

Pros and Cons of the article:
"Relationship between Initial
Vancomycin
Concentration-Time Profile and
Nephrotoxicity among
Hospitalized Patients"

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Relationship between Initial Vancomycin
Concentration-Time Profile and
Nephrotoxicity among Hospitalized
Patients

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Nephrotoxicity

- Definition
 - Increase in serum creatinine by at least 0.5 mg/dL or 50%
 - Single value or sustained increase
 - Evaluation only during therapy or include several days after discontinuing the agent in question

Background

- Mississippi Mud
 - Hypotension, fever, phlebitis, nephrotoxicity
- Purification of product
- History of vancomycin nephrotoxicity

Nephrotoxicity – 1970-1990

- 168 pts received vancomycin alone
- 63 pts received vancomycin with an aminoglycoside
- 103 patients received gentamicin alone
- Nephrotoxicity
 - 8 patients (5%) - vancomycin alone
 - 14 patients (22%) - vancomycin with an aminoglycoside
 - 11 patients (11%) - gentamicin alone
- Factors associated with increased risk of nephrotoxicity
 - concurrent therapy with an aminoglycoside
 - length of treatment with vancomycin (>21 days)
 - trough serum concentration (> 10 mg/l)

Rybak MJ, et al. J Antimicrob Chemother. 1990 Apr;25(4):679-87

Nephrotoxicity – 1970-1990

- A prospective evaluation of the safety of vancomycin was conducted in 54 consecutive patients over a 16-month period
- Reactions included:
 - Thrombophlebitis (20/54 patients)
 - Rash (4/54), proteinuria (1/50)
 - Nephrotoxicity (4/50 (8%)), and ototoxicity (1/11 patients tested by audiometry)
- Nephrotoxicity and ototoxicity were confined to patients receiving an aminoglycoside plus vancomycin

Sorrell TC, et al. J Antimicrob Chemother. 1985 Aug;16(2):235-41

Nephrotoxicity – 1970-1990

- Retrospective review of 98 patients/100 courses of vancomycin
- 6 courses could not be evaluated
- 34/94 received an aminoglycoside
 - 12/34 (35%) developed nephrotoxicity
- 60 pts received vancomycin alone
 - 3 (5%) developed nephrotoxicity

Farber & Moellering Antimicrob Agents Chemother. 1983 Jan;23(1):138-41

Nephrotoxicity – 1970-1990

Age (years)	Sex	Diagnosis*	Daily dose (g)	Length of prescription (days)	Change in serum creatinine (mg/dl)	Peak/trough levels (µg/ml) [†]	Other drugs
73	F	<i>S. aureus</i> sepsis	2.0	30	1.0 → 3.2	76/65	
59	M	<i>S. epidermidis</i> PVE	2.0	70	1.3 → 2.3	/39	
65	M	<i>S. pyogenes</i> cellulitis	1.0	26	1.2 → 1.7	35/30	Gentamicin
60	M	<i>S. aureus</i> sepsis	1.5	28	2.0 → 6.4	49/48	Furosemide-rifampin
54	M	Wound infection	2.0	7	1.1 → 3.4	25	Gentamicin
61	M	Prosthetic hip infection	1.5	30	1.0 → 2.0	19/12	Tobramycin
82	F	SBE	1.5	30	0.7 → 1.6	20/	Tobramycin-furosemide
61	M	SBE	2.0	26	1.1 → 2.8	36/21	Gentamicin
31	M	Burns, <i>S. epidermidis</i> sepsis		4	1.2 → 1.7		Gentamicin
74	F	Enterococcal PVE	2.7	13	2.1 → 4.0	37/24	Gentamicin
55	F	Osteomyelitis	1.5	17	1.0 → 1.5	30/19	Gentamicin
37	F	<i>S. epidermidis</i> PVE	2.0	26	0.8 → 2.6	26/	Gentamicin
52	F	<i>S. epidermidis</i> PVE	2.0	70	1.1 → 1.8	38/27	Gentamicin
22	M	<i>S. epidermidis</i> sepsis, VSD	2.0	28	1.3 → 2.2	22/	Gentamicin
85	F	<i>S. aureus</i> sepsis	1.5	30	1.5 → 2.1	30/27	Tobramycin

* PVE, Prosthetic valve endocarditis; SBE, subacute bacterial endocarditis; VSD, ventricular septal defect.
[†] Before rise in serum creatinine.

Farber & Moellering Antimicrob Agents Chemother. 1983 Jan;23(1):138-41

Nephrotoxicity – 1990-1999

- 198 cancer patients
 - 134 treated with other nephrotoxic agents
 - Nephrotoxicity rates were the same to those on vancomycin alone
- Trough serum levels > 15 mcg/mL were associated with significantly more nephrotoxicity (33.3% vs. 11.1%, $P < 0.03$) than low levels in the subgroups of either pretreated patients or untreated with other nephrotoxic drugs

Kralovcová K et al. J Chemother. 1997 Dec;9(6):420-6

Nephrotoxicity – 1990-1999

- 1276 patients in Europe and the United States were enrolled into 11 randomized clinical trials
- 625 patients received vancomycin at a dose of either 750-1000 mg, or 8-30 mg/kg every 12 h, over a period of 8-16 days

Wood MJ. J Antimicrob Chemother (1996) 37, 209-222

Nephrotoxicity – 1990-1999

Parameter	Teicoplanin (%)	Vancomycin (%)	P value
Clinical response ^a	435/552 (78.8%)	405/523 (77.2%)	ns
Bacteriological response ^a	220/263 (83.7%)	204/247 (82.6%)	ns
Patients with adverse events	91/651 (13.9%)	137/625 (21.9%)	0.0003
Patients with nephrotoxicity ^a	28/585 (4.8%)	58/544 (10.7%)	0.0005

Total number of teicoplanin patients = 651.
 Total number of vancomycin patients = 625.
 ns, Not statistically significant.
^aEvaluable patients.

Wood MJ. J Antimicrob Chemother (1996) 37, 209-222

Nephrotoxicity – 1990-1999

Investigator	Teicoplanin (n)	Vancomycin (n)	Number of patients with nephrotoxicity (%) teicoplanin	Number of patients with nephrotoxicity (%) vancomycin	P value
Smith et al. (1989)	35	37	1/35 (2.7%)	5/37 (14.3%)	ns ^a
Kureshi et al. (1991)	26	27	0/26 (0%)	6/27 (22%)	0.02
Charbonneau et al. (1994)	24	32	6/24 (25%)	15/32 (47%)	ns
Neville et al. (1995)	26	28	1/28 (4%)	5/28 (18%)	ns ^a
Van der Auwera et al. (1991)	37	37	0/37 (0%)	3/37 (8%)	ns
Van Laethem et al. (1988)	12	9	2/12 (17%)	2/9 (22%)	ns
Gerard et al. (1987)	21	19	no information given	no information given	—
Cony-Makhoul et al. (1990)	24	35	none reported in this study	none reported in this study	—
Hedström (1994)	53	27	2/37 (5.4%)	3/21 (14.3%)	ns
Kulmala et al. (1990)	118	122	12/111 (11%)	17/101 (17%)	ns
Menichetti et al. (1994)	275	252	4/275 (1.4%)	2/252 (0.8%)	ns

ns, Not statistically significant; n, number of patients.
^a0.5 < P < 1.0.
 NB. Each study reported had different criteria for defining nephrotoxicity. Details are given in the text.

Wood MJ. J Antimicrob Chemother (1996) 37, 209-222

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- The aim of the study was to delineate the pharmacodynamic index that best describes that relationship between vancomycin exposure and onset of nephrotoxicity
- A retrospective study from 1 January 2005 through 31 December 2006 at Albany Medical Center Hospital

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

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- 1,412 patients received vancomycin for at least 48 hours, 351 charts were randomly selected (25%)
- Inclusion criteria:
 - ≥ 18 years old
 - ANC ≥ 1000 cells/mm³
 - Received vancomycin for >48 h
 - 1 vancomycin trough level collected within 96 h of initiating therapy
 - Baseline serum creatinine level of <2.0 mg/dL
- Exclusion criteria:
 - Cystic fibrosis
 - Intravenous contrast dye within 7 days of starting vancomycin or during therapy
 - Vasopressor support during therapy

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

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- Only the initial vancomycin trough concentration was evaluated
- Modeled 3 ways:
 - Continuous variable
 - Dichotomous variable (by use of a classification and regression tree [CART]-derived breakpoint)
 - Categorical variable (with initial vancomycin trough values of ≥ 10 mg/L, 10-15 mg/L, 15-20 mg/L, and 20 mg/L)

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Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- The vancomycin AUC value from 0 to 24h at steady state (AUC_{0-24ss}) for each patient was estimated by a 2-compartment open vancomycin model
- Nephrotoxicity was defined as an increase in the sCr level of 0.5 mg/dL or 50%, whichever was greater, on at least 2 consecutive days during the period from initiation of vancomycin therapy to 72h after completion of therapy

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Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- 166/351 met the inclusion criteria
- Median baseline sCr level was 0.8 mg/dL
 - 9 (5.4%) of the 166 patients had a baseline sCr >1.5 mg/dL, and the highest was 1.8 mg/dL
- Median baseline CrCl value was 69.5 mL/min
- 21/166 (12.7%) developed nephrotoxicity
- The median peak sCr level was 2.0 mg/dL

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

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

- The median time to nephrotoxicity was 6 days
- The median duration that the sCr level remained 50% greater than baseline was 7 days
- Vancomycin therapy was discontinued in 13 (62.0%) of the 21 patients who experienced nephrotoxicity

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

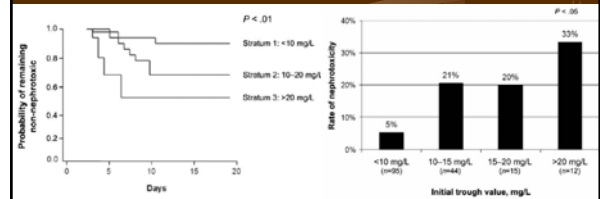
Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

Antibiotic exposure profile	Patients with nephrotoxicity (n = 21)	Patients without nephrotoxicity (n = 145)	P
Initial vancomycin trough value, mean mg/L ± SD	14.6 ± 8.3	9.6 ± 5.1	.014
Initial vancomycin trough value ≥9.9 mg/L	16 (76.2)	56 (38.6)	.00
AUC _{0-24h} value, mean mg × h/L ± SD	1318.4 ± 1147.2	898.5 ± 475.9	.11
AUC _{0-24h} value >1300 mg × h/L	7 (33.3)	20 (13.8)	.05

NOTE: Data are no. (%) of patients, unless otherwise noted. AUC_{0-24h}, vancomycin area under the curve from 0 to 24 h at steady state; SD, standard deviation.

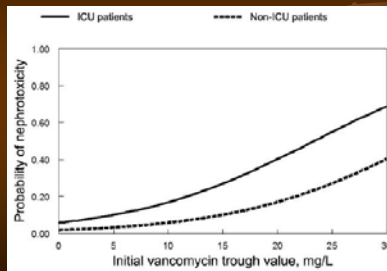
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Table 4. Cox Proportional Hazards Model for Time to Nephrotoxicity

Parameter	aHR (95% CI)	P
Empiric trough value ^a	1.13 (1.06-1.20)	<.001
Residence in ICU	2.67 (1.071-6.56)	.035
Weight ≥101 kg	3.17 (1.18-8.53)	.022

NOTE: CI, confidence interval; ICU, intensive care unit.
^a The adjusted hazard ratio (aHR) for the initial vancomycin trough value reflects the increased hazards of nephrotoxicity for each 1-unit change in the initial vancomycin trough value.

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Pros & Cons

- **Pro:** Using only the 1st trough concentration
 - Cause and effect
- **Pro:** No standardized dosing practices at the facility
- **Con:** Dosing practices to achieve higher trough concentrations were variable

Pros & Cons

- **Pro & Con:** AUC calculated using 2-compartment model
- **Pro:** Definition of nephrotoxicity & evaluation 72 hours after therapy discontinued
- **Pro:** Statistical analysis of the data
- **Con:** Sample size
 - No sample size calculation for power analysis
 - 166 patients of 1,412 possible (~12%)
 - Only 21 nephrotoxic patients

Pros & Cons

- Pro: Stratification of trough concentrations
- Pro: Discussion fair and accurate with regard to the historical nephrotoxicity rates in the literature
- Pro: Discussion of their results and those of other recent trials looking at efficacy and toxicity of higher trough concentrations

Pros & Cons

- Pro: Conclusion appropriate: caution extrapolation and the need for a multicenter, prospective study to verify their findings
- Con: If they had looked at more of their patient population would it have changed the interpretation

Thank you for your attention