Comparative Evaluation of Pharmacist-Managed Vancomycin Dosing in a Community Hospital Following Implementation of a System-Wide Vancomycin Dosing Guideline

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Abstract: Purpose: Evaluate the implementation of a large hospital system vancomycin dosing guideline in a community hospital with pharmacist vancomycin management. Design: Single center, retrospective and prospective quality assessment study. Methods: Pharmacist-managed vancomycin therapy was evaluated pre and post-implementation of a new dosing guideline in a study population of 586 from one community hospital. Results: Of the study population, 274 patients evaluated pre-implementation were compared to 312 patients post-implementation of the large hospital-system guideline (46.8% and 53.2%, respectively). There was no significant difference in demographics between both patient populations. Days of vancomycin therapy was shorter in the post-implementation group (4.32 ± 2.241) versus the pre-implementation group [(4.81 ± 2.764) , $p = 0.018$]. Days to goal trough was longer in the post-implementation group (3.51 ± 1.622) compared to the pre-implementation group [(3.09 ± 2.046) , $p = 0.054$]. A post-hoc regression analysis was conducted, showing that age, days of vancomycin therapy and goal trough are predictors for 77% of cases within the post-implementation group. Conclusion: The implementation of a new vancomycin dosing guideline significantly impacted days of vancomycin therapy and days to goal trough in patients on vancomycin managed by pharmacists. Our results encourage completion of future studies utilizing the regression analysis data, which may impact the future care of patient on vancomycin managed by pharmacists.

Key words: Vancomycin, therapeutic drug monitoring, pharmacokinetic monitoring, pharmacists, hospital, antibiotic.

1. Introduction

Vancomycin is one of the most commonly-used antimicrobials in the treatment of gram positive infections, especially those colonized with MRSA (methicillin-resistant *Staphylococcus aureus*). Vancomycin's effectiveness as a bactericidal agent is dependent on its time above the MIC (minimum inhibitory concentration) [1]. Due to its complex PK (pharmacokinetic) and PD (pharmacodynamic) properties, dosing vancomycin can be challenging for clinicians.

In January 2017, TJC (The Joint Commission) mandated ASPs (antimicrobial stewardship programs) within hospitals and nursing care centers [2]. According to standard MM.09.01.01, the purpose of ASPs is to improve and measure the appropriate use of antibiotic agents. This is achieved through promoting the selection of optimal antibiotics, including dose, duration of therapy, and route of administration. Pharmacists are a critical member of the ASP multidisciplinary team, and help improve patient outcomes and reduce antibiotic adverse events [2, 3, 4].

Vancomycin dosing and monitoring is one of many facets of ASPs. TJC recommends hospitals implement PK monitoring and adjustment programs for

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vancomycin [3]. In a meta-analysis of studies evaluating vancomycin dosing, hospitals with vancomycin TDM (therapeutic drug monitoring) produced more favorable outcomes of clinical efficacy than those without TDM (OR 2.62, 95% CI 1.34-5.11, $p = 0.005$) [5, 6]. When comparing patients on vancomycin pre and post-implementation of a pharmacist-directed pilot program, the percentage of patients who received optimal (i.e. ≥ 30 mg/kg/day within 24 h of initiation of therapy) vancomycin doses was significantly greater in the pharmacist-managed vancomycin group compared to those not managed by pharmacists (96.8% vs. 40.4%, respectively) [7]. Over 50% more patients were optimally dosed and had a shorter duration of therapy (10.0 vs. 8.4 days, $p < 0.003$) [7].

In addition to achieving optimal dosing, pharmacist vancomycin management provides clinical and economic benefits. In hospitals without pharmacist-managed aminoglycoside and vancomycin therapy, length of stay was 12.28% greater (131,660 excess patient days) and death rates were 6.71% higher (1,048 excess deaths) ($p < 0.0001$). Laboratory charges were 7.80% increased (\$22,530,474 in excess charges) and total Medicare charges were 6.30% higher (\$34,769,250) ($p < 0.0001$) compared to hospitals that have pharmacist-managed vancomycin and aminoglycoside therapy. Lastly, in hospitals lacking pharmacist management, there was an excess of \$34,769,250 in drug charges [8]. Pharmacists play an important role in achieving and improving patient clinical outcomes and benefiting the health system through multiple cost-savings.

The IDSA (Infectious Diseases Society of America), ASHP (American Society of Health-System Pharmacists), and the SIDP (Society of Infectious Diseases Pharmacists) released consensus hospital recommendations for vancomycin therapeutic guidelines in 2009. Some of the recommendations were calculating initial vancomycin doses based on actual body weight, with subsequent doses

administered based on serum trough concentrations. Trough concentrations are deemed the most accurate and effective method of monitoring vancomycin, and should be drawn before the fourth dose as this is approximately the time when vancomycin is at steady-state within the body [9]. Lastly, the consensus statement identifies concentration ranges to improve vancomycin penetration and clinical outcomes. In patients with more severe infections such as bacteremia, sepsis, osteomyelitis, endocarditis, meningitis and pneumonia, trough serum concentrations of 15-20 mg/L are recommended. Lower trough concentrations of 10-15 mg/L are appropriate for SSTIs (skin and soft tissue infections) and UTIs (urinary tract infections) [9].

Following the 2009 guidelines a survey of U.S. hospitals was conducted to identify similarities and inconsistencies in vancomycin dosing. Of 163 respondents, pharmacy services were automatically consulted to dose vancomycin in 51% of the institutions [10]. Even with the consensus guidelines and pharmacist vancomycin management, actual vancomycin dosing practices are not universal among hospitals. Of the recommendations, a majority of hospitals do use trough target concentrations of 15-20 mg/L for more complicated infections. However, there is great variability in timing of trough concentrations and use of loading doses [10].

UHSJMC (University Hospitals St. John Medical Center) is a 204-bed nonprofit teaching community hospital that provides care to patients in northeast Ohio. Since 2011, pharmacists at UHSJMC have been consulted to dose and monitor vancomycin. While utilizing the established protocol (Fig. 1), pharmacists have hypothesized that adjustments may be necessary in the young, renally impaired, and elderly populations. Following incorporation into UH (University Hospitals) health system in late 2015, UHSJMC adopted UH's vancomycin dosing guideline (Fig. 2). The new vancomycin guideline provides clear, concise, and conservative dosing recommendations

St. John Medical Center Vancomycin Dosing and Monitoring		
Weight (Kg)	Dose (mg) Trough Goal 10-15mg/L (~15mg/kg/dose)	Dose (mg) Trough Goal 15-20 mg/L (~20mg/kg/dose)
< 60	750	1000
60 – 70	1000	1250
71-80	1250	1500
81 - 100	1500	1750
>100	1500	2000
Est CrCl (ml/min)	Dosing Interval	
> 50*	Q 12 hours	
30 – 49	Q 24 hours	
< 30	Give one dose, then check random vancomycin level in 24 hours. Re-dose when level is within target trough range <u>OR</u> Q 48 hours and check level prior to second dose	

Fig. 1 UHSJMC vancomycin dosing guideline (Pre-UH guideline).

in an organized manner compared to the original dosing guideline utilized by pharmacists at UHSJMC. The purpose of this study is to evaluate the implementation of a large hospital system vancomycin dosing guideline in a community hospital with pharmacist-managed vancomycin dosing.

2. Materials and Methods

2.1 Study Design

This was a single center, retrospective and prospective quality assessment study conducted at UHSJMC in Westlake, Ohio. We evaluated patients on vancomycin managed by pharmacists from November 1, 2015 to March 31, 2016 (“Pre-UH guideline”). In September 2016, we re-designed the UHSJMC hospital vancomycin guideline to match that of UH (Fig. 2). The new dosing guideline was approved by the PNT (Pharmacy, Nutrition, and Therapeutics) committee, the ID (infectious disease) physician, and the UH institutional review board (IRB # NHR-16-102). Pharmacists and prescribers were

educated on the new vancomycin dosing changes and the new guideline was fully implemented in October 2016. Pre-UH guideline data was then compared to patients on vancomycin managed by pharmacists from November 1, 2016 to March 31, 2017 (“Post-UH guideline”). Patients in both groups were included if they were ≥ 18 years old and initiated on vancomycin therapy managed by pharmacists in the aforementioned time frame. Patients were excluded if they were < 18 years old, pregnant, cognitively impaired, diagnosed with ESRD (end stage renal disease), or those without vancomycin trough levels. Patients with ESRD were excluded due to the complexity and variability of vancomycin dosing and monitoring. Those without a vancomycin trough level drawn during the consult were also excluded because of the inability to evaluate the primary outcome.

The primary objectives of this study were days to goal serum trough concentration and total days of vancomycin therapy. These data endpoints were based upon previous studies evaluating vancomycin dosing

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Pharmacy Vancomycin Dosing & Monitoring

Usual empiric dose: 15-20mg/kg/dose

Note: a loading dose of 25-30 mg/kg can be considered for certain severe infections

Dose based on actual body weight (NOT to exceed 2g per dose); round each dose to nearest 250mg

Weight (kg)	CrCl (mL/min) – based on cockcroft-gault equation				
	≥ 50 ¹	30 – 49	< 30 ²	Intermittent HD	CRRT
< 40	500mg Q12H	500mg Q24H	500mg X 1 dose	< 70kg 1g load; Then 500mg after each HD	15 – 25 mg/kg loading dose; Then 10-15 mg/kg Q24H
40 - 54	750mg Q12H	750mg Q24H	750mg X 1 dose		
55 - 74	1g Q12H	1g Q24H	1g X 1 dose		
75 - 89	1.25g Q12H	1.25g Q24H	1.25g X 1 dose	70 – 100kg 1.25g load; Then 750mg after each HD	
90 - 109	1.5g Q12H	1.5g Q24H	1.5g X 1 dose	> 100kg 1.5g load; Then 1g after each HD	
110 - 125	1.75g Q12H	1.75g Q24H	1.75g X 1 dose		
> 125	2g Q12H	2g Q24H	2g X 1 dose		

¹ Higher frequency (i.e. Q8H) may be needed when rapid drug clearance is anticipated, such as younger patients with normal renal function, etc. Lower initial frequency may be warranted in elderly patients (i.e. > 75 years) due to age-related reduction in renal function.

² CrCl < 30 and AKI with changing renal function: Give one time dose, check vancomycin level 24 hours after dose is administered. Re-dose vancomycin if level is ≤ goal trough. If level is > goal trough, check another random level in 24-48 hours.

(A)

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Pharmacy Vancomycin Dosing & Monitoring

Target Vancomycin Trough Levels Based on Condition		
10 – 15 mg/L	Other infections, including: SSTI, UTI, etc.	
15 – 20 mg/L	Pneumonia, sepsis, bacteremia, meningitis, endocarditis, osteomyelitis, etc.	
Vancomycin Dose Adjustments Based on Trough Level		
Trough (mg/L) ³	Goal 10 – 15 mg/L	Goal 15 – 20 mg/L
< 10	Increase dose by 250 – 500mg OR Increase frequency (e.g. Q24 → Q12)	Increase dose by 250 – 500mg OR Increase frequency (e.g. Q24 → Q12)
10 – 15	No change	Increase dose by 250 – 500mg
15 – 20	Decrease dose by 250 – 500mg	No change
20 – 25	Decrease dose by 250 – 500mg OR Decrease frequency (e.g. Q12 → Q24)	Decrease dose by 250 – 500mg
> 25	Hold dose & re-check level after 24 hours; adjust therapy accordingly	Hold dose & re-check level after 12 – 24 hours; adjust therapy accordingly

³ Note: it is essential to check timing of trough level collection in comparison to time vancomycin dose was given to ensure a true trough value. Troughs should be drawn 30 minutes before the 4th dose, unless if patient on HD (check before HD session)

(B)

Fig. 2 UHSJMC vancomycin dosing guideline (Post-UH guideline) card with empiric dosing (A) and dosing adjustments (B).

protocols in the hospital setting. Additional data collected were patient weight (kg), white blood cell count (WBC), temperature (T), age divided into categories (young: < 40 years, middle-age: 40-64

years, and elderly: ≥ 65 years), serum creatinine (sCr), creatinine clearance (CrCl; using Cockcroft-Gault equation) divided into categories (normal > 50 mL/min, mild impairment 30-49 mL/min, and severe

impairment < 30 mL/min), and vancomycin indication.

2.2 Statistical Analysis

It was determined that a sample size of 84 patients per study group (pre and post-UH guideline) was required to achieve a power of 90%. Continuous data are displayed as mean $\pm$ SD (standard deviation) and were compared using the student's *t* test. Categorical data were evaluated using proportions and were compared using the χ^2 test. A post-hoc regression analysis was conducted to correlate study variables pre and post-UH guideline with clinical outcomes. A *p* value of ≤ 0.05 was considered statistically significant.

3. Results and Discussion

3.1 Results

A total of 1,096 patients were reviewed for inclusion in the study with a total of 586 patients enrolled, 274 and 312 in the pre and post-UH guideline groups, respectively (Fig. 3). A majority of patients in both groups were in the elderly age category and normal renal function category. There were no statistically significant differences in baseline demographics between the two groups (Table 1).

Of the 586 patients, the most common infections treated with vancomycin were SSTIs, pneumonia, and sepsis (Fig. 4). In the pre and post-UH guideline groups, 138 (50.4%) and 148 (47.4%) of patients achieved their goal serum concentration. Of the 138 patients in the pre-UH group, 57 (41.3%) had a goal trough of 10-15 mg/L and 81 (58.7%) had a goal trough of 15-20 mg/L. The mean days to goal trough in both groups were 2.70 and 3.95 respectively. Furthermore, of the 148 patients in the post-UH group, 55 (37.2%) had a goal trough of 10-15 mg/L and 93 (62.8%) had a goal trough of 15-20 mg/L. The mean days to goal trough in this group were 3.18 and 3.74.

The mean days of vancomycin therapy were statistically reduced in the post-UH guideline group

(*p* = 0.018) versus days to goal serum trough concentration, which was greater in the post-UH guideline group (*p* = 0.054) (Table 2).

3.2 Discussion

Previous data has proven that pharmacists play an important role in ASPs. According to vancomycin guidelines published by the IDSA, ASHP and SIDP in 2009, vancomycin should be monitored via serum trough concentrations prior to the fourth dose. Concentrations of 10-15 mg/L are recommended for UTIs and SSTIs, and concentrations of 15-20 mg/L are recommended for sepsis, osteomyelitis, meningitis, and pneumonia. In hospitals surveyed, approximately 50% have pharmacists consulted to dose vancomycin. However, with ASPs, vancomycin guidelines and pharmacist involvement, hospitals still lack universal vancomycin management [1-10].

Prior to the initiation of the UH vancomycin dosing guideline, pharmacists at UHSJMC hypothesized that adjustments may be necessary in certain populations

Fig. 3 Patient enrollment.

Fig. 4 Most common vancomycin indications (%).

Table 1 Baseline demographics.

	Pre-UH Guideline (n = 274, 46.8%)	Post-UH Guideline (n = 312, 53.2%)	<i>p</i> Value
Age category, n (%)			
Young	18 (6.6)	25 (8.0)	0.786
Middle-age	97 (35.4)	111 (35.6)	0.786
Elderly	159 (58.0)	176 (56.4)	0.786
Renal function category, n (%)			
Normal	136 (49.6)	162 (51.9)	0.550
Mild impairment	67 (24.5)	67 (21.5)	0.550
Severe impairment	70 (25.5)	78 (25.0)	0.550
Male, n (%)	152 (55.5)	154 (49.4)	0.204
Female, n (%)	122 (44.5)	158 (50.6)	0.987
Age (mean $\pm$ SD)	66.63 $\pm$ 15.59	66.65 $\pm$ 17.26	0.987
sCr (mean $\pm$ SD)	1.514 $\pm$ 1.12	1.529 $\pm$ 4.14	0.955
CrCl (mean $\pm$ SD)	54.292 $\pm$ 34.44	62.428 $\pm$ 100.49	0.219
WBC (mean $\pm$ SD)	12.235 $\pm$ 7.04	11.767 $\pm$ 6.23	0.394
Temp (mean $\pm$ SD)	36.985 $\pm$ 0.81	36.837 $\pm$ 3.10	0.447
Height (mean $\pm$ SD)	169.39 $\pm$ 18.87	166.86 $\pm$ 25.23	0.188
Weight (mean $\pm$ SD)	121.86 $\pm$ 54.23	93.60 $\pm$ 81.56	0.363
IBW (mean $\pm$ SD)	63.89 $\pm$ 13.45	62.559 $\pm$ 14.41	0.269
Goal trough 10-15 mcg/L, n (%)	92 (33.6)	96 (30.8)	0.474
Goal trough 15-20 mcg/L, n (%)	182 (66.4)	216 (69.2)	0.474
Goal attained, n (%)	138 (50.4)	148 (47.4)	0.479

UH = University Hospitals, SD = standard deviation, sCr = serum creatinine, CrCl = creatinine clearance, WBC = white blood cell count, Temp = temperature, IBW = ideal body weight.

Table 2 Primary outcomes.

	Pre-UH guideline (n = 274, 46.8%)	Post-UH guideline (n = 312, 53.2%)	<i>p</i> Value
Days of vancomycin therapy (mean $\pm$ SD)	4.81 $\pm$ 2.764	4.32 $\pm$ 2.241	0.018
Time to goal serum trough concentration (mean $\pm$ SD)	3.09 $\pm$ 2.046	3.51 $\pm$ 1.622	0.054

due to differences in pharmacokinetic and pharmacodynamic characteristics. Empiric vancomycin dosing pre-UH was based on weight and goal trough concentrations, with the dosing interval based on CrCl. While the new vancomycin dosing guideline at UHSJMC is similar to the old version, there are a few differences. Empiric vancomycin dosing is solely based upon the patient weight and renal function and does not take the goal trough concentration into consideration. In the same manner as the original vancomycin guideline, the UH guideline formats its dosing frequency based on the patient's renal function, or CrCl. Both guidelines utilize the same CrCl ranges, with the UH guideline

more clearly stating the recommendations for patients with intermittent HD (hemodialysis) and CRRT (continuous renal replacement therapy). There are also more dosing ranges based on weight in the new dosing guideline, which is beneficial for those patients who weigh less than 60 kg.

The following is an example of the dosing differences between the two vancomycin protocols:

JR is an 83 year old male who weighs 76kg with a CrCl = 32 mL/min. You are consulted to dose vancomycin for presumed pneumonia in JR. Based on the old vancomycin dosing guideline, JR would be prescribed vancomycin 1.5 g IV every 24 h. However, based on the new vancomycin guideline, JR would

receive vancomycin 1.25 g every 24 h. Although the differences are minimal in this example, this illustrates the more conservative approach of vancomycin dosing in the new vancomycin guideline.

In the process of collecting data for the study, an issue regarding the appropriate dosing of vancomycin was identified. Consensus guidelines recommend the use of ABW (adjusted body weight) to calculate CrCl in patients who are obese. Most pharmacists did not calculate or use ABW when dosing vancomycin in patients whose actual body weight was 30% greater than their IBW. This was identified at study completion. While this would not have significantly impacted the results of this study, it is important to assure correct doses of vancomycin which are provided to obese patients. As a result of this finding, pharmacists were re-educated on identifying appropriate patients to use ABW when dosing vancomycin.

In this study, 138 patients in the pre-UH guideline group (50.4%) and 148 patients in the post-UH guideline group (47.4%) reached goal trough. This rate of achieving goal trough is appropriate with both groups, as patients tend to be discharged or vancomycin is discontinued before reaching goal serum trough concentration. There was no significant difference in demographics between both groups. Of the primary endpoints, both days of vancomycin therapy and days to goal trough concentration were statistically significant. In the post-UH guideline group, days of vancomycin therapy was significantly lower ($p = 0.018$). Our reasoning for this result is that with the recent increase in pharmacist involvement in the ASP, pharmacists at UHSJMC are more vigilant in monitoring antimicrobial use 48 h post-initiation and recommending de-escalation of therapy when appropriate. In addition, days to goal serum trough concentration was significantly higher in the post-UH guideline group ($p = 0.054$). Reasoning for this abnormal change is the variability in vancomycin dosing frequency, which impacts the time the trough

concentration is drawn. For example, with vancomycin that is dosed every 8 h a trough is typically drawn on day two of vancomycin therapy (i.e. before the fourth dose). On the other hand, with vancomycin that is dosed every 24 h a trough concentration is drawn on the fourth day of therapy (i.e. before the fourth dose). In this study we evaluated time to goal trough in days, rather than in number of doses which is why our data is skewed in favor of the old vancomycin dosing guideline.

There are several strengths and limitations to this study. First, there was no significant difference in demographics, which is beneficial when comparing the patient populations in both study groups. The new vancomycin guideline provided clear and concise dosing recommendations in an organized manner, and was more conservative than the original dosing guideline utilized by UHSJMC. This is a strength as it addressed the issue of inappropriately dosing certain patient populations at UHSJMC.

During the pre-UH guideline era, pharmacists at UHSJMC rounded sCr to 1 while calculating CrCl if the patient was older than 65 and had a serum creatinine less than 1. In September 2016, around the time of the post-UH guideline study phase, this rounding policy was found unfavorable at UHSJMC and the practice was discontinued prior to the initiation of the new UH vancomycin dosing guideline. This change in the sCr rounding and CrCl calculations is one of the limitations to our study. In addition to the rounding policy, pharmacists did not use ABW when determining vancomycin therapy in obese patients. Following study completion, pharmacists were re-educated regarding the correct calculation of vancomycin dosing in the obese. The evaluation of days to goal trough is our final limitation to the study. This value is dependent on whether the vancomycin is dosed every 8 h versus daily. We would like to re-evaluate this endpoint based on number of vancomycin doses in future studies.

A post-hoc regression analysis was completed and

revealed the patient's age, total days of vancomycin therapy, and goal serum trough concentration are predictors for 77% of the cases in the post-UH guideline group. Although this study was not powered for a regression analysis, these results are promising for future vancomycin studies. If an equation utilizing these three variables was generated to develop a vancomycin dosing regimen, it is hypothesized it could accurately predict an appropriate vancomycin course of therapy 77% of the time in our patient population. This information can be used as a predictive model for future studies in analyzing vancomycin therapeutic drug monitoring in a community hospital setting.

4. Conclusions

Literature comparing various vancomycin dosing protocols is limited. This study contributes to current practice via the comparison of two different vancomycin dosing protocols managed by pharmacists in a community hospital. Of key endpoints identified in previous vancomycin literature, our study specifically evaluated days of vancomycin therapy and days to goal trough concentration. The results of these endpoints were statistically significant. Clinically, our results support previous data on pharmacist-managed vancomycin dosing and achieving favorable outcomes. Our research not only supports and fulfills TJC standard for ASPs, but also provides insight on some of the differences between hospital vancomycin dosing protocols. It is our hope that this data can be used in other hospitals to ignite conversation regarding a more universalized approach to vancomycin dosing. There is more information on the subject of therapeutic vancomycin dosing to be determined, and we are on the forefront of combining our data with others in the production of future studies to optimize patient care.

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