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Lee H. Nguyen
*Loma Linda University*

Martin Breen
*St. Jude Medical Center*

Jason Yamaki
*Chapman University*, yamaki@chapman.edu

Geraldine Cadalin
*Loma Linda University*

Nilomi Shah
*Loma Linda University*

***See next page for additional authors***

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# Assessing Vancomycin Dosing Per Pharmacy in Elderly Patients Over the Age of 74 Years

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**Authors**
Lee H. Nguyen, Martin Breen, Jason Yamaki, Geraldine Cadalin, Nilomi Shah, and Linda Lumintaintang

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# Assessing Vancomycin Dosing Per Pharmacy in Elderly Patients Over the Age of 74 Years

Lee H. Nguyen, PharmD, BCPS-AQ ID, APh; Martin Breen, PharmD; Jason Yamaki, PharmD, PhD; Geraldine Cadalin, BS; Nilomi Shah, BA; Linda Lumintaintang, BS

## Abstract

Vancomycin has a complex pharmacokinetic profile and carries potential risks for nephrotoxicity and ototoxicity. The pharmacokinetic profile in elderly patients significantly differs from that of younger patients. It is common practice in many institutions for pharmacists to intentionally round serum creatinine levels to 1 mg/dl in elderly patients with levels <1 mg/dl to avoid overestimating clearance and toxicities. This can potentially lead to underestimation of creatinine clearance, and subsequently lead to vancomycin under dosing. The aim of this study was to evaluate vancomycin target trough attainment and the time to trough attainment with vancomycin dosing per pharmacy in elderly patients.

## Methods

In this retrospective study, patients 75 years and older who received vancomycin at our institution were evaluated. Subjects were included in the study if they were at least 75 years of age, received intravenous vancomycin therapy, and had a vancomycin trough drawn after the third dose. The study patients were divided into three serum creatinine groups; <0.8 mg/dl (LSCr), 0.8-0.9 mg/dl (MSCr), and ≥1 mg/dl (HSCr). Patients were excluded from the study if they did not meet inclusion criteria, had no trough levels drawn, or were <75 years of age.

## Results

Two hundred and four patients 75 years or older were included in the study. The target trough attainment was highest in the HSCr group (n = 37, 80%), which was significantly higher than the LSCr (n=21, 31%; p<0.0001) and MSCr (n=42, 46%; p<0.0001) groups. The time to target trough goals (days, mean ± SD) differed between the three groups, with the LSCr group taking the longest duration: LSCr: 5.14 ± 2.5; MSCr: 3.74 ± 1.1; HSCr: 3.78 ± 1.6, p=0.005.

## Conclusion

Adjustments need to be done to improve vancomycin dosing per pharmacy in patients 75 years of age and older. This study shows that LSCr patients (<0.8 mg/dl) had the lowest rates of target trough level attainment. Intentionally rounding serum creatinine to 1 mg/dl if values are less when estimating renal function in this older patient population may not be predictive of true renal function and can decrease the likelihood of target attainment or increase time to target attainment.

## Background

Vancomycin is a glycopeptide antibiotic used to treat drug-resistant gram-positive bacteria, including methicillin-resistant Staphylococcus aureus.[1] It has been a widely used antibiotic since inception despite its complex pharmacokinetic profile and carries potential risks for nephrotoxicity and ototoxicity.[2-7] The vancomycin elimination rate constant and creatinine clearance have been suggested to be related to age. Additionally, there remains a sufficient amount of variability in clearance and volume of distribution observed in elderly patients.[8] Elderly patients may also have decreased muscle mass, which can lead to decreases in serum creatinine and affect drug distribution.[9] It has also been described that serum creatinine production in elderly patients may be within normal limits, but renal function may be lower than expected.[10]

In many institutions, pharmacists perform vancomycin dosing, order serum concentrations for therapeutic drug monitoring, and adjust the vancomycin dose accordingly based on specific target trough goals, site of infection, and causative organism.[5] Despite the clinical evidence that recommends against rounding serum creatinine when estimating clearance creatinine with the Cockcroft-Gault method, the practice remains.[9,11-17] Many institutions, including ours, have pharmacists who utilize serum creatinine rounding with the Cockcroft-Gault equation.[18-21] A common practice by the institutional pharmacists is to round up serum creatinine levels to 1 mg/dl if measured levels are <1 mg/dl prior to use in creatinine clearance calculations in patients 65 years of age or older. The rationale behind this is to account for lower muscle mass in the elderly, which can lead to lower serum creatinine levels and thus potentially an artificially high creatinine clearance, as previously described above.

National guidance on appropriate dosing of vancomycin in elderly patients is lacking. The vancomycin guidelines endorsed by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) do not provide best practices for dosing in older patients.[5] In addition, published reports pertaining to vancomycin dosing in elderly patients have been limited. However, a discussion of appropriate vancomycin dosing in elderly patients was recently started with Young and colleagues.[22]

Based on the data described above, limited national dosing guidelines, and the common practice of rounding serum creatinine to 1 mg/dl in elderly patients with serum creatinine levels of <1 mg/dl, more clinical data is needed to better understand the vancomycin utilization in the elderly population. The aim of this study was to evaluate vancomycin target trough attainment and the time to target trough attainment with vancomycin dosing per pharmacy in elderly patients, specifically in patients 75 years of age or older. We hypothesized that rounding of serum creatinine to 1 mg/dl in patients with serum creatinine levels of <1 mg/dl would lead to under dosing as evident by not achieving trough attainment or increasing time to trough target attainment.

## Methods

St. Joseph Health's Institutional Review Board approved this study. In this retrospective study, patients 75 years and older who received vancomycin at our institution during the time period of January 1, 2014, to December 31, 2014, were evaluated for inclusion. All subjects were identified through Meditech™ Electronic Medical Record reports and pharmacy records. The study institution is a non-academic community hospital with 325 beds. Subjects were included in the study if they were at least 75 years of age, received intravenous vancomycin therapy, and had a vancomycin trough drawn after the third dose. The study patients were divided into three groups: serum creatinine <0.8 mg/dl (LSCr), serum creatinine 0.8-0.9 mg/dl (MSCr), and serum creatinine ≥1 mg/dl (HSCr). The group designation was based on the value of serum creatinine when vancomycin was initiated. Only the first occurrence of vancomycin utilization was included in the study. Patients were excluded from the study if they did not meet inclusion criteria, had no trough levels drawn, or were less than 75 years of age. Vancomycin daily doses were based on the amount of vancomycin received in a 24-hour period. Patient chart reviews were performed to extract pertinent demographics, laboratory, and clinical data, including gender, age, height, weight, infection, renal function tests, and vancomycin dosing and levels.

## Statistical Analysis

Descriptive statistics were computed for all study variables that were measured on an interval or ratio scale. Discrete data were presented as frequencies and percentages. An independent student t-test was used to compare mean serum creatinine values and other continuous variables. The Pearson's chi-square or Fisher's test was used to measure the association between dichotomous variables. All tests were two-tailed and a P-value of <0.05 was considered significant. Statistical analyses were carried out with SPSS version 20.0 (Chicago, IL, USA) and GraphPad Prism version 6.0 (San Diego, CA, USA).

## Results

Two hundred and four patients 75 years of age or older were identified as receiving vancomycin and a trough level after the third dose of vancomycin. The patient characteristics (mean ± SD) include age 85.7 ± 5.98 years, weight 68.6 ± 16.94 kg, and serum creatinine 1.25 ± 0.78 mg/dl, and consisted of mostly women, 65% (Table 1). The three serum creatinine groups were distributed as LSCr (n=67), MSCr (n=91), and HSCr (n=46). The demographic characteristics are shown in Table 1. The majority of the differences between the groups were due to the HSCr group being significantly different from the LSCr and MSCr groups. The LSCr group had more female subjects (75%) overall, and shorter (mean ± SD, 63.9 ± 3.7 inches) patients than the MSCr group (65.6 ± 3.8). The HSCr group had a lower total daily mg/kg dose of vancomycin (mean ± SD) than the other two groups (HSCR 15.2 ± 3.3 vs MSCr 18.4 ± 6.2, LSCr 18.5 ± 5.6), p=0.001. All three groups had more than half of the vancomycin trough goals set as 15-20 mg/dl and did not differ between the groups, p=0.148.

The overall vancomycin trough target attainment (Table 1) was highest in the HSCr group (n=37, 80%), which was significantly higher than the LSCr (n=21, 31%; p<0.0001) and MSCr (n=42, 46%; p<0.0001) groups. The rates of the 10-15 mg/dl vancomycin trough target attainment did not statistically differ between groups, LSCr, n=10 (15%); MSCr, n=23 (25%); HSCr, n=15 (33%), p=0.0813. The rates of target attainment for the 15-20 mg/dl vancomycin troughs were higher in the HSCr group (n=22, 48%) compared to the other two groups, LSCr, n=11 (16%); p<0.0001 and MSCr, n=19 (21%); p=0.0003. There were no significant differences in target trough attainment between low and high trough levels within each group (data not shown). The time to target trough goals (days, mean ± SD), differed between the three groups, LSCr: 5.14 ± 2.5; MSCr: 3.74 ± 1.1; HSCr: 3.78 ± 1.6, p=0.005. The LSCr group took significantly longer to reach target trough goals compared to the other two groups (LSCr vs MSCr, p=0.02 and LSCr vs HSCr, p=0.04).

## Discussion

The current ASHP/IDSA/SIDP guidelines on vancomycin dosing do not address how vancomycin clearance should be calculated, or how to estimate creatinine clearance. Rather, the guidelines focus on what troughs or AUC/MIC to target for specific disease states and toxicity risks with vancomycin.5 This study evaluated a current practice of vancomycin dosing based on the knowledge that renal function declines in older patients. The groups included vancomycin per pharmacy in patients 75 years of age or older and grouped by serum creatinine values (<0.8 mg/dl [LSCr], serum creatinine 0.8-0.9 mg/dl [MSCr], and serum creatinine ≥1 mg/dl [HSCr]). The study results show that the majority of patients were female and on average more than 10 years older than the minimal inclusion age. The mean total body weights of each patient group did not differ, but the height of the LSCr group was statistically lower than that of the MSCr group. Patients with lower serum creatinine (<0.8 mg/dl) had the lowest rates of vancomycin trough attainment. When examining trough attainment with the higher trough goal of 15-20 mg/dl, we found patients with serum creatinine levels <1.0 mg/dl were less likely to achieve target attainment. In addition to the reduced rates of target attainment, the time to target trough was longer in patients with lower serum creatinine levels. The HSCr group had significantly higher levels of serum creatinine, suggesting true decreases in renal function, which likely attributed to achieving the trough goals.

Young and colleagues recently evaluated the impact of rounding serum creatinine levels to 1 mg/dl to dose vancomycin in patients ≥65 years of age. The study results suggest that actual serum creatinine levels may more accurately predict vancomycin troughs than rounded serum creatinine values.[22] The results of this study produced similar results to our own, suggesting older patients with rounded low serum creatinine values did not achieve vancomycin trough levels as readily as patients with higher serum creatinine levels, nor is the up-rounded serum creatinine value indicative of true renal function. Bourguignon and colleagues evaluated the pharmacokinetics of patients over the age of 80 years on vancomycin and found that there can be large inter-individual variability of vancomycin pharmacokinetic parameters.[8] Additional variabilities in protein binding and volume of distribution may also account for the differences in target trough attainment between groups.[23,24] Moreover, the use of serum creatinine as an estimate of renal function in elderly pa-

tients may not be reliable. Lower serum creatinine levels may be due to lower body mass, but as seen from our data, renal function may or may not be decreased. Renal function is thought to decline with age25, but the extent of renal function decline is difficult to ascertain. It has been described that one-third of elderly patients may not have a decline in renal function.26 Because of the variability seen in elderly patients, alternative strategies need to be considered.

Because of the limited body of clinical evidence, it would difficult to makes assumptions that vancomycin should be dosing by any specific method in elderly patients. The addition of this study reinforces the data presented by Young and colleagues that suggest vancomycin dosing in elderly patients is complex, and room for improvement is vast. Alternatively, instead of searching for correction factors or adjustments to dose vancomycin in elderly patients, adoption of new approaches should be considered. One potential approach to minimizing variability is to acquire two vancomycin levels to better determine the elimination rates. Hong and colleagues have used this technique to improve target trough attainment in the obese patient population.[27] Similar results of higher target trough steady-state achievement were seen in critically ill patients who had multiple vancomycin levels to predict renal function changes.[28]

## Limitations

Our study has several limitations. The study is retrospective in design at a single institution, which limits the assessment to only the variables collected. This lack of randomization of the three groups may potentially cause a selection bias. The selection of serum creatinine cut-off values was arbitrary. Winter and colleagues similarly evaluated serum creatinine rounding with a threshold of 0.8 mg/dl and 1 mg/dl for rounding.[17] Evaluating the groups based on serum creatinine above and below 0.8 mg/dl seemed reasonable. The rationale for the three groups was to have a single group act as a control group and the other groups with low-normal levels of creatinine as comparators. Clinical evidence is scarce when describing vancomycin dosing in elderly patients with low serum creatinine levels. Vancomycin dosing is based on variables such as gender, age, weight, and serum creatinine.[8,11,29,30] In our study, the patients in the LSCr and MSCr were similar in age, weight, and serum creatinine, thus allowing for comparisons with the HSCr group. Another limitation to the study is the potential for variations in clinical judgement by the clinical pharmacists despite the standardized protocol for dosing vancomycin. At our institution, only a handful of the same clinical pharmacists rotate to dose vancomycin as part of their clinical duties, which may limit some variation but not all. Lastly, the study did not control for critically ill patients or collect data on quantitative renal adjustment in various ages. Critically ill patients generally have different pharmacodynamics than stable patients.[28]

## Conclusions

Adjustments need to be done to improve vancomycin per pharmacy in patients 75 years of age and older. This study shows that patients with low serum creatinine <0.8 mg/dl had the lowest rates of target trough level attainment, specifically for higher trough goals of 15-20 mg/dl. Use of serum creatinine to estimate renal function in older patients may not be predictive of true renal function. Further studies that investigate alternative dosing strategies with vancomycin need to be explored.

## About the Authors

Dr. Lee Nguyen, PharmD, APh, BCPS-AQ ID is an associate professor at Loma Linda University and is part of the Antimicrobial Stewardship Program at St. Jude Medical Center. His areas of interest include outcomes associated with antimicrobial stewardship and resistance.

Dr. Martin Breen, PharmD is the clinical manager and clinical pharmacist at St. Jude Medical Center. His interest includes critical care pharmacy, anticoagulation, cardiology, and infectious diseases.

Dr. Jason Yamaki is an assistant professor of pharmacy practice at Chapman University School of Pharmacy. His area of research interests is in Infectious Diseases, and his research combines clinical, molecular, and pharmacological approaches to address the therapeutic challenges of treating multidrug resistant and highly virulent bacteria. Dr. Yamaki's research focuses on the epidemiology of Methicillin-Resistant Staphylococcus aureus (MRSA) and Extended Spectrum Beta-lactamase producing Enterobacteriaceae, patient outcomes and host response in various types of infections, and the effects of inadequate antibiotic dosing on virulence and disease severity. Thus far his research methods have encompassed in-vitro cellular and in-vivo murine models of infection, epidemiologic and retrospective patient outcome studies, and prospective clinical studies.

Geraldine Cadalin is a Doctorate of Pharmacy candidate graduating from Loma Linda University School of Pharmacy in 2018. She graduated from the University of Hawaii at Manoa with a Bachelor of Science in Biology and a concurrent Bachelor of Arts in Music. Upon graduation, she aspires to use her pharmacy degree to continue serving underserved populations.

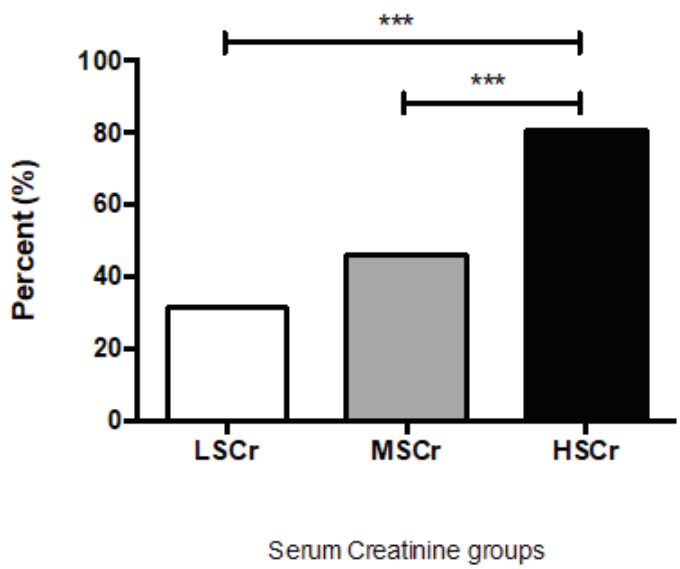
Linda Lumintaintang is a Doctorate of Pharmacy candidate graduating from Loma Linda University School of Pharmacy in 2018. Prior to her pursuing her Doctorate of Pharmacy degree, she received her Bachelor of Science in Health Communication at Pacific Union College. Her current clinical interests are ambulatory care and infectious disease. Postgraduate plans include an ambulatory care PGY-1 residency at Desert Oasis Healthcare.

Nilomi Shah is a Doctorate of Pharmacy candidate graduating from Loma Linda University School of Pharmacy in 2018. Ms. Shah received her Bachelor of Arts in Integrative Biology at University of California, Berkeley in 2013. She has been a member of California Pharmacists Association since 2014. Her clinical interests include infectious diseases, oncology, and pain management. She hopes to build on these interests during her PGY-1 pharmacy residency at Santa Clara Valley Health and Hospital System.

Table 1. Patient Demographics and Clinical Characteristics

| Variables | LSCr SrCR<0.8 (n=67) | MSCr SrCr 0.8-0.9 (n=91) | HSCr SrCr≥1 (n=46) | P=value |
|---|---|---|---|---|
| Age (years), mean ±SD | 84.7 ±6.3 | 84.2 ±5.8 | 90 ±4.6 | 0.0001 |
| Female, no. (%) | 51 (75) | 53 (58) | 26 (57) | 0.0356 |
| Height (inches), mean ±SD | 63.9 ±3.7 | 65.5 ±3.8 | 64.8 ±4.6 | 0.036 |
| Actual body weight (kg), mean ±SD | 65 ±17 | 71.4 ±19 | 66.8 ±12.8 | 0.0649 |
| BUN (mg/dl), mean ±SD | 16.4 ±9.1 | 19.2 ±9.7 | 45.8 ±29 | <0.0001 |
| Serum creatinine (mg/dl) mean ±SD | 0.61 ±0.08 | 0.85 ±0.05 | 2.08 ±1.28 | <0.0001 |
| Hospital location | | | | |
| Medicine floor, no. (%) | 45 (67) | 63 (69) | 22 (48) | 0.0375 |
| ICU floor, no. (%) | 14 (21) | 23 (25) | 19 (41) | 0.0475 |
| Other, no. (%) | 8 (12) | 5 (6) | 5 (11) | 0.3163 |
| Vancomycin (mg/kg/d) mean ±SD | 18.5 ±5.6 | 18.4 ±6.2 | 15.2 ±3.3 | 0.0024 |
| Vancomycin trough goals | | | | |
| 10-15 mg/dl | 22 (33) | 42 (46) | 15 (33) | 0.1480 |
| 15-20 mg/dl | 45 (67) | 49 (54) | 31 (67) | 0.1480 |

Figure 1. Rate of Overall Target Trough Attainment by Serum Creatinine Group




Vancomycin trough target attainment was highest in the HSCr group (80%), which was significantly higher than both the LSCr (31%) and MSCr (46%) groups (p<0.0001).

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