Relationships between creatinine increase and mortality rates in patients given vancomycin in 76 hospitals: The increasing role of infectious disease pharmacists

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Purpose. Vancomycin is a commonly used antimicrobial with the potential for renal toxicity. We evaluated vancomycin duration, changes in renal function after vancomycin initiation ("post-vancomycin" renal function changes), and associated mortality risk among hospitalized patients.

Methods. We analyzed data from 76 hospitals and excluded patients with a baseline serum creatinine concentration (SCr) of >3.35 mg/dL. We estimated mortality risk relative to vancomycin duration and the magnitude of post-vancomycin SCr change, controlling for demographics, baseline SCr, underlying diseases, clinical acuity, and comorbidities.

Results. Among 128,993 adult inpatients treated with vancomycin, 49.0% did not experience SCr elevation. Among the remaining patients, 26.0%, 11.4%, 8.8% and 4.8% experienced increases in post-vancomycin SCr of 1% to 20%, 21% to 40%, 41% to 100%, and greater than 100%, respectively. Compared to mortality risk among patients with a vancomycin therapy duration between 4 and 5 days (the lowest-mortality group), longer vancomycin therapy duration was not independently associated with higher mortality risk after adjusting for confounders. In contrast, there was a graded relationship between post-vancomycin SCr elevation and mortality. Multivariable adjusted mortality odds ratios ranged from 1.60 to 13.66, corresponding to SCr increases of 10% and greater than 200%, respectively.

Conclusion. Half of patients given vancomycin did not experience SCr elevation and had the lowest mortality, suggesting that vancomycin can be used safely if renal function is stabilized. In the large study cohort, vancomycin duration itself was not an independent predictor of mortality. Post-vancomycin SCr elevation appeared to be a driver of in-hospital mortality. Even a 10% post-vancomycin SCr increase was associated with an increased mortality risk. This finding stresses the importance of closely monitoring renal function and may support the value of pharmacokinetic dosing.

Keywords: infectious disease pharmacist, mortality, renal function, stewardship, vancomycin

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Vancomycin is one of the top-prescribed antimicrobials in the acute care setting, with usage ranging from empirical therapy for hospital-acquired infections, definitive therapy for invasive methicillin-resistant Staphylococcus aureus (MRSA) infections, and prophylaxis for certain clinical indications such as surgery when a patient is β-lactam allergic. The potential for both overprescribing and renal toxicity have been well characterized, with attempts to mitigate such adverse events through vancomycin treatment guidelines (a 2009 consensus guideline endorsed by ASHP, the Infectious Diseases Society of America [IDSA] and the Society of Infectious Diseases...
Pharmacists [SIDP], which was revised in 2020 by ASHP, IDSA, SIDP, and the Pediatric Infectious Diseases Society) to support pharmacokinetic dosing of vancomycin for MRSA infections. In parallel to this effort, the Centers for Medicare and Medicaid Services (CMS) recently joined the Joint Commission in supporting antimicrobial stewardship programs (ASPs) by codifying use of an ASP as a condition of participation (CoP) starting in March 2020. A major component of that CoP is to have a trained clinical pharmacist at the helm of stewardship. The CMS CoP cites as a supporting reference the Centers for Disease Control and Prevention (CDC) recommendations for appropriate antimicrobial use in acute care settings and the antibiotic use (AU) component of CDC’s Antimicrobial Use and Resistance (AUR) Module as a first-of-its-kind infrastructure for monitoring use of key antimicrobials, of which anti-MRSA agents and vancomycin constitute a key category. Given that mitigating vancomycin overuse is often cited as a target for ASPs in real-world evidence and given recent expert pharmacist consensus for pharmacokinetic vancomycin dosing, we sought to better characterize the relationship between duration of vancomycin use and level of renal function change with calculations of mortality risk. As better antimicrobial stewardship activities are propagated through regulatory auspices and pharmacy society expert guidelines, better understanding of safer vancomycin administration may help inform appropriate vancomycin use and dosing.

**Methods**

**Data source.** We analyzed electronic microbiological, pharmacy, and administrative data from 76 acute care hospitals in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ). The facility geographic distribution was as follows: Midwest, 32.9%; Northeast, 7.9%; South, 47.4%; and West, 11.8%. Teaching hospitals accounted for 27.6% of facilities; and nonteaching hospitals, 72.4%. The hospital size distribution (number of beds) was 10.5% (<100), 47.4% (100-300), and 42.1% (>300). The BD Insights Research Database is continuously updated and used for aggregated epidemiology and outcomes studies, mostly on topics related to hospital infections and antimicrobial use trends. It includes deidentified patient demographics, claims data, and electronic health record (EHR) data (general laboratory and pharmacy order data). The study was approved as involving use of a limited retrospective data set for an epidemiology study and was exempted from consent by the New England Institutional Review Board/ Human Subjects Research Committee (Wellesley, MA) and conducted in compliance with Health Insurance Portability and Accountability Act (HIPAA) requirements.

**Patients.** We included consecutive adult patients (18 years of age or older) admitted to one of the 76 acute care hospitals from October 1, 2015, through June 30, 2017. The inclusion criteria were as follows: any intravenous vancomycin use in the inpatient setting and at least 2 serum creatinine (SCr) measurements, 1 at baseline (prior to the nearest measured SCr prior to the highest measured absolute SCr value after the first dose of vancomycin was given during the hospital stay. We reported the time from the baseline to the highest SCr value after vancomycin initiation (ie, the highest “post-vancomycin value”). We calculated the change between the baseline and the highest post-vancomycin SCr values and presented it as a percentage change.

**Other covariates.** In addition to baseline SCr and SCr change, potential and known confounders for mortality outcomes in our study included epidemiological demographics and healthcare-associated admissions (previous hospitalization within 30 days or admissions from other healthcare settings such as a skilled nursing, long-term care, or other acute care facility). We also included 3 measures of clinical acuity: admission to intensive care unit; underlying disease (the principal diagnosis-based disease category per the Agency for Healthcare Research and Quality [AHRQ] Clinical Classification System software); and a published aggregated disease severity score, the...
Acute Laboratory Risk of Mortality Score (aLRMS). The aLRMS, which is calculated using demographics and 24 laboratory test results to score patients’ probability of mortality during a hospital stay, has been used as a risk adjustment tool in previous publications. For comorbidity, we used the Elixhauser Comorbidity Software from AHRQ, which aggregates relevant secondary diagnoses into 29 comorbidities.

Statistical analysis. We conducted univariate analysis of the relationship of vancomycin use duration, baseline SCr, change in SCr, and in-hospital mortality. We estimated the risk of mortality relative to vancomycin duration and the magnitude of post-vancomycin SCr change, with controlling for demographics, baseline SCr, underlying diseases, clinical acuity, comorbidities, and other potential confounders, using a multivariable logistic regression model. All analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics. Our cohort comprised a total of 128,993 adult patients treated with vancomycin who had at least 1 baseline (“pre-vancomycin”) SCr value below the 90th percentile for all patients treated with vancomycin (3.35 mg/dL). Because we endeavored to characterize signals between creatinine change and mortality in patients who received vancomycin, the 90th percentile was chosen as the SCr cutoff to help mitigate, within reason, the inclusion of patients who likely had chronic renal failure in the cohort. The baseline SCr distribution (in mg/dL) was as follows: SCr of ≤1.00, 53.1%; SCr of 1.01-1.20, 14.9%; SCr of 1.21-2.00, 23.1%; and SCr of 2.01-3.35, 8.9% (Table 1). The mean (standard deviation [SD]) age was 62.4 (17.1) years, and the median (1st quartile, 3rd quartile) age was 62 (52, 75) years. The cohort was 52.8% male and 47.2% female. The overall in-hospital mortality rate was 7.2% (9,350 of 128,993 patients).

Among the 128,993 patients in the final analysis, 49.0% did not experience SCr elevation during the hospital stay; in this subgroup, 91% of patients had a baseline SCr of <1.0 to 2.0 mg/dL. (Table 1), suggesting that most patients in this subpopulation did not have chronic renal failure and, therefore, the stable SCr was likely due to continued stable renal function. In the remaining patients, the proportions with increased SCr (by magnitude of increase) were 26.0% (SCr change of >0% to 20%), 11.4% (SCr change of >20% to 40%), 8.8% (SCr change of >40% to 100%) and 4.8% (SCr change of >100%), respectively. The mean (SD) duration of vancomycin therapy from the baseline SCr to the highest post-vancomycin SCr was 2.9 (4.4) days. Patients with higher post-vancomycin SCr elevation were more likely to be severely ill and have more comorbidities. The distribution of vancomycin duration (in DOT) was as follows: ≤3 days, 53.7%; 4 to 5 days, 23.7%; 6 to 7 days, 10.4%; 8 to 9 days, 5.2%; and >9 days, 7.0% (Table 1).

SCr elevation, vancomycin duration, and in-hospital mortality. There was a graded relationship between the magnitude of post-vancomycin SCr elevation and the in-hospital mortality rate across all baseline SCr strata (Figure 1). When the level of post-vancomycin SCr elevation was stratified by vancomycin duration, there was a striking trend of association with mortality: Patients with the highest SCr changes experienced a higher mortality rate. Moreover, the mortality risk incrementally increased with greater SCr change. This phenomenon was seen throughout all vancomycin duration demarcations (Figure 2). When stratified by levels of SCr elevation, vancomycin duration had a lesser impact (Figure 3).

Multivariable adjusted model results. After adjusting for demographics, underlying diseases, disease severity, comorbidities, and other covariates in the model (Table 2), the multivariable regression model showed that, compared to patients with a vancomycin duration of 4 to 5 days (the lowest-mortality group), those with longer vancomycin duration did not have higher mortality risk (P > 0.05 for all comparisons). In contrast to duration of vancomycin, the level of net change of post-vancomycin SCr elevation was highly correlated with mortality risk in a graded fashion (adjusted odds ratios ranged from 1.60 [corresponding to a 10% increase in SCr level] to 13.66 [corresponding to a >200% increase in SCr level]; P < 0.0001 for all comparisons). The model C statistic was 0.89.

Discussion

Vancomycin is a main therapy for serious gram-positive infections. An important known adverse effect is its potential for renal toxicity. The value of trough-based dosing and increasing maximum trough demarcations has been reported at times to be minimally helpful with clinical outcomes but may help in assessing risk of nephrotoxicity. How to use vancomycin safely remains a challenge to the clinical community, as reflected by continued updating of society guidelines and culminating thus far in the 2020 joint ASHP/SIDP/IDSA/PIDS vancomycin pharmacokinetic dosing guideline. The increasing burden to pharmacists, then, will be not only dosing of vancomycin but also monitoring of kidney function. With that likelihood in mind, we evaluated the data that a pharmacist would use in this endeavor, namely vancomycin duration, post-vancomycin renal function change, and associated mortality risk among hospitalized patients, using EHR data in conjunction with administrative data for all adult patients receiving vancomycin in the real-world setting at 76 hospitals. For all patients in the study cohort, we found evidence indicating that if the renal function is stable, vancomycin duration is likely not an independent risk factor for mortality. In contrast, elevated post-vancomycin SCr appears to be a driver of mortality risk after adjusting for demographics, vancomycin duration, baseline SCr, disease severity, and comorbidities.
Table 1. Patient Characteristics by Degree of Serum Creatinine Change After Vancomycin Initiation

| Variable                     | Total                | ≤0%       | 0.01%-20%  | 20.01%-40% | 40.01%-100% | >100%     | P Value  |
|------------------------------|----------------------|-----------|------------|------------|-------------|-----------|----------|
| Admissions                   | 128,993              | 63,184 (49.0) | 33,548 (26.0) | 14,733 (11.4) | 11,299 (8.8) | 6,229 (4.8) | <0.0001  |
| Deaths                       | 9,350                | 2,252 (3.6)  | 1,859 (5.5)  | 1,276 (8.7)  | 2,033 (18.0) | 1,894 (30.4) | <0.0001  |
| Baseline SCr, mg/dL          |                      |           |            |            |             |           | <0.0001  |
| ≤1.00                        | 68,505               | 29,943 (43.7) | 19,315 (28.2) | 9,208 (13.4) | 6,440 (9.4)  | 3,599 (5.3)  |          |
| 1.01–1.20                    | 19,163               | 10,519 (54.9) | 4,878 (25.5)  | 1,678 (8.8)  | 1,323 (6.9)  | 765 (4.0)   |          |
| 1.21–2.00                    | 29,818               | 16,879 (56.6) | 6,700 (22.5)  | 2,740 (9.2)  | 2,236 (7.5)  | 1,263 (4.2)  |          |
| 2.01–3.35                    | 11,507               | 5,843 (50.8)  | 2,655 (23.1)  | 1,107 (9.6)  | 1,300 (11.3) | 602 (5.2)   |          |
| Age                          |                      |           |            |            |             |           | <0.0001  |
| Mean (SD), y                 | 62.4 (17.1)          | 62.1 (17.4)  | 62.8 (17.0)  | 63.2 (16.6)  | 63.3 (16.4)  | 60.0 (16.5) |          |
| Median (1st quartile, 3rd quartile), y | 62 (52, 75) | 64 (51, 75)  | 64 (52, 76)  | 65 (53, 76)  | 63 (53, 76)  | 61 (49, 72) |          |
| Sex                          |                      |           |            |            |             |           | 0.0005   |
| Male                         | 68,159               | 33,354 (48.9) | 18,347 (26.9) | 7,578 (11.1) | 5,685 (8.3)  | 3,195 (4.7)  |          |
| Female                       | 60,834               | 29,830 (49.0) | 15,201 (25.0) | 7,155 (11.8) | 5,614 (9.2)  | 3,034 (5.0)  |          |
| Healthcare-associated admission |                      |           |            |            |             |           | <0.0001  |
| Yes                          | 65,734               | 30,835 (46.9) | 17,191 (26.2) | 7,915 (12.0) | 6,409 (9.7)  | 3,384 (5.1)  |          |
| No                           | 63,259               | 32,349 (51.1) | 16,357 (25.9) | 6,818 (10.8) | 4,890 (7.7)  | 2,845 (4.5)  |          |
| ICU admission                 |                      |           |            |            |             |           | <0.0001  |
| Yes                          | 45,966               | 18,737 (40.8) | 10,825 (23.6) | 6,214 (13.5) | 6,204 (13.5) | 3,986 (8.7)  |          |
| No                           | 83,027               | 44,447 (53.5) | 22,723 (27.4) | 8,519 (10.3) | 5,095 (6.1)  | 2,243 (2.7)  |          |
| Disease severity (ALaRMS)  c |                      |           |            |            |             |           | <0.0001  |
| 1st quartile                 | 32,490               | 16,962 (52.2) | 9,100 (28.0)  | 3,376 (10.4) | 1,940 (6.0)  | 1,112 (3.4)  |          |
| 2nd quartile                 | 32,925               | 16,351 (49.7) | 9,041 (27.5)  | 3,728 (11.3) | 2,490 (7.6)  | 1,315 (4.0)  |          |
| 3rd quartile                 | 32,822               | 15,924 (48.5) | 8,293 (25.3)  | 3,978 (12.1) | 3,072 (9.4)  | 1,555 (4.7)  |          |
| 4th quartile                 | 30,756               | 13,947 (45.3) | 7,114 (23.1)  | 3,651 (11.9) | 3,797 (12.3) | 2,247 (7.3)  |          |

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| Variable                                           | Total                  | ≤0%       | 0.01%-20%  | 20.01%-40% | 40.01%-100% | >100%  | P Value |
|----------------------------------------------------|------------------------|-----------|------------|------------|-------------|--------|---------|
| Underlying disease (per Clinical Classification System software) |                        |           |            |            |             |        |         |
| Diseases of skin, musculoskeletal & all other       | 33,889                 | 18,006 (53.1) | 9,445 (27.9) | 3,353 (9.9) | 2,016 (5.9) | 1,069 (3.2) | <0.0001 |
| Infectious and parasitic diseases (primarily sepsis) | 27,888                 | 15,324 (54.9) | 6,023 (21.6) | 2,635 (9.4) | 2,339 (8.4) | 1,567 (5.6) |         |
| Diseases of the respiratory system                  | 16,933                 | 7,728 (45.6) | 4,597 (27.1) | 2,173 (12.8) | 1,598 (9.4) | 837 (4.9) |         |
| Diseases of the circulatory system                  | 15,997                 | 5,557 (34.7) | 4,675 (29.2) | 2,621 (16.4) | 2,228 (13.9) | 916 (5.7) |         |
| Injury and poisoning                                 | 14,000                 | 6,760 (48.3) | 3,716 (26.5) | 1,701 (12.2) | 1,199 (8.6) | 624 (4.5) |         |
| Diseases of the digestive system                    | 5,683                  | 2,618 (46.1) | 1,400 (24.6) | 671 (11.8) | 616 (10.8) | 378 (6.7) |         |
| Symptoms; signs; and ill-defined conditions         | 5,407                  | 2,932 (54.2) | 1,290 (23.9) | 521 (9.6) | 424 (7.8) | 240 (4.4) |         |
| Neoplasms                                           | 3,109                  | 1,192 (36.0) | 914 (27.6) | 446 (13.5) | 423 (12.8) | 335 (10.1) |         |
| Diseases of the nervous system and sense organs     | 3,109                  | 1,699 (54.6) | 764 (24.6) | 320 (10.3) | 208 (6.7) | 118 (3.8) |         |
| Residual codes; unclassified; all E codes           | 2,777                  | 1,368 (49.3) | 724 (26.1) | 292 (10.5) | 248 (8.9) | 145 (5.2) |         |
| No. of comorbidities (per Elixhauser Comorbidity Software) |                        |           |            |            |             |        |         |
| Mean (SD)                                           | 4.0 (2.1)              | 3.8 (2.1) | 4.0 (2.1) | 4.2 (2.2) | 4.7 (2.2) | 4.9 (2.2) | <0.0001 |
| Median (1st quartile, 3rd quartile)                 | 4 (2, 5)               | 4 (2, 5) | 4 (2, 5) | 4 (3, 6) | 5 (3, 6) | 5 (3, 6) |         |
| Vancomycin duration, DOT                            |                        |           |            |            |             |        |         |
| ≤3                                                  | 69,252                 | 36,573 (52.8) | 18,139 (26.2) | 7,339 (10.6) | 5,002 (7.2) | 2,199 (3.2) | <0.0001 |
| 4–5                                                | 30,634                 | 15,165 (49.5) | 8,143 (26.6) | 3,447 (11.3) | 2,497 (8.2) | 1,382 (4.5) |         |
| 6–7                                                | 13,429                 | 5,998 (44.7) | 3,571 (26.6) | 1,651 (12.3) | 1,370 (10.2) | 839 (6.2) |         |
| 8–9                                                | 6,683                  | 2,647 (39.6) | 1,683 (25.2) | 954 (14.3) | 871 (13.0) | 528 (7.9) |         |
| >9                                                 | 8,995                  | 2,801 (31.1) | 2,012 (22.4) | 1,342 (14.9) | 1,559 (17.3) | 1,281 (14.2) |         |

Abbreviations: ALaRMS, Acute Laboratory Risk for Mortality Score; ICU, intensive care unit; SCr, serum creatinine concentration; resolved in its own country.

*aAll data are number (percentage) unless indicated otherwise.

*bPatients with a baseline SCr of >3.35 mg/dL (ie, those in the 90th percentile of SCr values for all patients treated with vancomycin) were excluded.

cALaRMS is calculated using age, gender, and 24 laboratory test results to score the predicted probability of inpatient mortality.14
Using EHR and administrative data from a large number of hospitals of different sizes and geographic locations allowed us to quantify the relationship of post-vancomycin SCr elevation and mortality on a granular scale. It also allowed us to include and assess the entirety of patients who receive vancomycin as a result of the frontline practice of giving vancomycin indiscriminately to patients who are first assessed in the emergency room or newly admitted. Inappropriate vancomycin use has been estimated to occur 25% to 70% of the time when vancomycin is used and remains a challenge for ASP teams in the United States. Furthermore, by assessing the totality of patients who receive vancomycin, the resultant graded relationship we report offers more precise clinical insights that may help guide renal function monitoring, mitigate potential vancomycin toxicity risk, and thereby contribute to improving patient safety via stewardship programs in the real world. Of note, previous randomized clinical trials evaluating the effect of vancomycin on outcomes used a SCr increase of 0.5 mg/dL or 50% as a dichotomized measure of acute kidney injury. The dichotomized measure would not be able to depict graded precision of the estimated impact of SCr elevation on mortality. The precision of the graded estimates from our study may be a helpful corroborative lens for pharmacists tasked with dosing and monitoring vancomycin. Thus, the analysis presented here can complement established studies on vancomycin use overall, while our study aimed to include signals in patients given vancomycin as part of empiric or inappropriate therapy as well. Given that ASP pharmacists are often tasked with both identifying inappropriate vancomycin use and monitoring vancomycin dosing when the drug is used as appropriate definitive therapy, this analysis may help provide insight to both populations.

Another strength of the study is that we were able to use detailed laboratory data from EHRs not only to measure the baseline SCr and its subsequent changes but also to score clinical severity based on a set of laboratory test results. Using laboratory data that quantify injury to organ systems and allow objective assessment of physiologic acuity of illness—in conjunction with ICU admission and underlying disease diagnoses—enhances clinical plausibility when studying outcomes. The high predictivity (C statistic = 0.89) of our multivariable model suggests that important confounders and contributing factors for mortality for our study population were largely accounted for in the model.
The use of pharmacokinetic and area under the curve (AUC) dosing of vancomycin has been debated in the past, with a more definitive guideline recommended the first time in the United States earlier this year. The newly supported AUC-based dosing involves tenets of individual patient-level dosing, relying less on repeated trough levels and more on individual SCr clearance using Bayesian or other models to help guide dosing. Vancomycin causes damage to the kidney through glomerular inflammation (glomerular nephritis), which on average occurs 2 to 5 days into therapy. The risk of glomerular nephritis is reportedly highest 5 to 10 days into therapy, with an estimated 3% of patients requiring hemodialysis. For practicing clinicians, this has suggested that prolonged duration of vancomycin therapy may represent higher risk of mortality. Our findings that (1) vancomycin duration is not likely an independent risk factor for in-hospital mortality when assessing all patients who receive vancomycin as either empiric or definitive therapy.

Conventional pharmacokinetic dosing of vancomycin requires that serum samples for determination of trough levels be drawn at steady state, and previous recommendations were to dose vancomycin to the target trough level of 15 to 20 mg/L (this is referred to as trough-based vancomycin dosing) as a surrogate for the recommended ratio of AUC to minimum inhibitory concentration (MIC) of ≥400. A recently revised consensus guideline, however, changed these recommendations, as studies have suggested that it has resulted in higher vancomycin dosing and an increased incidence of nephrotoxicity. The new consensus guideline recommends an AUC/MIC ratio (assuming a MIC of 1 mg/L) of 400 to 600 mg/L to achieve clinical efficacy and ensure safety for patients being treated for serious MRSA infections. Results of our study further support the importance of this recommendation, as we have shown that even small percentage increases in post-vancomycin SCr were associated with increased mortality risk. The clinical conundrum of balancing the potential mortality risk with achieving the desired AUC/MIC ratio remains, and it is our hope that the work presented here adds another aid to the decisions clinicians have to make when treating invasive MRSA infections.

Our study had limitations. First, as our intent was to characterize SCr change in all patients who received vancomycin from a stewardship perspective, we included all patients who received vancomycin for any reason and had a baseline and a post-vancomycin SCr measured. As such, patients in our cohort may have received as little as 1 DOT of vancomycin. While our cohort also included patients who were treated definitively with prolonged vancomycin therapy, it is important to note that the aggregate findings we report pertain to vancomycin doses given in both demographics in real-world settings across 76 hospitals. As a result, our findings may differ from those of focused clinical trials that assessed outcomes of vancomycin when used as definitive therapy only. Second, although we included objective laboratory data-based assessments of severity and other assessments, there might have been unmeasured confounders that might have contributed to the outcome. In our study approximately 32% of the cohort had a “baseline” SCr above the standard normal range (>1.2 mg/dL). Some of these patients could have had a predialysis diagnosis of renal insufficiency. Conversely, it is also possible that some patients had a normal renal function but suffered an acute renal injury as part of their acute illness that was further complicated by subsequent vancomycin administration. To address the baseline SCr variation, we stratified the SCr changes by baseline value, which indeed showed that patients with higher baseline SCr had steeper increases in mortality risk.
### Table 2. Multivariable Regression Model Results for In-Hospital Mortality Risk

| Variable                                                                 | Odds Ratio (95% CI) | P Value |
|--------------------------------------------------------------------------|---------------------|---------|
| Age (per 10-year increment)                                               | 1.11 (1.09-1.13)    | <0.0001 |
| Male vs female                                                           | 0.92 (0.87-0.96)    | 0.0004  |
| Healthcare-associated vs non–healthcare-associated admission            | 1.37 (1.30-1.44)    | <0.0001 |
| ICU vs non-ICU admission                                                 | 4.81 (4.52-5.11)    | <0.0001 |
| Disease severity (ALaRMS)<sup>a</sup>                                    |                     |         |
| 1st quartile Reference                                                   |                     |         |
| 2nd quartile                                                             | 1.70 (1.47-1.96)    | <0.0001 |
| 3rd quartile                                                             | 2.83 (2.47-3.24)    | <0.0001 |
| 4th quartile                                                             | 7.05 (6.17-8.06)    | <0.0001 |
| Underlying disease (principal diagnosis)                                 |                     |         |
| Diseases of skin, musculoskeletal & all other                            | Reference           |         |
| Neoplasms                                                                | 4.95 (4.30-5.69)    | <0.0001 |
| Diseases of the respiratory system                                       | 2.40 (2.16-2.66)    | <0.0001 |
| Infectious and parasitic diseases                                        | 2.22 (2.01-2.45)    | <0.0001 |
| Diseases of the nervous system and sense organs                          | 2.07 (1.71-2.52)    | <0.0001 |
| Residual codes; unclassified; all E codes                                | 1.97 (1.66-2.32)    | <0.0001 |
| Diseases of the digestive system                                         | 1.93 (1.68-2.21)    | <0.0001 |
| Symptoms; signs; and ill-defined conditions                              | 1.69 (1.45-1.96)    | <0.0001 |
| Injury and poisoning                                                     | 1.38 (1.22-1.57)    | <0.0001 |
| Diseases of the circulatory system                                       | 1.32 (1.18-1.47)    | <0.0001 |
| No. of comorbidities                                                    | 0.99 (0.98-1.00)    | 0.1495  |
| Baseline SCr, mg/dL                                                      |                     |         |
| ≤1.00                                                                    | Reference           |         |
| 1.01–1.20                                                                | 1.23 (1.14-1.33)    | <0.0001 |
| 1.21–2.00                                                                | 1.61 (1.51-1.71)    | <0.0001 |
| 2.01–3.35                                                                | 2.42 (2.25-2.60)    | <0.0001 |
| Vancomycin duration, DOT                                                 |                     |         |
| ≤3                                                                       | Reference           |         |
| 6–7                                                                      | 0.99 6 (0.91-1.09)   | 0.9358  |
| 8–9                                                                      | 1.00 (0.89-1.12)    | 0.9960  |
| >9                                                                       | 0.93 (0.85-1.02)    | 0.1144  |
| Post-vancomycin SCr change, %                                            |                     |         |
| ≤0                                                                       | Reference           |         |
| >0 to 10                                                                 | 1.60 (1.47-1.75)    | <0.0001 |
| >10 to 20                                                                | 1.91 (1.76-2.08)    | <0.0001 |
| >20 to 30                                                                | 2.30 (2.09-2.53)    | <0.0001 |
| >30 to 40                                                                | 2.75 (2.48-3.06)    | <0.0001 |
| >40 to 50                                                                | 3.72 (3.32-4.18)    | <0.0001 |

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than those who presented with normal SCr baseline values, with similar percentage changes in SCr. When baseline SCr was included in the multivariable model, it had a further independent effect on mortality above and beyond that of post-vancomycin SCr change and other covariates in the model. It should be pointed out that the observed graded relationship between the magnitude of SCr elevation and in-hospital mortality constituted a correlation and did not establish causality. Furthermore, it was beyond the scope of the study to evaluate the extent to which SCr elevation can be attributed to vancomycin use versus underlying disease progression. However, the fact that the average duration from baseline to the maximum SCr measure was approximately 4 days for patients experiencing SCr elevations seems to imply that vancomycin use was a contributing factor. Thirdly, our data set only allowed for analysis of maximal SCr change during the entire hospital stay irrespective of daily concurrent active vancomycin use during that maximal SCr collection time. As such, we draw conclusions from the standpoint of population health and from the point of view of antimicrobial stewardship, which endeavors to guard and monitor the safety of all patients who have received an antimicrobial during the hospital stay, inclusive of downstream consequences of antimicrobial use. Finally, we used pharmacy order data in DOT, which is a commonly used metric for quantifying antimicrobial use. The ability to assess other concurrent nephrotoxic agents was beyond the scope of our data set analysis. More direct measures of administered vancomycin such as trough levels, dose, duration, and rate of infusion may further elucidate the relationship of vancomycin pharmacokinetic features and renal function change. Also, stratifying outcomes by baseline preadmission renal function and other simultaneously administered nephrotoxic agents may help unpack the relationship between SCr change and mortality in more specific patient populations to guide targeted stewardship practices when vancomycin use is considered for either empiric or definitive therapy. With further EHR integration and with pharmacist-led ASPs gaining regulatory and public policy traction, this type of longitudinal data analysis would become possible in the future.

**Conclusion**

Half of patients treated with vancomycin did not experience SCr elevation. These patients had the lowest mortality, suggesting that vancomycin can be tolerated and used safely in patients with stabilized renal function. In the evaluated general cohort of inpatients given vancomycin in 76 hospitals, vancomycin duration itself was likely not an independent predictor of mortality. Post-vancomycin elevation of SCr appeared to be a driver of in-hospital mortality. Even small percentage increases in post-vancomycin SCr were associated with increased mortality risk. These findings stress the increasing role of pharmacist-led stewardship programs, highlights the importance of closely monitoring renal function, and support newly endorsed AUC-based pharmacokinetic vancomycin dosing.

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**Disclosures**

All authors were current or former employees of Becton, Dickinson and Company (BD) at the time of the study. BD is a medical, diagnostics, and analytics technology company whose Medication Management Solutions business unit develops, manufactures, and sells medication dispensing and infusion devices as part of its business.

**Additional information**

Study concept and design, Drs. Tabak, Yu, Vankeepuram, Yamaga; data analysis and interpretation, Drs. Tabak, Yu, Vankeepuram, Yamaga; drafting of manuscript, Drs. Yu, Yamage, and Tabak; and critical revision and
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