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Practical Vancomycin Dosing in Hemodialysis Patients in the Era of Emerging Vancomycin Resistance: A Single-Center Experience

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Vancomycin is used commonly to treat Gram-positive bacteremia in hemodialysis patients [1]. The most accurate and practical method to monitor vancomycin effectiveness is to measure the trough vancomycin concentration prior to the fourth dose [1]. Because vancomycin is cleared by renal excretion, it can be dosed following each dialysis session to maintain therapeutic plasma concentrations [2]. Vancomycin clearance during hemodialysis is negligible with low-flux dialyzers, but substantial (~40%) with high-flux dialyzers [3, 4]. Administration of vancomycin at the end of each dialysis session avoids intra-dialytic clearance and ensures therapeutic concentrations [3, 4]. However, this practice is logistically challenging in the outpatient dialysis setting. For this reason, vancomycin is frequently infused during the last hour of each dialysis session. Using such a regimen, Ariano et al achieved pre-dialysis serum vancomycin concentrations of 5 to 20 mg/L in most hemodialysis patients [5]. We have been using a similar protocol (a loading dose of 20 mg/kg during the first dialysis session, followed by 500 mg during the last 30 min of each subsequent session) to administer vancomycin at our institution.

Until recently, the recommended trough serum vancomycin concentrations were 5-20 mg/L. However, the frequency of *Staphylococcus aureus* and *Enterococcus* infections with relative resistance to vancomycin has been increasing [1, 6]. Recent studies have documented an association between trough vancomycin serum concentrations < 10 mg/L and therapeutic failure, which could potentially promote the emergence of vancomycin resistance [7, 8]. These observations have led to new consensus guidelines, which recommend maintaining a minimal vancomycin trough of >10 mg/L to avoid development of vancomycin resistance, and a concentration of 15 to 20 mg/L to optimize tissue penetration and clinical outcomes in patients with complicated infections [1].

Most U.S. hemodialysis units are at freestanding locations, and patient blood samples are shipped to a remote laboratory for testing [9, 10]. As a result, serum vancomycin

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concentrations are not readily available. Thus, it would be desirable to have a dosing regimen that achieves therapeutic trough vancomycin concentrations in the vast majority of patients without requiring routine drug monitoring. We performed a quality assurance study to determine whether a higher fixed dose of vancomycin administered during the last hour of dialysis sessions could reliably achieve the new target trough vancomycin concentrations in hemodialysis patients.

During a six-month period, we enrolled 34 hospitalized hemodialysis patients (32 with end-stage renal disease and 2 with acute renal failure; 50% female; age range, 21-80 yr; weight range, 50-118 kg; 62% with catheters) receiving vancomycin to treat suspected or documented bacteremia (Table 1). The duration of antibiotics was determined by the infection type. The first dose of administered vancomycin (Hospira Inc, www.hospira.com) was 20 mg/kg (actual weight) (rounded to the nearest 250 mg) and infused at 1000 mg/hr, timed to end with the dialysis session. Subsequent doses of 1000 mg vancomycin were infused during the last hour of each dialysis session. A trough vancomycin concentration was measured after the third dose of vancomycin, and immediately prior to the fourth dialysis session. Serum vancomycin concentrations were measured using the enhanced turbidimetric inhibition immunoassay (SYNCHRON; Beckman Coulter, www.beckman-coulter.com). Our Institutional Review Board approved retrospective data analysis for research purposes.

Standard descriptive statistics were calculated using the GraphPad Prism software (version 4.0a, GraphPad Software, www.graphpad.com). The mean $\pm$ SD trough serum vancomycin concentration was 19.0 ± 6.6 mg/L (95% CI, 16.7 to 21.3 mg/L)(Figure 1). Twelve patients (or 35%) had trough vancomycin concentrations between 15-20 mg/L, and 27 (or 79%) had concentrations between 10-25 mg/L. Only two patients had trough vancomycin concentrations less than 10 mg/L (8.4 and 9.9 mg/L, respectively), requiring an increase in their maintenance vancomycin dose. Five patients (15%) had concentrations > 25 mg/L.

Our protocol achieved vancomycin concentrations >10 mg/L prior to the fourth dose in nearly all patients. Our study has some limitations. First, it was performed at a single medical center, and would need to be validated at other centers. Second, we did not perform formal pharmacokinetic studies to quantify vancomycin clearance by the dialyzer. Thus, the actual systemic vancomycin dose received by each patient is unknown. Third, we used a single type of high-flux dialyzer, and vancomycin clearance may differ with other dialyzers. Fourth, we did not quantify residual kidney function. In patients with significant endogenous vancomycin clearance, this protocol might produce subtherapeutic vancomycin concentrations. Finally, we employed a “one-size-fits-all” approach to maintenance vancomycin dosing. This strategy offers the advantage of simplicity in the outpatient dialysis setting, in which serum vancomycin concentrations are not readily available. However, it carries the potential risk of underdosing vancomycin in some patients. Thus, therapeutic drug monitoring may still be indicated in patients with morbid obesity (body mass index >40 kg/m²), those with significant residual kidney function, and those with a dialysis duration >4 h. Conversely, vancomycin overdosing may occur in small individuals using this protocol.

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Figure 1. Distribution of trough serum vancomycin concentrations in the study population. The solid line represents the mean value, and the dotted line is the recommended minimum trough vancomycin concentration (10 mg/L) to avoid development of vancomycin resistance. The mean $\pm$ SD trough serum vancomycin concentration was 19.0 ± 6.6 mg/L (95% CI, 16.7 to 21.3 mg/L).

Table 1

Clinical and dialysis features of the study population

Pt No.	Age/Sex	Admit diagnosis	Weight (kg)	HD prescription				Trough vancomycin (mg/L)
				Access type	Blood flow (mL/min)	Dialysate flow (mL/min)	HD time (h)	
1	57/F	CRB	86.7	TC	400	800	3.5	11.5
2	59/M	Gangrene, CRB	81.4	TC	400	800	3.5	21.0
3	36/F	Cellulitis	95.7	TC	400	800	3.0	17.3
4	57/M	Cellulitis	74.8	AVF	400	800	3.5	17.0
5	44/F	CRB	71.4	TC	400	800	3.0	25.3
6	59/M	Empyema	72.8	AVF	400	800	3.0	26.9
7	69/M	Cardiac arrest, pneumonia	90.9	TC	300	800	3.5	18.2
8	61/M	Osteomyelitis	70.0	TC	400	800	3.0	26.9
9	40/F	CRB	50.0	TC	400	800	3.0	39.5
10	80/F	CRB	64.0	TC	400	800	2.9	15.8
11	32/F	AVG infection	107.8	TC	330	800	3.3	15.2
12	58/M	Myeloma, CRB	72.5	TC	300	800	4.0	23.1
13	41/M	UTI with sepsis	63.9	TC	300	800	4.0	23.8
14	67/M	Peripheral graft infection	100.0	AVF	400	800	3.2	14.9
15	50/M	ARF, pneumonia	89.2	TC	250	800	4.0	23.9
16	38/F	AVG infection	62.3	NTC	400	800	3.5	9.9
17	57/F	CRB	83.4	TC	250	800	4.0	19.4
18	59/F	Peritonitis	103.5	TC	400	800	3.0	33.1
19	52/M	Cirrhosis, sepsis	67.2	TC	400	800	4.0	23.2
20	49/M	Gangrene, sepsis	114.3	AVF	400	800	4.0	8.4
21	59/M	AVR	73.9	AVF	400	800	3.0	10.6
22	60/F	Hip infection	50.0	TC	400	800	3.0	13.8
23	59/F	CVA, sepsis	88.5	AVG	400	800	3.0	19.6
24	79/F	CRB	62.0	TC	400	800	4.0	21.4
25	58/M	Gangrene, sepsis	66.2	AVF	400	800	3.0	15.9

Pt No.	Age/Sex	Admit diagnosis	Weight (kg)	HD prescription				Trough vancomycin (mg/L)
				Access type	Blood flow (mL/min)	Dialysate flow (mL/min)	HD time (h)	
26	53/M	Pneumonia, ARF	91.9	NTC	400	800	4.0	12.6
27	43/F	Endocarditis	74.8	AVF	400	800	4.0	19.6
28	56/F	AIDS, sepsis	74.0	AVF	400	800	3.5	20.1
29	21/M	AVF infection	85.7	AVF	400	800	4.0	19.3
30	63/M	Osteomyelitis	118.0	AVF	400	800	4.0	17.0
31	70/F	Pacemaker infection	79.4	AVF	400	800	3.0	12.2
32	65/F	Biliary colic	101.6	TC	400	800	4.0	13.4
33	40/F	Cellulitis	60.0	TC	400	800	3.0	20.6
34	75/M	Decubitus ulcer infection	71.5	TC	400	800	3.0	15.9

Note: all patients were dialyzed with Revaclear MAX (high-flux polysulfone dialyzer).

Abbreviations: CVA, cerebrovascular accident; AIDS, acquired immunodeficiency syndrome; UTI, urinary tract infection; CRB, dialysis catheter-related bacteremia; ARF, acute renal failure; AVR, aortic valve replacement; TC, tunneled catheter; NTC, non-tunneled catheter; AVF, arteriovenous fistula; AVG, arteriovenous graft.