IDENTIFICATION OF RISK FACTORS FOR VANCOMYCIN-ASSOCIATED NEPHROTOXCITY IN PATIENTS RECEIVING EXTENDED HIGH-TARGET THERAPY

Claire Contreiras, BSc(Pharm); Mike Legal, PharmD, ACPR; Tim T.Y. Lau, PharmD, ACPR, FCSHP;
Rosanne Thalakada, BSc, BSc(Pharm), ACPR; Stephen Shalansky, PharmD, FCSHP; Mary H.H. Ensom, PharmD, FASHP, FCCP, FCSHP, FCAHS

Background

- Impurities in original vancomycin formulation were believed to be associated with nephrotoxicity.
- Purified formulation is associated with low incidence of nephrotoxicity when conventional doses are used in absence of known nephrotoxins.
- Recent guidelines recommend higher vancomycin trough levels (15-20 mg/L) to treat invasive infections.
- With higher trough levels, concern regarding vancomycin-associated nephrotoxicity has again surfaced.
- Trough levels ≥ 14 mg/L and duration of therapy ≥ 7 days were previously identified as thresholds for development of nephrotoxicity.
- Extent to which other factors may contribute to nephrotoxicity is not yet clearly defined.

Objectives

- To determine occurrence of nephrotoxicity* in patients receiving > 7 days of vancomycin at high-target trough levels (15-20 mg/L).
- To identify and evaluate specific risk factors, in this population, related to development of vancomycin-associated nephrotoxicity.
- To describe time course and clinical outcome of nephrotoxicity.

Inclusion Criteria

- Adults receiving > 7 days intravenous vancomycin therapy
- Serum Creatinine (SCr) measurements prior to or within first week of vancomycin therapy
- Steady-state vancomycin trough level between 15-20 mg/L
- Stable renal function** during first 7 days of therapy

Exclusion Criteria

- Patients in renal failure (Creatinine Clearance (CrCl) < 10 mL/min) or receiving hemodialysis
- Patients with unclear or missing dosage and/or sampling times

Methods

- A retrospective health care record review was conducted at St Paul's Hospital and Vancouver General Hospital (Jan 2008 – Mar 2011).
- Previously identified patients reaching high-target trough levels were screened for eligibility against inclusion and exclusion criteria.
- Relevant patient data were collected and baseline characteristics are summarized in Table 1.
- Univariate analysis was used to identify possible nephrotoxicity risk factors.
- Multivariate logistic regression was performed on those risk factors identified.

* ↑SCr ≥ 26.2 µmol/L or ↑ ≥ 50 % in SCr from baseline on 2 consecutive days

** ≤ 25% increase in SCr from baseline

Table 1. Patient Demographics

	Study Population (n=176)
Male (%)	119 (67.6)
Mean Age (years)	57.8 ± 17.7
Mean Weight (kg)	73.1 ± 17.1
Median Daily Vancomycin Dose (mg)	2000 (1000)
Mean Baseline CrCl (mL/min)	100.8 ± 48.8
Median Length of Stay (days)	26 (30)
Median Length of Treatment (days)	15 (12)
Median Length of Treatment (weeks)	3 (2)
Clinical Area – Medicine (%)	84 (47.7)
Concurrent Nephrotoxins Received (%)	113 (64.2)
Developed Nephrotoxicity (%)	24 (14)

Table 2. Clinical Course of Nephrotoxicity

Mean Peak SCr (µmol/L)	134.5 ± 53.4
Median No. of days to first rise in SCr (from start of therapy)	14 (11)
Median No. of days to peak SCr (from start of therapy)	15.5 (11)
Median No. of days to resolution (from peak SCr)	7 (6)

Figure 1. Response to Nephrotoxicity

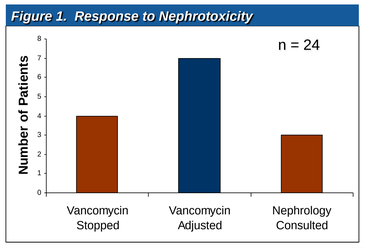


Figure 2. Resolution of Nephrotoxicity Prior to Discharge

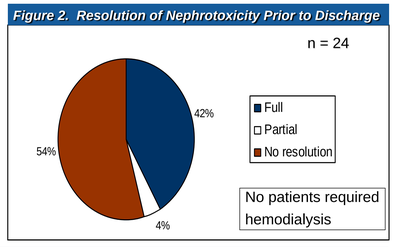


Table 3. Nephrotoxicity: Univariate Analysis

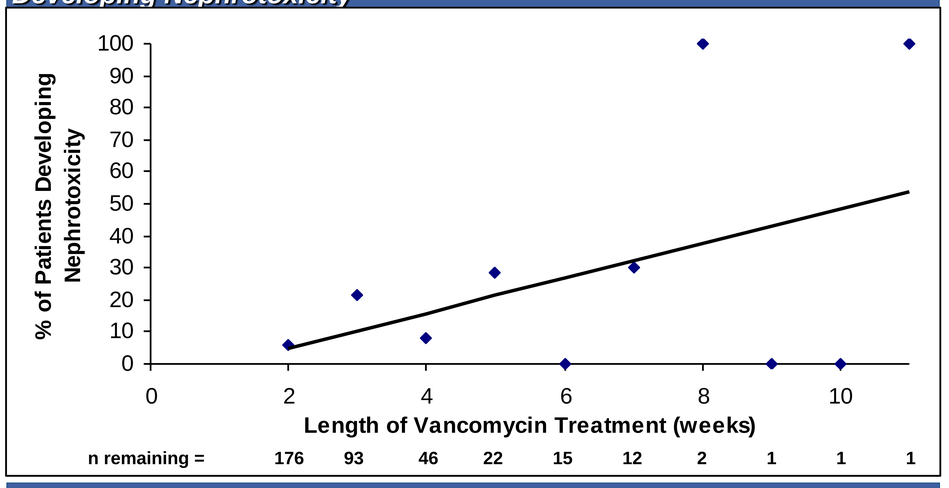
	Nephrotoxicity		
	Yes (n=24)	**No (n=152)**	**P-value**
Mean Age (years)	60 ± 19	57 ± 17	0.43
Mean Weight (kg)	74.5 ± 17.6	72.9 ± 17.1	0.68
Mean Baseline CrCl (mL/min)	103.3 ± 49	100.4 ± 48.9	0.79
Mean Baseline SCr (µmol/L)*	84.6 ± 43.1	84.5 ± 38	1
Length of Vancomycin Treatment (days)	24.8 ± 16.1	17.5 ± 10.3	0.04
Length of Vancomycin Treatment (weeks)*	**3.8 ± 2.2**	**2.9 ± 1.3**	**0.08**
Clinical Area – Medicine (%)*	**16 (66.7)**	**68 (44.7)**	**0.05**
Clinical Area – ICU (%)	2 (8.3)	14 (9.2)	0.9
Febrile Neutropenia (%)	2 (8.3)	2 (1.3)	0.03
Comorbidity – Diabetes (%)	6 (25)	30 (19.6)	0.62
Comorbidity – Hypertension (%)	9 (37.5)	49 (32)	0.71
Concurrent Nephrotoxin – Any (%)	11 (45.8)	102 (66.7)	0.04
Concurrent Nephrotoxin – ACEI or ARB (%)*	1 (4.2)	36 (23.5)	0.03
Concurrent Nephrotoxin – IV contrast dye (%)	2 (8.3)	40 (26.1)	0.05
Concurrent Nephrotoxin – NSAIDs (%)	1 (4.2)	25 (16.3)	0.1

*Variables included in multivariate logistic regression

Table 4. Predictors of Nephrotoxicity: Multivariate Model

	Adjusted Odds Ratio	95% CI	P-value
Clinical Area – Medicine	2.57	1.01-6.75	0.05
Length of Vancomycin Treatment (weeks)	1.35	1.04-1.76	0.03

Figure 3. Length of Vancomycin Treatment (weeks) vs. % of Patients Developing Nephrotoxicity



Discussion

- Length of vancomycin treatment and clinical area (Medicine) are consistent predictors of nephrotoxicity despite different approaches to expressing length of treatment (i.e. days vs. weeks) – thereby indicating stability of the multivariate model.
- Concurrent use of known nephrotoxins was not identified as a predictor of vancomycin-associated nephrotoxicity.
- Although surprising, this finding can be explained by likely increased monitoring of patients on a known nephrotoxin and avoiding their use in patients with poor renal function.

Conclusions and Recommendations

- Patients being treated on the medicine unit and receiving vancomycin courses > 7 days appear to have an increased likelihood of developing nephrotoxicity.
- The increased risk of developing nephrotoxicity in patients on the Medicine unit is likely multifactorial.
- The relationship between length of treatment and risk of nephrotoxicity appears to follow a linear trend.
- When using extended high-target vancomycin therapy, increased vigilance should be practiced to monitor for nephrotoxicity.

Future Research

- Increase sample size to try to strengthen these associations and reveal additional variables associated with an increased incidence of nephrotoxicity.
- Validate current multivariate model by evaluating and testing its predictive performance in a separate cohort of patients.

UBC · fraserhealth Better health. Best in health care. · Providence HEALTH CARE How you want to be treated. · Provincial Health Services Authority Province-wide solutions. Better health. · Vancouver CoastalHealth Promoting wellness. Ensuring care.