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CLINICAL THERAPEUTICS

Renoprotective Effects of Melatonin against Vancomycin-Related Acute Kidney Injury in Hospitalized Patients: a Retrospective Cohort Study

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ABSTRACT Vancomycin is associated with nephrotoxicity, and the mechanism may in part be related to oxidative stress. *In vitro* and preclinical studies suggest that melatonin supplementation decreases oxidative stress. The objective of this study was to evaluate concomitant use of melatonin and vancomycin and the incidence of acute kidney injury (AKI). We performed a retrospective cohort study at a large community medical center. All consecutive patients admitted to the medical center between January 2016 and September 2020 who received vancomycin therapy alone or concomitantly with melatonin as part of ordinary care were considered for inclusion. The primary endpoint was the development of AKI, defined as an absolute increase in serum creatinine of ≥0.3 mg/dl or a ≥50% increase in serum creatinine. All data were analyzed using descriptive statistics. A multivariable logistic regression was constructed to account for potential confounding variables. We identified a total of 303 adult patients meeting inclusion and exclusion criteria treated with vancomycin, 101 of which received melatonin concomitantly. Overall baseline characteristics were similar between the two groups except for the incidence of bacteremia/sepsis. After controlling for the vancomycin area under the curve, baseline creatinine clearance, and intensive care unit admission in a multivariable logistic regression analysis, melatonin use was associated with a 63% decrease in AKI (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.14 to 0.96; $P = 0.041$). Melatonin use was associated with a significant reduction in vancomycin-related AKI. Although this was a retrospective study with a small sample size, given the magnitude of the difference seen, further large prospective studies are warranted.

KEYWORDS acute kidney injury, antioxidant, melatonin, vancomycin

Vancomycin was introduced into clinical practice in 1956 as a first line of invasive treatment for Gram-positive infections. Vancomycin is a glycopeptide antibiotic effective against Gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). In many severe MRSA infections, vancomycin dose adjustment is recommended to achieve an area under the curve (AUC)/MIC ratio for better response. However, vancomycin causes acute kidney injury (AKI) with prolonged and higher doses (1–3). Initially, the nephrotoxicity and ototoxicity were attributed to the earlier formulations of vancomycin, which contained product impurities and were termed "Mississippi mud" (4–6). Despite formulation improvements, the reported incidence of AKI with vancomycin use ranges between 5% and 43%, based on the dose and duration of therapy (7–10). In a recent study, approximately 9% of hospitalized patients with acute bacterial skin and skin structure infections, a population with a relatively

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low risk of AKI, treated with vancomycin developed AKI (11). Furthermore, each additional day of vancomycin therapy beyond 72 h was associated with a 14%-increased risk of AKI, with a >2-fold-higher risk with treatment durations exceeding 7 days (11).

Although the exact mechanism of vancomycin-related AKI is not clearly defined, reported preclinical data suggest that vancomycin may cause renal damage by inducing oxidative stress in proximal tubules (12–17). There are some preclinical studies conducted in mice that have indicated that vancomycin is associated with the downregulation of antioxidant genes and, subsequently, a negative impact on mitochondrial bioenergetics (18–20).

A variety of antioxidants have been investigated for protection against vancomycin-related AKI, primarily in preclinical studies. These have included vitamin E (21), gingko biloba, vitamin C, *N*-acetylcysteine, curcumin, and melatonin (22, 23). First isolated in 1958, *N*-acetyl-5-methoxytryptamine, commonly known as melatonin, is a synthetic product of the vertebrate pineal gland. Melatonin was initially discovered as a mediator of circadian rhythm, but it has since been studied as a direct scavenger of free radicals and a general antioxidant (24–26). Melatonin has a receptor-mediated mechanism, and its structure itself helps to reinforce the inhibition of oxidatively mediated stress. The main advantage of using melatonin as an antioxidant is that it is selectively taken up by the mitochondrial membrane, which is not applicable to other antioxidants (27). Melatonin is now well recognized as an antioxidant, and several preclinical studies demonstrate its renoprotective properties against oxidative-stress-induced nephrotoxicity, including that caused by vancomycin (12, 28, 29). The consideration of melatonin for renoprotection is an interesting option, since it is commonly used as a sleep aid in hospitalized patients due to an efficacy similar to and a safety profile better than that of non-benzodiazepine hypnotics, as we have previously reported (30). In this study, we evaluated the association between melatonin use and the development of AKI in hospitalized adult patients receiving vancomycin.

RESULTS

We identified a total of 303 adult patients who were treated with vancomycin during the specified time period, 101 of which were on melatonin in combination with vancomycin. The mean number of melatonin doses was 6.5 ± 8.1 doses per patient in the treatment group. More than half of patients (53.5%) received melatonin before or on the same day as vancomycin therapy initiation. Table 1 provides a summary of the patient demographics and vancomycin dosing characteristics. Overall, baseline characteristics were similar between the two groups except for the incidence of bacteremia/sepsis (25.2% for the control group versus 37.6% for the treatment group [$P = 0.026$]).

Patients frequently received other antibiotics (Table 2), with the most common agent being piperacillin-tazobactam (49.5% for the control versus 46.5% for the treatment group [$P = 0.626$]). Most patients also received other nephrotoxins (73.3% for the control versus 78.2% for the treatment group [$P = 0.349$]), such as nonsteroidal anti-inflammatory drugs (NSAIDs), loop diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), all of which were similar between groups. The most common vancomycin dosing frequency was every 8 h (Q8h) for the control group (46.0%) and Q12h for the treatment group (57.4%). The total daily dose of vancomycin was higher in the control group (2.8 ± 1.2 g/day for the control versus 2.6 ± 1.1 g/day for the treatment group [$P = 0.186$]), but this difference was not statistically significant. The total number of days of vancomycin therapy was longer for the treatment group (4.2 ± 2.5 days for the control versus 4.8 ± 3.1 days for the treatment group [$P = 0.068$]), but this difference was also not statistically significant. The initial mean trough concentrations at steady state were similar between the two groups (16.2 ± 6.6 μg/ml for the control versus 16.7 ± 6.6 μg/ml for the treatment group [$P = 0.632$]). The mean AUCs, estimated with a Bayesian model, were also similar between the two groups (487.4 ± 215.9 mg · h/liter for the control versus 479.2 ± 256.7 mg · h/liter for the treatment group [$P = 0.770$]). The median changes in creatinine clearance (CL_{CR}) from the start of vancomycin therapy to discontinuation of therapy

TABLE 1 Baseline comparison between groups[a]

Parameter	Value(s) for: Control group ($n = 202$)	Melatonin group ($n = 101$)	*P* value
Mean age (yrs) ± SD	60.9 ± 19.3	64.4 ± 18.3	0.131
Mean ht (cm) ± SD	171.0 ± 10.8	171.6 ± 10.0	0.658
Mean wt (kg) ± SD	88.2 ± 27.5	89.2 ± 27.6	0.774
Mean body mass index (kg/m^2) ± SD	30.2 ± 9.1	30.3 ± 9.3	0.925
Mean initial BUN (mg/dl) ± SD	20.2 ± 11.1	20.6 ± 12.5	0.774
Mean initial sCr (mg/dl) ± SD	0.87 ± 0.37	0.93 ± 0.42	0.204
Mean initial albumin (g/dl) ± SD	3.5 ± 0.67	3.36 ± 0.55	0.149
Mean initial CL_{CR} (ml/min) ± SD	122.1 ± 71.5	112.4 ± 73.4	0.263
$CL_{CR} \geq 90$ ml/min (no., %, of patients)	124, 61.4	58, 57.4	0.509
CL_{CR} of 60–89 ml/min (no., %, of patients)	46, 22.8	22, 21.8	0.854
CL_{CR} of 30–59 ml/min (no., %, of patients)	32, 15.8	21, 20.8	0.292
Female (no., %, of patients)	76, 37.6	31, 30.7	0.376
Race and/or ethnicity (no., %, of patients):			
White only	153, 75.7	80, 79.0	0.879
White and Hispanic/Latino	13, 6.4	7, 6.9	
Black	17, 8.4	5, 5.0	
Black and Hispanic/Latino	2, 0.1	1, 1.0	
Asian or Pacific Islander	4, 2.0	3, 3.0	
Other	13, 6.4	5, 5.0	
Obesity (no., %, of patients)	87, 43.1	43, 42.6	0.935
Hypertension (no., %, of patients)	108, 53.5	56,55.4	0.744
Heart failure (no., %, of patients)	56, 27.7	21, 20.8	0.191
Diabetes (no., %, of patients)	70, 34.6	41, 40.6	0.312
ICU admission (no., %, of patients)	51, 25.2	23, 22.3	0.636
Infections present (no., %, of patients):			
Bacteremia/sepsis	51, 25.2	38, 37.6	0.026
Osteomyelitis	3, 1.5	0, 0	0.533
Pneumonia	31, 15.3	15, 14.9	0.910
Skin and soft structure infection	8, 4.0	4, 4.0	1.000
Urinary tract infection	21, 10.4	16, 15.8	0.172
Empiric	110, 54.5	46, 45.5	0.143
CCI ± SD	2.4 ± 2.5	2.2 ± 2.3	0.493
Mean total daily dose (g/day) of vancomycin ± SD	2.8 ± 1.2	2.6 ± 1.1	0.186
Mean total no. of days of vancomycin ± SD	4.2 ± 2.5	4.8 ± 3.1	0.068
Vancomycin dosing frequency (no., %, of patients):			0.111
Q48h	1, 0.01	0, 0	
Q24h	21, 10.4	9, 9.0	
Q12h	87, 43.1	58, 57.4	
Q8h	93, 46.0	34, 33.4	
No., %, of patients with the following daily dose of melatonin:			
5 mg	NA	69, 68.3	
3 mg	NA	32, 31.7	
No., %, of patients with indicated day of initiation of melatonin:			
Before or on the same day	NA	54, 53.5	NA
Started after vancomycin	NA	47, 46.0	NA
Mean no. of days of concomitant melatonin, SD	NA	3.0, 2.3	NA

[a]BUN, blood urea nitrogen; NA, not available.

were significantly different between the two groups (3.5 ml/min for the control versus 11.0 ml/min for the treatment group [$P = 0.047$]). However, the mean change in serum creatinine (sCr) from the start of vancomycin therapy to discontinuation of therapy was lower in the treatment group (0.1 ± 0.5 mg/dl for the control versus −0.1 ± 0.4 mg/dl for the treatment group [$P = 0.007$]) (Table 3). Furthermore, patients who experienced AKI had significantly longer median lengths of stay (LOS) than the patients who did not experience AKI (6.0 days for patients without AKI versus 11.0 days for patients with AKI [$P < 0.001$]). For patients who developed AKI in the treatment group, there was no statistically significant

TABLE 2 Comparison of other prescribed antibiotics and nephrotoxins between patients receiving concomitant vancomycin and melatonin and those receiving vancomycin alone

Antibiotic(s)	No., %, of patients in: Control group ($n = 202$)	Melatonin group ($n = 101$)	*P* value
Cephalosporins	104, 51.5	57, 56.4	0.416
Cefazolin	24, 11.9	23, 22.7	0.014
Cefepime	40, 19.8	18, 17.8	0.680
Cefoxitin	0, 0	2, 2.0	0.110
Cefpodoxime	3, 1.5	2, 2.0	1.000
Ceftriaxone	60, 29.7	31, 30.7	0.859
Cephalexin	4, 2.0	3, 3.0	0.690
Penicillins	109, 54.0	55, 54.5	0.935
Ampicillin-sulbactam	12, 5.9	7, 6.9	0.738
Amoxicillin-clavulanic acid	3, 1.5	4, 4.0	0.227
Oxacillin	2, 1.0	3, 3.0	0.338
Piperacillin-tazobactam	100, 49.5	47, 46.5	0.626
Aminoglycosides	5, 2.5	1, 1.0	0.667
Amikacin	0, 0.0	1, 1.0	0.333
Gentamicin	5, 2.5	0, 0	0.173
Fluoroquinolones	20, 9.9	9, 8.9	0.782
Ciprofloxacin	7, 3.5	1, 1.0	0.277
Levofloxacin	13, 6.4	9, 8.9	0.434
Tetracyclines	10, 5.0	7, 6.9	0.480
Doxycycline	10, 5.0	7, 6.9	0.480
Carbapenems	27, 13.4	18, 18.2	0.304
Aztreonam	3, 1.5	1, 1.0	0.627
Ertapenem	11, 5.4	3, 3.0	0.399
Imipenem	1, 0.1	0, 0	1.000
Meropenem	11, 5.4	14, 13.9	0.015
Macrolides	32, 16.2	12, 12.1	0.356
Azithromycin	24, 12.0	10, 10.1	0.607
Lincosamides	8, 4.0	2, 2.0	0.505
Clindamycin	8, 4.0	2, 2.0	0.505
Other	49, 24.3	25, 25.3	0.925
Trimethoprim-sulfamethoxazole	7, 3.5	5, 5.1	0.532
Daptomycin	10, 5.0	4, 4.0	0.781
Linezolid	5, 2.5	1, 1.0	0.667
Metronidazole	33, 16.3	15, 15.2	0.739
Nitrofurantoin	1, 0.1	2, 2.0	0.259
Other nephrotoxins[a]	148, 73.3	79, 78.2	0.349
NSAIDs	99, 49.0	47, 46.5	0.684
ACEI/ARB	51, 25.2	29, 28.7	0.519
Loop diuretics	69, 34.1	46, 45.5	0.054
Contrast media	87, 43.1	36, 35.6	0.264

[a]NSAIDs, nonsteroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

difference between the patients who started melatonin before or on the same day as vancomycin therapy initiation and the patients who started melatonin after vancomycin therapy initiation (2/54 versus 6/47 [$P = 0.141$]).

Results of the univariate and multivariable analyses on the risk factors associated with the onset of AKI are shown in Table 4. The incidence of AKI was lower in patients treated with melatonin than in the control group (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.20 to 0.99; *P* value = 0.048). In the univariate analysis, concomitant piperacillin-tazobactam use during the vancomycin therapy was associated with a significantly increased risk of developing AKI (OR, 3.90; 95% CI, 1.83 to 8.29; *P* value < 0.001). The use of a loop diuretic, which was one of the common nephrotoxic agents used in both groups, was also a major risk factor for developing AKI (OR, 3.37; 95% CI, 1.70 to 6.7; *P* value = 0.001). We have also

TABLE 3 Comparison of clinical characteristics and outcomes

Parameter	Values for: Control group ($n = 202$)	Melatonin group ($n = 101$)	*P* value
No. (%) of patients with acute kidney injury	33 (16.3)	8 (7.9)	0.043
No. (%) of patients with an sCr >0.3 mg/dl from baseline	32 (15.8)	8 (7.9)	0.055
No. (%) of patients with an sCr increase >50% from baseline	18 (8.9)	5 (5.0)	0.220
Mean length of stay (days) ± SD	8.4 ± 7.8	12.1 ± 17.1	0.044
Mean AUC (mg · h/liter) ± SD	487.4 ± 215.9	479.2 ± 256.7	0.770
Mean initial trough (μg/ml) ± SD	16.2 ± 6.6	16.7 ± 6.6	0.632
Median change in CL_{CR} from baseline (ml/min) [IQR][a]	3.5 [17.1]	11.0 [27.2]	0.047
Mean change in sCr (mg/dl) from baseline ± SD	0.1 ± 0.5	−0.1 ± 0.4	0.007

[a]IQR, interquartile range.

identified other risk factors in univariate analysis, such as an AUC of >600 mg · h/liter, a Charlson-Deyo comorbidity index (CCI) of >3, and admission to an intensive care unit (ICU). However, only covariates for which the *P* was ≤0.1 were considered for further evaluation in the multivariable analysis. After controlling for an AUC of >600 mg · h/liter, a CL_{CR} of ≥60 ml/min, and admission to the ICU in multivariable logistic regression, melatonin use was associated with a 63% decrease in AKI (OR, 0.37; 95% CI, 0.14 to 0.96; *P* value = 0.041).

DISCUSSION

To our knowledge, this is the first human study assessing the association between melatonin and vancomycin-related nephrotoxicity in hospitalized patients. Although the impact of melatonin on drug-related nephrotoxicity in *in vitro* models has been previously reported, its clinical applicability has not been evaluated in hospitalized patients. In this study, the use of melatonin during the vancomycin therapy was associated with a 63% reduction in AKI.

In our univariate analysis, an age of ≥65 years, AUC values of >600 mg · h/liter, a CCI score of >3, loop diuretics, ICU admission, and concomitant piperacillin-tazobactam use were associated with an increased risk of developing AKI. Previous studies have reported on the increased risk of nephrotoxicity with the concomitant use of piperacillin-tazobactam and vancomycin therapy (31–33).

Preclinical studies have demonstrated that vancomycin may induce kidney injury through oxidative stress and mitochondrial damage (18, 34). As melatonin can restore the renal mitochondrial dynamic balance by inhibiting fission and promoting fusion activities (35), melatonin may prevent vancomycin-related nephrotoxicity by improving renal mitochondrial function. Melatonin also increases the anti-inflammatory cytokines, thus reducing oxidative stress (19, 36). Furthermore, since a CL_{CR} of ≥60 ml/min was identified in our multivariable analysis to significantly lower the risk of developing AKI (OR, 0.45; 95% CI, 0.21 to 0.95; *P* value = 0.036), improving CL_{CR} should be prioritized to prevent hospitalized patients from developing vancomycin-related AKI.

TABLE 4 Multivariable logistic regression for factors associated with AKI[a]

Parameter	Univariate OR (95% CI)	Univariate *P* value	Multivariable[b] OR (95% CI)	Multivariable[b] *P* value
Melatonin	0.44 (0.20–0.99)	0.048	0.37 (0.14–0.96)	0.041
Age ≥ 65 yrs	1.75 (0.90–3.41)	0.100		
AUC > 600 mg · h/liter	11.6 (5.61–24.28)	<0.001	11.6 (5.15–26.2)	<0.001
CCI > 3	2.52 (1.26–5.06)	0.030		
CL_{CR} ≥ 60 ml/min	0.45 (0.21–0.95)	0.036	0.36 (0.15– 0.91)	0.030
Use of loop diuretics	3.37 (1.70–6.7)	0.001		
ICU admission	5.99 (2.99–11.98)	<0.001	4.17 (1.90–9.18)	<0.001
Piperacillin-tazobactam	3.90 (1.83–8.29)	<0.001		

[a]Abbreviations: AUC, area under the curve; CCI, Charlson-Deyo comorbidity index; CL_{CR}, creatinine clearance; ICU, intensive care unit.
[b]Only covariates with a *P* of ≤0.1 were considered for further testing in the multivariable model.

AKI is commonly observed in hospitalized patients and is associated with an increased likelihood of mortality, hospital LOS, and cost (37–39). Similarly, in our study, patients who experienced AKI had a significantly longer median LOS than the patients who did not experience AKI (6.0 days for patients without AKI versus 11.0 days for patients with AKI [$P < 0.001$]). Since each case of AKI increases the hospitalization costs by $11,016 to $42,077 per case (40), this additional cost related to AKI indicates that melatonin may not only attenuate vancomycin-related AKI but also reduce the overall hospital LOS, further driving down the total cost for inpatient stay.

There are some limitations to our study that should be considered. First, the melatonin serum levels were not collected due to the lack of data availability. The oral bioavailability of melatonin in humans has a wide range, with melatonin serum levels differing up to 28-fold (41). Therefore, the melatonin serum levels for each patient may vary substantially based on the patient's other clinical factors. Second, the doses and frequency of melatonin administration were not consistent among the patients in the treatment group. The mean number of melatonin doses was 6.5 ± 8.1 doses per patient in the treatment group. However, there were some variations in the dosage of melatonin administered. Most patients received 5 mg of melatonin, while some patients received 3 mg of melatonin (68.3% for 5 mg, 31.7% for 3 mg). Several preclinical studies in mice (42), rats (29, 43, 44), and rabbits (45) have investigated the benefits of melatonin for protection against nephrotoxicity secondary to various insults. Dosing has varied among the studies; however, rats dosed with melatonin at 500 μg/kg of body weight orally (43) and 1 mg/kg (44) appreciated a reduction in markers of kidney injury. These doses translate to approximately 5 to 10 mg in a 70-kg human using allometric scaling (46). Moreover, melatonin concentrations in highly perfused organs, such as the kidney, may be higher than those quantitated in plasma based on previous physiologically based pharmacokinetic modeling (47). As such, the dose used in the current retrospective cohort reasonably recapitulates what has been appreciated in animal models. Nonetheless, the optimal dose and frequency of melatonin for its renoprotective effects still need further investigation. Similarly, although the timing of the melatonin administered did not significantly impact the incidence of vancomycin-related AKI in the treatment group, there may be a greater benefit if the melatonin is started prior to the vancomycin therapy initiation. The race and gender of our study population were mostly white and male. This limits applicability to other patient populations, as the average rate of kidney function decline differs among different racial and ethnic groups (48). Moreover, our study included patients who received at least three doses of vancomycin regardless of their treatment indications. Therefore, the levels of severity of a disease may have differed among the patient populations, which may directly or indirectly impact their kidney functions. Even though most of the patients were treated with vancomycin empirically, the treatment group had a significantly greater number of patients treated for bacteremia/sepsis than the control group (25.2% for the control versus 37.6% for the treatment group [$P = 0.026$]). Nevertheless, we did account for overall comorbidity by adjusting our primary outcome for the CCI. We utilized sCr as a biomarker for AKI in our study. sCr is not an ideal biomarker because it may be influenced by other factors. Nonetheless, the current standard of care for assessing renal function is sCr. Finally, since this was a retrospective cohort study, there are inherent limitations with this study design. Confounding factors are always a concern in observational studies. We considered propensity score matching using covariates known to influence the incidence of AKI; however, the conclusions were unchanged (see Table S1 in the supplemental material). Despite these limitations, our findings provide valuable information about the impact of melatonin on hospitalized patients treated with vancomycin.

MATERIALS AND METHODS

Data source and patient selection. We performed a single-center, retrospective, institution review board (IRB)-approved cohort study using data from electronic patient medical records at a large community medical center. All consecutive patients (aged 18 years or older) discharged from the hospital

between January 2016 and September 2020 who received at least three doses of vancomycin alone or with melatonin (GenDose Pharmaceuticals, Davidson, NC) were screened for inclusion. Patients were required to have a creatinine clearance (CL_{CR}) greater than or equal to 30 ml/min at baseline (first vancomycin dose). Patients who were on hemodialysis, peritoneal dialysis, or had severe kidney dysfunction, defined as a CL_{CR} of $<$30 ml/min at baseline, were excluded.

Data extraction and collection. All data were extracted from the electronic health record (Allscripts Sunrise Clinical Manager). Patient age, sex, race/ethnicity, concomitant nephrotoxic agents, concomitant antibiotics, vancomycin indications, height, weight, and other relevant laboratory data were extracted from the medical record. Serum creatinine (sCr) concentrations were collected and used as a marker of vancomycin-related AKI. Baseline sCr concentrations were collected prior to the vancomycin therapy initiation, and the highest sCr concentrations during the vancomycin therapy were collected after vancomycin therapy initiation and until 24 h after the last dose. Patient comorbidities were identified using International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) codes, and subsequently, the Charlson-Deyo comorbidity index (CCI) was calculated to capture patient overall comorbidity. CL_{CR} was calculated with the Cockcroft-Gault equation using actual body weight. Area under the curve (AUC) data were estimated with DoseMe software (Tabula Rasa Healthcare, Moorsetown, NJ), which utilizes the Bayesian approach based on a published model (49).

Outcome. Patients were divided into all those who received vancomycin concomitantly with melatonin and a random sample of those who did not receive melatonin using a 1-to-2 ratio. The primary endpoint of AKI was defined as an absolute increase in serum creatinine of $\geq$0.3 mg/dl or a $\geq$50% increase in serum creatinine from the start of vancomycin therapy (50–52). Patients were evaluated for vancomycin-related AKI at any point after the first dose of vancomycin was initiated and until 24 h after the last dose. Two consecutive elevated sCr measurements were required to establish an AKI. Secondary endpoints included a change in CL_{CR} and sCr from baseline levels to completion of vancomycin therapy.

Statistical analysis. Patient demographics were summarized using descriptive statistics. Continuous data are reported as means and standard deviations, and nominal data are reported as percentages. The differences in the baseline characteristics, vancomycin dosing variables, and clinical outcomes were tested using the *t* test for continuous data and the chi-square test or Fisher's exact test for categorical data. Normality testing was performed using visual inspection of histograms and the Mann-Whitney U test. For data that were not normally distributed, results are reported as medians and interquartile ranges and were compared using the Kruskal-Wallis test. The paired *t* test was used to assess significance in covariates from baseline to posttreatment. A multivariable logistic regression was constructed using melatonin as the exposure variable and AKI as the outcome variable. Covariates were selected for inclusion based on previous literature and results of univariate analysis. Variables were retained in the final model if *P* was $<$0.05. All analyses were performed in SPSS v26 (IBM Corporation, Armonk, NY).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.03 MB.

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