

# Feasibility of serum Cystatin C for predicting Vancomycin concentration in abdominal cancer patients with severe infectious disease

Xiaowu Zhang (✉ [zhangxiaowu1986@163.com](mailto:zhangxiaowu1986@163.com))

Tianjin medical University Cancer Institute and Hospital <https://orcid.org/0000-0002-3751-6348>

Donghao Wang

Tianjin Medical University Cancer Institute and Hospital

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## Research article

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## Abstract

**Background:** This study was designed to investigate the population pharmacokinetics and impact indicator of vancomycin in abdominal cancer patients complicated with severe infectious disease.

**Methods:** A total of 78 patients abdominal cancer patients complicated with severe infectious disease were included. Vancomycin serum trough concentrations were measured using the fluorescence polarization immunoassay (FPIA) method. The patients were divided into early and delayed groups based on whether they achieve the target concentration. And clinical factors were compared between two groups.

**Results:** The average initial therapeutic dose of vancomycin was  $15.18 \pm 3.29$  mg/kg (q12h). The research revealed that the abdominal cancer patients complicated with severe infectious disease had significantly lower initial vancomycin trough concentrations (median [IQR]: 6.90[5.28-11.20] mg/L). Multiple regression analysis revealed that Cys-C was the most important variable for vancomycin target trough achievement. The duration of mechanical ventilation in Early group was considerably shorter compared with group Delayed group ( $\chi^2=4.532$ ;  $p < 0.05$ ; Fig 1E). Propensity score weighting further confirmed that the duration of mechanical ventilation ( $\chi^2=6.607$ ;  $p < 0.05$ ; Fig 1F) and vasoactive agent ( $\chi^2=6.106$ ;  $p < 0.05$ ; Fig 1D) was considerably shorter compared with group Delayed group.

**Conclusions:** The steady-state initial vancomycin trough concentration was significantly reduced in abdominal cancer patients complicated with severe infectious disease. The baseline Cys-C level measured prior to administration of vancomycin is suggested to be the most suitable parameter to predict whether vancomycin trough concentration is up to standard dosage.

## Introduction

Vancomycin is a bactericidal glycopeptide antibiotic which inhibits bacterial growth by hindering the synthesis of cell wall in bacteria. It has strong antibiotic effect on Gram-positive bacteria. It includes *methicillin-resistant Staphylococcus aureus* (MRSA), *Enterococcus*, or *methicillin-resistant Staphylococcus epidermidis* (MRSE) [1]. The pharmacokinetic-pharmacodynamic breakpoint of vancomycin is defined as the ratio of the area from 0 to 24 hours (area under the curve (AUC) 0–24) under the concentration-time curve to minimal inhibitory concentration (MIC), and is at least 400 h in adults with *Staphylococcus aureus* pneumonia [2]. Intravenous vancomycin mainly combined with albumin and IgA, protein-bound protein is 25% to 50%, almost completely eliminated by the renal pathway. Therefore, the most important factor in determining vancomycin dosage is renal function [3]. Therapeutic drug monitoring (TDM) as an optimizing vancomycin therapy is widely recommended for avoiding secondary clinical complications because of its narrow therapeutic window, such as vancomycin toxicity due to over-dosing or resistance due to under-dosing [3].

Patients with malignant tumors represent a critical population in whom empirical antibacterial therapy deficiency may significantly increase infection-related morbidity and mortality. In addition, previous studies have demonstrated that the pharmacokinetic parameters of cancer patients often exhibit different characteristics compared to non-cancer patients [4] [5], so optimizing drug dosing regimens is critical. Researches have shown that vancomycin has a significantly increased clearance rate in adults with hematologic malignancies compared to adults without malignant tumors, but there is insufficient pharmacokinetic data. [6] [7]. Therefore, we aimed to elucidate the possible effects of this pharmacokinetic difference on conventional vancomycin treatment and conducted a retrospective researcher to study the influencing factors of the trough concentrations for vancomycin dose adjustment in abdominal cancer patients complicated with severe infectious disease.

## Methods

**Subjects:** From February 2014 to June 2017, we retrospectively reviewed 78 patients of abdominal cancer aged more than 18 years who were complicated with severe infectious disease and who were treated in the intensive care unit of Tianjin Cancer Hospital (Tianjin, China). This clinical trial was agreed by the Ethics Committee and approval from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and complied with the Declaration of Helsinki. And their data were collected from the clinical charts. All patients received vancomycin therapy for more than five estimated terminal disposition half-

lives, by which time serum vancomycin levels were supposed to have reached a steady state. Human subjects with poor kidney function (CLCr <50 mL/min), pregnant and lactating women, hemodialysis patients were excluded. Other anti-infective treatments were administered if patient condition needs.

## Pharmacokinetic analysis and Vancomycin therapeutic drug monitoring (TDM):

The vancomycin dosage was administered over a 1-hour period. The steady state vancomycin trough concentration was measured prior to subsequent treatment to adjust dose and dose intervals [8]. The target serum vancomycin trough concentrations ranged from 10–15 or 15–20 mg/L[9]. Serum vancomycin concentrations were measured by FPIA method using a Cobas 6000 c501 analyzer (Roche Diagnostics, China). Meanwhile, the laboratory staff records information about each specimen, including gender, age, body weight, serum creatinine concentration, daily dosage, dose interval, infusion time, sampling time since infusion end and measure concentration for pharmacokinetic analysis.

## Data collection:

Demographic data obtained included age, gender, admission diagnosis, acute physiology and chronic health assessment II score (Apache II score) at admission to the ICU. For the treatment program, daily doses, interval time, and the occurrence of acute kidney injury (AKI) and renal replacement therapy (RRT) were recorded. New-onset acute kidney injury was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) stage II criteria after at least 24 hours and within 7 days of vancomycin administration initiation [10]. The duration of the vasoactive agent, the duration of mechanical ventilation, the duration of the antibiotic, and the 28-day all-cause mortality were also recorded. The definition of clinical outcomes after cessation of the study drug, including clinical success and clinical failure, are shown in Table 1. Finally, inverse probability of treatment weighting (IPTW) was used to measure participants based on the estimated exposure probability (the propensity score) for a given confounding factor to balance the observed confounding factors between the early and delayed groups.

## Statistical analysis

Values for categorical variables are given as count (percentage), for continuous variables, as mean±standard deviation or as median [interquartile range]. Pearson <sup>2</sup> test was used for categorical variables, and *t* test was used for continuous variables. Univariate and multivariate analysis is used for covariates associated with target trough achievement. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using the SPSS statistical package (version 24.0, SPSS Inc., Chicago), *P* < 0.05 was considered statistically significant.

## Results

A total of 78 patients were enrolled, all of whom received recommended standard vancomycin dosage adjustment. Clinical characteristics, pharmacokinetic parameters and clinical outcomes of the included patients were summarized in Table 2 and Table 3. Our research revealed that the abdominal cancer patients complicated with severe infectious disease have a significantly lower initial vancomycin trough concentration (median [IQR]: 6.90[5.28–11.20] mg/L) than the recommended standard vancomycin trough concentrations (10–15 or 15–20 mg/L). The overall relationship between trough concentrations and potential covariates was screened by Univariate and multivariate analysis to explore potential information covariates. There was a strong correlation between vancomycin trough concentration and age, body weight, serum creatinine and serum Cystatin C level (Cys-C) (Table 4). Multivariate regression analysis revealed that the Cys-C was the most important variable for vancomycin target trough achievement (odds ratio, 5.274; 95% CI, 1.780 to 15.627; *p* = 0.003) (Table 4).

We divided patients into Early group and Delayed group based on whether the initial trough concentration **achieved** the target concentration. Although the Clinical outcomes were similar between two groups in Table 5 (e. g., the incidence of new-onset AKI or RRT, clinical success rate, 28-day all-cause mortality), the duration of **mechanical ventilation** in Early group was considerably shorter compared with Delayed group ( $\chi^2 = 4.532$ ; *p* < 0.05; Fig 1E). Compared with Delayed group, propensity score weighting

(IPTW) further confirmed that the duration of **mechanical ventilation** ( $\chi^2 = 6.607$ ;  $p < 0.05$ ; Fig 1F) and vasoactive agent ( $\chi^2 = 6.106$ ;  $p < 0.05$ ; Fig 1D) in Early group were considerably decreased.

## Discussion

Of these 78 patients, small number of patients achieved the target level. The standard vancomycin dose recommended in the package instructions approved by the Chinese authorities appears to be too low to achieve the target trough concentrations in clinical **practice**. The reason for this result may be because the standard vancomycin administration algorithm was developed based on data from relatively healthy patients. Therapeutic drug monitoring of vancomycin is widely recommended for clinical treatment[11] [9]. However, few studies have been available to evaluate vancomycin (VCM) pharmacokinetics in abdominal cancer patients complicated with severe infectious disease. The aim of this study was to address the above issues and sought to find clinically useful information to predict and estimate the appropriate dosage of vancomycin. The conclusion is that initial vancomycin trough concentrations are significantly reduced in these patients. We also found that Cys-C was associated with target trough achievement. Accordingly, the traditional standard dose of vancomycin may result in a high risk of failing to achieve the recommended standard vancomycin trough concentrations. This finding confirms the need to design more effective guidelines for individualized vancomycin anti-infective treatment in patients with abdominal cancers with severe infectious diseases.

Previous studies have shown that malignant tumors themselves may have an impact on VCM PKs [12], in addition to changes in volume of distribution due to edema, peritoneum or pleural effusion. Chang et al. reported a significant increase in VCM clearance(CL) in pediatric cancer patients using the 2-compartment Bayesian PK approach has been reported, which has also been demonstrated in adult hematological malignancies [13]. Meanwhile, there are also different **opinions**, Omote's findings suggest that there is no significant differences in estimated VCM clearance between cancer patients and non-cancer patients, indicating that the dosage can be adjusted only by conventional TDM [14]. Nevertheless, Shimada et al. proposed that direct activation of renal organic anion/cation transporters (OCT1/2, OATs) by cytokines such as TNF- $\alpha$  leads to an increase in renal clearance, which is confirmed by *in vivo* experiments [15] [16].

Severe infectious disease was **frequently** combined with the development of systemic inflammatory response syndrome (SIRS). This inflammatory response leads to vasodilatation, capillary leakage and the development of hyperdynamic cardiovascular state characterized by third-space, high cardiac output and increased blood flow to the major **tissue and organ** [17].As water soluble, vancomycin is primarily cleared by the kidneys. Increased CL is **very likely** due to increase in renal blood flow, which enhances the elimination of vancomycin by urine and leads to a decrease in plasma vancomycin concentration. And increased volume of distribution (Vd) is usually attributed to the third space induced by SIRS [18], which results in significant overhydration. However, the underlying mechanism for increasing vancomycin CL and Vd still need further studied.

Recently, some studies have proposed augmented renal clearance (ARC) to describe the enhancement of renal elimination of circulating solutes observed in critically ill patients [19]. Most studies have shown that hyperdynamic circulation characterized by increased renal blood flow and increased in glomerular filtration rate are potential mechanism [20]. Nevertheless, in these studies, no information was given concerning the number of oncological patients in these studies. Previous study found that the risk factors for ARC are age, sepsis, and SIRS [19]. Thus, the increased vancomycin CL observed in this study was very likely to be related to ARC but not oncological status. However, Curth et al. had different opinions [21]. They believed that oncological status can also cause occurrence of ARC. Considering that the study is only a case report, this opinion should be treated with caution. In practice, there is no guidance for this treatment and ARC has not been taken seriously in clinical work in China. Clinicians usually do not seriously consider increasing the dose even though dose adjustment is allowed at their discretion and the actual therapeutic drug monitoring results showed very low concentrations. And our research strongly recommends that abdominal cancer patients require higher dose regimens.

In this research, we observed a strong correlation between vancomycin trough concentrations and age, body weight, serum creatinine and especially the Cys-C. This research confirmed the relationship between Cys-C and vancomycin trough concentrations for the first time in abdominal cancer patients. Cys-C is a non-glycosylated, low molecular weight basic protein composed of 120 amino acids [22]. Human Cys-C is a housekeeping gene and is stably produced by all human nucleated cells

[22]. In earlier studies, Cys-C was considered to be independent of age, muscle mass or body mass index in healthy individuals [23]. Although [previous](#) studies have shown a significant correlation between serum Cys-C levels and malignant progression of colorectal cancer, melanoma and ovarian cancer [24], recent studies confirmed that Cys-C can be very effective in predicting renal function in cancer patients [25] [26]. These features partially explain the relationship between Cys-C and vancomycin trough concentrations.

This observational study was done on a real-time clinical practice. Since the serum Cys-C is readily available in clinical practice, these parameters may allow physicians and/or pharmacists to predict vancomycin dose requirements in a short period of time. Earlier identification of insufficient vancomycin trough concentrations could be used to optimize antimicrobial adequacy. Earlier initial goal vancomycin trough concentration achievement means shorter duration of mechanical ventilation, and shorter duration of vasoactive agent, which means earlier hemodynamic stability. With this conclusion, clinicians should be able to adjust the dose of vancomycin confidently. For specific dose adjustment algorithm, we need further research. Recently, Erin Frazee et al have confirmed that vancomycin dosing algorithm based on estimated glomerular filtration rate from creatinine and Cys-C levels significantly improved goal trough achievement compared to Cockcroft-Gault creatinine clearance among ICU patients with stable kidney function [27].

There are several potential limitations in research. Firstly, the samples collected in this study were too limited to accurately assess the pharmacokinetics of vancomycin. Secondly, this is single-center and observational study with bias in case selection. Thirdly, inappropriately timed vancomycin trough concentration determination is a general challenge for therapeutic drug monitoring and is present regardless of the vancomycin administration algorithm used.

## Conclusion

The serum initial trough concentration of vancomycin was significantly reduced in abdominal cancer patients complicated with severe infectious disease. Clinicians should pay special attention to changes in vancomycin pharmacokinetic, and higher dosage regimens are needed to ensure clinical effectiveness. The Cys-C level measured prior to vancomycin was administered is considered to be a potentially valuable parameter for predicting whether the vancomycin trough concentration is up to standard. Further, this study is promising, prospective validation of this or a similar Cystatin C-inclusive dosing model is warranted.

## Declarations

### *Acknowledgment*

We thank the health professional staff from Department of Clinical Laboratory, Tianjin Medical University Cancer Institute and Hospital.

### *Ethics approval and consent to participate*

This retrospective cohort study was agreed by the Ethics Committee and approval from the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and waived the requirement to obtain informed consent

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Competing Interest*

All authors reported no competing interests.

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### Authors' Contributions

Xiaowu Zhang and Donghao Wang were involved in the concept, interpretation of the data and writing of the manuscript. Xiaowu Zhang was involved in the statistical analyses and the writing of the manuscript.

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## Tables

### Table 1 Clinical outcome definitions after study drug cessation

Clinical response	Definition
Clinical success	1. Cure or improvement of all signs and symptoms caused by the infection 2. No additional antibiotic therapy required
Clinical failure	1. Persistent or worsening of any one of the clinical symptoms 2. New clinical signs and symptoms of infection 3. Other systemic antimicrobial therapy required

**Table 2. Vancomycin Levels Achieved and Clinical Outcomes (n=78)**

Characteristics	
Sex (male/female)	17/61
Age (years)	65.04±12.72 65[57-63]
Body weight(kg)	24.74±3.68 79[71.5-86]
Apache II score	20.05±2.92 19[18-22]
SOFA score	13.15±2.25 13[12-15]
Albumin (g/L)	27.89±6.14 28.20[24.85-32.30]
Serum creatinine (µmol/L)	68.74±22.97 56.0[46.0-84.5]
Cys-C(mg/L)	1.237±0.560 1.105[0.770-1.418]
<b>Cancer type, n(%)</b>	
Hepatocellular carcinoma	16(20.5)
Pancreatic cancer	6(7.7)
Colorectal cancer	22(28.2)
Gastric cancer	32(41.0)
Gallbladder cancer	2(2.6%)
<b>Suspected source of infection</b>	
Pulmonary	39(50)
Intra-abdominal	28(35.9)
Surgical incision	3(3.8)
Other/unknown	8(10.3)
<b>Identified pathogens, n (%)</b>	
<i>methicillin-resistant Staphylococcus aureus</i>	21(26.9)
<i>methicillin-resistant Staphylococcus epidermidis</i>	12(15.4)
<i>Enterococcus</i>	35(44.9)
Other Gram-positive coccus	10(12.8)

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; Cys-C, Cystatin C.

**Table 3. Vancomycin Levels Achieved and Clinical Outcomes (n=78)**

Characteristic	
<b>Initial dose (daily), n (%)</b>	
1000-2000 mg	4 (5.1)
2001-3000 mg	50 (64.1)
≥3000 mg	24 (30.8)
Average daily dosage (mg/kg, q12h)	15.18±3.29
	15.38[14.29-19.27]
<b>Vancomycin trough concentration, n (%)</b>	
≤10mg/L	55 (70.5)
10-15 mg/L	15 (19.3)
15-20 mg/L	8 (10.3)
Average trough concentration (mg/L)	8.26±5.01
	6.90[5.28-11.20]
Duration of vasoactive agent(day)	4[2-5]
Duration of ventilation(day)	4[3-5]
Duration of antibiotics(day)	5[5-7]
Composite outcome of new-onset AKI or RRT	7 (9.0)
Clinical success rate, n (%)	58(74.4)
28-day all-cause mortality	4 (5.1)

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

**Table 4. Univariate and Multivariate Analysis of Covariates Associated With Target Trough Achievement**

Variants	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Sex	1.470	0.423-5.105	0.544			
Age (years)	1.057	1.003-1.114	0.039*	1.152	0.997-1.331	0.054
Body weight(kg)	1.057	1.002-1.116	0.043*	0.929	0.804-1.073	0.315
Apache II score	1.016	0.863-1.198	0.846			
SOFA score	1.006	0.809-1.250	0.959			
Albumin (g/L)	1.007	0.925-1.097	0.864			
Serum creatinine (μmol/L)	1.018	1.002-1.035	0.032*	1.018	0.993-1.045	0.158
Cys-C(mg/L)	5.249	1.972-13.972	0.001*	5.274	1.780-15.627	0.003*

\**p*≤0.05

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; Cys-C, Cystatin C.

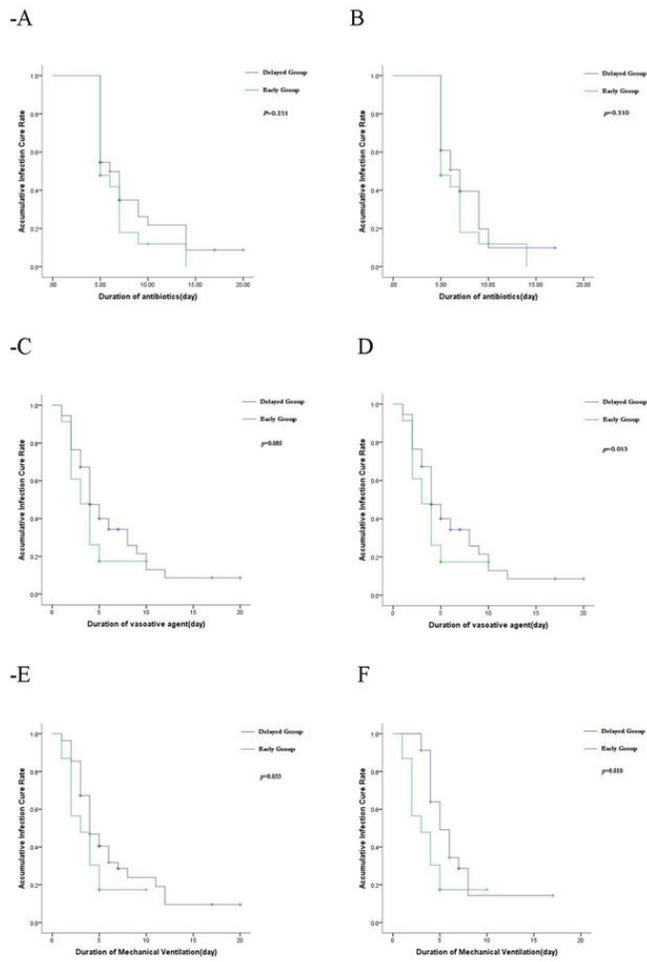
**Table 5 Patients' Baseline Data Before and After Propensity Score Weighting (n=78)**

Characteristics	Entire Cohort		$\chi^2$	<i>P</i>	Propensity Score Weighting		$\chi^2$	<i>P</i>
	Delayed group (n=55)	Early group (n=23)			Delayed group (n=23)	Early group (n=23)		
Age, years								
Mean±S.D.	62.65±11.87	68.78±10.45		0.035*	65.22±10.76	68.78±10.45		0.260
Median(range)	65(56-70)	68(61-76)			67(60-74)	68(61-76)		
Sex, n(%)				0.542				0.381
Male	42[76.4%]	19[82.6%]			21[91.3%]	19[82.6%]		
Female	13[23.6%]	4[17.4%]			2(8.7%)	4[17.4%]		
Body weight, kg								
Mean±S.D.	75.53±12.38	81.61±9.302		0.038*	78.52±11.63	81.61±9.30		0.326
Median(range)	77(69-83)	84(75-88)			80(72-87)	84(75-88)		
Apache II score on ICU								
Mean±S.D.	19.51±2.73	19.65±3.60		0.849	20.00±2.73	19.65±3.60		0.714
Median(range)	19(18-22)	20(17-22)			20(17-22)	20(17-22)		
SOFA score								
Mean±S.D.	13.15±2.41	13.17±1.87		0.974	13.70±2.55	13.17±1.87		0.307
Median(range)	13[11-15]	13[12-14]			13[12-15]	13[12-14]		
Albumin (g/L)								
Mean±S.D.	27.86±5.50	28.10±6.53		0.867	27.24±3.70	28.10±6.53		0.587
Median(range)	28.0(25.7-32.3)	29.4(23.7-33.5)			27.7(25.7-29.4)	29.4(23.7-33.5)		
Serum creatinine (μmol/L)								
Mean±S.D.	62.73±29.81	79.00±26.24		0.026*	81.09±32.46	79.00±26.24		0.812
Median(range)	50(42-77)	76(63-89)			74(53-105)	76[63-89]		
<b>Clinical Outcomes</b>								
Composite outcome of new-onset AKI or RRT	4(7.3)	3(13.0)	0.143	0.705	4(17.4)	3(13.0)	0.000	1.000
Clinical success rate, n (%)	39(70.9)	19(82.6)	1.164	0.281	16(69.6)	19(82.6)	1.075	0.300
28-day all-cause mortality	4	0	0.585	0.444	3(13.0)	1(4.3)	0.274	0.601

\**p*≤0.05

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; RRT, renal replacement therapy.

## Figures



**Figure 1**

Kaplan-Meier curves for (A) Duration of Antibiotics between the two groups before weighting; (B) Duration of Antibiotics after weighting; (C) Duration of Vasoactive Agent between the two groups before weighting; (D) Duration of Vasoactive Agent after weighting; (E) Duration of Mechanical Ventilation between the two groups before weighting; (D) Duration of Mechanical Ventilation after weighting.