



Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects

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ABSTRACT

Optimising antibiotic administration is critical when dealing with pathogens with reduced susceptibility. Vancomycin activity is dependent on the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration (AUC/MIC), making continuous infusion (CI) or conventional twice daily administration pharmacodynamically equipotent. Because CI facilitates drug administration and serum level monitoring, we have implemented a protocol for CI of vancomycin by: (i) examining whether maintaining stable serum concentrations (set at 25–30 mg/L based on local susceptibility data of Gram-positive target organisms) can be achieved in patients suffering from difficult-to-treat infections; (ii) assessing toxicity ($n=94$) and overall efficacy ($n=59$); and (iii) examining the correlation between AUC/MIC and the clinical outcome in patients for whom vancomycin was the only active agent against a single causative pathogen ($n=20$). Stable serum levels at the expected target were obtained at the population level (loading dose 20 mg/kg; infusion of 2.57 g/24 h adjusted for creatinine clearance) for up to 44 days, but large inpatient variations required frequent dose re-adjustments (increase in 57% and decrease in 16% of the total population). Recursive partitioning analysis of AUC/MIC ratios versus success or failure suggested threshold values of 667 (total serum level) and 451 (free serum level), corresponding to organisms with a MIC > 1 mg/L. Nephrotoxicity potentially related to vancomycin was observed in 10% of patients, but treatment had to be discontinued in only two of them.

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1. Introduction

The pharmacokinetic/pharmacodynamic index governing the antibacterial activity of vancomycin is the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration [1] (AUC/MIC; see [2] for definition), with a value of at least 400 for optimal activity [3]. Thus, vancomycin could be administered by discontinuous infusion as well as by continuous infusion (CI) as far as efficacy is concerned. North American guidelines recommend administering vancomycin

as a twice daily or three times daily schedule (doses given in ca. 1 h every 12 h or 8 h apart) and to monitor trough levels [4]. This, however, does not allow accurate determination of the AUC since peak levels, primarily influenced by the volume of distribution (V_d), remain undetermined. In contrast, CI may provide an immediate reading of the AUC value. Actually, CI of vancomycin was shown to allow for a better attainment of target concentrations [5] and to ensure at least equal efficacy, whilst affording equal or decreased toxicity (see [6] for a recent meta-analysis). CI also greatly facilitates the monitoring of vancomycin (since serum levels should not be affected by the time of sampling) and has practical advantages for nursing [5,7,8]. It also allows for a centralised preparation of ready-to-use infusion sets, adapted for administration through volumetric devices, further minimising the risks of dose and timing errors [9]. We report here on the hospital-wide implementation of vancomycin administration for non-intensive care unit (non-ICU) patients under the supervision of a clinical pharmacist and an infectious diseases physician, and we present an analysis of the pharmacokinetics (including the determination of free versus total

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serum levels), the clinical outcomes and the correlations between AUC/MIC and clinical success.

2. Materials and methods

2.1. Overall design, setting, patients and ethical considerations

The investigation was performed over a 13-month period in the non-ICU wards (see caption of Fig. 1) of a 420-bed teaching hospital. Eligible patients were those for whom vancomycin treatment was prescribed for suspected or documented infection according to local guidelines. Excluded patients were those with life expectancy <1 week, baseline serum creatinine >2.3 mg/L or a creatinine clearance <30 mL/min at initiation of treatment, or those who already received vancomycin within 48 h prior to the current infection. All enrolled patients were examined for quality of administration, overall clinical efficacy and side effects, and benefited from dose adaptation based on availability of serum levels (usually once a week). A subset of patients who provided specific informed consent was included for detailed pharmacokinetic analysis with daily follow-up of serum levels and subsequent/eventual dose adaptation. The protocol of the study was approved prior to initiation by the Ethical Committee of the CHU Mont-Godinne (Yvoir, Belgium) and written informed consent was obtained from all patients (or a close relative if the patient was unable to co-operate) for investigations beyond the local standard of care.

2.2. Treatment

Vancomycin (Vancocin®; Lilly, Illkirch, France) 10 g/L in 5% glucose solution for infusion was prepared in the Central Pharmacy and was administered by volumetric infusion pump (Volumed® 7000;

Arcomed AG, Regensdorf, Switzerland). Patients received a loading dose of 20 mg/kg (based on actual body weight and an estimated V_d of 0.7 L/kg [10–12]) administered over 1 h for doses <2 g or over 2 h for larger doses. This was immediately followed by CI at a rate K_0 (mg/min) calculated according to Eq. (1):

$$K_0 = C_{ss} \times 0.65 \times \text{CCrCl} \quad (1)$$

where C_{ss} (mg/L) is the total serum target concentration at steady state, CCrCl is the calculated creatinine clearance (in L/min, based on the Cockcroft–Gault formula [13] using total body weight) and 0.65 is a correction factor for prediction of vancomycin clearance from CCrCl [12,14]. Because of the limitations of the Cockcroft–Gault formula, CCrCl values >120 mL/min were ignored (38/94 patients) and those patients were dosed as if having a creatinine clearance of 120 mL/min. Our initial serum concentration target value was 27.5 mg/L, corresponding to a daily dose of 2.57 g for an ideal patient (CCrCl=0.1 L/min; male), and, based on the preparation made, an infusion at 10.7 mL/h (rounded to 11 mL/h for practical purposes). For patients not enrolled in the detailed pharmacokinetic analysis (described in Section 2.5), a first sample was obtained within 8–12 h after initiation of CI and dosing was re-adjusted by increasing or decreasing the speed of the volumetric device by 500 mg increments. A new loading dose was administered if the total vancomycin serum concentration was <15 mg/L. Sampling and dose adjustments were repeated daily using pre-defined criteria (see Supplementary Table SP1) until two consecutive levels in the target range (25–30 mg/L) were obtained, after which samples were taken at least once weekly. Additional details regarding the stability of vancomycin and its compatibility with other antibiotics and other drugs have been published recently [15].

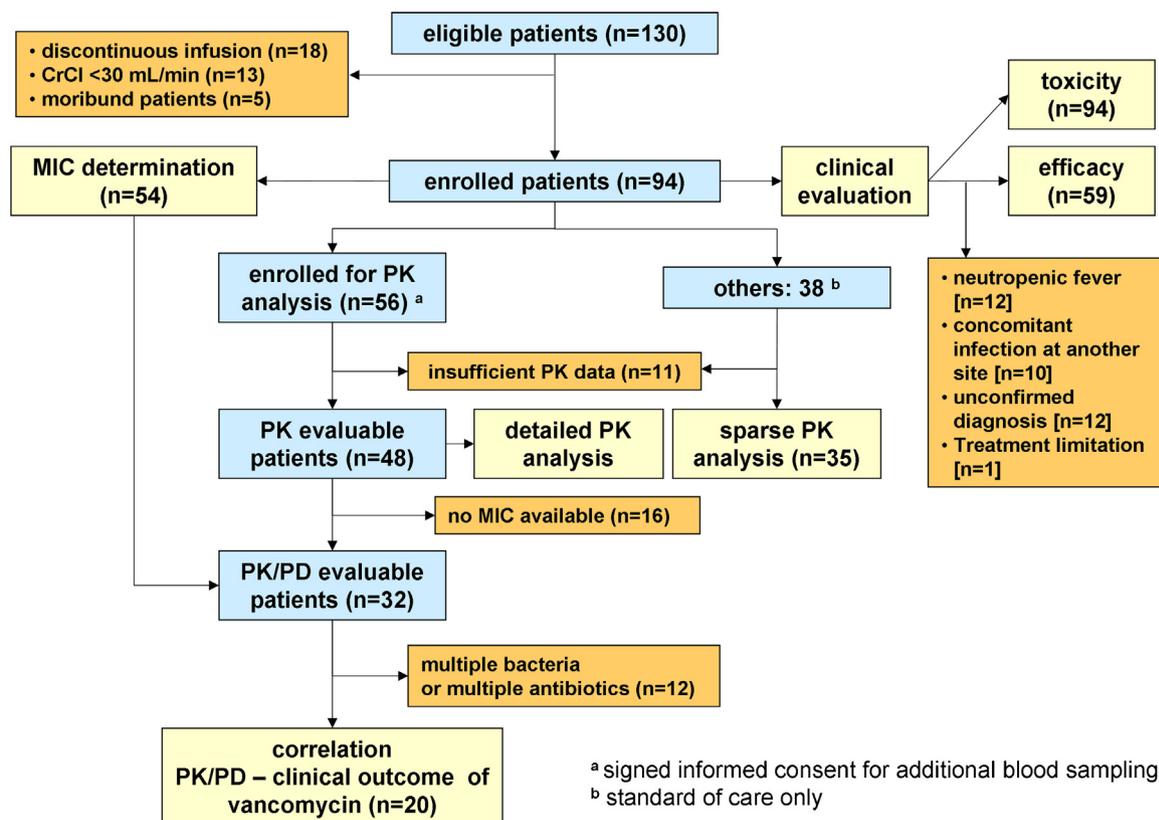


Fig. 1. General outline of the study and number of patients in each group or subgroup. Patients were from the following wards: cardiology ($n=4$); cardiovascular surgery ($n=7$); general surgery ($n=7$); gastroenterology ($n=3$); geriatrics ($n=7$); haematology ($n=31$); internal medicine ($n=8$); neurosurgery ($n=2$); oncology ($n=6$); orthopaedic surgery ($n=10$); pneumology ($n=6$); and urology ($n=3$). CrCl, creatinine clearance; MIC, minimum inhibitory concentration; PK, pharmacokinetics; PD, pharmacodynamics.

2.3. Clinical analysis (efficacy and safety)

Age, sex and weight were recorded before or at initiation of treatment, and the following parameters were recorded on a daily basis: peripheral white blood cell (WBC) count; C-reactive protein (CRP) level; minimum and maximum body temperature; arterial blood pressure; serum creatinine; serum albumin; patient comorbidities (see [16] for classification); consciousness; signs and symptoms of infection; and all concomitant treatments.

Clinical and bacteriological outcomes were assessed both during and at the end of treatment. Clinical cure was defined as the disappearance of all major signs of infection, normalisation of body temperature and marked decrease of CRP. Improvement was defined as substantial positive change of the above criteria. Failure was defined as persistent signs or symptoms of infection (e.g. fever, increased WBC count), appearance of new signs or symptoms of infection, or their worsening after ≥ 5 days of therapy. Criteria for bacteriological cure were a negative culture from the originally sampled site and absence of signs of persisting infection at this site. Relapses were evaluated over a 6-month period. Assessment of treatment outcomes was retrospectively validated by an external infectious diseases physician not previously involved in the study. As pathologies were diverse, no general rule could be established, but all cases of failure or recurrence were re-examined by three of the investigators (EA, BD and PMT) for confirmation as 'vancomycin failure' based on the best available evidence for each specific patient.

Side effects presumably attributable to vancomycin (based on the drug's official labelling [17]) were recorded, with renal toxicity evaluated until 1 week after the end of treatment [4]. Nephrotoxicity was defined as corresponding to two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or $\geq 50\%$ increase from baseline) or a drop in CCrCl of 50% from baseline documented after >3 days of therapy. We prospectively evaluated risk factors for non-vancomycin-induced nephrotoxicity using a list of criteria validated by infectious diseases physicians and clinical pharmacists that included age, pre-existing renal failure, diabetes, concomitant nephrotoxic medication, and medical conditions known to be associated with nephrotoxicity such as sepsis, hepatic impairment, obstructive uropathy and pancreatitis [4].

2.4. Laboratory studies

Samples for microbiology were processed according to standard methods and MICs of Gram-positive pathogens were determined in parallel by microbroth dilution according to Clinical and Laboratory Standards Institute (CLSI) standards [18] and by Etest (bioMérieux, Marcy l'Étoile, France). Total and free vancomycin serum levels were measured by an automated method (Architect[®]; Abbott Laboratories, Abbott Park, IL) (coefficient of variation $\leq 2.75\%$; between-day sample precision, 1.35%) using untreated samples and materials collected after ultrafiltration through Centrifree[®] centrifugal filter devices (Millipore, Billerica, MA) (20 min, 2000 \times g, room temperature), respectively, as previously described [19].

2.5. Pharmacokinetics and pharmacodynamics

For patients enrolled for detailed pharmacokinetic analysis, serum samples were obtained on Day 1 at 1, 3 and 6 h after the end of the loading dose and once daily from Day 2 onwards, and the values were used to construct a concentration–time profile for each patient. The AUC for the entire duration of treatment [and expressed as the value for 24 h (AUC_{24h})] was determined using GraphPad Prism v.4.3 (GraphPad Software Inc., La Jolla, CA).

AUC_{24h}/MIC values were calculated with MICs arbitrarily set at 0.25 mg/L if reported to be <0.5 mg/L.

2.6. Statistical methods

Statistical analyses were performed using JMP v.9.03 (SAS Software Inc., Cary, NC) and GraphPad InStat v.3.10 (GraphPad Software Inc.). Logistic fit regression and recursive partitioning were used to examine associations between continuous and categorical variables, respectively.

3. Results

3.1. Patient and sample characteristics

Fig. 1 shows the general outline of the study, the number of patients in each group or subgroup, and the reasons for exclusion at each step. In brief: (i) 94 patients were evaluated for toxicity and for quality of administration, 59 for clinical efficacy and 54 for measurement of vancomycin MIC against the putative pathogen; (ii) 48 patients could be evaluated for pharmacokinetics; (iii) pharmacodynamic analysis (AUC_{24h}/MIC) was performed in a subset of 20 patients with a documented Gram-positive infection and who had been treated with vancomycin as the only anti-Gram-positive antibiotic. Table 1 shows the populations' demographic and major clinical characteristics. The mean duration of treatment was 11.7 ± 8.4 days, with no significant difference between subgroups with respect to all criteria listed.

3.2. Global efficacy and safety

Of the 59 patients who could be evaluated for clinical outcome, 44 (74.6%) were considered as cured, 6 (10.2%) as improved and 9 (15.3%) as failing. Stratifying failures according to the MIC of the putative Gram-positive organism (obtained for 59 patients; see details in Supplementary Table SP2) showed values of 0/3, 3/18, 4/27 (1 was a relapse) and 2/6 for organisms with MICs of 0.25, 0.5, 1 and 2 mg/L, respectively. Relapse (at 6 months) was observed in only three patients (see detailed overview of treatment failures and recurrent infections in Supplementary Table SP3).

Table 2 shows that 13 patients (13.8%) experienced one or more adverse events possibly related to vancomycin treatment, with nephrotoxicity being predominant (10/13; see detailed overview of treatment-emergent toxicity events in Supplementary Table SP4). Seven of those patients had at least one vancomycin serum level >35 mg/L before the onset of toxicity, six had pre-existing mild to moderate renal failure and four had received either vancomycin for >14 days or a large cumulative dose (25 g). However, all those patients also had at least one other risk factor besides vancomycin administration: (i) all had received concomitant nephrotoxic drugs; (ii) eight received diuretics and two suffered from dehydration, making hypovolaemic renal failure not implausible; and (iii) nine were >65 years of age. Of four patients receiving a combination of vancomycin and aminoglycoside, one developed nephrotoxicity after 23 days of treatment. Vancomycin had to be discontinued due to nephrotoxicity in two patients (both presenting several other risk factors for nephrotoxicity, but showing a return of creatinine levels to baseline 1 week after treatment discontinuation).

A third patient developed general erythrodermia and fever after 10 days of treatment that could be ascribed either to vancomycin or to cefepime (both antibiotics were discontinued).

3.3. Pharmacokinetics/pharmacodynamics

Fig. 2A shows the profile of total serum vancomycin concentration over time for all patients with more than three determinations

Table 1
Demographic characteristics of all patients included.

Characteristic	Ratio, mean \pm S.D. or prevalence [n (%)] in patients evaluated for:				
	Toxicity (n = 94)	Efficacy (n = 59)	PK (n = 48)	PK/PD (n = 32)	PK/PD and vancomycin treatment outcome (n = 20)
Sex (M/F ratio) ^a	0.75/0.25	0.71/0.29	0.73/0.27	0.74/0.26	0.70/0.30
Age (years) ^a	63.3 \pm 13.8	65.1 \pm 13.9	62.3 \pm 13.2	62.6 \pm 14.0	65.6 \pm 12.6
CrCl (mL/min) ^a	100.6 \pm 42.4	94.4 \pm 41.2	105.8 \pm 46.7	103.7 \pm 41.5	99.0 \pm 44.4
Type of infection (n) ^b					
Foreign body ^c	21 (22.3)	14 (23.7)	12 (25.0)	10 (31.3)	8 (40.0)
Osteomyelitis	9 (9.6)	8 (13.6)	7 (14.6)	5 (15.6)	5 (25.0)
Septicaemia	31 (33.0)	20 (33.9)	14 (29.2)	11 (34.4)	4 (20.0)
Skin and soft tissue	7 (7.4)	5 (8.5)	4 (8.3)	0 (0.0)	0 (0.0)
Other	26 (27.7)	12 (20.3)	11 (22.9)	6 (18.8)	3 (15.0)
Organism isolated (n) ^b					
MSSA	7 (7.4)	4 (6.8)	3 (6.3)	2 (6.3)	2 (10.0)
MRSA	30 (31.9)	19 (32.2)	12 (25.0)	10 (31.3)	7 (35.0)
CoNS	25 (26.6)	15 (25.4)	12 (25.0)	11 (34.4)	8 (40.0)
Enterococci	7 (7.4)	4 (6.8)	4 (8.3)	2 (6.3)	0 (0.0)
Other	25 (26.6)	17 (28.8)	17 (35.4)	7 (21.9)	3 (15.0)
Nephrotoxic medication (%) ^b	58 (61.7)	38 (64.4)	35 (72.9)	24 (75.0)	13 (65.0)
Cytostatic drugs	30 (31.9)	18 (30.5)	15 (31.3)	10 (31.3)	4 (20.0)
Aminoglycosides	4 (4.3)	4 (6.8)	4 (8.3)	2 (6.3)	0 (0.0)
Diuretics	60 (63.8)	37 (62.7)	28 (58.3)	21 (65.6)	12 (60.0)
Treatment duration (days) ^a	11.7 \pm 8.4	12.6 \pm 7.9	13.9 \pm 9.6	15.6 \pm 7.6	15.4 \pm 7.3

PK, pharmacokinetics; PD, pharmacodynamics; CrCl, creatinine clearance; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci.

^a No significant difference between patients groups [$P < 0.05$, one-way analysis of variance (ANOVA)].

^b No significant difference between patient groups ($P < 0.05$, χ^2 test).

^c Patients with at least one prosthesis [cardiovascular, 12.8% ($n = 12$); orthopaedic, 11.7% ($n = 11$); 2 patients had both types of prostheses].

Table 2
Adverse events observed in all enrolled patients ($n = 94$).

Type	Occurrence [n (%)]	Treatment discontinuation [n (%)]
All ^a	13 (13.8)	3 (3.2)
Nephrotoxicity ^b	10 (10.6)	2 (2.1)
Hypersensitivity reactions ^c	2 (2.1)	0 (0.0)
Leukopenia ^d	1 (1.1)	1 (1.1)

^a Details of each case are given in Supplementary Table SP4.

^b Two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or $\geq 50\%$ above baseline) or a drop of calculated creatinine clearance $\geq 50\%$ from baseline after several days of therapy.

^c Red man syndrome ($n = 2$) and erythrodermia (late in treatment and no hypotension) ($n = 1$); 1 patient had both adverse events.

^d Decrease of total white blood cell to lowest limit of normal values ($1800/\text{mm}^3$) followed by further decrease of polymorphonuclear neutrophils.

at any time ($n = 91$). The mean concentration reached after administration of the loading dose (time 0 h) matched the targeted level (27.5 mg/L). We examined whether the apparent vancomycin V_d (in L/kg) was influenced by the total body weight using a subset of 53 patients for whom pertinent data were available [serum level at 1 h after loading dose and initiation of the CI, 26.7 ± 5.5 mg/L (range 10.2–40.9 mg/L; interquartile range (IQR) 23.8–29.7 mg/L); weight, 77.7 ± 21.9 kg (range 42.0–155.0 kg; IQR 61–92 kg)]. The mean V_d was 0.82 ± 0.23 L/kg (range 0.48–1.96 L/kg; IQR 0.68–0.89 L/kg) and was essentially unrelated to patient weight (linear regression slope, -0.0026 ± 0.0011 ; $R^2 = 0.113$). Serum levels, however, fell rapidly to ca. 20 mg/L within 6 h. After increasing the rate of infusion (57.4% of all patients), the mean concentration again reached the targeted value within 96 h and was thereafter maintained at 27.8 ± 5.7 mg/L for the whole duration of treatment. Based on the first stable steady-state level (defined as the first of two successive levels differing by $< 10\%$; $n = 49$), we observed a vancomycin clearance of 79.6 ± 26.9 mL/min (range 21.9–132.4 mL/min) and an apparent half-life of 10.0 ± 4.9 h (range 4.2–28.3 h). The correlation between vancomycin clearance and CCrCl was further explored using both linear and non-linear regression. A linear function and a one-phase exponential association fitted the data

almost equally well ($R^2 = 0.68$ and 0.72 , respectively). The former yielded a slope of 0.47 (95% confidence interval 0.38–0.57) and an intercept (non-renal clearance) at 29.0 ± 5.5 mL/min. The second showed no non-renal clearance (zero intercept), a ratio of vancomycin to creatinine clearance varying from 1.01 to 0.52 in the range of CCrCl values examined (32–237 mL/min) and saturation of vancomycin clearance at 150.3 mL/min (95% confidence interval 111.5–189.0 mL/min). The mean $\text{AUC}_{24\text{h}}$ calculated from data points recorded after 48 h of infusion up to the end of treatment was 661 ± 60 mg h/L (range 441–756 mg h/L; $n = 32$).

Although stable at the whole population level, important variations in serum concentrations (10 mg/L or more) were observed in 40 out of 52 patients for whom more than three successive samples were obtained after 96 h of treatment (Fig. 2B). These variations were not related to age, weight, serum creatinine, serum protein, sex, underlying pathology or hospitalisation in haematology. Conversely, they were positively associated with an increased CCrCl (threshold at > 104 mL/min) and negatively associated with the use of diuretics [multivariate modelling prediction expression, $y = 26.81 + (-0.046 \times \text{CCrCl}) \pm 1.65$ where the last term relates to the use (+) or not (–) of diuretics; $P < 0.01$].

Free vancomycin concentrations were measured in samples from a subgroup of 30 patients. Fig. 3 (upper and middle panels) shows that although the correlation between free and total concentrations was satisfactory at the population level ($r^2 = 0.77$), there was a large variation in the free/total concentration ratio between different samples. We looked for a correlation between free concentrations and several potential pertinent clinical factors (including CCrCl and plasma protein levels) but none showed statistical significance. The pattern of free concentration values over time was, however, globally similar to that of total concentrations but with even larger variations (9.15 ± 6.83 mg/L; range 2.0–39.2 mg/L) and a trend towards a sustained increase over time.

The average $\text{AUC}_{24\text{h}}/\text{MIC}$ ratio in the 20 patients who received vancomycin as single active drug was then correlated with clinical outcome (cure/failure). Recursive partitioning analysis pointed to 667 and 451 as best split values separating failure from success using total and free vancomycin concentrations, respectively, and

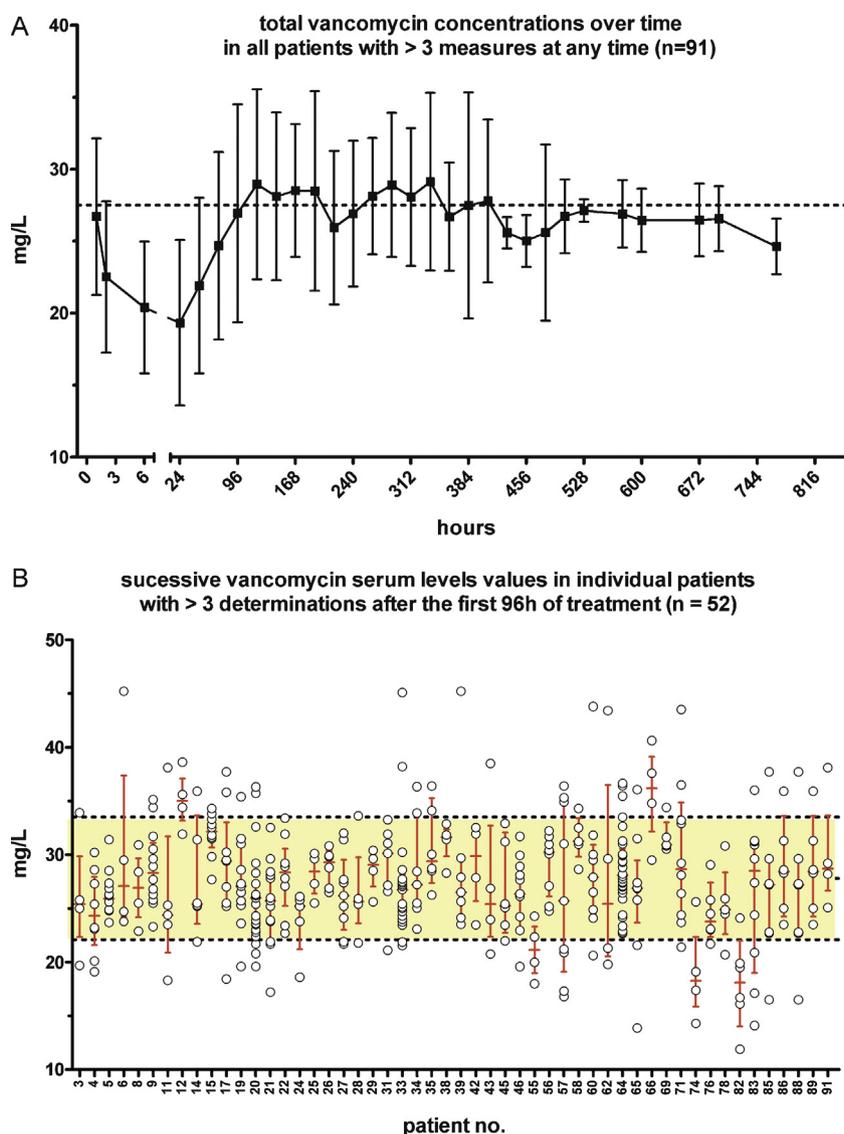


Fig. 2. Total vancomycin serum concentrations. (A) All patients with more than three successive determinations ($n=91$) over time. Data are presented as concentrations (\pm S.D.) observed at the corresponding times for the first 6 h of the observation period, and at the closest rounded value (in days) after 24 h. The dotted line shows the targeted serum concentration (27.5 mg/L). Number of patients per data point, 41–80 between 1 h and 168 h; 28–40 between 192 h and 360 h; and 3–7 for longer times. (B) Individual serum levels in individual patients with more than three successive determinations after the first 96 h infusion. Each point represents one value. The red bars show the median and the interquartile range. The highlighted zone shows the mean \pm S.D. for all samples. S.D., standard deviation.

MICs determined by microdilution method (Fig. 4; see Supplementary Fig. SP1 for a similar analysis using MICs determined by Etest; although the P -value exceeded 0.05 for some of these analyses, the trend was quite obvious).

3.4. Pharmacokinetics/toxicodynamics

Vancomycin serum levels were compared in the 10 patients who developed nephrotoxicity using all values from Day 1 to the time of onset of nephrotoxicity (mean 14.5 days) and in all patients with no evidence of nephrotoxicity and for whom serum levels over a period of 14 successive days were available ($n=19$). No correlation between increased vancomycin serum level and nephrotoxicity was observed (see Supplementary Fig. SP2).

4. Discussion

Administration of vancomycin by CI has been advocated because of its practical advantages for nursing and serum level monitoring

as well as its potential for increased efficacy and decreased toxicity. Contrasting views, however, have been clearly expressed in this context [see, e.g., [20] (systematic review) versus [6] (meta-analysis)]. The present study adds to this large body of knowledge by: (i) showing how CI can be implemented in non-ICU wards of a whole hospital; (ii) providing information on its clinical efficacy and safety; and (iii) presenting information about the ratio of drug exposure (AUC) to the MIC of the offending organism that may separate clinical success versus failure. ICU patients were not included because (i) administration of vancomycin by CI in this population has already been studied by several authors (see [21] for review) and (ii) because using the widely accepted Cockcroft–Gault formula for calculation of creatinine clearance to adjust vancomycin infusion rates is questionable in ICU patients [22].

With respect to pharmacokinetics, our protocol allowed achieving initial serum concentrations close to the target value, indicating that the assumed V_d of 0.7 L/kg was almost correct for most patients. Interestingly enough, no major correction had to be introduced based on actual body weight (within the limits of

weights observed). This does not preclude that other patients, such as those experiencing sepsis, could require higher loading doses [23], which will need to be assessed at the individual level. Conversely, the rapid concentration fall observed when starting the infusion cannot be attributed to an underestimation of the true

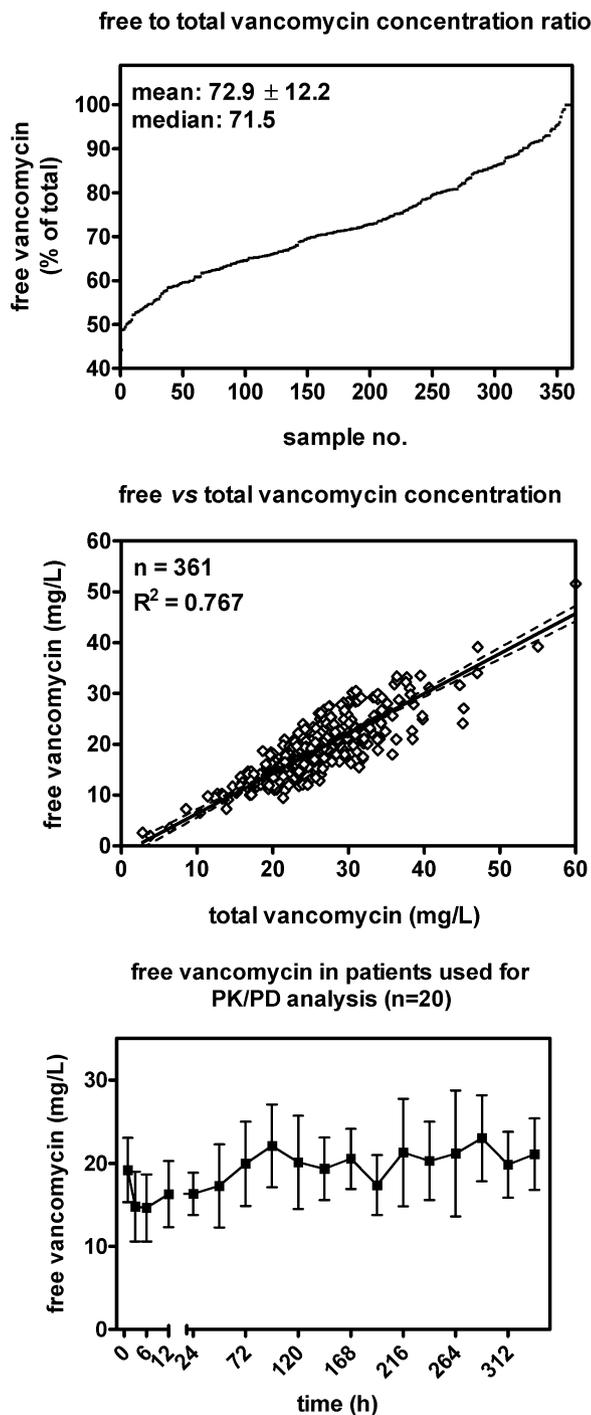
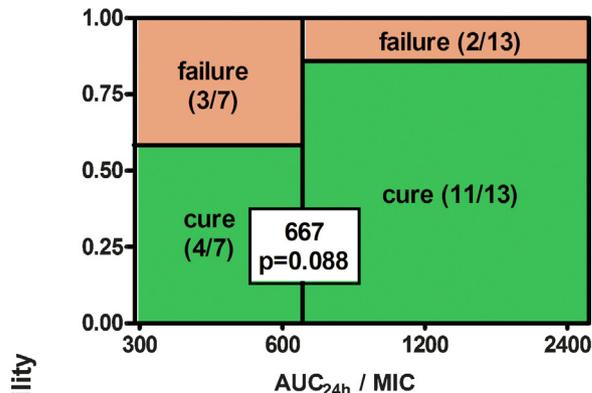


Fig. 3. Free serum vancomycin concentrations. Upper panel: distribution of free fraction of vancomycin in serum samples ($n = 361$). Each point is an individual sample, and samples are ranked by low to high free to total vancomycin concentration ratio. Middle panel: correlation between free and total vancomycin serum levels in the 361 samples shown in the upper panel. The solid line shows the regression line (linear regression) and the dotted lines show the 95% confidence interval band. Lower panel: free vancomycin serum concentrations over time for patients for whom a correlation was made between pharmacokinetic/pharmacodynamic data and clinical outcome ($n = 20$; see Fig. 1). Data are presented as mean (\pm standard deviation) observed at the corresponding times for the first 12-h observation period and at the closest rounded value (in days) after 24 h.

A. Total vancomycin serum concentration



B. Free vancomycin serum concentration

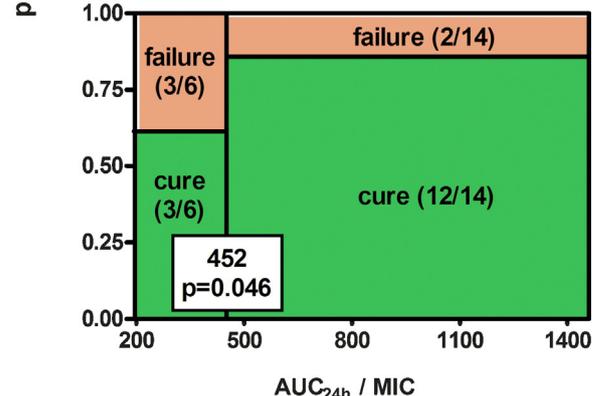


Fig. 4. Pharmacokinetic/pharmacodynamic analysis of clinical outcomes in 20 patients (i) infected by a single Gram-positive organism and having received vancomycin as the only agent active against this organism, and (ii) for whom assignment to antibiotic treatment success or failure could be established. The figure shows the probability of cure or failure as a function of the AUC_{24h}/MIC ratio observed for each individual patient using her/his mean AUC data for the entire duration of treatment and the MIC value (microdilution) of the causative organism. Upper graph, total vancomycin concentration; lower graph, free vancomycin concentration. Data were analysed by recursive partitioning to determine the dichotomous split in AUC_{24h}/MIC distributions that best separates values with low versus high probability of clinical success. Node splitting is based on the LogWorth statistic and the results analysed by χ^2 test (contingency tables). See Supplementary Fig. SP1 for the same analysis using MIC values obtained by Etest. AUC_{24h}, area under the concentration–time curve over 24 h at steady-state; MIC, minimum inhibitory concentration.

vancomycin clearance by using the well-accepted ratio of 0.65 to CCrCl [12,14] to guide dosing since its actual ratio was lower if assuming a linear relationship between both clearances. However, this ratio could be higher in patients with low CCrCl if accepting the non-linear model. Possibly also, we simply may have underestimated the true creatinine clearance by using the Cockcroft–Gault equation. More sophisticated equations could have been used but these are not validated for medication dosage adjustment. We could also have measured the actual creatinine clearance, but this is not routine practice in non-ICU wards and was therefore considered unsuited in a context of hospital-wide implementation of CI. Actually, the main message is that maintaining the serum level at its targeted value requires careful monitoring-based dosage re-adjustment. This could be related to higher than anticipated renal clearance, as recently also pointed out by others [23–25], but also to many other factors beyond the clinician's direct control. In our setting, this may have been increased by the decision to disregard CCrCl values >120 mL/min, and a revision of our protocol may be warranted in this context.

We found a direct correlation between the proportion of treatment failures and the MIC of the assumed causative organism when considering the whole group of patients. When limiting the pharmacokinetic/pharmacodynamic analysis to patients for whom vancomycin was the only active agent against the putative causal Gram-positive pathogen, we could confirm that low AUC_{24h}/MIC values were associated with a larger proportion of failures, with a threshold at values higher than that of 400 originally proposed [3]. Thus, considering the serum levels reached, organisms with a $MIC \geq 2$ mg/L will obviously prove difficult to be correctly covered, lending further support to the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) vancomycin clinical breakpoints for staphylococci [susceptible (S), ≤ 2 mg/L; resistant (R), >2 mg/L [26]] and questioning the validity of the corresponding current CLSI breakpoints (S, ≤ 2 mg/L; R, ≥ 16 mg/L [18]) as also stressed for patients treated with intermittent dosing [27]. Doses and target serum levels could, however, be decreased for infections caused by organisms with MICs <1 mg/L, which may offer both toxicological and economical advantages. A study performed in a large cohort of patients receiving intermittent administration has indeed clearly demonstrated a relationship between initial trough levels and the risk of nephrotoxicity (with a threshold value of ca. 10 mg/L but with a clear difference in disfavour of ICU versus non-ICU patients) [28]. With CI, ICU and outpatients appear to be at a higher risk of nephrotoxicity if concentrations exceed 28 mg/L and 30 mg/L, respectively [29,30]. Yet we saw no correlation in our population, questioning the validity of defining any threshold in this context. The weakness of our study, however, is that although a rather high rate of nephrotoxicity was observed, its association with vancomycin remains uncertain as several other causes of renal failure were present. Other toxicities, including thrombophlebitis, were rarely encountered or not seen.

Altogether, our study demonstrates that hospital-wide implementation of vancomycin administration by CI may be a practical and appropriate option for the treatment of patients with severe Gram-positive infections provided that the corresponding MICs remain <2 mg/L. CI, however, will still require monitoring blood levels because of (i) the difficulties in correctly predicting vancomycin serum concentrations (using presently accepted models based on CCrCl) as well as unanticipated large inpatient and interpatient variations and (ii) the necessity to adjust these levels to the MIC of the causative organism. Whilst vancomycin stability will not cause issues (even under poorly controlled room temperatures as evidenced from many reports), independent lines (or multi-lumen catheters) will need to be used for co-administration of other intravenous medications as vancomycin is reported to be incompatible with many other drugs [17].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://www.facm.ucl.ac.be/downloads/IJAA-D12-00806-SM.pdf>.

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Supplementary Material

Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic, and toxicological aspects.

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Contents:

Table SP1: Dose adaptations for deviations of the targeted serum level	2
Table SP2: Organism, MIC (microdilution; Etest®) and clinical outcomes	3
Table SP3: Detailed overview of treatment failures and recurrent infections.....	5
Table SP4: Detailed overview of treatment-emergent toxicity events	8
Table SP5: Clinical and bacteriological features of patients with PK/PD analysis	10
Figure SP1: Success/failures partitioning based on Etest MICs	12
Figure SP2: Total and free vancomycin serum concentrations in patients without and with signs of nephrotoxicity	13

Table SP1: Dose adaptations for deviations of the targeted serum level

Target level: 25-30 mg/L

Actual concentration (measured)	Dose adaptation
0-5 mg/L	<ul style="list-style-type: none"> • Add a loading dose (20 mg/kg) • Increase of the rate of infusion (+ 8 mL/h) ^a
6-10 mg/L	<ul style="list-style-type: none"> • Add a loading dose (15 mg/kg) • Increase of the rate of infusion (+ 6 mL/h) ^a
11-15 mg/L	<ul style="list-style-type: none"> • Add a loading dose (10 mg/kg) • Increase of the rate of infusion (+ 4 mL/h) ^a
16-25 mg/L	<ul style="list-style-type: none"> • Increase of the rate of infusion (+ 2 mL/h) ^a
26-30 mg/L	<ul style="list-style-type: none"> • No change
31-35 mg/L	<ul style="list-style-type: none"> • Decrease of the rate of infusion (- 2 mL/h) ^a
> 35 mg/L	<ul style="list-style-type: none"> • STOP infusion for 6 h • Decrease of the rate of infusion (- 4 mL/h) ^a • Control serum level the next day

^a standard infusion solution at 10 mg/mL

Table SP2: Organism, MIC (microdilution; Etest®) and clinical outcomes

Data of patients with failures are highlighted in grey.

Patients are ranked by order of increasing MIC (microdilution)

patient no.	organism ^a	MIC (mg/L)		clinical outcome ^d	used in PK/PD analysis ^e
		microdil. ^b	Etest ^{®c}		
14	<i>E. faecium</i>	0.25	0.25	cure	
41	<i>Streptococcus</i> spp.	0.25	1	cure	
43	<i>S. equisimilis</i>	0.25	0.5	cure	X
3	<i>S. epidermidis</i>	1	1.5	cure	
5	<i>S. hominis</i>	0.5	1.5	cure	
16	MRSA	0.5	1.5	cure	
18	MSSA	0.5	1.5	cure	
21	MSSA	0.5	0.5	improvement	X
25	MRSA	0.5	1	cure	X
26	MRSA	0.5	1.5	failure	X
27	MRSA	0.5	1.5	failure	X
31	<i>Corynebacterium</i> spp.	0.5	0.75	cure	X
32	MSSA	0.5	1.5	cure	
37	MRSA	0.5	1.5	improvement	X
38	CNS	0.5	1.5	cure	X
45	MRSA	0.5	2	cure	
57	MRSA	0.5	1.5	cure	
61	MRSA	0.5	1.5	cure	
13	MRSA	0.5	1.5	unevaluable	
82	MRSA	0.5	1.5	unevaluable	
66	MRSA	0.5	2	cure	
83	MRSA	0.5	2	failure	
23	MSSA	1	1	unevaluable	
6	<i>S. epidermidis</i>	1	1	failure ^f	X
2	MSSA	1	1.5	cure	X
50	MSSA	1	1.5	unevaluable	
8	<i>S. epidermidis</i>	1	1.5	cure	X
9	MRSA	1	1.5	cure	X
11	MRSA	1	1.5	cure	X
78	<i>E. faecalis</i>	1	1.5	relapse	
75	<i>E. faecium</i>	1	1.5	unevaluable	
71	MRSA	1	1.5	cure	
8	CNS	1	1.5	improvement	
87	MRSA	1	1.5	cure	
74	MRSA	1	1.5	cure	
15	<i>S. haemolyticus</i>	1	2	cure	X
17	MRSA	1	2	cure	X

4	MRSA	1	2	unevaluable	
30	<i>S. epidermidis</i>	1	2	cure	
39	<i>S. epidermidis</i>	1	2	failure	
81	MRSA	1	2	cure	
12	<i>S. epidermidis</i>	1	2	failure	
29	MRSA	1	2	unevaluable	
79	<i>E. faecium</i>	1	1.5	unevaluable	
42	CNS	1	3	cure	X
54	MRSA	1	2	failure ^f	X
60	<i>S. epidermidis</i>	1	2	cure	
65	<i>E. faecium</i>	1	1.5	cure	
76	MRSA	2	2	cure	
1	<i>E. faecalis</i>	2	3	failure	
24	<i>S. haemolyticus</i>	2	3	improvement	X
34	<i>S. epidermidis</i>	2	3	improvement	X
46	<i>S. epidermidis</i>	2	2	failure ^g	X
62	MRSA	2	3	cure	

^a MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*;
CNS: coagulase-negative *staphylococci* .

^b according to the recommendations of the Clinical Laboratory Standards Institute (Performance Standards of Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. M100-S22: 1-183. Clinical and Laboratory Standards Institute, Wayne, PA (2012).

^c bioMérieux SA, Marcy l'Etoile, France

^d with respect to the causative organism as listed in the Table

^e patients (i) enrolled in the pharmacokinetic study and for whom sufficient data could be assembled, and (ii) infected by an organism against which vancomycin could be considered as the only active agent (monotherapy)

^f relapse considered as due to vancomycin lack of efficacy

^g death possibly due to infection

Table SP3: Detailed overview of treatment failures and recurrent infections

patient no.	Organisms ^a and source ^b	vancomycin MIC (mg/L) microdil. / Etest®	vancomycin treatment duration (days)	clinical outcome
1	CNS (centr. catheter) <i>E. faecalis</i> (HC 1fl/4) <i>C. freundii</i> (HC 1fl/4) <i>Enterobacter</i> spp. (HC 1fl/4)	2/3 (<i>E. faecalis</i>)	4	Vancomycin treatment for suspected catheter related infection Antibiotic switched to ampicillin + cefepime after 4 days. Death 4 days after switch from gastro-intestinal hemorrhagic shock and sepsis of gastrointestinal origin due to <i>Enterobacter</i> spp. and <i>Enterococcus</i> spp. There is evidence that death resulted from a non-infectious cause but the patient was still infected
6	<i>S. epidermidis</i> (peroperative bone biopsy)	1/1	10	Conservative treatment of prosthetic device infection at weeks after prosthesis (no removal of prosthetic device) Surgical debridement at day 8 Switch to ciprofloxacin + rifampin at day 10 for the next 6 weeks Recurrence of the collection with removal of prosthesis at day 35
12	<i>S. epidermidis</i> , <i>Enterococcus</i> spp., <i>E. coli</i> (collection samplig)	1/2 (<i>S. epidermidis</i>)	14	Vancomycin + cefepime for 2 weeks for retroperitoneal abscess (post nephrectomy) - no drainage Switch to teicoplanin + cefepime for 2 weeks Reappearance of retroperitoneal collection; residual cutaneous fistula with culture positive for <i>E. faecalis</i> and CNS (ampicillin susceptible) at the end of antibiotic treatment. Percutaneous drainage and initiation of a second treatment with vancomycin and meropenem Thereafter, clinical success after 15 days (no sample available)
26	MRSA (hemoculture)	0.5/1.5	10	Septicemia of unknown origin Persistence of fever and several positive haemocultures until 3 weeks after the end of treatment
27	MRSA (superficial wound culture)	0.5/1.5	20	MRSA surgical wound infection toe despite amputation and postoperative vancomycin treatment Persistence of the infection and new amputation
36	<i>S. pyogenes</i> (wound culture)	/	3	Skin and soft tissue infection. Switch to cefazolin after 3 days for 2 weeks CRP increase during treatment and reoccurrence of erysipelas at the end of the antibiotic treatment.

46	CNS (<i>S. epidermidis</i> in perioperative cultures)	2/2	28	Wound infection with suspicion of vascular prosthesis infection. Treatment with vancomycin and ceftazidime, followed by ciprofloxacin and rifampicin No removal of prosthesis (debridement only). Wound necrosis and several perioperative positive cultures after 2 months
54	MRSA (sputum culture)	1/2	7	Respiratory tract (COPD exacerbation). Death (clinical deterioration with fever, dyspnoea and sputum after 6 days of therapy)
55	<i>Helococcus kunzii</i> (bone biopsy)	/	8	Relapse of chronic osteomyelitis 2 months after surgical debridement and initiation of antibiotic therapy (no prosthesis) vancomycin treatment for 8 days switch to ceftriaxone + rifampicin after 3 weeks switch to rifampicin + cotrimoxazole for a total duration of 2 months with no sign of infection healing Patient refuses surgical treatment.
78	<i>E. faecalis</i> <i>K. oxytoca</i> <i>C. albicans</i> (perioperative culture abscess)	1/1.5 (<i>E. faecalis</i>)	10	Abdominal abscess with surgical debridement followed by vancomycin + meropenem + fluconazole Recurrence of abdominal abscess due to <i>E. faecalis</i> and MRSA at 3 months
83	MRSA haemocultures (5fl/6)	0.5/2	17	Septic thrombophlebitis switch to oral linezolid for 2 weeks Haemoculture at day 20 Confirmation of cervical spondylodiscitis at the end of linezolid therapy Considered as a failure of the antibiotic treatment
86	<i>S. epidermidis</i> <i>E. coli</i> (perioperative bone biopsy)	/	16	Chronic knee prosthesis infection (prosthesis not removed; conservative treatment)) first biopsy negative concomitant to treatment with cefuroxime (haemocultures positive for <i>E. coli</i>) At day 16, switch to minocycline for 6 weeks Biopsy positive for <i>S. epidermidis</i> and <i>E. coli</i> at the end of antibiotic treatment Removal of prosthesis Considered as failure of the suppressive treatment

¹ to protect patients' anonymity, the age and the underlying disease(s) are not reported but the data are available from the authors if deemed important for scientific reasons. Stratification on age showed an equal distribution between <70 and ≥70 years. Prosthesis and diabetes accounted for the most frequent underlying illnesses (4 and 3 cases, respectively).

^a MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; CNS: coagulase-negative staphylococci.

^b HC: hemoculture (with the number of positive flasks over the total number of samples)

Table SP4: Detailed overview of treatment-emergent toxicity events

Patient no.	Age (y)	Infection type	Baseline CiCr (mL/min)	Duration VAN before onset of toxicity (days)	Cumulative VAN dose before onset of toxicity (g)	Highest VAN conc. measured (mg/L)	Risk factors for toxicity - related to vancomycin treatment - other	Type	Description	End of VAN due to toxicity?
12	73	urinary tract infection (renal abscess)	39.2	14	16.0	39.8	age, loop diuretic, enoxaparin, contrast agent, chronic renal insufficiency nephrectomy, renal abscess	renal	Serum creatinine 2.3 at D0. Increase to 2.7 at D12 leading to VAN stop. After treatment stop further increase to 5.1 at D+7. dialysis at D+15. Then decrease to 2.8 at D+21 and to 2.2 at D+35.	yes
21	73	sternal osteomyelitis	42.3	31	38.5	34.2	enoxaparin, diabetes, dehydration, age, duration, dose	renal	Serum creatinine 1.2 at D0. Increase to 1.7 at D31, leading to VAN stop. Thereafter increase to 1.8 at D+2 then decrease to 1.1 at D+7.	yes
35	60	catheter sepsis	>12 0.0	10	34.1	36.4	enoxaparin, dose, diabetes, dehydration, surgery	renal	Serum creatinine 0.8 at D0. Increase to 1.4 at D11 during several days leading to two consecutive dose decreases. Thereafter normalisation to 0.9 at D13.	no
64	73	central nervous system (postsurgical cerebral abscess)	41.0	21	33.6	36.4	loop diuretic, allopurinol, glucose-1-phosphate, age, diabetes, dehydration, duration, dose	renal	Increase of serum creatinine from 1.9 to 3.0 at D30 during 7 days. Stop Van at D35. Thereafter, stabilisation of serum creatinin at 2.6 until D+22.	no
65	66	abdominal (colitis)	103. 1	8	24.8	27.5	loop diuretic, enoxaparin, cytarabine, dehydration	renal	Increase of serum creatinine from 0.5 to 1.0 at D8 during 6 days. . Stop VAN at D7. Thereafter normalisation to 0.6 at D+12.	no

66	85	Skin and soft tissue	31.0	9	9.4	40.6	loop diuretic, enoxaparin, mild chronic renal insufficiency, dehydration, age	renal	increase of serum creatinine from 1.6 to 2.1 after a 9 day treatment from D+1 until D+18. Thereafter: decrease to 1.7 at D+21.	no
75	76	foreign body (pacemaker)	59.3	7	11.7	47.5	loop diuretic, enoxaparin, age	renal	Increase of serum creatinine from 0.9 to 1.7 after a 7 day treatment from D+2. Thereafter: decrease to 1.4 from D+4 to D+15.	no
86	78	foreign body (orthopaedic)	71.0	3	5.6	34.4	loop diuretic, age, sepsis, dehydration, serum conc.,	renal	Increase serum creatinine from 1.4 to 2.1 at D3 during 3 days leading to dose decrease. Return serum creatinine to 1.4 at D6.	no
93	67	Foreign body infection (pacemaker)	95.0	21	29.5	40.1	aminoglycosides, loop diuretic, duration, dose serum concentration	renal	Increase of serum creatinine from 1.0 to 1.5 from D21 during 6 days. Stop VAN at D23. No serum creatinine determination afterwards.	no
89	84	respiratory tract (exacerbation of COPD)	48.0	9	13.0	36.7	diuretic, dehydration, serum conc.,	renal	Increase serum creatinine from 0.9 to 1.4 at D9. Stop VAN at D10. Rise serum creatinine to 1.8 at D+2. creatinine until D+14. Normalisation to 0.9 AT D+22.	no
85	71	catheter sepsis	73.0	10	28.0	37.7	dose, serum concentration	Hypersensitivity	Red men at loading dose (1800 mg/2h). General erythrodermia and fever at D10 due to vancomycin or cefepime	no
92	56	foreign body infection (vascular)	66.0	0	1.0	NA	none	red man	Red men at loading dose (1000 mg/1h). Stop after 45 min during 45 min than rest of loading dose administered in 15 min.	no
5	34	foreign body infection (orthopaedic)	109.6	16	56.0	31.4	enoxaparin, duration, dose	hematologic	Decrease of WBC and neutrophils count respectively to 4.8/ μ L (4-10) and 2.5/ μ l (2.1-6.3) from D17. Further decrease of neutrophil count to 1.8 at D32.	yes

- To protect patients' anonymity, the reason for admission is not reported but is available from the authors if deemed important for scientific reasons.
- Our analysis did not disclose meaningful association of the reason of admission and the occurrence of a toxic event.

Table SP5: Clinical and bacteriological features of patients with PK/PD analysis

Patients (n=20) with

- detailed pharmacokinetic analysis,
- available MIC value of a Gram-positive organism considered as the cause of the infection, and
- receiving vancomycin as the only anti-Gram-positive antibiotic.

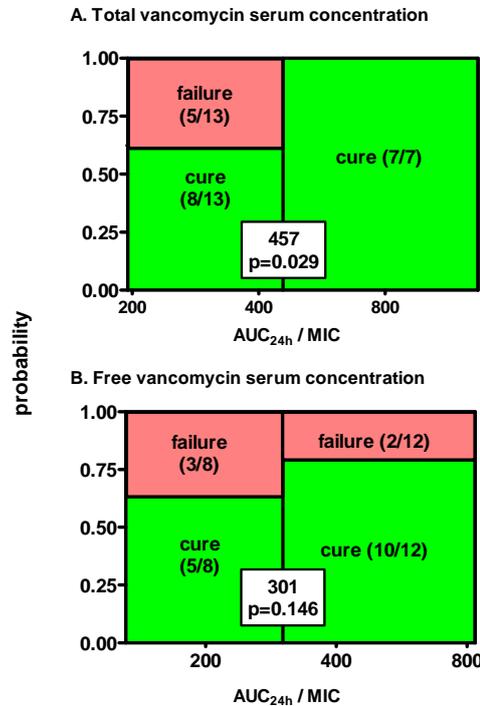
no.	infection type	organism ^a	MIC (mg/L) Etest® / microdil.	treatment duration (days)	clinical outcome
3	catheter sepsis	<i>S. epidermidis</i>	1.5/1	9	cure
6	foreign body infection (orthopaedic)	<i>S. epidermidis</i>	1/1	10	failure ^b
8	foreign body infection (orthopaedic)	<i>S. epidermidis</i>	1.5/1	15	cure
9	foreign body infection (ventriculo-peritoneal drain)	MRSA	1.5/1	28	cure
11	osteomyelitis	MRSA	1.5/1	14	cure
15	catheter sepsis	<i>S. haemolyticus</i>	2/1	14	cure
17	osteomyelitis	MRSA	2/1	22	cure (slow improvement over time)
21	osteomyelitis (sternal)	MSSA	0.5/0.5	32	improvement
24	osteomyelitis	<i>S. haemolyticus</i>	3/2	14	improvement
25	Central nerve system	MRSA	1.5/0.5	17	cure

26	bacteraemia of unknown origin	MRSA	1.5/0.5	10	failure (persistence of fever and relapse of infection 3 weeks after the end of treatment)
27	osteomyelitis	MRSA	1.5/0.5	20	failure (MRSA surgical wound infection despite amputation and postoperative vancomycin treatment)
31	bacteraemia of unknown origin	<i>Corynebacterium</i> spp.	0.75/0.5	12	cure
34	foreign body infection (orthopaedic)	<i>S. epidermidis</i>	3/2	16	improvement
37	respiratory tract	MRSA	1.5/0.5	7	improvement
38	foreign body infection (pacemaker)	CNS	1.5/0.5	10	cure
42	Foreign body infection (pacemaker)	CNS	3/1	9	cure
43	foreign body infection (vascular)	<i>S. equisimilis</i>	0.5/0.25	11	cure
46	foreign body infection (vascular)	CNS	2/2	28	failure (relapse of wound infection due to coagulase negative <i>Staphylococcus</i> after 2 months)
54	respiratory tract	MRSA	2/1	7	Failure (clinical deterioration; patient died after 6 days of therapy)

- To protect patients' anonymity, the age and the underlying disease(s) are not reported but the data are available from the authors if deemed important for scientific reasons.
- Stratification on age: <70 years: n=11 - ≥70 years: n=9. There was no specific association between underlying disease and cure or failure.

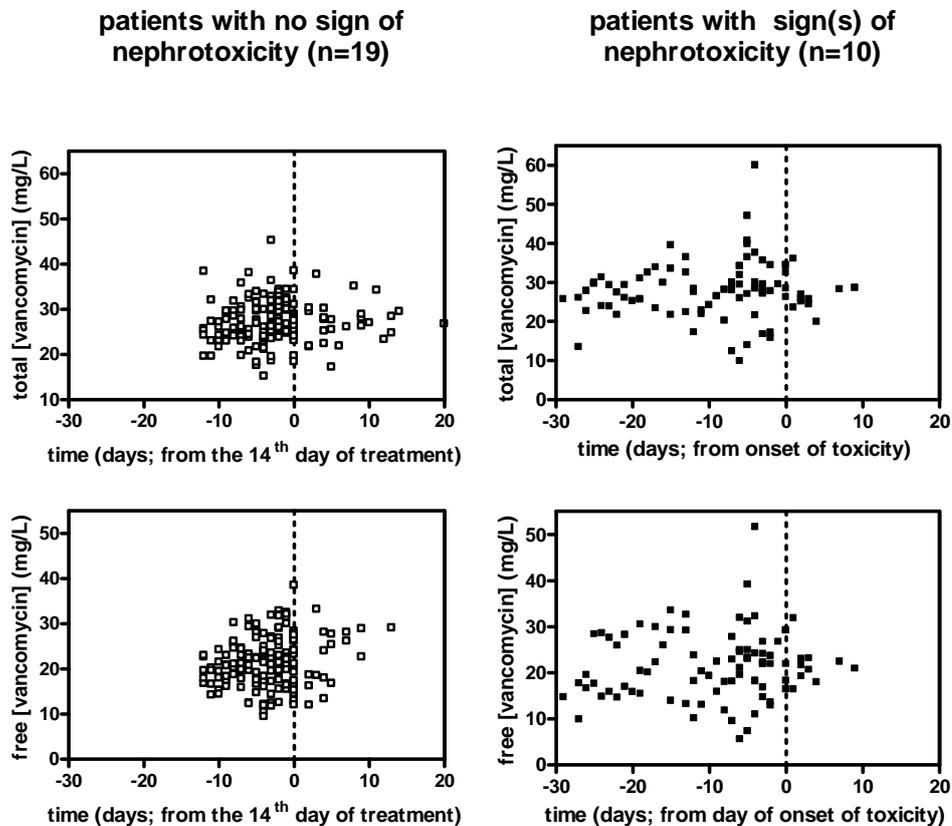
^a MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; CNS: coagulase-negative staphylococci.

^b relapse considered as due to vancomycin lack of efficacy

Figure SP1: Success/failures partitioning based on Etest MICs

Caption of Figure SP1: Pharmacokinetic/pharmacodynamic analysis of the clinical outcomes in patients (n = 20) infected by a single Gram-positive organism and having received vancomycin as the only agent active against this organism (monotherapy). The figure shows the probability of cure or failure as a function of the AUC/MIC observed for each individual patient using the mean AUC data of each patient for the entire duration of the treatment (upper graph: total vancomycin concentrations; lower graph: free vancomycin concentration) and the MIC data of the causative organism as determined by Etest® (see Table SP3 for a comparison of individual MIC values as determined in broth). Data were analyzed by recursive partitioning to determine the dichotomous split in AUC/MIC distributions that best separates values with low vs. high probability of clinical success. Node splitting is based on the LogWorth statistics and analyzed by Chi-square test (contingency table).

Figure SP2: Total and free vancomycin serum concentrations in patients without and with signs of nephrotoxicity



Caption to Figure SP2: Total (upper panels) and free (lower panels) vancomycin serum levels in patients without (left panels; n=19) vs. patients with signs of nephrotoxicity (right panel; n=10). Nephrotoxicity was defined as two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or $\geq 50\%$ increase from baseline) or a drop in calculated creatinine clearance of 50% from baseline documented after > 3 days of therapy. For patients with nephrotoxicity, the dotted line refers to the day of the diagnostic, and the data points correspond to the levels measured in these patients before and after that day. For patients without evidence of nephrotoxicity, the dotted line corresponds to the 14th day of treatment with vancomycin and the data points correspond to all available serum levels measured before and after that day.