JNI 20es Journées Nationales d'Infectiologie
Lyon
et la région Auvergne-Rhône-Alpes
du mercredi 5 juin 2019
au vendredi 7 juin 2019

The role of pharmacokinetic monitoring in the clinical management of severe infections

Glycopeptides and Lipopeptides

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Hospices Civils de Lyon & Université Lyon 1

ESCMID
MANAGING INFECTIONS
PROMOTING SCIENCE

Hospices Civils de Lyon

LBBE
BIOMETRIE ET BIOLOGIE EVOLUTIVE

Lyon 1

Déclaration d'intérêts de 2014 à 2018

- **Intérêts financiers : Aucun**
- **Liens durables ou permanents : Aucun**
- **Interventions ponctuelles : Symposiums MSD (Lyon 2018), Pfizer (SFAR, Paris 2018), CSL-Behring (ECTH, Marseille 2018), Correvio (JNI, Lyon 2019)**
- **Intérêts indirects : Aucun**

PK monitoring of glycopeptides and lipopeptides

- Vancomycin, teicoplanin, daptomycin

- Why monitoring drug concentration ?
  - Concentration-effect relationships
  - Concentration-related toxicities
  - Clinical benefits of TDM interventions

- How to perform TDM for those drugs ?
  - PK and PK/PD target
  - Dosing issues
  - Role of MIC determination
  - Role of model-based dose adjustment

Vancomycin

Vancomycin: concentration-effect relationships

Both nephrotoxicity and clinical response depend on vancomycin exposure

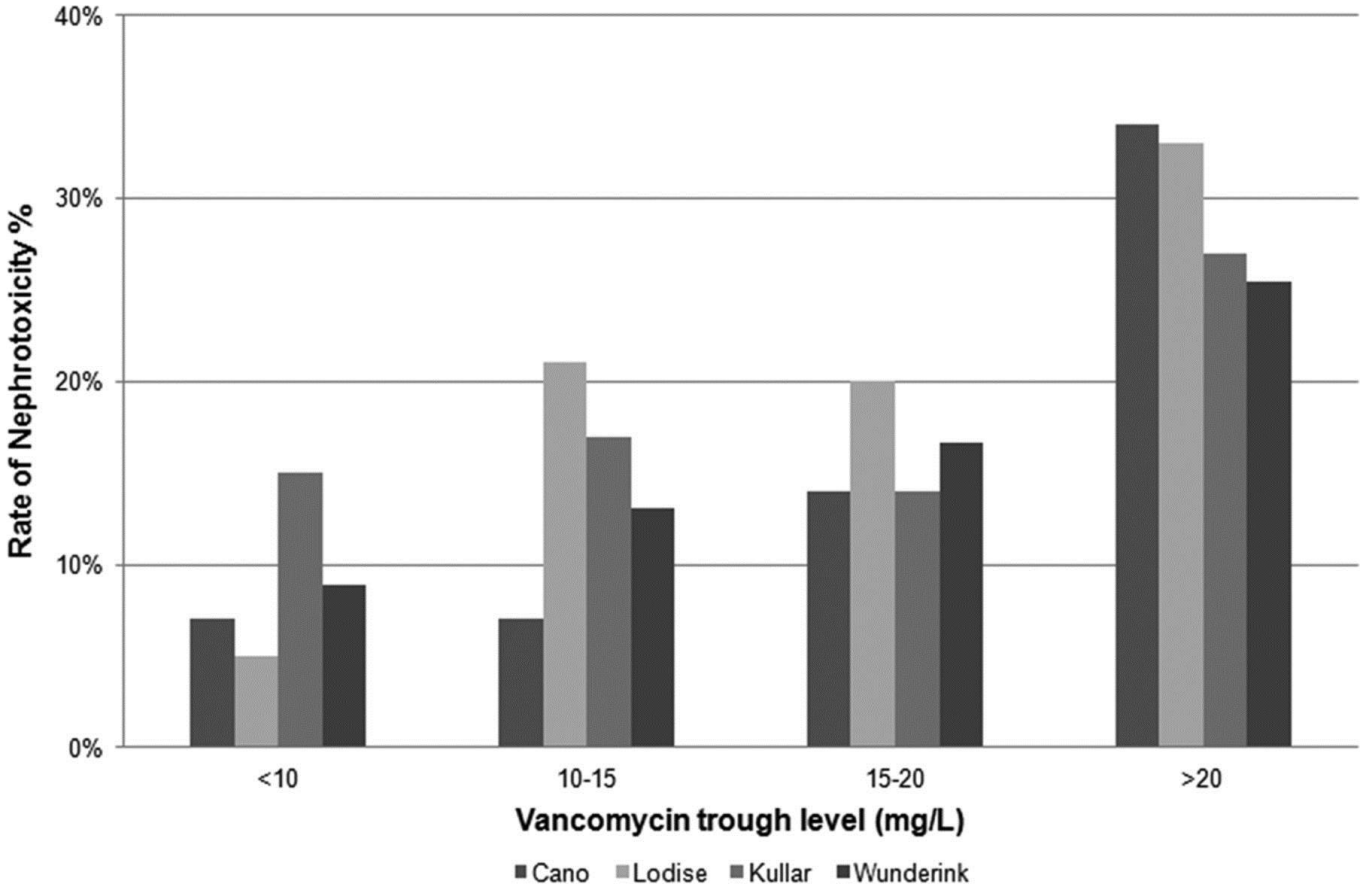
Characteristic N = 308	Vancomycin failure n (%)	P (vs reference category)	Nephrotoxicity n (%)	P (vs reference category)
Trough <10 mg/L (n=70)	**46 (65.7%)**	**0.001**	10/65 (15.4%)	.682
Trough 10–14.9 mg/L (n=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L (n=86)	34 (39.5%)	REF	10/77 (13.0%)	REF
Trough >20 mg/L (n=62)	31 (50.0%)	0.206	**17/62 (27.4%)**	**.032**

308 patients, S. aureus bacteremia
Failure: 30-day mortality OR persistent signs and symptoms of infection at the end of therapy OR persistent bacteremia ≥7 days

Kullar et al. CID 2011

Vancomycin: concentration-effect relationships

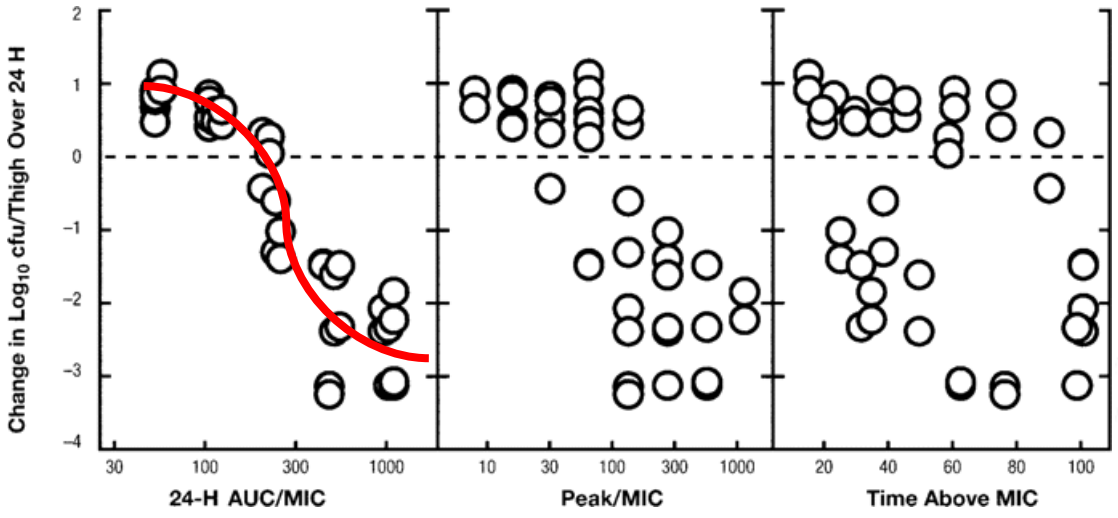
Vancomycin nephrotoxicity increases steadily with Cmin

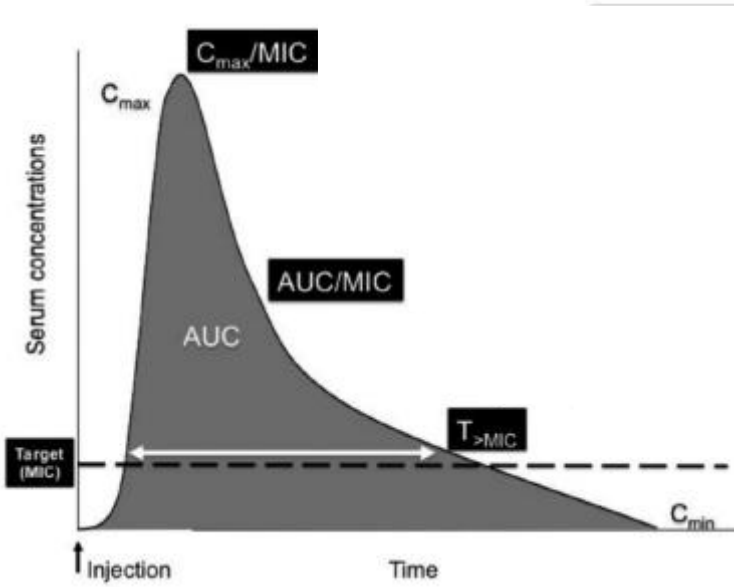


Van Hal et al. AAC 2013

Vancomycin PK/PD: the rise of the AUC

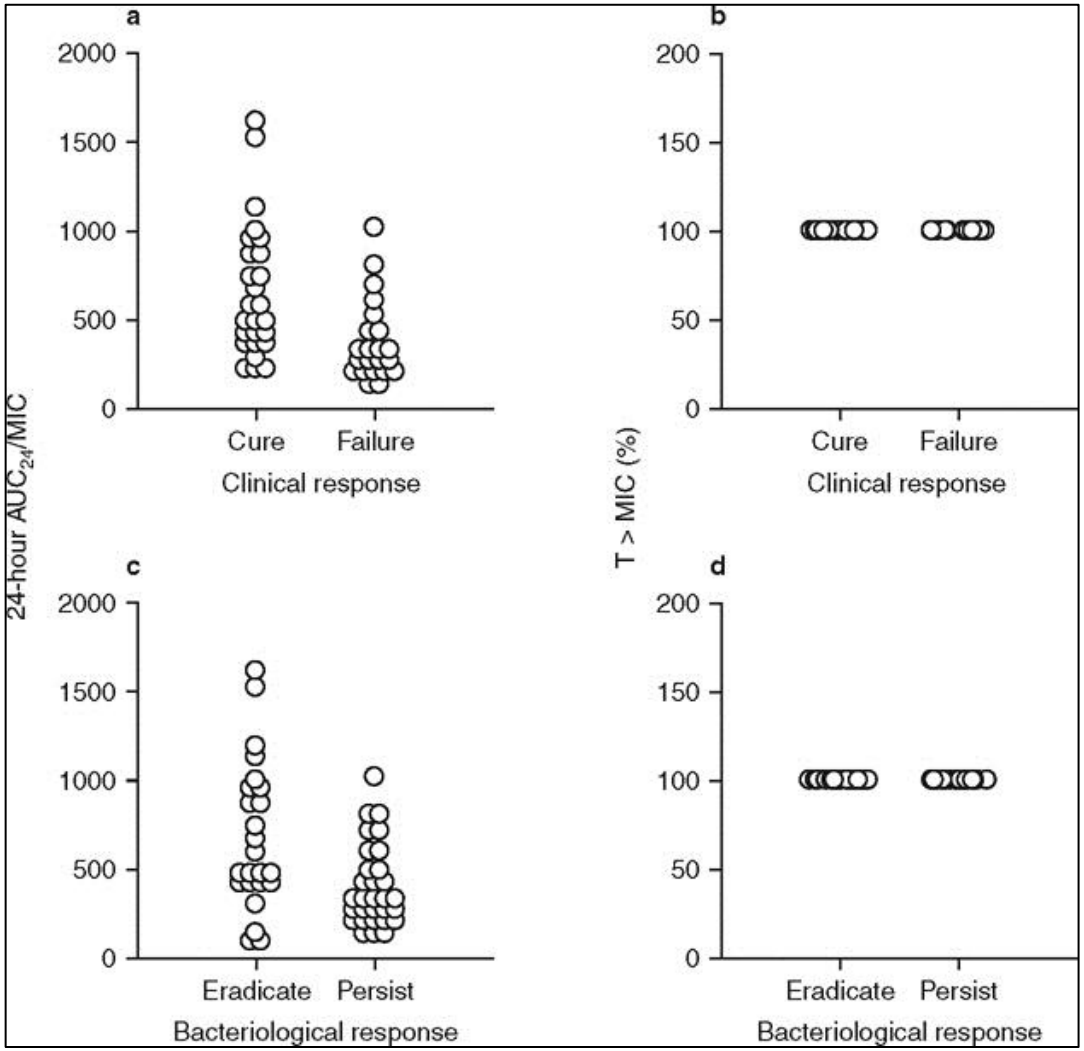
Vancomycin killing effect is concentration-dependent
AUC/MIC best correlates with effect





Rybak CID 2006; Jager et al. Expert Rev Clin Pharmacol 2016

Vancomycin PK/PD: the rise of the AUC



108 patients with S. aureus lower respiratory tract infection

AUC_{24}/MIC cut-off for clinical response ≥ 350

Moise-Broder et al. Clin Pharmacokinet 2004

Vancomycin PK/PD : the rise of the AUC

Reference (year)	Outcomes available in systematic review	All-cause mortality (deaths/total)		Infection treatment failure (failures/total)		Breakpoints of AUC_{0-24}/MIC ratio	MIC determination methods
		Higher than breakpoint	Lower than breakpoint	Higher than breakpoint	Lower than breakpoint		
Ampe et al. (2013)	Infection treatment failure	/	/	2/14	3/6	451	BMD
Brown et al. (2012)	All-cause mortality	6/37	6/7	/	/	211	Etest
Gawronski et al.(2013)	All-cause mortality; Infection treatment failure	0/23	1/36	2/23	7/36	293	Etest
Ghosh et al. (2014)	Infection treatment failure	/	/	18/77	27/50	398	BMD
Holmes et al. (2013)	All-cause mortality	17/108	21/74	/	/	373	BMD
Jung et al. (2014)	Infection treatment failure	/	/	10/52	10/24	398.5	BMD
Kullar et al. (2011)	Infection treatment failure	/	/	107/221	61/99	421	BMD
Moise et al. (2000)	Infection treatment failure	/	/	7/32	16/21	345	BMD
Zelenitsky et al.(2013)	All-cause mortality	6/20	12/15	/	/	451	BMD

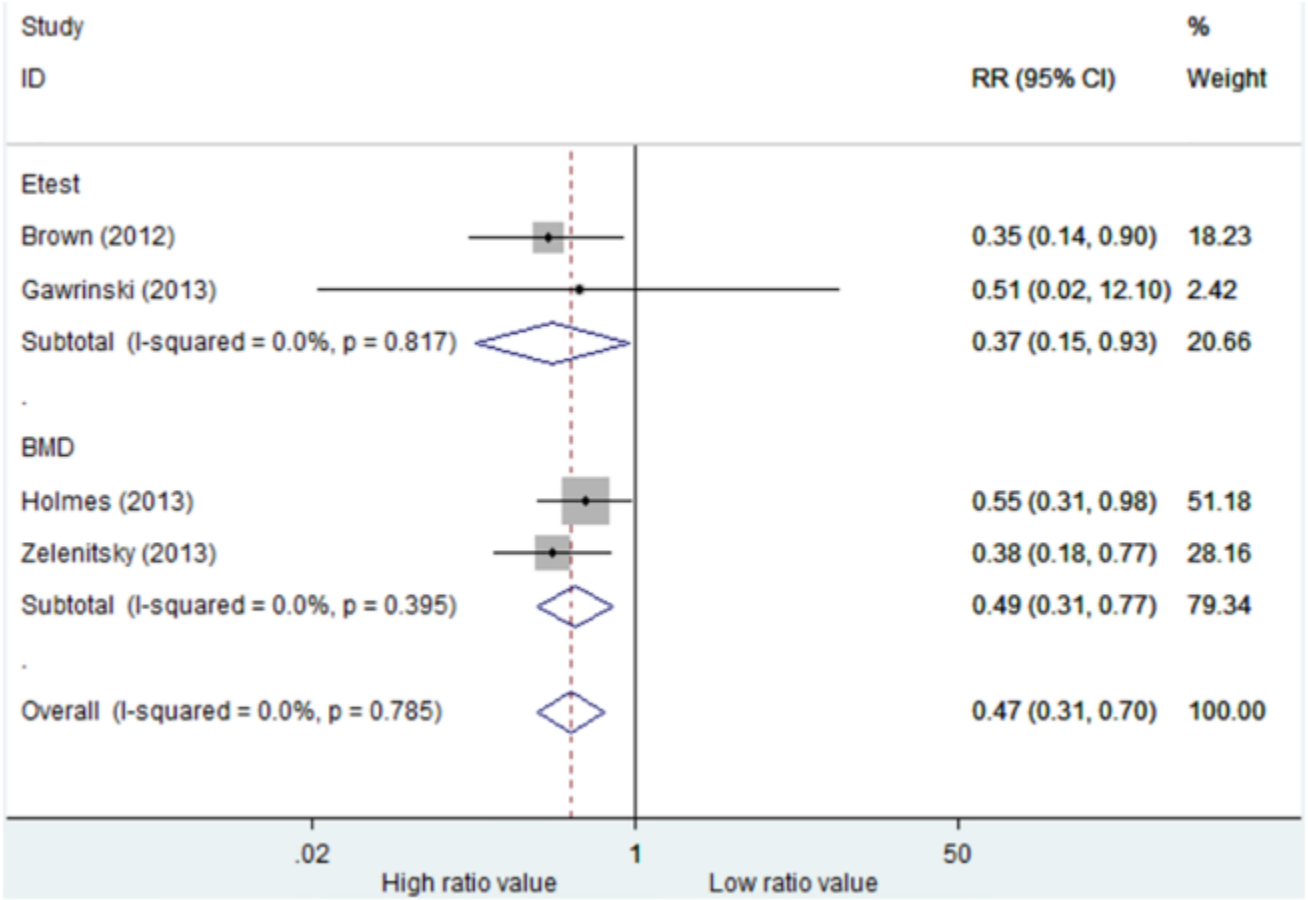
doi:10.1371/journal.pone.0146224.t003

Outcomes, breakpoints of AUC_{0-24}/MIC ratio and MIC determination methods of studies included in the meta-analysis.

Targeting AUC_{24}/MIC ratio ~ 400 for efficacy

Men et al, Plos One 2016

Vancomycin PK/PD : the rise of the AUC



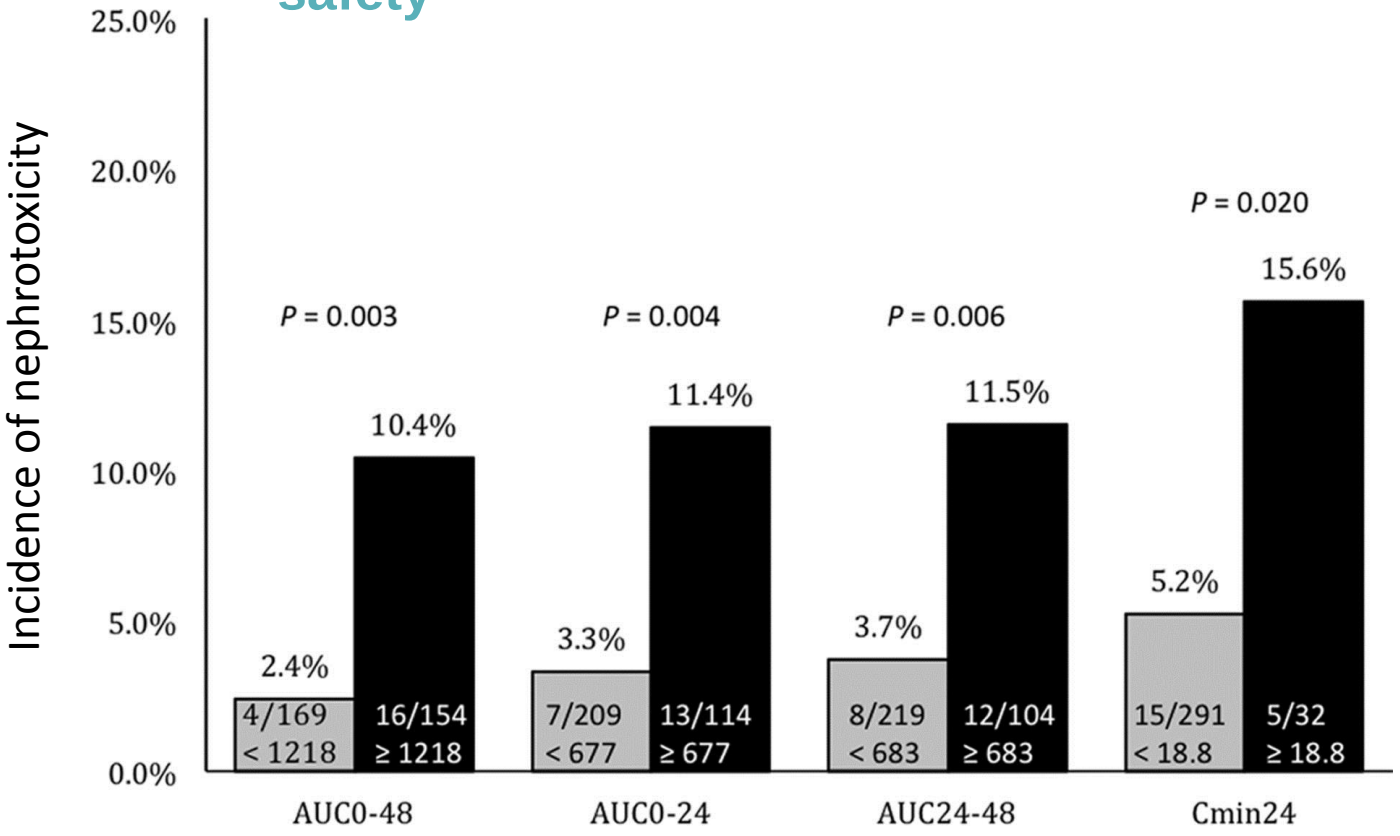
Achieving the AUC_{24}/MIC target is associated with decreased mortality

Risk ratios of all-cause mortality rates: high versus low $AUC_{0\text{-}24}$/MIC ratio

Men et al, Plos One 2016

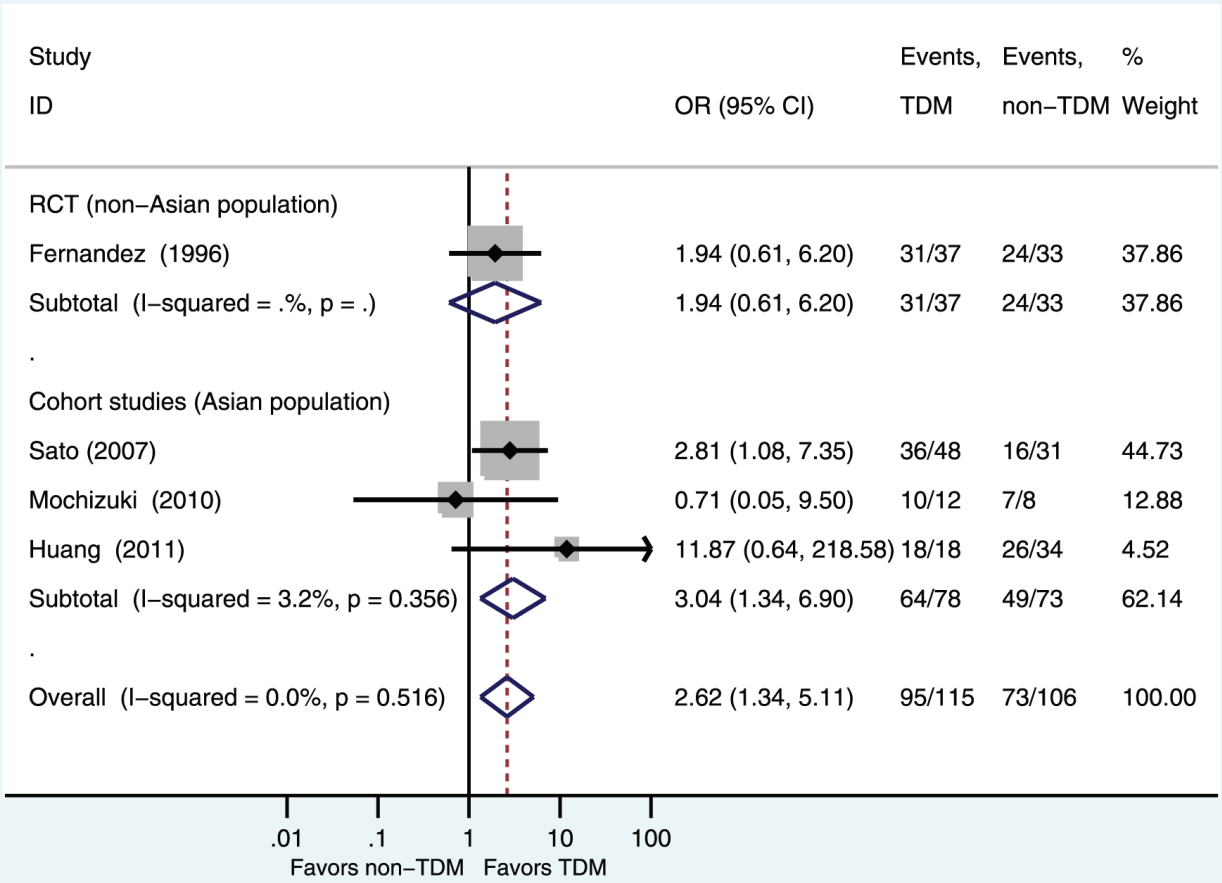
Vancomycin PK/PD : the rise of the AUC

Targeting vancomycin AUC_{24} < 700 mg.h/L for safety



Zasowski et al. AAC 2018

Vancomycin TDM : clinical benefits

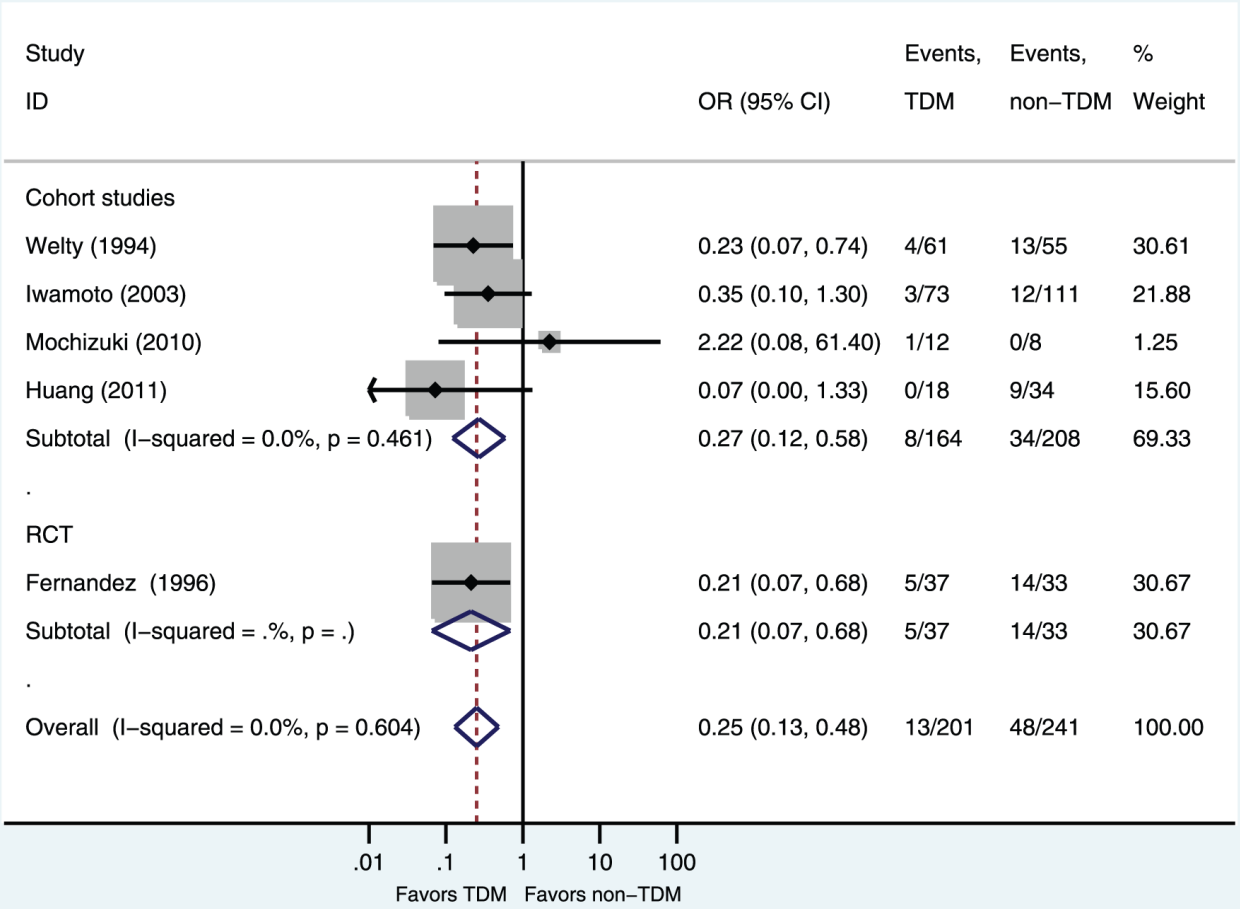


Vancomycin TDM improves clinical response

Meta-analysis of vancomycin TDM - Effect on clinical efficacy

Ye Plos One 2013

Vancomycin TDM : clinical benefits



Vancomycin TDM reduces nephrotoxicity

Meta-analysis of vancomycin TDM - Effect on nephrotoxicity

Ye PlosOne 2013

Vancomycin TDM : concentration targets

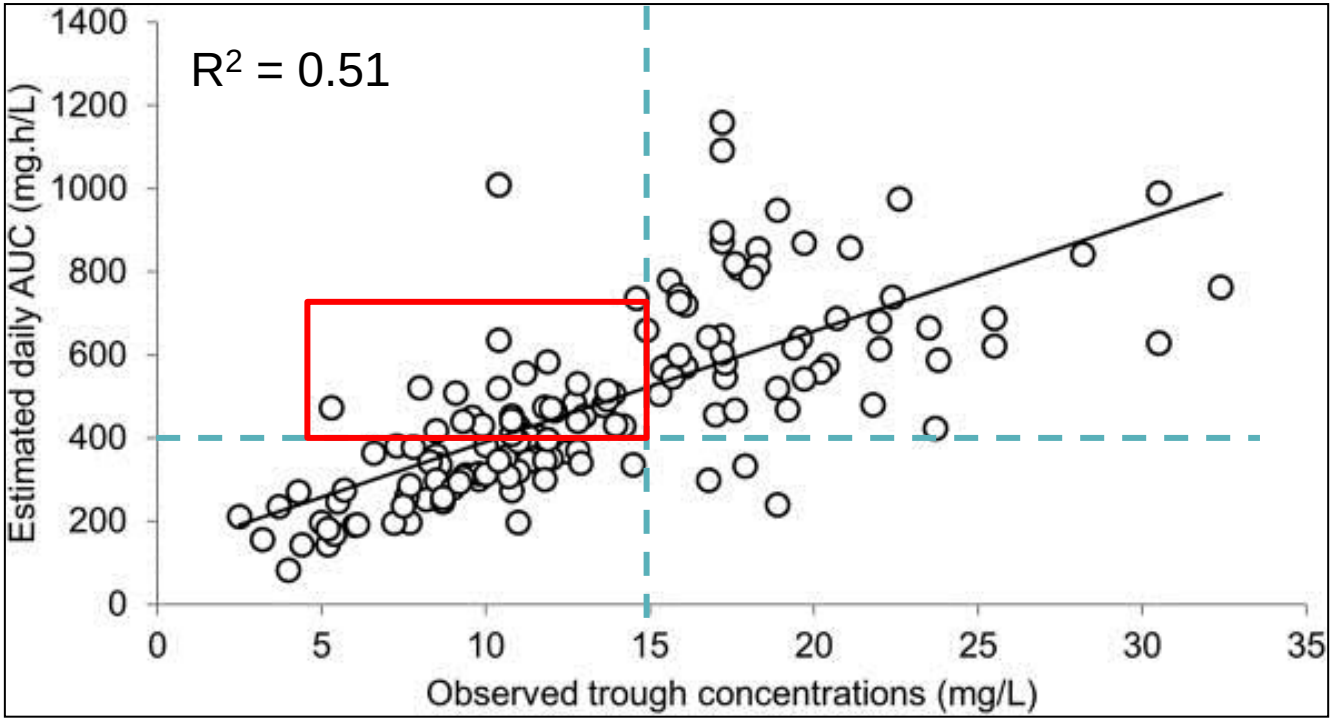
PK/PD index	Lower bound	Upper bound
Cmin (intermittent infusion)	10 to 15 mg/L	20 mg/L
Css (continuous infusion)	15 mg/L	28 mg/L
AUC_{24}	AUC_{24}/MIC ≥ 400	AUC < 700 mg.h/L

Css = AUC_{24} /24

Rybak et al. Am J Health System Pharm 2009 ; Ingram et al. JAC 2008 ; Zasowski et al. AAC 2018

Vancomycin TDM : Cmin or AUC ?

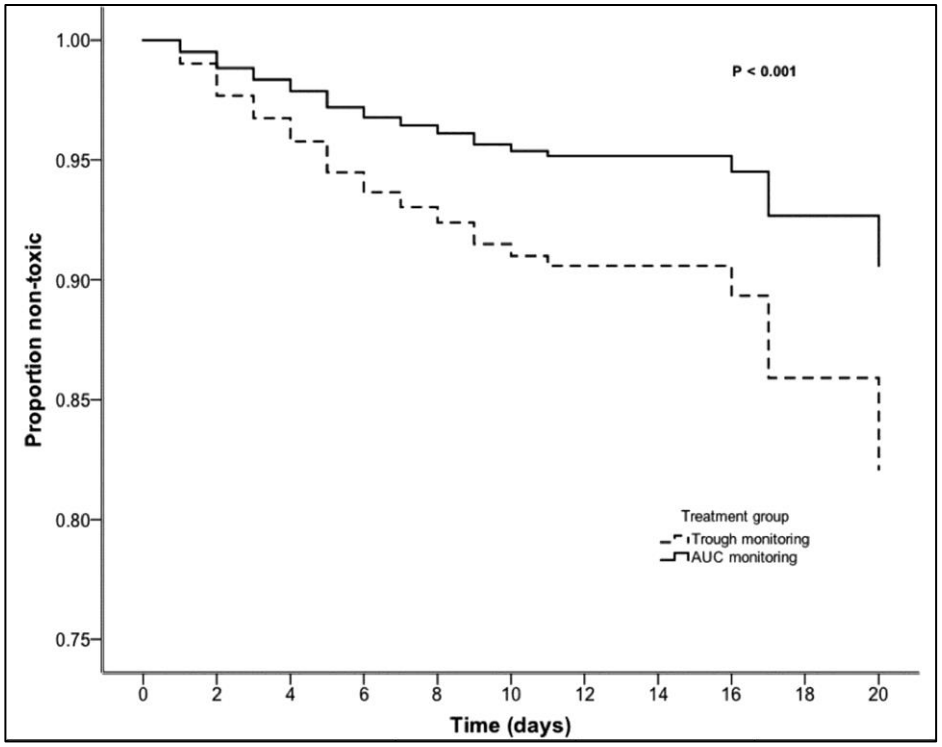
Cmin is not an accurate predictor of AUC_{24}



150 Cmin – AUC pairs from 95 elderly patients

Bel Kamel et al. TDM 2017

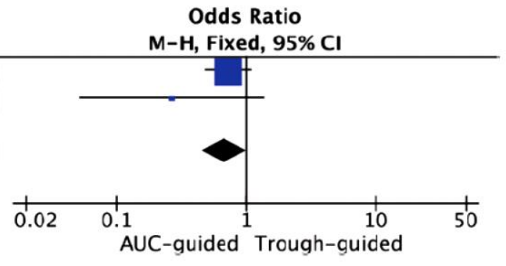
Vancomycin TDM : Cmin or AUC ?



Vancomycin TDM based on the AUC is associated with less nephrotoxicity compared with Cmin monitoring

Study or Subgroup	AUC guided Events	Total	Trough guided Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Finch 2017	54	734	54	546	90.1%	0.72 [0.49, 1.07]
Neely 2017	2	88	6	75	9.9%	0.27 [0.05, 1.37]
Total (95% CI)		**822**		**621**	**100.0%**	**0.68 [0.46, 0.99]**
Total events	56		60			

Heterogeneity: $Chi^2 = 1.35$, df = 1 (P = 0.24); $I^2 = 26\%$
Test for overall effect: Z = 2.00 (P = 0.05)



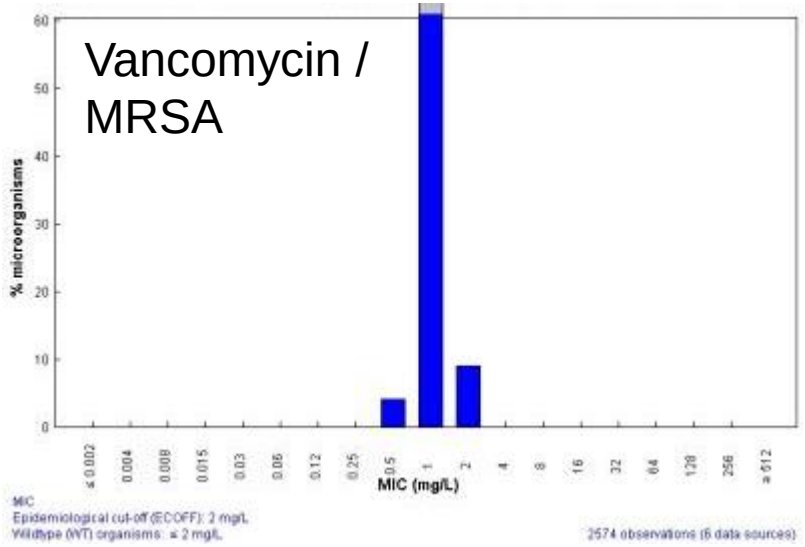
Finch et al. AAC 2017;
Neely et al. AAC 2018;
Aljefri et al. CID 2018

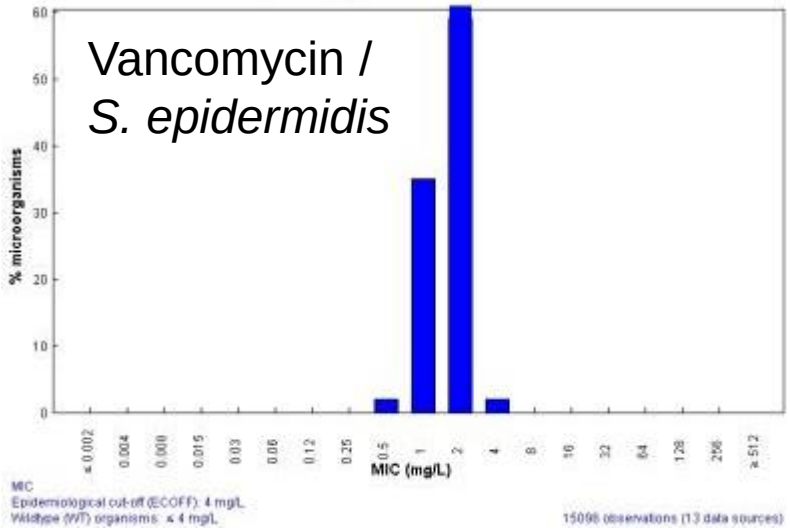
Vancomycin TDM : importance of MIC determination

Probability of Achieving an AUC/MIC Ratio of 400 for Each Vancomycin Regimen Stratified by Renal Function

CLCR	20 ml/min	40 ml/min	60 ml/min	80 ml/min	100 ml/min	120 ml/min
1000 mg IV every 12 h						
0.5 mg/L	98%	97%	**95%**	92%	86%	80%
1.0 mg/L	94%	87%	**75%**	61%	49%	39%
2.0 mg/L	77%	49%	**29%**	17%	10%	6%
1500 mg IV every 12 h						
0.5 mg/L	99%	98%	**98%**	97%	96%	93%
1.0 mg/L	97%	95%	**90%**	82%	74%	66%
2.0 mg/L	89%	75%	**57%**	42%	30%	22%
2000 mg IV every 12 h						
0.5 mg/L	99%	99%	**99%**	99%	98%	97%
1.0 mg/L	98%	97%	**95%**	92%	87%	81%
2.0 mg/L	94%	87%	**75%**	61%	49%	39%

Drusano et al. CID 2011





Teicoplanin

Teicoplanin: concentration-effect relationships

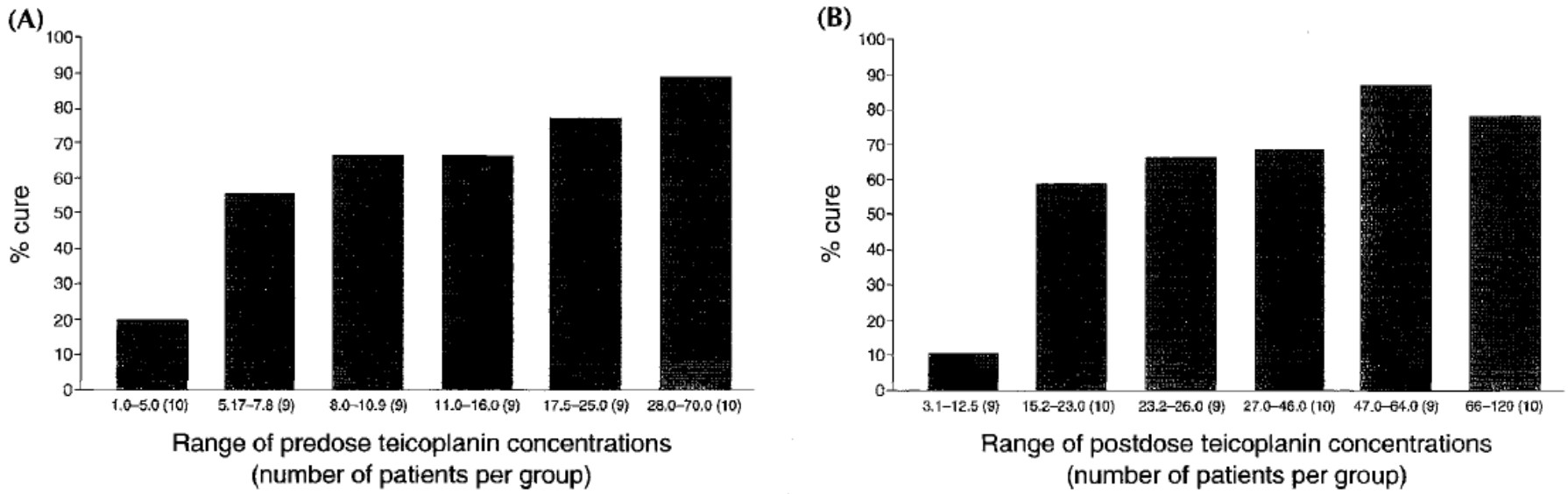
Characteristic	Cured (n = 36)	Not cured (n = 22)	*P* value
Bacterial Isolate			
S. aureus	11	9	
Staphylococcus spp.	2	9	
S. epidermidis	6	1	
Viridans streptococci	7	0	
E. faecalis	4	1	
S. bovis	2	1	
Other coagulase-negative staphylococci, including			
Micrococcus spp.	3	1	
JK Corynebacteria	1	0	
Site of Infection			
Infective endocarditis	21	4	
Osteomyelitis	9	7	
Septicemia	5	7	
Abscess	1	4	
~~Isolate MIC (mg/L)~~	~~0.6 ± 1.3 (36)~~	~~1.2 ± 2.1 (22)~~	~~NS~~
Teicoplanin postdose (mg/L)	46.6 ± 27.6 (36)	25.0 ± 20.8 (21)	$P < 0.05$
Teicoplanin predose (mg/L)	18.8 ± 14.1 (35)	9.0 ± 9.1 (21)	$P < 0.05$
Postdose/MIC ratio	939 ± 2957 (36)	140 ± 250 (21)	$P < 0.05$
Predose/MIC ratio	289 ± 696 (35)	61 ± 122 (21)	$P < 0.05$
Teicoplanin/maintenance dose			
mg/day	330 ± 162 (9)	220 ± 75 (15)	NS
mg/kg/day	8.4 ± 3.8 (27)	8.1 ± 4.4 (7)	NS

Teicoplanin serum concentration and outcomes in 58 patients from clinical trials

MacGowan et al. J Infect Chemother

Teicoplanin: concentration-effect relationships

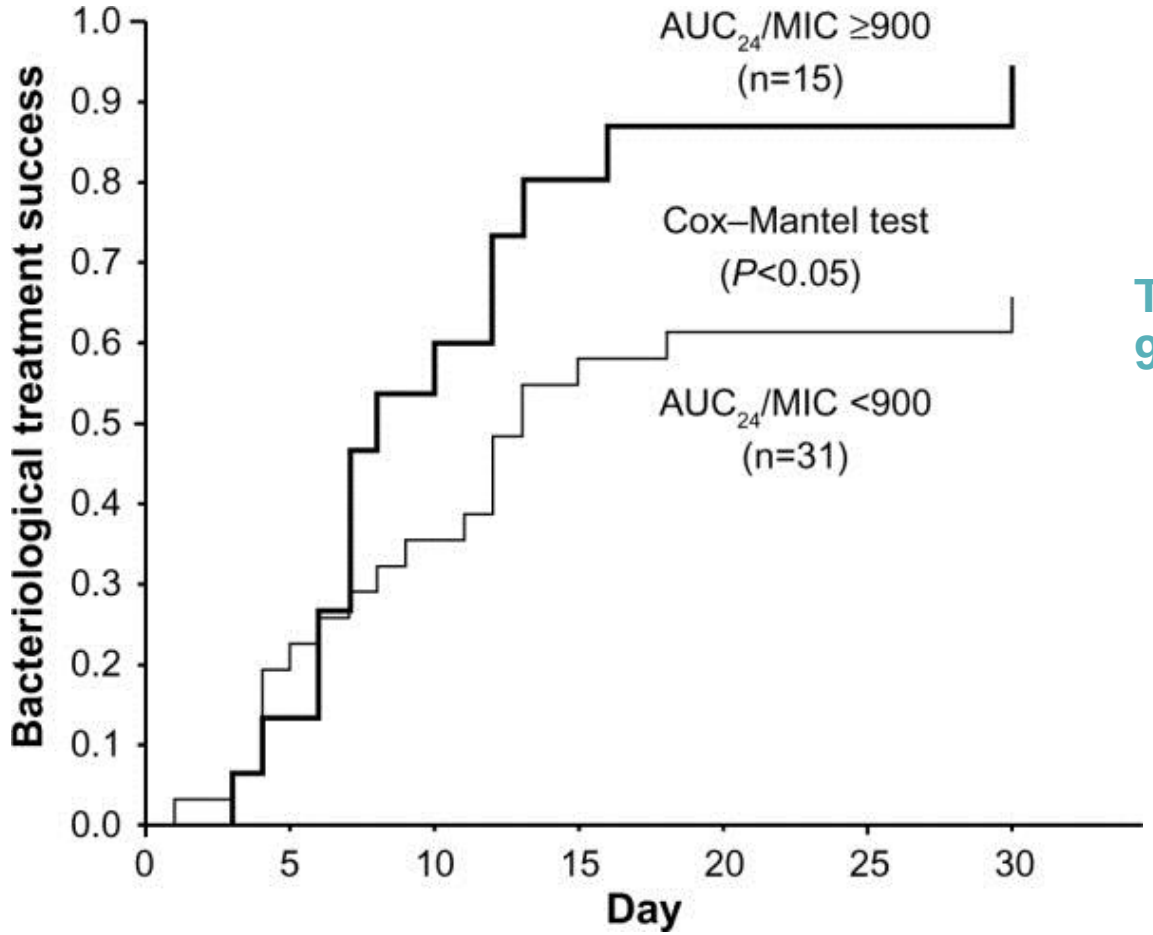
Targeting teicoplanin Cmin > 10 mg/L for efficacy



Teicoplanin serum concentration and outcomes in 58 patients from clinical trials

MacGowan et al. J Infect Chemother 1996

Teicoplanin: concentration-effect relationships



Targeting AUC/MIC ≥ 900 for efficacy ?

Retrospective analysis – 46 patients with MRSA infections

Matsumoto et al. Clin Pharmacol 2016

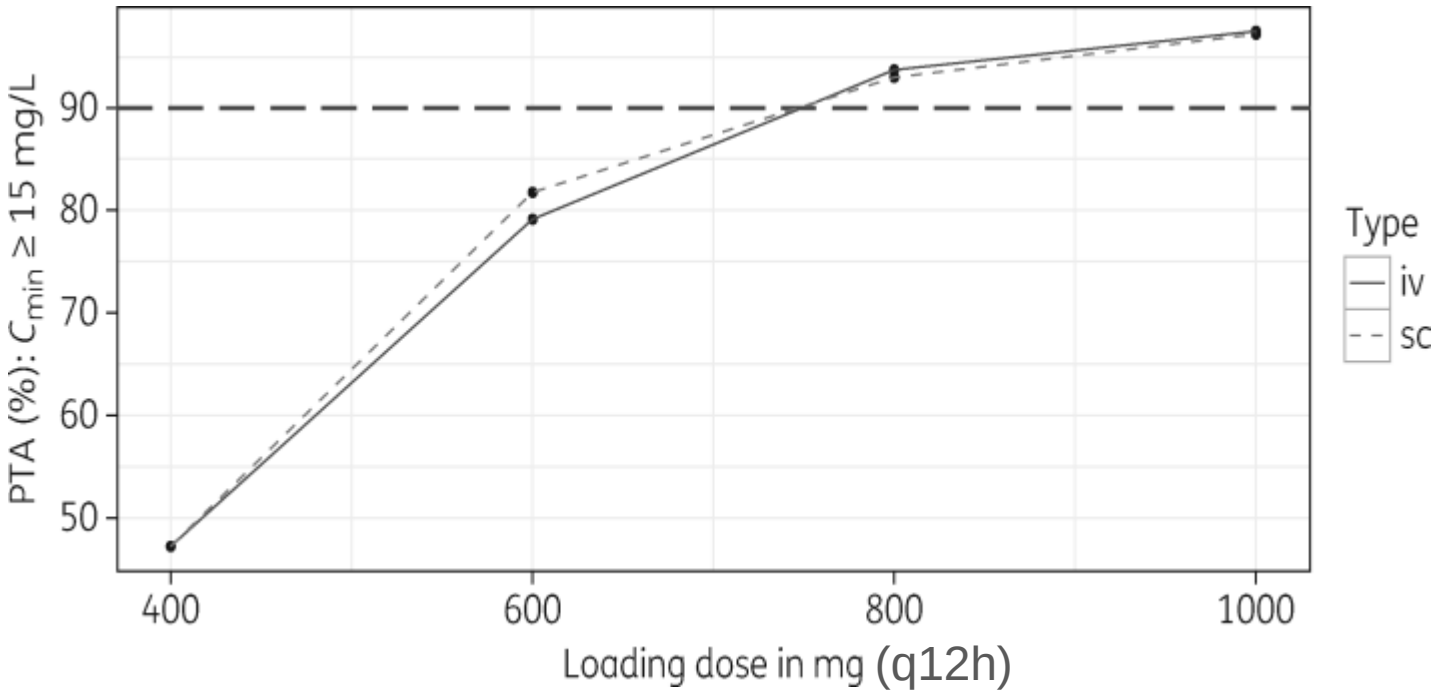
Teicoplanin TDM : concentration targets

Indication	Lower Cmin target (FPIA assay)	Upper Cmin target
Complicated skin and soft tissues Pneumonia Complicated urinary tract	> 15 mg/L	< 60 mg/L ?
Bone and joint	> 20 mg/L	
Infective endocarditis	> 30 mg/L	

Teicoplanin summary of product characteristics ; Wilson Clin Pharmacokinet 2000

Teicoplanin: dosing issues

Loading doses higher than recommended are necessary for early achievement of concentration targets

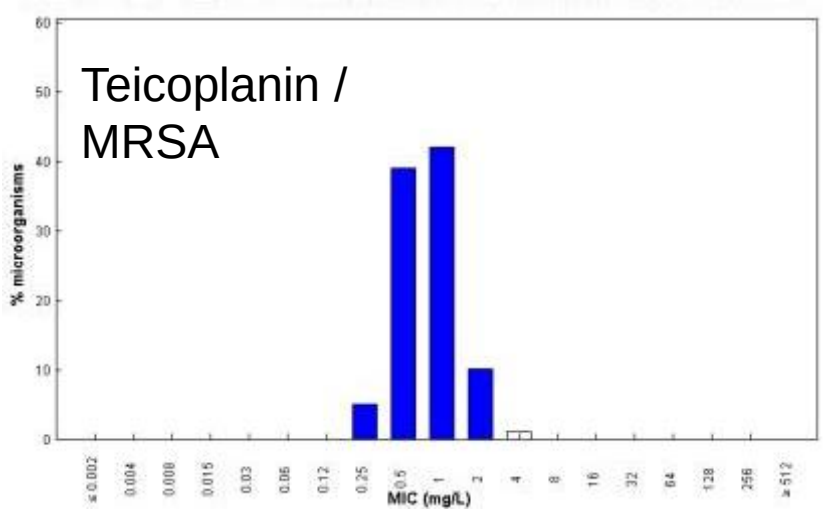


Simulated probabilities of C_{min} target attainment for iv and sc routes of administration at day 3

Cazaubon et al. JAC 2017

Teicoplanin : role of MIC determination

Achieving AUC_{24}/MIC > 900 would be associated with toxic Cmin if MIC > 1 mg/L

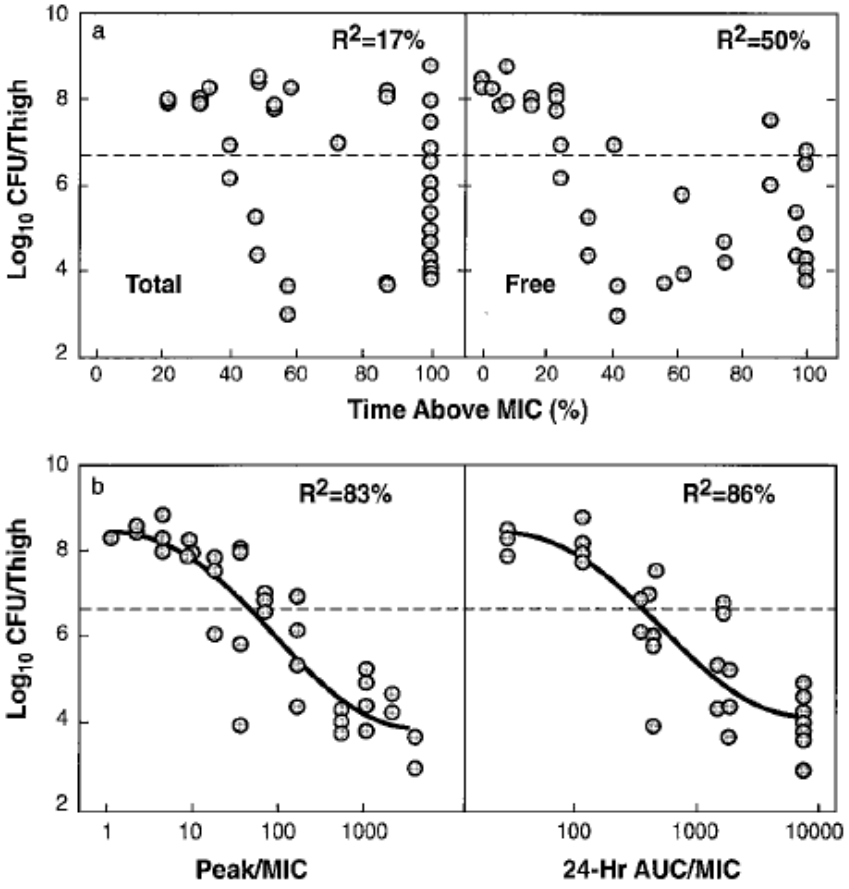


Simulated IV dosage q12h from 0 to 48h q24h from Day 2 to 15	AUC_{24} Day 15 (mg.h/L)	Cmin Day 15 (mg/L)
400 mg	810 ± 196	29 ± 8
600 mg	1215 ± 294	44 ± 12
800 mg	1619 ± 392	59 ± 16
1000 mg	2024 ± 490	73 ± 20

Cazaubon et al. JAC 2017

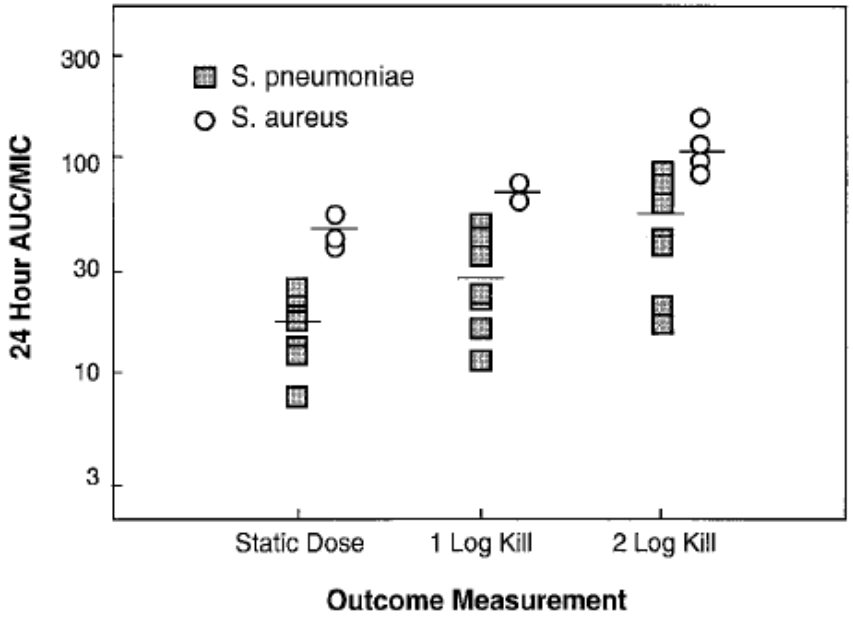
Daptomycin

Daptomycin: concentration-effect relationships



Neutropenic mouse thigh infection model

Safdar et al. AAC 2004



Suggested target for S. aureus infections

$fAUC_{24}$/MIC > 66

AUC_{24}/MIC ≥ 666 (90% protein binding)

AUC_{24} ≥ 666 (ECOFF = 1 mg/L)

Daptomycin : concentration-effect relationships

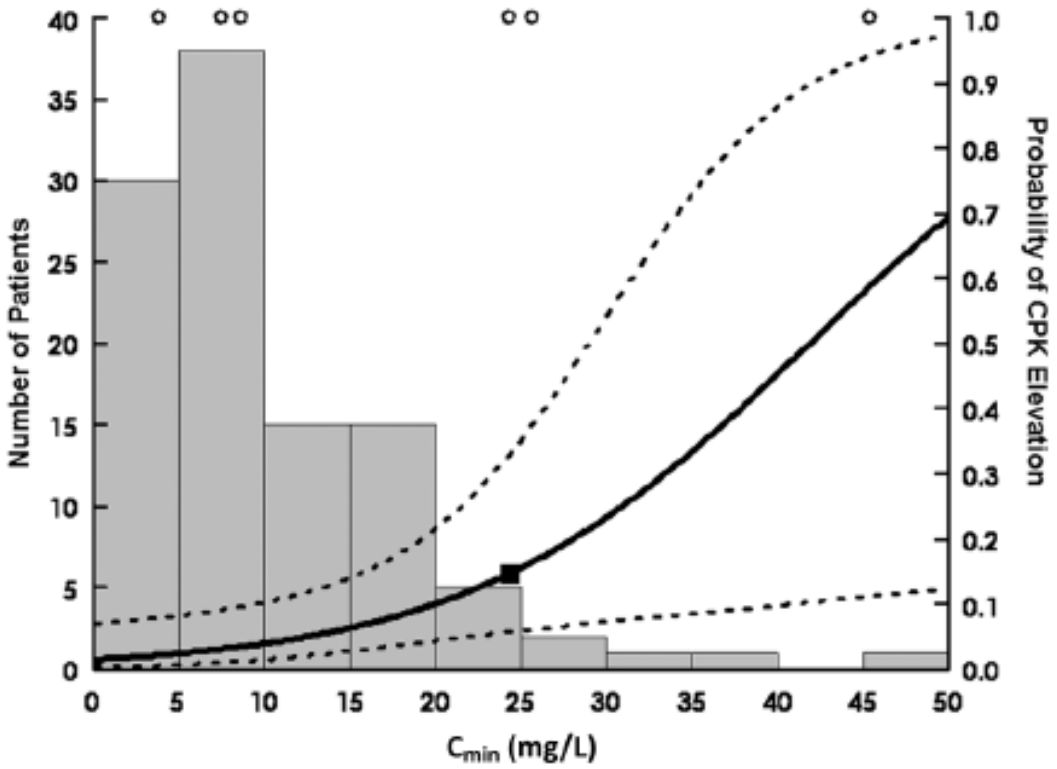
Table 6 Multivariate analysis of factors associated with poor outcome

Variable	*p*	OR (95 % CI)
AUC/MIC <666	0.032	1.24 (1.18–1.3)
ICU acquisition of infection	0.02	1.93 (1.48–2.56)
Hypoalbuminemia	0.02	3.82 (2.21–39.03)

35 patients, Gram + infections
Daptomycin 6 or 8 mg/kg/j
Poor outcome = death

Falcone et al. J Infect Chemother 2013

Daptomycin: concentration-effect relationships



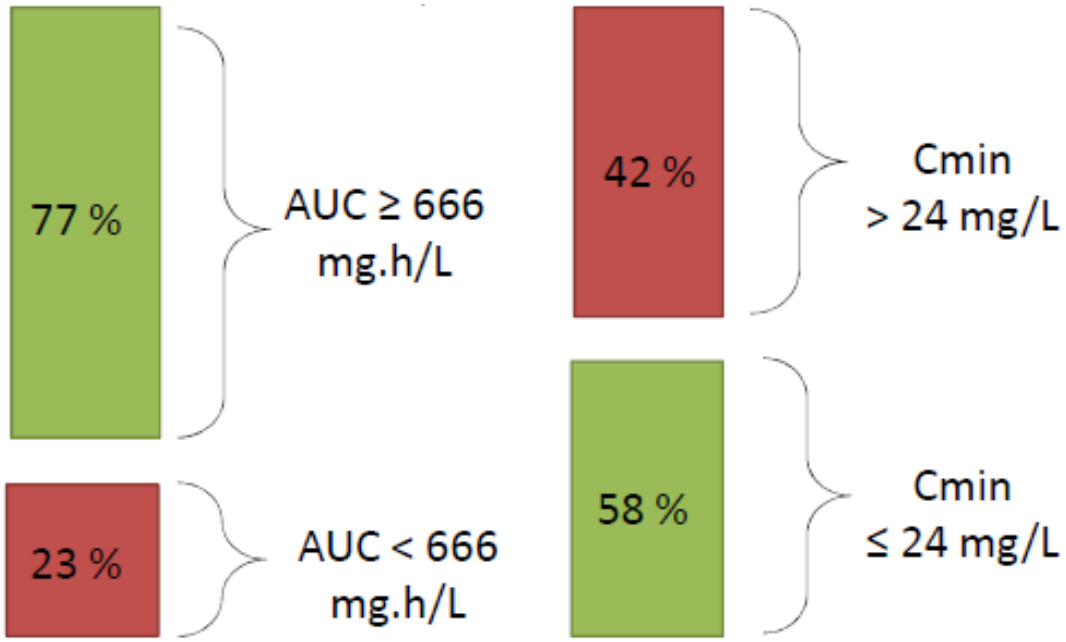
Daptomycin muscular toxicity correlates with Cmin

Suggested target Cmin < 24 mg/L at 24h

Phase III study - 120 patients with bacteremia or endocarditis
Daptomycin 6 mg/kg/day

Bhavnani et al. CID 2010

Daptomycin : dosing issues



Go and see our poster ! (IOA-19 Heitzmann et al.)

Retrospective PK analysis
94 patients with BJI treated with daptomycin
Mean dose of 7.6 ± 1.3 mg/kg/day
Results on the first TDM occasion

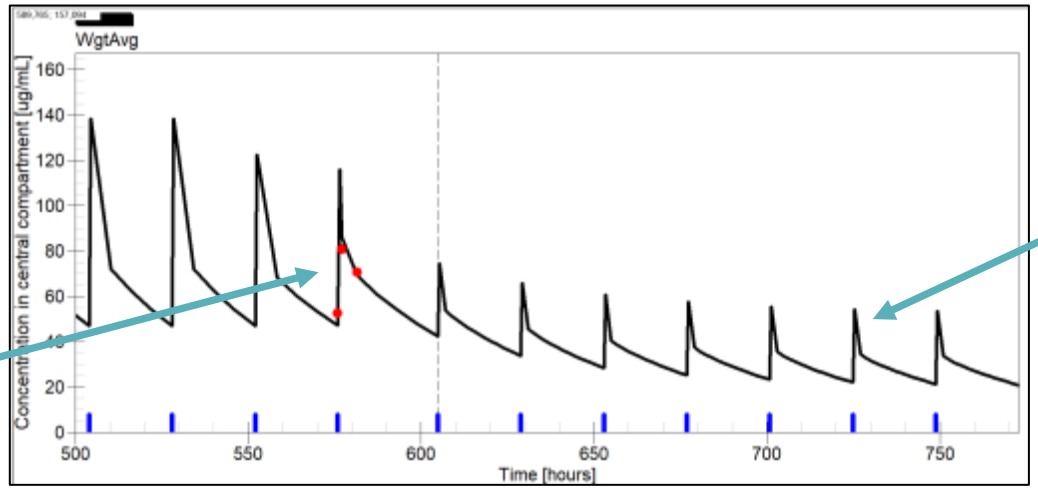
Daptomycin TDM : model-based dose adjustment

- Case study
  - 88 year-old men, 90 kg, Scr = 123 µmol/L, eGFR ~ 40 ml/min
  - Septic arthritis and sepsis caused by MRSA (MIC = 0.125)
  - Daptomycin 700 mg/day (7.8 mg/kg)

Measurements
Cmin = 52.5
C1h = 80.8
C5H = 70.7

Bayesian estimation of past PK profile

AUC_{24} = 1700



Implementation of our population PK model (Bricca et al. JAC 2019) in the BestDose software

Simulation of future regimen

300 mg/24h
Cmin = 19.5
AUC_{24} = 660
AUC/MIC > 5000

BestDose software: http://www.lapk.org/

PK monitoring of glycopeptides and lipopeptides: take-home messages

- Strong evidence of concentration-effect relationships
- AUC as the PK index linked with antibacterial effect
- Clinical benefits of TDM are established for vancomycin
- New TDM targets : switching from Cmin to AUC
- MIC determination is key in interpretation
- One size does NOT fit all: individualize dosage to achieve targets
- AUC estimation and dose adjustment in routine

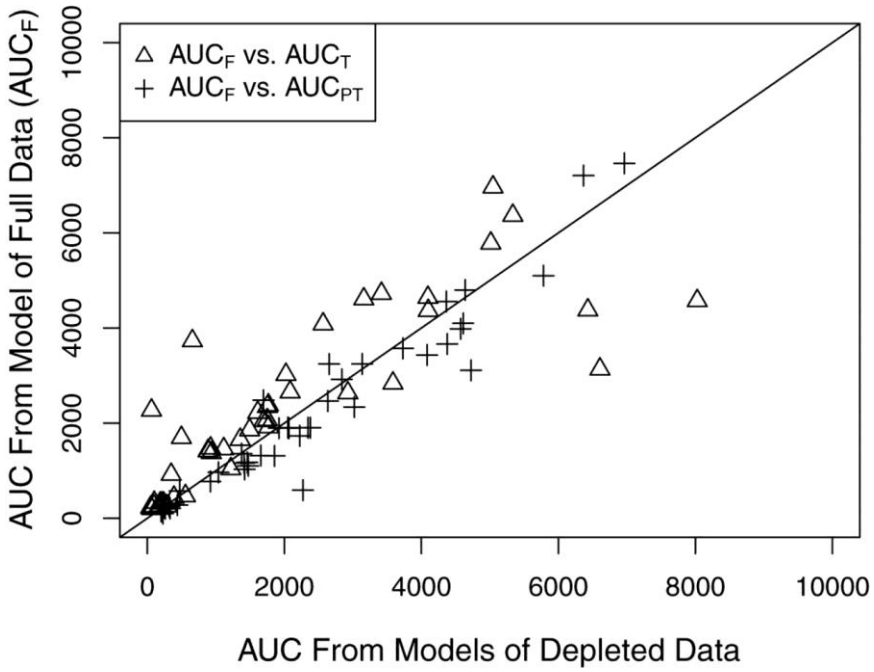
Back-up

Vancomycin TDM: model-based dose adjustment

AAC
Journals.ASM.org

Are Vancomycin Trough Concentrations Adequate for Optimal Dosing?

Michael N. Neely,[a,b] Gilmer Youn,[a] Brenda Jones,[a] Roger W. Jelliffe,[a,b] George L. Drusano,[c] Keith A. Rodvold,[d] Thomas P. Lodise[e]

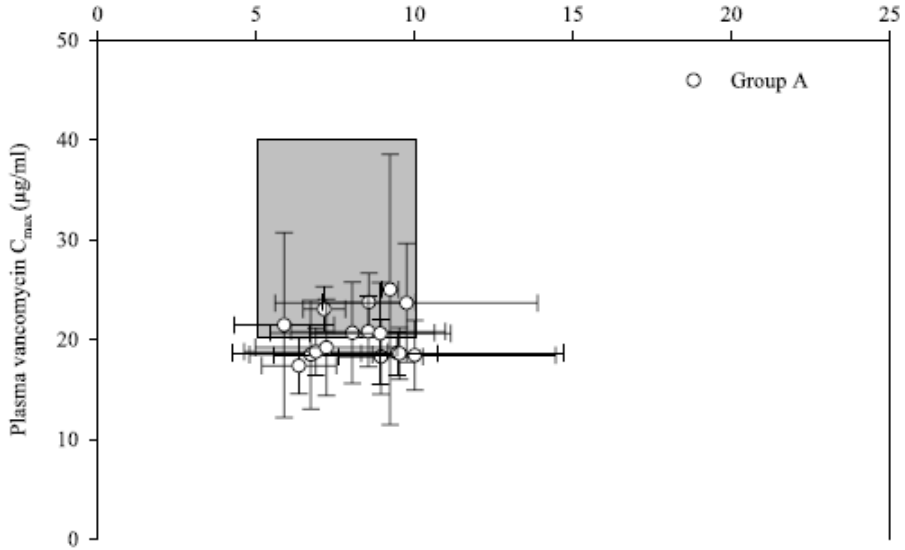


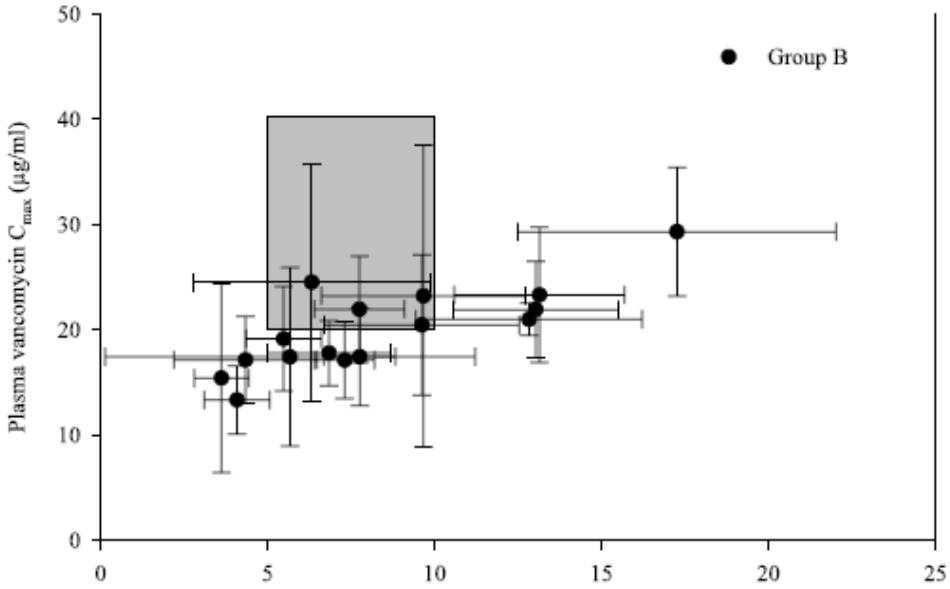
Neely et al. AAC 2016

Vancomycin TDM: model-based dose adjustment

TDM coupled with Bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients

Federico Pea [a,*], Massimo Bertolissi [b], Adriana Di Silvestre [b], Donatella Poz [a], Francesco Giordano [b], Mario Furlanut [a]

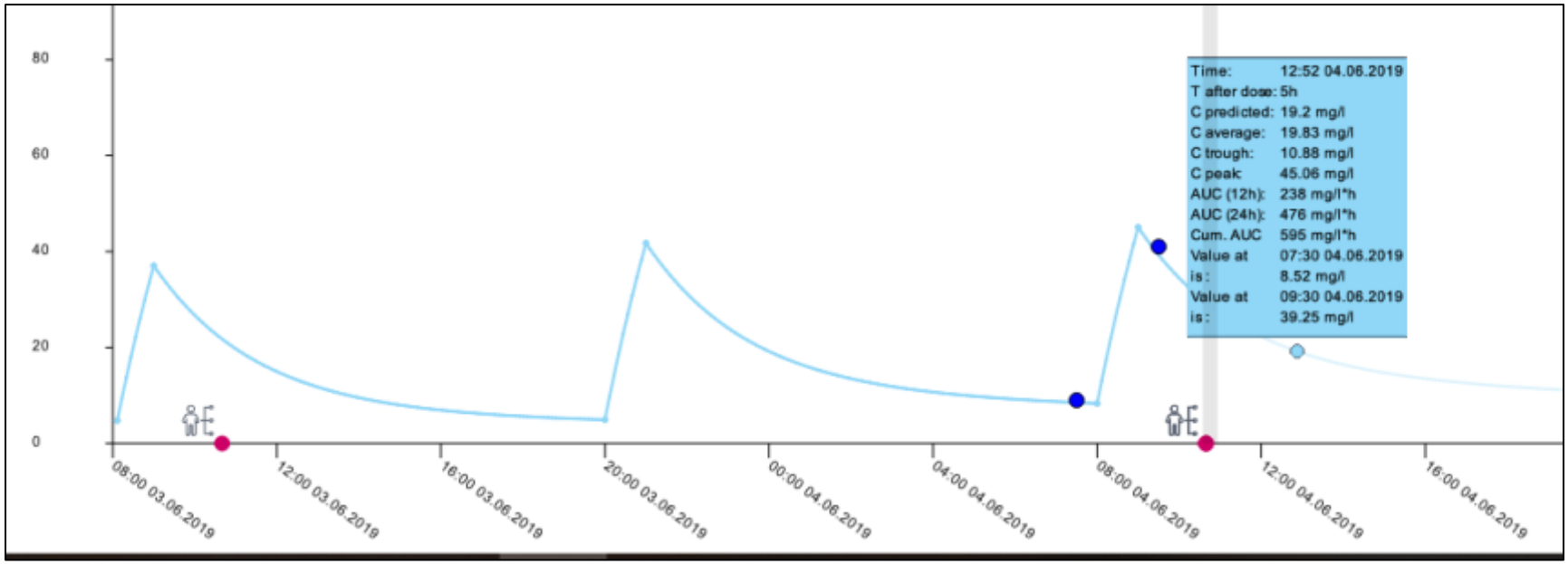




IJAA 2002

Vancomycin TDM: model-based dose adjustment

Bayesian estimation using a population PK model is a convenient approach to estimate AUC based on a few measured serum concentrations



Tucuxi software http://www.tucuxi.ch/

Teicoplanin: concentration-effect relationships

Targeting teicoplanin higher Cmin (>20 mg/L) in staphylococcal infections ?

Characteristic	Cured (n = 22)	Not cured (n = 20)	*P* value
Bacterial Isolate			
S. aureus	11	9	
Coagulase-negative staphylococci	9	2	
Staphylococcus spp.	2	9	
Type of Infection			
Osteomyelitis	7	6	
Septicemia	5	7	
Infective endocarditis	9	3	
Abscess	1	4	
Isolate MIC (mg/L)	1.0 ± 1.6 (21)	1.3 ± 2.2 (20)	NS
Teicoplanin postdose (mg/L)	55.0 ± 31.8 (21)	25.7 ± 21.6 (19)	$P < 0.05$
Teicoplanin predose (mg/L)	23.0 ± 16.4 (20)	9.3 ± 9.5 (19)	$P < 0.05$
Postdose/MIC ratio	171 ± 208 (21)	85 ± 132 (19)	$P < 0.05$
Predose/MIC ratio	67 ± 80 (20)	37 ± 77 (19)	$P < 0.05$
Teicoplanin/maintenance dose			
mg/day	200 (5)	220 ± 75 (15)	NS
mg/kg/day	10.1 ± 3.9 (16)	10.1 ± 3.6 (5)	NS

Teicoplanin serum concentration and outcomes in 44 patients with staphylococcal infections from clinical trials

MacGowan et al. J Infect Chemother 1996