Evaluation of Vancomycin Dosing in Patients With Cirrhosis: Beginning De-liver-ations about a New Nomogram

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Abstract

Background: Reduced hepatic production of creatinine precursors in patients with decompensated cirrhosis leads to falsely low serum creatinine values. Therefore, when performing empiric dosing of vancomycin, an overestimation of creatinine clearance may result in significantly supratherapeutic vancomycin levels and increased risks of nephrotoxicity. **Objective:** The objective of the study is to evaluate vancomycin dosing requirements in patients with cirrhosis stratified by Child-Pugh Score, with subsequent comparison with doses that are recommended in the previously published and validated Kullar nomogram. **Methods:** A retrospective evaluation of patients with cirrhosis who received vancomycin for at least 3 full days and had at least 1 serum concentration drawn. Vancomycin daily dose and corresponding serum concentration were collected with patients stratified by Child-Pugh Score for comparison. Each patient had their vancomycin dose compared with the dose suggested by a published nomogram. **Results:** A total of 201 courses of vancomycin were followed. There were no significant differences between the Child-Pugh cohorts with respect to initial vancomycin dosing. There was also no significant difference in the median initial vancomycin trough concentration between the 3 cohorts (Child-Pugh A: 13.7 µg/mL [interquartile range, IQR: 10.4-22.1]; Child-Pugh B: 20.2 µg/mL [IQR: 15.1-25.9]; Child-Pugh C: 19.3 µg/mL [IQR: 14.9-25.2, $P = .08$]. The median vancomycin dose using the Kullar nomogram would have been 3.0 g/day (IQR: 2.0-3.75, $P < .001$), but the median dose actually used in this patient population was significantly less at 2.0 g/day. Nonetheless, the median vancomycin trough concentration in the entire patient population was 19.8 µg/mL (IQR: 15.4-25.9). **Conclusion:** In patients with cirrhosis, there was a high incidence of supratherapeutic vancomycin serum concentrations despite the fact that dosing was significantly less than that suggested by the published Kullar nomogram.

Keywords

anti-infectives, infectious diseases, monitoring drug therapy

Introduction

Vancomycin was first marketed in the United States in 1968. Its generic name was derived from the term “vanquish,” which was apparently how researchers described the drug’s impressive effect on eradicating colonies of staphylococci.^{1,2} Once marketed, there emerged ever-increasing awareness of dose-related toxicities that could be correlated with high serum levels, and higher serum levels tended to occur in patients with concomitant renal impairment.^{3,4} In response to these observations, and the fact that pharmacokinetic studies showed that the drug was 80% to 90% renally excreted unchanged, dosing nomograms based upon creatinine clearance began to appear in the literature with advancing regularity.^{3,5,6}

As vancomycin was found to have a volume of distribution that correlated reasonably well to actual body weight, most of the nomograms would include actual body weight on one axis and creatinine clearance on the other.^{1,6} “Therapeutic” peaks

and troughs were also promulgated. Moving into the 1980s, the use of target peaks was gradually dismissed on several grounds. Initially, the therapeutic trough range was established as 5 to 10 µg/mL. That was until the National Accrediting Agency for Clinical Laboratory Standards changed their breakpoints in 1999, whereupon target troughs increased to a diagnosis-dependent 10 to 20 µg/mL range. These changes in breakpoints, and the concomitant growing involvement of

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	Creatinine Clearance (mL/min)							
		40-49	50-59	60-69	70-79	80-89	90-99	>100
Weight (kg)	50-54	500mg q 12h	750mg q 12h	1000mg q12h	750mg q8h	1000mg q8h	1000mg q8h	1250mg q8h
	55-59	750mg q 12h	1000mg q12h	1250mg q12h	750mg q8h	1000mg q8h	1000mg q8h	1250mg q8h
	60-64	750mg q 12h	1000mg q12h	1250mg q12h	750mg q8h	1000mg q8h	1250mg q8h	1500mg q8h
	65-69	750mg q 12h	1000mg q12h	1250mg q12h	1000mg q8h	1000mg q8h	1250mg q8h	1500mg q8h
	70-74	750mg q 12h	1250mg q12h	750mg q8h	1000mg q8h	1250mg q8h	1500mg q8h	1500mg q8h
	75-79	1000mg q12h	1250mg q12h	750mg q8h	1000mg q8h	1250mg q8h	1500mg q8h	1750mg q8h
	80-84	1000mg q12h	1250mg q12h	1000mg q8h	1250mg q8h	1250mg q8h	1500mg q8h	1750mg q8h
	85-89	1000mg q12h	1250mg q12h	1000mg q8h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h
	90-94	1000mg q12h	1500mg q12h	1000mg q8h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h
	95-99	1250mg q12h	1500mg q12h	1000mg q8h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h
	100-104	1250mg q12h	1500mg q12h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h	2000mg q8h
	105-109	1250mg q12h	1500mg q12h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h	2250mg q8h
	≥110	1250mg q12h	1500mg q12h	1250mg q8h	1500mg q8h	1750mg q8h	2000mg q8h	2250mg q8h

Figure 1. Vancomycin dosing nomogram of Kullar et al.⁷

pharmacists in dosing and monitoring vancomycin as a standard of care, led to further refinement of the nomograms.⁷ Of course, these nomogram adjustments endeavored to further optimize efficacy and minimize toxicity.

Despite these improvements and enhancements through use of the dosing nomograms, not all populations can be generalized to these guidelines.⁵ One such population may be patients with hepatic cirrhosis.⁵ Because patients with cirrhosis have fewer functional hepatocytes, they produce less creatine, the precursor to creatinine. They also have less muscle mass, and therefore have lower quantities of stored creatine and circulating creatinine. Thus, creatinine clearance estimates using a formula such as Cockcroft-Gault may overestimate true glomerular filtration rate (GFR) in patients with cirrhosis by about 1.5-fold to 2-fold.⁸⁻¹¹ However, as vancomycin volume of distribution correlates with fluid load, the higher fluid volume found in patients with cirrhosis and ascites could result in larger volumes of distribution.⁹ To add further importance to the need to account for these differences, patients with cirrhosis are also more prone to drug-induced renal failure, which may lead to hepatorenal syndrome, a condition that portends very high mortality rates.¹⁰

For these reasons, we sought to evaluate dosing of vancomycin in patients with cirrhosis by comparing the doses actually used and monitored by clinical pharmacists in a large university hospital with the dosing that would have been recommended using a recently published and validated nomogram by Kullar et al.⁷ (Figure 1). The Kullar nomogram targets vancomycin trough concentrations between 15 and 20 µg/mL. Patients who were not included in the Kullar study included those weighing greater than 110 kg, had a creatinine clearance less than 30 mL/min or greater than 110 mL/min, did not have unstable renal function or volume of distribution, transplant procedure within previous 6 months, had surgery within preceding 24 hours, were receiving

vasopressor therapy, or had a serum creatinine concentration below 0.6 mg/dL.

Methods

This was a retrospective observational study evaluating initial vancomycin dosing in adults with cirrhosis admitted to the gastroenterology service. Patients were identified over a 4-year period (January 2011 through December 2015). Other inclusion criteria included duration of vancomycin therapy of at least 3 full days and the measurement of at least 1 vancomycin trough concentration. Use of trough concentrations was limited to those collected no sooner than prior to the fourth dose of vancomycin. Patients were stratified by Child-Pugh Score to evaluate vancomycin dosing requirements. Patients who were not receiving scheduled dosing of vancomycin (eg, hemodialysis patients) were excluded from the study. The dosing of vancomycin within the institution was managed by pharmacists. Although there was an in-house vancomycin dosing nomogram, pharmacists were not obligated to use it; thus, actual practice varied by clinician.

Data collected included demographic information (sex, age, height, weight) and serum laboratory values including serum creatinine, blood urea nitrogen, albumin, bilirubin, and international normalized ratio (INR). Clinical information included presence of ascites or hepatic encephalopathy. Vancomycin data collected included dosing regimen, serum trough concentration measured at steady state, and duration of therapy. Calculation of creatinine clearance was determined using the Cockcroft-Gault formula.

The primary outcome of the study was to compare median vancomycin trough concentrations achieved among the 3 Child-Pugh cohorts (A, B, or C). Vancomycin dosing required to achieve initial concentrations was also assessed. The proportion of patients who achieved therapeutic troughs was also

Table 1. Baseline Demographics (Medians With IQR).

	Child-Pugh Class			P value
	A (n = 12)	B (n = 90)	C (n = 99)	
M/F	8/4	46/44	47/52	
Age (y)	53.0 (47.0-54.8)	58.5 (53.0-62.5)	55.0 (46.0-61.0)	.002 ^a
Weight (kg)	81.2 (71.8-101.6)	86.5 (73.7-99.8)	83.5 (68.6-94.0)	.33
Creatinine (mg/dL)	0.8 (0.6-1.0)	1.2 (0.8-1.6)	1.2 (0.8-1.8)	.009 ^b
Bilirubin (mg/dL)	0.9 (0.4-1.4)	1.5 (0.9-2.5)	6.4 (3.7-14.1)	<.001 ^a
INR	1.15 (1.1-1.2)	1.2 (1.1-1.5)	1.8 (1.6-2.2)	<.001 ^a
Albumin (g/dL) ^c	3.4 + 0.7	2.8 + 0.6	2.6 + 0.6	<.001 ^d
Initial vancomycin dose (g/24 h)	2.0 (2.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	.17
Creatinine clearance (mL/min)	89.5 (71.5-137.5)	63.0 (45.1-82.8)	61.0 (44.3-88.9)	.003 ^b
Indications				
Pneumonia	5	18	32	
Peritonitis	2	8	19	
Sepsis	1	20	21	
Bacteremia	1	7	8	
Cellulitis	1	11	7	
Urinary tract infection		2	3	
Empiric	1	23	8	
Wound	1		1	
Osteomyelitis		1		

Note. IQR = interquartile range; INR = international normalized ratio.

^aBetween A and C; B and C.

^bBetween A and B; A and C.

^cMean + SD.

^dBetween each class.

Table 2. Vancomycin Serum Concentrations and Incidence of Supratherapeutic Concentrations (Median With IQR).

	Child-Pugh Class			P value
	A (n = 12)	B (n = 90)	C (n = 99)	
All patients				
Initial vancomycin dose (g/24 h)	2.0 (2.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	.17
Vancomycin concentration mg/dL	13.7 (10.4-22.1)	20.2 (15.1-25.9)	19.3 (14.9-25.2)	.08
Supratherapeutic concentration, n (%)	4 (33.3%)	47 (52.2%)	46 (46.5%)	.41

Note. IQR = interquartile range.

compared. Subset analysis of patients with normal renal function was performed. Finally, dosing regimens used in each patient were compared with the recommended vancomycin dosing regimen on the Kullar vancomycin nomogram.

Data Analysis

Continuous data that were normally distributed were analyzed using the 1-way analysis of variance with post hoc Sheffe test and nonnormally distributed data were analyzed using the Kruskal-Wallis test or the Wilcoxon signed rank test. Determination of normality was performed using the Shapiro-Wilk test. Categorical data were analyzed using chi-square or Fisher exact test. A *P* value of <.05 was considered significant. All data are reported as median with interquartile ranges (IQR) unless indicated otherwise.

Results

A total 201 patients were included in the study. The majority of patients were in Child-Pugh Classes B (n = 90) and C (n = 99), with relatively few patients in Child-Pugh Class A (n = 12) (Table 1). Stratified by Child-Pugh class, patients were significantly different with respect to several baseline demographic characteristics. Indices of hepatic function (bilirubin, INR, albumin) were significantly different between each of the Child-Pugh classes.

Patients who received 1500 mg of vancomycin per day or less were dosed once daily, those receiving doses between 1500 mg and 3.0 g/day were dosed every 12 hours, whereas those dosed greater than 3.0 g/day were dosed every 8 hours. There were no significant differences between the cohorts with respect to initial vancomycin dosing (Table 2). There

was also no difference in the median initial vancomycin trough concentration between the 3 cohorts (Child-Pugh A: 13.7 µg/mL [IQR: 10.4-22.1]; Child-Pugh B: 20.2 µg/mL [IQR: 15.1-25.9]; Child-Pugh C: 19.3 µg/mL [IQR: 14.9-25.2, $P = .08$]). Overall, there were 97 patients (48.3%) who had an initial vancomycin trough concentration >20 µg/mL. The incidence of supratherapeutic vancomycin concentration was not significantly different among the cohorts (Child-Pugh A: 33%, Child-Pugh B: 52%; Child-Pugh C: 46.5%, $P = .41$). Finally, there were 9 patients who had vancomycin concentrations that were less than 10 µg/mL (Child-Pugh A: 17%; Child-Pugh B: 4.4%; Child-Pugh C: 3%, $P = .09$).

Comparison to Nomogram

There were 134 patients (Child-Pugh A = 7 patients, B = 57 patients, C = 70 patients) who met criteria for dosing via the Kullar nomogram. The median empiric vancomycin dose in this cohort was 2.0 g/day (IQR: 1.0-2.0). The median vancomycin trough concentration was 19.8 µg/mL (IQR: 15.4-25.9). There were 66 patients (49.3%) who had an initial vancomycin trough concentration >20 µg/mL. The median vancomycin dose that would have been recommended via the Kullar nomogram was 3.0 g/day (IQR: 2.0-3.75, $P < .001$).

Subgroup analysis showed supratherapeutic concentrations occurred in 29% of Child-Pugh A patients and 49% in each of the Child-Pugh B and C cohorts. The median vancomycin trough concentrations among the 3 cohorts were not significantly different (Child-Pugh A: 13.4 µg/mL [IQR: 10.8-22.2]; Child-Pugh B: 20.0 µg/mL [IQR: 15.7-25.9]; Child-Pugh C: 19.8 µg/mL [IQR: 15.7-27.1], $P = .31$). The median dose used in the Child-Pugh B group was 2.0 g/day (IQR: 1.0-2.0) compared with the Kullar recommended dose of 2.5 g/day (IQR: 2.0-3.0, $P < .001$). Finally, the median dose used in the Child-Pugh C group was 2.0 g/day (IQR: 1.0-2.0) compared with the Kullar recommended dose of 2.75 g/day (IQR: 2.0-3.75, $P < .001$).

Discussion

The Kullar nomogram was selected for comparison because it was recently published, and is well known to be an “aggressive” nomogram targeting a trough of 15 to 20 µg/mL. Adding validity to using Kullar as a standard from which to measure, about 80% of the Kullar subjects had troughs between a range of 13 and 22 mg/mL,⁷ which would be a reasonable and desirable outcome when dealing with empiric therapy in acutely ill hospitalized patients.

In the cohort that met criteria for the Kullar nomogram, the empiric vancomycin dosing used was about two-thirds of dosing that would have been recommended by the Kullar nomogram. Despite the lower doses in this subset, the median vancomycin trough concentration was 19.8 µg/mL, whereas the median trough concentration in the Kullar study cohort was 17.5 µg/mL (IQR: 15.0-20.0). Furthermore, there was a

much higher rate of supratherapeutic concentrations in this cohort (49.3%) compared with that seen in the Kullar study (22.5%). Given that patients with cirrhosis may possess “cryptic renal impairment,” this result was expected. The falsely low serum creatinine concentrations in cirrhosis are thought to be a manifestation of long-term malnutrition, hormonal imbalances leading to gradual muscle wasting, and reduced hepatic production of creatine due to the declining numbers of viable hepatocytes.⁸⁻¹¹

Creatine is an essential nutrient formed by the bonding of the 2 amino acids, glycine and arginine. It is produced mainly by the liver, and to a lesser extent in the kidneys, then transported and stored in skeletal muscle and other tissues. It is then phosphorylated and converted to phosphocreatine and/or creatinine, which act as energy buffers for skeletal muscle contraction.¹¹ Creatine is produced endogenously at a rate of about 1.0 g/day in patients with normal hepatic function. It is also obtained exogenously through diet. Dietary intake averages are also thought to be about 1.0 g/day with a typical omnivorous diet.¹²⁻¹⁴

As cirrhosis progresses, creatine production declines.¹⁵ Earlier studies with cirrhosis concluded that the disease caused average reductions in creatine synthesis on the order of 40% to 50%.^{10,16,17} More studies followed in patients with decompensated cirrhosis that showed significant overestimation of renal clearance compared with patients without cirrhosis when serum creatinine was used in the estimate.^{9,18,19} Many papers have opined that most methods of estimating creatinine clearance that use the serum creatinine would overestimate true renal function by about 50% (1½ times) in patients with decompensated cirrhosis,^{9,10,20} and that factor may even as high as a 2-fold overestimation in patients with more advanced cirrhosis.¹⁷

The empiric vancomycin dosing in our study population of about 2.0 g/day was already much lower than what would have been recommended using most vancomycin nomograms, and certainly far lower than the 3.0 g/day on corresponding the Kullar tables. However, despite these lower empiric doses, the median initial troughs were still supratherapeutic almost half the time, with patients in Child-Pugh Classes B and C manifesting median concentrations near or greater than 20 µg/mL. Although analysis revealed no significant difference in vancomycin trough concentrations between the Child-Pugh cohorts, there was a trend toward significance. Lack of significance between the mild cirrhosis in Class A versus Classes B and C may be due to an inadequate number of patients in the Class A cohort. Of course, a lack of sample size power could have also been the reason there was no difference seen between Classes B and C, as well. It would be expected that decreases in vancomycin dosing requirements should occur incrementally as liver disease progresses from Classes A to B to C. This is because as cirrhosis advances, the ability to produce creatine declines and muscle wasting advances, and true GFR may actually decline even though the serum creatinine may not change.^{15,20}

Currently, there is a dearth of information available regarding dose adjustments of vancomycin in patients with cirrhosis. Of note, a study by Aldaz et al²¹ looked at the effects of hepatic function on vancomycin pharmacokinetics in cancer patients. They studied 130 patients without hepatic failure and 24 patients with varying degrees of hepatic failure, 7 of whom had ascites. They concluded that vancomycin clearance was not influenced by degree of liver failure when the patients with ascites were excluded. The investigators attributed the reduced clearance in the patients with ascites to an increase in vancomycin volume of distribution of just over 50%, which is a reasonable explanation for at least some of the difference. Because those with ascites may also fall into the category of “decompensated” liver disease, reduced renal clearance may also have played a role. However, given that then only 17 patients were in the hepatic failure without ascites group, and the fact that the type of liver failure in these cancer patients was likely much different than that seen with chronic liver disease leading to cirrhosis, these conclusions do not appear readily generalizable to our study population.

There are some limitations to the study that need to be considered. First, this was a retrospective study; thus, data collection is subject to accuracy of documentation. Also, the number of patients per cohort and the significant imbalance of subjects among the cohorts may have resulted in either a type I or type II statistical error.

Further studies could be done to validate the findings in this study. From our study, it does appear as if patients with decompensated cirrhosis (generally Child-Pugh Classes B and C) require about half to one-third less vancomycin than patients without cirrhosis when compared with a published nomogram (Kullar). Eventually, with the accumulation of more data, it is hoped that a nomogram specific to patients with cirrhosis could be actually be synthesized and validated.

Declaration of Conflicting Interests

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