Vancomycin Trough Concentrations and Clinical Outcomes in Non-Deep Seated Infections: A Retrospective Study

Michael Wan,[1] BScPhm, PharmD; Sandra A.N. Walker,[1,2,3,4*] BSc, BScPhm, ACPR, PharmD, FCSHP; Elaine Martin,[2] PharmD student, Marion Elligsen,[1] BScPhm, ACPR; Lesley Palmay,[1] BSc, BScPhm, ACPR, MScPhm; Jerome A. Leis, MD, MSc, FRCPC[3,4,5]
[1]Sunnybrook Health Sciences Centre (SHSC), Department of Pharmacy; [2]University of Toronto, Leslie Dan Faculty of Pharmacy; [3]SHSC, Division of Infectious Diseases; [4]SHSC, Sunnybrook Research Institute; [5]University of Toronto, Faculty of Medicine
Underlined Author: Pharmacy Resident working under supervision of Sandra Walker at time of study; *Senior Author; sequence determines credit approach to authorship

ABSTRACT

Rationale: Vancomycin guidelines recommend dosing to attain trough concentrations >10mg/L in non-deep seated infections. However, no studies have evaluated a risk of clinical failure or demonstrated development of bacterial resistance to vancomycin used for non-deep seated infections for ≤14 days; thereby, calling into question the value of these recommendations.
Objective: The primary objective was to evaluate patients with non-deep seated infections treated with vancomycin for ≤14 days to determine whether there were differences in clinical outcome with serum trough concentrations of vancomycin <10 mg/L (low trough) versus ≥10 mg/L (high trough). The secondary objective was to identify factors that affected clinical outcome.
Methods: A retrospective chart review of patients who received vancomycin, had at least one steady state trough concentration, and were hospitalized between March 10, 2010 and December 31, 2015 was completed. Demographic and clinical outcomes for patients in the low and high trough groups were compared using appropriate statistical tests (t-test, Fisher's exact, or Mann-Whitney) and binary logistic regression was completed to identify factors associated with clinical outcome. Statistical significance was defined as p<0.05.
Results: A total of 1579/2098 patients (75%) on vancomycin were screened for eligibility and 71 patients met inclusion criteria. There was no difference in clinical cure between the low (35/39 [90%]) and high trough (24/32 [75%]) groups (p = 0.12). Patients in the high trough group had a larger change in serum creatinine from baseline (p = 0.0458) and incidence of nephrotoxicity (p = 0.037). Vancomycin trough concentration was not associated with clinical outcome (p=0.102).
Conclusion: The results indicate that there is no difference in clinical outcome based on vancomycin trough concentrations in patients with non-deep seated infections, treated with vancomycin for ≤14 days. Targeting higher troughs may be associated with increased nephrotoxicity with no corresponding benefit in clinical outcome in these patients.

BACKGROUND

- Vancomycin is a broad spectrum glycopeptide antibiotic that is widely used to treat infections from resistant organisms, including:
  - Methicillin-resistant *S. aureus* (MRSA)
  - Coagulase-negative Staphylococci (CNST)
  - *Enterococcus faecium*
- Current guidelines recommend:
  - Maintaining a minimum trough level above 10mg/L in all infections to prevent the development of resistance – based on limited data (IIIB recommendation)
- No studies to date to demonstrate the emergence of resistance to vancomycin in patients with non-deep seated infections receiving a short course of vancomycin therapy (e.g. ≤14 days).
- Targeting a trough above 10mg/L in these patients may have no clinical benefit and may:
  - Increase dosing and monitoring complexity, which may translate to increased workload, and medication error
  - Increase the risk of nephrotoxicity (dose-dependent)
  - Increase healthcare costs
  - Increase risk of infection (due to increased vascular access)

OBJECTIVES

Primary: To determine if there was a difference in clinical outcome when targeting trough concentrations of <10mg/L (low trough) versus ≥10mg/L (high trough), in patients diagnosed with non-deep seated infections, treated with vancomycin for ≤14 days.

Secondary: To identify whether known clinical or demographic factors affected clinical outcome

METHODS

Study Design and Inclusion/Exclusion Criteria
- Retrospective chart review of inpatients at Sunnybrook Health Sciences Centre (SHSC)
- Adult (age ≥18y) patients were included if:
  - Inpatient between March 12, 2010 and December 31, 2015 (SPIRIT database limits)
  - Treated with vancomycin for ≥48h and ≤14d with at least one steady state vancomycin level recorded. Steady state was defined as:
    - ≥Q12H dosing: Prior to 3rd dose, at earliest
    - ≤Q8H dosing: Prior to 4th dose, at earliest
    - Continuous infusion: 24h after dose adjustment, at earliest
  - Had presumed or confirmed non-deep seated infection for any organism that vancomycin may be indicated to treat. Non-deep seated infections were defined as:
    - Uncomplicated skin and soft tissue infections (SSTIs, such as folliculitis, carbuncle(s), surgical site infections, wound infections, non-suppurative cellulitis or erysipelas)
    - Uncomplicated urinary tract infections (without renal abscesses, renal stones, anatomic abnormalities)
    - Bacteremia (without seeding to lungs, brain, joint, bone, heart)
    - Coagulase-negative staphylococci (CNST) line-related infections (excluding tunnel infection or vascular graft infections)
  - Patients were excluded if:
    - Diagnosed with a deep seated infection (Examples: abscess at any site, endocarditis, intra-abdominal infection, meningitis, osteomyelitis, pneumonia, septic arthritis)
    - Switched from vancomycin to another antibiotic on day 2 or 3 after a culture and sensitivity report
    - Received renal replacement therapy
    - Diagnosed with febrile neutropenia
    - Received antibiotics with no documented infection (e.g. prophylactic antibiotics)
    - Vancomycin was discontinued due to palliation
  - If patients received more than one course of vancomycin over their hospital stay, only data from the 1st course of treatment was included

Outcomes

Primary outcome:
- Clinical Cure, defined as all of the following:
  - Resolution of all presenting signs and symptoms of infection within ≤14 days therapy with vancomycin
    - Patients could be discharged home on a short course of vancomycin (total duration ≤14 days) with documentation of improvement during hospital stay
  - Maintained resolution of all presenting signs and symptoms of infection for 14 days following vancomycin discontinuation
  - No additional course of antibiotics within 14 days with the same indication as vancomycin

Secondary outcome:
- Identification of clinical or demographic factors affecting clinical cure

Sample Size and Statistical Analysis
- Treatment failure rate of non-deep seated infections was estimated to be between 10-25%. Using a standard sample size equation for dichotomous data, 219 to 348 patients in each group was required to detect a difference in treatment failure of 10 percentage points (2 tailed, p=0.05, power=0.8)
- Data were analyzed using GraphPad InStat (version 3.05, 32-bit for Win95/NT; GraphPad Software Inc, La Jolla, California)
- Nominal data were compared with Fisher's Exact test
- Normally distributed Interval data with equal standard deviations were compared with the two-sided unpaired t-test
- Normally distributed Interval data with unequal standard deviations were compared using the two-sided unpaired t-test with Welch correction.
- Interval data that failed the test for normality were compared using a two-tailed Mann-Whitney test.
- Univariable (Pearson's correlation) and multivariable (binary logistic regression) analyses were used to identify clinical or demographic factors that affected clinical outcome.
- Statistical significant was defined as $p < 0.05$.

RESULTS

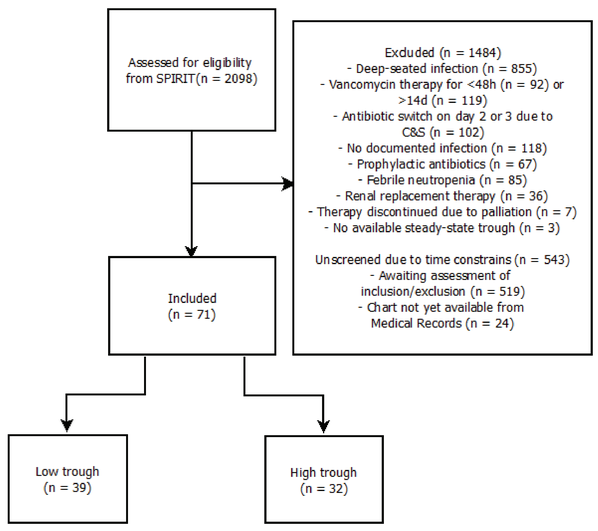

Figure 1. Inclusion and Exclusion Flow Diagram

RESULTS

Table 1. Patient Characteristics (N=71)	Low Trough (N=39)	High Trough (N=32)	P-value	Odds Ratio	95% Confidence Interval for Odds Ratio
Demographics and Baseline Clinical Factors					
Age (years; mean)	59 ± 20	63 ± 23	0.42		
(Range)	(21 - 91)	(19 - 92)			
Gender (Male)	21 (54%)	18 (56%)	>0.99	0.91	0.35-2.32
Hospital Location at Vancomycin Initiation (Ward vs. ICU)	30 (77%)	24 (75%)	>0.99	1.11	0.37-3.32
Length of Stay at Vancomycin Initiation (days; median)	2	2	0.80		
(Range)	(0 - 70)	(0 - 187)			
Any Comorbidity[a]	16 (41%)	16 (50%)	0.48	0.70	0.271-1.785
- Heart Failure	3 (8%)	5 (16%)	0.45	0.45	0.099-2.050
- Chronic Obstructive Pulmonary Disease	2 (5%)	4 (13%)	0.40	0.38	0.064-2.216
- Diabetes Mellitus	5 (13%)	5 (16%)	0.75	0.80	0.208-3.030
- Immunosuppression Due to Disease[b]	7 (18%)	3 (9%)	0.49	2.12	0.499-8.954
- Immunosuppression Due to Drug[c]	6 (15%)	1 (3%)	0.12	5.64	0.641-49.541
APACHE II[d] (ICU patients)	24 ± 6	22 ± 13	0.46		
(Range)	(11 - 25)	(6 - 41)			
Critically Ill Ward Patients (Pitt[e] ≥ 4)	1 (3%)	3 (9%)	0.32	0.25	0.025-2.575
Baseline Serum Creatinine (mmol/L)	76 ± 32	85 ± 38	0.31		
(Range)	(23 - 185)	(35 - 206)			
Use of Concomitant Antibiotics[f]	16 (41%)	13 (41%)	>0.99	1.02	0.39-2.63
Use of Concomitant Antibiotics for Same Indication as Vancomycin	13 (33%)	11 (34%)	>0.99	0.79	0.11-5.60
Included Infections					
All Skin and Soft Tissue Infections (SSTIs)	24 (62%)	23 (72%)	0.45	0.63	0.23-1.71
- Cellulitis	18 (46%)	16 (50%)	0.75	1.31	0.36-4.73
- Wound/Surgical Site Infection	6 (15%)	7 (22%)			
All Urinary Tract Infections (UTIs)	9 (23%)	3 (9%)	0.20	2.9	0.72-11.80
- Enterococcal UTI	7 (18%)	2 (6%)			
- MRSA UTI	2 (5%)	1 (3%)	>0.99	1.75	0.10-30.86
All Bacteremias	6 (15%)	6 (19%)	0.76	0.79	0.23-2.73
- Enterococcal Bacteremia	1 (3%)	0 (0%)	>0.99	0.28	0.009-8.43
- CNST Bacteremia	5 (13%)	6 (19%)			
Microbiology					
Patients With Positive Non-Screening Cultures for Resistant Gram Positives[g]	10 (26%)	11 (34%)	0.44	0.66	0.236-1.834
Patients with MRSA Clinical Culture	2 (5%)	3 (9%)	0.65	0.52	0.082-3.34
Patients with CNST Clinical Culture	8 (21%)	8 (25%)	0.78	0.77	0.25-2.36
MRSA-colonized Patients	1 (3%)	3 (9%)	0.32	0.25	0.025-2.575
VRE-colonized Patients	1 (3%)	0 (0%)	>0.99	2.53	0.100-64.35

[a] Patients may have had more than 1 comorbidity, thus totals for specific comorbidities sum to a value greater than the number of patients with any comorbidity
[b] e.g. HIV/AIDS, asplenia, hematological malignancies, transplantation
[c] e.g. Corticosteroids (prednisone >5mg/day), chemotherapy, TNF-α inhibitors, transplant medications
[d] Acute Physiology and Chronic Health Evaluation II; Arterial blood gases were not available for all ICU patients and APACHE II scoring could not be completed for these patients
[e] Pitt Bacteremia Score
[f] Concomitant antibiotic defined as: ≥48h overlap with vancomycin and administered for ≥48h
[g] Methicillin Resistant *Staphylococcus aureus*, Coagulase-negative *Staphylococci*, Vancomycin Resistant *Enterococci*

Table 2. Results (N=71)	Low Trough (N=39)	High Trough (N=32)	P-value	Odds Ratio	95% Confidence Interval for Odds Ratio
Clinical Outcomes					
Primary Outcome: Clinical Cure	35 (90%)	24 (75%)	0.12	2.92	0.79-10.79
Survival	39 (100%)	31 (97%)	0.45	3.76	0.148-95.621
Vancomycin Use and Dosing					
Final Total Daily Dose, median (mg)	2000	2000	0.43		
(Range)	(500 - 3000)	(666 - 4000)			
Patients With Daily Dose ≥3g/day	4 (10%)	9 (28%)	0.07	0.29	0.08-1.061
Initial Steady State Trough (mg/L)[a]	6.99 ± 2.27	11.54 ± 5.55	<0.001		
(Range)	(2.54 - 11.81)	(2.00 - 27.06)			
Final Steady State Trough (mg/L)[a]	7.21 ± 2.04	16.49 ± 6.72	<0.001		
(Range)	(2.95 - 9.85)	(10.22 - 38.55)			
Duration of Vancomycin Therapy (days)[b]	7 ± 3	8 ± 3	0.36		
(Range)	(3 - 15)	(3 - 15)			
Patients Requiring Dose Adjustment	7 (18%)	12 (38%)	0.10	0.36	0.123-1.081
# of Dose Adjustments Per Patient	0.21 ± 0.47	0.59 ± 0.91	0.11		
(Range)	(0 - 2)	(0 - 3)			
Time Estimate for Dose Adjustments Per Patient (minutes)	11 ± 25	31 ± 48	0.11		
(Range)	(0 - 106)	(0 - 159)			
Renal Function Outcomes					
Final Serum Creatinine (mmol/L)	69 ± 25	90 ± 47	0.02		
(Range)	(24 - 155)	(32 - 225)			
% Change in Serum Creatinine	-6% ± 19	9% ± 36	0.046		
(Range)	(-63 - 40)	(-42 - 96)			
Nephrotoxicity[c]	0 (0%)	4 (13%)	0.037	0.08	0.004-1.550

[a] Initial vs Final steady state trough concentration comparisons within groups: Low trough p-value = 0.6395; High trough p-value = 0.0021
[b] Patients were included if the intent was to treat for ≤14 days
[c] ≥50% increase from baseline serum creatinine

Table 3. Univariable and Multivariable Analyses
(Except for Trough Concentration, only variables with significant univariable analysis are shown[a])

Independent Variables	Univariable (Pearson's Correlation)		Multivariable (Binary Logistic Regression)	
	Correlation	P-value	Correlation	P-value
Low/High Trough Categorization	-0.196	0.102	-	-
Heart Failure	-0.315	0.008	4.748	0.213
Initial Steady State Vancomycin Levels	-0.253	0.033	0.973	0.784
Final Steady Stage Vancomycin Levels	-0.27	0.023	0.96	0.502
Final Serum Creatinine	-0.319	0.007	0.999	0.918
% Change in Serum Creatinine	-0.247	0.038	2.401	0.657
Nephrotoxicity	-0.379	0.001	30.855	0.168
Indication for Vancomycin	0.243	0.041	2.01	0.046[b]

[a] Clinical outcome was the dependent variable and all other factors in Tables 1 and 2 were included as independent variables in the Pearson's Correlation matrix (34 independent variables); Ratio of patients : independent variables entered into binary logistic regression was 9:1
[b] No significant difference between indications when tested with Chi-square test for multiple proportions with Marascuilo procedure

DISCUSSION

- Our results indicate no difference in clinical cure between patients with low and high vancomycin trough concentrations when vancomycin was used for the treatment of non-deep seated infections.
- This was coupled with an increased risk of harm (nephrotoxicity; p=0.037) and potential negative outcomes associated with an increased dosing complexity in the high trough group.
- Our study is the first of its kind - no studies have evaluated clinical outcomes when targeting vancomycin trough concentrations <10 mg/L versus ≥10 mg/L in patients being treated for non-deep seated infection with vancomycin for ≤14 days.
- Current infectious diseases practice guidelines recommend maintaining vancomycin serum trough concentrations above 10 mg/L in all infections to prevent the development of resistance, based on limited data (Level IIIB recommendation).
- Real-life application of these guidelines varies amongst institutions and clinicians, likely due to differing experiences and opinions regarding the current literature.
- In patients with non-deep seated infection being treated with a short course of vancomycin, the emergence of vancomycin resistance has never been reported in the literature. We did not observe the emergence of any resistance to vancomycin in our study. The emergence of vancomycin-resistant *S. aureus* has only been seen in patients with end-stage renal disease with recent hemo- or peritoneal dialysis that had recurrent MRSA infections, and had prolonged vancomycin exposure (6-18 weeks) preceding the emergence of vancomycin tolerance. No association between vancomycin trough concentrations and emergence of vancomycin resistance has been observed for any other bacteria for which vancomycin may be indicated.

Limitations:
- Our current sample size is sufficient to detect only a minimal difference of 30% points between the two groups. However, patient screening will continue to increase overall sample size and thus, reduce the minimal detectable difference.
- As a single-centre, retrospective study, unidentified confounders may exist. However, the two groups were well-balanced for all identified baseline factors (Table 1).
- Several assumptions were made (e.g. definition of steady state trough levels, definition of clinical cure/failure) due to the retrospective nature of this study.
- Patients with concomitant antibiotic treatment were included in this study, which may affect our clinical outcome. However, the number of patients with concomitant antibiotics, as well as the number of patients with concomitant antibiotics for the same indication as vancomycin, did not differ between the two groups (p > 0.99 for both).
- APACHE II scoring could not be completed for all ICU patients as arterial blood gases (ABGs) were not available for all patients. As these patients were of sufficient stability to not require ABGs, this exclusion would skew our observed APACHE II score towards a higher severity.
- Patients were excluded to avoid bias due to inadequate duration of vancomycin (<48h); thus, potentially introducing selection bias due to early mortality. However, early death attributable to infection would not be anticipated with non-deep seated infections (see "Survival" in Table 2).

Future steps:
- To achieve a larger sample size, screening of patients will continue. For a further increase in recruitment, the inclusion timeframe will be extended (i.e. beyond December 2015).

CONCLUSION

- In patients with non-deep seated infections, treated with vancomycin for ≤14 days, our results indicate:
  - No difference in clinical outcome based on vancomycin trough concentrations (<10 mg/L vs. ≥10 mg/L).
  - Higher vancomycin troughs (≥10 mg/L) may be associated with increased nephrotoxicity with no corresponding benefit in clinical outcome.
  - A potential for increased dosing and monitoring complexity, resulting in increased staff workload, potential for error, and potential introduction of infection with increased vascular access exists with the higher vancomycin trough concentration target.
- Based on our results, for patients with non-deep seated infections, targeting vancomycin troughs ≥10 mg/L is unnecessary and may increase the risk of harm.

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Disclosure:
No author has any conflict of interest related to this study.