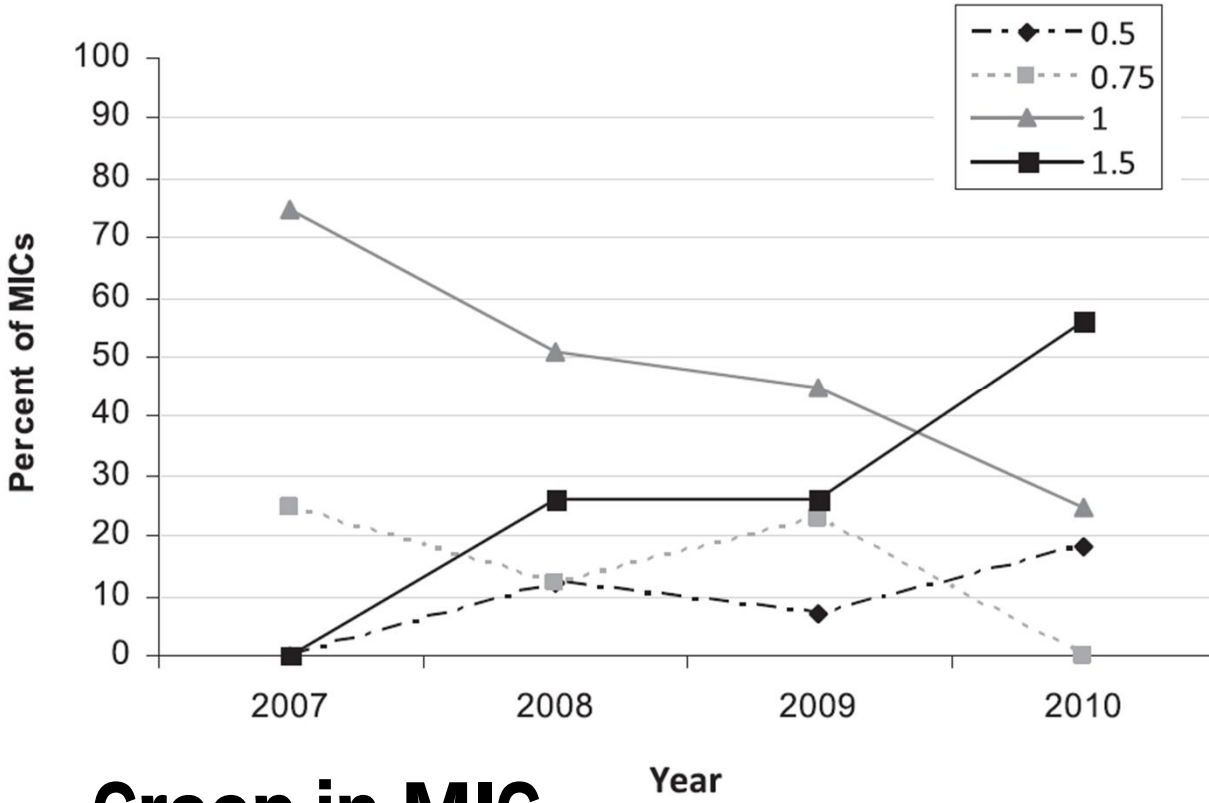
- Neutropenic mouse
- 2 different MRSA strains
- High (triangle) and low (circle) inoculum injected in opposite tight

Lee, AAC, 2013, 57, 1434-1441.

Therapeutic effect

hVISA & creep in MIC





hVISA

Creep in MIC

Liu, *AAC*, 2003,47:3040-5.

Edwards, J Clin Microbiol 2012;50:318-325

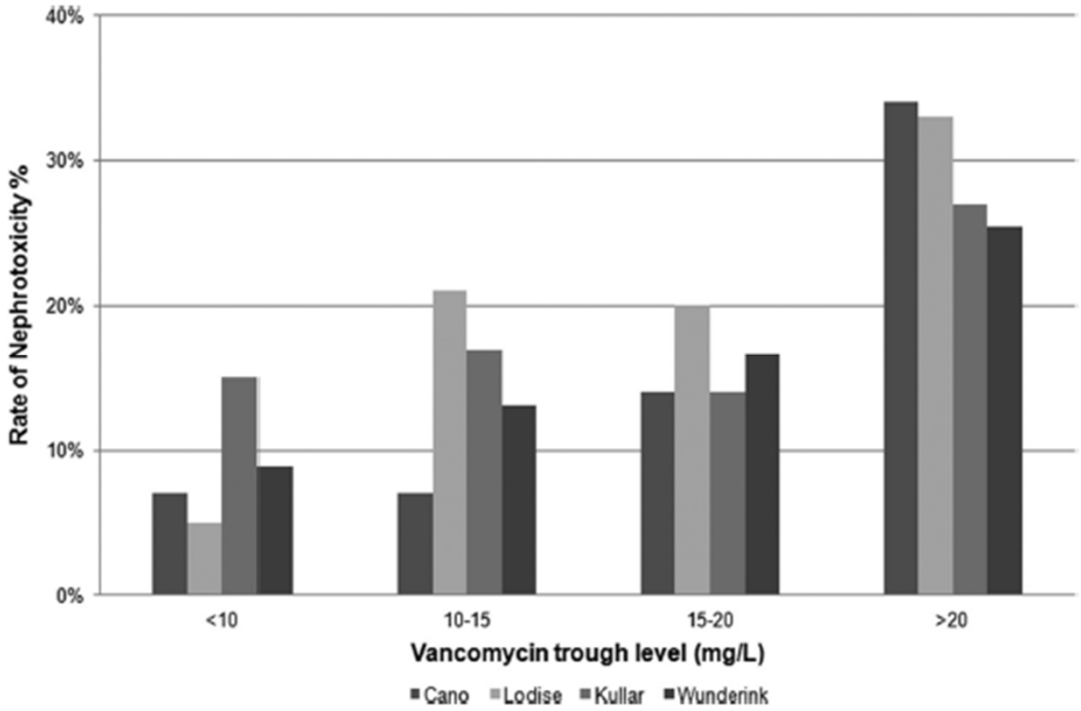
Toxic effect

Inherent toxicity: nephrotoxicity

- **12 – 43 %**; dialysis needed in 5 – 30 % of the severely ill

Vandecasteele, 2010, KI, 77, 760-64
Van Hal, AAC, 2013, 57, 734-744.

- **Incremental with dose (amount and duration)**



Lodise, 2008,AAC, 52, 1330-1336
Lodise, 2009,CID, 49, 507-514
Carreno, 2013, Infect Dis Therapeut, 2, 201-208
Hanrahan, 2014, Crit Care Med, 42, 2527-2536
Van Hal, AAC, 2013, 57, 734-744.

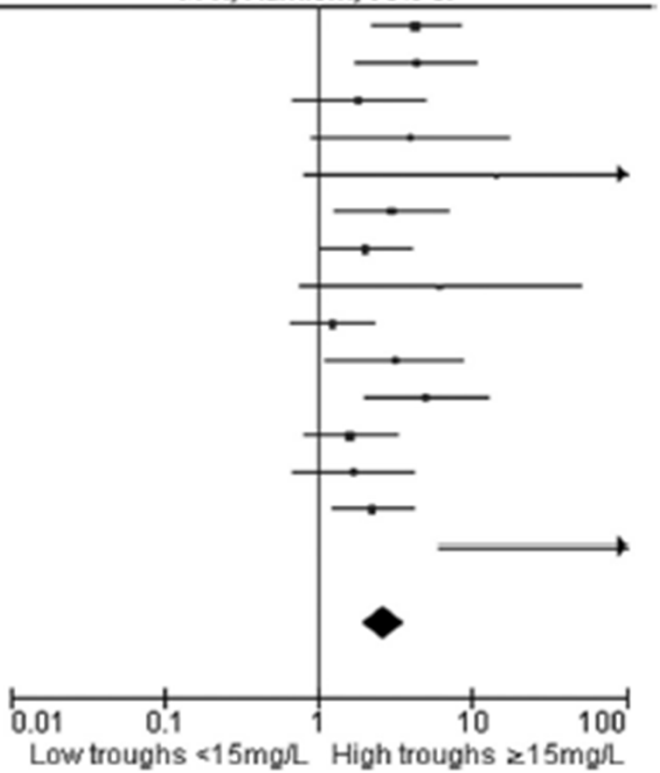
Toxic effect

Inherent toxicity: nephrotoxicity

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 23.89$, $df = 14$ ($P = 0.05$); $I^2 = 41\%$

Test for overall effect: $Z = 6.13$ ($P < 0.00001$)



Van Hal, AAC, 2013, 57, 734-744.

Toxic effect

Inherent toxicity: nephrotoxicity

- Risk is higher for IA than for CI → peak concentration ??

Cataldo, 2012 , JAC, 67, 17-24.
Hanrahan, 2014, Crit Care Med, 42, 2527-2536

- Increased with co-administration of other nephrotoxic drugs, e.g. aminoglycosides , loop diuretics, vasopression, ...

Ryback,1990, JAC, 55,679-687
Hanrahan, 2014, Crit Care Med, 42, 2527-2536

Toxic effect

Inherent toxicity: nephrotoxicity

Retrospective analysis, 1430 treatment courses, ICU, Rifle criteria

- OR 1,112 [1,038-1,139] for medium vanco concentration p<0,001
- OR 1,041 [1,028-1,054] for duration (days) p<0,001

TABLE 5. Precision of Predicting Nephrotoxicity and Incremental Risk Increase of Different Threshold Values for Highest Measured Vancomycin Serum Concentrations

Threshold Level (mg/L)	Nephrotoxicity (%)	Relative Risk Increase[a]	Sensitivity	Specificity	Youden Index	Positive Predictive Value	Negative Predictive Value
10	21.7%		1	0.043	0.043	0.217	1
15	23.2%	1.069	0.936	0.178	0.115	0.232	0.914
20	26.2%	1.207	0.84	0.372	0.212	0.262	0.898
25	33.1%	1.525	0.747	0.600	0.346	0.331	0.899
30	41.5%	1.912	0.603	0.774	0.377	0.415	0.880
> 30	47.9%	2.207	0.303	0.912	0.216	0.478	0.831

[a]Relative to first threshold level (10 mg/L).

Hanrahan, 2014, Crit Care Med, 42, 2527-2536

Toxic effect

Inherent toxicity: ototoxicity

high frequency hearing loss - in up to 12 % of the patients when used longer time.

Forouzesh, 2009, AAC, 53, 483-486.

Ideosyncratic toxicity

neutropenia, hypersensitivity reactions, ...

Matzke, 1986, Clinical Pharmacokinetics, 11 257-280

Therapeutic effect

Evidence based

1. Bactericidal antibiotic with
   i. Slow mode of action
   ii. Time dependent killing activity
   iii. Important inoculum and stationary phase effect

Toxic effect

2. Major problem of nephrotoxicity
   i. Incremental with dose (amount and duration)
   ii. Most pronounced in case of other nephrotoxic factors (medication, hypoperfusion)
   iii. Less in CI than in IA: peak effect ?

Therapeutic effect

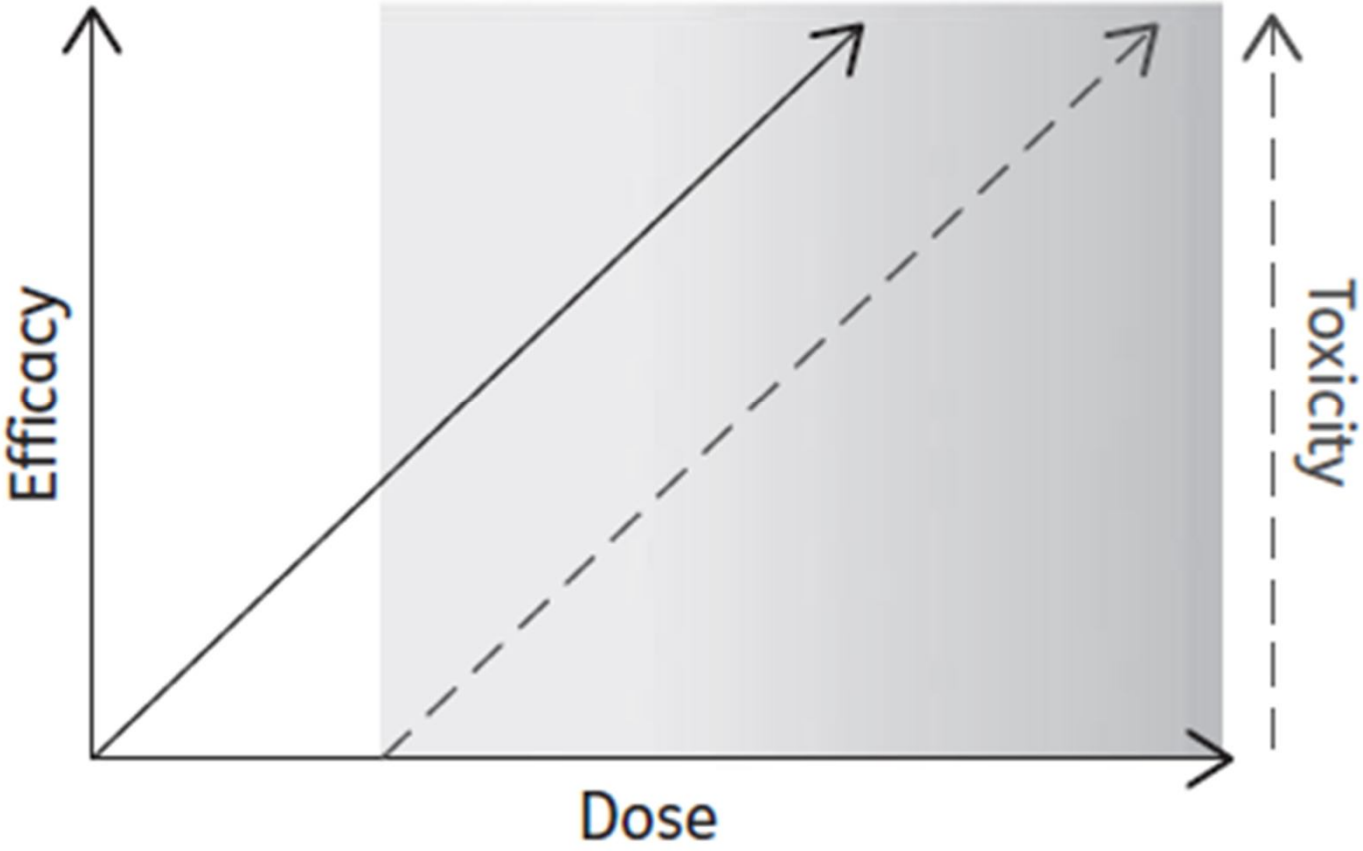
GUESS

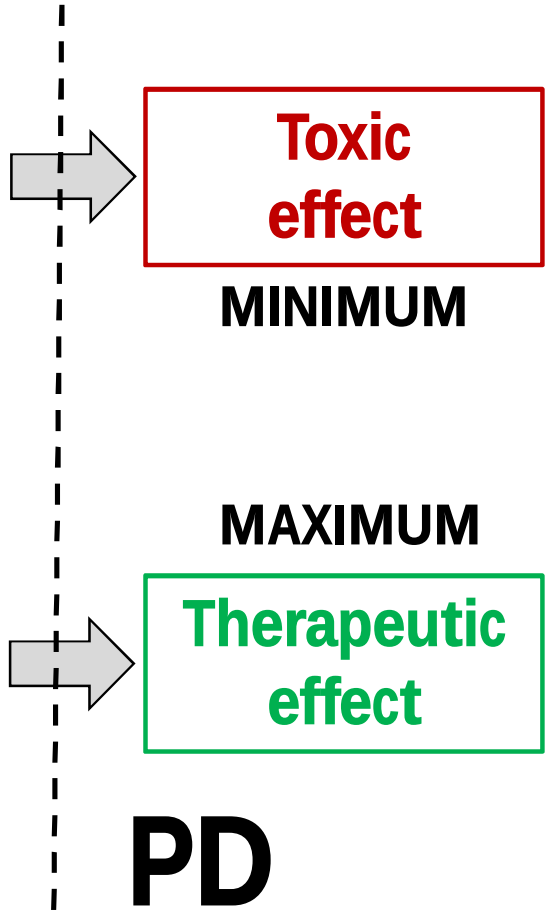
Toxic effect

Unresolved issues

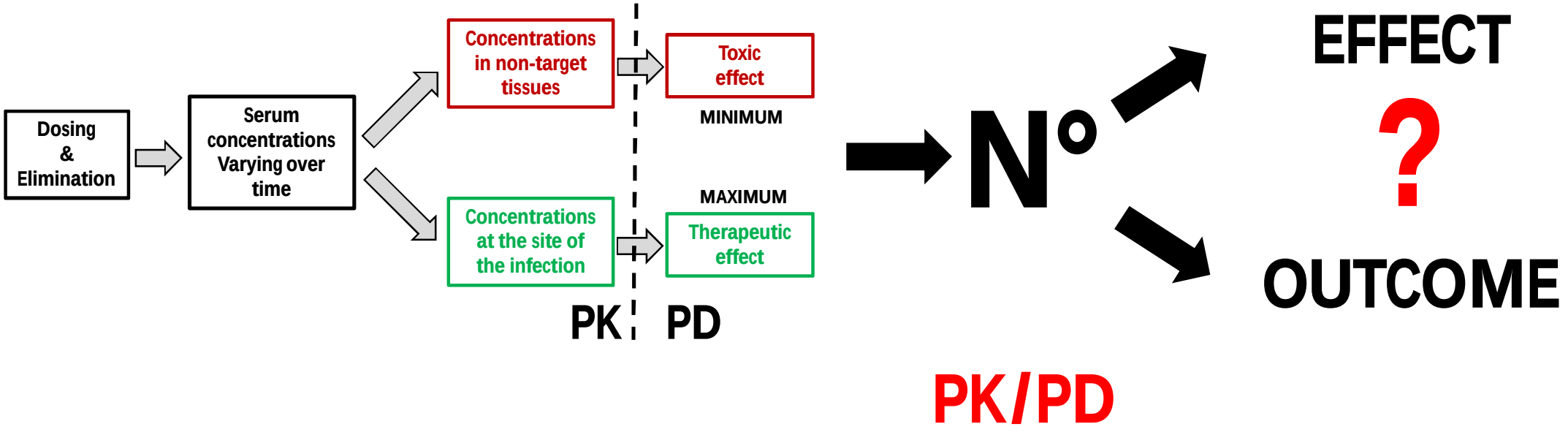
1. Impact of inoculum effect? Growth mode? Biofilm formation? Creep in MIC? hVISA?
2. Exact dose/effect correlation?
3. Exact dose/renal toxicity correlation?
4. Reversibility renal toxicity?
5. Effect renal toxicity on outcome?
6. ...

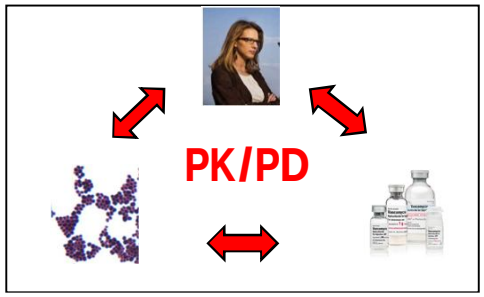
Pharmacodynamics of vancomycin (PD)



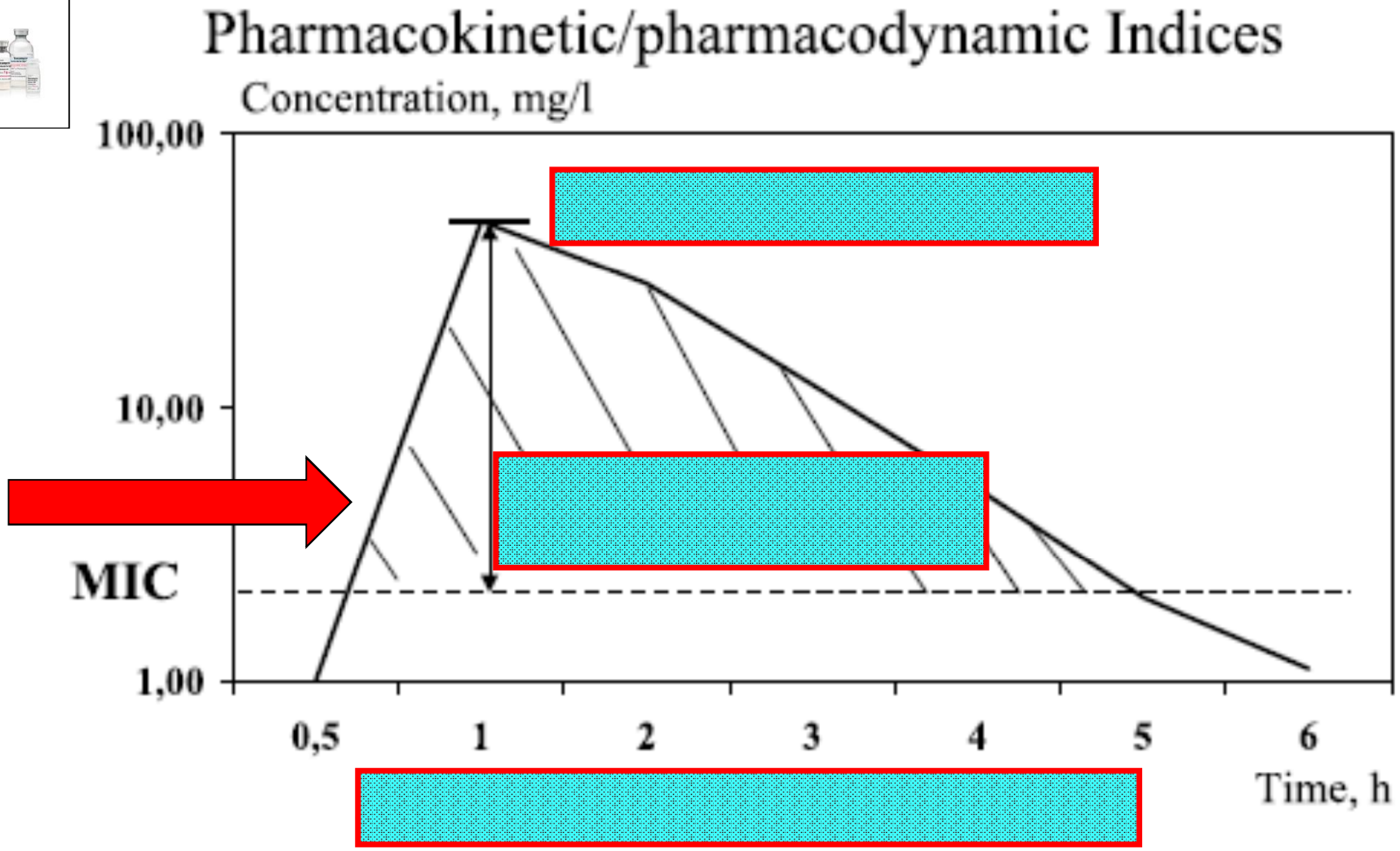


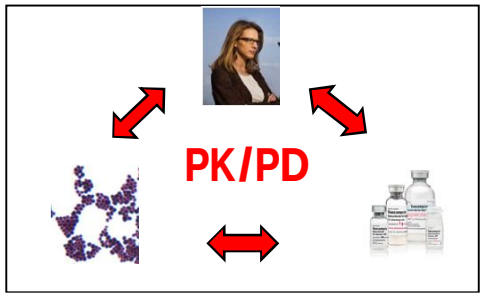
3. PK/PD of vancomycin



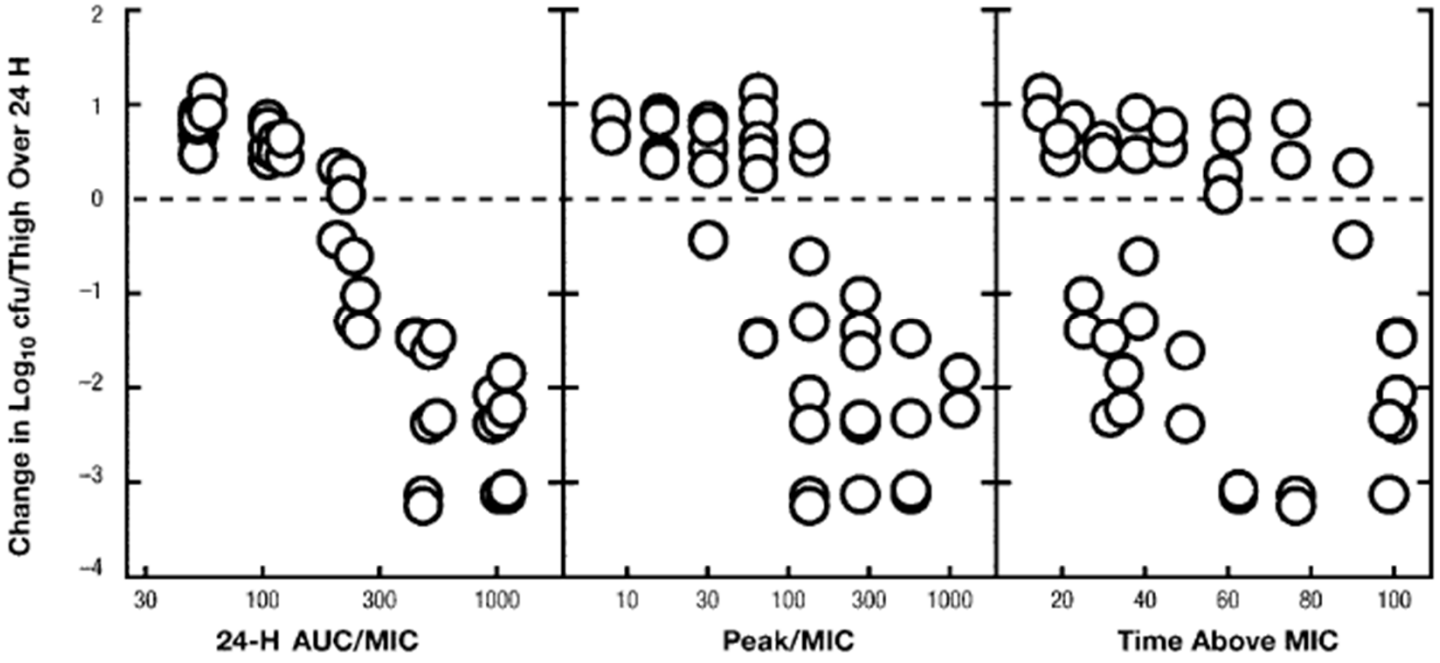


AUC_{24}/MIC as vancomycin PK/PD index ?



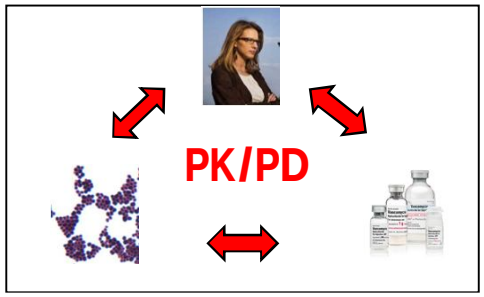


Experimental ground of AUC/MIC model:

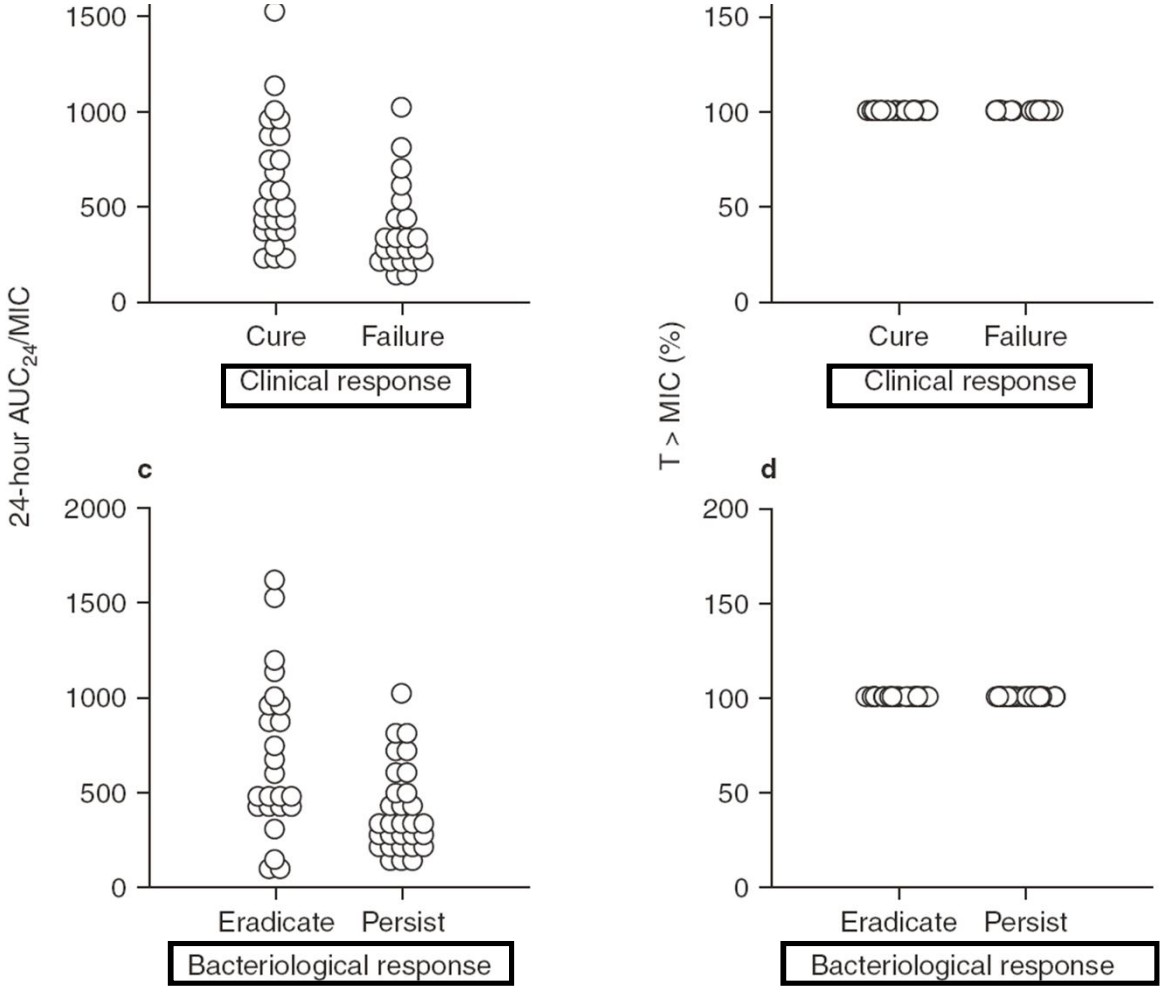


Experimental mouse model
Never published; 1987 ICAAC

Ryder, CID, 2006; 42: S35–9



Clinical grounds of AUC/MIC model:

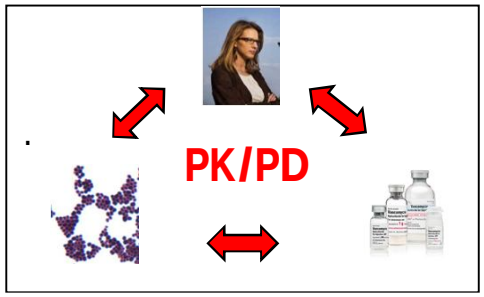


1) 108 ptn with pneumonia calculated AUC_{24} in 78 (!) ptn

AUC_{24}/MIC:

- 345 clinical cure
- 850 microbiological cure

Moise-Broder, Clin Pharmacokinet, 2004;43: 925-942



Clinical grounds of AUC/MIC model:

2) 102 ptn HA pneumonia, calculated AUC_{24}
No correlation through or AUC with outcome

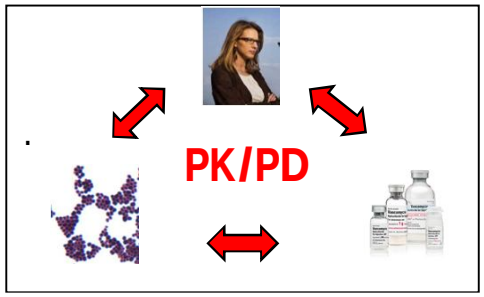
Jeffres' 2006 Chest, 130, .947-955

3) 50 complicated MRSA bacteremia
retrospective, calculated AUC_{24}
correlation outcome (4x higher mortality) with AUC_{24}/MIC of < or **> 211**

Brown, AAC, 2012, 56, 634-638.

4) Retrospective cohort of 182 SAB, calculated AUC_{24}/MIC
No correlation with 30-day mortality for AUC_{24}/MIC ≥ 400, but **correlation** when cut-off of **> 375** is used (p=0,043)

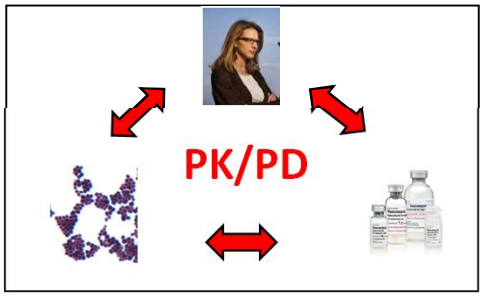
Holmes, AAC, 2013, 57, 1654-1663



Clinical grounds of AUC/MIC model:

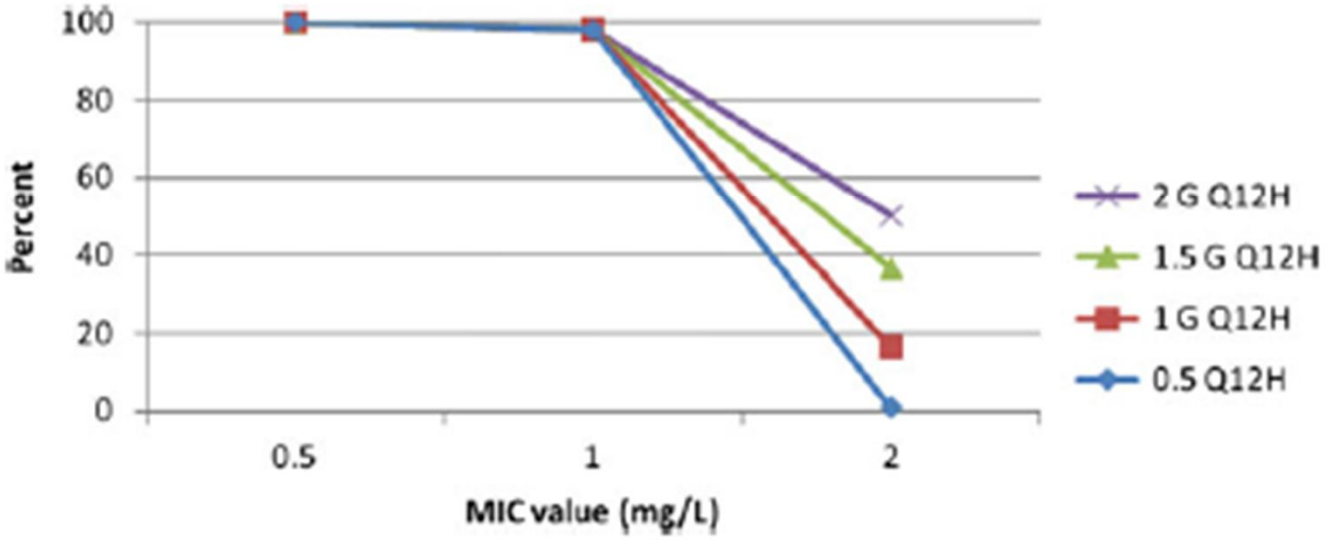
5) 139 ptn MRSA endocarditis, 76,3 % right-side
failure = 30 d mortality or > 7 d bacteremia
calculated $AUC_{24,}$ retrospective cohort
Correlation with **failure** 69,8 versus 54,7 % for AUC < or > than 600
p =0,073

Casapao,2015, AAC, Eprint.



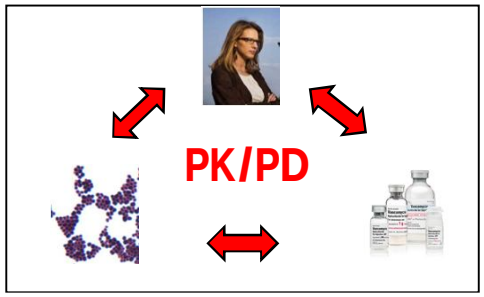
Which AUC/MIC is feasible?

MIC value	AUC/MIC ratio ≥400			Nephrotoxic event	
	0.5mg/L (%)	1.0mg/L (%)	2.0mg/L (%)	Non-ICU (%)	ICU (%)
500 mg IV Q12H	57	15	0.7	3	10
1000 mg IV Q12H	90	57	15	6	16
1500 mg IV Q12H	97	79	38	9	25
2000 mg IV Q12H	98	90	57	14	34



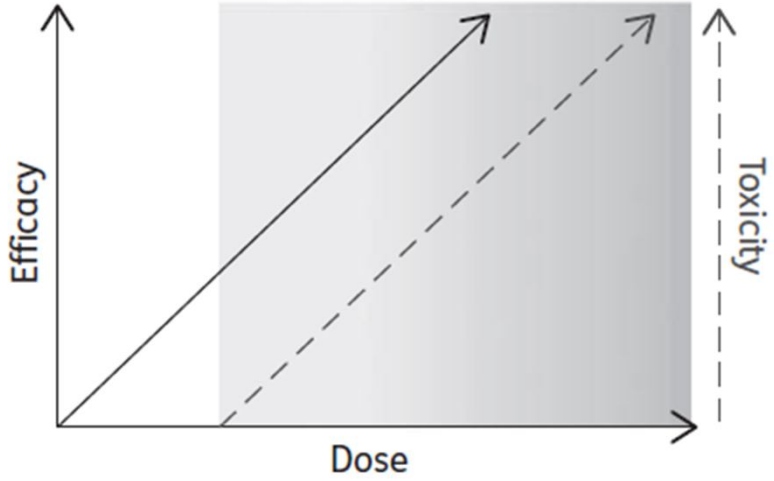
Extensive modelling
Data from 37 patients

Patel *et al*. Clin Infect Dis 2011;52:969–974



Target levels:

No hard outcome data !!

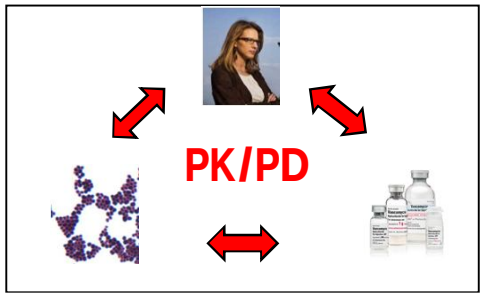


Efficacy: the higher, the better

Toxicity: the lower, the better ...

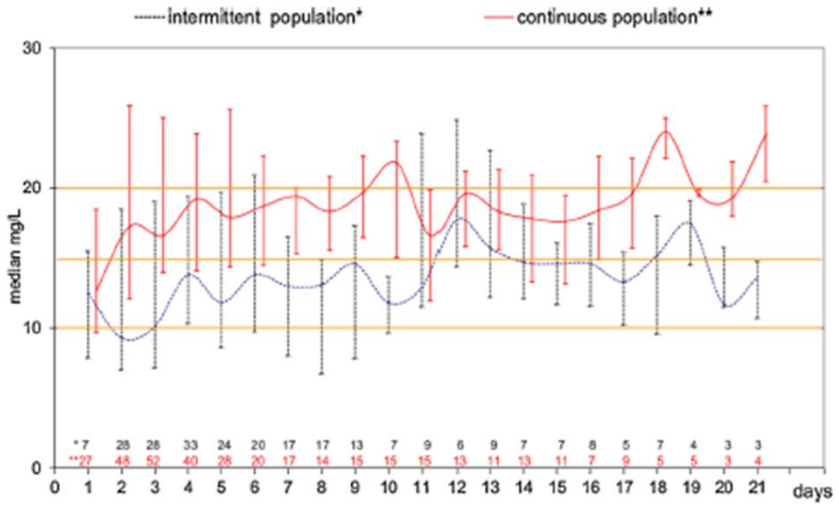
Data derived from AUC/MIC modelling:

- **Intermittent administration: 15-20 µg/ml**
- **Continuous infusion: 20-25 µg/ml**

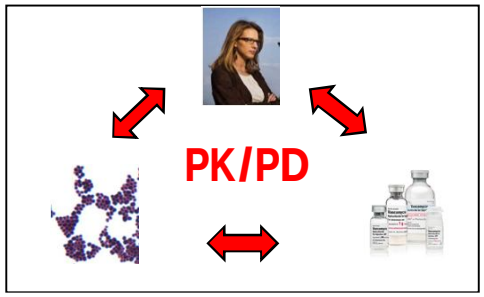


CI or IA ? → time dependent AB
→ No hard outcome data !!

- Less renal toxicity for CI
- More rapid target attainment (3 versus 4 days – p=0,022)
- Less sub-therapeutic levels (41 versus 11 % - p<0,001)
  (125 ptn, prospective, surgical ICU)

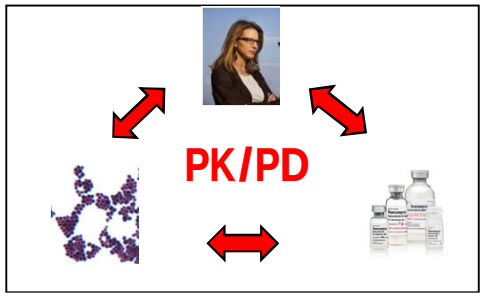


Tafelski, J of Infection and Public Health, 2015, Eprint
Cataldo, 2012 , JAC, 67, 17-24.
Hanrahan, 2014, Crit Care Med, 42, 2527-2536



Evidence based

1. There is a correlation between effect and AUC/MIC: the higher, the more effect.
2. Continuous infusion seems to be safer and results in more rapidly target attainment.



Unresolved issues

1. What PK/PD parameter best predicts effect?
2. How does this PK/PD parameter correlate with outcome?
3. Does TDM predict this PK/PD parameter?
4. Do through levels predict effect?
5. What are the best target through levels?
6. Should vancomycin be administered as CI or IA?
7. ...

CONCLUSION

Can optimization of vancomycin dosing improve outcome (mortality and morbidity) ?