



## Plasma and interstitial fluid population pharmacokinetics of vancomycin in critically ill patients with sepsis

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### ABSTRACT

Vancomycin is a commonly prescribed antibiotic in the intensive care unit. However, there are limited data describing its distribution into the interstitial fluid (ISF) of tissues. The aim of this study was to describe the plasma and tissue ISF population pharmacokinetics of vancomycin in critically ill patients with sepsis. Serial vancomycin blood and ISF samples were collected at pre-specified time intervals in critically ill patients with sepsis. ISF sampling occurred using a subcutaneously inserted microdialysis catheter. Bioanalysis was undertaken using a validated spectrometric assay method. Population pharmacokinetic analysis was performed using Pmetrics<sup>®</sup>. Seven patients were recruited and pharmacokinetic data were available for six of them. The median (interquartile range) age, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score and measured creatinine clearance (CL<sub>Cr</sub>) were 55 (44–67) years, 85 (81–102) kg, 20 (16–29), 5 (4–8) and 90 (83–98) mL/min, respectively. Vancomycin pharmacokinetics was best described by a three-compartment linear model. Measured CL<sub>Cr</sub> (on vancomycin clearance) and weight (on volume of distribution of the central compartment) were the only patient covariates that improved the model fit. Coefficients of variation for the vancomycin rate constants into and out of the peripheral and tissue ISF compartments were also high, ranging from 47% to 134%. There is significant variability of vancomycin distribution into tissue ISF, which it was not possible to explain with patient characteristics.

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### 1. Introduction

Severe sepsis and septic shock account for a significant proportion of admissions to the intensive care unit (ICU) and are a leading cause of mortality in critically ill patients [1]. Early treatment with appropriate antimicrobial therapy is an important determinant of survival. However, conventional dosing strategies consistently fail to achieve therapeutic exposures in plasma owing

to altered drug clearance and volume of distribution in many critically ill patients [2–4]. Furthermore, the effect of critical illness on antimicrobial concentrations in the interstitial fluid (ISF) of tissues, the focus of most infections, is poorly understood [5,6]. Whilst it has traditionally been assumed that ISF antimicrobial concentrations are similar to those achieved in plasma, data from studies of  $\beta$ -lactam antibiotics have shown major differences between plasma and ISF exposures in critically ill patients. This potential lack of antimicrobial penetration into the ISF may have important implications for therapeutic efficacy [7,8].

Vancomycin, a bacteriostatic glycopeptide antibiotic, remains the most frequently used antibiotic in critically ill patients for the treatment of bacterial infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) [9]. Previous studies in patients

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following cardiac surgery or with traumatic brain injury have demonstrated reduced vancomycin penetration into ISF of the thigh and cerebral interstitial fluid [10,11]. However, the penetration of antibiotics in the context of severe sepsis cannot be extrapolated from the above studies in normal volunteers or diabetic patients to critically ill patients as the pathophysiological changes that occur in sepsis alter vancomycin pharmacokinetics [12]. There are limited data regarding the pharmacokinetics of vancomycin in critically ill patients with sepsis. In particular, the concentration of vancomycin in the subcutaneous ISF has not been reported by microdialysis [13,14]. The aim of the current study was to describe the plasma and tissue ISF population pharmacokinetics of vancomycin in critically ill patients with sepsis, using microdialysis to measure ISF vancomycin concentrations.

## 2. Methods

### 2.1. Setting

This prospective, single-centre, pharmacokinetic study was conducted in critically ill patients admitted to the ICU of The Queen Elizabeth Hospital (Adelaide, SA, Australia) between August 2011 and October 2013. Ethical approval was obtained from the Human Research Ethics Committee of The Queen Elizabeth Hospital. Prior informed written consent was obtained either from the patient or the patient's legally authorised representative before entry into the study.

### 2.2. Study population

Patients were eligible for enrolment in the study if they met all of the following inclusion criteria: (i) age  $\geq 18$  years and  $\leq 80$  years; (ii) documented evidence of sepsis at the time of enrolment; (iii) arterial and indwelling urinary catheters in situ or planned insertion; (iv) serum creatinine (SCr)  $< 180$   $\mu\text{mol/L}$ ; and (v) prescribed intravenous intermittent bolus dose vancomycin by the treating clinician. Sepsis was defined as the presence of a suspected or confirmed infection and two or more of the following systemic inflammatory response syndrome criteria documented in the previous 24 h: (i) core temperature  $< 36.0^\circ\text{C}$  or  $> 38.0^\circ\text{C}$ ; (ii) heart rate  $> 90$  beats/min; (iii) respiratory rate  $> 20$  breaths/min or partial pressure of carbon dioxide in the arterial blood  $< 32$  mm Hg, or the requirement for mechanical ventilation for an acute process; and (iv) white blood cell count of  $> 12.0 \times 10^9/\text{L}$  or  $< 4.0 \times 10^9/\text{L}$ , or  $> 10\%$  immature bands.

Patients with a suspected allergy to vancomycin or benzylpenicillin, prescribed continuous infusion of vancomycin or with a SCr  $> 180$   $\mu\text{mol/L}$  and those patients in whom consent could not be obtained prior to commencement of the study were excluded.

### 2.3. Study protocol

Vancomycin was initiated at the discretion of the treating physician based on the clinical requirement. Sampling occurred prior to administration of the third prescribed dose of vancomycin. Nine arterial blood samples (3 mL each) for plasma vancomycin measurement were obtained on each sampling day. Blood samples were drawn immediately prior to commencing vancomycin infusion and at 30, 60, 75, 90, 120, 240, 360 and 720 min post-commencement.

Clinical and demographic data included: (i) demographic data (age, sex, weight); (ii) severity of illness and organ injury scores [Acute Physiology and Chronic Health Evaluation (APACHE) II score calculated on data available for the 24 h prior to study enrolment and Sequential Organ Failure Assessment (SOFA) score]; and (iii) serum albumin concentration, SCr concentration and measured

creatinine clearance ( $\text{CL}_{\text{Cr}}$ ) on both sampling days.  $\text{CL}_{\text{Cr}}$  was assessed by performing an 8-h urine collection post-commencement of each vancomycin dose.

### 2.4. Microdialysis

A flexible microdialysis probe (CMA 60 microdialysis catheter; Dipylon Medical, Solna, Sweden) with a membrane length of 20 mm, an outer diameter of 0.6 mm and molecular weight cut-off of 20 000 Da was inserted prior to commencement of the third dose of vancomycin in preparation for sampling. The microdialysis probe was inserted into the subcutaneous tissue of the upper arm as previously described [7,15]. The microdialysis system comprised a microinfusion pump with benzylpenicillin (10 mg/L) perfusing as an internal standard at 1.5  $\mu\text{L}/\text{min}$ . Benzylpenicillin was chosen as the internal standard for analytical purposes. Following a 30-min equilibration period, microdialysis samples for determination of antibiotic concentrations in the soft tissue were collected at 20-min intervals between 0–2 h after starting the vancomycin infusion and then at 30-min intervals for the following 10 h. Microdialysate samples were stored in microvials at  $-80^\circ\text{C}$  until analysis.

Recovery of vancomycin in the microdialysate solution was interpolated from the loss of benzylpenicillin across the microdialysis membrane: % vancomycin recovery =  $100 \times (C_{\text{in}} - \text{mean } C_{\text{out}}/C_{\text{in}})$ , where  $C_{\text{in}}$  = benzylpenicillin 10 mg/L (perfusate) and  $C_{\text{out}}$  = measured benzylpenicillin concentration in the microdialysate [16]. Estimated concentrations from microdialysis samples were corrected using the in vivo recovery calculated for vancomycin prior to pharmacokinetic analyses with the following equation:  $C_{\text{ISF}} = 100 \times (C_{\text{microdialysate}}/\text{percent recovery in vivo})$ , where  $C_{\text{ISF}}$  is the drug concentration in ISF and  $C_{\text{microdialysate}}$  is the vancomycin concentration in the microdialysate.

### 2.5. Bioanalysis

Vancomycin in plasma was measured by high-performance liquid chromatography (HPLC) with ultraviolet detection on a Shimadzu Prominence system (Shimadzu Corp., Kyoto, Japan). Calibration standards and quality controls at three concentrations were assayed alongside clinical samples and were subjected to batch acceptance criteria [17]. The calibration was linear over the range 1–100  $\mu\text{g}/\text{mL}$ . The precision and accuracy at the lower limit of quantification (LLOQ) was  $\leq 13.4\%$ , and at three concentration levels over three separate occasions were  $\leq 4.5\%$ .

Vancomycin and benzylpenicillin in microdialysate were measured by a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method on a Shimadzu Nexera X2 LC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu Corp.). Calibration standards and quality control at three concentrations were assayed alongside clinical samples and were subjected to batch acceptance criteria. The calibration line was 0.2–100  $\mu\text{g}/\text{mL}$  for vancomycin and 0.5–100  $\mu\text{g}/\text{mL}$  for benzylpenicillin. The precision and accuracy at the LLOQ was  $\leq 13.2\%$  for vancomycin and  $\leq 17.6\%$  for benzylpenicillin. The precision and accuracy at three quality control levels were  $\leq 12.1\%$  for vancomycin and  $\leq 14.3\%$  for benzylpenicillin.

### 2.6. Population pharmacokinetic modelling

Two- and three-compartment models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the Pmetrics® package for R (Laboratory of Applied Pharmacokinetics and Bioinformatics, University of Southern California, Los Angeles, CA) [18]. Elimination from the central compartment and intercompartmental distribution into the ISF compartment and other

compartments were modelled as first-order processes using differential equations. Estimates of assay error were included in the modelling process. The area under the concentration–time curve from 0–24 h (AUC<sub>0–24</sub>) in plasma and ISF was also calculated by doubling the AUC from 0–12 h (AUC<sub>0–12</sub>), which was calculated using Pmetrics. Demographic and clinical characteristics (age, weight, CL<sub>CR</sub>) that were considered biologically plausible to affect vancomycin pharmacokinetics were tested for inclusion as covariates. If sequential inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood (*P* < 0.05) and/or improved the goodness-of-fit plots, then it was supported for inclusion. The vancomycin penetration ratio was calculated as the ratio of the observed AUC<sub>0–12</sub> in ISF relative to plasma.

2.6.1. Model diagnostics

The goodness of fit was assessed by visual inspection of the observed–predicted plot, the coefficient of determination of the linear regression of the observed–predicted values, and the log-likelihood values from each run. Predictive performance evaluation was based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models both in plasma and ISF compartments.

2.7. Statistical analysis

Descriptive statistics were used to describe patient clinical and demographic data, presented as the median [interquartile range (IQR)].

3. Results

Seven patients were enrolled in the study. Sampling for one patient was ceased at 8 h owing to the development of anuria and the requirement for commencement of renal replacement therapy. This patient was excluded from the pharmacokinetic analysis. The data presented relate to the remaining six patients. Four patients were male and the median APACHE II score at enrolment was 20 (IQR 16–29). The median (IQR) daily dose of vancomycin administered was 24.5 (19.2–26.1) mg/kg/24 h. Patient clinical and demographic details are summarised in Table 1.

3.1. Individual plasma and interstitial fluid concentrations

A total of 410 samples were collected (126 blood and 284 microdialysis). Plasma and ISF concentration–time data for the six patients are shown in Fig. 1. The median (IQR) total vancomycin AUC<sub>0–24</sub> in plasma was 346 (328–373) mg·h/L. The median (IQR) ISF vancomycin AUC<sub>0–24</sub> was 123 (90–148) mg·h/L. The median (IQR) in vivo vancomycin recovery rate for microdialysis was 36% (17–50%). Median (IQR) vancomycin ISF penetration was 0.37 (0.30–0.53).

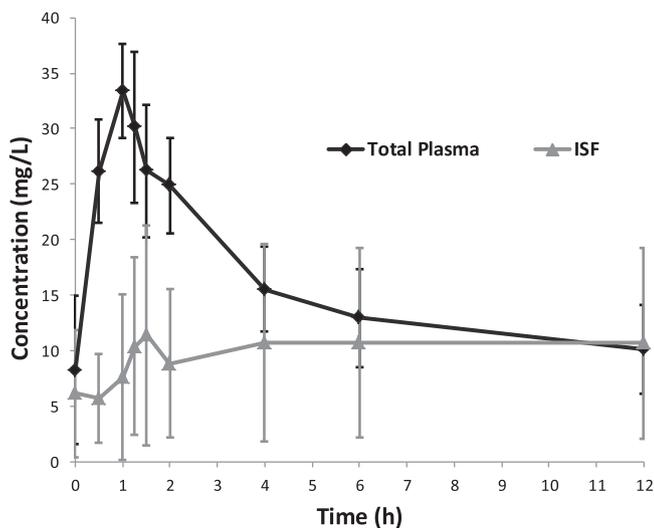
3.2. Population pharmacokinetic model building

The time course of total plasma and ISF concentrations of vancomycin was best described by a three-compartment linear model. This model included zero-order input of drug into the central compartment. The only covariates that improved the model fit with a statistically significant improvement in the log likelihood were: (i) CL<sub>CR</sub> normalised to 100 mL/min for vancomycin clearance and; (ii) total body weight normalised to 80 kg (to the power of 0.75)

Table 1 Patient characteristics and laboratory variables.

Patient	Age (years)	Weight (kg)	Diagnosis	APACHE II score	Vasopressor use (maximum/mean) (µg/h)	Ventilation	SOFA score	Fluid balance status (24 h to the study date) (L)	Serum albumin (g/L)	Vancomycin dose (mg/kg/24 h)	Measured CL <sub>CR</sub> (mL/min)
1	48	90	Staphylococcal bacteraemia	11	N/A	Yes	4	-0.5	37	33.4	170
2	77	83	Streptococcal bacteraemia	15	N/A	No	2	-1.2	20	24.1	98
3	73	85	Septic shock	21	7/3	Yes	8	+1.0	31	17.6	60
4	55	80	Acute osteomyelitis	17	22/14	No	5	+2.0	15	25.0	82
5	61	113	Staphylococcal bacteraemia	20	N/A	Yes	4	+1.8	20	26.5	84
6	39	157	Septic shock	37	20/13	Yes	8	+1.8	19	12.7	96
Median (IQR)	58.0 (49.7–70.0)	87.5 (83.5–107.2)		18.5 (15.5–20.7)		4 (67%)	4.5 (4–8)		20 (19.2–28.2)	24.6 (19.2–26.1)	90.0 (83.0–98.0)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CL<sub>CR</sub>, creatinine clearance; N/A, not applicable; IQR, interquartile range.



**Fig. 1.** Observed concentration–time profile of vancomycin in plasma and tissue interstitial fluid (ISF) on the first sampling interval (Day 1) in six critically ill patients with sepsis. Data are the mean  $\pm$  standard deviation.

**Table 2**

Parameter estimates for vancomycin from the final covariate three-compartment population pharmacokinetic model.

Parameter	Mean $\pm$ S.D.	CV (%)	Median	% shrinkage
CL (L/h)	3.33 $\pm$ 1.19	35.64	3.45	0
$V_c$ (L)	10.87 $\pm$ 3.73	34.32	9.75	0
$k_{ct}$ ( $h^{-1}$ )	9.17 $\pm$ 10.38	113.11	3.18	0
$k_{tc}$ ( $h^{-1}$ )	12.54 $\pm$ 16.77	133.77	1.11	0
$k_{cp}$ ( $h^{-1}$ )	2.28 $\pm$ 1.08	47.49	1.95	0
$k_{pc}$ ( $h^{-1}$ )	4.64 $\pm$ 5.46	117.64	2.82	0

S.D., standard deviation; CV, coefficient of variation; CL, vancomycin clearance;  $V_c$ , volume of distribution of the central compartment;  $k_{ct}$ , rate constant for drug distribution from the central to interstitial fluid compartment;  $k_{tc}$ , rate constant for drug distribution from the interstitial fluid to central compartment;  $k_{cp}$ , rate constant for drug distribution from the central to peripheral compartment;  $k_{pc}$ , rate constant for drug distribution from the peripheral to central compartment.

for volume of distribution of the central compartment. No patient characteristics could explain the variation in distribution rate constants. The final models were described as follows:

$$TVVCL = CL * CL_{Cr}/100 \text{ and } TVV_c = V_c * (wt/80)^{0.75}$$

where TVVCL is the typical value of vancomycin clearance, TVV<sub>c</sub> is the typical value of  $V_c$ , CL is the population parameter estimate of vancomycin clearance,  $CL_{Cr}$  is the measured creatinine clearance,  $V_c$  is the population parameter estimate of the volume of distribution of the central compartment and wt is total body weight.

The population pharmacokinetic parameter estimates from the final covariate model are shown in Table 2, and diagnostic plots to confirm model goodness of fit are shown in Figs 2 and 3.

#### 4. Discussion

These data suggest that vancomycin distributed incompletely, and highly variably, from plasma into subcutaneous ISF in this cohort of critically ill patients with sepsis.

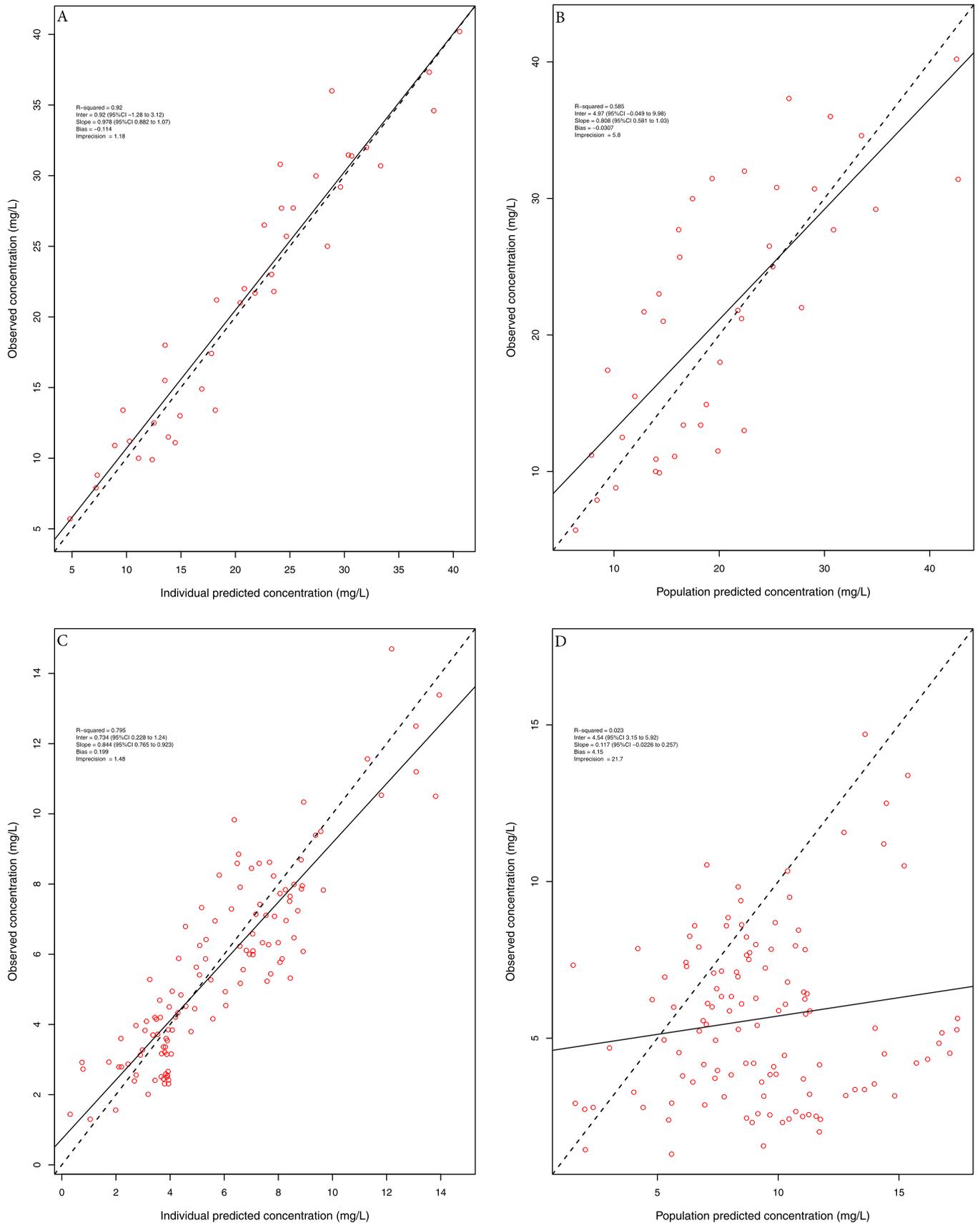
There is a paucity of studies investigating vancomycin penetration into subcutaneous ISF, and none from critically ill patients

with sepsis. In patients with diabetic lower-limb infections, Housman et al. reported a near complete distribution of vancomycin (mean  $\pm$  standard deviation  $fAUC_{ISF}/fAUC_{plasma}$  of  $0.8 \pm 0.2$ ) [19]. Skhirtladze et al. investigated steady-state vancomycin penetration into subcutaneous ISF in cardiac surgery patients with sternal wound infections [11]. In that study, the median (IQR) ISF to plasma vancomycin concentration ratio was 0.10 (0.01–0.45) in patients with diabetes (2 of 6 patients were on vasopressors and 3 were in the ICU) and 0.30 (0.46–0.94) in patients without diabetes (4 of 6 patients were on vasopressors and all were in the ICU). The observed ISF distribution ratio in the current study is similar to non-diabetic patients in the study by Skhirtladze et al. [11] [median (IQR) 0.37 (0.30–0.53) vs. 0.30 (0.46–0.94)]. Given the near complete ISF distribution in non-ICU diabetic patients and the reduced ISF distribution in patients with and without diabetes but receiving vasopressors and in the ICU may suggest that sepsis may have a role in reduced ISF distribution.

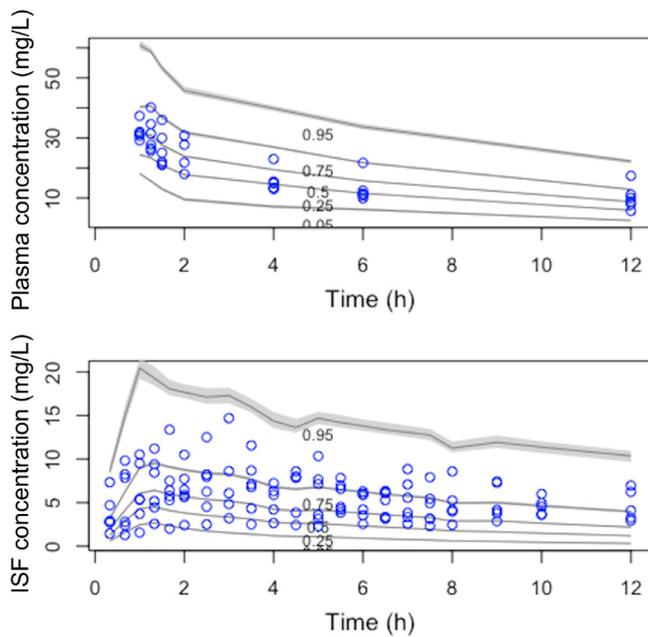
The current study cohort comprised severe sepsis patients with a high APACHE II score and evidence of organ dysfunction, with one-half to two-thirds of patients requiring vasopressors and/or invasive mechanical ventilation. There was significant interindividual variation in subcutaneous ISF penetration, with coefficients of variation for the vancomycin rate constants into and out of the peripheral and tissue ISF compartments ranging from 47% to 134% (Table 2). However, we could not find any correlation between ISF distribution and use of vasopressors, mechanical ventilation or fluid balance status. Previous microdialysis studies with piperacillin and fluconazole in similar patient cohorts have shown that these factors could play a role in the limited and heterogeneous subcutaneous ISF penetration of vancomycin observed in the current study [8,15,20]. Given the heterogeneous distribution and lack of readily identifiable clinical and pharmacokinetic factors to identify patients with reduced distribution into the ISF, it is suggested that care should be taken when adjusting doses based only on the measured plasma concentration.

There are some limitations to this study that should be declared. First, we have only provided pharmacokinetic data from six patients and, whilst this is not a large patient sample, the observed data demonstrate heterogeneous ISF distribution of vancomycin in patients with sepsis. Second, we did not measure the unbound concentrations of vancomycin in plasma, which may have provided a much stronger correlation with ISF concentrations. As such, we cannot rule out that possibility that impaired penetration of vancomycin is associated with altered protein binding. Third, the pharmacokinetics of vancomycin in the subcutaneous ISF peripheral site chosen for this study may be different from other sites such as intra-abdominal infection or within the epithelial lining fluid. However, for patient safety and comfort we considered these data to be useful, as have been used previously [7,20]. Finally, this study was not powered to assess the effect of antibiotic concentrations in the ISF on patient outcome, and a larger study would be required for this analysis.

In summary, it was found that vancomycin distributes incompletely from plasma into subcutaneous ISF with substantial variability between patients. Given the heterogeneous distribution and lack of clinically identifiable factors to recognise patients with reduced distribution and suboptimal therapeutic exposure, we recommend therapeutic drug monitoring-guided dosing aiming at concentrations at the higher end of the therapeutic range in an attempt to maximise ISF concentrations in critically ill patients with sepsis.



**Fig. 2.** Diagnostic plots for the final population pharmacokinetic covariate model in plasma and tissue interstitial fluid (ISF): (A) observed plasma vancomycin concentration versus individual predicted plasma vancomycin concentration ( $R^2 = 0.920$ ); (B) observed plasma vancomycin concentration versus population predicted plasma vancomycin concentration ( $R^2 = 0.585$ ); (C) observed ISF vancomycin concentration versus individual predicted ISF vancomycin concentration ( $R^2 = 0.795$ ); and (D) observed ISF vancomycin concentration versus population predicted ISF vancomycin concentration ( $R^2 = 0.023$ ).



**Fig. 3.** Visual predictive checks ( $n=1000$  simulations) of plasma (top panel) and tissue interstitial fluid (ISF) data (lower panel) (open circles represent observed data and the lines represent the 5th, 25th, 50th, 75th and 95th percentiles based on simulations of the pharmacokinetic model).

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### Competing Interests

None declared.

### Ethical Approval

Ethical approval was obtained from the Human Research Ethics Committee of The Queen Elizabeth Hospital.

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