A Retrospective Quality Improvement Study of Pharmacist-Directed Vancomycin Dosing Among Adult Home Infusion Patients

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ABSTRACT

Background

Vancomycin is widely used to treat gram-positive infections. Vancomycin therapy is accompanied by the clinical monitoring of trough levels in order to maintain therapeutic efficacy and patient safety. The home infusion patients receiving vancomycin therapy may undergo physiologic changes from inpatient care to home infusion that could affect their response to therapy. Home infusion pharmacists are uniquely positioned to facilitate continued acute monitoring, assess pharmacokinetic changes, and further support the patient transitioning to the post-acute care setting. There is insufficient data regarding the impact of pharmacist-directed vancomycin dosing and utilizing a standardized protocol within the home infusion setting. Using results from this study, this institution intends to demonstrate the value that pharmacists have in recommending therapeutic adjustments, developing a formal pharmacist-directed dosing protocol, and providing education to clinical pharmacists about the use of that protocol.

Methods

This retrospective, quality improvement study characterized data from patients receiving pharmacist-directed vancomycin dosing. This study included patients ≥18 years of age who received vancomycin dosed to a goal trough of 15-20 mg/L and were on service between January 1, 2021, and December 31, 2021. The primary objective of this study was to evaluate the efficacy of pharmacist-directed vancomycin therapy in a home infusion setting by analyzing rates of therapeutic trough levels, duration of therapy, and resolution of infection. The secondary objective of this study was to evaluate safety outcomes in patients receiving vancomycin in a home infusion setting by analyzing the incidence of acute kidney injury (AKI).

Results

Thirty-one patients met the inclusion criteria for retrospective analysis. Eighteen patients (58.06%) experienced resolution of infection. Of the patients who did not meet the criteria for resolution of infection, 11 (78.6%) had therapeutic extensions. The median duration for therapeutic extensions was 12 days. The average trough with pharmacist-directed dosing was 16.71 ± 4.84 mg/mL. When assessing the secondary outcomes of patients with supratherapeutic troughs, it was reported that 4 patients (13%) experienced adverse safety events. Two patients (6.5%) experienced AKI secondary to vancomycin therapy. Both patients had supratherapeutic vancomycin troughs at the time of AKI appearance.

Conclusion

Pharmacist-directed dosing led to sustained improvements in therapeutic troughs and maintained a low incidence of AKI.

Keywords: Vancomycin, pharmacokinetic dosing, clinical monitoring, antibiotic, infectious disease, home infusion

Background

Vancomycin, a glycopeptide antibiotic, is widely used to treat various gram-positive infections in inpatient, outpatient, and home infusion health care settings. Vancomycin therapy is accompanied by the clinical monitoring of trough levels in order to maintain therapeutic efficacy and patient safety. Therapeutic efficacy is frequently described as achieving and maintaining vancomycin troughs within goal ranges. Maintenance of therapeutic safety involves the prevention of adverse drug reactions (ADRs), including acute kidney injury (AKI). Vancomycin is associated with a broad incidence of AKI dependent on the study referenced (0-40%).[1] The patients at the greatest risk of experiencing adverse safety outcomes are those who reach supratherapeutic trough levels.[1] Patients more susceptible to reaching supratherapeutic trough levels are those treated to higher goal troughs of 15-20 mg/L.[2]

Pharmacokinetic vancomycin dosing protocols are widely developed and utilized in inpatient health care settings as they generally have been proven to improve efficacy and safety outcomes associated with patient care. Marquis et al. completed a pre-post study to evaluate the impact and utility of implementing a pharmacist-driven protocol in an inpatient setting.[3] The pre-implementation phase involved retrospective audits of medical records for patients receiving vancomycin therapy during a defined time range, and the post-implementation phase involved the utilization of a pharmacist-driven vancomycin protocol, which employed traditional, trough-based, and area under the curve (AUC) pharmacokinetic dosing strategies.[3] Data analyses from this study showed improved patient outcomes, including increases in optimal dosing, decreases in nephrotoxicity, and reduced duration of vancomycin therapy after implementation.[3] Analyses from this study and studies with similar designs in the inpatient setting also allow institutions to see a pharmacist-driven impact on patient outcomes as they refine vancomycin dosing practices.[3-7] Unfortunately, there is currently insufficient data regarding the impact of pharmacist-directed vancomycin dosing and utilizing a standardized protocol within the home infusion setting.

Patients receiving prolonged courses of vancomycin in the home not only require assessment of therapy-specific parameters on a clinically appropriate schedule, but also, these lab assessments need to be coordinated with the individual patient's vancomycin administration time. Additionally, patients discharged from the hospital to the home after an acute hospital stay may undergo physiologic changes, including hydration status, from inpatient care to home infusion that could affect their response to vancomycin therapy. Home infusion pharmacists are uniquely positioned to facilitate continued acute monitoring, assess pharmacokinetic changes, and further support patients transitioning to the post-acute care setting. Using results from this study, this institution intends to demonstrate the value that pharmacists have on recommending therapeutic adjustments, develop a formal pharmacist-directed dosing protocol, and provide education to clinical pharmacists about the use of that protocol.

Methods
Study Design

This was a retrospective, quality improvement study, which characterized data from a 12-month sample of patients receiving pharmacist-directed vancomycin dosing. Pharmacist-directed dosing is defined as pharmacist-recommended dose changes provided to and accepted by the prescribing/managing provider. This study included patients ≥18 years of age who received vancomycin dosed to a goal trough of 15-20 mg/L and on service with a home infusion provider servicing Pennsylvania, northeastern West Virginia, eastern Ohio, and western New York between January 1, 2021, and December 31, 2021. The goal trough range was chosen to evaluate outcomes in patients at a higher risk of negative safety outcomes, including AKI. Patients must also have received initial vancomycin therapy or loading doses in the inpatient setting, before transitioning to therapeutic continuation in the home infusion setting. Patients receiving vancomycin for surgical prophylaxis were excluded.

The study received approval from the institution's Quality Review Board (QRB) and was exempt from Institutional Review Board (IRB) approval. Data was de-identified and maintained confidentially. Data was collected via retrospective electronic health record (EHR) review.

The primary objective of this study was to evaluate the efficacy of pharmacist-directed vancomycin therapy in a home infusion setting by analyzing

rates of therapeutic trough levels, duration of therapy, and resolution of infection. Therapeutic trough levels included troughs that were collected at appropriate intervals relative to dosing and were within the goal range of 15-20 mg/L. Duration of therapy was analyzed to determine whether therapeutic extensions were required to resolve infection. Resolution of infection was defined as completion of vancomycin therapy for expected duration (without extension) and without therapeutic change to an alternative antibiotic. Data collected to assess the primary objective included vancomycin troughs, vancomycin regimens and changes, and intended (as originally ordered) and actual therapy duration.

The secondary objective of this study was to evaluate safety outcomes in patients receiving vancomycin in a home infusion setting by analyzing the incidence of AKI defined by KDIGO guidelines (1.5 times increase in serum creatinine from baseline within the last 7 days), non-AKI ADRs, and premature discontinuation of therapy.[8] The specific definition for AKI from KDIGO guidelines was selected due to the weekly frequency with which labs are typically collected for home health patients. Premature discontinuation of therapy was defined as discontinuation secondary to safety reasons (AKI, non-AKI ADRs, and patient death). Data collected to assess the secondary objectives included laboratory markers of renal function (BUN, SCr), supratherapeutic trough values (troughs >20 mg/L), concomitant nephrotoxic therapies associated with acute tubular injury (antimicrobials, chemotherapeutic agents, calcineurin inhibitors, diuretics), concomitant disease states considered susceptibilities for AKI (chronic kidney disease, congestive heart failure, hypertension, diabetes mellitus, malignancy, anemia), and therapeutic discontinuation secondary to AKI and non-AKI ADRs.[3-6, 9]

Statistical Analysis
Data was analyzed and tabulated using descriptive statistics to identify central tendency. Statistical means were used to characterize continuous data sets with normal distributions. Standard deviations (SD) were used to represent the spread of data sets with calculated means. Statistical medians were

used to characterize continuous data sets with skewed distributions. Interquartile ranges (IQR) were used to represent the spread of data sets with calculated medians.

Results
Patients with vancomycin therapy in their institutional profile were screened for inclusion in the study. Thirty-one patients ultimately met inclusion criteria for retrospective analysis. Most patient exclusions occurred due to the following reasons: physician-directed vancomycin dosing was used, patients had goal troughs outside of the study range, and patients did not ultimately receive vancomycin after they were referred for onboarding (due to change in antibiotic therapy after initial referral or decision for patients to complete vancomycin courses in the hospital). The baseline characteristics represented a relatively uniform patient population. There were more males than females with the majority of patients being white males without underlying renal insufficiency (Table 1). Osteomyelitis was the most common indication for vancomycin therapy, occurring in 14 patients (45.16%). Methicillin-

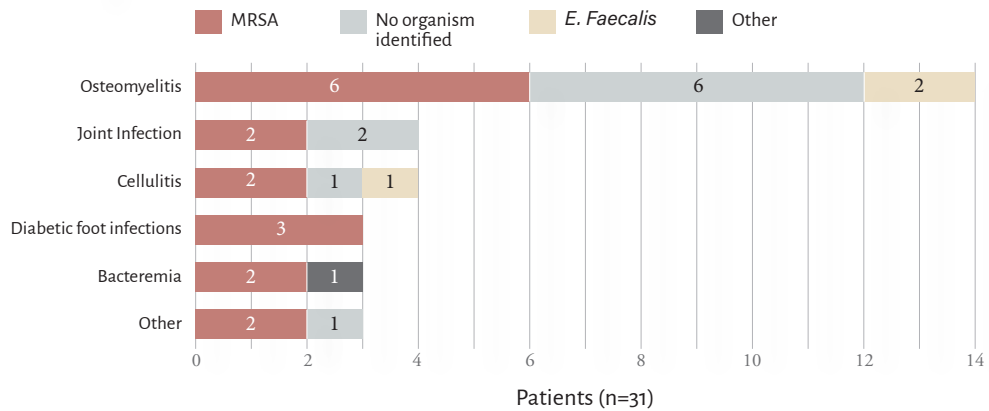TABLE 1 | Baseline Characteristics of Home Infusion Patients Receiving Vancomycin

Patient Characteristics (n = 31)	
Age, years[a]	61.29 ± 14.13
Male sex assigned at birth, n (%)	21 (67.74)
Race (non-Hispanic/white), n (%)	31 (100)
Height, inches[a]	68.6 ± 4.81
Ideal body weight, kg[a,b]	68.32 ± 12.64
Adjusted body weight, kg[a,b]	79.98 ± 11.05
Total body weight, kg[a,b]	97.47 ± 22.65
Renal Function (n = 31)	
SCr, mg/dL[a,b]	1.05 ± 0.58
BUN, mg/dL[a,b]	19.58 ± 11.90
CrCl, mL/min[a,b]	93.37 ± 43.39
Concomitant Nephrotoxic Therapy (n = 31)	
Loop diuretics, n (%)	9 (29.03)

Abbreviations: SCr, serum creatinine; BUN, blood urea nitrogen; CrCl, creatinine clearance
   a. Data presented as mean ± SD.
   b. Values at the time of outpatient onboarding

FIGURE 1 | Infection Characteristics of Vancomycin Patients

Legend: MRSA, No organism identified, *E. Faecalis*, Other

Osteomyelitis: 6 (MRSA), 6 (No organism identified), 2 (*E. Faecalis*)
Joint Infection: 2 (MRSA), 2 (No organism identified)
Cellulitis: 2 (MRSA), 1 (No organism identified), 1 (*E. Faecalis*)
Diabetic foot infections: 3 (MRSA)
Bacteremia: 2 (MRSA), 1 (Other)
Other: 2 (MRSA), 1 (No organism identified)

Patients (n=31)

resistant *Staphylococcus aureus* (MRSA) was the most frequently identified organism among available cultures (17 patients, 51.61%) (Figure 1).

Eighteen patients (58.06%) experienced a resolution of infection as defined in the study design (Table 2). Of the patients who did not meet the criteria for resolution of infection, 11 (78.6%) had therapeutic extensions. The median duration for therapeutic extensions was 12 days. Of the 11 patients with therapeutic extensions, 9 (81.8%) had at least 1 subtherapeutic trough throughout therapy. The average trough with pharmacist-directed dosing was 16.71 ± 4.84 mg/mL (Table 2). All trough values after the first outpatient trough reflected pharmacist-directed vancomycin dosing. The first outpatient troughs reflected the initial outpatient dosing regimen provided at the time of inpatient discharge and home infusion onboarding. Six (20.7%) patients with detectable first outpatient troughs had therapeutic troughs prior to pharmacist-directed dosing, while 14 (50%) patients had therapeutic second troughs after initiating pharmacist-directed dosing (Figure 2). The authors suspect that the achievement of therapeutic troughs after initiation of pharmacist-directed dosing

FIGURE 2 | Characteristics of Detectable Outpatient Troughs

Percent of total troughs
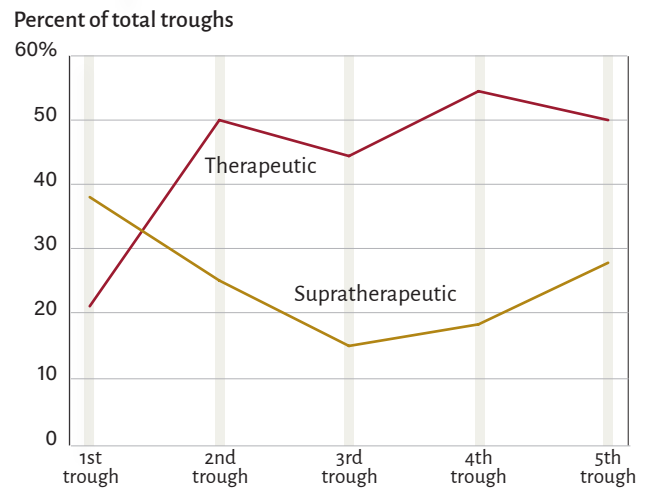
was directly related to pharmacist interventions; however, this finding should be further evaluated with correlative objective data in future studies. The trend line in Figure 2 also reflects the maintenance of therapeutic drug levels through the fifth trough measurement. Analyzed data did not expand past the fifth trough due to a median duration of therapy of 38 days (Figure 2).

Safety data regarding supratherapeutic troughs is reported in Table 3. Four patients (13%) experienced adverse safety events (Figure 3). Two patients (6.5%) experienced AKI secondary to vancomycin therapy. Both patients had supratherapeutic vancomycin troughs at the time of AKI appearance. The first patient met KDIGO criteria for AKI at the second trough draw (day 11 of home infusion vancomycin therapy), and the second met these criteria at the fifth trough draw (day 26 of home infusion vancomycin therapy). Additionally, both had pauses in therapy after experiencing AKI. The first patient with AKI

TABLE 2 | Primary Outcomes and Evidence of Efficacy

Efficacy Outcomes	
Patients with resolution of infection[a], n (%)	18 (58.06)
Average trough with pharmacist-directed dosing, mg/L[b]	16.71 ± 4.84
Actual duration of therapy, days[c]	38 [25-42]

a. Defined as completion of vancomycin therapy for expected duration (without extension) and without therapeutic change to another antibiotic.
b. Data presented as mean ± SD.
c. Data presented as median [IQR].

TABLE 3 | Secondary Outcomes and Evidence of Safety

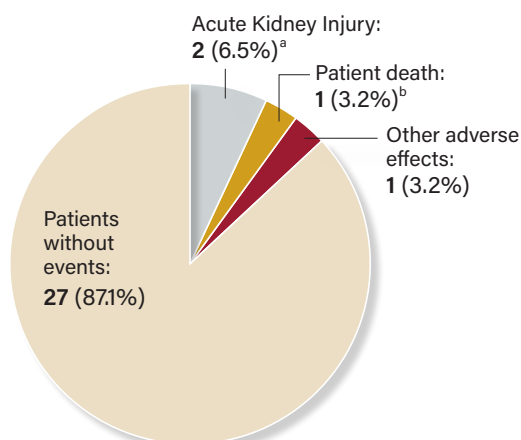| Safety Outcomes	
Total number of supratherapeutic troughs, n (%)[a]	32 (21.77)
Total daily dose associated with supratherapeutic troughs, gram[a,b]	2.5 [1.5-2.88]
Total daily weight-based dose for supratherapeutic troughs, mg/kg (mean)[a]	31.29

a. Troughs > 20 mg/L
b. Data presented as median [IQR].

did not resume dosing after an initial pause in therapy, and the second resumed therapy at a lower dose. One patient (3%) reported a non-AKI ADR, characterized as nausea and vomiting. One patient death (3%) was reported while on vancomycin therapy; however, this was found to be unrelated to vancomycin. Overall, safety results represent tolerability of vancomycin, made evident by the low incidence of adverse safety outcomes attributed to vancomycin itself (3 patients, 9.7%) and an even lower incidence of vancomycin discontinuation due to adverse outcomes (2 patients, 6.5%).

Discussion

The results of this study show an increase in the number of therapeutic troughs and a decrease in the number of supratherapeutic troughs after the initiation of pharmacist-directed dosing in the home infusion setting. Subsequent troughs reflected similar trends. This indicates that most pharmacist-directed interventions led to the successful achievement of therapeutic goals in the absence of regularly scheduled inpatient care and daily lab monitoring.

FIGURE 3 |

Secondary Outcomes – Adverse Events Reported, n (%)

Acute Kidney Injury: 2 (6.5%)[a]
Patient death: 1 (3.2%)[b]
Other adverse effects: 1 (3.2%)
Patients without events: 27 (87.1%)

a. Defined by KDIGO guidelines as an increase in serum creatinine ≥ 1.5 times baseline within 7 days
b. Death determined as not vancomycin-related

The incidence of vancomycin-related ADRs remained low with home infusion vancomycin therapy and pharmacist-directed dosing. Although the exact incidence of AKI and additional vancomycin-related ADRs are unknown, there is evidence that patients receiving vancomycin have an increased risk of AKI (relative risk of 2.45).[11] In a pre-post study from Philips, et al., researchers examined the outcomes of a clinical practice guideline for pharmacist-led vancomycin dosing, and 6 patients (11.32%) developed nephrotoxicity pre-protocol.[4] In a similar study from the Marquis, et al., 14 patients (8.7%) developed nephrotoxicity pre-protocol.[3] These results closely reflect this study's findings for the incidence of AKI.

The average creatinine clearance for the study population upon onboarding may have been contributory to observed lower risks of AKI. The authors suspect the baseline renal function may have been affected by the hydration status of patients while in the hospital. Altered hydration status is common after hospital discharge due to the reduction or elimination of supplemental IV hydrations. Expansion of the study population may demonstrate how dynamic changes in hydration status may affect rates of AKI. Furthermore, minimized rates of AKI may partially be attributed to the reduced presence of concomitant nephrotoxic therapy in the study population. Loop diuretics were the only identified drug class from the list of screened medications that could potentiate AKI.

Although the preferred method of therapeutic drug monitoring (TDM) for vancomycin involves ratios of the area under the curve (AUC) compared to the minimum inhibitory concentration (MIC), the home infusion setting is unique because most patients receive labs on a weekly basis due to factors that affect patients and home health nursing agencies.[2] Because there is minimal existing data for trough-based protocolized dosing in the home infusion setting, there is a similar deficiency of information for AUC:MIC protocolized dosing in this setting. Additionally, Bayesian software used for recommendations to vancomycin dosing may prove cost-prohibitive to institutions, and it is more accurate when using both peaks and troughs instead of troughs only.[2,10] Resultantly, trough-based dosing continues to be the mainstay of vancomycin management in a home infusion setting and is the most appropriate method for protocol development based on current home health practices.

Limitations from this study resulted from the small sample size, the limited number of prescribers that employed pharmacist-directed dosing, and the retrospective study design. Although there were initially 1,208 patients with vancomycin in their institutional profiles during the study's timeframe, these patients had to be evaluated individually for adherence to inclusion criteria due to the institution's lack of therapy-specific search criteria during the data-collection process. The limited search criteria contributed to a large population of excluded patients. This study did not require a large sample size to be adequately powered since it was observational in nature and no comparator group was utilized. The small sample size, however, represented a narrow demographic of patients receiving vancomycin from this institution, thereby limiting the external validity of findings. The low sample size also indicates that a small portion of this institution's collaborating prescribing physicians currently utilize pharmacists for the purpose of TDM and dose adjustments for vancomycin. The retrospective study design limited data collection to information obtained from onboarding documentation and patient EHRs. Furthermore, limited access to many of the patients' EHRs restricted thorough analysis of the collected data points. For example, the rationale for therapeutic extensions could not be investigated secondary to a lack of EHR accessibility.

In order to address the limitations of this study for future investigations, this institution can market the ability of the clinical pharmacists to monitor and make recommendations for patients on vancomycin therapy to providers' offices. Additionally, following implementation of a standardized pharmacokinetic dosing model, this institution plans to expand our study population to further explore the impact of pharmacist-directed vancomycin dosing in the home infusion setting. This would increase the potential sample size and create a population more reflective of the patients serviced with this institution.

Conclusion

Overall, the results indicate that pharmacist-directed dosing led to sustained improvements in therapeutic troughs. Additionally, low incidences of ADRs, including AKI, occurred following pharmacist-directed dosing. Results from this study will be considered to establish educational modules for the clinical pharmacist staff, develop an institutional pharmacist-directed vancomycin dosing protocol, and assess efficacy of this protocol once implemented.

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