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Influence of Vancomycin on Renal Function in Critically Ill Patients after Cardiac Surgery

Continuous versus *Intermittent Infusion*

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Background: **Vancomycin is frequently used in clinical practice to treat severe wound and systemic infections caused by Gram-positive bacteria after cardiac surgery. The drug is excreted almost entirely by glomerular filtration and might exhibit nephrotoxic side effects. This study compared the nephrotoxic impact of vancomycin during continuous *versus* intermittent administration.**

Methods: **The authors analyzed 149 patients admitted to the intensive care unit during a 5-yr period. All patients were treated at the intensive care unit after elective open heart surgery. Thirty patients received a dosage of 1325 ± 603 mg/d vancomycin (range 300–3400 mg/d) by intermittent infusion, and 119 patients received a mean dosage of 1935 ± 688 mg/d (range 352–3411 mg/d) by continuous infusion.**

Results: **Nephrotoxicity occurred in 11 patients (36.7%) in the intermittent treatment group and in 33 patients (27.7%) in the continuous treatment group ($P = 0.3$; 95% CI = 0.283). Continuous veno-venous hemofiltration after vancomycin administration was required for 9 patients (9 of 30; 30%) in the intermittent treatment group and for 28 (28 of 119; 23.5%) in the continuous treatment group ($P = 0.053$; 95% CI = 0.256). A change of one unit (1 mg/l) in vancomycin serum concentration (ΔVancoC) induced an average change of 0.04 mg/dl in creatinine (ΔCrea) in the intermittent treatment group *versus* 0.006 mg/dl in the continuous treatment group ($P < 0.001$).**

Conclusions: **The data show that both the intermittent and also the continuous application modality of vancomycin are associated with deterioration of renal function in critically ill patients after cardiac surgery. However, continuous infusion showed the tendency to be less nephrotoxic than the intermittent infusion of vancomycin.**

THE beneficial effect of antibiotic treatment during and after major surgery has been clearly demonstrated in a number of clinical trials.[1,2] Surgical site infections and particularly sternal and mediastinal wound infections have implications for significantly increasing both morbidity and mortality in critically ill patients after cardiac surgery (CS).[3,4]

The actual incidence of sternal and wound infections after CS in our institution is on average 11%. However, reports focus on an increasing number of sternal infections and wound infections after CS caused by resistant Gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococcus.[5,6] Intravenously administered vancomycin remains the drug of choice for treatment of infections caused by staphylococci and enterococci.[7,8] The use of vancomycin continues to increase as resistant Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* strains and other ß-lactam–resistant staphylococci and streptococci become more prevalent in critically ill patients.[9]

Vancomycin, a glycopeptide antibiotic, is excreted almost entirely by glomerular filtration and might exhibit nephrotoxic side effects.[10,11] Inaccurate vancomycin dosing can lead to toxic drug levels, associated with acute and severe worsening of kidney function. Nevertheless, there is a lack of definitive evidence linking concentrations to either outcome or toxicity.[12]

Critically ill patients after CS present on the intensive care unit (ICU) with different extents of organ dysfunction, especially with postoperative acute renal dysfunction. Renal function is likely to be influenced by hemodynamic changes during and after extracorporeal circulation, perioperative volume-shifting to the interstitial space, and catecholamine support.

Intermittent intravenous administration of antibiotics seems to be standard clinical practice, but there is an intensified interest among intensivists in examining the benefits of continuous application of antibiotics.[13] The continuous infusion of vancomycin has already been suggested as a less toxic mode of administration.[14] However, there are several clinical studies comparing the effectiveness and toxicity of continuous *versus* intermittent intravenous administration of vancomycin with conflicting results.[15,16,17,18,19,20] Little is known about the influence on renal function between the two different application modalities of vancomycin. However, it has been speculated that continuous administration causes less deterioration of renal function compared to intermittent administration.

Renal failure is associated with an increased mortality.[21] Therefore, it is of high importance to use the least nephrotoxic antibiotic therapy in ICU-patients suffering

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from severe infections after open heart surgery. If vancomycin is required for efficient antibiotic therapy, the mode of application might have significant influence on nephrotoxic side effects. To evaluate the nephrotoxic side effects of intermittent *versus* continuous infusion of vancomycin, we performed a retrospective study analyzing data of 149 ICU patients receiving vancomycin during their ICU stay.

Materials and Methods

This explorative study retrospectively analyzed anonymous data of 149 critically ill patients admitted during a 5-yr period (from January 2001 to December 2005). All patients underwent elective CS. They received vancomycin intravenously after microbiologic confirmation of infection or strong indirect evidence of infection with Gram-positive strains. Vancomycin was administered intermittently in 30 patients (IIV-group) and continuously in 119 patients (CIV-group). We analyzed the renal parameters of patients of the two groups before and during antibiotic treatment with vancomycin to investigate the different impact of vancomycin on renal function after continuous *versus* intermittent intravenous administration.

The study was approved by the local ethics committee (Ethics-Committee of the Medical University of Vienna and the Vienna General Hospital–AKH, Vienna, Austria). Study patients were treated in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission. Our institutional ethics committee does not require written informed consent from study patients for retrospectively performed studies.

Inclusion criteria are specified to minimize the risk of confounders. Initially, 375 records are sent to analysis. Only 149 patients achieved enrolment due to inclusion and exclusion criteria. Inclusion and exclusion criteria are given in table 1. Parameters characterizing the study population are listed in table 2. Predisposing factors for renal failure for both treatment groups are given in table 3.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Female/male
Age > 19 years
ICU-admission after elective CS
Vancomycin therapy for suspected or documented infection
Preoperative creatinine concentration (Crea) ≤ 1.5 mg/dl
No preoperative period of acute or chronic renal failure
No preoperative renal replacement therapy (CVVHF/CVVHD)
Exclusion criteria
Preoperative
Clinical signs of infection
SIRS
Increased body temperature > 37.5°C
Crea > 1.5 mg/dl
Necessity of renal replacement therapy (CVVHF/CVVHD)
Vancomycin therapy 72 h before elective CS
Verified β-lactam allergy
Intraoperative
Prolonged extracorporeal circulation (ECC ≥ 500 min)
Bleeding (> 4 red packed cells)
Hemofiltration on CPB
Perioperative and/or postoperative
Acute kidney injury in accordance with the AKIN classification
Hemodynamic instability
Increased vasopressor support
Norepinephrine dosage > 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Epinephrine dosage > 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Increased inotropic support
Dobutamin dosage > 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Hypotension (decrease in mean arterial blood pressure > 35% of baseline)
Urine production < 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$
Necessity of additional administration of proven nephrotoxic drugs (immunsuppressive drugs)
Two or more organ failures (MOD Score ≥ 9)
SAPS II score > 70 on ICU admission

AKIN = Acute Kidney Injury Network; CPB = cardiopulmonary bypass; CS = cardiac surgery; CVVHF/CVVHD = continuous veno-venous hemofiltration or hemodialysis; ECC = extracorporeal circulation time in min; ICU = intensive care unit; MOD = Multiple Organ Dysfunction score by Marschall; SAPS II Score = Simplified Acute Physiology score; SIRS = systemic inflammatory response syndrome.

Treatment and Measurements

Patients were treated with vancomycin intravenously after microbiologic confirmation of infection with Gram-positive pathogens susceptible to glycopeptides (methicillin-resistant *Staphylococcus aureus* or coagulase-negative *Staphylococcus*) or clinically suspected infection. All patients enrolled in this study received a purified commercial form of vancomycin hydrochloride (Vancomycin®; Eli Lilly, Vienna, Austria). Vancomycin was administered intermittently or continuously depending on the preference of the supervising ICU physican. Continuous infusion of vancomycin was performed with 0.025 $mg \cdot kg^{-1} \cdot min^{-1}$ *via* a central venous catheter (Arrow International, Inc, Reading, PA). In both groups, vancomycin was initiated with a 20 mg/kg bolus administered intravenously over 60 min and than adjusted in accordance to the serum level and serum creatinine concentration. A serum through concentration of 15 mg/l was aspired for intermittent administration and a plateau concentration of 20 to 25 mg/l for continuous infusion.

After this initial administration, patients in the IIV group received an adjusted treatment, based on trough vancomycin concentration in serum, by increasing or decreasing the daily dose.

Dosing adjustment in patients in the CIV group was performed by either increasing or decreasing the amount of vancomycin administered per kg per min.

The serum concentration of vancomycin was selected in the range of 20–25 mg/l according to available data on the MIC_{90} value of vancomycin against *Staphylococcus* species, its protein binding, and its diffusion into tissues.[22]

A target trough vancomycin serum concentration of 15 mg/l for intermittent administration and a plateau van-

Table 2. Patient Characteristics, Surgical Treatment Data, Site of Infection, and Pathogens

	IIV Group, n = 30	CIV Group, n = 119	*P* Value
Patients characteristics			
Age, yr	59 ± 14 (37–83)	59 ± 14 (19–86)	0.85
Gender, female/male	9 (30)/21 (70)	47 (39)/72 (61)	0.76
Height, cm	173 ± 9 (151–185)	171 ± 8 (151–194)	0.28
Weight, kg	75 ± 16 (47–110)	75 ± 16 (43–126)	0.84
SAPS II	34 ± 14 (11–64)	37 ± 13 (13–70)	0.84
Type of surgical procedure			
Valve replacement, AKE, MKE	8 (25)	19 (16)	0.21
CABG	11 (34)	42 (35.3)	0.99
CABG+KE	7 (23)	31 (26.1)	0.67
MKE+AKE	1 (3)	10 (8.4)	0.33
Aortic aneurysm replacement	1 (3)	5 (4.2)	0.81
PTEA	2 (6)	5 (4.2)	0.60
HTX	1 (3)	7 (5.9)	0.56
Surgical treatment data			
ACC, min	156 ± 71 (90–210)	131 ± 49 (76–199)	0.67
ECC, min	200 ± 98 (102–469)	214 ± 113 (89–395)	0.53
Infection site/pathogens (multiple answers possible)			
Wound infection	9 (29)	36 (30)	0.90
Sternal infection	5 (16)	19 (16)	0.99
Mediastinitis	1 (3)	8 (7)	0.47
Catheter-related infection	5 (16)	18 (15)	0.89
Hospital-acquired pneumonia	6 (19)	21 (18)	0.82
Infection with bacteremia	5 (16)	17 (14)	0.80
Staphylococcus aureus infection	8 (26)	26 (22)	0.64
CNS infection	3 (10)	13 (11)	0.85

This table describes the demographic and surgical treatment data of patients in the two treatment groups. Additionally, it shows the infections site and most relevant pathogens. Metrically scaled variables are described with mean ± standard deviation (range), nominally scaled variables are described with absolute frequency (percentage).

ACC = aortic cross clamp time; AKE = aortic valve replacement; CABG = coronary artery bypass grafting; CIV group = continuous treatment group (patients in this group received a continuous infusion of vancomycin); CNS infection = coagulase-negative *Staphylococcus*; ECC = extracorporeal circulation time; HTX = heart transplantation; IIV group = intermittent treatment group (patients in this group received an intermittent infusion of vancomycin); MKE = mitral valve replacement; PTEA = pulmonary thromendarterectomie; SAPS II = Simplified Acute Physiology Score II.

comycin serum concentration of 20–25 mg/l for continuous infusion were determined by experts of the Department of Infections Disease and were used as standard in our ICU. Vancomycin serum concentration (VancoC) was determined on a daily basis in all patients.

At our institution, it is a clinical standard to collect blood for analysis in the central laboratory at predefined time intervals. Collection of blood is routinely performed at 7 AM and at 7 PM daily. Every 4 h, we also performed arterial blood gas analysis with a device located on our ICU.

Determination of serum blood levels of vancomycin depends on the frequency of vancomycin administration. The determination of vancomycin serum levels dependent on the frequency of administration is the clinical standard and therefore routinely performed at our institution. Serum concentrations of vancomycin were routinely determined together with this standard blood analysis when vancomycin was administered continuously. When vancomycin was administered intermittently, vancomycin serum concentration was determined immediately before the administration of the next vancomycin bolus (trough level).

To evaluate the nephrotoxicity of the two different application modalities of vancomycin, we determined serum creatinine (Crea) and calculated creatinine clearance (CreaCl) before CS, before administration of vancomycin, and throughout the whole application period of vancomycin. Crea was analyzed on AU5400 Olympus Analyser (Workstation Consolidation XXL Laboratories, Olympus Austria Ges.m.b.H, Vienna, Austria) by using the Jaffé-method.[23] CreaCl was calculated with the following formula: urine-creatinine × urine-volume/serum-creatinine × time in minutes (ml/min).

To evaluate the antimicrobial efficacy of vancomycin, we measured the C-reactive protein (CRP) in mg/dl and in addition leukocytes count (number/μl) on a daily basis and focused on their change during therapy.

Fluid balance was calculated for each patient of the two groups on a daily basis. Calculation of fluid balance included the intravenous and oral nutrition, fluid administration, the amount of drug infusions, the urine production, and the loss of drainages. Blood and coagulation products were excluded from total fluid balance. In patients treated with continuous veno-venous hemofiltration or hemodialysis (CVVHF/CVVHDF), withdrawal of fluid by means of hemofiltration was included in total fluid balance.

Nephrotoxicity was defined using the classification of the Acute Kidney Injury Network (AKIN).[24] An abrupt

Table 3. Predisposing Factors for Renal Failure

	IIV Group, n = 30	CIV Group, n = 119	*P* Value
Baseline serum creatinine, mg/dl	0.9 ± 0.7	0.9 ± 0.5	0.86
Diabetes mellitus, n (%)	3 (10)	13 (10.9)	0.89
LVEF < 30%, n (%)	2 (6.7)	9 (7.6)	0.87
PAPsyst > 60 mm Hg, n (%)	3 (10)	12 (10.1)	0.99
COPD, n (%)	5 (16.7)	20 (16.8)	0.99
Age > 75 yrs, n (%)	6 (20)	27 (22.7)	0.76
Extracardiac arteriopathy, n (%)	4 (13.3)	14 (11.8)	0.82
Acute liver failure, n (%)	—	2 (1.7)	0.48
Infection/sepsis, n (%)	30 (100)	119 (100)	1
DIC, n (%)	1 (3.3)	4 (3.4)	0.99
Diuretics, n (%)	3 (10)	15 (12.6)	0.70
Concomitant antibiotic therapy, n (%)			
Carbapenemes or cephalosporins	8 (26.6)	31 (26.1)	0.95
Aminoglycosides	3 (10)	14 (11.8)	0.79

Baseline serum creatinine is given in mg/dl ± SD. The other values are given with absolute frequency (percentage)/n (%).

CIV group = continuous treatment group (patients in this group received a continuous infusion of vancomycin); COPD = chronic obstructive pulmonary disease; DIC = disseminated intravascular coagulation; IIV group = intermittent treatment group (patients in this group received an intermittent infusion of vancomycin); LVEF = left ventricular ejection fraction; PAPsyst = systolic pulmonary artery pressure.

reduction in kidney function within 48 h, currently defined as an absolute increase in Crea of at least 0.3 mg/dl (at least 26.4 μM), a percentage increase in Crea of at least 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml · kg^{-1} · h^{-1} for more than 6 h).

Postoperative oliguria or oliguria during vancomycin therapy was treated with diuretics (furosemide). To avoid the possible influence of the nephrotoxic potential of diuretics, the therapy with diuretics was limited to 24 h. In case of prolonged postoperative oliguria (more than 24 h) or persistent oliguria during diuretic therapy, patients received CVVHF/CVVHDF.

Sepsis, severe sepsis, and septic shock were defined in accordance with the Consensus Conference of the American College of Chest Physicians/Society of Critical Care Medicine held in 1992.

Treatment duration with vancomycin was 7 days or longer, depending on the site and severity of infection. Administration of nonglycopeptide antibiotics in combination with vancomycin was permitted after microbiologic detection of strains beyond the spectrum of vancomycin activity or pathogens being unsusceptible to glycopeptides.

Laboratory Analysis

Vancomycin was prescribed for infections defined in accordance with the criteria of the Centers for Disease Control and Prevention,[25] except for hospital-acquired pneumonia. We used the definition given by the 1992 International Consensus Conference for hospital-acquired pneumonia, which requires a quantitative culture of protected strains obtained from lower respiratory tract. Catheter-related infection was defined as a quantitative culture of the catheter tip yielding the same pathogen obtained from a peripheral-blood culture.

VancoC was measured by cloned enzyme donor Immuno-Assay (CEDIA-Immunotest) (fluorescence polarization immunoassay, 823 HITACHI 917 Analyser; Boehringer Ges.m.b.H, Mannheim, Deutschland). The routine practice, considered as standard, was to measure trough and peak concentrations depending on the method of administration.

Statistical Analysis and Measurements

Statistical calculations and data analysis were performed by using commercially available computer programs, SAS (SAS Institute Inc., Cary, NC), SPSS (SPSS Inc., Chicago, IL) and σ-Stat (Statistica, StatSoft Inc., Tulsa, OK).

Noncompartmental pharmacokinetic analysis was performed by using a commercially available computer program (Kinetica; Innaphase, PA).

The area under the serum concentration time curve (AUC_{24h}) of vancomycin was calculated for 24-h intervals by using the log-trapezoidal rule, assuming a monoexponential decrease in the drug level in serum when it was given intermittently and a constant drug level in serum for the 24 h when vancomycin was given continuously.

Metrically scaled variables (patients characteristics, Simplified Acute Physiology Score II , duration of vancomycin treatment, duration of CVVHF/CVVHDF, the amount of days on CVVHF/CVVHDF, duration of ICU stay, ICU mortality and in-hospital mortality) are described with mean ± SD and range. Nominally scaled variables (surgical treatment data, type of surgical procedure, infection site, and pathogens) are described with absolute frequencies (percentages).

A summary measures approach was used to characterize dynamic variables. These variables, such as trough and plateau VancoC, vancomycin dosage, Crea, CreaCl, total fluid balance, urine production, withdrawal of fluid during CVVHF/CVVHDF, CRP levels, and catecholamine support were measured on a daily basis during vancomycin treatment. This statistical analysis was based on the calculation of a mean value for each dynamic variable per patient.[26] The obtained single mean value for each dynamic variable is described as usual with mean ± SD and range. Due to clinical relevance, Crea and CreaCl were described as maximum values or minimum values instead of mean values.

Whenever data were normally distributed, an unpaired Student *t* test was used for comparisons of patients in both groups. We used Wilcoxon Mann–Whitney U test for analysis of not normally distributed data. Differences between patients in the IIV and CIV groups were assessed with the Pearson chi-square test. A repeated measures regression approach (Proc Mixed of SAS) was used

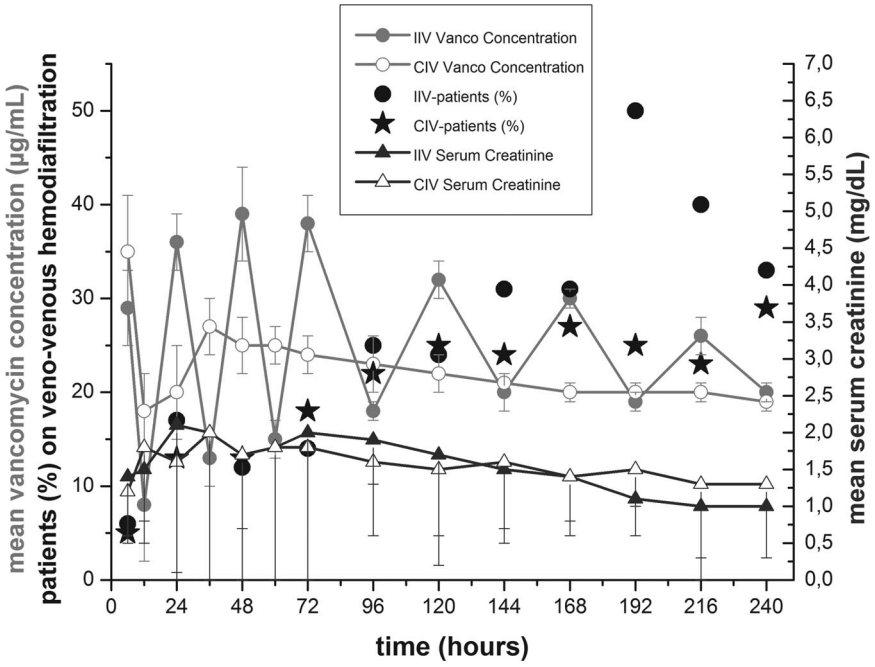

Fig. 1. Changes of vancomycin serum concentration in µg/ml over the time (h) in the intermittent treatment group (IIV group; *filled circles*) and in the continuous treatment group (CIV group; *blank circles*). It also shows the changes of serum creatinine (mg/ml) over the time (h) during vancomycin administration in both treatment groups (IIV group in *filled triangles*, CIV group in *blank triangles*). The values are given as means ± SD (range). Time 0 is the time of intensive care unit admission. In addition, this figure shows the percentage of patients on veno-venous hemofiltration/hemodiafiltration over time (h) during vancomycin therapy in the two groups (IIV group in *circles*, CIV group in *asterisks*). CIV group = continuous treatment group (patients in this group received a continuous infusion of vancomycin); IIV group = intermittent treatment group (patients in this group received an intermittent infusion of vancomycin); Vanco = vancomycin.

to assess the effect of a change of one unit (1 mg/l) of vancomycin serum concentration (ΔVancoC) on a change (mg/dl) of Crea (ΔCrea).

$P < 0.05$ was considered statistically significant. All P values are results of two-sided tests. No adjustment for multiple testing was performed because the goals of this retrospective study were rather exploratory than confirmatory.

Results

We retrospectively analyzed the data of 149 ICU patients requiring treatment with vancomycin after elective CS. Initially, 375 patients were sent to analysis; 226 patients failed enrollment because of predefined inclusion and exclusion criteria.

Analysis period was extended from January 2001 to December 2005 (60 months). We evaluated the influence of vancomycin on renal function by comparing the different impacts of intermittent (IIV group, n = 30 patients) *versus* continuous (CIVgroup, n = 119 patients) administration.

All patients had suspected or established hospital-acquired staphylococcal infections susceptible to vancomycin. Demographic characteristics, surgical treatment data, severity of underlying disease, and infection sites were similar in the two treatment groups (table 2).

The incidence of severe sepsis was 3.3% (n = 1) in the IIV group and 5.0% (n = 6) in the CIV group ($P = 0.70$). Septic shock occurred in 1 patient (0.9%) in the CIV group.

Trough and plateau VancoC were 17.0 ± 4.7 mg/l (mean, range 9–22 mg/l) in the IIV group and 25.0 ± 4.0 mg/l (mean, 7–30 mg/l) in the CIV group ($P = 0.42$), respectively. Changes in vancomycin concentration in serum over time in the two treatment groups are given in figure 1. The daily doses of infused vancomycin were comparable between treatment groups ($P = 0.2$). Patients in the IIV group received an average dosage of 1325 ± 603 mg/d by intermittent infusion (mean ± SD, range 300–3400 mg/d) and a continuous infusion of 1935 ± 688 mg/d (mean ± SD, range 352–3411 mg/d) in the CIV group.

Twenty-five patients (83.3%) in the IIV group received a single daily dose of vancomycin to reach a vancomycin serum concentration of at least 15 mg/l. Five patients (16.7%) received a second dose of vancomycin within 48 h to reach the target vancomycin serum concentration of 15 mg/l. It required 50 ± 21 h to establish a vancomycin trough serum concentration above 15 mg/l in the IIV-group but only 16 ± 8 h to establish a plateau concentration above 20 mg/l in the CIV group ($P < 0.001$).

The AUC_{24h} was 612 ± 213 $\mu g \cdot ml^{-1} \cdot h^{-1}$ in the IIV group and 529 ± 98 $\mu g \cdot ml^{-1} \cdot h^{-1}$ in the CIV group.

Crea values measured at the end of surgery ($P = 0.41$) and immediately before starting vancomycin treatment ($P = 0.16$) were comparable between both groups (table 4). CreaCl calculated 24 h and 48 h after ICU admission ($P = 0.56$) and before starting vancomycin treatment ($P = 0.79$) showed no significant difference between the two groups. In both groups, Crea increased and calculated CreaCl decreased nonsignificantly from the baseline to the end of vancomycin treatment ($P = 0.11$ and $P = 0.23$, respectively). During vancomycin therapy, maximum Crea was 1.7 ± 0.7 mg/dl (mean, range 0.7–3.6 mg/dl) in the IIV group and 1.5 ± 0.7 mg/dl (mean, range 0.6–5.0 mg/dl) in the CIV group ($P = 0.21$). The mean of minimum CreaCl during van-

Table 4. Major Laboratory Findings, Fluid Balance, and Catecholamine Dosage

	IIV Group, mean ± SD (range)	CIV Group, mean ± SD (range)	*P* Value
Crea			
Before CS, mg/dl	0.9 ± 0.7 (0.4–1.5)	0.9 ± 0.5 (0.5–1.5)	0.86
Before Vanco, mg/dl	1.4 ± 0.6 (0.5–3.4)	1.2 ± 0.6 (0.6–4.3)	0.16
Maximum during Vanco, mg/dl	1.7 ± 0.7 (0.7–4.6)	1.5 ± 0.7 (0.6–5.0	0.21
CreaCl			
Before CS, ml/min	103 ± 30 (85–156)	119 ± 21 (81–172)	0.56
Before Vanco, ml/min	53 ± 31 (1–102)	54 ± 40 (1–254)	0.79
Minimum during Vanco, ml/min	22 ± 23 (1–89)	36 ± 29 (1–146)	0.015*
CRP			
Before CS, mg/l	5.7 ± 7.4 (0.5–26.8)	3.7 ± 5.1 (0.5–25.1)	0.44
At start of Vanco, mg/l	15.3 ± 8.6 (1.5–37.4)	22.64 ± 10.1 (7.3–55)	0.001*
On tenth day of Vanco, mg/l	9.5 ± 8.4 (0.4–28.3)	7.6 ± 5.9 (0.7–32.1)	0.62
Fluid balance during Vanco, ml/d	1559 ± 3100 (−1607–12205)	788 ± 1465 (−1478–7001)	0.70
Urine production during Vanco, ml/d	1982 ± 1121 (25–4442)	2006 ± 1036 (90–4610)	0.87
Withdrawal on CVVHF/CVVHDF, ml/d	760 ± 380 (297–1240)	820 ± 275 (540–1390)	0.22
Dose			
Epinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.18 ± 0.1 (0.03–0.25), n = 7	0.15 ± 0.1 (0.02–0.37), n = 20	0.50
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.16 ± 0.2 (0.02–0.32), n = 7	0.13 ± 0.2 (0.01–0.39), n = 48	0.84
Dobutamin, $\mu g \cdot kg^{-1} \cdot min^{-1}$	3.4 ± 1.0 (1.0–4.4), n = 10	3.5 ± 0.9 (1.0–5.0), n = 61	0.73

This table shows the serum creatinine in mg/dL and calculated clearence in mL/min measured before CS and vancomycin therapy in the IIV-group compared to the CIV-group. The table describes the CRP levels after operation, before vancomycin therapy and additionally on the tenth day of vancomycin therapy. Additionally, this table implies the maximum serum ceatinine and minimum creatinine clearance during vancomycin treatment.

CIV group = continuous treatment group (patients in this group received a continuous infusion of vancomycin); Crea = serum creatinine; CreaCl = creatinine clearance; CRP = C-reactive protein; CS = cardiac surgery; CVVHF/CVVHDF = continuous veno-venous hemofiltration/hemodiafiltration; IIV group = intermittent treatment group (patients in this group received an intermittent infusion of vancomycin); Vanco = vancomycin therapy.

comycin therapy was 22 ± 23 ml/min (mean, range 1–89 ml/min) in the IIV group and 36 ± 29 ml/min (mean, range 1–146 ml/min) ($P = 0.015$) (table 4).

A change of one unit (1 mg/l) in vancomycin serum concentration (ΔVancoC) induced an average change of 0.04 mg/dl in Crea (ΔCrea) in the IIV group *versus* 0.006 mg/dl in the CIV group ($P < 0.001$).

Nephrotoxicicty occurred in 11 patients (36.7%) in the IIV group and in 33 patients (27.7%) in the CIV group ($P = 0.3$) during vancomycin treatment (95% confidence interval [CI] = 0.283]. CVVHF/CVVHDF after vancomycin administration was required for 9 patients (30%) in the IIV group and for 28 (23.5%) in the CIV group ($P = 0.053$; 95% CI = 0.256).

We scored patients of both treatment groups according to the AKIN categorization and according to the Risk, Injury, Failure, Loss, and End-stage (RIFLE) categorization (table 5). A total of 93.3% of patients in the IIV group (n = 28) and 92.4% of patients in the CIV group (n = 110) were classified to AKIN categorization by Crea criteria and urine output criteria ($P = 0.87$). The remaining two patients in the IIV group (6.7%) and the remaining nine patients in the CIV group (7.5%) were only classified by their Crea levels.

In the cohort of patients requiring CVVHF/CVVHDF during vancomycin therapy, the number of patients (%) per CVVHF/CVVHDF-day did not show significant difference between the IIV group and the CIV group ($P = 0.25$) (fig. 1).

Total fluid balance values, including urine production calculated over 24 h, were nonsignificantly different during vancomycin therapy in both treatment groups and are given in table 4. Withdrawal of fluid during CVVHF/CVVHDF was entered into total fluid balance and was 760 ± 380 ml/d (mean ± SD, range 297–1240 ml/d) in the IIV group and 820 ± 275 ml/d (mean ± SD, range 540–1390 ml/d) in the CIV group during vancomycin therapy.

We found an increase of Crea from the beginning of vancomycin therapy to the tenth day of vancomycin therapy (iΔCrea 10th) of 0.7 ± 0.3 mg/dl in patients who failed sufficient vancomycin therapy (n = 36 of 149; 24.2%) and an iΔCrea 10th of 0.2 ± 0.15 mg/dl in

Table 5. Classification of Nephrotoxicity Using the RIFLE Categorization and the AKIN Categorization

	IIV Group, n = 30	CIV Group, n = 119	*P* Value
RIFLE groups			
No classification (N)	19 (63.3)	72 (60.5)	0.78
Risk (R)	8 (26.7)	36 (30.3)	0.70
Injury (I)	2 (6.7)	5 (4.2)	0.57
Failure (F)	(0)	3 (2.5)	0.39
AKIN groups			
No stage	17 (56.7)	60 (50.4)	0.54
Stage 1	7 (23.3)	35 (29.4)	0.51
Stage 2	4 (13.3)	14 (11.8)	0.82
Stage 3	2 (6.7)	10 (8.4)	0.76

Classification is described with absolute frequency (percentage).

AKIN = acute kidney injury network; CIV group = continuous treatment group (patients in this group received a continuous infusion of vancomycin); IIV group = intermittent treatment group (patients in this group received an intermittent infusion of vancomycin); RIFLE = The Risk, Injury, Failure, Loss and End stage categorization.

patients who achieved treatment success (n = 113 of 149; 75.8%) ($P = 0.023$).

Mean duration of vancomycin treatment was 8.5 ± 7 days (range 2–18 days) in the IIV group and 9 ± 6 days (range 3–19 days) in the CIV group ($P = 0.4$). The time elapsed between cardiac intervention and beginning of vancomycin therapy was comparable between treatment groups (mean 5.1 ± 2.4 days in the IIV group and 4.9 ± 1.8 days in CIV group).

The time period from starting vancomycin therapy to the beginning of CVVHF/CVVHDF did not show significant difference between the groups with mean 2.8 ± 2.4 days (range 1–6 days) in the IIV-group and mean 3.0 ± 3.9 days (range 1–18 days) in the CIV group ($P = 0.72$). The amount of days on CVVHF/CVVHDF during vancomycin therapy were mean 10 ± 5 days (range 2–23 days) in the IIV group and mean 7 ± 3 days (range 1–18 days) in the CIV group ($P = 0.1$).

The administration of diuretics (furosemide) during vancomycin therapy was necessary in three patients (10.0%) in the IIV group and in 15 patients (12.6%) in the CIV group ($P = 0.70$). The administration of furosemide was limited to 24 h. In case of persistent oliguria over 24 h, patients received CVVHF/CVVHDF. All patients requiring diuretic therapy initially received a single intravenous bolus of 20 mg of furosemide and a continuous infusion of furosemide. The continuous dose of furosemide in the three patients in the IIV group was 4 ± 2 mg/h; the 15 patients in the CIV group received 5 ± 0.3 mg/h ($P = 0.56$).

None of the patients in both groups received contrast agents during the time period of vancomycin therapy.

Concomitant antibiotic therapy with carbapenemes or cephalosporins was necessary in eight patients from the IIV group (26.7%) and in 31 patients from the CIV group (26.1%) ($P = 0.95$). A total of three patients in the IIV group (10%) and 14 patients in the CIV group (11.8%) required concomitant antibiotic therapy with aminoglycosides ($P = 0.79$).

A total of 22 patients (73.3%) in the IIV group and 85 patients (71.4%) in the CIV group required continuous catecholamine support for hemodynamic stabilization. Vasoactive support was defined as the need of epinephrine, norephinephrine, and dobutamine infusion alone and/or in combination at a total dosage of more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Mean concentrations of catecholamines are given in table 4 and did not show significant difference.

We noticed a vancomycin-induced red man syndrome in two patients (6.7%) in the IIV group and in none of the patients in the CIV group.

Mean stay in ICU was 16 ± 14 days (range 2–49 days) in the IIV group *versus* 15 ± 13 days (range 1–78 days) in the CIV group.

ICU mortality in our critically ill patients was 20.8% (31 of 149 patients). A total of six patients (20.0%) in the IIV group and 25 patients (21.0%) in the CIV group died during ICU-stay. In-hospital mortality was 30.9% (46 of 149 patients) and was comparable between groups (30.3% in the CIV group and 33.3% in the IIV group, respectively). The timing of death in the course of vancomycin administration (mean 9.8 ± 2.4 days [range 2–18 days] in the IIV group and mean 9.0 ± 3.3 days [range 1–20 days]) did not show significant difference between both groups ($P = 0.8$).

Discussion

This explorative study investigated the impact of continuous *versus* intermittent intravenous administration of vancomycin on renal function. We analyzed anonymous data of 149 critically ill patients after open heart surgery suffering from severe postoperative infections.

Vancomycin is well known to be a powerful glycopeptide antibiotic and is increasingly used owing to the emergence of highly resistant organisms such as MRSA. Initially, the intermittent intravenous modality of vancomycin administration was the standard clinical practice for administration of vancomycin. However, when the potential benefit of continuous intravenous vancomycin application was published,[16] the continuous infusion of vancomycin was rapidly considered to be a promising alternative administration modality. In our institution, change of practice was initiated in accordance with literature. We switched vancomycin administration from intermittent to continuous intravenous mode early in 2002. Vancomycin was administered intermittently or continuously depending on the preference of the supervising ICU-physican in the intermediate time period. This bias in patient randomization is an important limitation of the study. This change in vancomycin application modality accounts for the asymmetrical distribution of our two study groups. Incomplete documentation before 2000 eliminates any possibility of retrieving data of a comparable quality of additional patients with intermittent intravenous vancomycin application. Actually, asymmetrical distribution of patients between the two treatment groups is certainly a limitation of our study.

Severely ill patients after CS present on the ICU with different extent of organ dysfunction, and most of them require vasoactive drugs. To ensure that the observed renal injury was caused by vancomycin, patients were selected by rigorous inclusion and exclusion criteria (table 1). Initially, data of 375 patients were screened. However, 226 patients failed study enrollment to obtain comparable conditions.

In CS, therapeutic failures with minimal concentrations of vancomycin below 10 mg/l[27] are reported; also, concentrations above 10 mg/l have been shown to be insufficient in critically ill patients with severe infections.[28,29] Therefore, in our institution, intermittent vancomycin infusion was adjusted to maintain a trough

concentration of 15–20 mg/l. Continuous infusion of vancomycin was adjusted to obtain a plateau of 20–25 mg/l. Considering the pharmacokinetic properties of vancomycin and the trend toward an increase in concentrations[4] deemed necessary to inhibit *Staphylococcus* species, a target plateau of 20–25 mg/l is probably a safe and reasonable limit. Finally, Aeschlimann *et al.*[30] recently reported that a target plateau of 20–25 mg/l reached with continuous infusion is an alternative against *Staphylococcus* species with reduced susceptibility to vancomycin. It has been demonstrated that continuous administration of antibiotics offers better activity against resistant pathogens and reduces the development of antibiotic resistance.[17,30]

It is well known that the effectiveness of time-dependent antibiotics, such as vancomycin, increases with the duration of time that antibiotic serum concentrations are above the MIC_{90} of susceptible pathogens. In agreement with previous studies,[15,16] we found that the target concentrations were reached faster in the CIV group (fig. 1). The faster acquisition of target concentrations over the MIC_{90} value of susceptible pathogens is clinically relevant in critically ill patients. Faster achievement of target vancomycin concentrations might be associated with the ease of treatment adjustment with continuous infusion, as suggested by the lower variability between patients in the AUC_{24h} and in the daily dose that was seen with this infusion modality. As shown in our study, CRP levels before vancomycin therapy were significantly higher in the CIV group compared with the IIV group ($P < 0.001$) (table 4). On the tenth day of vancomycin therapy, both treatment arms showed comparable CRP levels ($P = 0.62$) (table 4). The far more pronounced decrease of initially higher infection parameters in the CIV group during vancomycin treatment might indicate the microbiologic superiority and better clinical efficacy of continuous infusion.

A meta-analysis[13] showed a potential benefit of continuous intravenous infusion of antibiotics in better pharmacokinetic and clinical results. However, in accordance with our findings, this meta-analysis did not confirm differences in nephrotoxicity between continuous *versus* intermittent antibiotic administration.

Nephrotoxicity was defined using the classification of AKIN. Although, RIFLE categorization[31] is very well established for risk, injury, and failure evaluation of renal function, Lassnigg *et al.*[32] showed that the most recent AKIN definitions improve detection of acute kidney injury in our postoperative cardiac surgical patients. In addition, we preferred using the AKIN categorization because AKIN improves sensitivity of acute kidney injury diagnosis in postoperative patients. Therefore, we evaluated both categorization methods for our patient population (table 5). A comparison of the methods showed interesting results. According to the RIFLE-categorization, 91 of 149 patients (61.1%) were not classified; according to AKIN categorization, 77 of 149 patients (51.7%) were not classified. In addition, severe changes in renal function were more likely to be detected with AKIN categorization in our postoperative patient population.

The AKIN classification includes an absolute and also a percentage change in Crea to accommodate variations related to age, gender, and body mass index and to reduce the need for a baseline Crea. However, it does require at least two Crea values within 48 h. The urine output criteria are included in the AKIN classification. They are based on the predictive importance of the urine output, with the awareness that urine output depends on various facts, such as hemodynamic changes with the need of catecholamine support or the necessity of administration of diuretics.

Renal replacement therapy remains the management for patients with severe acute kidney injury. Although several authors describe the technology for providing renal replacement therapy, the fundamental issues regarding its management, including timing of initiation, remain unresolved.[33] In our department, hemofiltration is initiated early in accordance with the findings of Demirkilic *et al.*[34]

Urinary interleukin (IL)-18 is an early predictor of acute kidney injury.[35] However, during our study period between 2001 and 2005, only few reports had been published examining this biomarker.[36,37] At this time IL-18 was under evaluation. Therefore, the analytical determination of urinary IL-18 levels was not established in clinical practice during our study period. Since 2007, when Bagshaw *et al.* [35] described urinary IL-18 to be an early predictor for acute kidney injury, we routinely determined this biomarker in our septic patients.

Only limited data are available concerning the influence of the intermittent and continuous intravenous administration of the antibiotic on renal function. It has been speculated by several experts[16] that continuous administration causes less deterioration of renal function compared to intermittent administration. Data in our study showed a moderate increase in Crea and a decrease in CreaCl during vancomycin therapy in both treatment groups. An interesting finding in our study was that a 1 mg/l change in VancoC induces a significantly higher increase of Crea (mg/dl) with intermittent than with continuous administration modality ($P < 0.001$). The more severe impact on renal function might be due to potentially high vancomycin peak concentrations during intermittent infusion. In contrast, plateau concentrations of vancomycin seem to inflict much less renal damage.

Although the daily vancomycin dose was slightly higher in the CIV group, the CreaCl showed less decrease during vancomycin treatment than in the IIV group. In addition, a smaller percentage of patients required CVVHF/CVVHDF in the CIV-group (23.5% in CIV

group *vs.* 30% in IIV group). A noticeable finding in our study, although not statistically significant, was that more patients in the IIV group required CVVHF/CVVHDF due to renal damage after 5 days of vancomycin therapy. These findings indirectly suggest a lower nephrotoxic potential of continuous vancomycin administration, but they marginally missed significant difference. One feasible explanation is in fact the limited number of patients in the IIV group. Another explanation is the previously described microbiologic superiority and better clinical efficacy of continuous administration of time-dependent antibiotic agents. Clinical failure of antimicrobial therapy due to continuous bacterial growth is one of the most predictive factors for progressive movement from sepsis to multiple organ failure and renal failure. Therefore, it is not surprising that CRP levels in serum on the tenth day of vancomycin therapy (table 4) were higher in patients who failed sufficient treatment of infection compared with those who achieved treatment success. However, in association with the higher CRP levels on the tenth day of vancomycin therapy, we found an increase of serum creatinine concentration (iΔCrea 10th) that was significantly higher in patients who failed sufficient antibiotic treatment ($P = 0.023$), suggesting that an increase of Crea during vancomycin therapy might be a marker of treatment failure rather than of vancomycin nephrotoxicity *per se*.[16]

Vancomycin is considered as a generally safe medication, but it is well known that vancomycin can cause histamine-mediated side effects, hypotension, and rash, well known as red man syndrome. This hypersensitivity reaction has often been associated with rapid infusion of the first dosage of the drug and was initially attributed to impurities found in vancomycin preparations.[38] We noticed the red man syndrome in two patients in the group receiving intermittent infusion of vancomycin. The vancomycin-related red man syndrome was not frequently observed in the present study, and the incidence of 6.7% in our population is comparable with findings of other clinical studies.[39]

Conclusions

Both the intermittent and also the continuous application modality of vancomycin are associated with deterioration of renal function. No significant disadvantage was observed with respect to nephrotoxicity between the continuous and the intermittent administration of vancomycin. Our data showed a tendency of continuous vancomycin administration to be less nephrotoxic compared with the intermittent administration. Statements about the two different treatment arms of vancomycin and their impact on renal function need to be individualized, as nephrotoxicity is influenced by a variety of other factors, including the type of infection, the responsible pathogen, and the patient's condition. However, our data suggest that is worthwhile to perform a prospective, randomized trial comparing the impact of continuous *versus* intermittent vancomycin infusion on renal function.

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