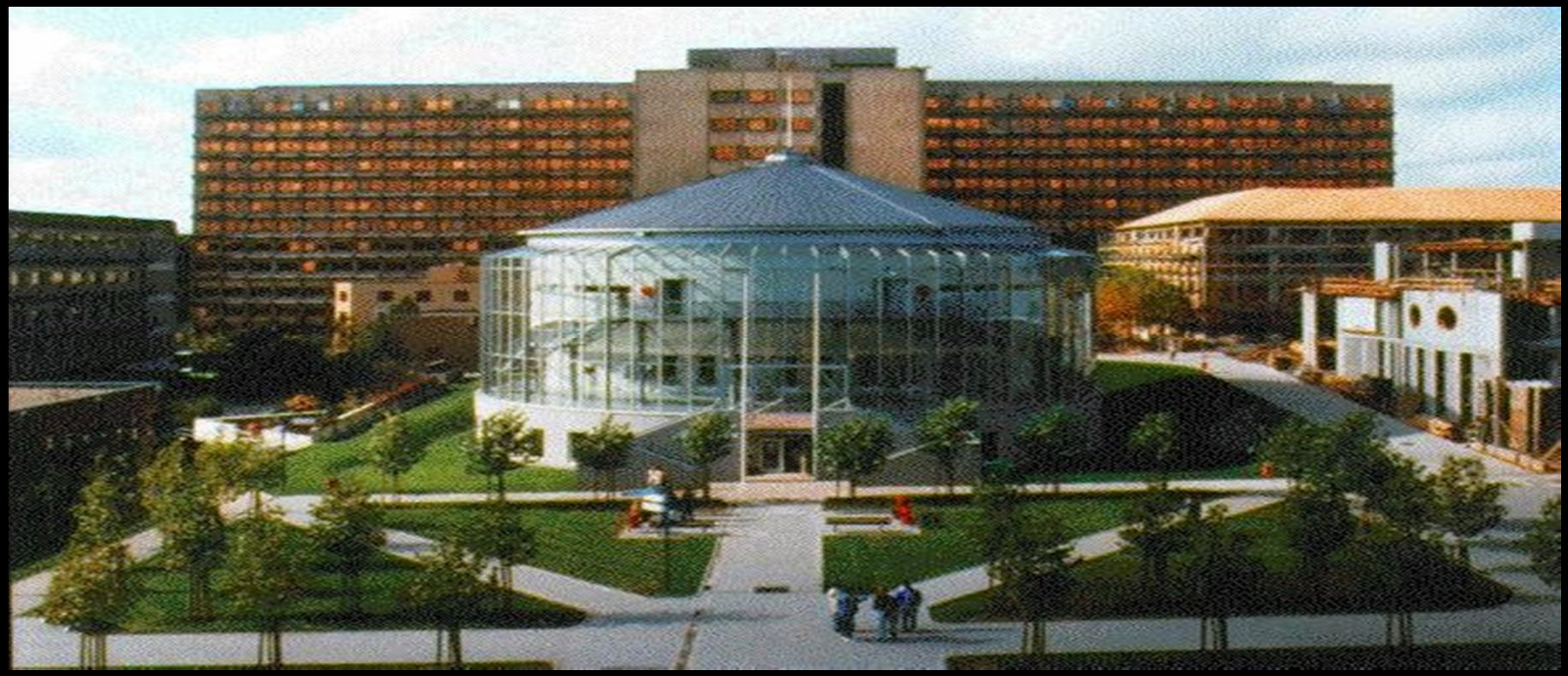
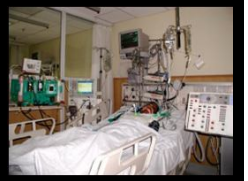
Vancomycin in the ICU: Use and Misuse



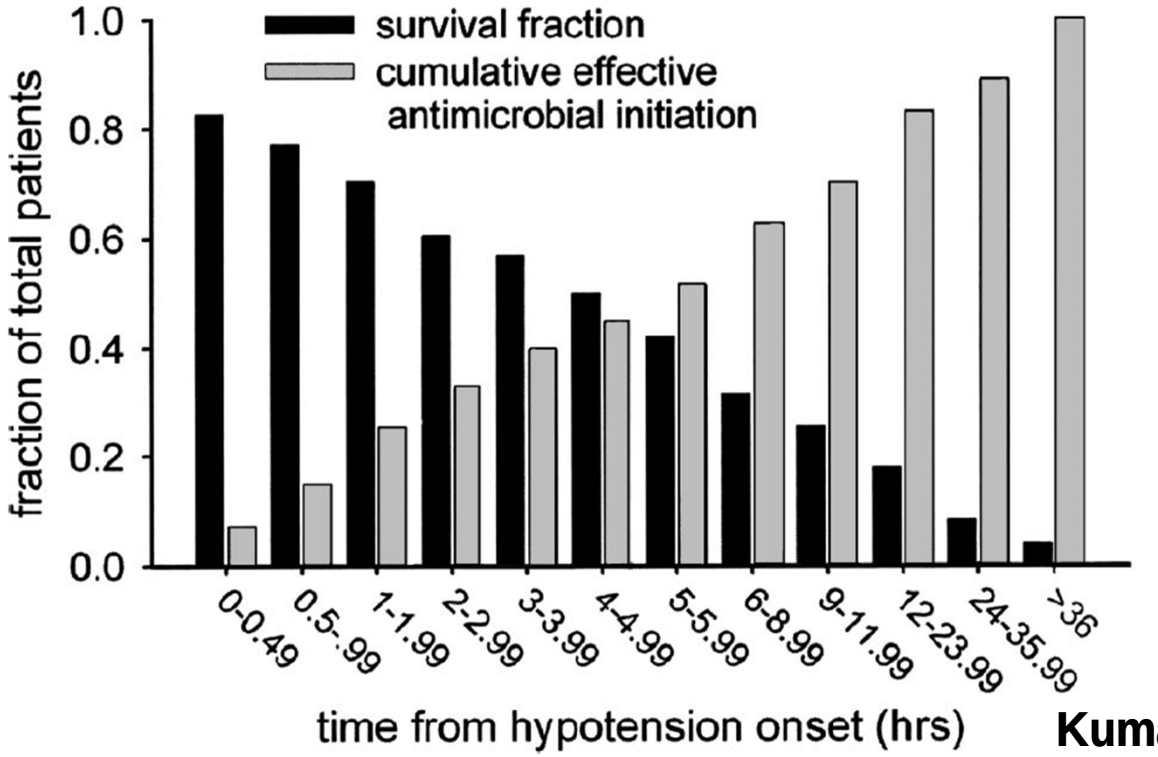
Dr Fabio Silvio TACCONE
Department of Intensive Care
Hôpital Erasme – Brussels (BELGIUM)

Background



Early antibiotic therapy is mandatory in ICU (septic) patients

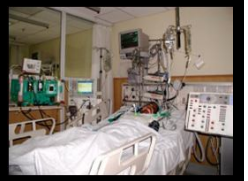
EARLY THERAPY



n = 2154 pts
septic shock

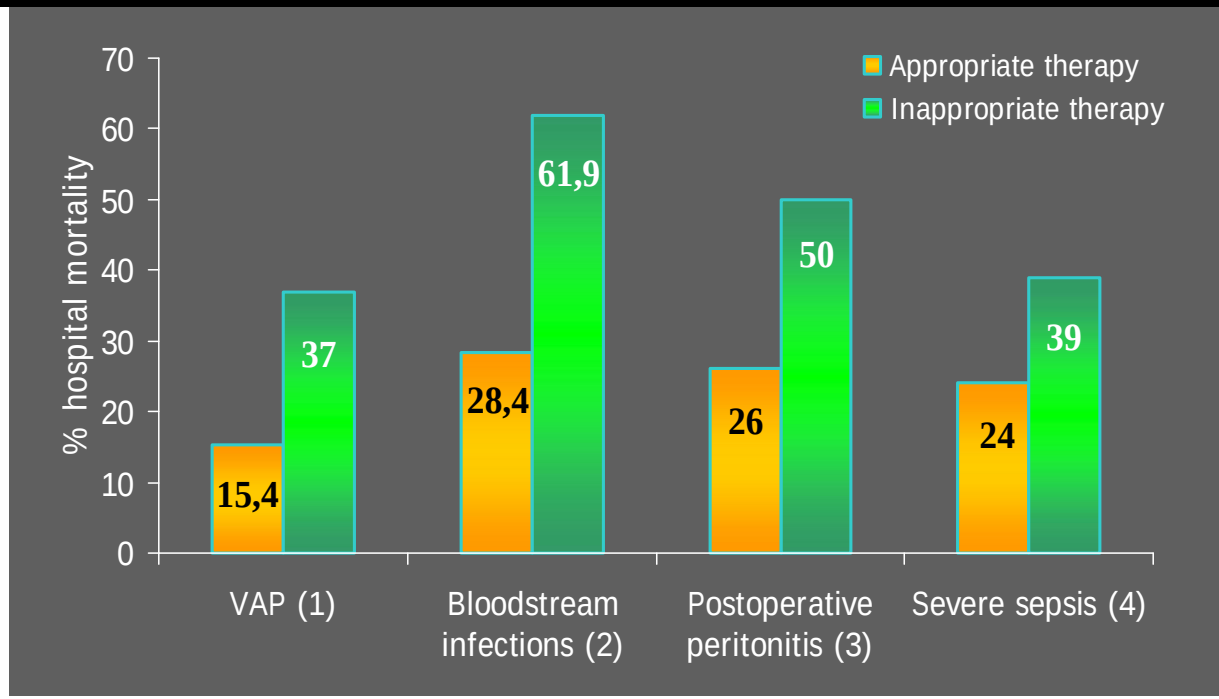
Kumar, Crit Care Med 2006

Background



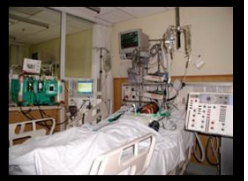
Appropriate antibiotic therapy is mandatory in ICU (septic) patients

INAPPROPRIATE INITIAL ANTIMICROBIALS



(1) J.Rello et al, Amer J Crit Care Med 1997 ; 156 : 196-200 / (2) E.Ibrahim, Chest 2000 ; 118 : 146-155 / (3) P.Montravers, Clin Inf Dis 1996 ; 23 : 486-494 / (4) S.Harbarth et al, Am J Med 2003 ; 115 : 529-535

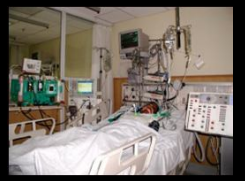
Appropriate Drug



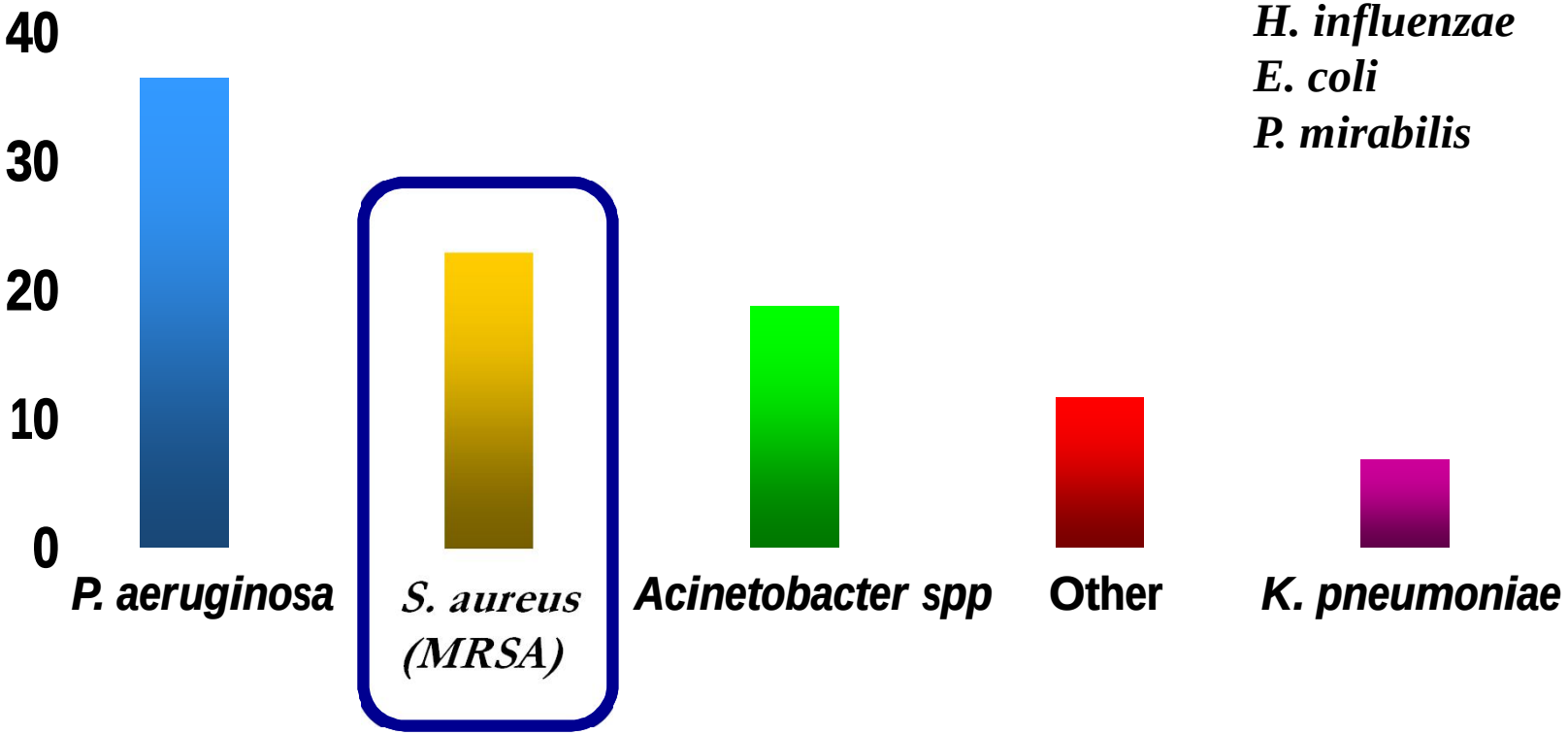
GRAM-NEGATIVE	Nosocomial Infections Neutropenic Immunocompromised Chronic Organ Failure
GRAM-POSITIVE	High level endemic MRSA Neutropenia Intravascular catheters Nosocomial pneumonia
FUNGI/YEASTS	IS unresponsive to ATBs Prolonged ATB therapy Positive fungal cultures High risk pts

ATB should cover 100% potential pathogens

Resistant Strains



Inadequate treatment (%)



Adapted from Kollef. Clin Infect Dis 2000;31(Suppl. 4):S131–S138

Prevalence of MRSA

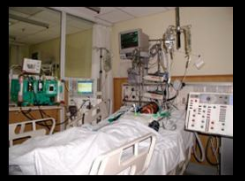
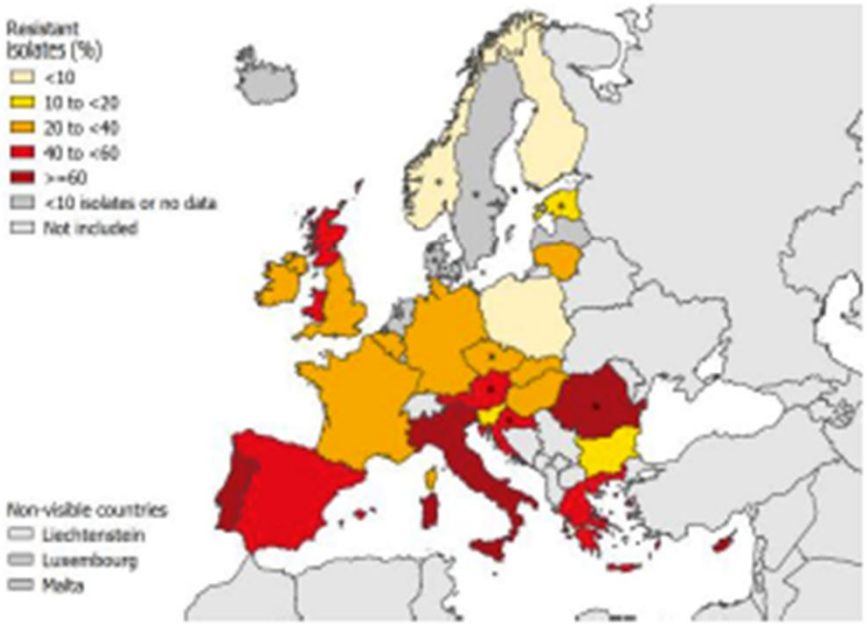


Figure 1: Percentage of resistant isolates among isolates from HAIs with known antimicrobial susceptibility testing (AST) results, by species and by country, ECDC PPS 2011–2012[3]

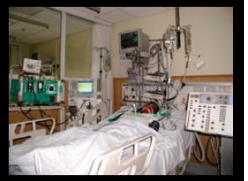
a. Meticillin-resistant *Staphylococcus aureus* (MRSA)



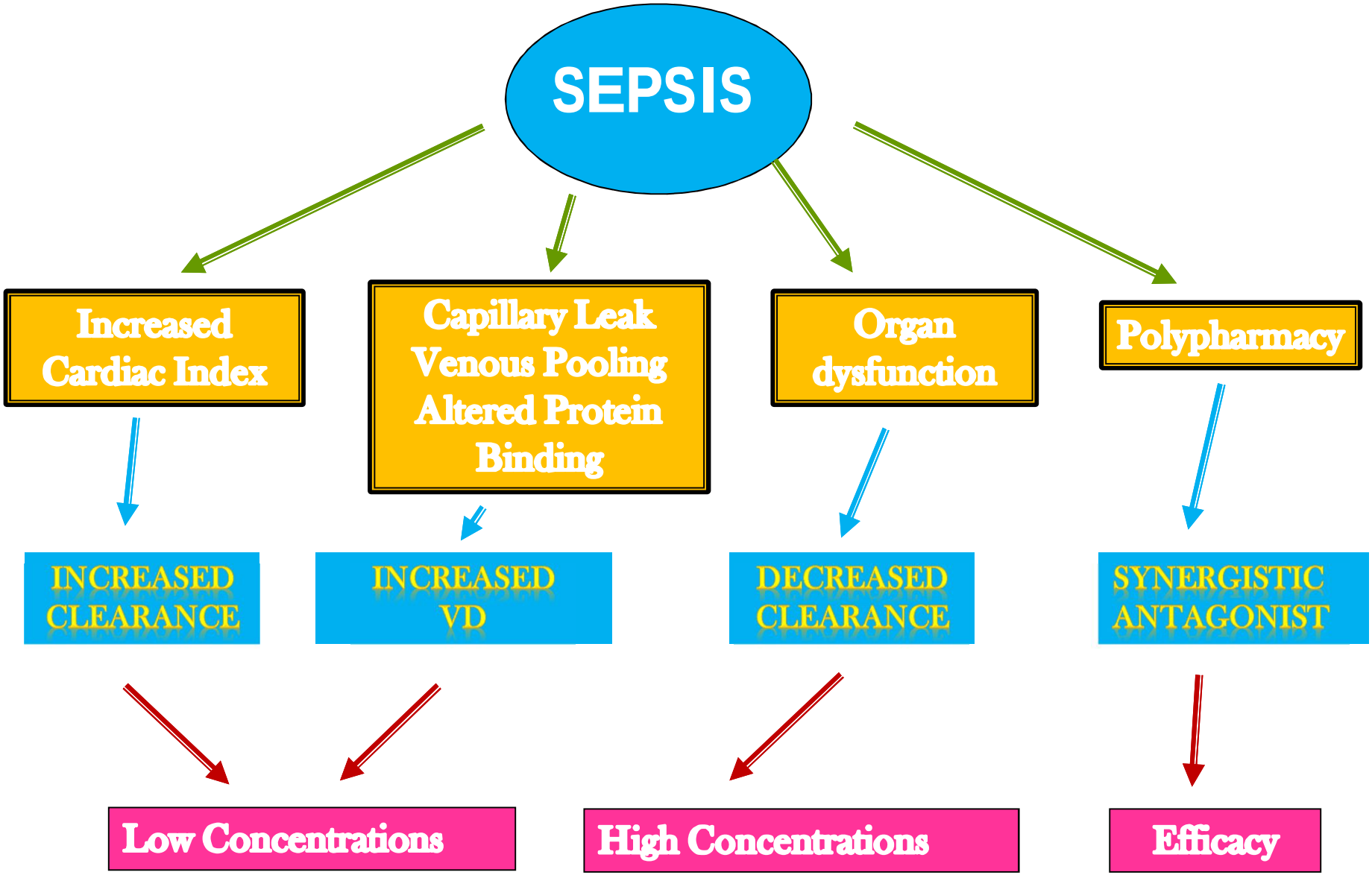
b. Vancomycin-resistant *Enterococcus species* (VRE)

ECDC surveillance

Vancomycin

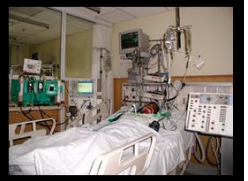


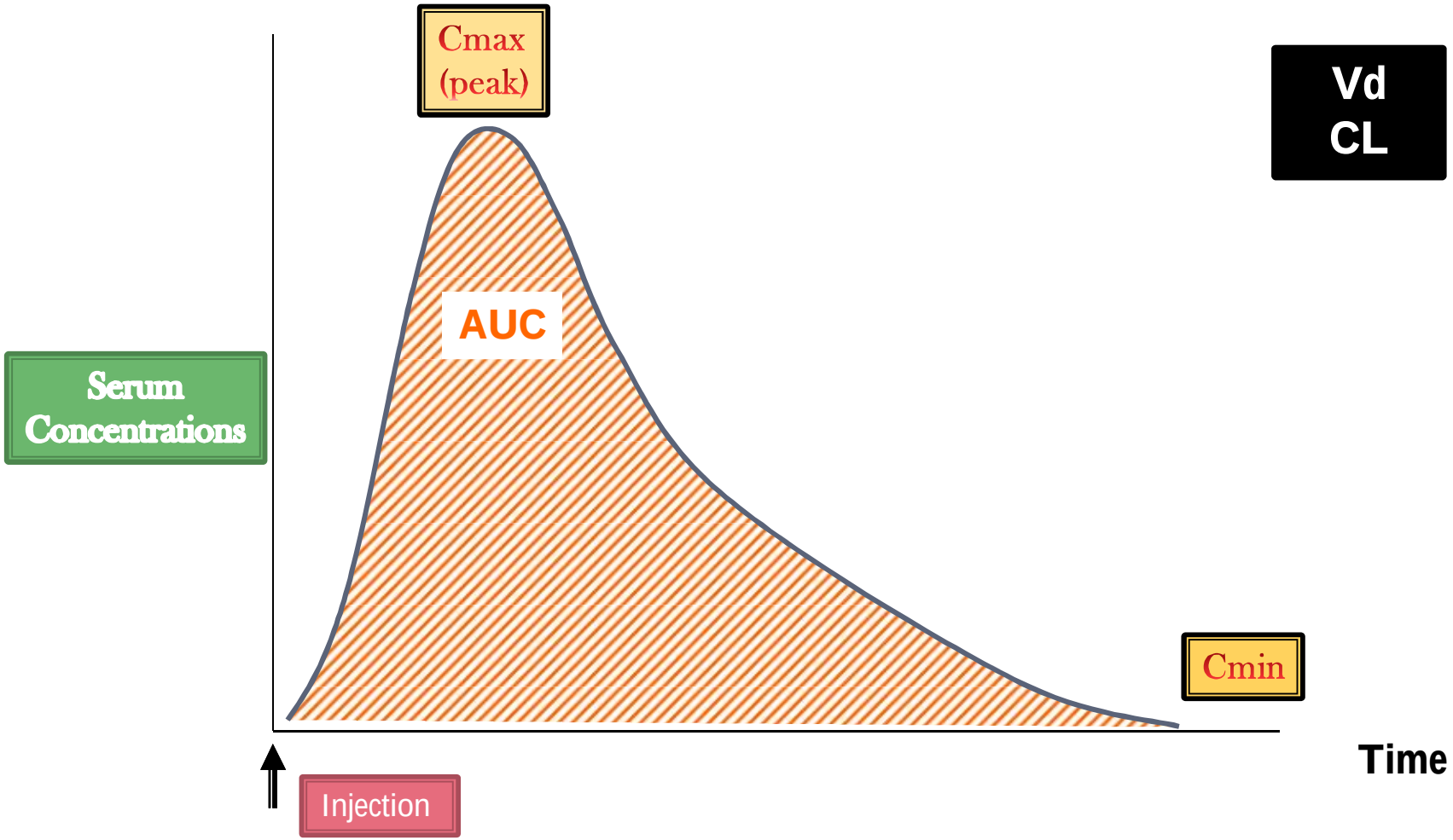
- **Tricyclic glycopeptide antibiotic**
- **Active against many GPB**
- **Used mainly for MRSA and *Enterococcus***
- **First-line therapy for allergic patients**



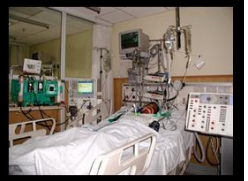
Adapted from : Roberts and Lipman. Springer 2007

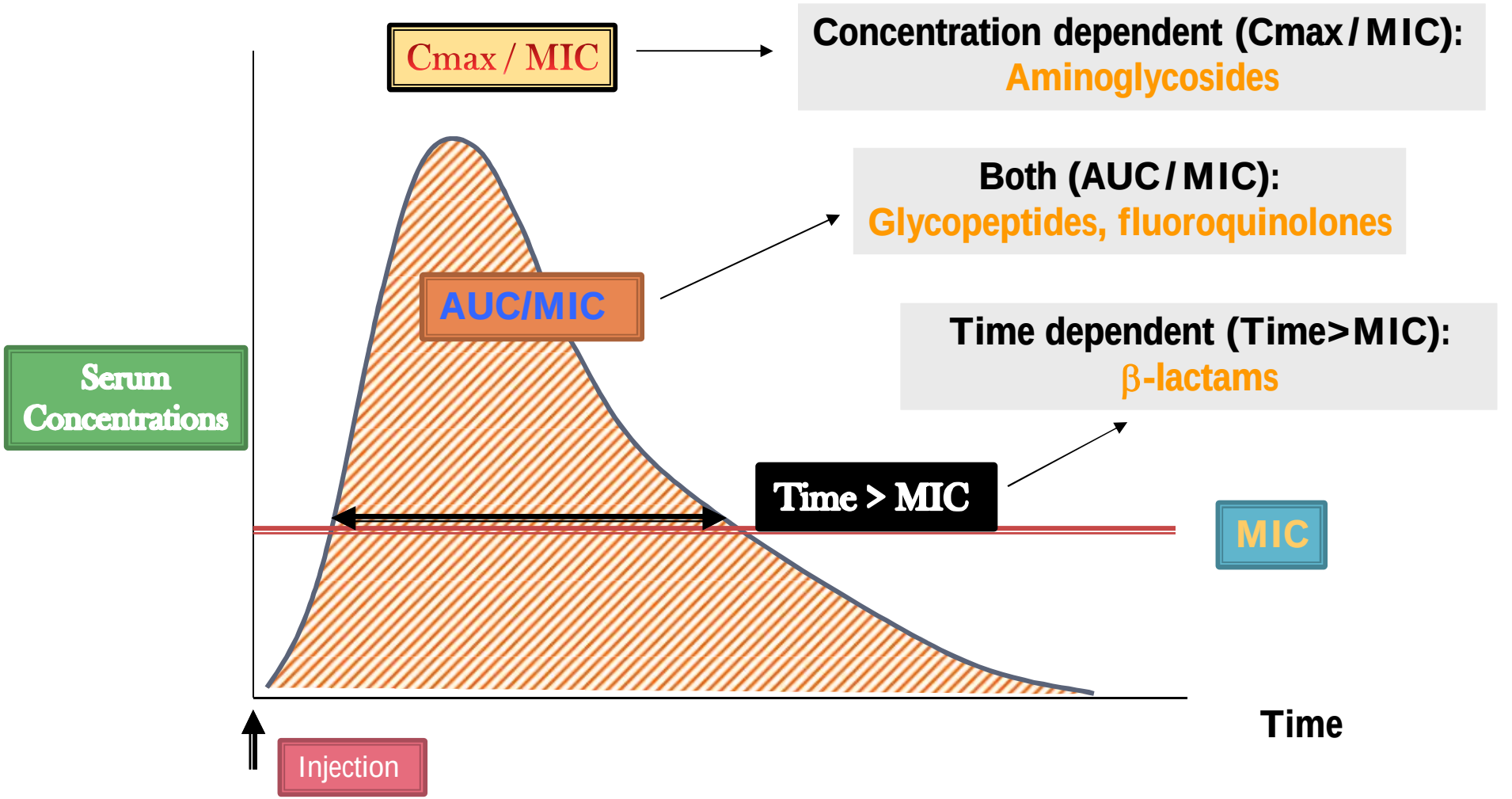
PK parameters



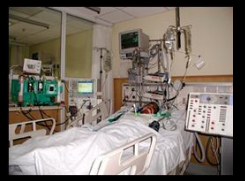


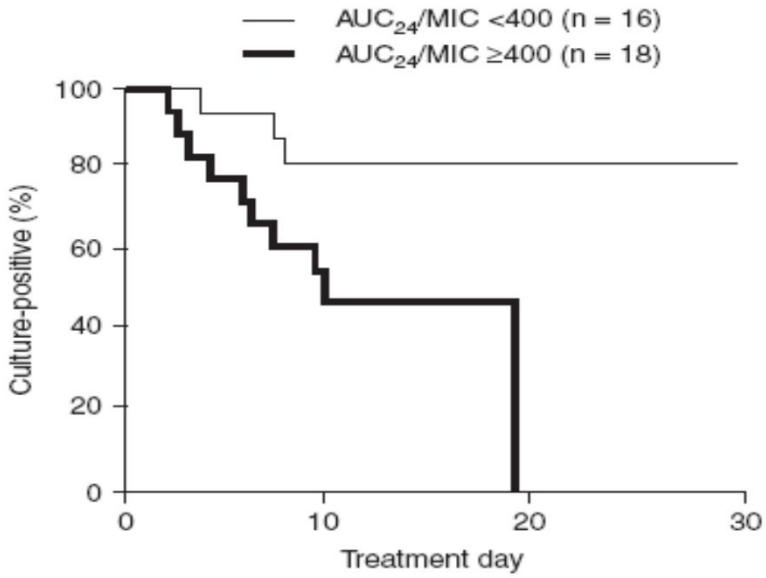
PD parameters





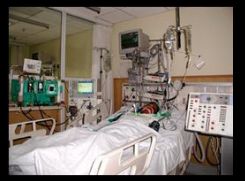
Vancomycin





Moise-Broder, Clin Pharmacokin 2004

Vancomycin



Impact of Vancomycin Minimum Inhibitory Concentration on Mortality among Critically Ill Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Christian J. Woods, MD;[1,2] Anindita Chowdhury, MD;[1]
Vinay M. Patel, MD;[1] Andrew F. Shorr, MD, MPH[1]

Retrospective Study – 2 years
n = 99
20% Endocarditis

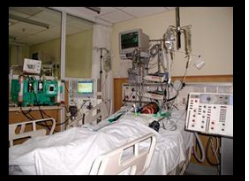
MIC of 2 mg/L only in 5 pts

TABLE 2. Factors Independently Associated with Mortality

Variable	Adjusted odds ratio	95% confidence interval	*P*
Age ≥65 years	5.81	2.04–16.55	.001
Endocarditis	4.53	1.35–15.22	.014
Shock	2.98	1.01–8.84	.049
Receipt of mechanical ventilation	2.89	0.98–8.52	.055
Vancomycin MIC of 2 mg/L	13.87	1.12–171.23	.014

NOTE. MIC, minimum inhibitory concentration.

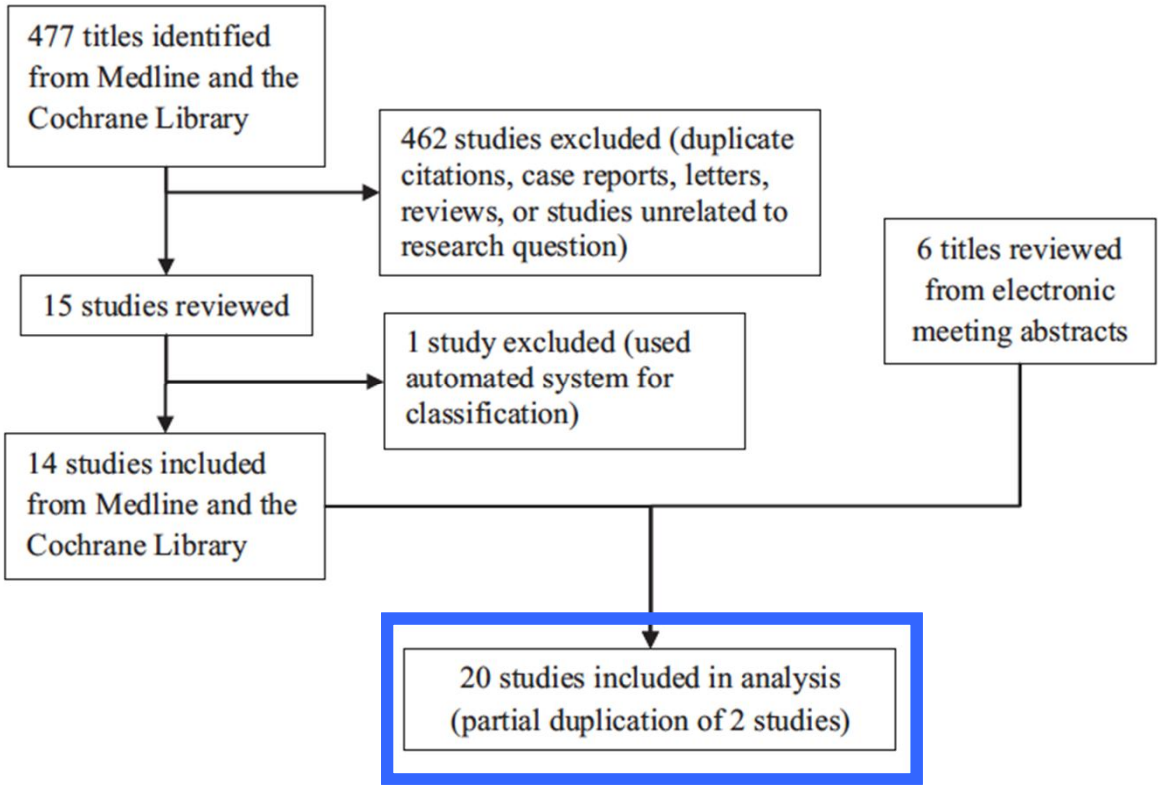
Vancomycin



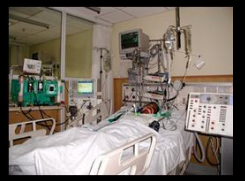
High vancomycin minimum inhibitory concentration and clinical outcomes in adults with methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis

International Journal of Infectious Diseases 17 (2013) e93–e100

Jesse T. Jacob [a,*], Carlos A. DiazGranados [b]



Vancomycin



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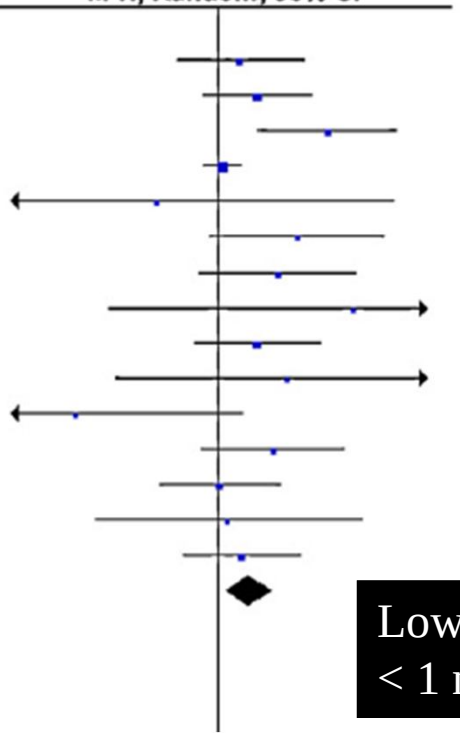
(A)

Study or Subgroup	High MIC Events	High MIC Total	Low MIC Events	Low MIC Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 E-test based studies						
Choi	12	34	10	36	6.1%	1.27 [0.63, 2.55]
Haque	41	115	10	43	7.5%	1.53 [0.84, 2.78]
Hidayat	20	44	7	51	5.3%	3.31 [1.55, 7.08]
Kullar	66	122	102	198	17.6%	1.05 [0.85, 1.30]
Lewis T	0	3	34	139	0.6%	0.51 [0.04, 6.89]
Lodise	24	66	4	26	3.7%	2.36 [0.91, 6.15]
Lustberg	16	66	6	47	4.4%	1.90 [0.80, 4.49]
Moore	36	116	0	6	0.5%	4.37 [0.30, 63.99]
Musta	74	249	7	36	6.1%	1.53 [0.77, 3.05]
Neuner	39	185	1	10	1.1%	2.11 [0.32, 13.82]
Price	1	8	14	23	1.1%	0.21 [0.03, 1.32]
Soriano	37	130	6	38	5.1%	1.80 [0.82, 3.94]
Swami	14	52	12	45	6.5%	1.01 [0.52, 1.95]
Wilhelm	3	18	3	20	1.7%	1.11 [0.26, 4.82]
Yamaki	12	57	20	123	6.8%	1.29 [0.68, 2.46]
Subtotal (95% CI)		**1265**		**841**	**74.1%**	**1.40 [1.11, 1.77]**
Total events	395		236			

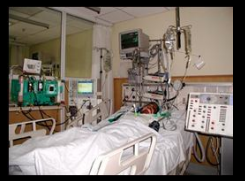
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 19.39$, df = 14 (P = 0.15); $I^2 = 28\%$

Test for overall effect: Z = 2.81 (P = 0.005)



Low MIC
< 1 mg/L

Vancomycin



Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Support for Consensus Guidelines Suggested Targets

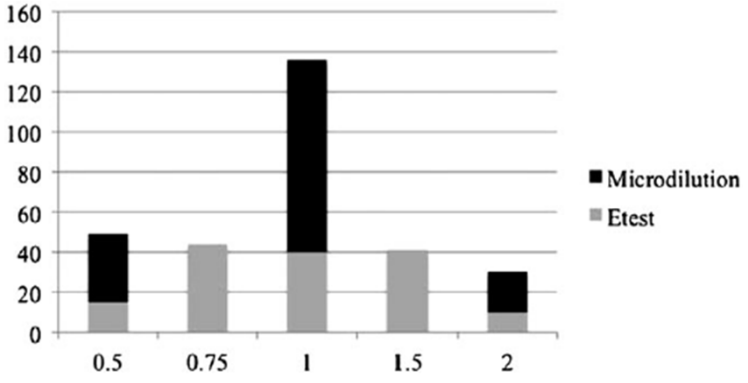
Detroit – 2005/2010
320 patients
52% Vanco Failure

Clinical Infectious Diseases 2011;52(8):975–981

Ravina Kullar,[1] Susan L. Davis,[1,3] Donald P. Levine,[2,3] and Michael J. Rybak[1,2,3]

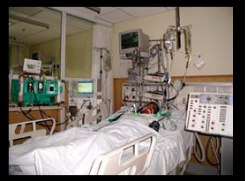
Characteristic $N = 308$[a]	Vancomycin failure *n* (%)	*P* (vs reference category)	Nephrotoxicity[b] *n* (%	*P* (vs reference category)
Trough <10 mg/L (*n*=70)	46 (65.7%)	0.001	10/65 (15.4%)	.682
Trough 10–14.9 mg/L(*n*=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L(n=86)	34 (39.5%)	REF	10/77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

Higher treatment failure observed in patients with AUC_{24h}/MIC < 421



But this strategy is poorly effective against MIC > 1 μg/mL

Vancomycin



Relationships between vancomycin minimum inhibitory concentration, dosing strategies, and outcomes in methicillin-resistant *Staphylococcus aureus* bacteremia☆

Evan C. Clemens[a], Jeannie D. Chan[a,*], John B. Lynch[b], Timothy H. Dellit[b]

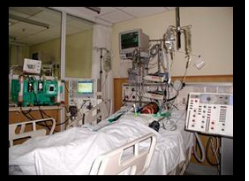
Table 2
Outcomes of treatment failure and mortality

	Vanco MIC ≤1.5 mg/L, *n* = 94 (%)	Vanco MIC = 2 mg/L, *n* = 24 (%)	Odds ratio (95% CI)	*P* value	Adjusted odds ratio* (95% CI)	*P* value
Treatment failure	20 (21.3)	7 (29.2)	1.52 (0.55–4.20)	0.416	1.11 (0.24–5.14)	0.891
30 day all-cause mortality	10 (10.6)	2 (8.3)	0.75 (0.15–3.72)	0.729	0.48 (0.05–4.27)	0.510
Infection-related mortality	8 (8.5)	2 (8.3)	0.97 (0.19–4.91)	0.967	0.58 (0.06–5.47)	0.631
Recurrence	4 (4.3)	2 (8.3)	2.05 (0.35–11.98)	0.428	2.18 (0.31–15.24)	0.433
Microbiological failure	8 (8.5)	3 (12.5)	1.54 (0.37–6.33)	0.553	0.88 (0.11–6.86)	0.902

* Multivariate analysis adjusted for age, source of bacteremia, duration of bacteremia ≥72 h, ICU care, received effective antibiotic within 24 h of positive blood culture, and renal insufficiency (SCr ≥1.3 mg/dL).

Diagnostic Microbiology and Infectious Disease 71 (2011) 408–414

Vancomycin

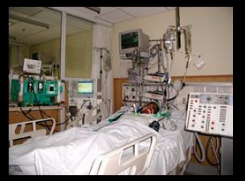


Exposure of vancomycin-sensitive *Staphylococcus aureus* to subinhibitory levels of vancomycin leads to up-regulated capsular gene expression.

Initial vancomycin trough level <15 mg/L was an independent risk factor for persistent MRSA bacteremia (OR, 4.25; 95% CI, 1.51-11.96)

Awad, Br J Biomed Sci 2013
Chong, Medicine 2013

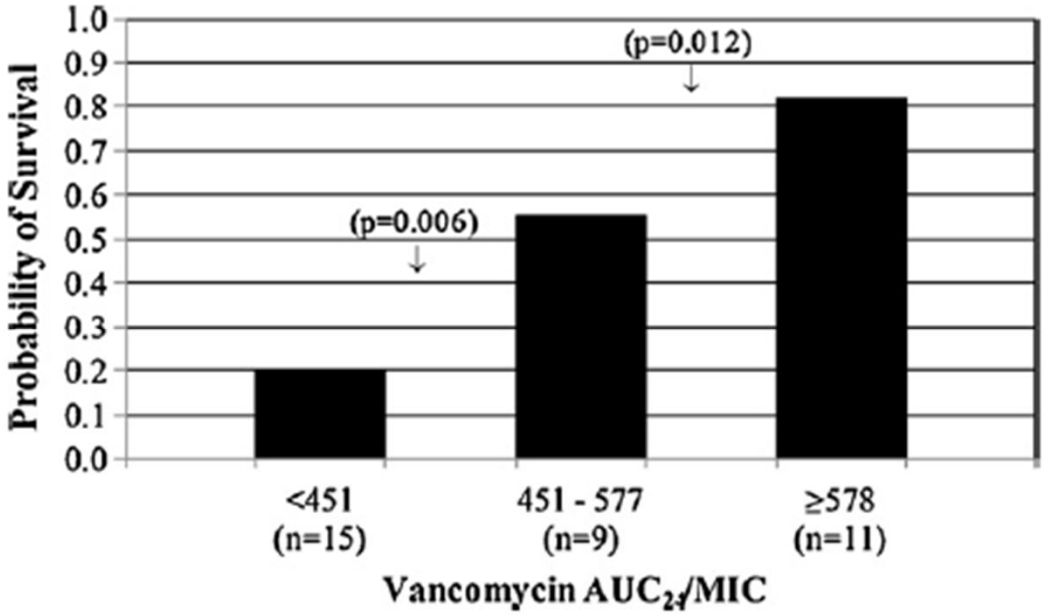
Vancomycin



Vancomycin pharmacodynamics and survival in patients with methicillin-resistant *Staphylococcus aureus*-associated septic shock☆

Sheryl Zelenitsky[a,b,*], Ethan Rubinstein[c], Robert Ariano[a,b], Harris Iacovides[a,b], Peter Dodek[d], Yazdan Mirzanejad[e], Anand Kumar[c,f], the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group

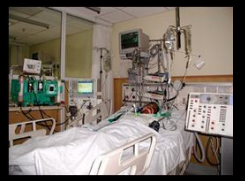
International Journal of Antimicrobial Agents 41 (2013) 255–260



35 patients

	Died (n = 18)	Survived (n = 17)
Vancomycin trough (mg/L)	13.3 ± 7.0	20.1 ± 8.6
≥15 mg/L	5 (27.8)	12 (70.6)

Vancomycin



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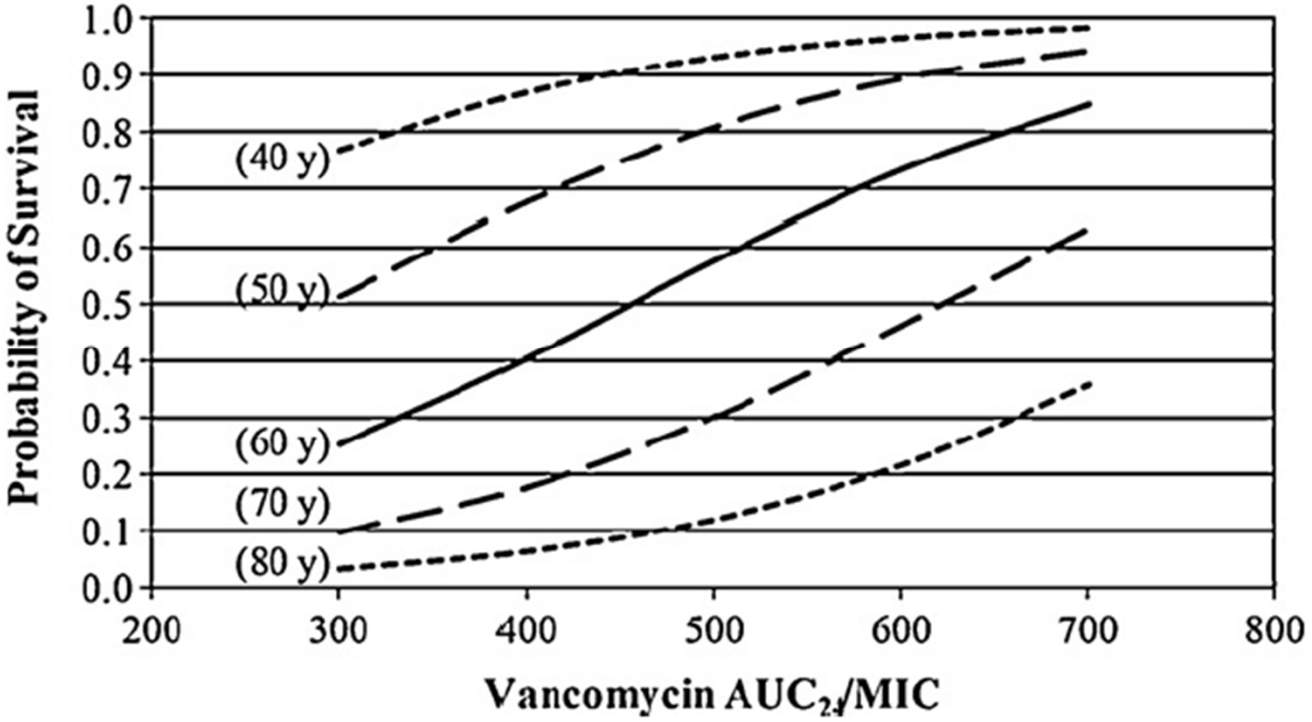


35 patients

Comparison of Conventional Dosing versus Continuous-Infusion Vancomycin Therapy for Patients with Suspected or Documented Gram-Positive Infections

JOSEPH K. JAMES,[1]† SHIRLEY M. PALMER,[1]‡ DONALD P. LEVINE,[2] AND MICHAEL J. RYBAK[1,2]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 696–700

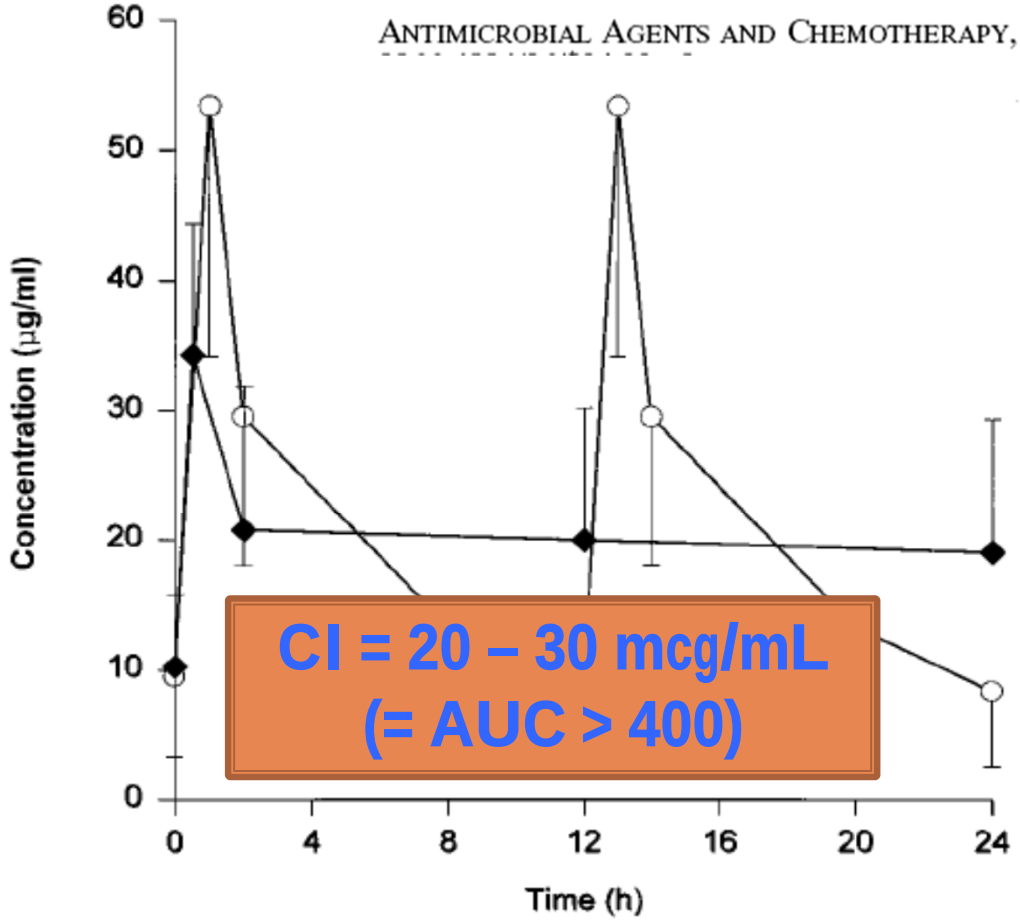
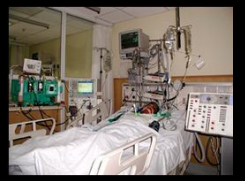
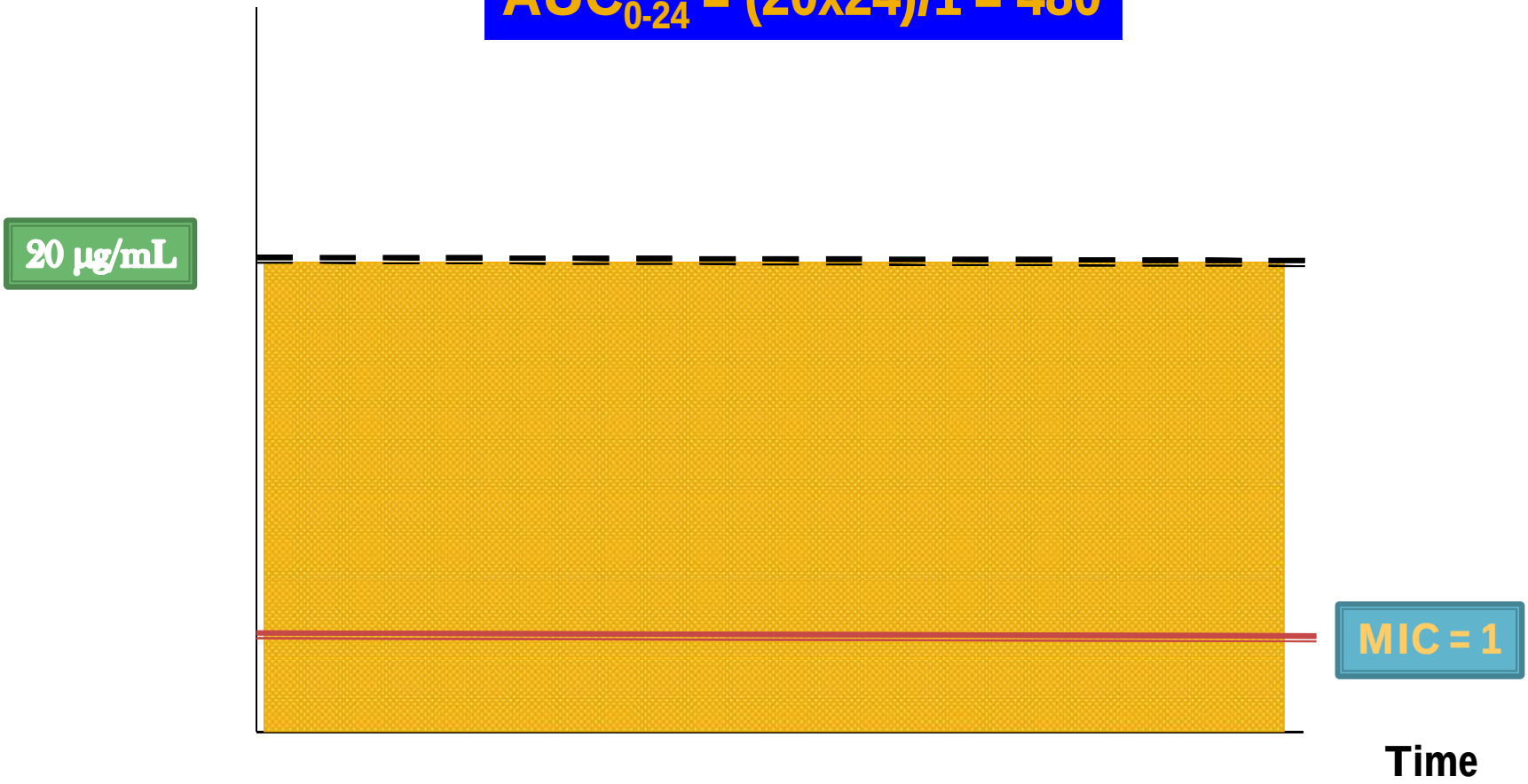


FIG. 1. Mean serum vancomycin concentrations adapted to a 24-h dosing interval. ○, CD; ◆, CI. The results for the concentration-time dosage interval of 12 to 24 h was simulated from mean data for 0 to 12 h.

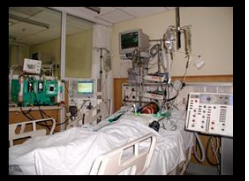
Vancomycin



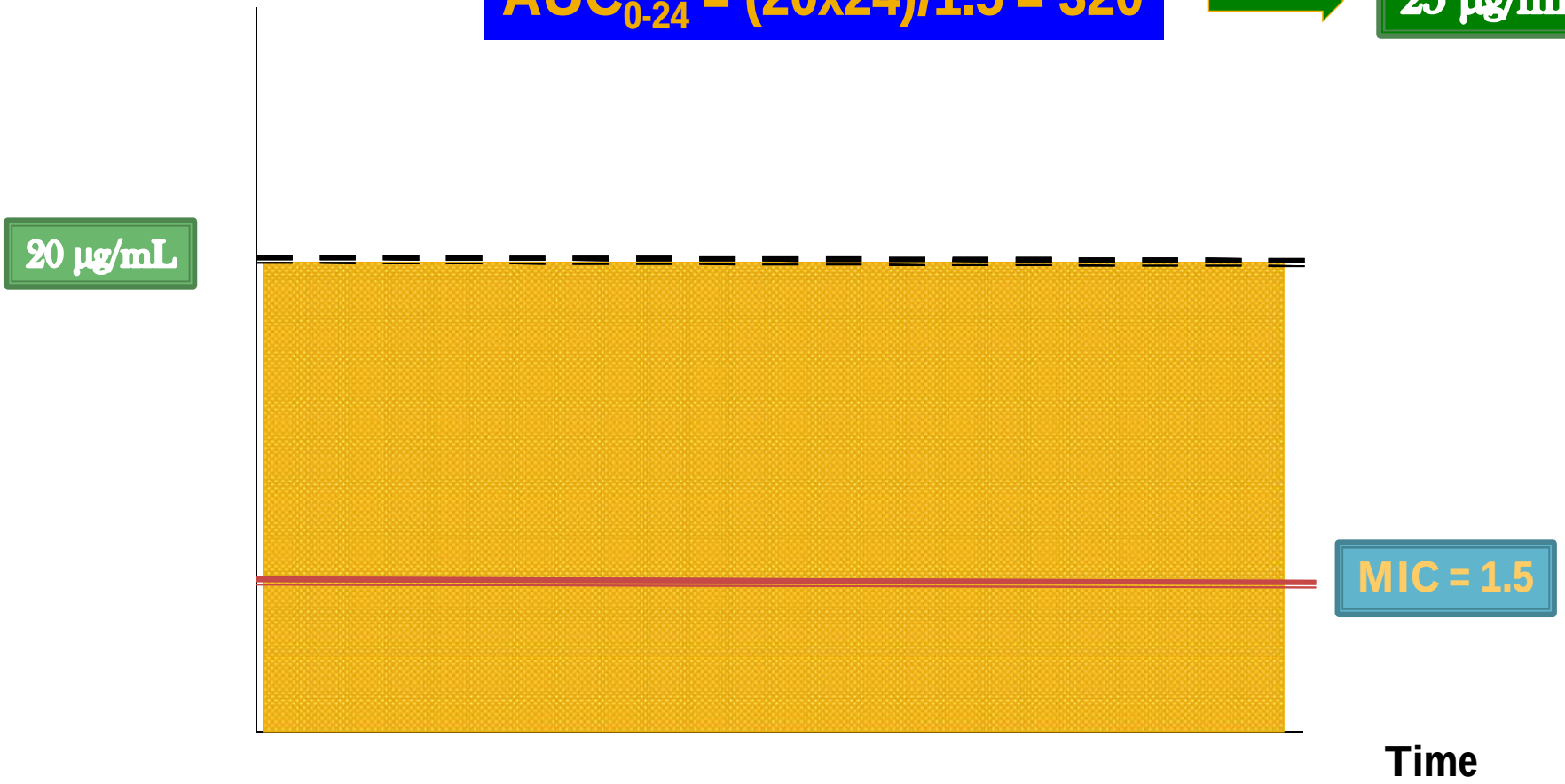
$AUC_{0\text{-}24}$ = (20x24)/1 = 480



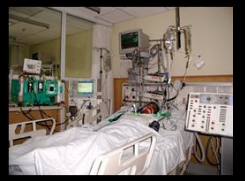
Vancomycin



$AUC_{0\text{-}24} = (20x24)/1.5 = 320$ → 25 µg/mL



Vancomycin



$AUC_{0-24} = (20x24)/2 = 240$

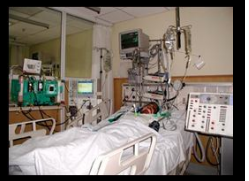
33 µg/mL

20 µg/mL

MIC = 2

Time

Vancomycin



A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals

F. M. Buyle · J. Decruyenaere · J. De Waele · P. M. Tulkens · T. Van Audenrode · P. Depuydt · G. Claeys · H. Robays · D. Vogelaers

	n	Non ICU				ICU			
		Intermittent infusions	Prolonged infusions		Combination	Intermittent infusions	Prolonged infusions		Combination
		II (%)	EC (%)	CI (%)	II/CI (%)	II (%)	EC (%)	CI (%)	II/CI (%)
Ceftazidime	32	19 (59)	0 (0)	13 (41)	0 (0)	6 (19)	0 (0)	26 (81)	0 (0)
Cefepime	20	18 (90)	1 (5)	1 (5)	0 (0)	13 (65)	5 (25)	2 (10)	0 (0)
Piperacillin–tazobactam	34	30 (88)	4 (12)	0 (0)	0 (0)	21 (62)	12 (35)	1 (3)	0 (0)
Meropenem	34	22 (65)	11 (32)	1 (3)	0 (0)	11 (32)	22 (65)	1 (3)	0 (0)
Vancomycin	34	19 (56)	0 (0)	12 (35)	3 (9)	7 (20)	0 (0)	24 (71)	3 (9)

Eur J Clin Microbiol Infect Dis (2013) 32:763–768

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

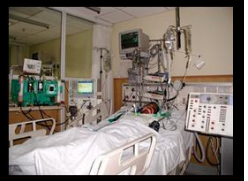
MARC WYSOCKI,[1]* FREDERIQUE DELATOUR,[2] FRANÇOIS FAURISSON,[2] ALAIN RAUSS, YVES PEAN,[4] BENOIT MISSET,[5] FRANK THOMAS,[6] JEAN-FRANÇOIS TIMSIT,[7] THOMAS SIMILOWSKI,[8] HERVE MENTEC,[9] LAURENCE MIER,[10] DIDIER DREYFUSS,[10] AND THE STUDY GROUP†

- **119 pts with MRSA infections (35% bacteremia; 45% pneumonia)**

- **Clinical outcome and safety similar**
- **Target concentrations reached faster**
- **Smaller variability of AUC**
- **Lower Costs**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2001, p. 2460–2467

PD of Vancomycin



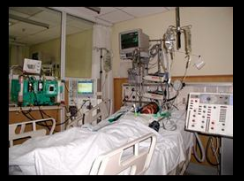
Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI Study

Table 2 Pharmacokinetic and pharmacodynamic parameters of vancomycin and clinical outcomes in critically ill patients

Parameter	All patients (n = 42)	Intermittent dosing (n = 18)	Continuous infusion (n = 24)	*p**
Vancomycin dose (mg/kg)	27 [18 – 32]	27 [22 – 30]	27 [17 – 33]	0.611
Elimination rate constant (h^{-1})**	0.09 [0.03 – 0.13]	0.09 [0.03 – 0.13]	-	-
Clearance (L/h)	3.6 [1.9 – 5.9]	5.1 [2.4 – 7.1]	2.7 [1.7 – 4.1]	0.038
Half-life (h)**	8.2 [5.4 – 24.1]	8.2 [5.4 – 24.1]	-	-
C_{min} (mg/L)	17 [8 – 23]	10 [7 – 17]	21 [14 – 26]	0.029
C_{min} ≥15 mg/L, n (percentage)	24 (57.1]	7 (38.9)	17 (70.8)	0.038
AUC_{0-24}/MIC	655 [368 – 911]	409 [246 – 712]	830 [529 – 952]	0.029
AUC_{0-24}/MIC > 400, n (percentage)	30 (71.4)	9 (50.0)	21 (87.5)	0.008
Length of vancomycin therapy on sampling date				
Days, n	4 [1 – 7]	2 [1 – 6]	4 [1 – 7]	0.314
>2 days, n (percentage)	23/41 (56.1)	8/18 (44.4)	15/23 (65.2)	0.183
>3 days, n (percentage)	22/41 (53.7)	8/18 (44.4)	14/23 (60.9)	0.295

CRITICAL CARE

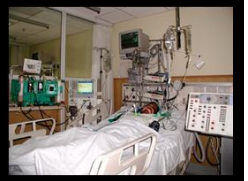
PD of Vancomycin



- **No evidence of better clinical outcome when CI is used**
- **Reduced incidence of nephrotoxicity**
- **No studies in septic patients concerning which is the best dosage regimen**

Vancomycin	2 g q8h/30 min	2 g/30 min loading dose+2 g q8h/3 h	
	15 mg/kg q12h/1 h		15 mg/kg/2 h loading dose+30 mg/kg q24h/24 h
	20 mg/kg q12h/1 h		20 mg/kg/2 h loading dose+30 mg/kg q24h/24 h

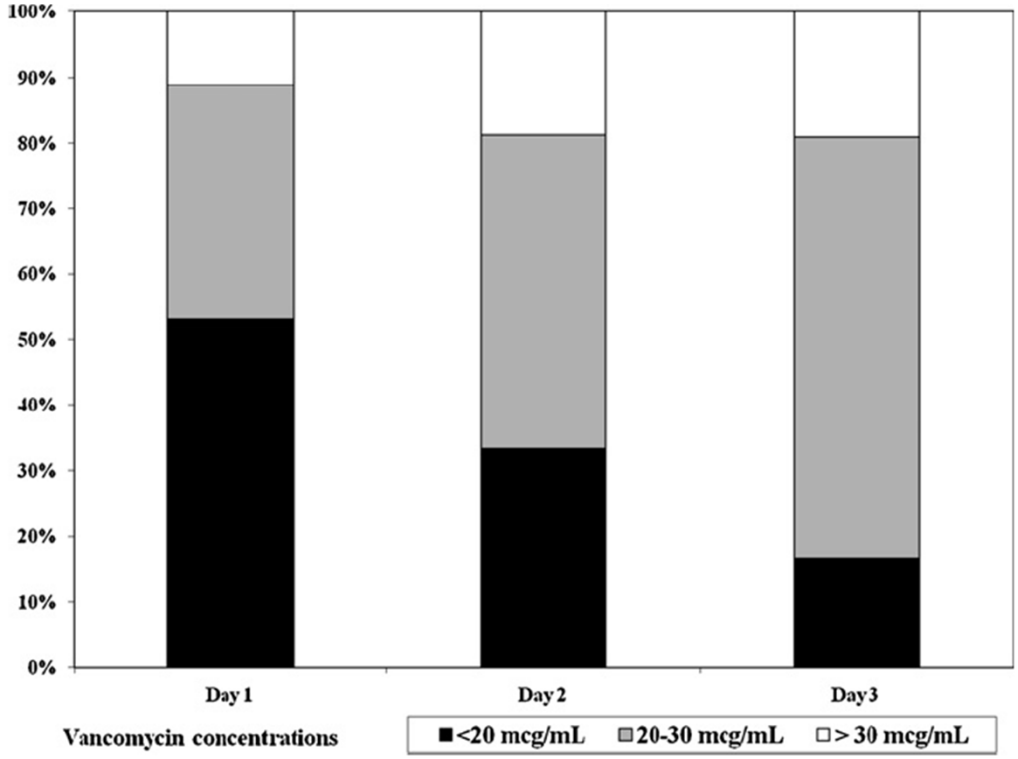
PD of Vancomycin

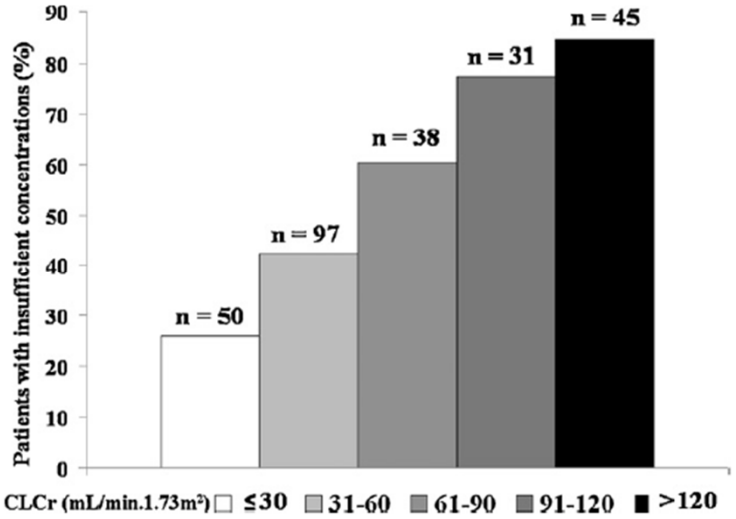


Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients

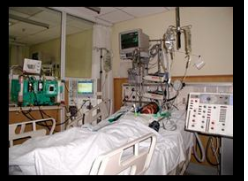
Eva Ocampos-Martinez[a], Laura Penaccini[a], Sabino Scolletta[a], Ali Abdelhadii[a], Alessandro Devigili[a], Silvia Cianferoni[a], Daniel de Backer[a], Frédérique Jacobs[b], Frédéric Cotton[c], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]

International Journal of Antimicrobial Agents 39 (2012) 332–337





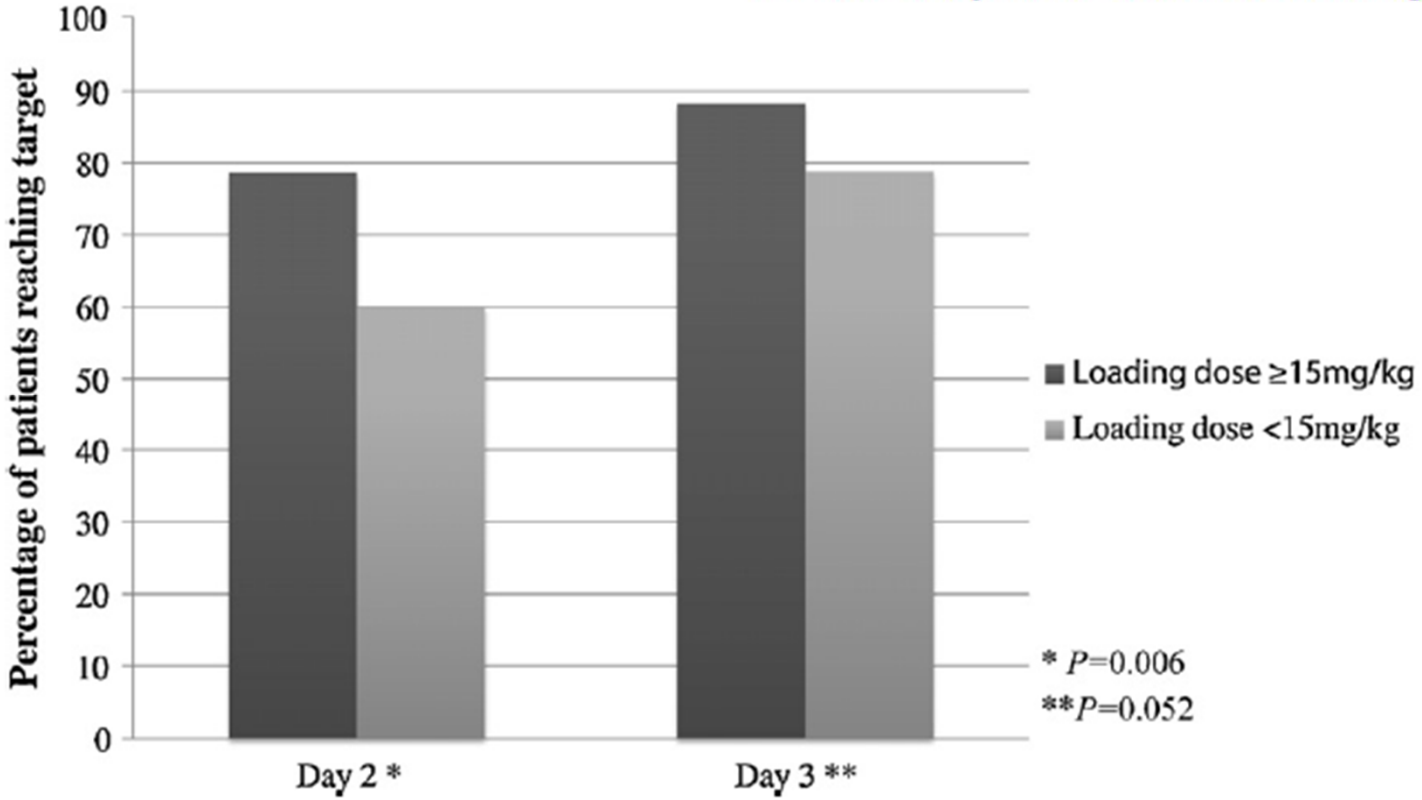
PD of Vancomycin



Factors associated with inadequate early vancomycin levels in critically ill patients treated with continuous infusion

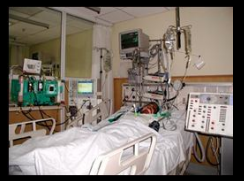
J.J. De Waele[a,*], I. Danneels[b], P. Depuydt[a], J. Decruyenaere[a], M. Bourgeois[c], E. Hoste[a]

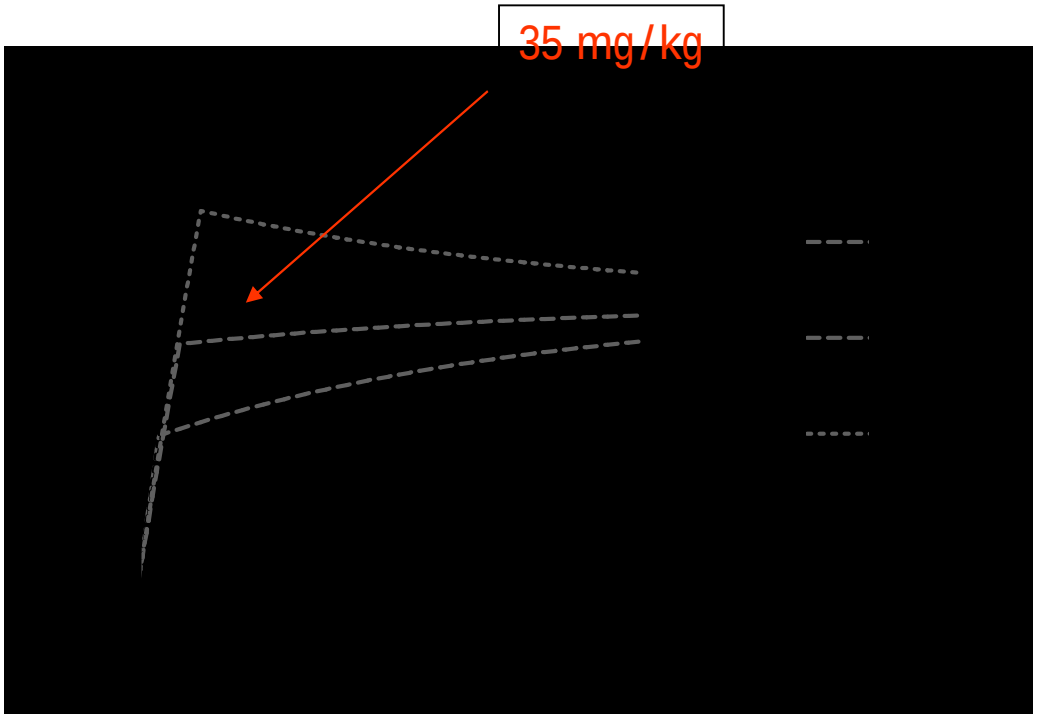
International Journal of Antimicrobial Agents 41 (2013) 434–438



Age
Male gender
sCr
Temperature
LD

Monte Carlo Simulation

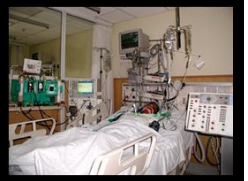




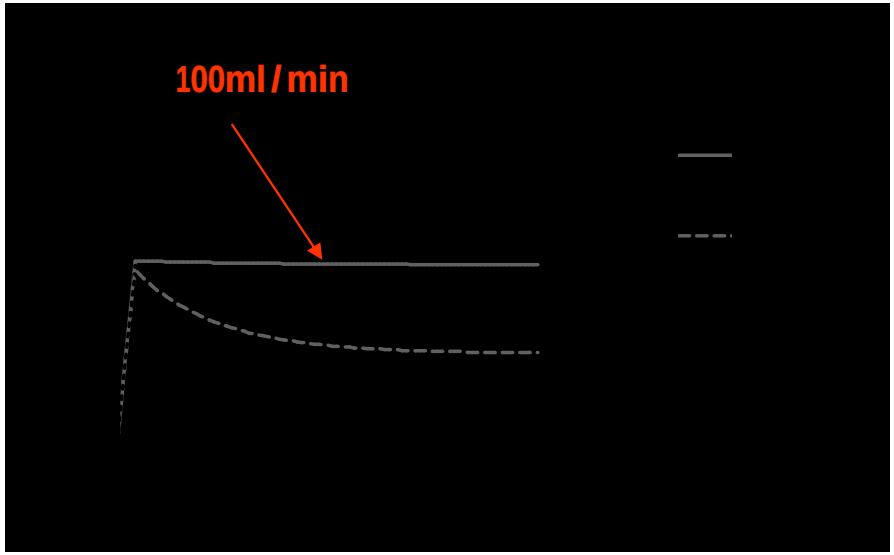
Roberts, Taccone et al. (AAC, 2011)

Simulations for identifying the best loading dose for a critically ill patient

Monte Carlo Simulation

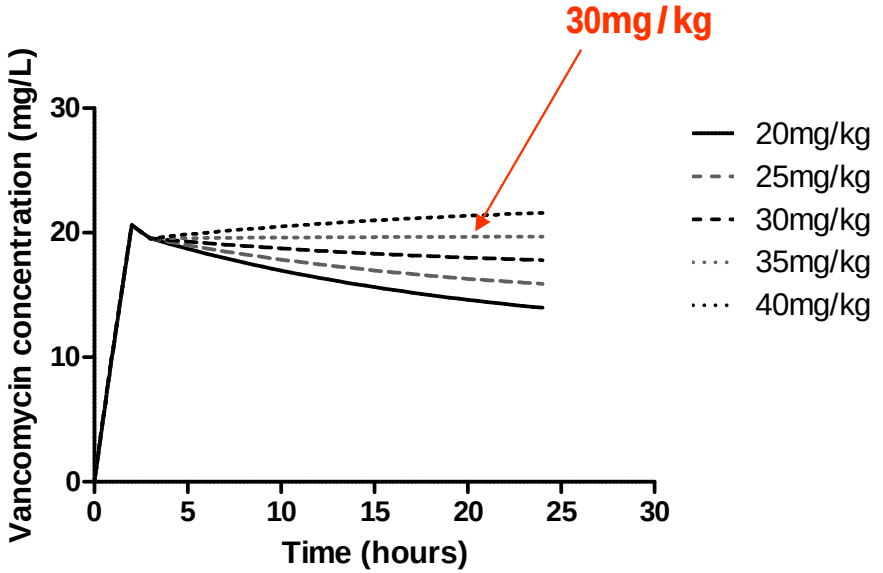


Creatinine clearance



Loading dose: 35mg / kg
CI: 30mg / kg

Daily dose



Loading dose: 35mg / kg
Creatinine clearance: 100ml / min x 1.73m²

Loading dose: 35mg / kg
then daily dose: 30mg / kg if clearance 100ml / min x 1.73m²

Validation

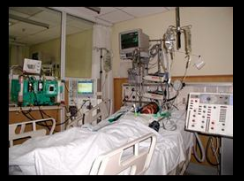
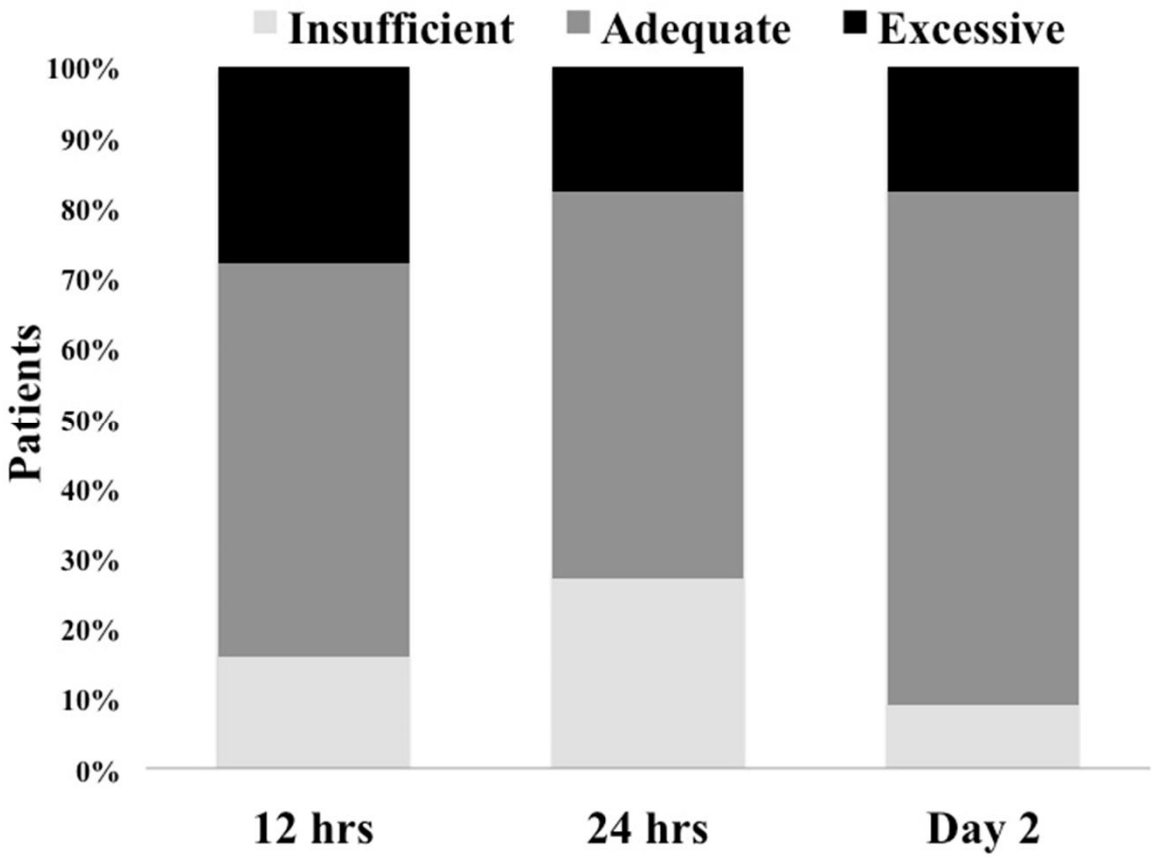
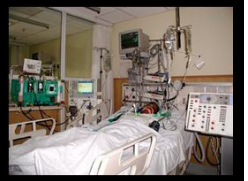


Table 1: Daily dose according to CrCl.	
CrCl (ml/min)	Daily dose (mg/kg/day)
> 150	45
120-150	40
80-120	35
50-80	25
25-50	14
< 25 or oliguria	7



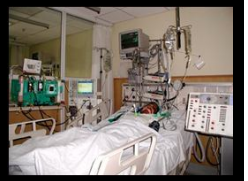
Cristallini, 42nd SCCM Congress 2013

Vancomycin: Side effects



- **Red-Man Syndrome**
- **Nephrotoxicity**
- **Ototoxicity**

Vancomycin: Side effects



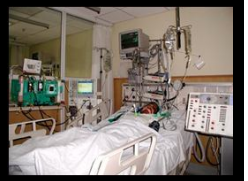
Vancomycin nephrotoxicity is not fully understood

- Early preparations were associated with nephrotoxicity
- Large doses and high trough levels have been correlated with nephrotoxicity
- Combination with aminoglycosides increases the risk of acute renal failure

Table 3 Summary of the most important articles, including adult intensive care unit (ICU) patients, which evaluated the incidence of acute kidney injury (AKI) during vancomycin therapy

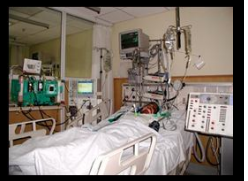
Reference	*n*	Type	%ICU	Age	Regimen	Definition of AKI	AKI incidence (%)	Mortality in AKI patients (%)	CRRT need	Vancomycin regimen	Vancomycin concentrations
Bosso et al. [11]	288	P	36	NA	II	Increase sCr ≥0.5 mg/l/50 %	30	NA	NA	–	C_{min} > 15 μg/ml had increased risk of AKI
Cano et al. [41]	188	R	100	58	II	Increase sCr ≥0.5 mg/l/50 %	15	33 %	NA	–	Initial C_{min} > 15 μg/ml had increased risk of AKI
Colares et al. [42]	19	R	57	51	II	50 % increase in baseline sCr	100	53	37	–	Highest C_{min} > 40 μg/ml in all patients with AKI
Hidayat et al. [29]	95	P	42	72	II	Increase sCr ≥0.5 mg/l	12	NA	NA	–	AKI occurred only if C_{min} > 15 μg/ml
Hutschala et al. [43]	149	R	100	59	II CI	Increase sCr ≥0.3 mg/l	37 27	NA	30 % 23 %	Similar daily doses between groups	Mean levels higher in CI (25 vs. 17 μg/ml)
Jeffres et al. [10]	94	R	NA[a]	59	II	Increase sCr ≥0.5 mg/l/50 %	43	NA	0 %	–	C_{min} > 15 μg/ml had increased risk of AKI
Lodise et al. [28]	166	R	36	56	II	Increase sCr ≥0.5 mg/l/50 %	13	NA	NA	–	Initial C_{min} was associated with AKI development
Lodise et al. [8]	246	R	41	58	II	Increase sCr ≥0.5 mg/l/50 %	12	NA	0 %	>4 g/day was associated with increased AKI	–
Minejima et al. [30]	227	P	33	70	II	Increase sCr ≥0.3 mg/l	19	19 %	0 %	Lower initial dose in AKI group	Vancomycin levels were not associated with AKI
Pritchard et al. [9]	129	R	NA[a]	61	II	Increase sCr ≥0.5 mg/l/50 %	16	NA	NA	Higher initial dose in patients with AKI	Higher mean C_{min} in patients with AKI
Shen et al. [35]	33	R	30	71	II	1.5-fold increase in sCr	45	40 %	6 %	–	–
Spapen et al. [18]	129	R	100	67	CI	Increase sCr ≥0.3 mg/l	29	53 %	0 %	–	C_{max} was associated with AKI

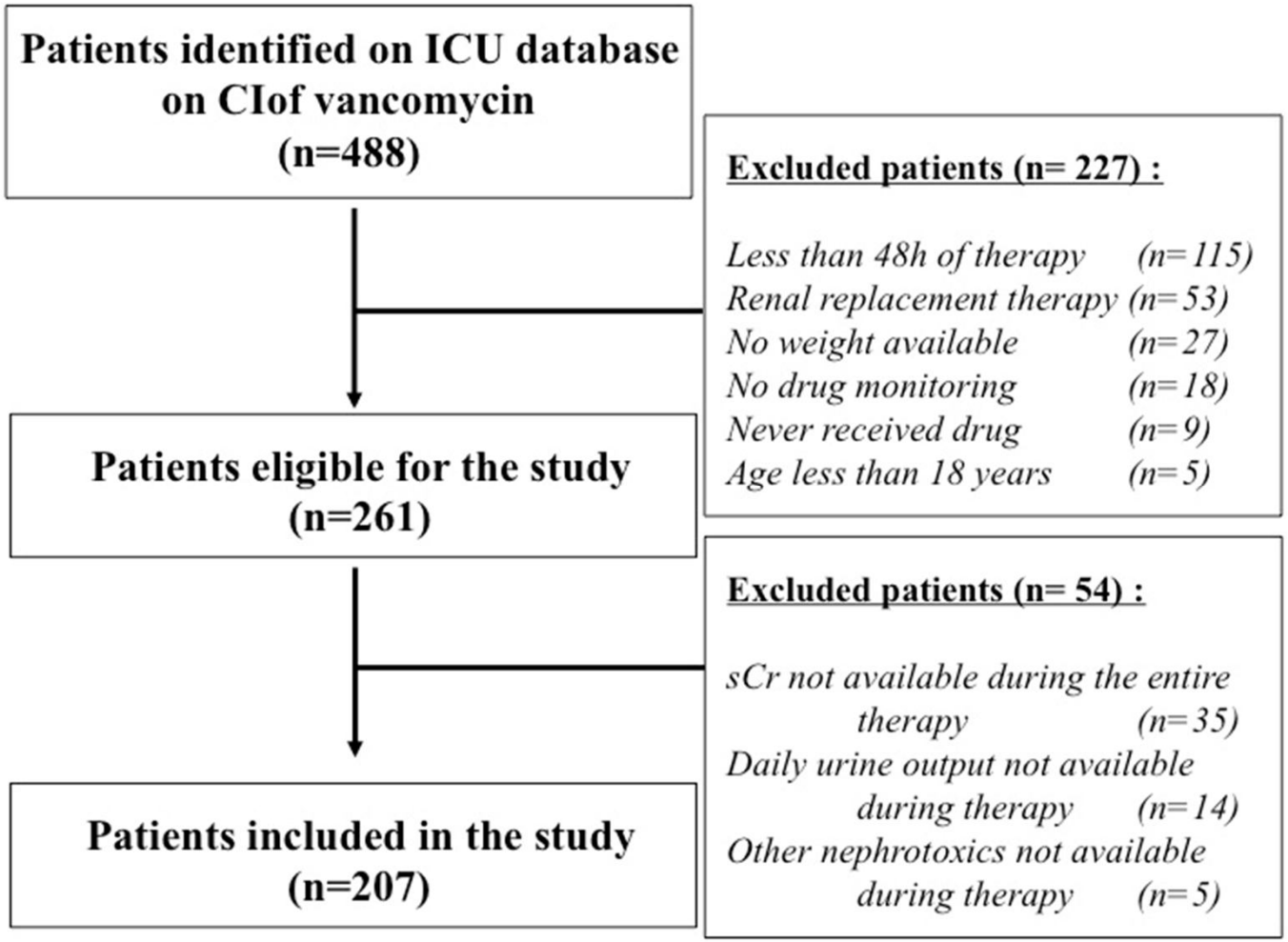
Toxicity of CI Vanco



- **Early vs. Late**
- **Exposure vs. One Measurement**
- **Long-Term Effects (Creat)**
- **Use of CRRT**

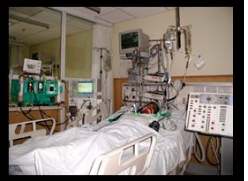
Toxicity of CI Vanco





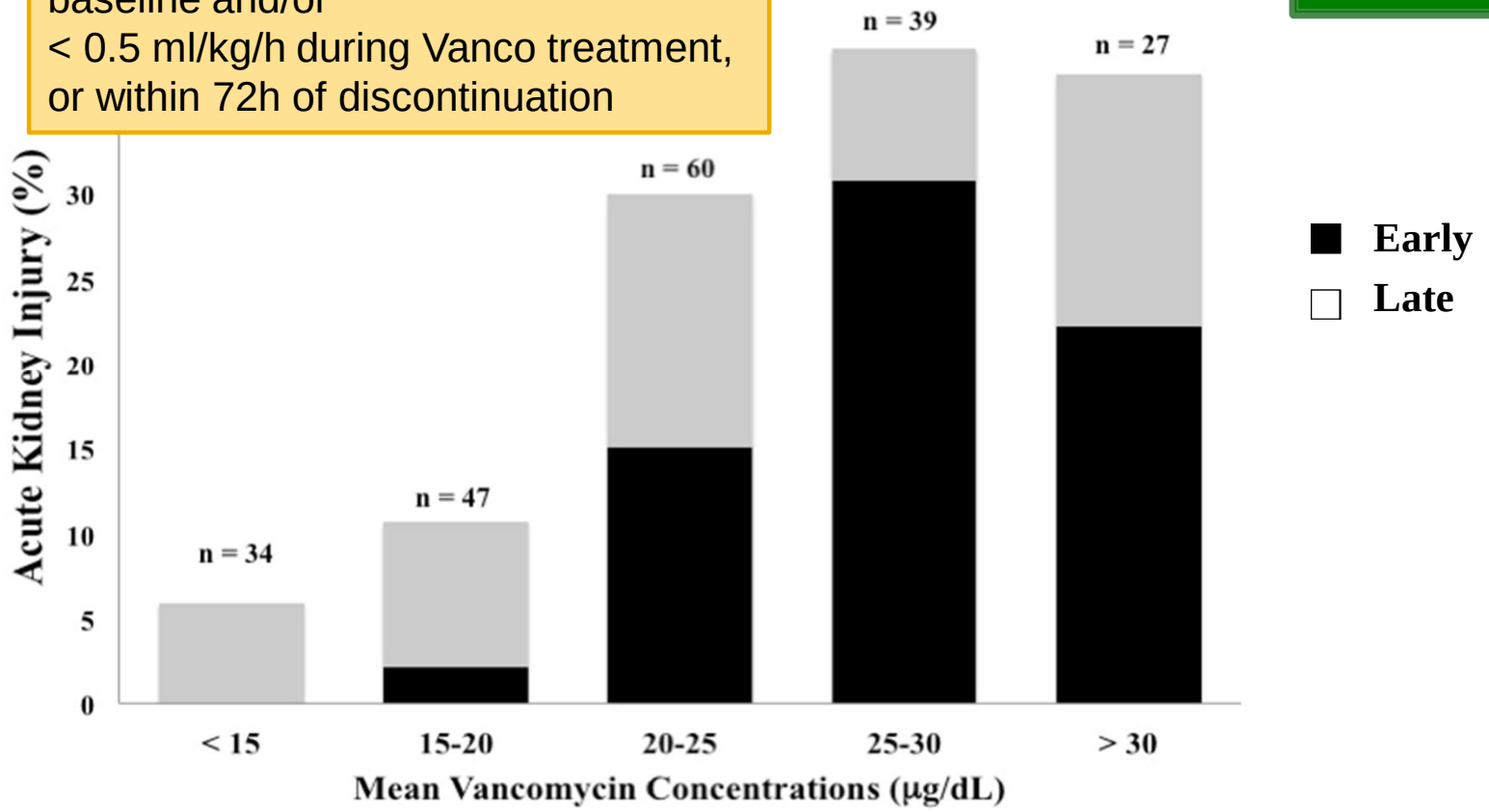
Cianferoni, Infection 2013

Toxicity of CI Vanco



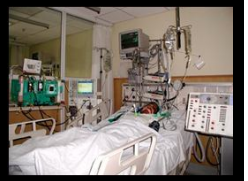
Definition of AKI:
Increase in >0.3 mg/dl sCr from baseline and/or
< 0.5 ml/kg/h during Vanco treatment, or within 72h of discontinuation

24% AKI



Cianferoni, Infection 2013

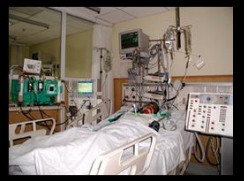
Toxicity of CI Vanco

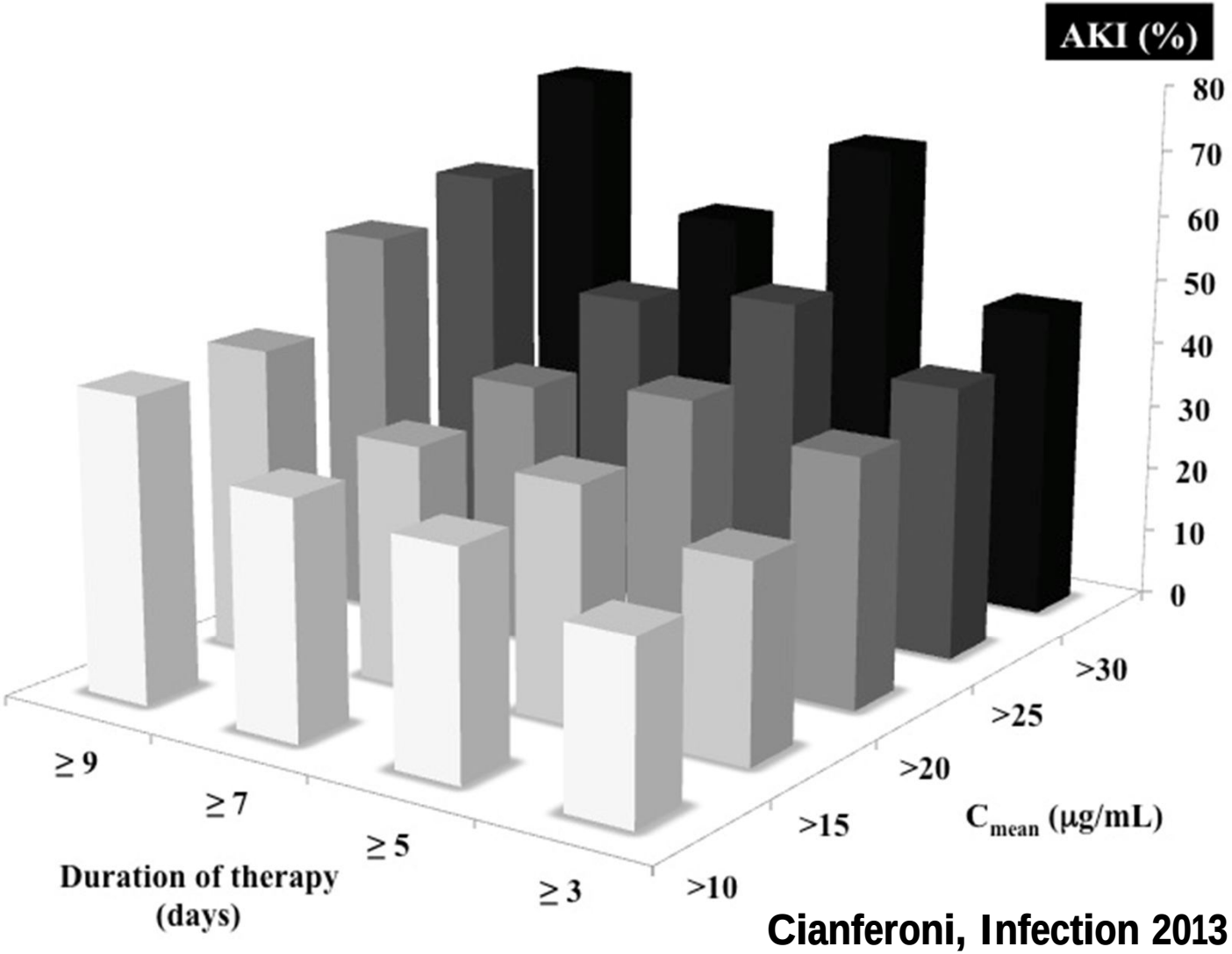


Variable	Multivariable analysis	
	p-Value	OR (95 % CI)
AKI		
C_{mean} (µg/ml)	<0.001	1.1 (1.04–1.15)
Duration of therapy (days)	0.049	1.12 (1.01–1.25)
Early AKI		
Bacteremia	0.008	1.76 (1.32–1.93)
C_{mean} (µg/ml)	<0.001	1.12 (1.01–1.20)
$Dose_{mean}$ (mg/day)	<0.001	0.98 (0.97–0.99)
Late AKI		
Diabetes	0.02	1.68 (1.16–1.88)
Duration of therapy (days)	0.02	1.17 (1.02–1.33)

Cianferoni, Infection 2013

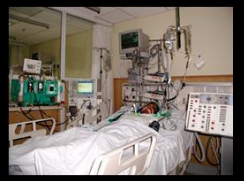
Toxicity of CI Vanco





Cianferoni, Infection 2013

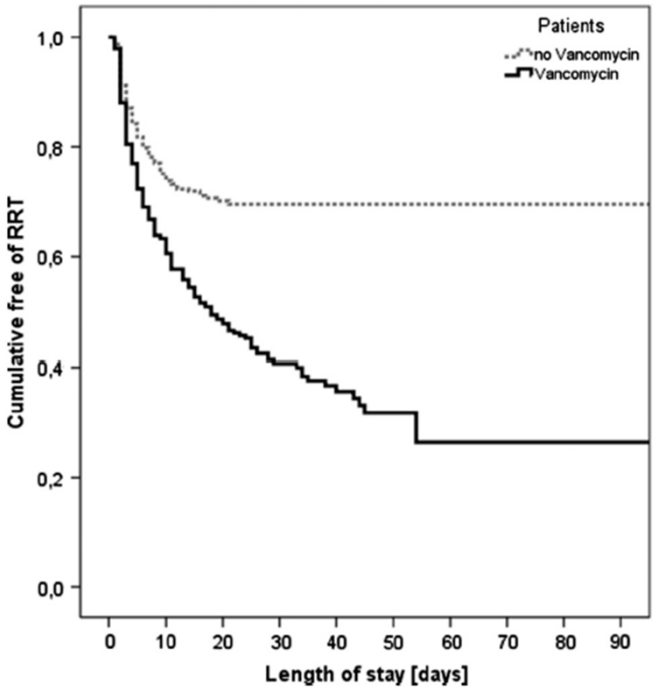
Toxicity of CI Vanco



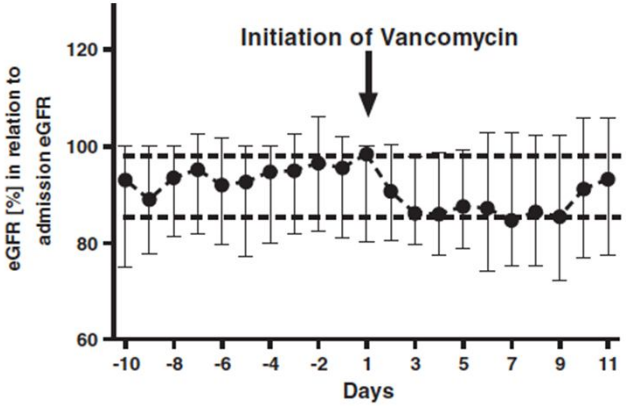
Renal outcome after vancomycin treatment and renal replacement therapy in patients with severe sepsis and septic shock: A retrospective study ☆

Gordon P. Otto, MD, MSc [a,b,*], Maik Sossdorf, PhD [a,b], Hannes Breuel, MD [b], Peter Schlattmann, MD, MSc [c], Ole Bayer, MD [b], Ralf A. Claus, PhD [a,b], Niels C. Riedemann, MD [a,b], Martin Busch, MD [d]

Journal of Critical Care xxx (2014) xxx–xxx



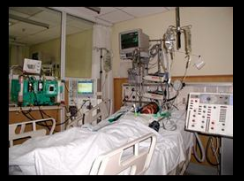
	Requirement of RRT at ICU discharge in all patients			Requirement of RRT at ICU discharge with vancomycin use before RRT initiation		
	OR	95% CI	P	OR	95% CI	P
Median SAPS II during LOS†	1.368	1.276-1.466	<.001	1.371	1.272-1.478	<.001
eGFR at admission‡	0.978	0.967-0.990	<.001	0.980	0.967-0.993	.002
Gentamicin treatment	1.266	0.685-2.339	.455	2.010	1.002-4.033	.049
Vancomycin treatment	2.659	1.878-3.766	<.001	1.648	1.067-2.546	.024



Dosing for « special » conditions

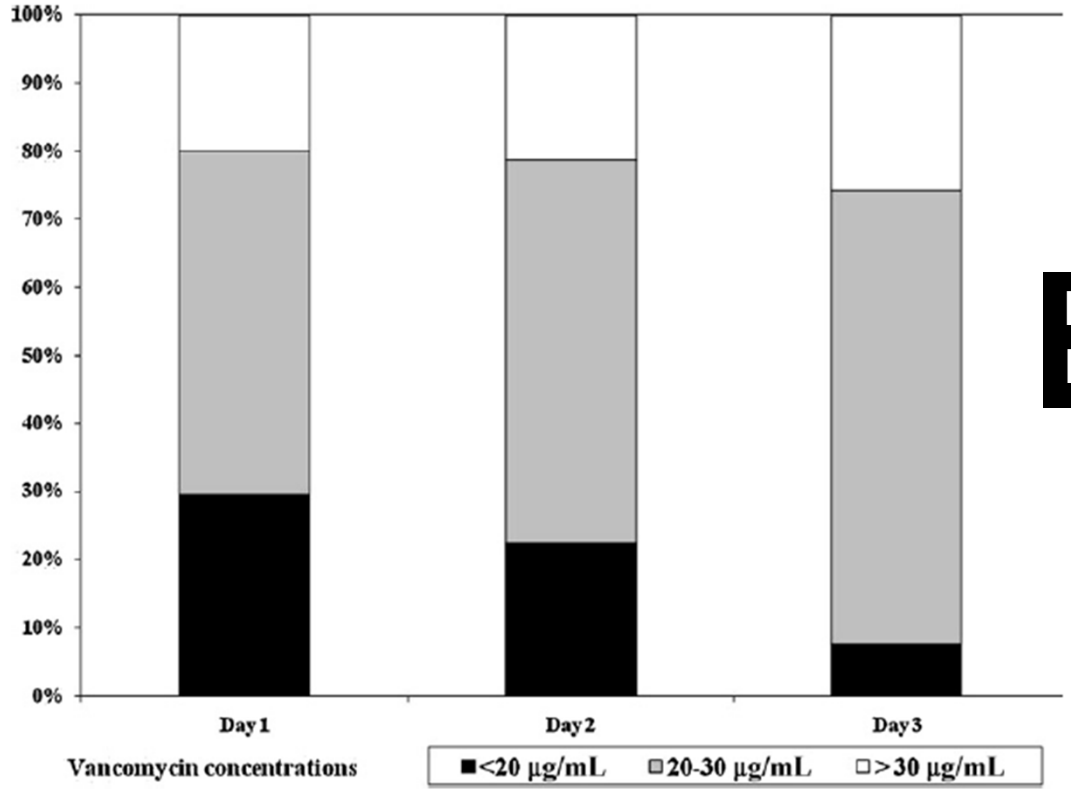
- **Continuous Renal Replacement Therapy (CRRT)**
- **Obese patients**
- **Liver cirrhosis / Burns**

CRRT



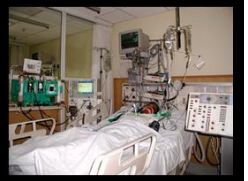
Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy

Cecilia Covajes[a], Sabino Scolletta[a], Laura Penaccini[a], Eva Ocampos-Martinez[a], Ali Abdelhadii[a], Marjorie Beumier[a], Frédérique Jacobs[b], Daniel de Backer[a], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]



LD = 15 mg/kg
DD = 20-30 mg/kg

CRRT



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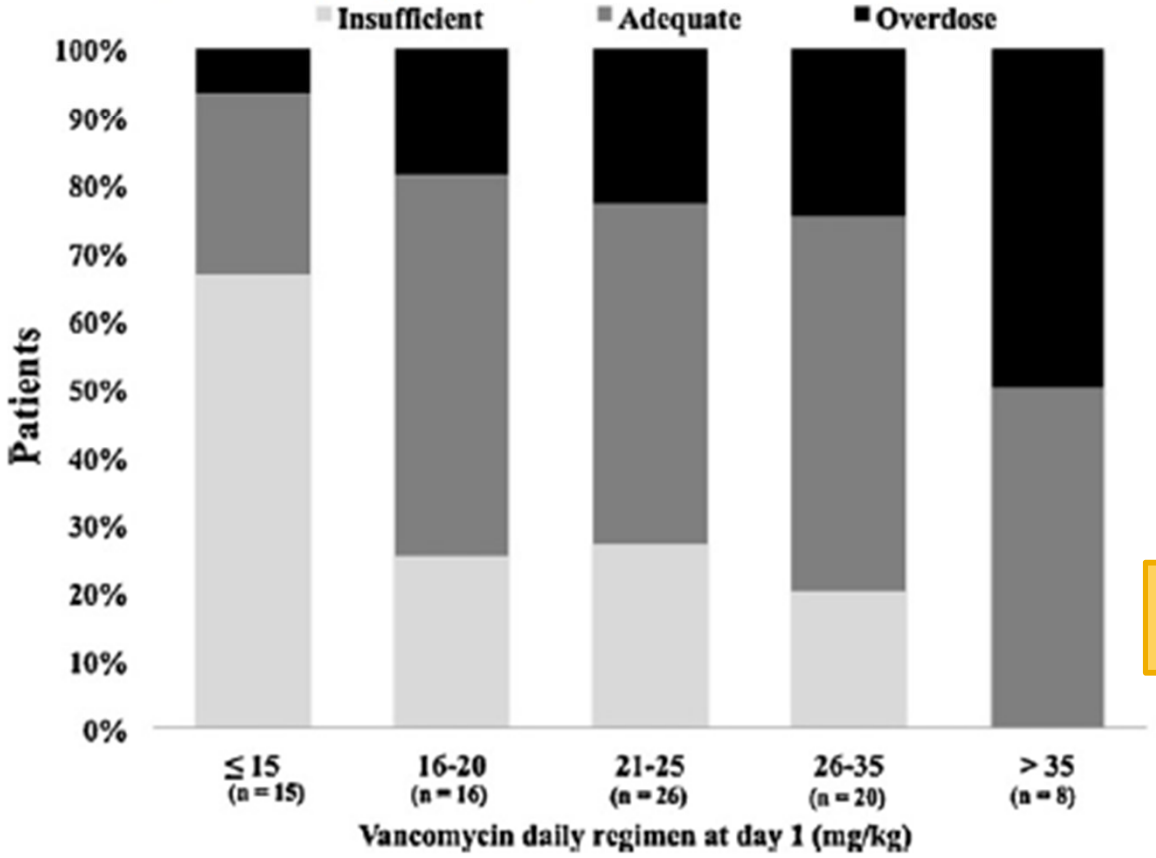
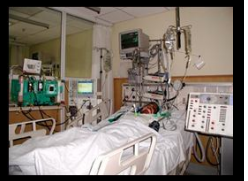


LD = 15 mg / kg
DD = 20-30 mg / kg

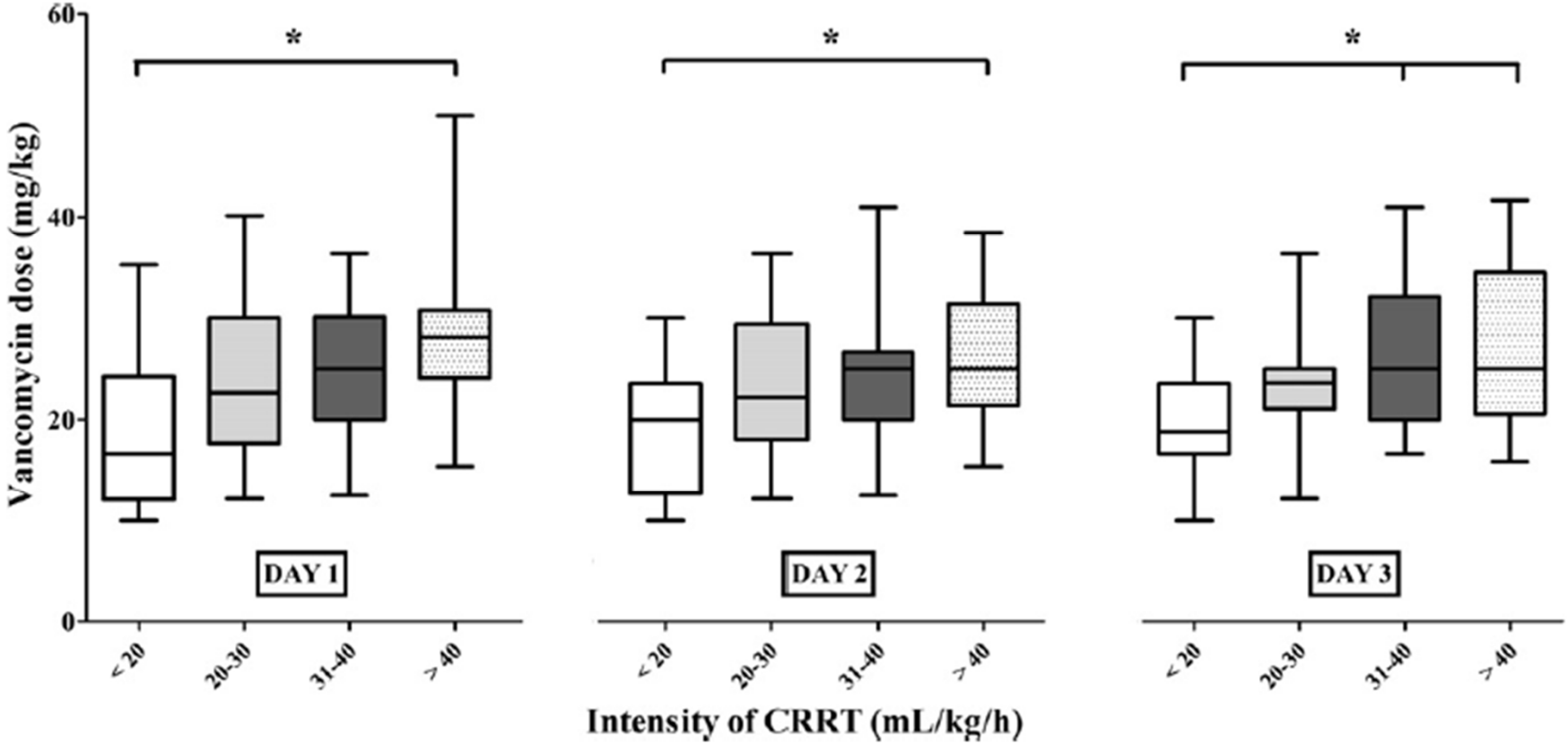
51% of patients had adequate serum concentrations at day1

CRRT



Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy

Cecilia Covajes[a], Sabino Scolletta[a], Laura Penaccini[a], Eva Ocampos-Martinez[a], Ali Abdelhadii[a], Marjorie Beumier[a], Frédérique Jacobs[b], Daniel de Backer[a], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]



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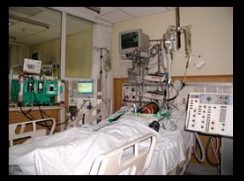
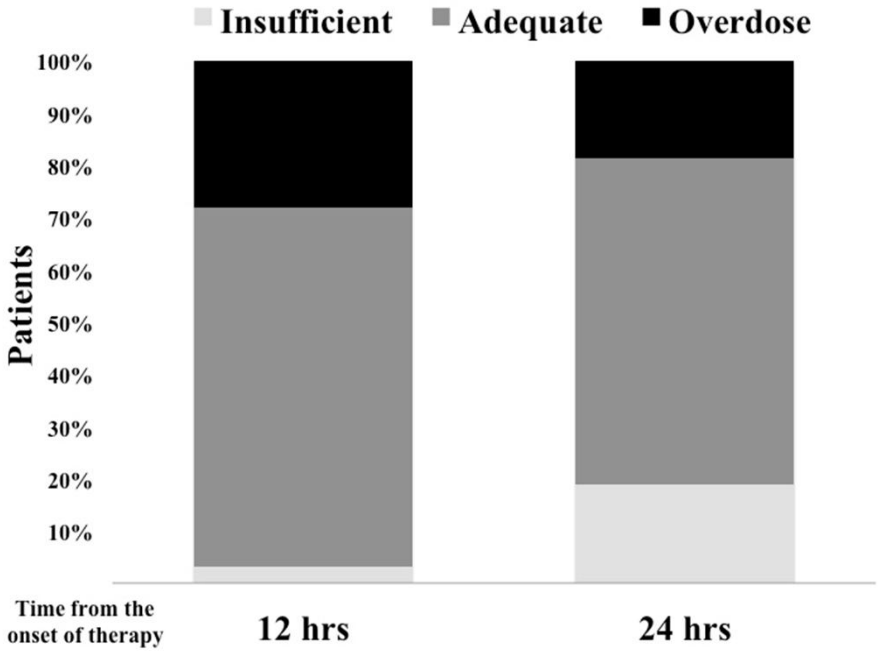
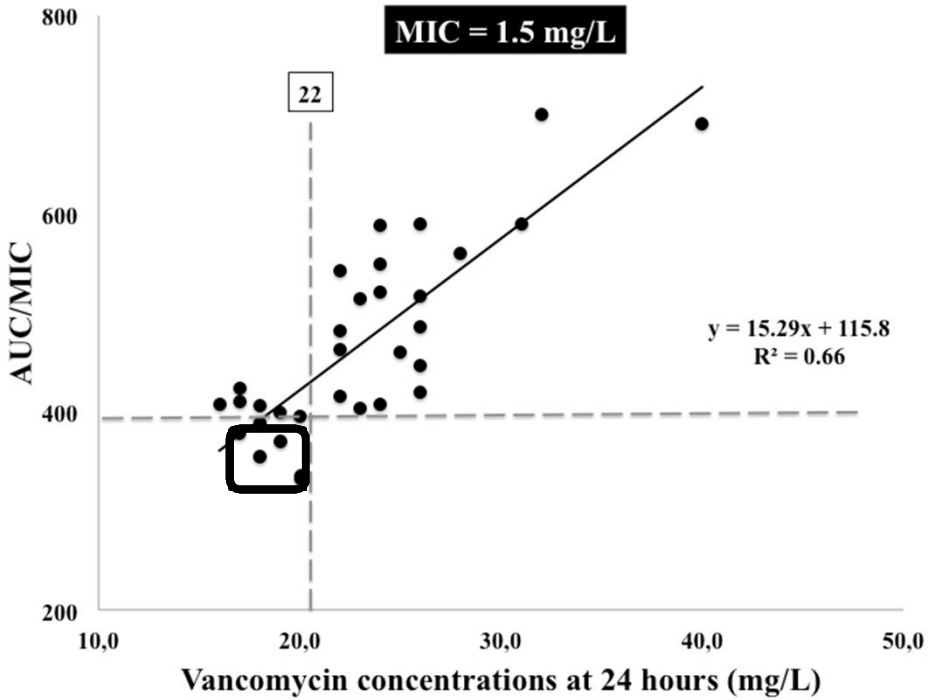


A new regimen for continuous infusion of vancomycin during continuous renal replacement therapy

Marjorie Beumier[1], Jason A. Roberts[2], Hakim Kabtouri[3], Maya Hites[3], Frederic Cotton[4], Fleur Wolff[4], Jeffrey Lipman[2], Frédérique Jacobs[3], Jean-Louis Vincent[1] and Fabio Silvio Taccone[1]*

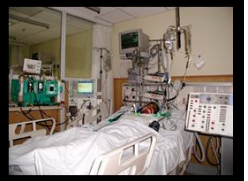
J Antimicrob Chemother 2013; **68**: 2859–2865





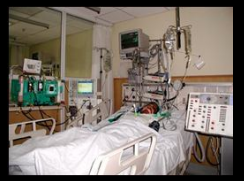
35 mg/kg LD + 14 mg/kg daily

Conclusions



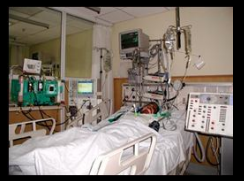
- **Vancomycin**
  - **Remains one of the first options to treat GP infections**
  - **Increasing MICs**
  - **Insufficient drug concentrations with standard regimens**
  - **CI > II ... but not better clinical response**

Conclusions



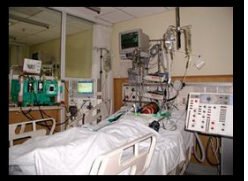
- **Nephrotoxicity**
  - **20-25%**
  - **Associated with concentrations in the early phase: chicken/egg?**
  - **Association with other nephrotoxics**
- **Drug regimen adjustment in other conditions**
  - **CRRT**
  - **Obese patients**
  - **ECMO**

Vancomycin: Alternatives



- **Linezolid**
- **Telavancine**
- **Daptomycine**
- **Tygecycline**
- **Ceftaroline**
- **Ceftobiprole**

Vancomycin: Alternatives



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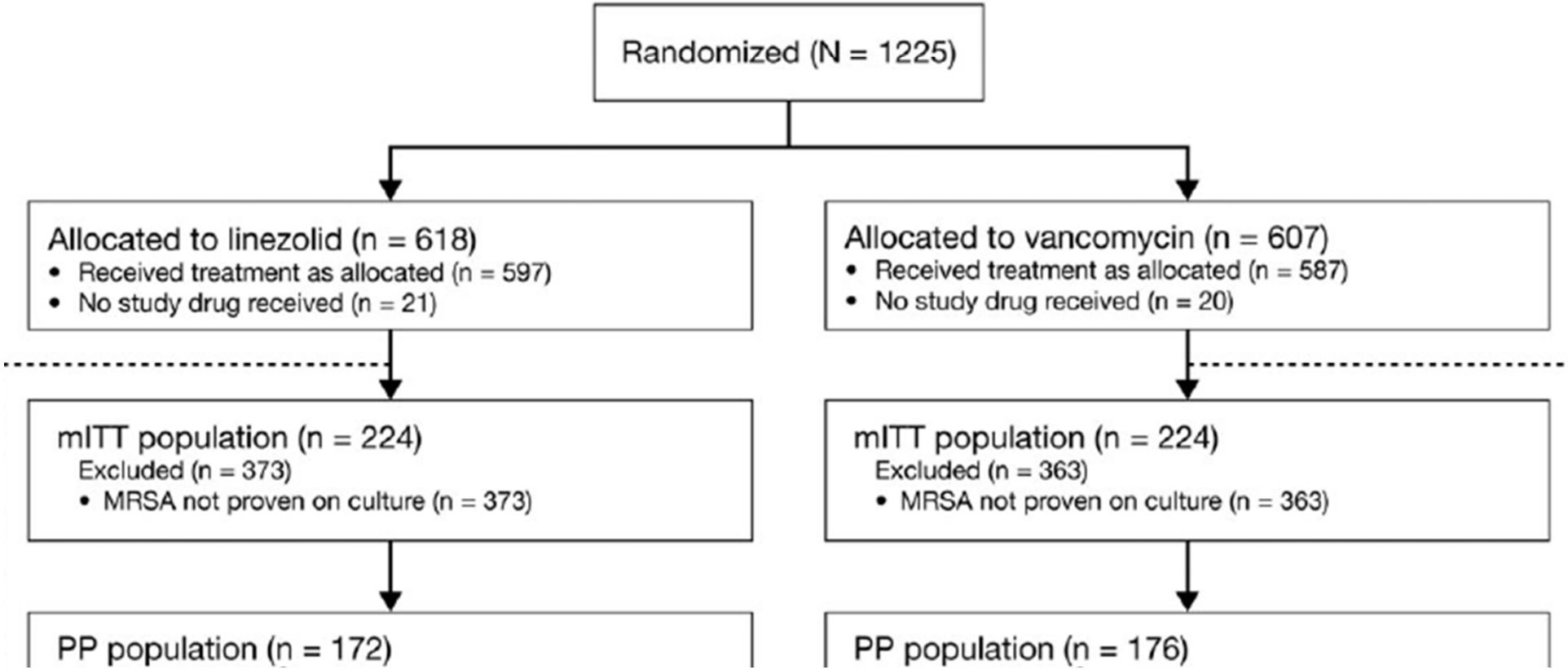
Clinical Infectious Diseases 2012;54(5):621–9



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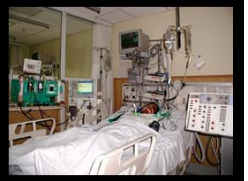

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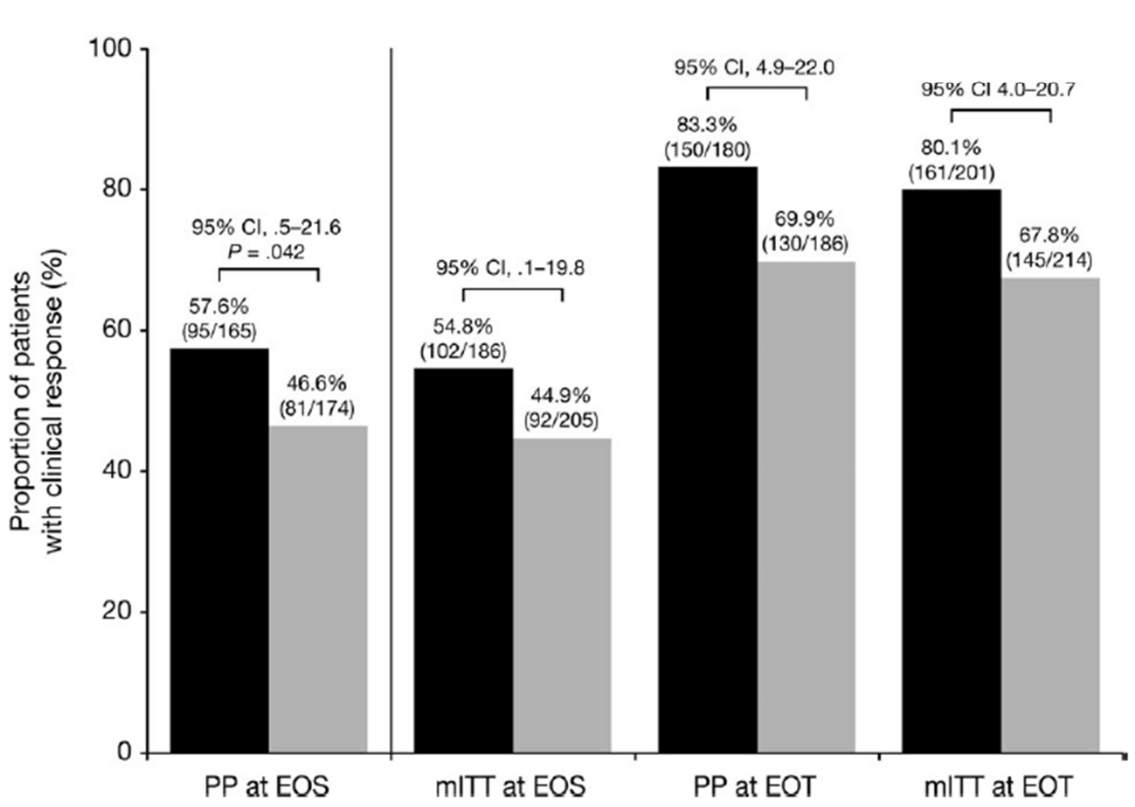

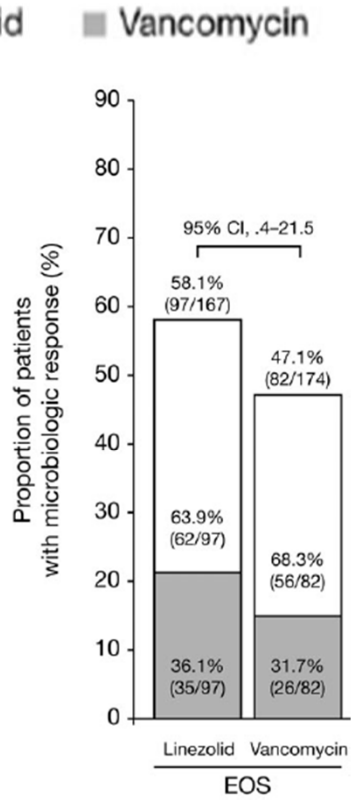

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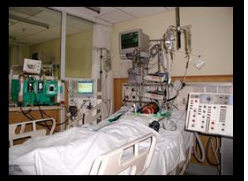

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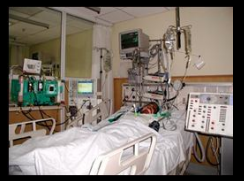
Vancomycin trough levels (day 3)			
0–7.9 μg/mL	…	17/35 (48.6)	
8–12.3 μg/mL	…	17/37 (46.0)	
12.4–17.4 μg/mL	…	15/33 (45.5)	
>17.4 μg/mL	…	15/33 (45.5)	
Vancomycin MIC			
<1 μg/mL	10/16 (62.5)	7/14 (50.0)	−22.8 to 47.8
1 μg/mL	77/122 (61.5)	64/134 (47.8)	1.6 to 25.8
≥2 μg/mL	3/8 (37.5)	7/13 (53.8)	−59.5 to 26.8

Vancomycin: Alternatives



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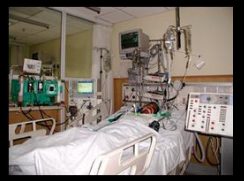
Adverse Event	Linezolid Arm, No. (%)(n = 597)	Vancomycin Arm, No. (%)(n = 587)
Anemia	30 (5.2)	42 (7.2)
Renal failure/ impairment/azotemia[a]	22 (3.7)	43 (7.3)
Cardiac arrest	11 (1.8)	13 (2.2)
Thrombocytopenia	8 (1.3)	13 (2.2)
Pancreatitis	5 (0.8)	1 (0.2)
Polyneuropathy	…	1 (0.2)
Pancytopenia/ neutropenia	4 (0.6)	2 (0.4)
Paresthesia	…	1 (0.2)

Vancomycin: Alternatives



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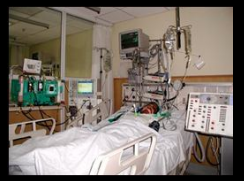
Vancomycin serum trough levels, median (interquartile range) µg/mL		
Day 3 (n = 140)	…	12.3 (9.45)
Day 6 (n = 90)	…	14.7 (10.40)
Day 9 (n = 33)	…	16.1 (11.30)

Glomerular filtration rate	■ Linezolid	■ Vancomycin	
<50 mL/min	12/28 (42.9)	15/35 (42.9)	−24.6 to 24.6
≥50 mL/min	82/134 (61.2)	64/133 (48.1)	1.2 to 24.9

Vancomycin: Alternatives



Linezolid versus vancomycin for meticillin-resistant *Staphylococcus aureus* infection: a meta-analysis of randomised controlled trials

Mao Mao An[a], Hui Shen[a], Jun Dong Zhang[a], Guo Tong Xu[a,**], Yuan Ying Jiang[a,b,*]

International Journal of Antimicrobial Agents 41 (2013) 426–433

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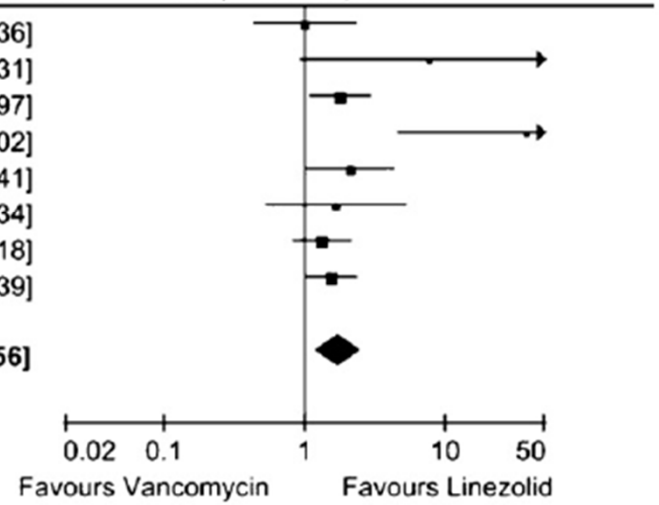
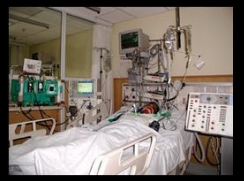
Study	linezolid Events	Total	Vancomycin Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Stevens [16]	41	56	38	52	11.7%	1.01 [0.43, 2.36]
Weigelt[15]	52	53	47	54	2.7%	7.74 [0.92, 65.31]
Weigelt [13]	436	462	394	436	19.5%	1.79 [1.08, 2.97]
Sharpe[14]	29	30	13	30	2.8%	37.92 [4.55, 316.02]
Kohno[12]	45	93	15	49	14.0%	2.13 [1.02, 4.41]
Wilcox[10]	39	45	31	39	7.7%	1.68 [0.53, 5.34]
Itani[9]	191	227	167	209	19.9%	1.33 [0.82, 2.18]
Wunderink [8]	95	165	81	174	21.7%	1.56 [1.01, 2.39]
Total (95% CI)		**1131**		**1043**	**100.0%**	**1.77 [1.22, 2.56]**
Total events	928		786			

Heterogeneity: Tau² = 0.12; Chi² = 13.29, df = 7 (P = 0.07); I² = 47%

Test for overall effect: Z = 3.02 (P = 0.003)



Vancomycin: Alternatives



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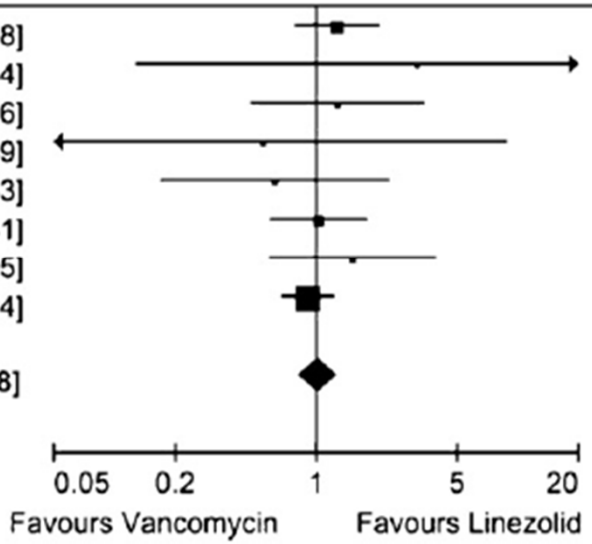
C

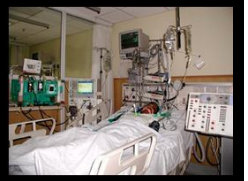
Stevens [16]	44	240	33	220	19.8%	1.27 [0.78, 2.08]
Weigelt[15]	1	66	0	69	0.5%	3.18 [0.13, 79.54]
Weigelt [13]	9	592	7	588	4.9%	1.28 [0.47, 3.46]
Kohno[12]	1	100	1	55	0.6%	0.55 [0.03, 8.89]
Wunderink [11]	4	74	6	72	2.8%	0.63 [0.17, 2.33]
Wilcox[10]	28	269	26	257	15.2%	1.03 [0.59, 1.81]
Itani[9]	11	537	7	515	5.3%	1.52 [0.58, 3.95]
Wunderink [8]	94	597	100	587	50.9%	0.91 [0.67, 1.24]
Total (95% CI)		**2475**		**2363**	**100.0%**	**1.03 [0.82, 1.28]**
Total events	192		180			

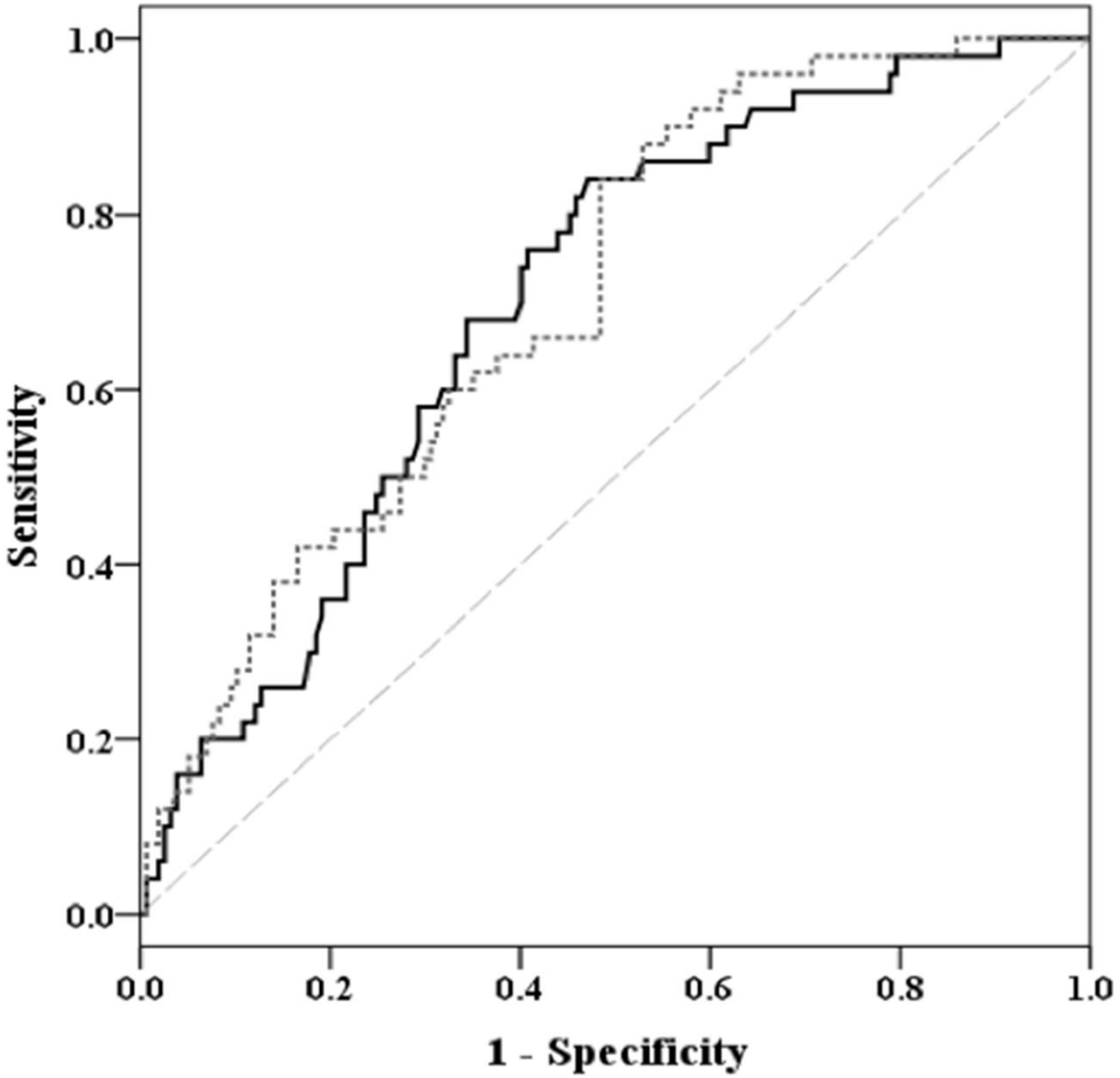
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 7 (P = 0.85); I² = 0%

Test for overall effect: Z = 0.24 (P = 0.81)



Toxicity of CI Vanco





AUC = 0.70 (C_{mean})
AUC = 0.71 (C_{mean} + Duration)

Cianferoni, Infection 2013

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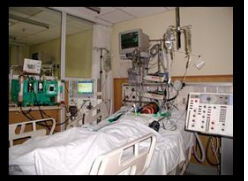
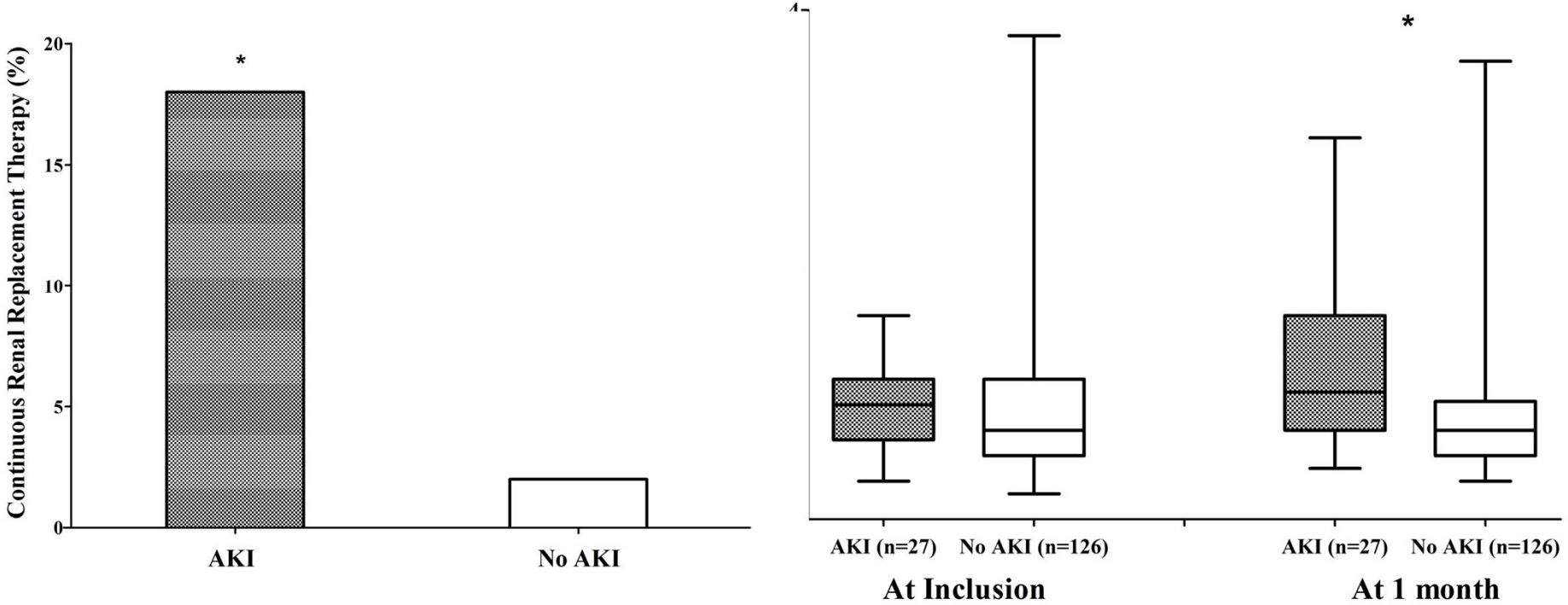
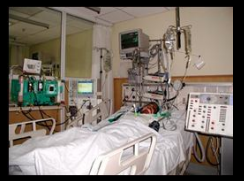




Cianferoni, Infection 2013

Conclusions



- **Vancomycin**
  - Remains one of the first options to treat GP infections
  - Increasing MICs
  - Insufficient drug concentrations with standard regimens
  - CI > II ... but not better clinical response
- **Alternative to Vancomycin**
  - Linezolid
  - Better clinical response but ... mortality ??
  - Costs