CLINICAL USE OF GLYCOPEPTIDES

Herbert Spapen
Intensive Care Department
University Hospital
Vrije Universiteit Brussel

Universitair Ziekenhuis Brussel

Glycopeptides

Natural

- Vancomycin → introduced in 1958
- Teicoplanin → introduced in Europe (1988) and Japan (1998)
  never licensed in USA

Semi-synthetic

- Telavancin
- Oritavancin
- Dalbavancin

FDA approved , mainly for treatment of acute or severe skin and soft tissue infections
Not licensed in Europe

Clinical Use

Treatment

- Severe infections caused by β-lactam resistant Gram-positive micro-organisms (methicillin-resistant and coagulase-negative *S.aureus*, penicillin-resistant *Streptococci*)

- Infections caused by Gram-positive micro-organisms in patients with serious (IgE-mediated) allergy to β-lactam agents

- Clostridium difficile-associated colitis (oral form)

Clinical use

Prophylaxis

Major surgical procedures involving implantation of prosthetic material or devices at institutions that have a high rate of MRSA or MRSE infection

Debatable indications

- Empirical treatment in febrile neutropenia or sepsis
- Treatment in response to a single blood culture positive for coagulase-negative *Staphylococci*

Vancomycin dosing

Intermittent treatment 15-20 mg/kg bid, not to exceed 2g/day

Continuous infusion 15 mg/kg loading dose, then 2g/24h
(to obtain plateau levels of 20-25µg/mL)

→ **dose adapted to renal function**

For complicated infections (bacteremia, hospital-acquired pneumonia, endocarditis, meningitis, osteomyelitis) and for infections caused by strains with MICs > 1µg/mL, vancomycin trough levels of 15-20µg/mL are recommended !

Liu C, et al. IDSA Clinical Practice Guidelines, Clin Infect Dis 2011

Teicoplanin dosing

- Long half-life → can be given IM or IV once daily

- 6mg/kg (400mg) daily results in too low mean trough levels
  6mg/kg twice daily for 48h is needed to attain serum levels > 10µg/mL in all infections and must be continued for complicated infections and sepsis

  Harding I, et al. J Antimicrob Ther 2000; Brink AJ, et al. Int J Antimicrob Agents 2008

- A meta-analysis of studies suggests that teicoplanin has equal clinical and microbiological efficacy as vancomycin, while having a lower incidence of infusion-related side-effects and nephrotoxicity

  (but only in less severely ill patients !)

  Svetitsky S, et al. Antimicrob Agents Chemother 2009

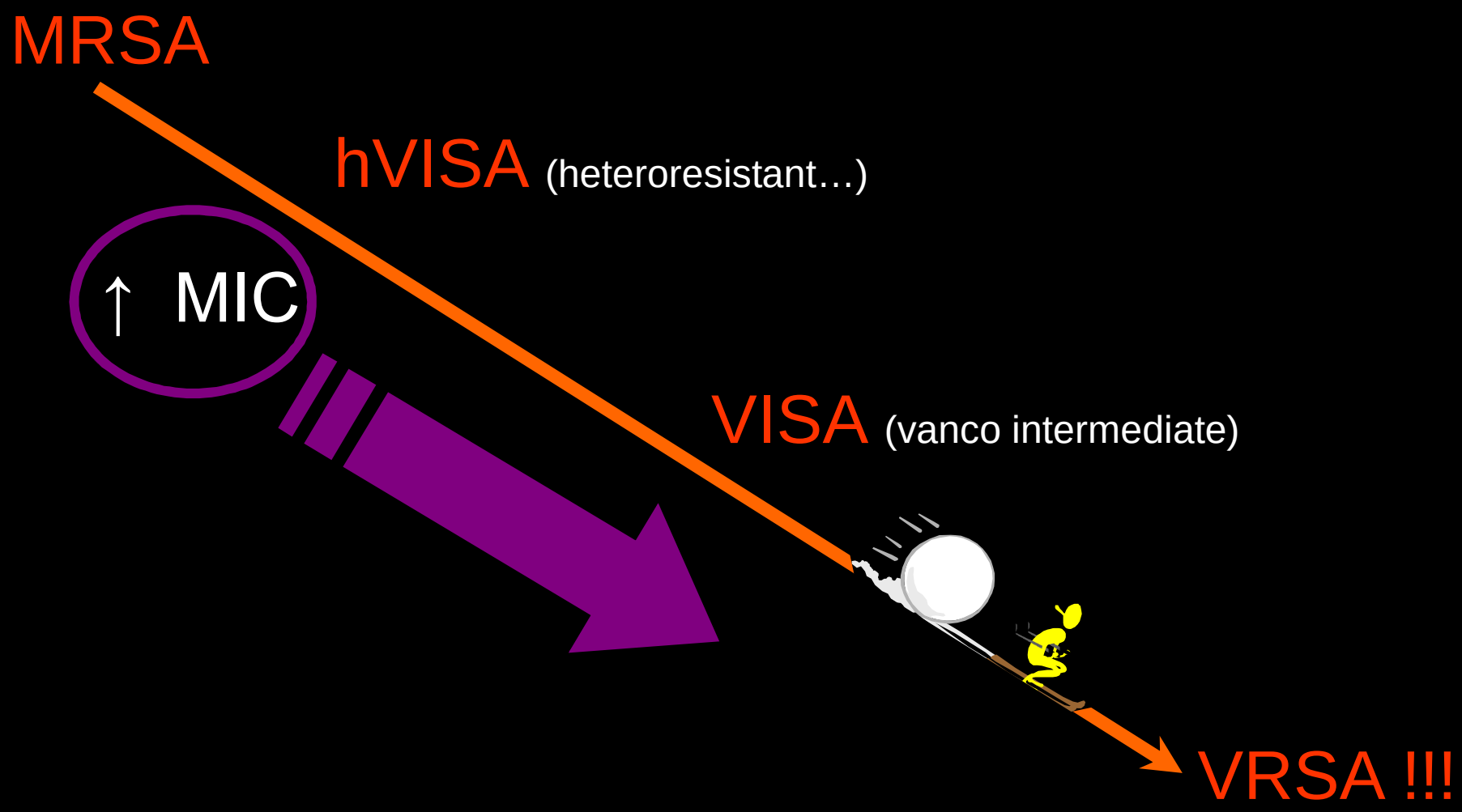
The problem with vancomycin

- **Efficacy**
- **Reduced susceptibility and resistance**
- **Safety and toxicity**

Vancomycin efficacy

- Slow bactericidal activity, particularly at high inocula
- Less activity against MSSA
- Poor tissue penetration
  - **meninges** (dependent on degree of inflammation)
  - **foreign devices** (orthopedic infections !)
  - **lungs**
    - → 45% penetration in post-lobectomy lung tissue
    - → 6:1 blood/epithelial lining fluid penetration ratio in ICU patients

Reduced susceptibility of S. aureus to vancomycin



Vancomycin breakpoints

Classification	MIC (µg/mL) CLSI	MIC (µg/mL) EUCAST
Susceptible (VSSA)	≤ 2	≤ 2
Intermediate (VISA)	4 – 8	
Resistant (VRSA)	> 8	> 2

CLSI Clinical Laboratory Standards Institute
EUCAST European Committee on Antimicrobial Susceptibility Testing

MIC should always be reported by method !!

MICs determined by E-test tend to be higher than those determined by broth method

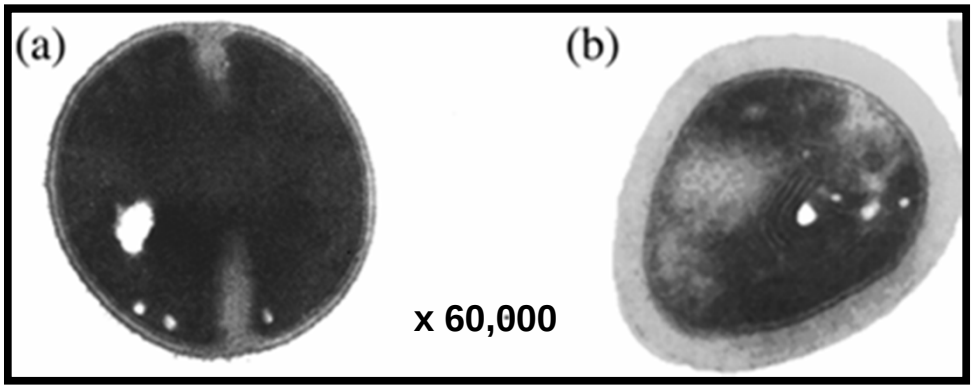
Vancomycin resistance

VRSA **"vancomycin resistant S.aureus"**

- conferred by transfer ***vanA resistance operon*** from vancomycin-resistant enterococci into S. aureus
- only handful of cases reported (USA, India, Iran)

VISA **"vancomycin intermediate resistant S.aureus"**

- heterogeneous distribution worldwide (e.g. up to 26% in Japan)
- does not possess *van resistance genes* but produce a thicker cell wall



Transmission electron micrograph of Vanco-susceptible MRSA (a) and VISA strain (b)

Denis O, et al. JAC 2002

Vancomycin resistance

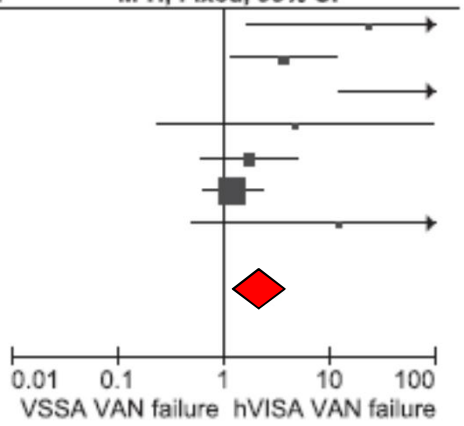
hVISA "heteroresistant vancomycin- intermediate S.aureus"

- Refers to a strain with a vancomycin MIC in the susceptible range (≤ 2µg/mL) which contains a subpopulation with higher MIC (2µg/mL)
- May be a VISA precursor
- Reported rates are variable due to differences in methods for identification
- Can disseminate even in the absence of glycopeptide pressure
- Patients harbouring hVISA strains may fail on vancomycin

hVISA- Treatment failure and Mortality

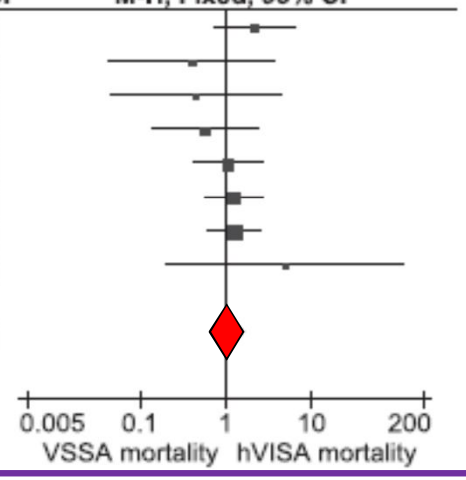
Study or Subgroup	hVISA Events	hVISA Total	VSSA Events	VSSA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ariza (2)	12	14	1	5	0.8%	24.00 [1.69, 340.99]
Bae et al (4)	13	19	17	46	12.2%	3.70 [1.18, 11.53]
Charles et al (8)	5	5	1	48	0.1%	348.33 [12.59, 9636.20]
Fong et al (16)*	9	9	21	26	2.3%	4.86 [0.24, 97.05]
Horne et al (24)	10	26	11	42	20.2%	1.76 [0.62, 5.02]
Musta et al (41)	20	43	101	242	63.5%	1.21 [0.63, 2.33]
Neoh et al (42)	2	2	5	18	1.0%	12.27 [0.50, 299.32]
Total (95% CI)		**118**		**427**	**100.0%**	**2.37 [1.53, 3.67]**
Total events	71		157			

Heterogeneity: Chi² = 17.79, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 3.88 (P = 0.0001)



Study or Subgroup	hVISA Events	hVISA Total	VSSA Events	VSSA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bae et al (4)	8	19	16	65	8.7%	2.23 [0.76, 6.50]
Bert et al (5)	1	13	6	35	6.2%	0.40 [0.04, 3.71]
Charles et al (8)	1	5	17	48	5.3%	0.46 [0.05, 4.41]
Fong et al (16)	5	10	19	30	9.9%	0.58 [0.14, 2.46]
Horne et al (24)	12	58	11	56	18.4%	1.07 [0.43, 2.67]
Maor et al (37)	14	27	103	223	22.2%	1.25 [0.56, 2.79]
Musta et al (41)	14	43	67	242	28.3%	1.26 [0.63, 2.53]
Neoh et al (42)	2	2	8	16	0.9%	5.00 [0.21, 120.44]
Total (95% CI)		**177**		**715**	**100.0%**	**1.18 [0.80, 1.72]**
Total events	57		247			

Heterogeneity: Chi² = 4.75, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)



Van Hal SJ and Paterson DL. Antimicrob Agents Chemother 2011

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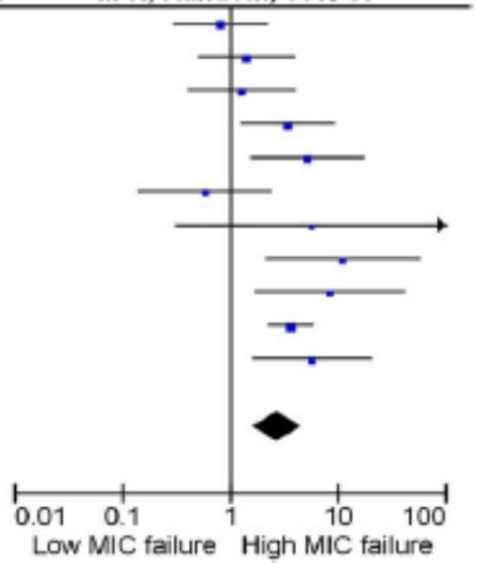
Clinical significance of Vancomycin MICs – S.aureus treatment failure

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, 40.66]
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: $Tau^2 = 0.38$; $Chi^2 = 22.59$, df = 10 (P = 0.01); $I^2 = 56\%$

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



Irrespective of source of infection and MIC methodology used

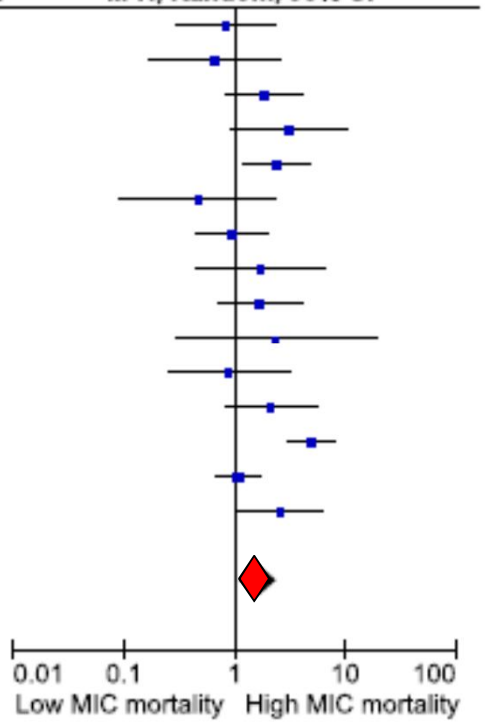
Van Hal SJ, et al. Clin Infect Dis 2012

Clinical significance of Vancomycin MICs – MRSA 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)



Irrespective of source of infection and MIC methodology used

Van Hal SJ, et al. Clin Infect Dis 2012

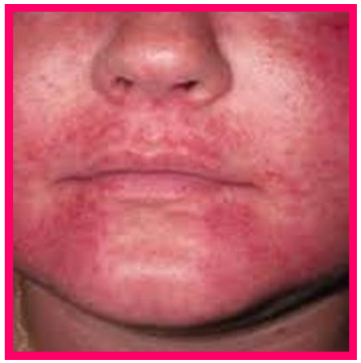
Vancomycin Safety & Toxicity

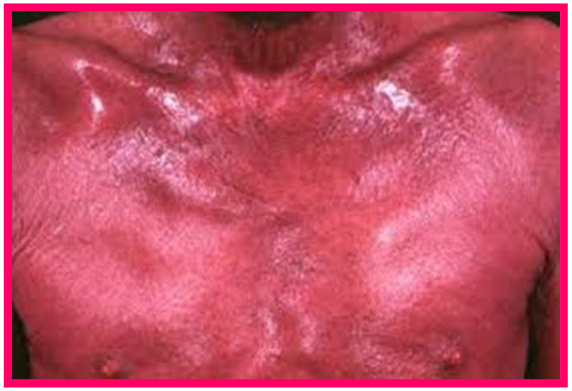
- ↑ Prevalence of vancomycin-resistant enterococci (VRE)
- Red (wo)man/red neck syndrome
- Toxicity

  - ototoxicity
  - nephrotoxicity

Red (wo)man/neck syndrome

- Caused by degranulation of mast cells and basophils resulting in histamine release (not IgE-mediated)
- Characterized by pruritus, erythematous rash, sometimes hypotension

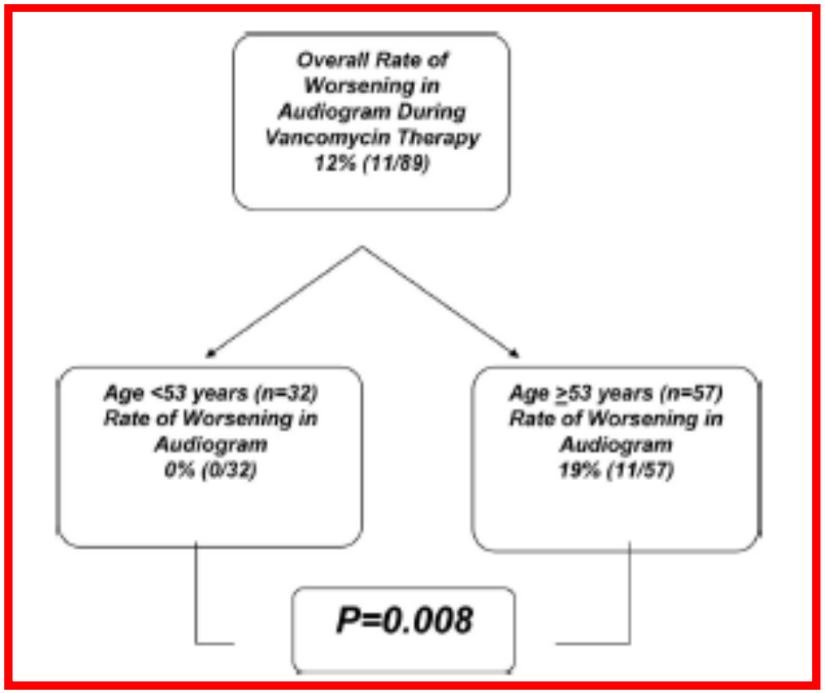




- Most severe reactions occur in patients < 40 years or with rapid infusion
- Treatment: discontinuation of infusion, antihistaminics, fluids (vasopressors)

Ototoxicity

Audiograms performed after an average of 27 days of vancomycin therapy aiming at trough levels between 10-20µg/mL



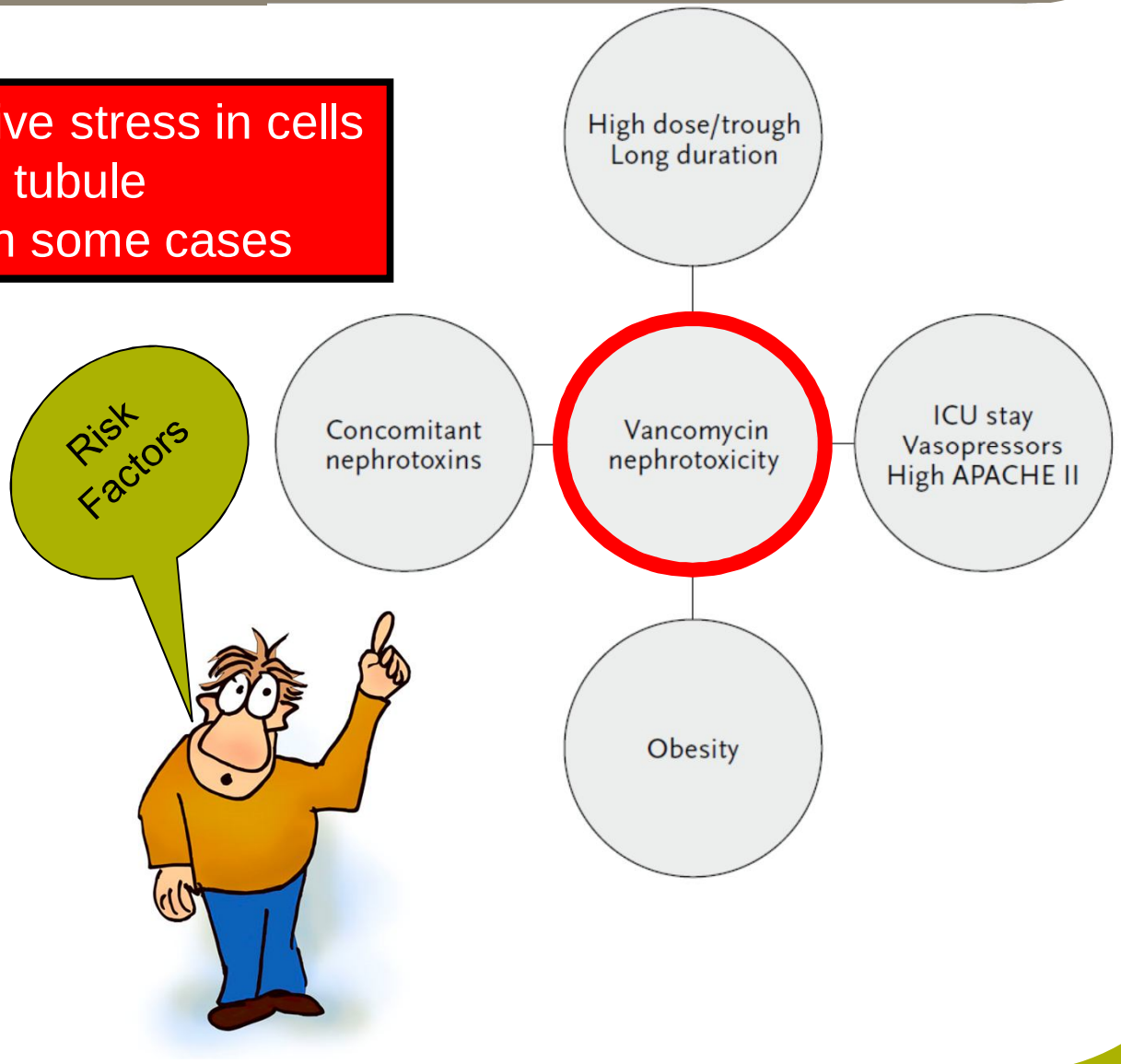
Ototoxicity risk depends upon:

- age
- abnormal baseline audiogram

Forouzesh A, et al. Antimicrob Agents Chemother 2009

Nephrotoxicity

Mechanism = oxidative stress in cells of the proximal renal tubule
Interstitial nephritis in some cases



Incidence of vancomycin-associated nephrotoxicity

Reference	N	Dose	Nephrotoxicity
Hermsen et al. [16]	55	Trough ≥15 vs <15	HD 31% SD 10%
Hidayat et al. [17]	95	Dose to achieve trough concentration of 4-5 times MIC of MRSA strain	HD 12% SD 0%
Jeffres et al. [18]	94	30 mg/kg/d to target trough of 15-20 µg/ml	42.6%
Lodise et al. [19]	291	≥4 g/d vs <4g/d	HD 34.6% SD 9.7%
Lodise et al. [5]	166	Trough ≥15 vs <15	25.9% vs 10.1%
Mora et al. [25]	163	Trough ≥15 vs <15	HD 8% SD 3%
Ingram et al. [27]	167	CI vs IA	15.6%
Hutschala et al. [28]	149	CI vs IA	29.5% overall 27.7% in CI 36.7% in IA
Vuagnat et al. [29]	44	CI vs IA	8.7% in CI* 42.9% in IA*

N = number of patients; HD = high dose; SD = standard dose; CI = continuous infusion; IA = intermittent administration; * = adverse drug effects.

Variable incidence, ranging from < 1 to > 40%

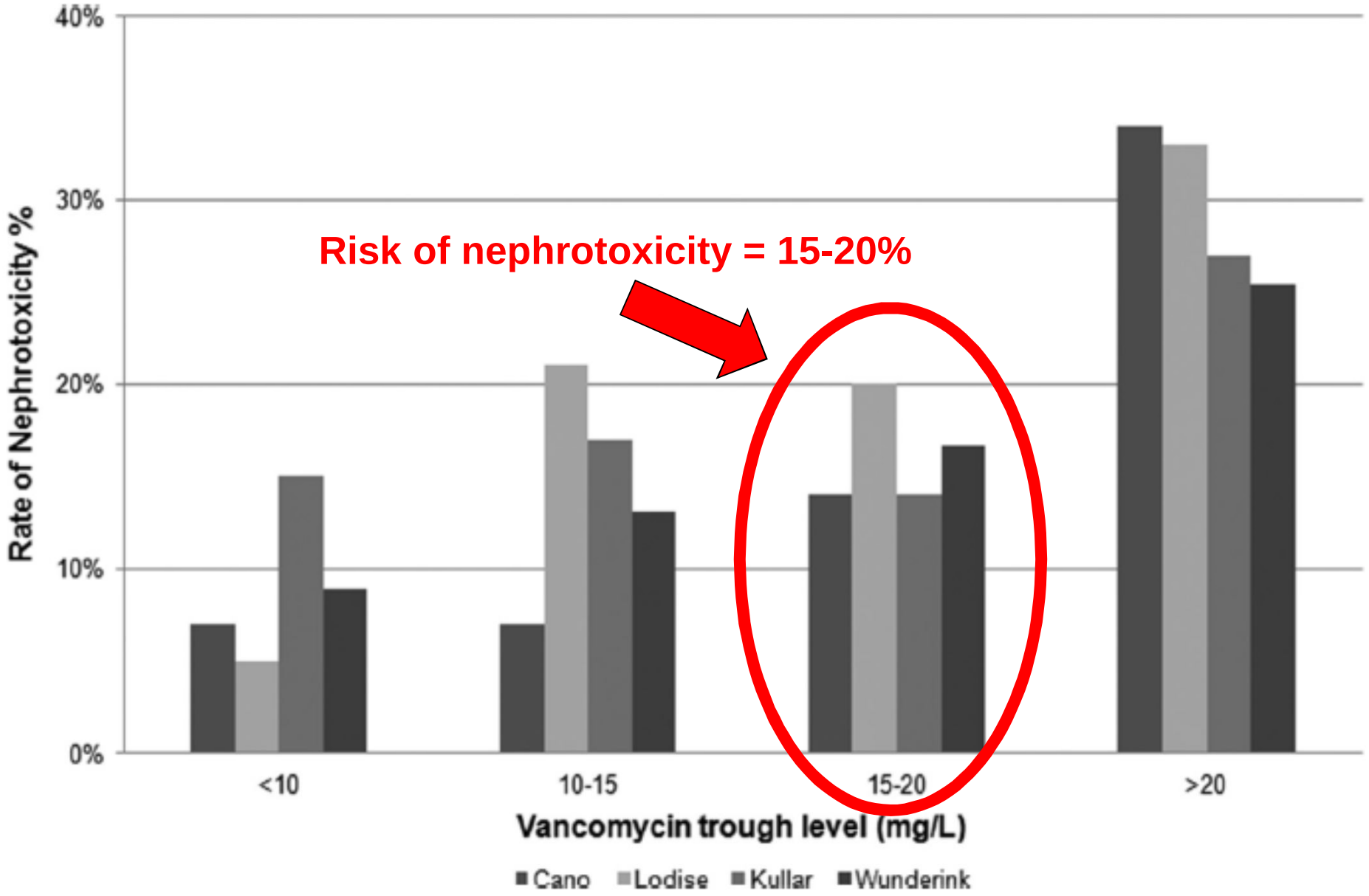
- different populations studied
- different dosing regimens
- different definition of nephrotoxicity

		RIFLE criteria	
		sCreatinine	Urine output criteria
Increasing severity	Risk	↑sCrea × 1.5	< 0.5 ml/kg per h × 6 h
	Injury	↑sCrea × 2	< 0.5 ml/kg per h × 12 h
	Failure	↑sCrea × 3 or ⩾ 0.5 mg/dl if baseline sCrea ↑ > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Outcome	Loss	Complete loss of renal function > 4 weeks	
	End-stage	End-stage renal disease	

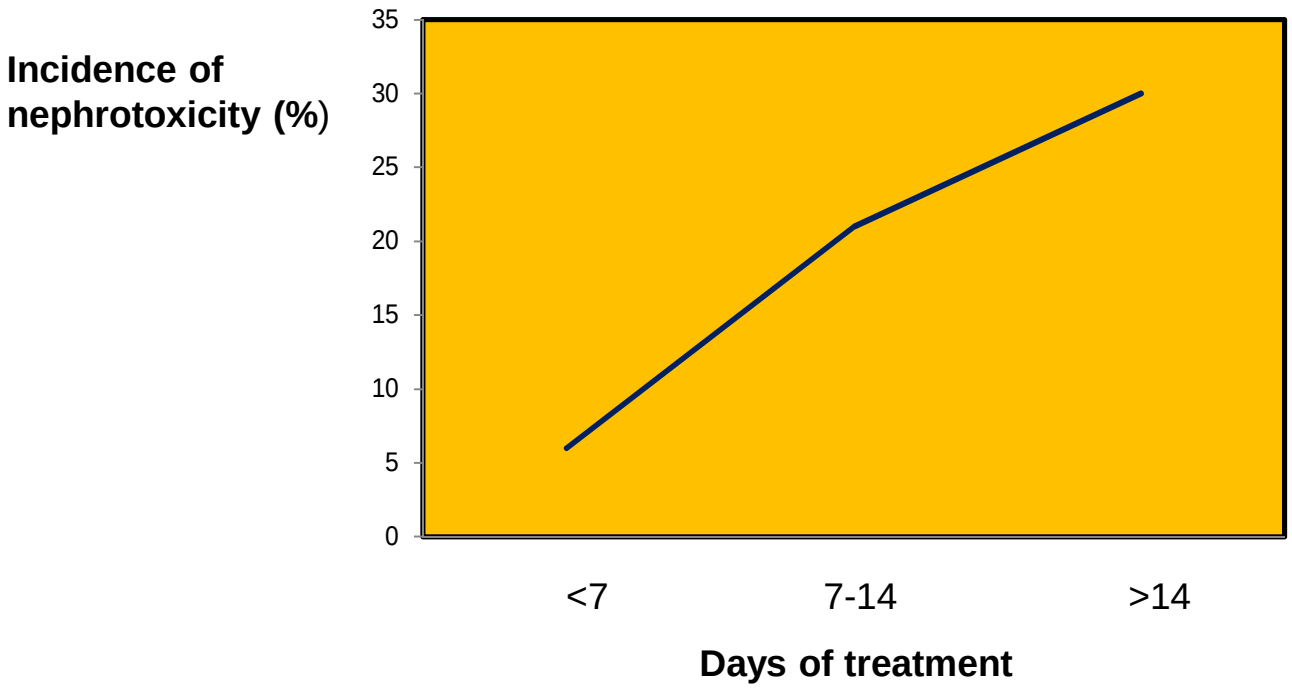
	AKIN criteria	
	sCreatinine	Urine output criteria
Stage 1	↑ sCrea × 1.5 or ↑⩾0.3 mg/dl in sCrea	< 0.5 ml/kg per h × 6 h
Stage 2	↑sCrea × 2	< 0.5 ml/kg per h × 12 h
Stage 3	↑sCrea × 3 or ↑⩾0.5 mg/dl if baseline sCrea > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Patients who receive RRT are considered to have met stage 3 criteria, irrespective of the stage they are in at the time of RRT		

Gupta A, et al. Neth J Med 2011

The “Trough-Toxicity” dilemma



Duration of therapy and nephrotoxicity



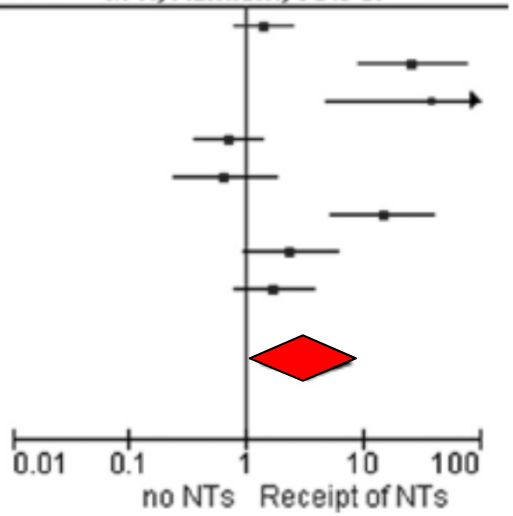
Lodise TP, et al. Clin Infect Dis 2009

Vancomycin and concomitant nephrotoxins

Study or Subgroup	Receipt of NTs Events	Total	no NTs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	26	55	90	233	14.0%	1.42 [0.79, 2.57]
Cano et al. (22)	16	29	7	159	12.4%	26.73 [9.32, 76.63]
Hidayat et al. (13)	10	11	17	84	8.4%	39.41 [4.71, 329.47]
Kralovicova et al. (31)	31	134	19	64	13.7%	0.71 [0.36, 1.39]
Lodise et al. (36)	6	21	55	145	12.6%	0.65 [0.24, 1.79]
McKamy et al. (38)	18	24	24	143	12.6%	14.88 [5.35, 41.36]
Minejima et al. (39)	37	169	6	58	12.9%	2.43 [0.97, 6.10]
Prabaker et al. (43)	21	31	174	317	13.4%	1.73 [0.79, 3.78]
Total (95% CI)		**474**		**1203**	**100.0%**	**3.30 [1.30, 8.39]**
Total events	165		392			

Heterogeneity: Tau² = 1.54; Chi² = 60.99, df = 7 (P < 0.00001); I² = 89%

Test for overall effect: Z = 2.50 (P = 0.01)



Nephrotoxins include any or all of the following: aminoglycosides, amphotericin B, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, colistin, contrast dye, cyclosporine, cisplatin, diuretics, nonsteroidal antiinflammatory drugs, tacrolimus, and **vasopressors (?)**.

Van Hal SJ, et al. Antimicrob Agents Chemother 2013

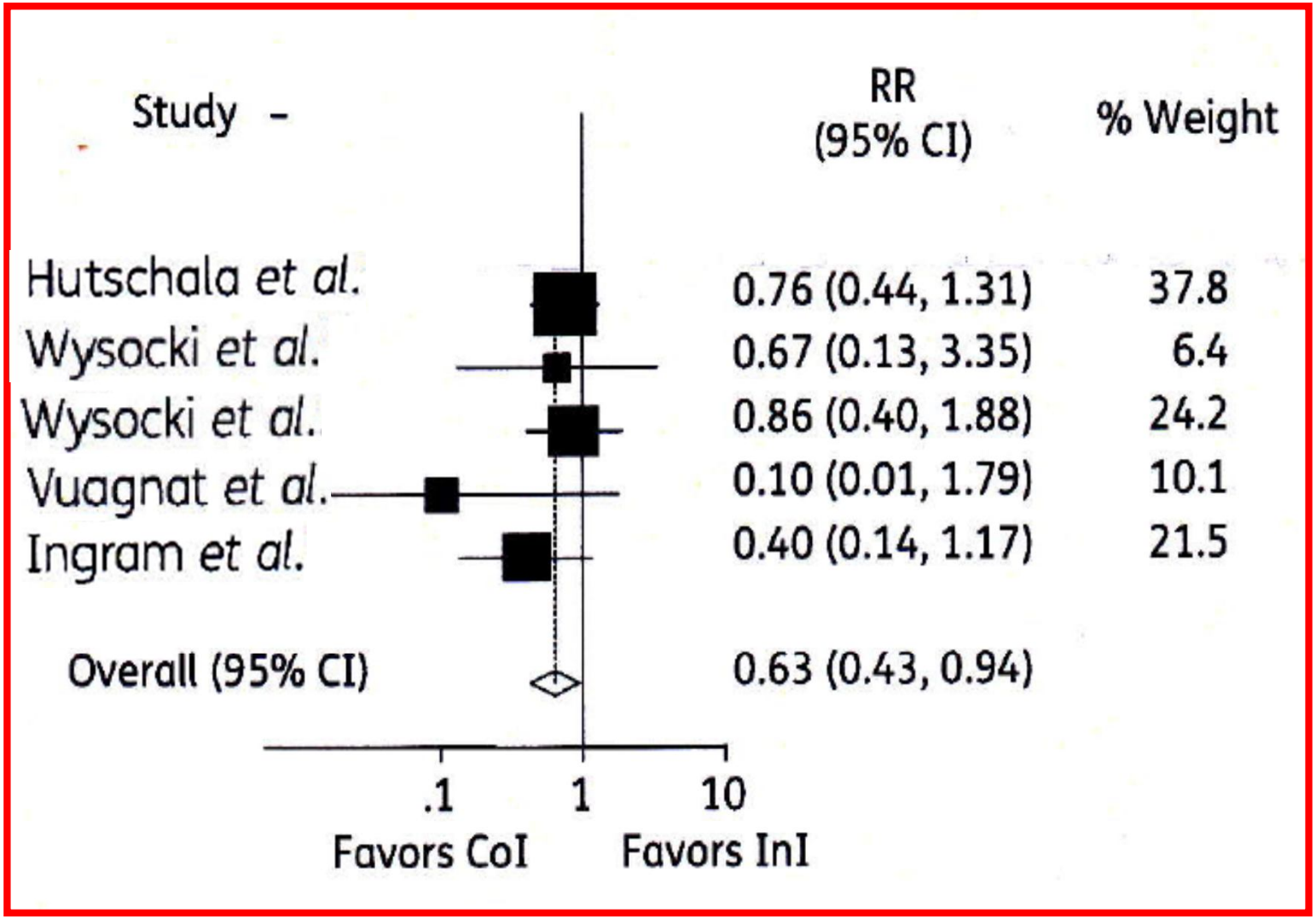
Some thoughts about vancomycin nephrotoxicity

1. Temporal relationship between elevated trough vancomycin levels and development of nephrotoxicity remains uncertain, precluding a definite cause-effect analysis
   Elevated levels may be consequence rather than cause of nephrotoxicity.

2. Degree of renal dysfunction remains modest with resolution occurring in > 70% of patients at discharge. Dialysis need in 5-30% of patients,

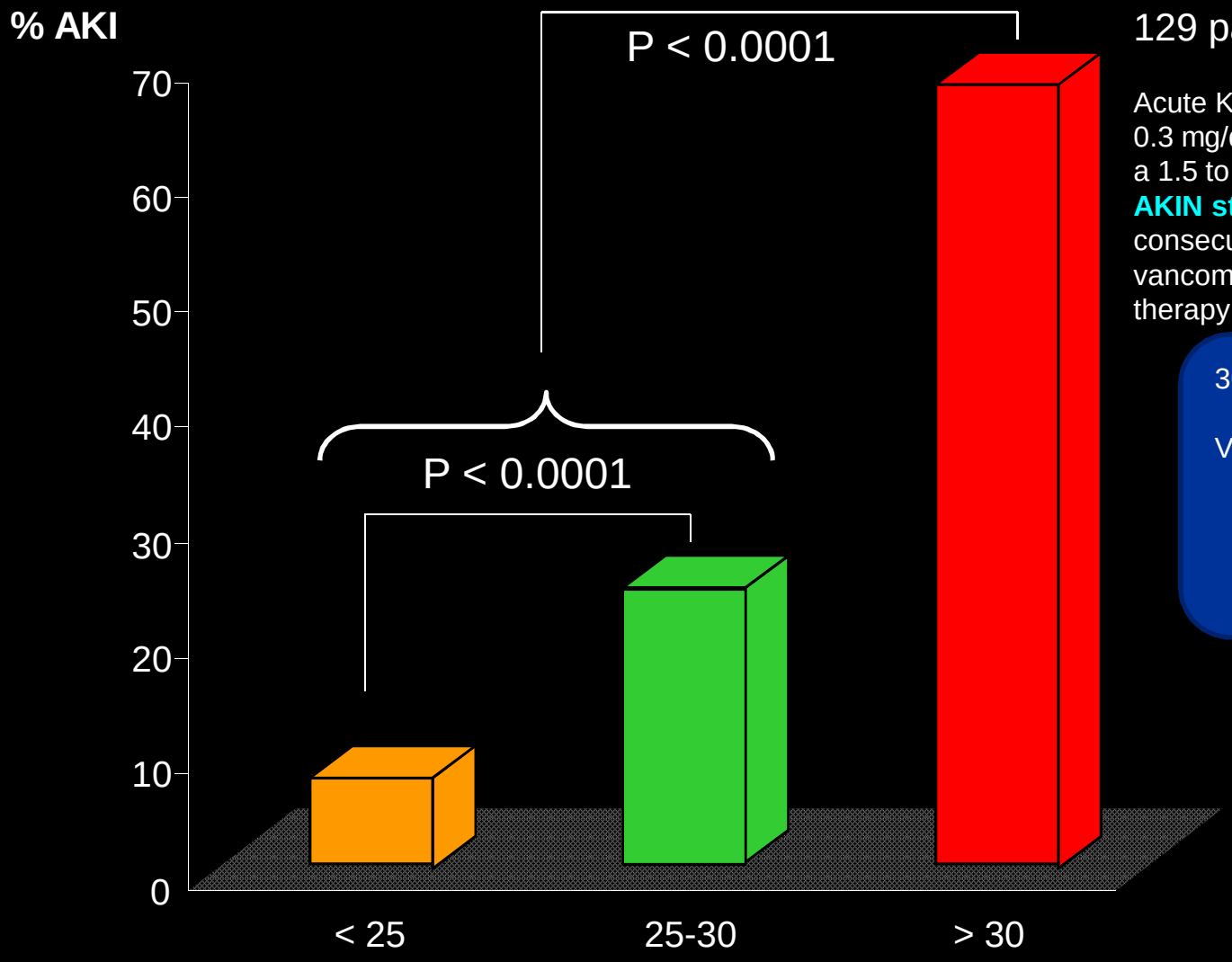
3. Less nephrotoxicity with continuous infusion of vancomycin?

Vancomycin continuous infusion and nephrotoxicity



Adapted from Cataldo MA, et al. J Antimicrob Chemother 2012

Vancomycin continuous infusion and nephrotoxicity



129 patients

Acute Kidney Injury (AKI) defined as a 0.3 mg/dL increase in creatinine level or a 1.5 to 2 x increase from baseline **(i.e. AKIN stage 1**) on at least two consecutive days from initiation of vancomycin till 72h after completion of therapy

30% developed AKI

Variables contributing to AKI:
- high vancomycin levels
- higher body weight
- severity of disease
- longer treatment duration

Spapen HD, et al. Ann Intensive Care 2011

Thank you for your attention !