Linezolid or Vancomycin in the Treatment of MRSA Pneumonia: Still Existing Dilemmas?

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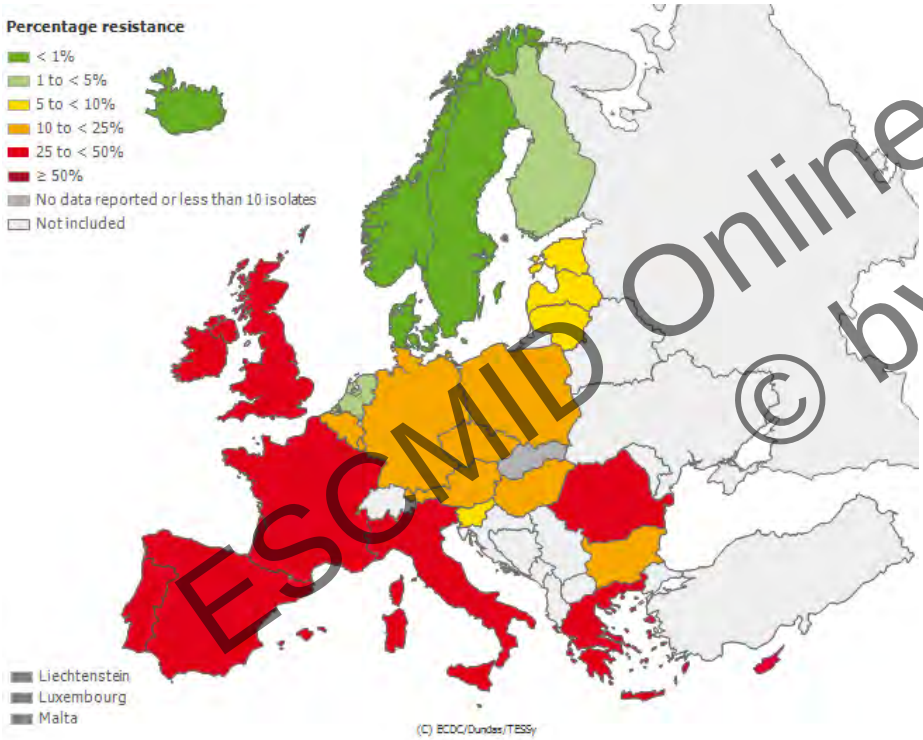
www.reamedpitie.com

Conflicts of interest

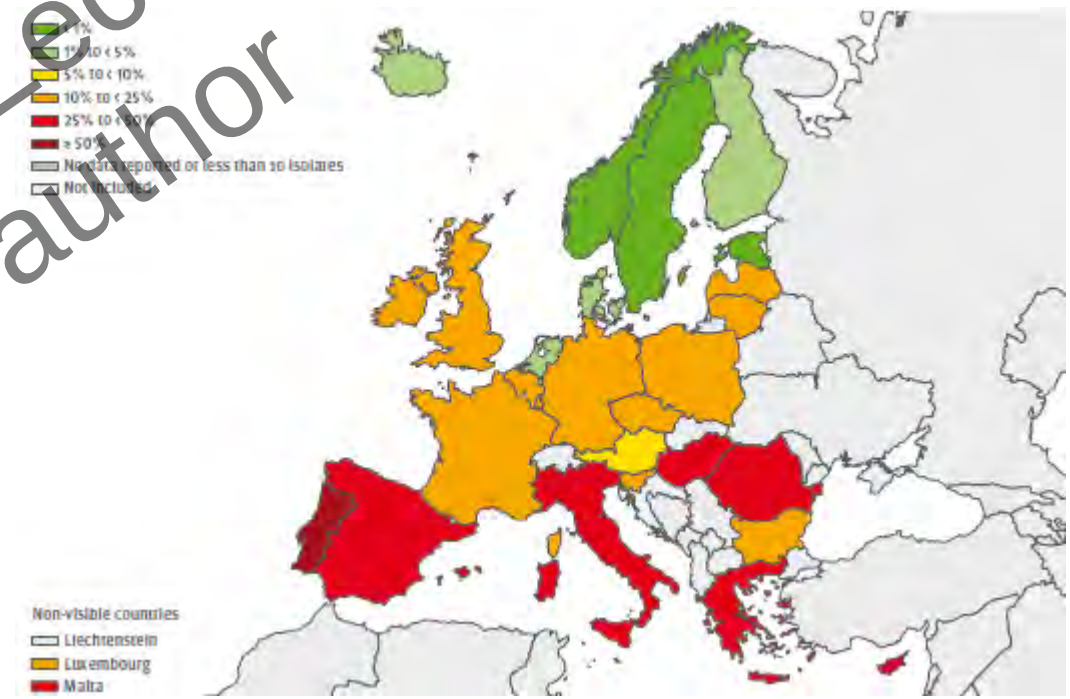
- Consulting or lecture fees:
  - Pfizer, Nektar-Bayer, Brahms, Cubist, sanofi-aventis, Janssen-Cilag, Ranbaxy, Astellas, Trius

The proportion of MRSA isolates remains above 25% in 1/3 European countries[a]

EARS-Net, 2007



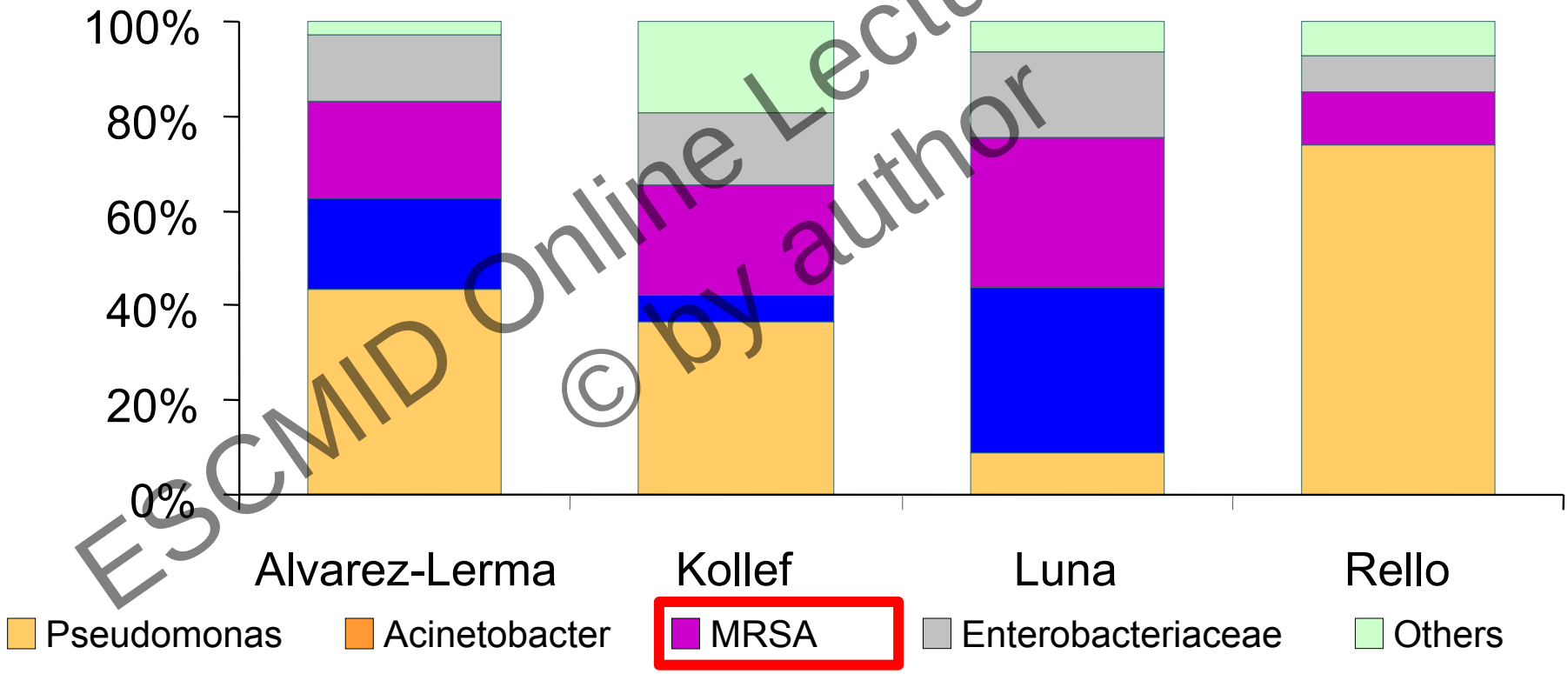
EARS-Net, 2010



[a]Despite decreasing proportions of MRSA in Austria, Cyprus, Estonia, France, Ireland, Latvia and the UK
EARS-Net, European Antimicrobial Resistance Surveillance Network

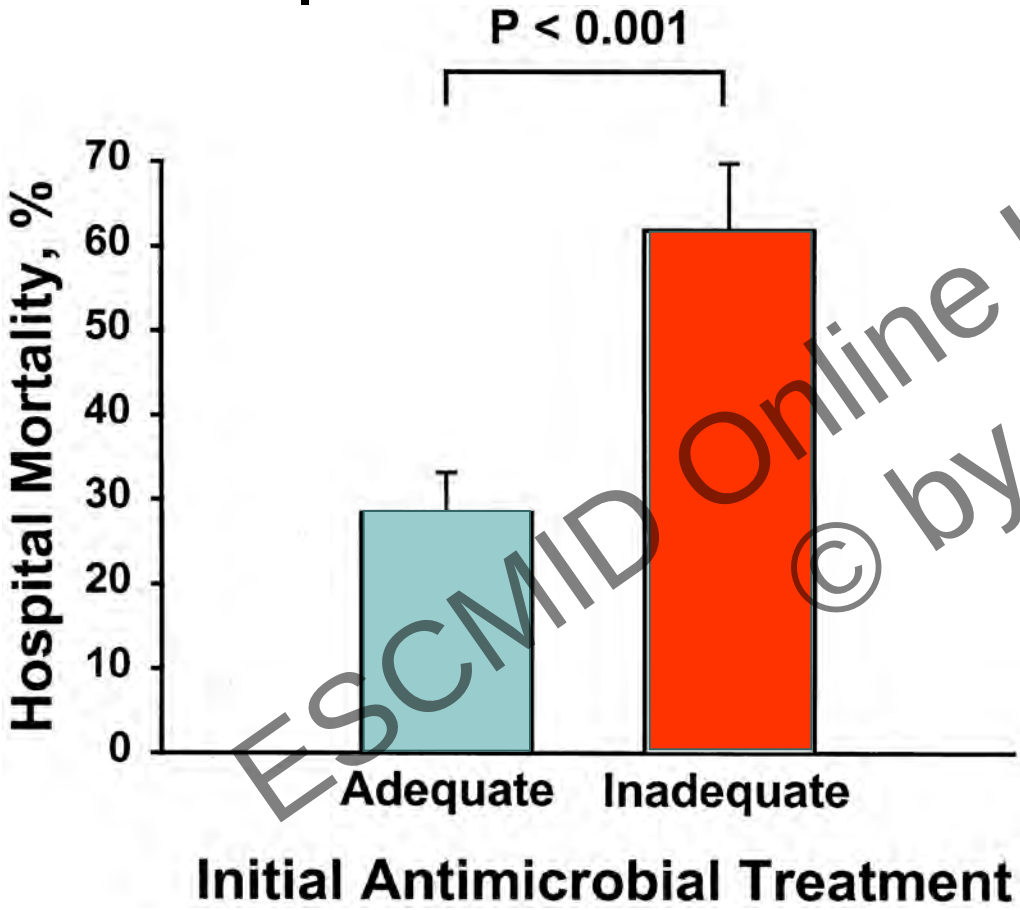
http://ecdc.europa.eu/en/publications/Publications/1111_SUR_AMR_data.pdf.pdf

Pathogens Associated with Inappropriate Initial Therapy in Patients with VAP



Alvarez-Lerma. Intensive Care Med 1996;22:387-394;
Kollef, Ward. Chest 1998;113:412-420;
Luna et al. Chest 1997;111:676-685;
Rello et al. Am J Respir Crit Care Med 1997;156:196-200

Delay in appropriate antibiotic treatment and mortality



	MSSA	MRSA
Pneumonia		
Noso	12%	60%
Commu	12%	42%
Bloodstream		
Noso	0	73%
Commu	13%	50%

% patients with delayed treatment

Kollef MH, et al. Chest. 1999 Feb;115:462-74
Ibrahim EH, et al. Chest. 2000 Jul;118:146-55

MSSA, methicillin-sensitive *S. aureus*

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of MRSA Infections

- For **HA-MRSA or CA-MRSA pneumonia, IV vancomycin** (**A-II**) **or linezolid** 600 mg PO/IV twice daily (**A-II**) **or clindamycin** 600 mg PO/IV three times daily (**B-III**) if the strain is susceptible **is recommended** for 7-21 days, depending on the extent of the infection

Liu C, et al. CID 2011;52(3):e18-e55

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of MRSA Infections

Liu C, et al. CID 2011;52(3):e18-e55

- **IV vancomycin 15–20 mg/kg/dose every 8–12 h**, not to exceed 2 g per dose, is recommended in patients with normal renal function (B-III)
- In seriously ill patients, a **loading dose** of 25–30 mg/kg may be considered
- **Trough vancomycin concentrations** are the most accurate method to guide dosing (B-II). Serum trough conc. should be obtained at steady state conditions, prior to the 4th or 5th dose
- For serious infections, **vancomycin trough conc. of 15–20 ug/mL** are recommended (B-II)

Intrinsic Limitations of Vancomycin for Treating MRSA Infections

1. Relatively slow bacterial killing
2. Poor tissue penetration, particularly in the lung
3. Decreased susceptibility to glycopeptides and emergence of strains with intermediate-level vancomycin resistance
4. Potential for toxicity

MRSA, methicillin-resistant *Staphylococcus aureus*;
VAP, ventilator-associated pneumonia

Vancomycin Pulmonary Penetration

Lamer C et al. *Antimicrob Agents Chemother.* 1993.

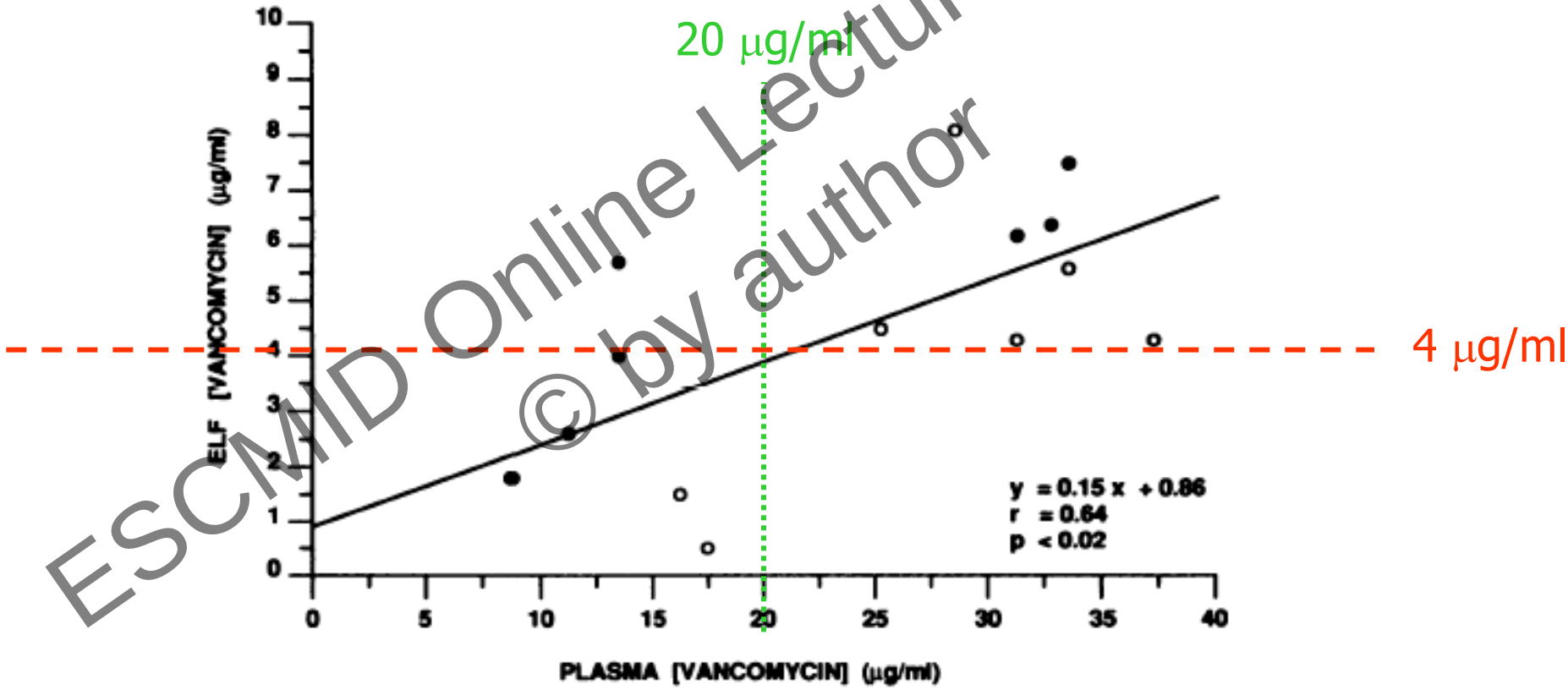
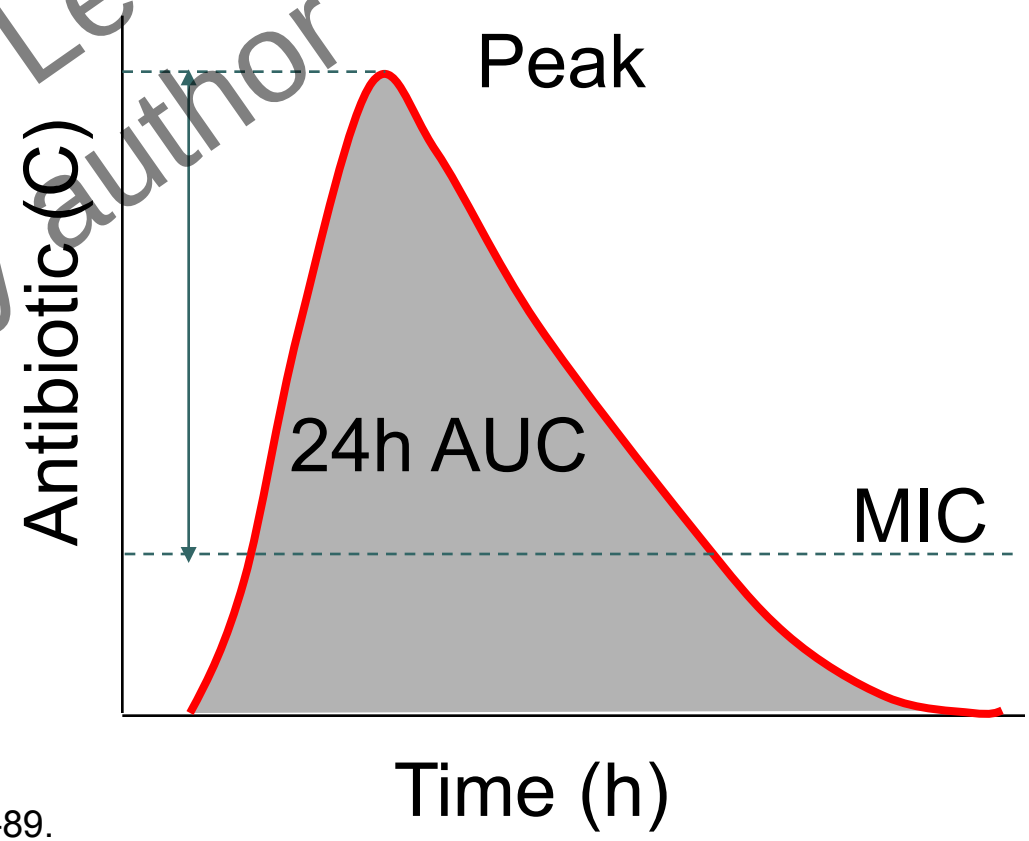


FIG. 1. Relationship between vancomycin concentrations in plasma and ELF. Symbols: ○, patients with albumin level in ELF of <3.4 mg/ml; ●, patients with albumin levels in ELF of ≥3.4 mg/ml.

PK-PD Parameters Required for Optimal Treatment of Patients with Severe MRSA Infection

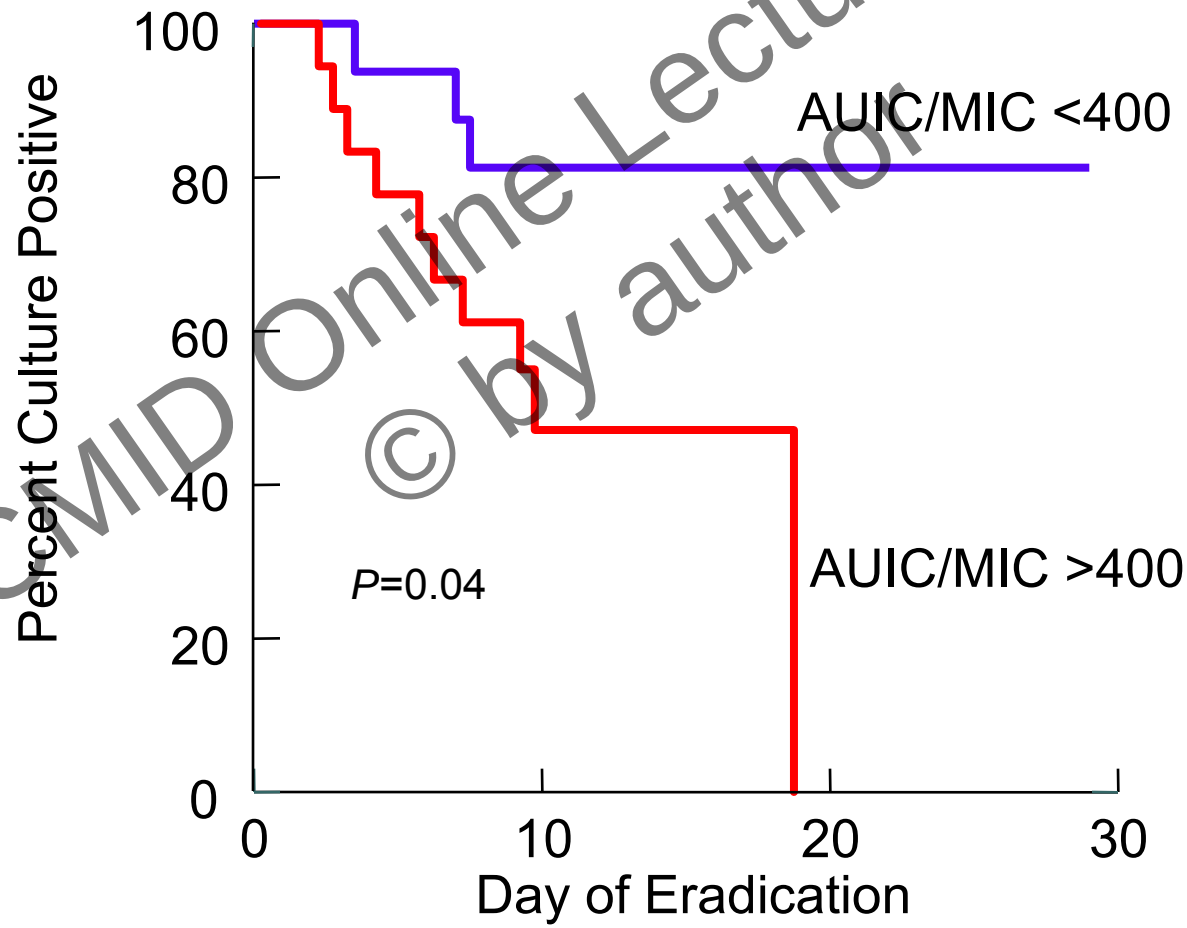
For vancomycin:
the most important PK-PD parameter seems to be the 24h AUC, although this antibiotic demonstrates some concentration independency.



Andes D et al. *Antimicrob Agents Chemother.* 2002;46:3484-89.
Moise PA et al. *Am J Health-Syst Pharm.* 2000;57:S4-S9.

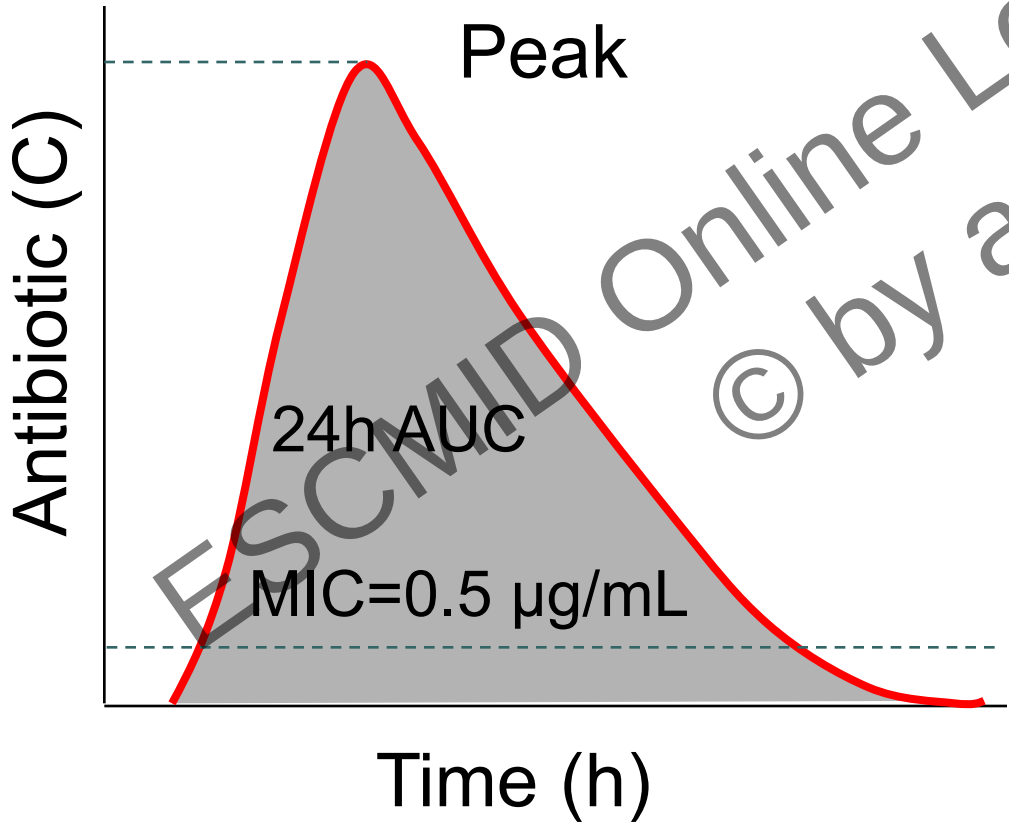
Vancomycin Pharmacodynamics and Days to Eradication for MRSA Infections

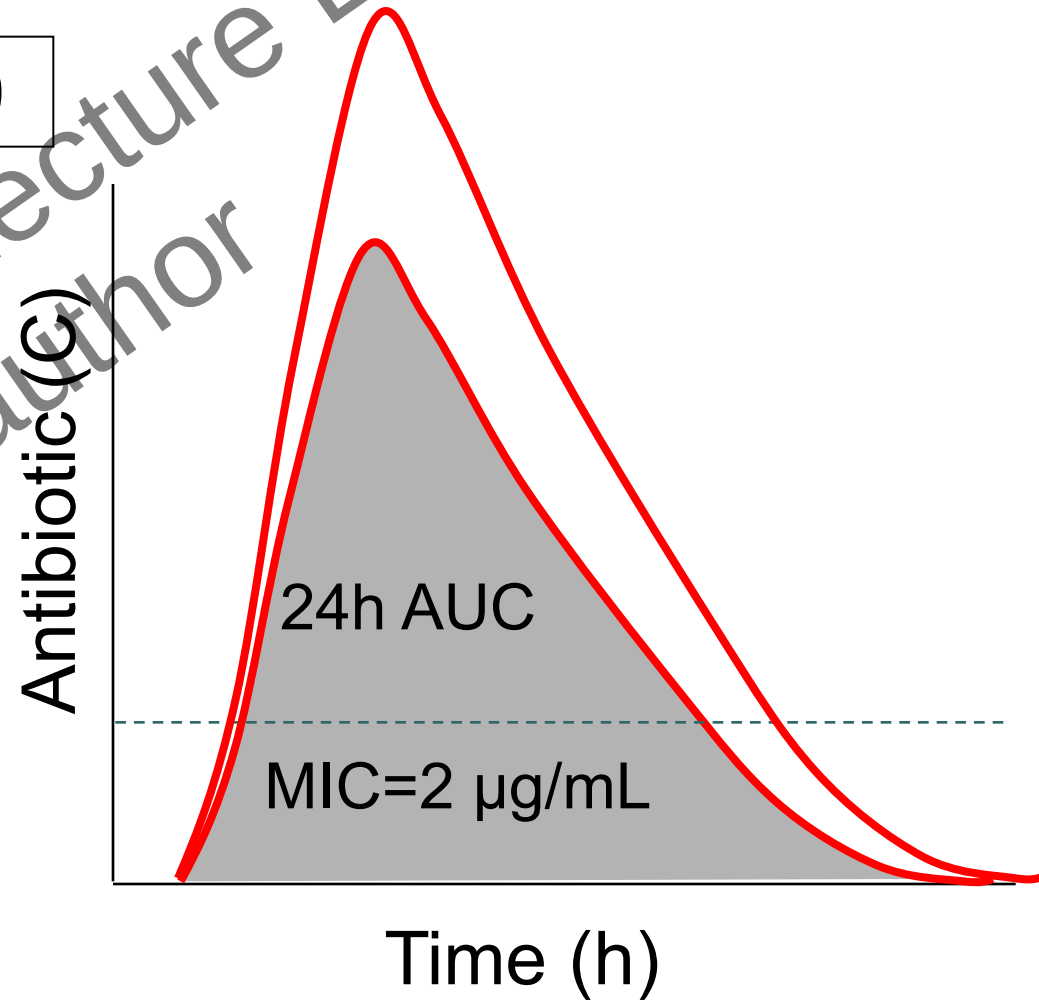
Moise & Schentag. Clinical Pharmacokinetics 2004;43:925-42



Using PK-PD Data to Optimize Vanco. Therapy

Target: AUIC/MIC >400





Drusano GL Clin Infect Dis. 2007 Jul 15;45 Suppl 1:S89-95
McKinnon PS, Davis SL Eur J Clin Microbiol Infect Dis. 2004;23:271-88

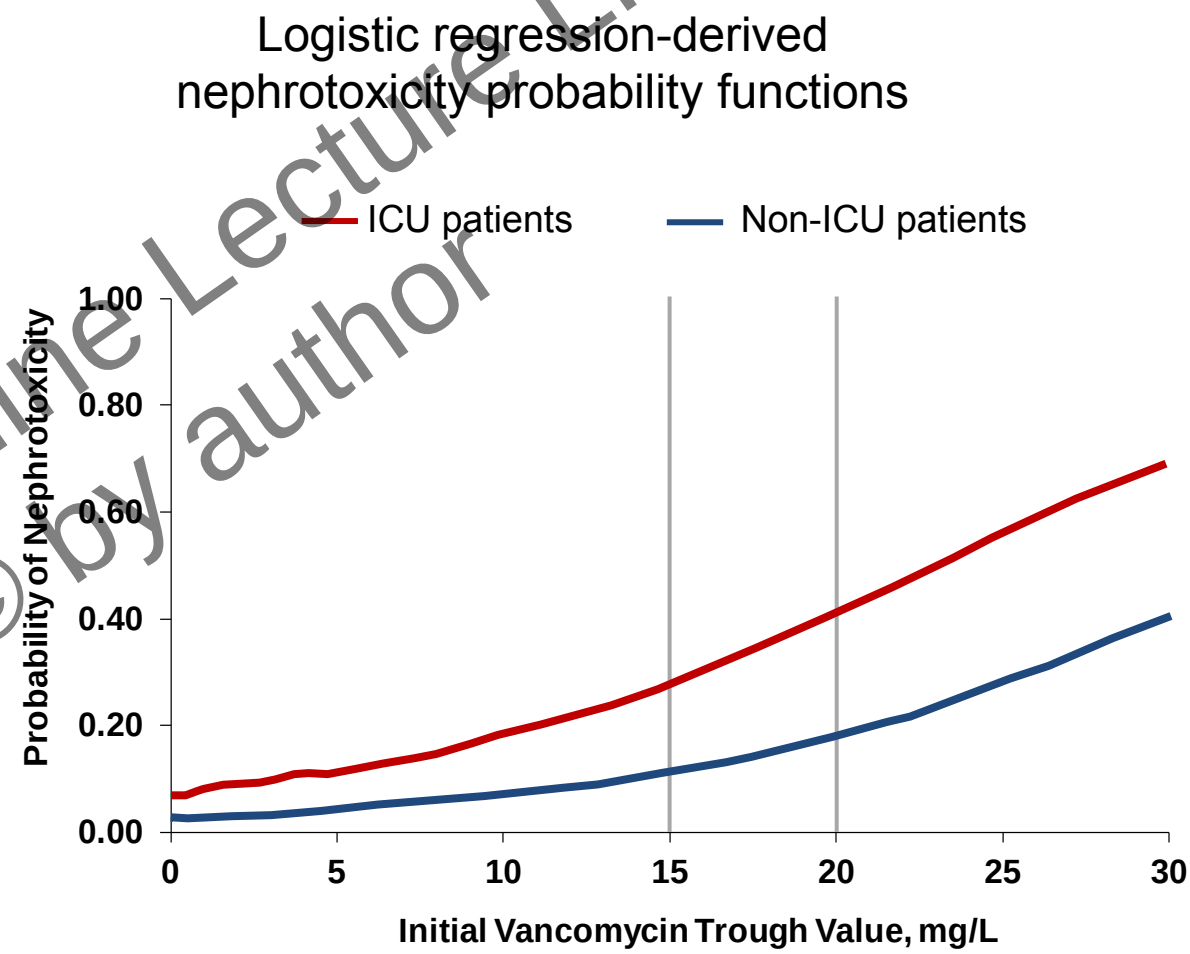
Vancomycin concentration-time profile

Retrospective US study correlating the vancomycin nephrotoxicity with its pharmacokinetics (PK) in 166 patients

Baseline creatinine <2.0 mg/dL

21 patients with nephrotoxicty (50% or 0.5 mg/dL increase in the serum creatinine level from baseline)

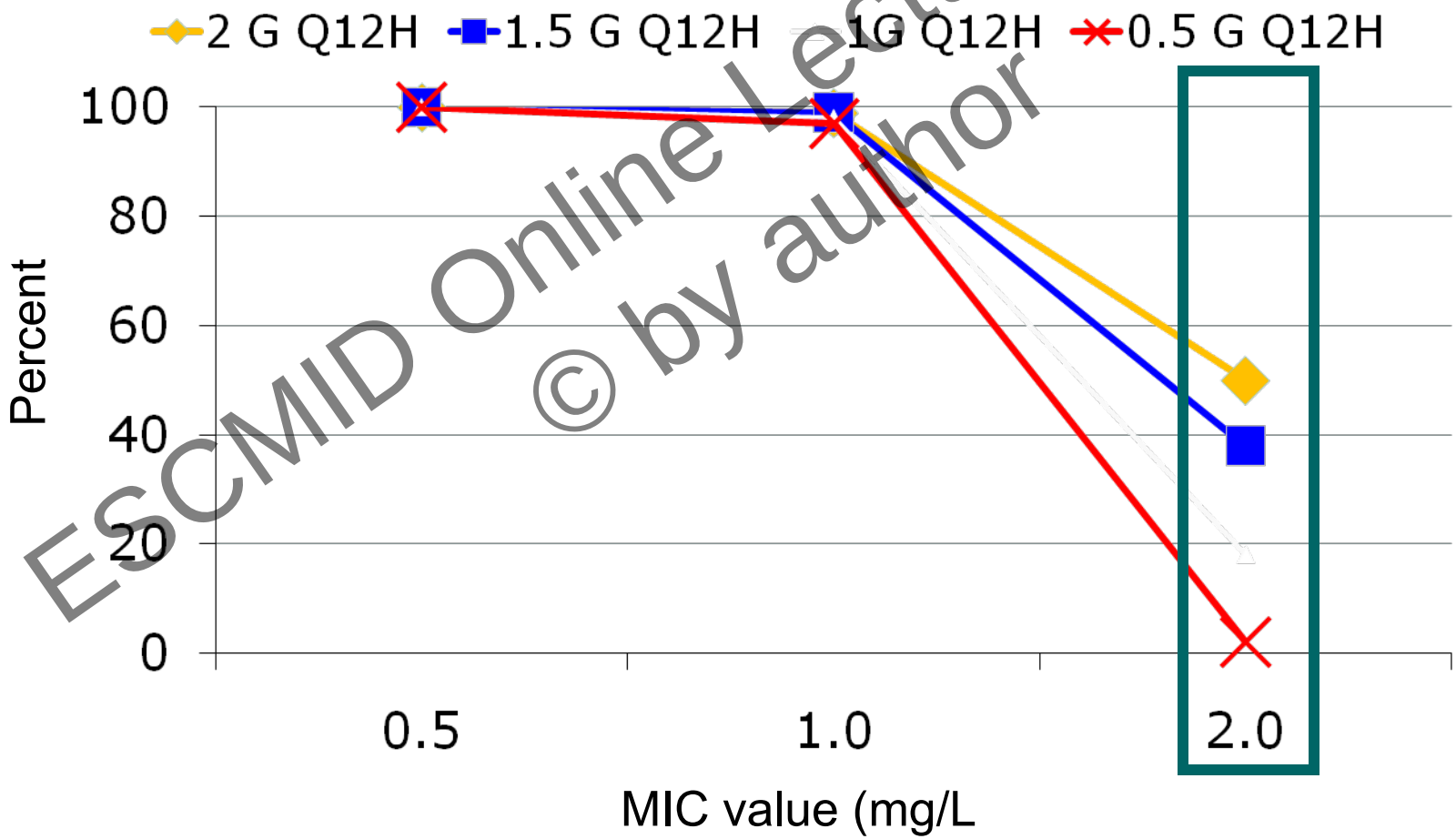
The results indicate that a vancomycin exposure–toxicity response relationship exists. The vancomycin trough value is the pharmacodynamic index that best describes this association



Lodise et al. Clin Infect Dis 2009;49:507-14

Probability of achieving AUC/MIC ≥400 for vancomycin regimens of varying intensity when Cmin were between 15 and 20 mg/L

Patel N, et al. CID 2011;52:969-74



The Clinical Significance of Vancomycin MIC in *S. aureus* Infections: A Systematic Review and Meta-analysis

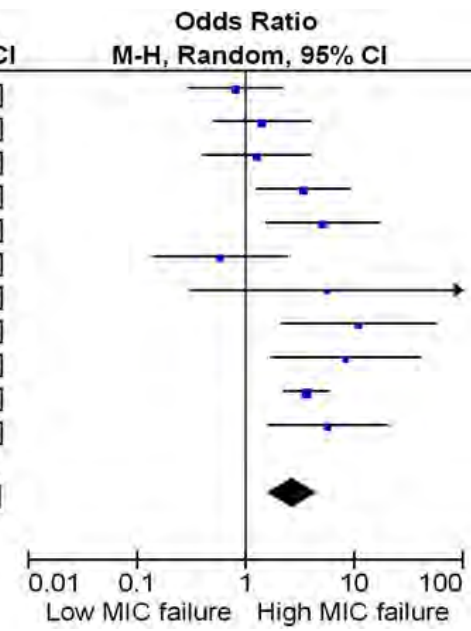
Van Hal S.J. et al. CID 2012;54:755-71

Treatment failure

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	14	37	12	28	10.9%	0.81 [0.30, 2.21]
Choi et al (15)	12	34	10	36	10.8%	1.42 [0.51, 3.91]
Ferry et al (17)	9	24	9	28	9.7%	1.27 [0.40, 3.98]
Hidayat et al (21)	20	51	7	44	11.0%	3.41 [1.27, 9.12]
Hsu et al (25)	17	45	4	38	9.3%	5.16 [1.56, 17.11]
Lalueza et al (32)	3	13	17	50	7.7%	0.58 [0.14, 2.40]
Lodise et al (36)	6	66	0	26	2.7%	5.69 [0.31, 104.78]
Moise et al (41)	11	14	5	20	6.5%	11.00 [2.16, 56.09]
Moise-Broder et al (42)	23	25	22	38	6.8%	8.36 [1.72, 40.68]
Takesue et al (53)	34	97	85	662	15.9%	3.66 [2.28, 5.89]
Yoon et al (58)	14	18	17	45	8.8%	5.76 [1.63, 20.41]
Total (95% CI)		**424**		**1015**	**100.0%**	**2.69 [1.60, 4.51]**
Total events	163		188			

Heterogeneity: Tau² = 0.38; Chi² = 22.59, df = 10 (P = 0.01); I² = 56%

Test for overall effect: Z = 3.75 (P = 0.0002)



The Clinical Significance of Vancomycin MIC in *S. aureus* Infections: A Systematic Review and Meta-analysis

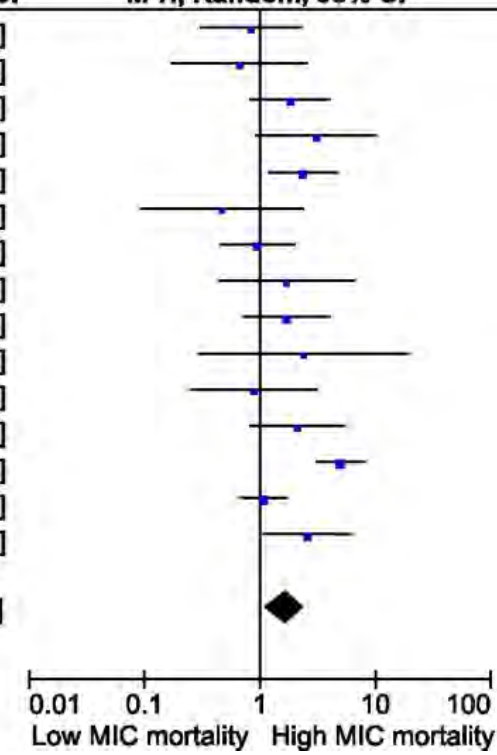
Van Hal S.J. et al. CID 2012;54:755-71

Mortality

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

Test for overall effect: Z = 2.65 (P = .008)



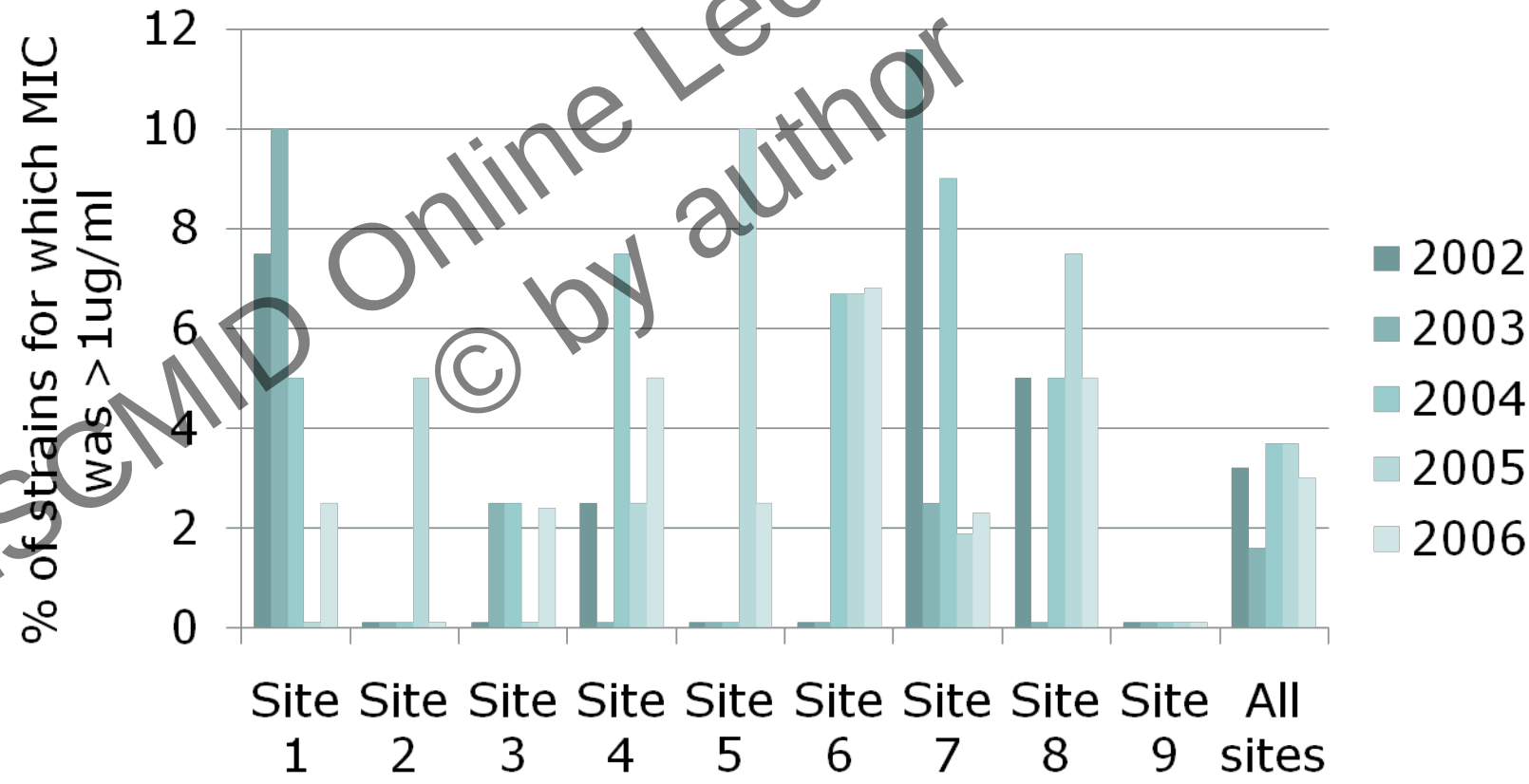
Changes in vancomycin MIC have been observed in the clinical setting

Hawser et al. Int J Antimicrob Agents 2011;37:219-24

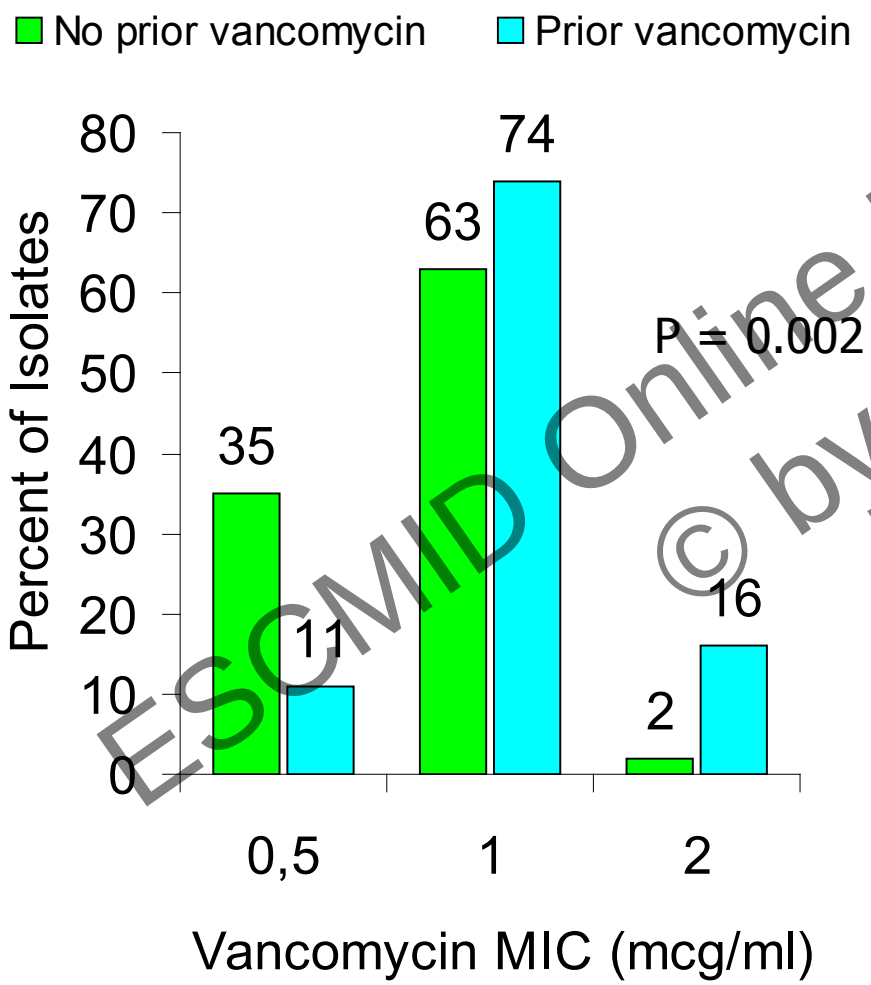
Year	Isolates	Phenotype		
		S. aureus	MRSA	MSSA
2004-2009	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	20,004 797 (4.0)	8249 439 (5.3)	11,755 358 (3.0)
2004	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	2525 101 (4.0)	1158 65 (5.6)	1367 36 (2.6)
2005	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	2930 62 (2.1)	1411 39 (2.8)	1519 23 (1.5)
2006	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	3612 94 (2.6)	1531 50 (3.3)	2081 44 (2.1)
2007	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	4944 160 (3.2)	2028 78 (3.8)	2916 82 (2.8)
2008	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	4348 253 (5.8)	1481 136 (9.2)	2867 117 (4.1)
2009	All (n) Vancomycin MIC ≥2 µg/mL, n (%)	1645 127 (7.7)	640 71 (11.1)	1005 56 (5.6)

Vancomycin Creep against MRSA Collected in 9 US Centers from 2002 to 2006

Sader HS, et al. AAC 2009;53:4127-32



Prior Vancomycin Use Predicts High MICs



Moise et al, JAC 2008;61:85–90

Logistic Regression Analysis of Risk Factors Associated with Vancomycin MIC ≥ 1.5 mcg/ml

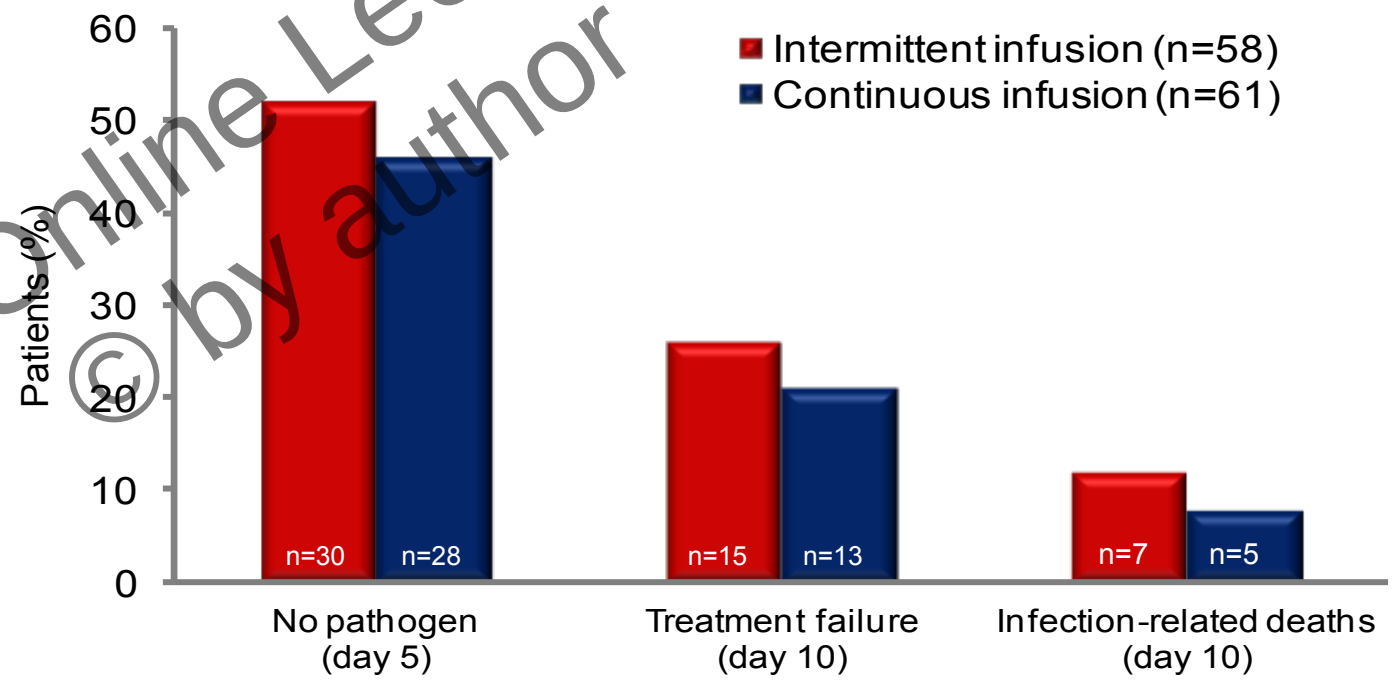
Variable	AOR (95% CI)	P value
Vancomycin last 30 days	9.4 (1.1-80.7)	0.04
ICU-acquired bacteremia	5.3 (1.4-20.4)	0.02

Lodise et al, JAC 2008;62:1138-41

Continuous vs intermittent infusion of vancomycin

Wysocki et al. Antimicrob Agents Chemother 2001;45:2460-7

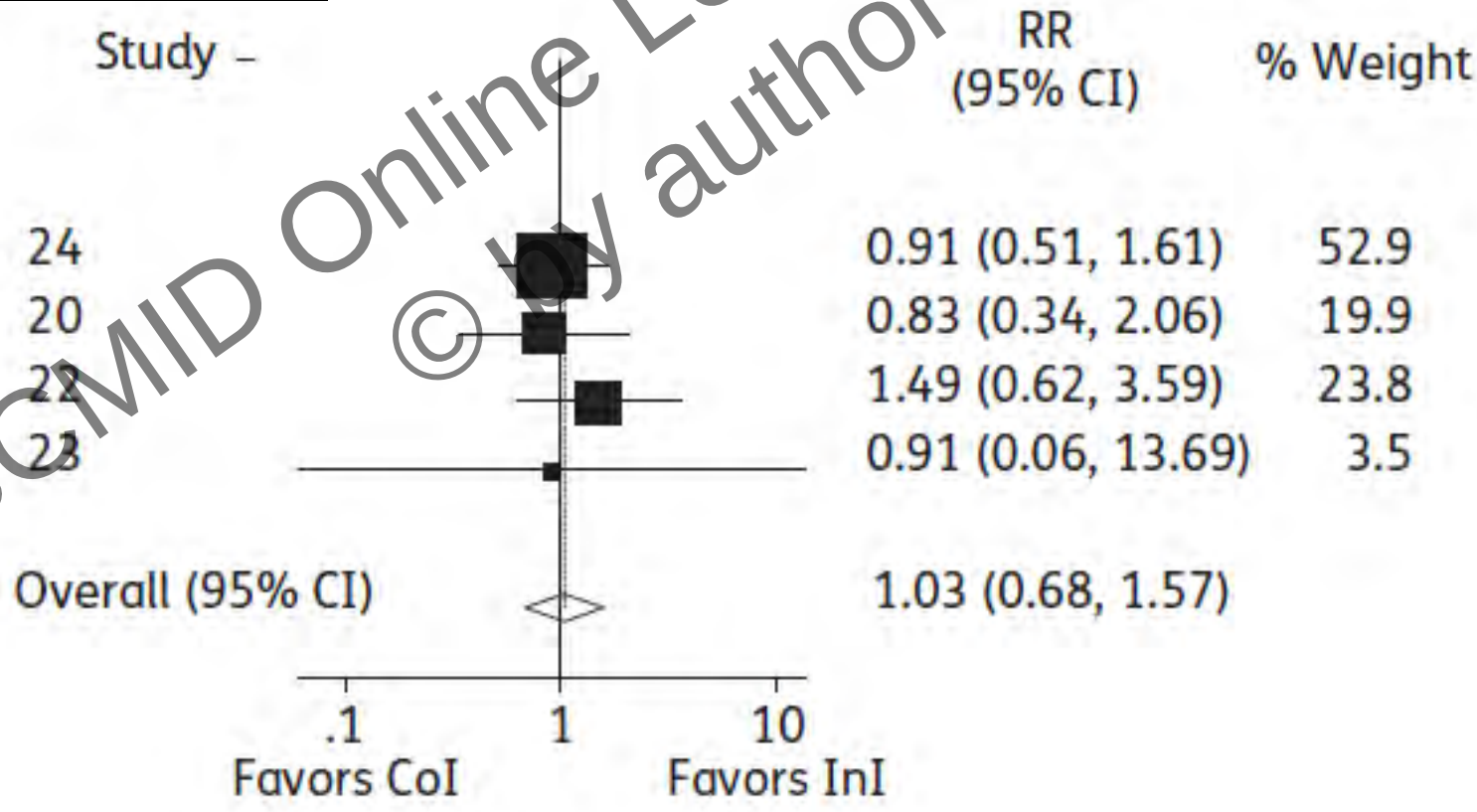
- Prospective randomised study
- Designed to compare continuous vs intermittent vancomycin in 119 critically ill patients with MRSA infections
- Microbiological and clinical outcomes and safety were similar
- No statistically significant difference was found between the two treatment groups



Continuous versus intermittent infusion of vancomycin for treatment of Gram-positive infections: A systematic review

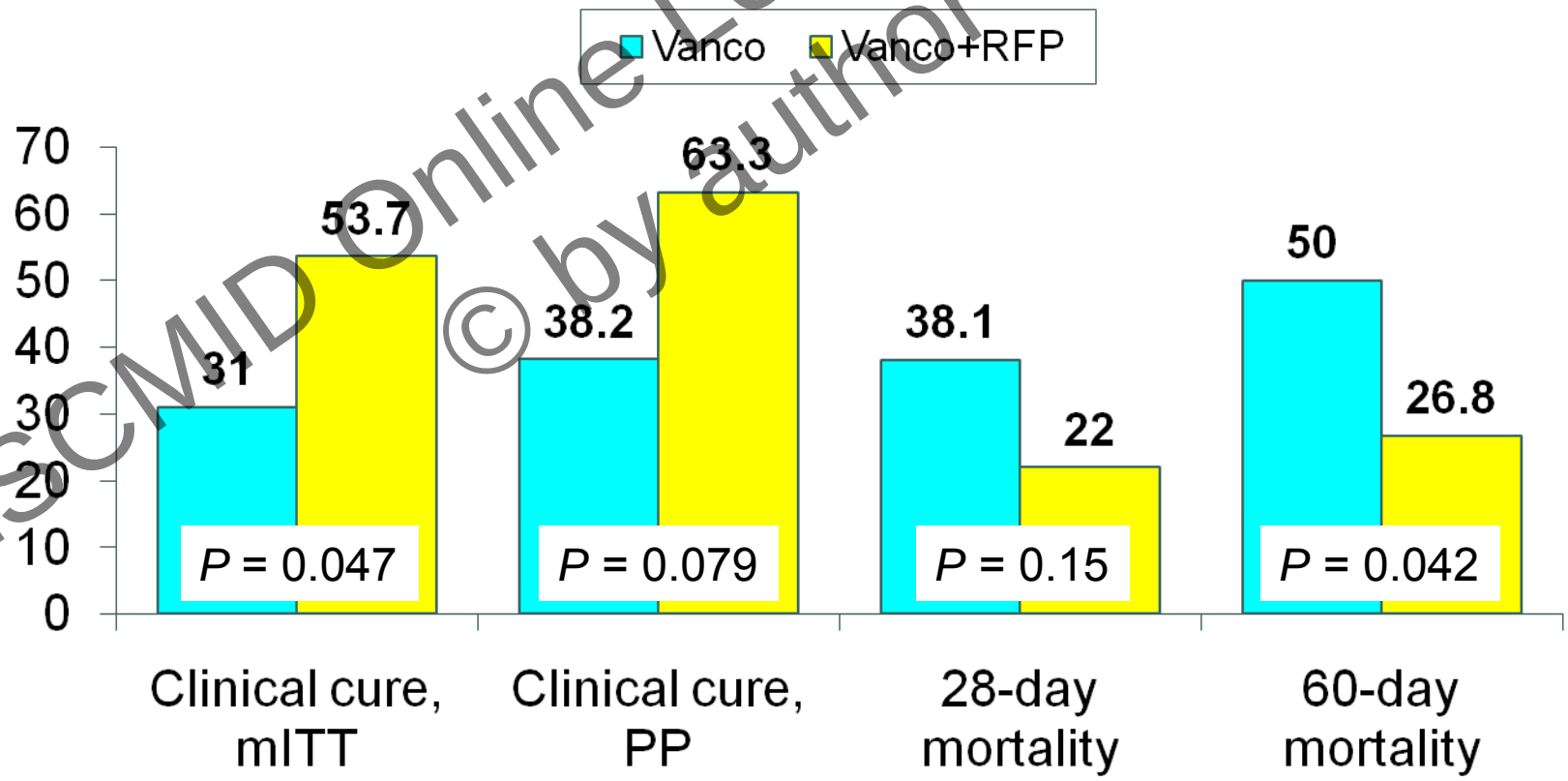
Cataldo A. et al. JAC 2012;67:17–24

Overall mortality



Effect of vancomycin plus rifampicin in the treatment of 83 episodes of nosocomial MRSA pneumonia

Jung YJ et al. Crit Care Med 2010;38:175–80

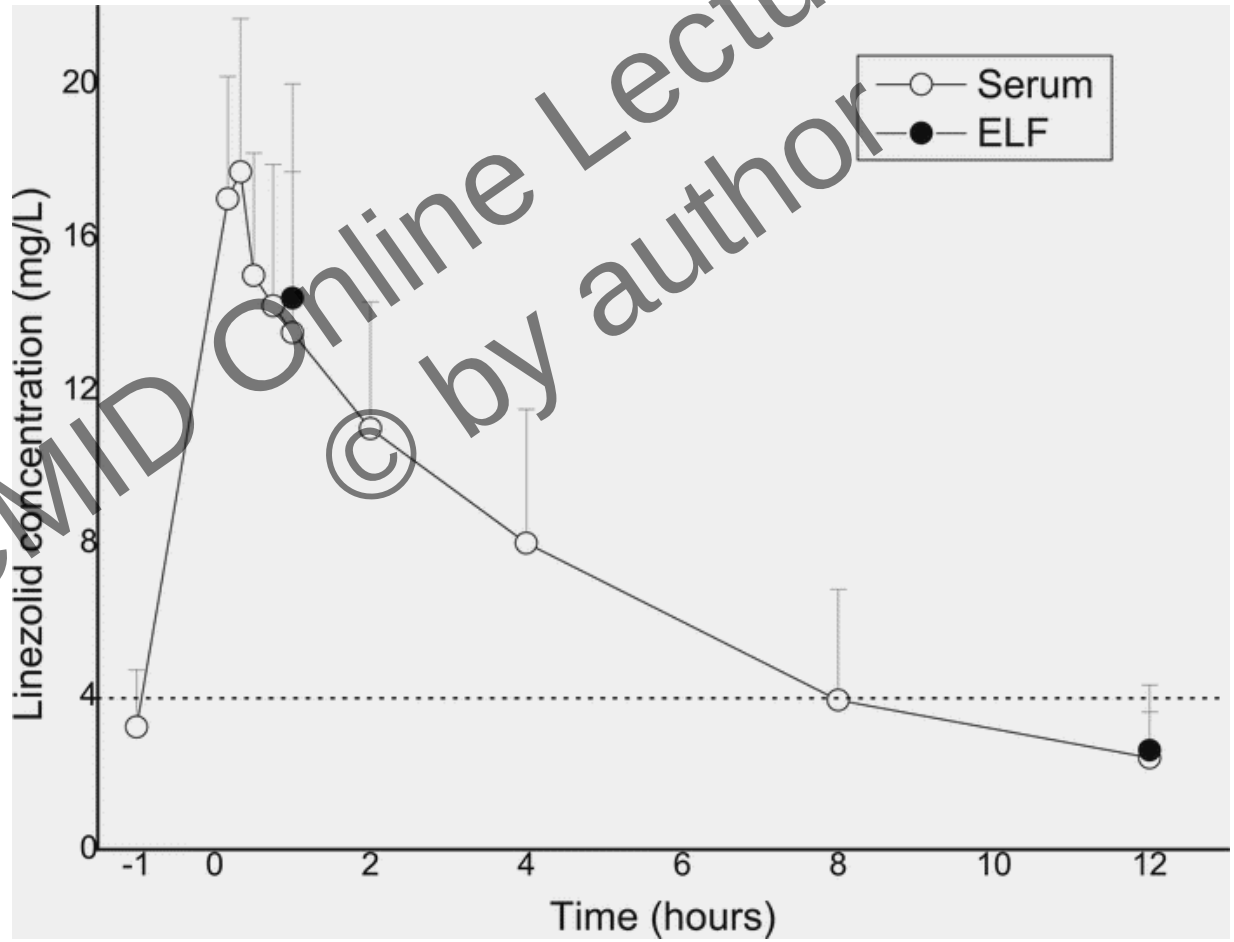


Potential Advantages of Linezolid

1. **Spectrum of activity** covering MRSA and other difficult-to-treat Gram pos. pathogens
2. 100% oral bioavailability
3. **Good tissue penetration**, including into the lung
4. Low propensity for selecting resistant strains
5. May inhibit toxin-mediated effects of bacteria
6. **Proved clinical and microbiological efficacy**
7. **Low toxicity**

Linezolid Penetrates Well and Rapidly into the Lung

Boselli et al. Crit Care Med 2005;33:1529-33

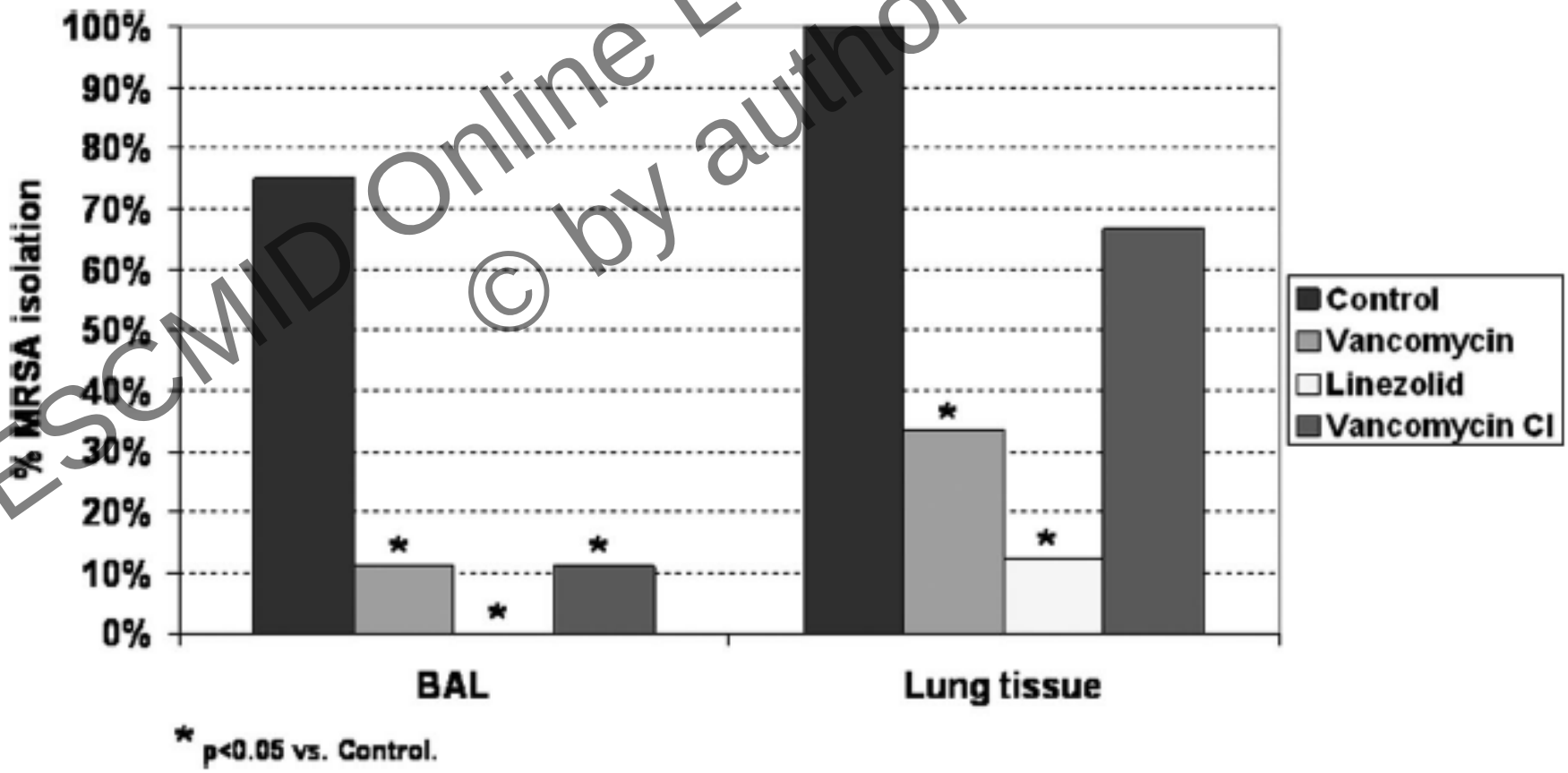


ELF, epithelial lining fluid

Efficacy of linezolid compared to vancomycin in an experimental model of VAP induced by MRSA in ventilated pigs

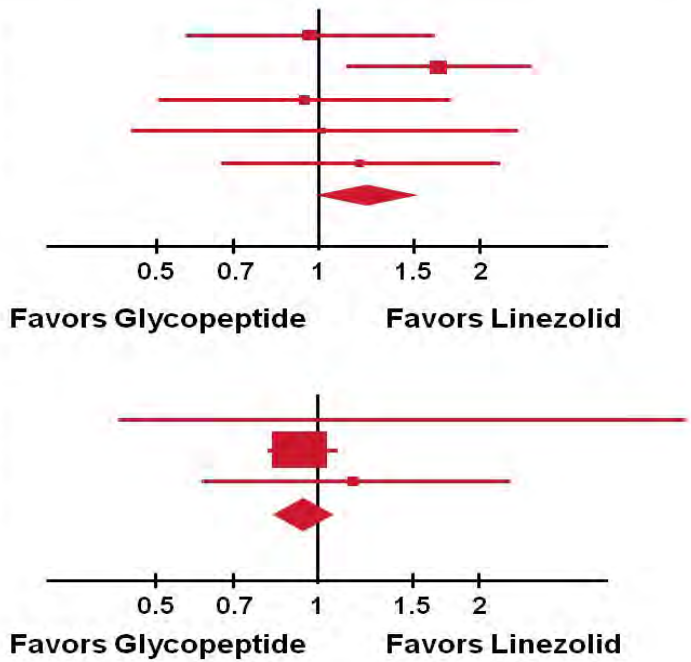
Martinez-Olondris P, et al. Crit Care Med 2011

Microbiological findings



Meta-analysis: Clinical Success in Subjects With or Without Culture-Positive MRSA Pneumonia

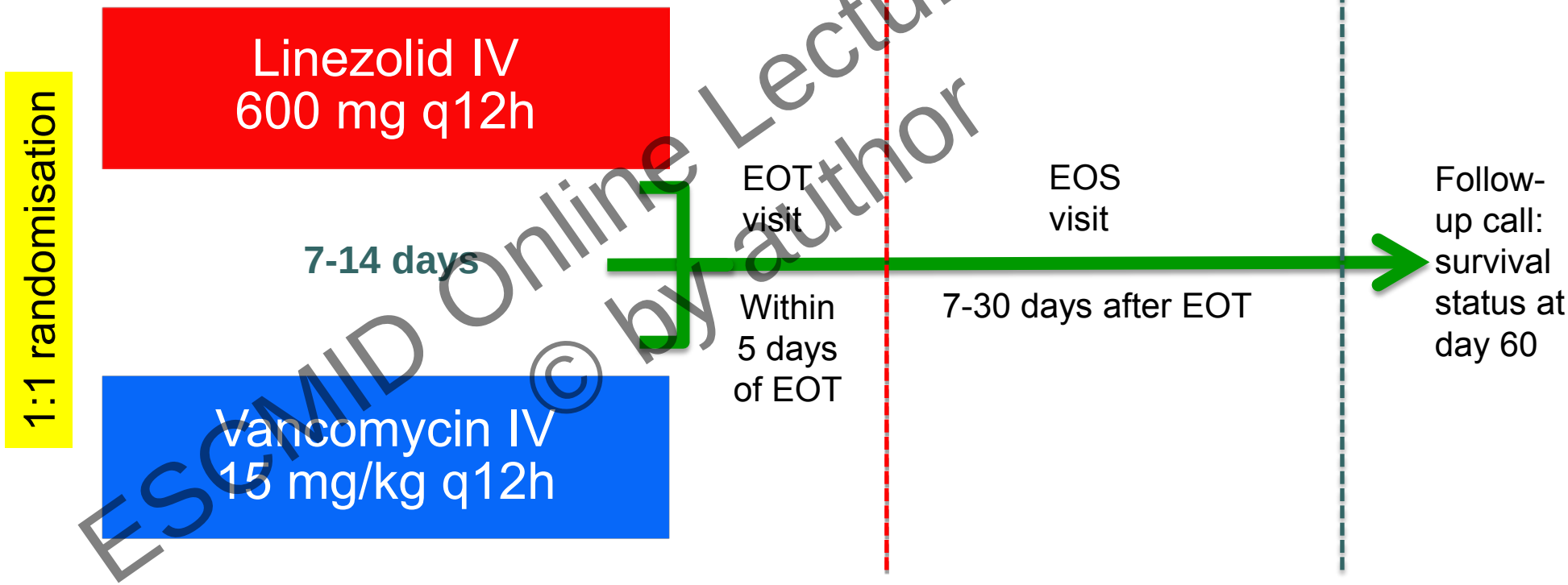
Study or Subgroup	#success/total Linezolid	#success/total Glycopeptide	Risk Ratio (95% CI)
Subjects With Culture-Positive Pneumonia			
Clinical Success, test of cure, MRSA			
Stevens et al 2002	12/23	14/26	0.97 (0.57, 1.64)
Wunderink et al 2003	36/61	22/62	1.66 (1.12, 2.47)
Cepeda et al 2004	9/17	9/16	0.94 (0.50, 1.75)
Kohno et al 2007	11/34	6/19	1.02 (0.45, 2.33)
Wunderink et al 2008	13/23	9/19	1.19 (0.66, 2.16)
Total Clinical Success, MRSA	81/158	60/142	1.23 (0.97, 1.57)
Heterogeneity χ^2 3.95, P=.41, I^2=0%			
Test for overall effect, P=.09			
Subjects Without Culture-Positive Pneumonia			
Clinical Success, test of cure, non-MRSA			
Stevens et al 2002	8/16	2/6	1.50 (0.44, 5.15)
Wunderink et al 2003	185/356	180/325	0.94 (0.82, 1.08)
Cepeda et al 2004	10/17	7/14	1.18 (0.61, 2.27)
Total Clinical Success, non-MRSA	203/389	189/345	0.95 (0.83, 1.09)
Heterogeneity χ^2 2.20, P=.96, I^2=0%			
Test for overall effect, P=.48			



*Includes data from Rubinstein et al 2001.

Walkey AJ et al. *Chest*. 2011;139(5):1148-1155.

Linezolid vs vancomycin in MRSA nosocomial pneumonia: the ZEPHyR trial



- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentrations
- Initial cefepime or other Gram-negative coverage (not MRSA-active) required

EOT, end of treatment; EOS, end of study; IV, intravenous

Wunderink et al. Clin Infect Dis 2012;54:621-629

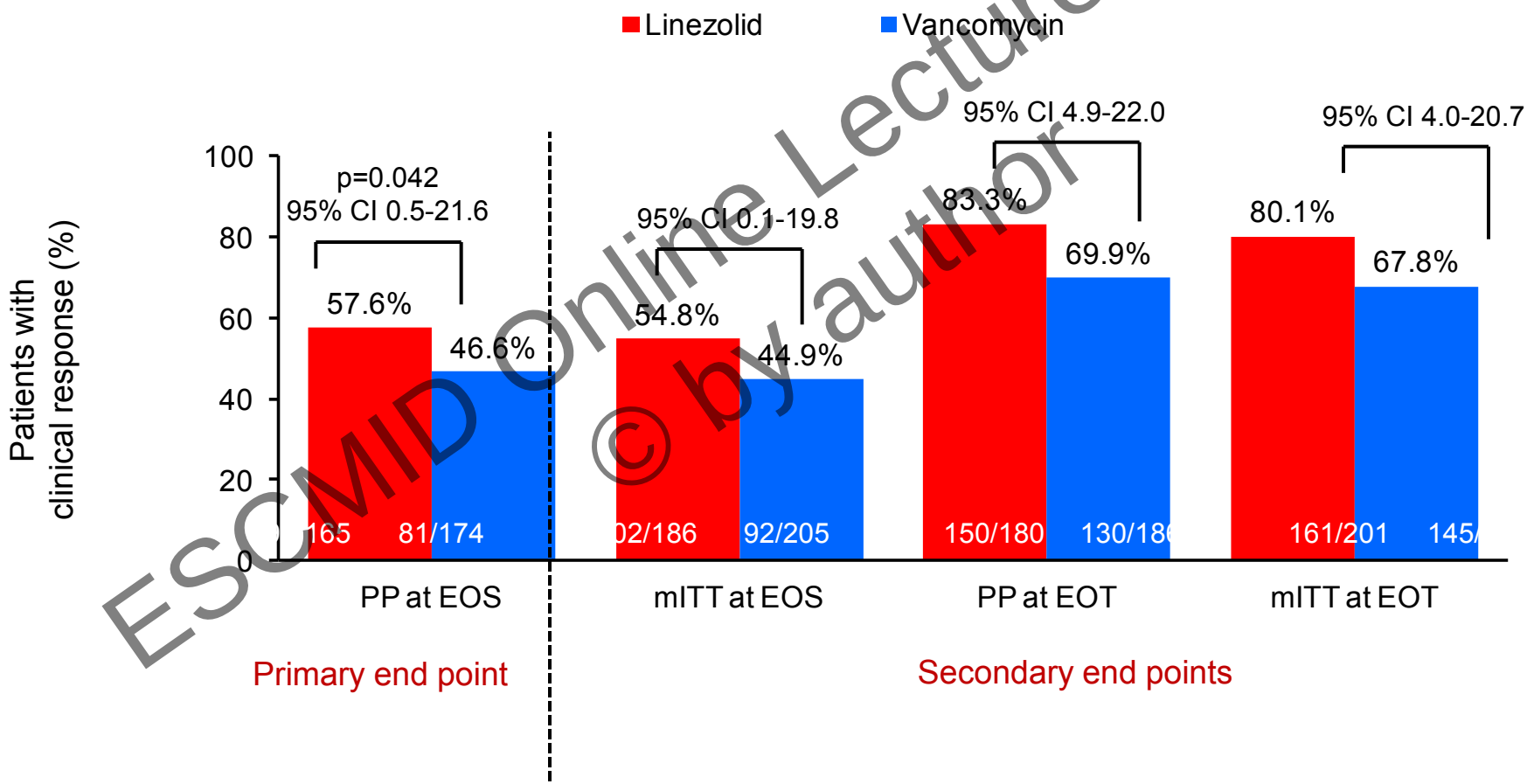
Vancomycin trough plasma concentrations in the PP population

Treatment day	n	Mean concentration (µg/mL)	Concentration range (µg/mL)
3	140	14.1	2.8-50.8
6	90	16.9	2.7-45.0
9	33	17.4	2.0-46.9

As a double-blind study, only the research pharmacist and unblinded monitor were aware of the levels
PP, per protocol

Wunderink et al. Clin Infect Dis 2012;54:621-629;
Niederman et al. Am J Respir Crit Care Med 183;2011:A3932

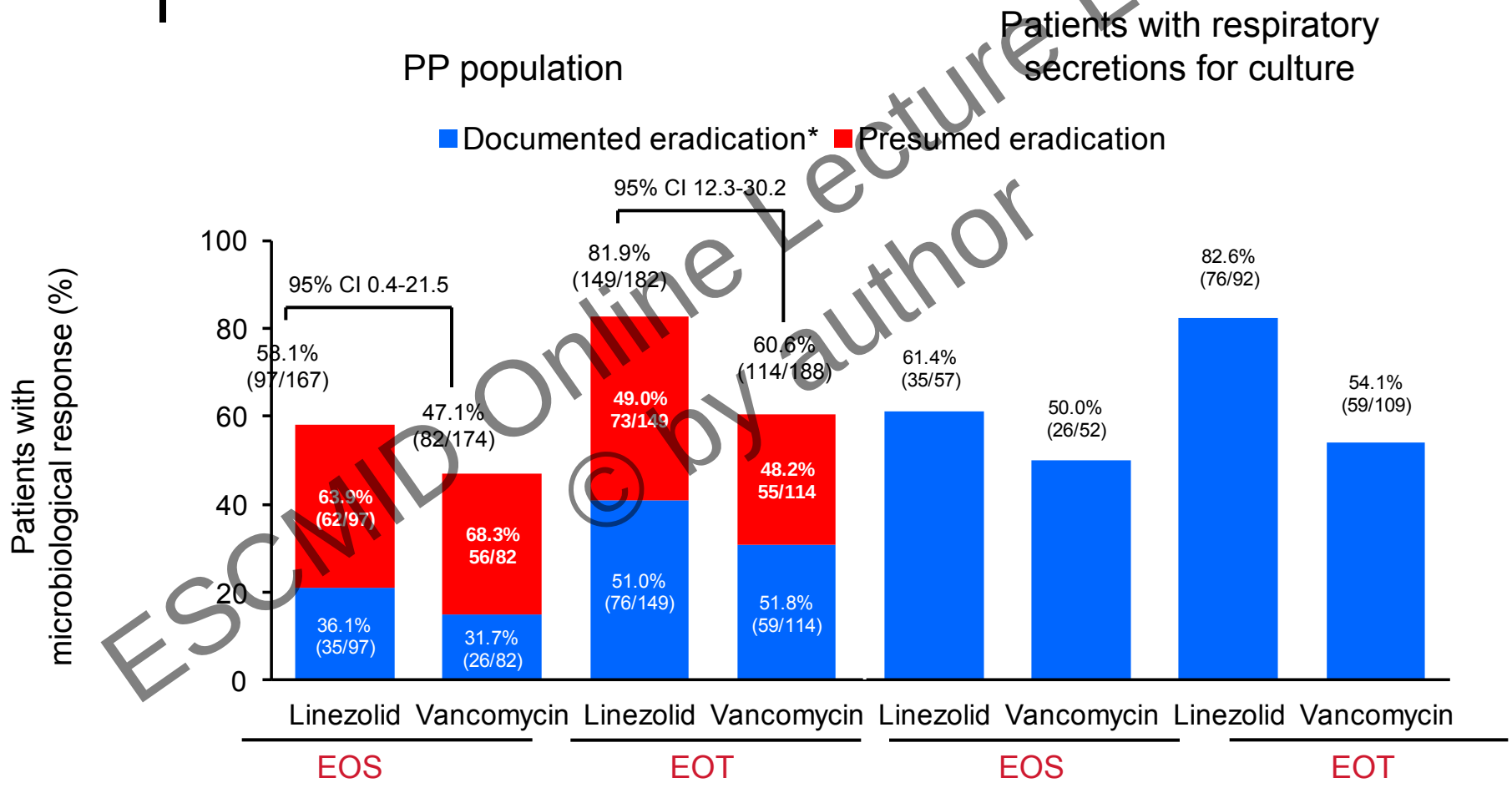
Clinical response at EOS and EOT in the PP and mITT populations



mITT, modified intent-to-treat

Wunderink et al. Clin Infect Dis 2012;54:621-629

Secondary end point: microbiological response rates at EOS and EOT



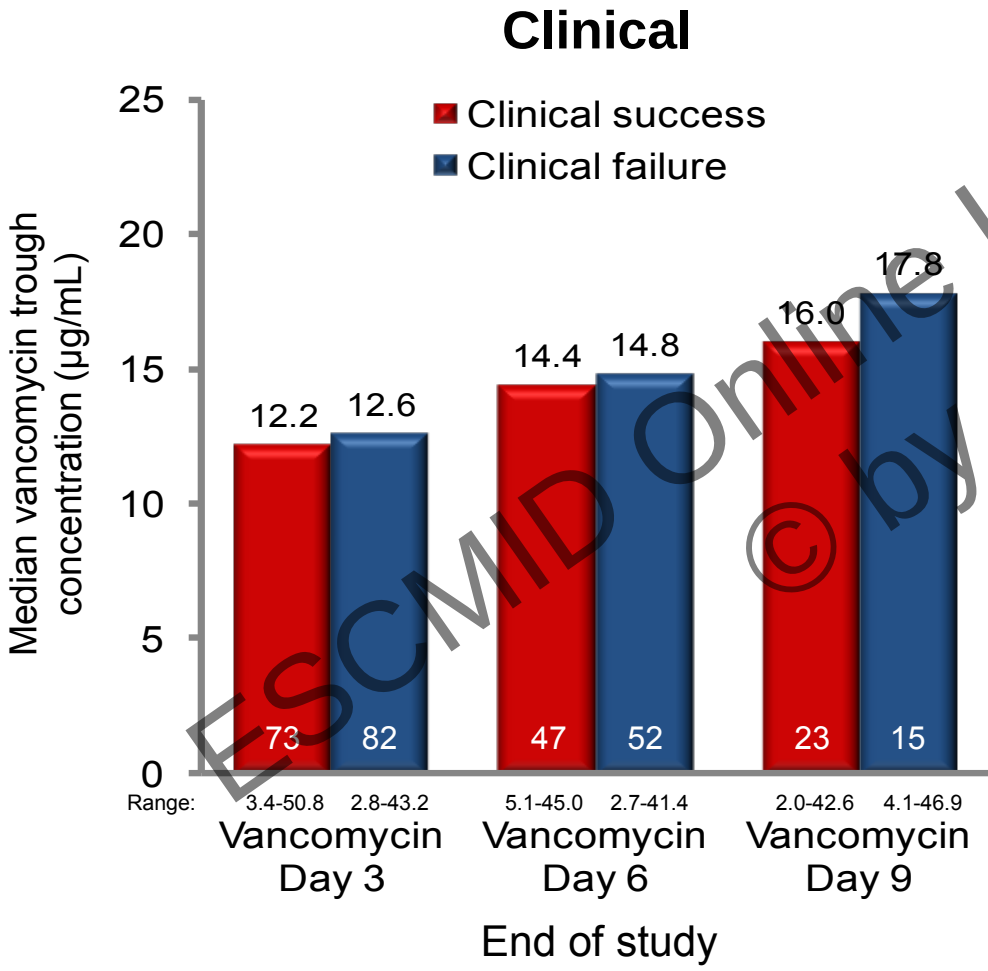
Patients with EOS outcome of 'indeterminate' were excluded from efficacy analysis
*Confirmed microbiological eradication

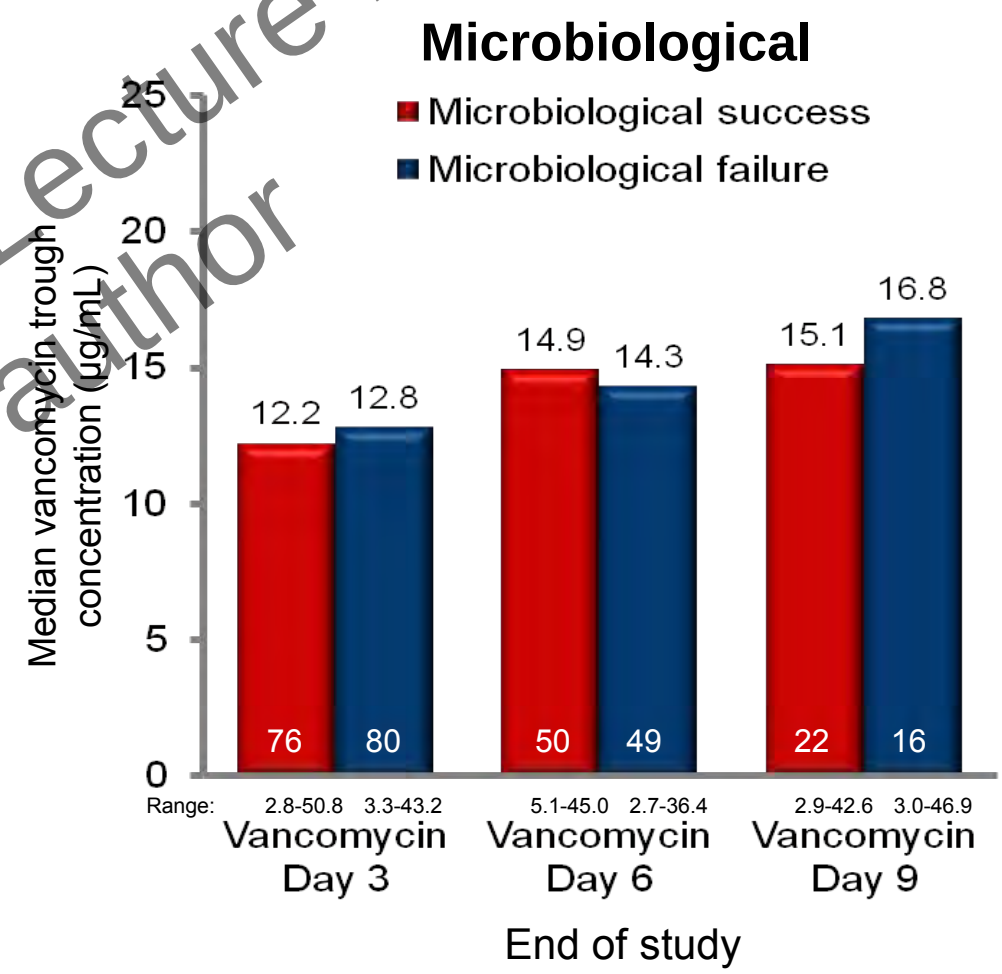
Wunderink et al. Clin Infect Dis 2012;54:621-629

Subgroup	Linezolid arm, No. (%)	Vancomycin arm, no. (%)	95% CI for Difference[a]
Evaluable for efficacy analyses[b]	165	174	
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
Diagnosis by quantitative culture			
Yes	30/58 (51.7)	31/72 (43.1)	−8.5 to 25.9
No	65/107 (60.8)	50/102 (49.0)	−1.7 to 25.1
Systemic steroids			
Yes	21/39 (53.9)	16/36 (44.4)	−13.1 to 32.0
No	74/126 (58.7)	65/138 (47.1)	−.3 to 23.6

Wundering RG, et al. Clin Infect Dis 2012, DOI: 10.1093/cid/cir895

No relationship between vancomycin trough level and outcomes in the ZEPHyR study

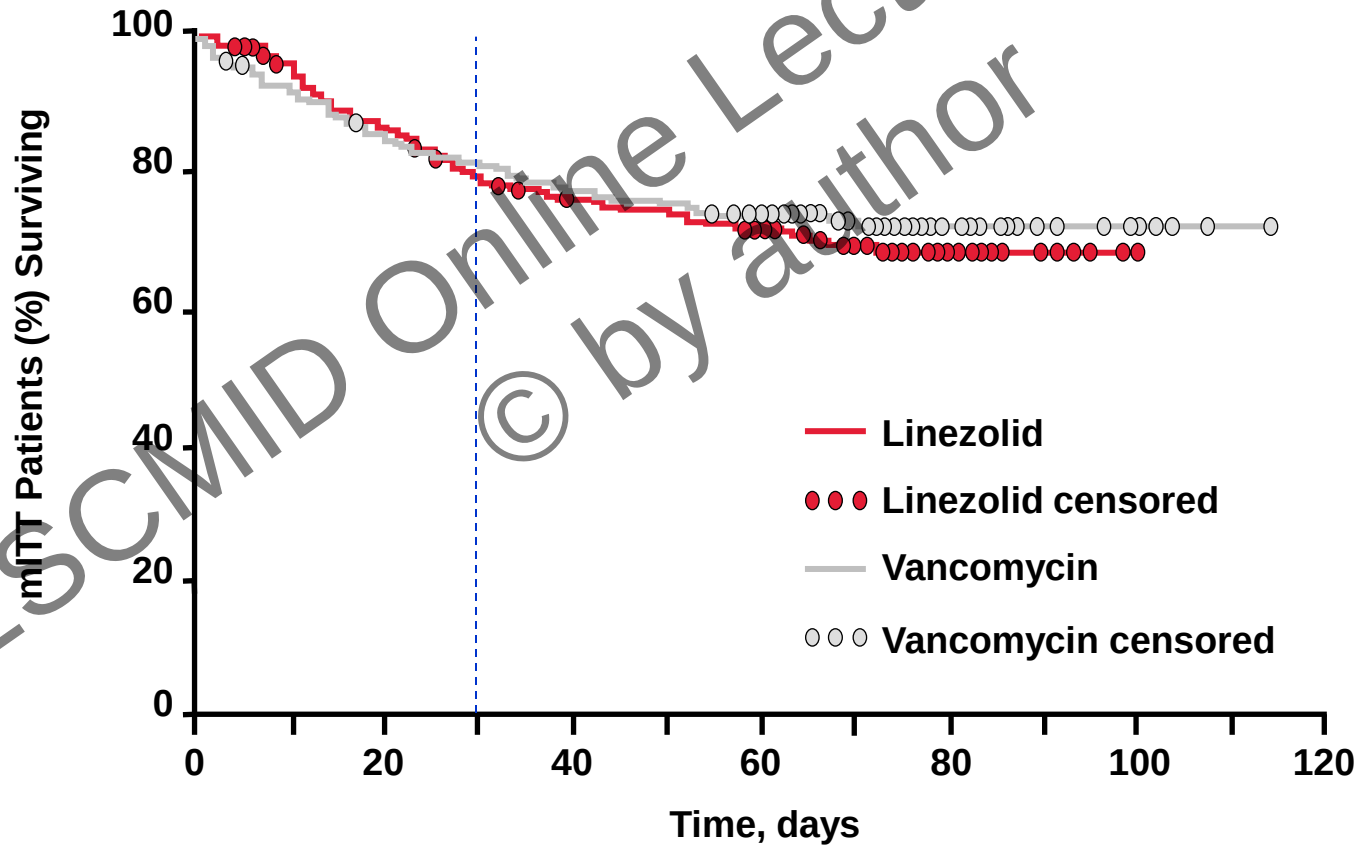




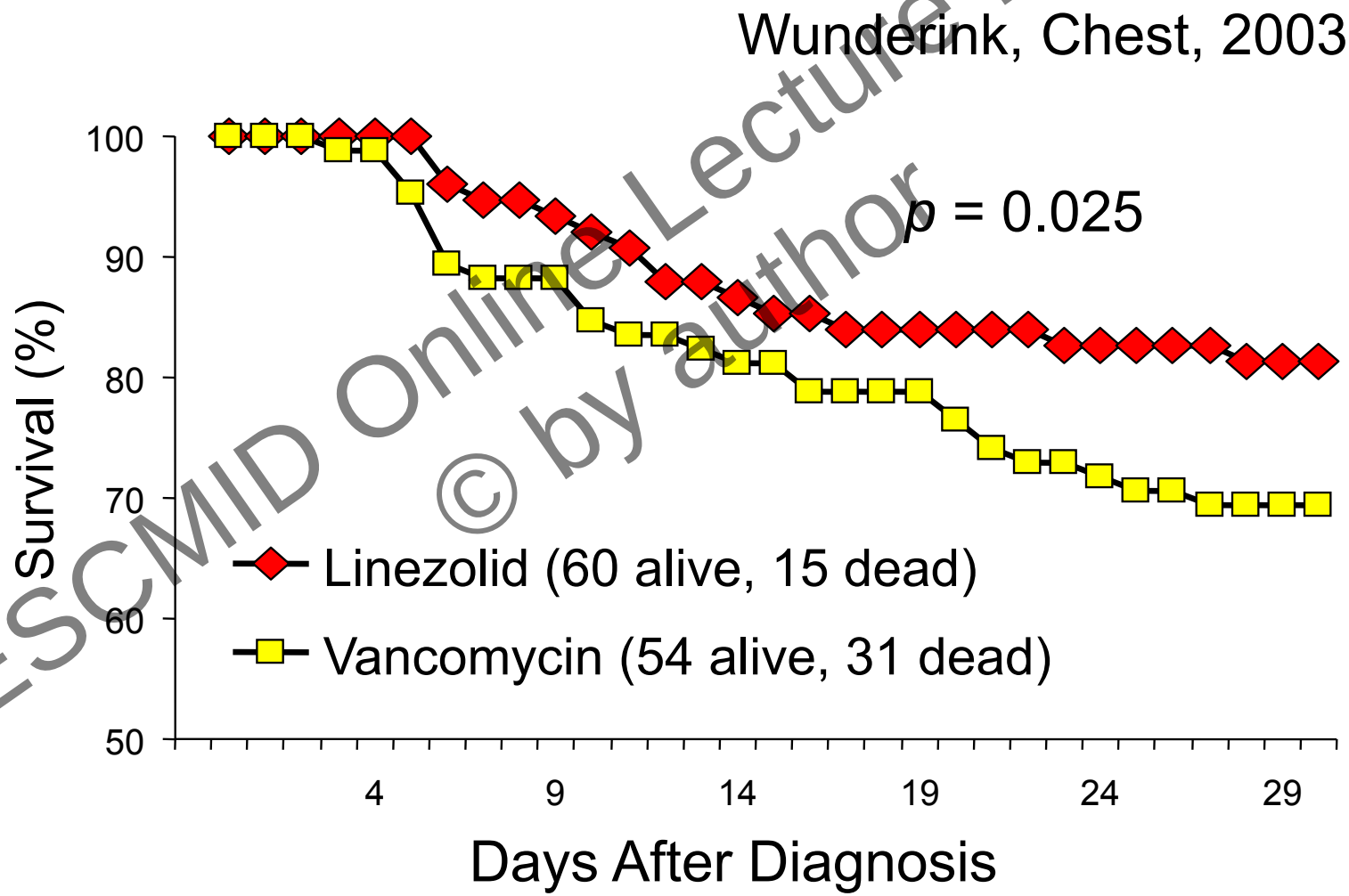
Adapted from Niederman et al. Am J Respir Crit Care Med 2011;183:A3932

Secondary End Point: 60-Day Survival (mITT Population)

Wunderink et al. Clin Infect Dis 2012;54:621-9; Appendix,Figure 2

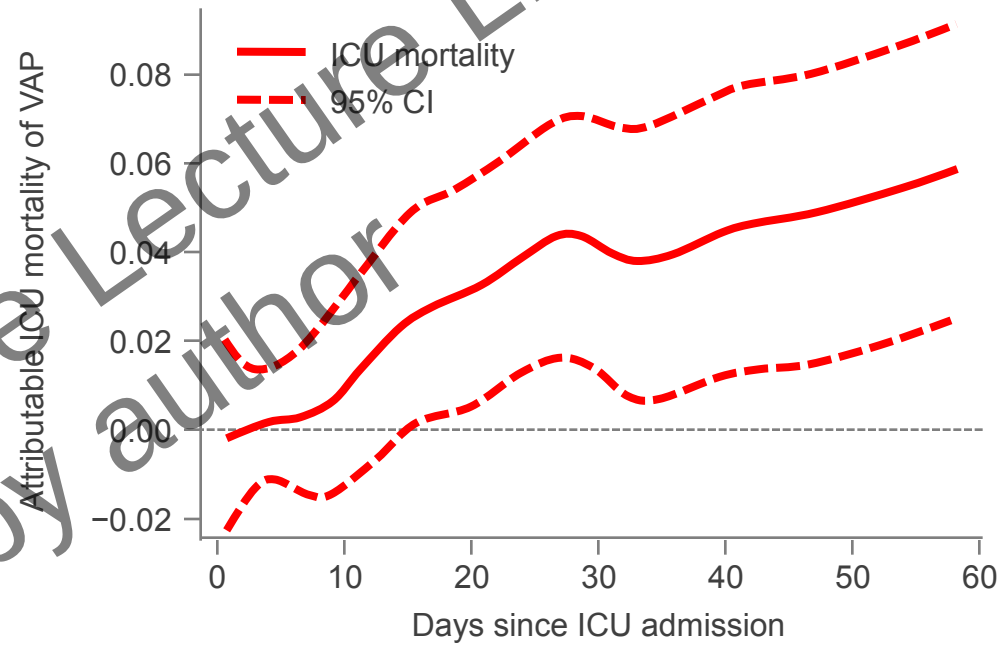


Hospital-acquired MRSA Pneumonia



Low mortality attributable to VAP

- Patients (n=4479) from a French multicentre database were included if they had stayed in the ICU for ≥2 days and received MV within 48 hours of admission
- Only about 1-1.5% of the ICU mortality rate was directly attributable to VAP



The attributable ICU mortality of VAP as a function of time, defined as the population-attributable fraction.

Solid line = % of ICU mortality that could be attributable to VAP or % of observed ICU deaths that could be avoided by preventing VAP.

Dashed line = corresponding 95% CI.

CI, confidence interval; ICU, intensive care unit; MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

Bekaert et al. *Am J Respir Crit Care Med* 2011;184:1133-9

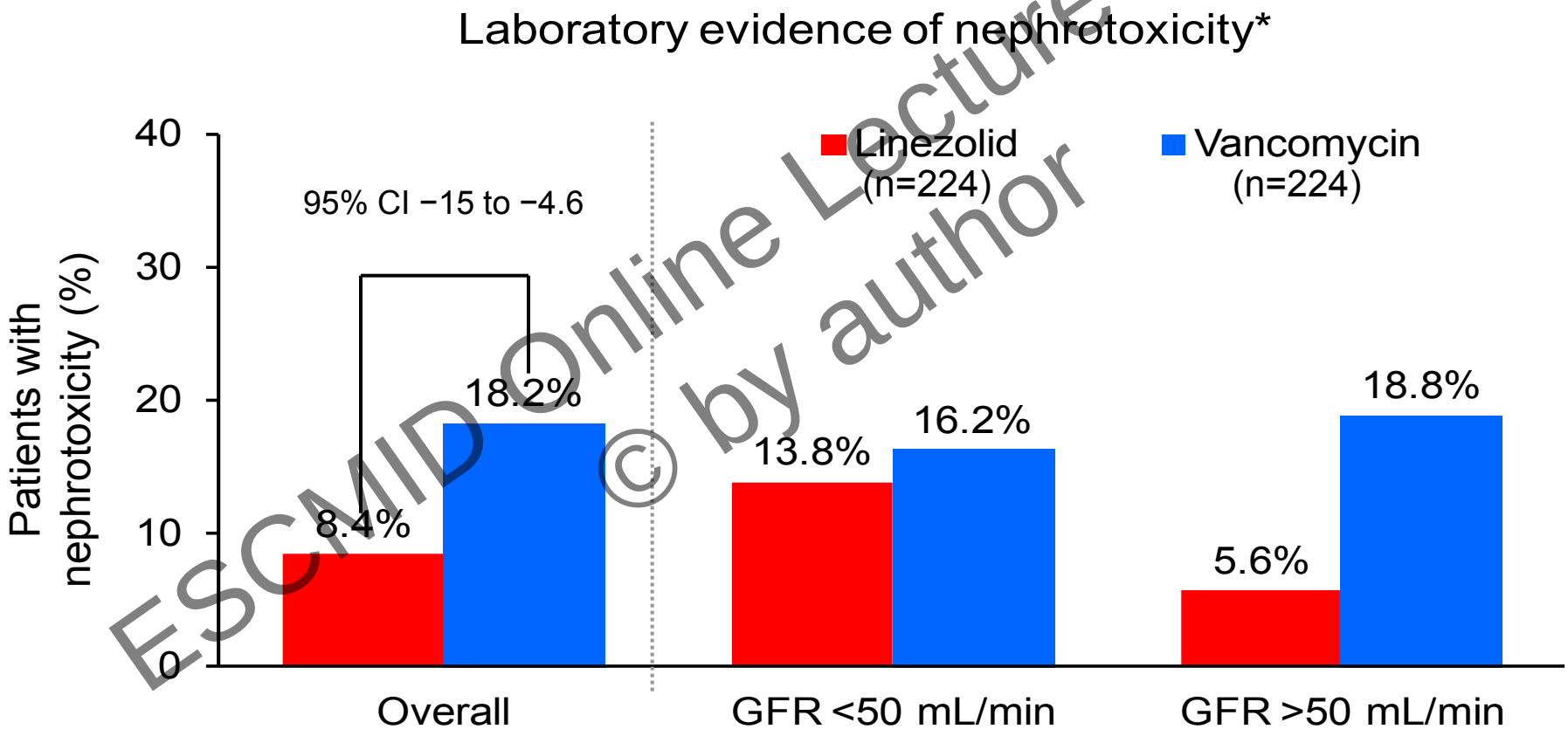
Secondary end point: clinically important investigator-reported all-cause AEs(ITT population)

AE, n (%)	Linezolid (n=597)	Vancomycin (n=587)
Anaemia	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)

[a]Patient was reported to have ≥1 of the following: renal failure, renal impairment and/or azotemia

Wunderink et al. Clin Infect Dis 2012;54:621-9

Secondary end point: nephrotoxicity in the mITT population



*0.5 mg/mL increase in serum creatinine if normal at baseline, or 50% increase if abnormal at baseline
GFR, glomerular filtration rate

Wunderink et al. Clin Infect Dis 2012;54:621-629

IMPACT-HAP Study

- The improving Medecine through Pathway Assessement of Critical Therapy in Hospital–Acquired Pneumonia (IMPACT-HAP) was a **US multicenter, retrospective, observational study of ICU patients with VAP due to MRSA** treated with linezolid or vancomycin
- The objective of this study was to compare **clinical success rates** for patients with VAP due to MRSA treated with **vancomycin versus linezolid**

Higher Clinical Success in Patients With Ventilator-Associated Pneumonia Due to MRSA Treated With Linezolid Compared to Vancomycin: Results From the IMPACT-HAP Study Oral Abstract Session 1283 IDSA 2012

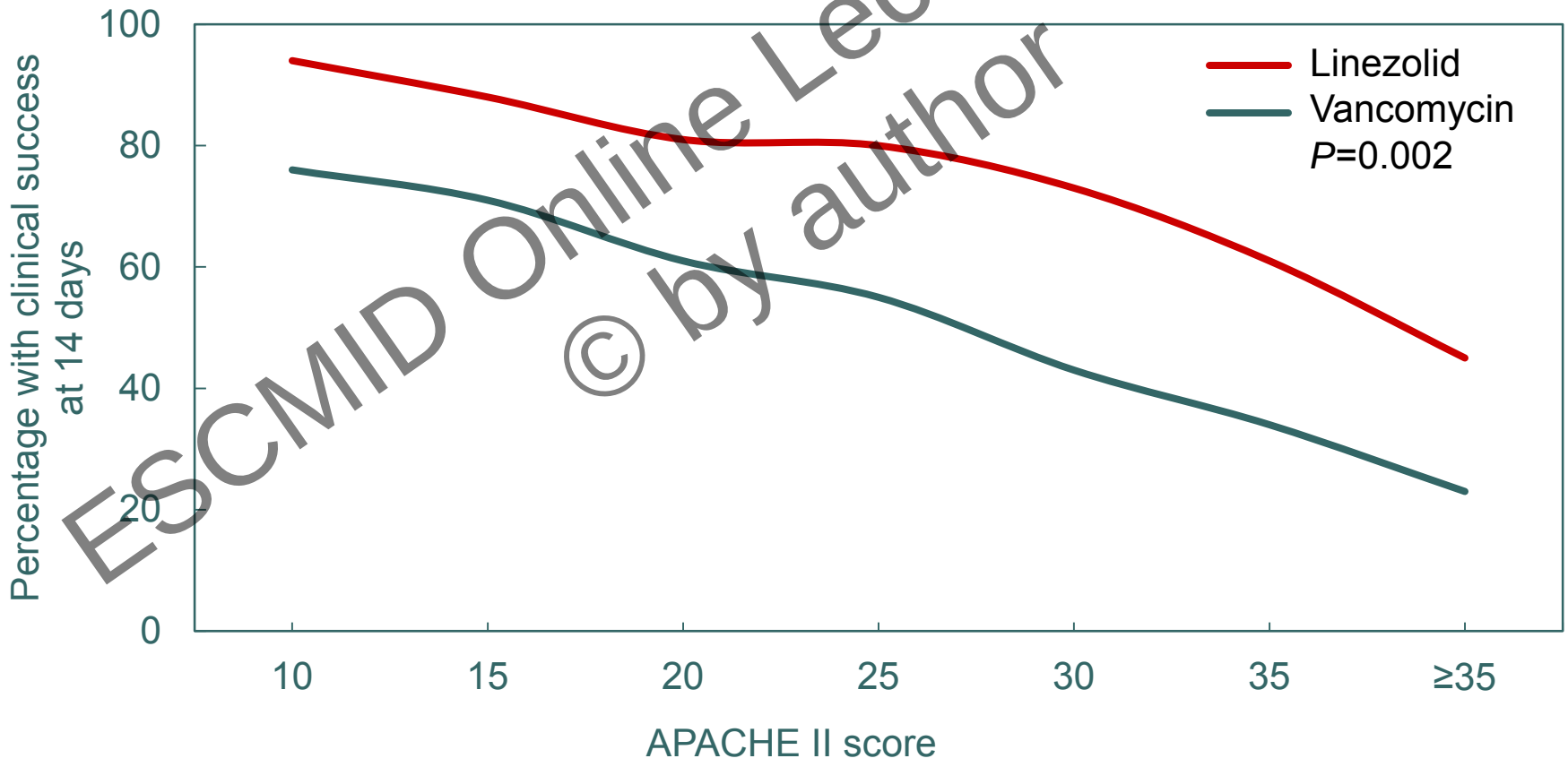
IMPACT-HAP Study: Results

- **A total of 144 patients** were evaluated, **81 patients treated with linezolid vs 63 patients treated with vancomycin**.
- **Patients receiving linezolid** had a **higher mean APACHE II** score compared to those receiving vancomycin (**22 vs 19; P=0.007**).
- **All-cause 14-day mortality was similar** (linezolid, 14% vs vancomycin, 13%; P=0.877).
- **Patients receiving linezolid achieved a significantly higher rate of clinical success** compared to vancomycin [63/81 (**78%**) vs 36/63 (**57%**); P=0.008].

Higher Clinical Success in Patients With Ventilator-Associated Pneumonia Due to MRSA Treated With Linezolid Compared to Vancomycin: Results From the IMPACT-HAP Study Oral Abstract Session 1283 IDSA 2012

IMPACT-HAP Study : Results

Propensity-adjusted regression model



Higher Clinical Success in Patients With Ventilator-Associated Pneumonia Due to MRSA Treated With Linezolid Compared to Vancomycin: Results From the IMPACT-HAP Study Oral Abstract Session 1283 IDSA 2012

Linezolid or Vancomycin in the Treatment of MRSA Pneumonia: Still Existing Dilemmas?

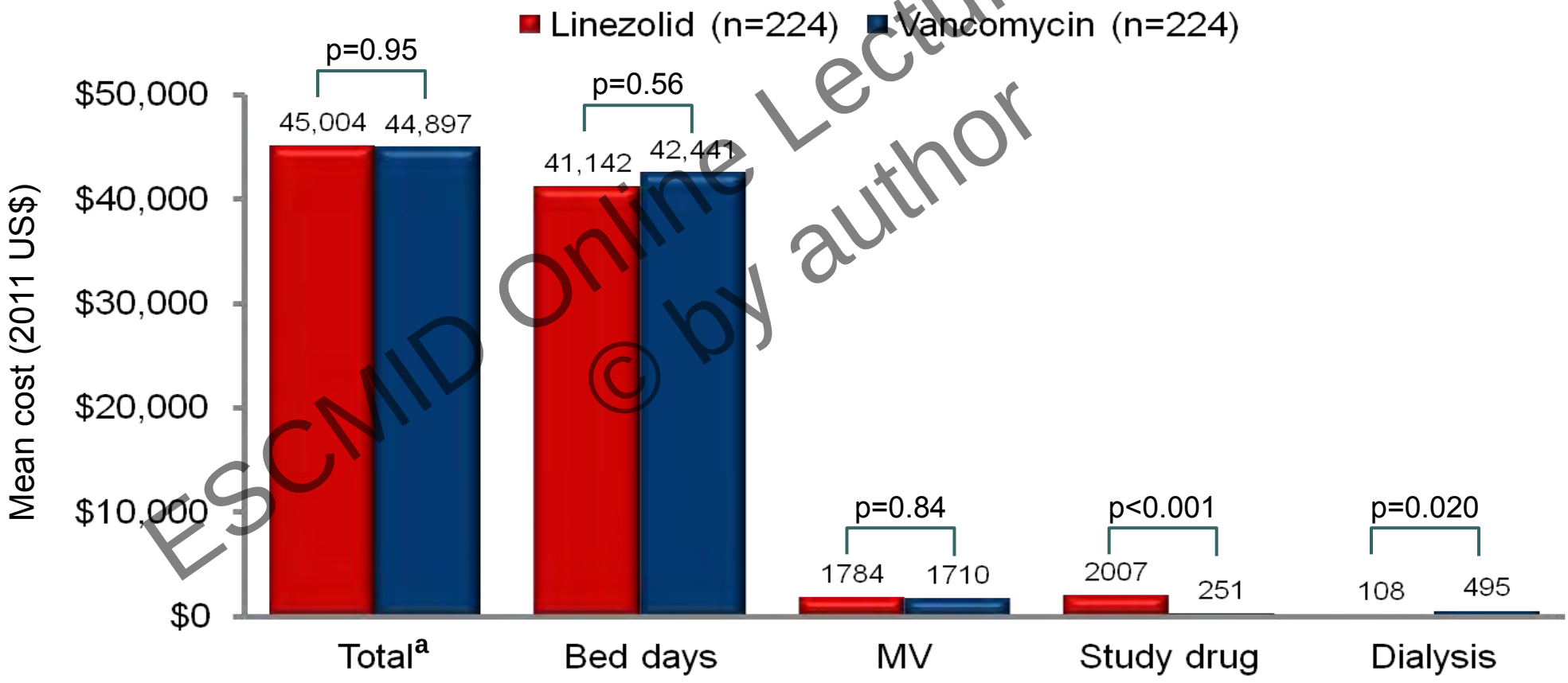
1. **MRSA VAP** is still a **common issue** in patients requiring prolonged MV
2. Optimizing antibiotic treatment **as soon as possible** is important
3. **Linezolid** has **documented superiority** over vancomycin
4. Using a **check list with prompting** may improve diagnosis and treatment

A Personal Care Bundle for Treating MRSA VAP in my Own ICU

C-E. Luyt, J. Chastre

1. **Obtain BAL specimens** for Gram staining and cultures before introduction of new ABs
2. **Start ABs less than 2 hrs** after BAL
3. Select initial treatment based on **risk factors for MRSA** using an **explicit algorithm**
4. When risk factors for MRSA are present, **immediately start linezolid**
5. **Streamline antibiotics** once culture results are available
6. **Shorten treatment duration** based on procalcitonin kinetic

Comparable overall treatment costs for vancomycin and linezolid in the ZEPHyR study



[a]total cost includes bed days, MV, study drug and dialysis