

*Teaching Point*  
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## Treatment of paediatric vancomycin intoxication: a case report and review of the literature

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### Introduction

Vancomycin is a 1.5-kDa molecular weight tricyclic glycopeptide antibiotic with a volume of distribution of 0.2–1.25 L/kg. It is primarily cleared by the kidneys. The half-life ( $T_{1/2}$ ) of vancomycin in patients with normal renal function is 4–6 h [1] and is prolonged to 54–180 h in patients with end-stage renal disease [2]. Most reported vancomycin intoxications occur because the patient's renal function declines while on treatment. Without appropriate dose adjustments, plasma vancomycin concentration inevitably rises. Prescription and/or administration errors account for the majority of additional cases. In general, children may be more at risk than adults for such a mishap [3]. An association with the concomitant use of other nephrotoxins, particularly aminoglycosides, is often noted [4]. A significant proportion of reported adult and paediatric cases have pre-existing renal pathology [5].

Several options for the treatment of vancomycin overdose have been described in the literature. These include supportive care, acute intermittent haemodialysis with high-flux dialysis membranes (AIHD<sub>HF</sub>), charcoal haemoperfusion, continuous renal replacement therapy (CRRT) and gastric dialysis with multiple-dose activated charcoal (MDAC). If renal function is well preserved and plasma vancomycin concentration is not markedly elevated, management with supportive care and optimization of diuresis to enhance renal vancomycin excretion has been successful [6]. When there is evidence of established renal dysfunction, the therapeutic approach should be more definitive. However, no clear threshold for the initiation of renal replacement therapy (RRT) has been defined, either in terms of the degree of renal dysfunction or plasma vancomycin levels.

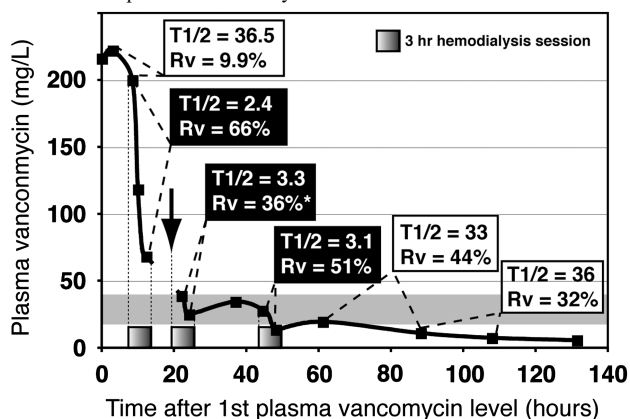
This case report focuses on the management of an infant who suffered an iatrogenic vancomycin overdose. It is accompanied by a summary of all previously published paediatric cases of vancomycin intoxications to illustrate the range of therapeutic options and associated outcomes. Altogether, it provides a useful guide for physicians faced with a similar situation.

### Case history

We report a case of iatrogenic vancomycin intoxication in a 3.3-kg premature infant with normal baseline renal function, with peak levels of plasma vancomycin ( $P_{\text{Vanco}}$ ) of 222 mg/L. The 31-week gestational age infant was 72 days old at presentation, giving a corrected age of 9 days. The inadvertent overdose period lasted 5 days, during which a total of 6000 mg of vancomycin was administered, instead of the intended 600 mg, due to a dispensing error. Plasma creatinine ( $P_{\text{Creat}}$ ) doubled from 38 to 78  $\mu\text{mol/L}$ , without any electrolyte disturbance. Urine output was well maintained (2–3 cc/kg/h). Vancomycin had been prescribed to treat multi-focal osteomyelitis, along with intravenous (IV) cefotaxime (150 mg/kg/day divided three times a day). The infant was also on empiric IV amphotericin B (1 mg/kg/day) for presumed renal fungal balls, diagnosed on renal ultrasound. Transfer to our institution for further management was organized shortly after discovery of the error.

### Treatment and management

RRT for our patient was considered early on for a variety of reasons. First, despite 'normal' urine output,  $P_{\text{Creat}}$  had doubled, indicating that the glomerular filtration rate (GFR) was reduced compared to baseline. Second, the calculated endogenous vancomycin removal from the in-



**Fig. 1.** Dynamics of vancomycin removal following three sessions of acute intermittent haemodialysis with a high-flux dialysis membrane. The half-life ( $T_{1/2}$ ) and percentage of plasma vancomycin removed ( $R_v$ ) are indicated for the various time intervals. White boxes indicate removal of plasma vancomycin via endogenous processes (renal) and the black boxes indicate removal during each 3-h haemodialysis session. The shaded area represents the therapeutic window for vancomycin. The downward arrow shows the time at which the second dialysis session was started as no pre-treatment vancomycin level was drawn. The asterisk indicates that the data are not representative of the whole session.

travascular compartment ( $R_v$ ) was 9.9% and the half-life ( $T_{1/2}$ ) was 36.5 h: both were markedly abnormal (normal  $T_{1/2}$  is 4–6 h) despite optimization of urine output with administration of isotonic saline, as per Panzarino *et al.*

[7]. Third, this infant was also on conventional amphotericin B, a well-known nephrotoxin. Amphotericin B was replaced by IV fluconazole (6 mg/kg/day), which is less nephrotoxic. IV cefotaxime was continued, and the dose adjusted for reduced renal function.

A right internal jugular vein 6-Fr double lumen Gam-Cath™ was inserted 3 h later. The parameters of the initial dialysis prescription are detailed in Table 2 ('New'). The infant was dialysed with a Fresenius™ 2008K dialysis machine using a high-flux dialysis membrane Fresenius™ F-40 (45 mL). Neonatal arterial (8 mL) and paediatric venous (25 mL) lines were used. As the total extracorporeal circuit volume (75 mL) was more than 10% of the patient's blood volume, blood priming with reconstituted packed red blood cells with a target haematocrit of 30–50% was used for all sessions. The blood flow rate ( $Q_B$ ) was 6 mL/kg/min and the dialysate flow rate ( $Q_D$ ) was 300 mL/min, with no ultrafiltration. Anticoagulation was provided with unfractionated heparin, with an initial heparin bolus of 10 IU/kg, followed by an infusion of 10 IU/kg/h adjusted to a target activated clotting time of 160–200 s. The composition of the dialysate was as follows: sodium 150–140 mmol/L with linear ramping, potassium 4 mmol/L, bicarbonate 35 mmol/L, calcium 1.25 mmol/L and phosphate 1 mmol/L. Three sessions were required in order to reduce the vancomycin levels to sub-therapeutic (Figure 1). All sessions were well tolerated and the vascular access performed well.

**Table 1.** Characteristics of this case and eight other paediatric cases from the literature

	Treatment modalities								
	AIHD <sub>HF</sub>					CH-H	CVVH	GD + MDAC	
Case ID	New	1	2	3	4	5	6	7 <sup>a</sup>	8
Age	3 months	–	–	9 years	8 years	14 months	14 years	47 days	17 days
Gender	M	F	M	F	M	F	M	M	F
Weight (kg)	3.3	22	5.6	17	27	8	39	1.2	4.2
Underlying diagnoses	P31	LT	Nil	CF	VPS	PBS	VPS	P35	AM
Prior renal disease	Nil	Nil	OU, RD	Nil	Nil	RD	Nil	Nil	Nil
Vancomycin peak (mg/L)	222	345	313	420	45.8	337	250	427	168
Baseline half-life (hours)	36.5	67.2	31	216	–	145	53	35	–
Vancomycin assay used	EMIT	–	–	–	–	FPIA	FPIA	EMIT	–
Other medications	Cftx, AmB	Nil	Gent	Gent	Cftx, Clox	Gent	Cftx, Rif	Gent, Amp	Cftx, Amp
Baseline creatinine (μmol/L)	38	–	–	–	33	309	53	27	62
Peak creatinine (μmol/L)	82	282	88	650	500	466	580	123	'N'
Urine output	NO	O	NO	NA	MO	NA	O	NO	NO
Mechanism of intoxication	IO	S	IO	IO	PPVT	IO	DRF	IO	IO
Renal outcome	N-2	–	–	N-1	ND	DD	ND	ND	ND
Otologic outcome	N-4	–	–	–	–	N-4	–	ND	ND
Reference	Herein	10	10	11	12	7	13	15	16

The en-dash indicates not mentioned in the original article.

Therapy: AIHD<sub>HF</sub>, acute intermittent haemodialysis with high-flux dialysis membrane; CH-H, charcoal haemoperfusion and haemodialysis; CVVH, continuous veno-venous haemodialysis; GD + MDAC, gastric dialysis with multiple-dose activated charcoal.

Diagnoses: P, prematurity (following number = number of weeks at birth); LT, liver transplantation; CF, cystic fibrosis; PBS, prune belly syndrome; VPSI, ventriculoperitoneal shunt; AM, Arnold–Chiari malformation.

Prior renal disease: OU, obstructive uropathy; RD, renal dysplasia. Vancomycin assay: EMIT, enzyme-multiplied immunoassay technique, Sylva Corp.; FPIA, fluorescence polarization immunoassay, AxSYM, Abbott.

Other medications: Acy, acyclovir; AmB, amphotericin B; Amp, ampicillin; Cftx, cefotaxime; Clox, cloxacillin; Gent, gentamicin; Rif, rifampin.

Urine output: NO, not oliguric; NA, not anuric; O, oliguric.

Mechanism of intoxication: IO, iatrogenic overdose; S, sepsis; DRF, decreased renal function unrelated to vancomycin; PPVT, presumed primary vancomycin toxicity.

Outcomes: N, normal (number indicates number of months since overdose); DD, dialysis dependent; ND, normal at discharge.

<sup>a</sup>This patient was also treated with 1.5 blood volume exchange transfusion.

**Table 2.** Characteristics of the different types of RRT prescriptions

	Treatment modalities						
	AIHD <sub>HF</sub>					CH-H	CVVH
Case ID	New	1	2	3	4	5	6
CVL site	Right internal jugular	Femoral	Femoral	Femoral	–	Femoral	Right subclavian
CVL type	6.0-Fr GamCath	9.0-Fr Cook	7.0-Fr Cook	9.0-Fr MedComp	–	2 × 9.6-Fr Hickman	11.5-Fr
Dialyser used	Fresenius 2008K	Baxter 550	Baxter 550	Gambro AK-100	–	–	–
Dialysis membrane	Fresenius F-40	Baxter CT110	Baxter CT110	Toray BK-F 1.3	Optiflux 200	Mini-Minor cartridge	HF 700 Renaflo Haemofilter
Kuf (mL/mmHg/h)	20	25	25	26	56	1–8	?
Type of membrane	PS	CTA	CTA	PMMA	PS	PS	PS
Surface area (m <sup>2</sup> )	0.7	1.1	1.1	1.3	2.0	0.08	0.71
Blood flow (mL/kg/min)	6	5	12	6	–	7.5	3.9
Dialysis flow (mL/min)	300	500	500	–	–	N/A	N/A
Ultrafiltration rate (mL/h)	0	–	–	1000	–	–	1800
Number of sessions	3	3	2	2	3	2	1
Duration (h)	3	3	3	4	4	4	38
Extracorporeal circuit volume (mL)	75	165	165	150	–	240	–
Priming	Blood	Blood	Blood	0.9% NaCl	–	Blood	–
Vancomycin removal ( $R_V$ ) (%)	66	67	60	73	79	42	85
Vancomycin $T_{1/2}$ (h)	2.4	1.9	2.3	2	–	12.5	13.7
Vancomycin rebound	Yes	Yes	No	No	Yes	–	No
Reference	Herein	10	10	11	12	7	13

The en-dash indicates not mentioned in the original article.

Therapy: AIHD<sub>HF</sub> acute intermittent haemodialysis with high-flux dialysis membrane; CH-H, charcoal haemoperfusion and haemodialysis; CVVH, continuous veno-venous haemodialysis.

Types of membrane: PS, polysulphone; CTA, cellulose triacetate; PMMA, polymethylmethacrylate.

### Short-term and long-term outcomes

The best  $R_V$  (66%) and  $T_{1/2}$  (2.4 h) were observed during the first treatment session (Figure 1). The initial  $Q_D$  of 300 mL/min was chosen to avoid excessive clearance of other plasma constituents, especially phosphate. Since the initial  $R_V$  and  $T_{1/2}$  observed were in the same range as that reported in the literature for AIHD<sub>HF</sub>,  $Q_D$  was not increased to 500 mL/min (Table 2; Cases 1–3). The only documented rebound in  $P_{\text{Vanco}}$  was noted between the second and third dialysis sessions (Figure 1).

$P_{\text{Creat}}$  remained abnormally elevated at 50  $\mu\text{mol/L}$  at the time of discharge home 5 days after initiation of dialysis (Figure 1). When repeated 2 months later, it was at the upper limit of normal for age at 35  $\mu\text{mol/L}$ . A normal hearing test was documented at 4 months corrected age.

### Literature review

A literature search was performed in Ovid Medline using the keywords: ‘clearance’, ‘dialysis’, ‘overdose’, ‘nephrotoxicity’, ‘renal replacement therapy’ and/or ‘vancomycin’. All potential articles were obtained and assessed for relevance, and the reference list of all chosen reports was also reviewed. Finally, ISI Web of Science was used to find relevant reports citing the articles identified. Both electronic resources were last accessed on 5 December 2009. Using this methodology, we identified 13 paediatric cases of

vancomycin overdose who were not on dialysis at baseline. The adult literature on this topic is scant (see Supplementary Table 1). The patient characteristics and the details of the renal replacement therapies instituted (if applicable) are presented in Tables 1 and 2, respectively.

$R_V$  obtained with older, low-flux dialysis membranes was historically low because of its relatively large molecular weight [8]. The emergence of high-efficiency dialysis membranes in the past 10 years has literally revolutionized the management of these patients, with reported  $R_V$  of at least 25–50% [9]. Based on the plasma  $R_V$  and  $T_{1/2}$  reported (Cases 1–4), it is clear that AIHD<sub>HF</sub> is superior to the other treatment modalities when the patient is haemodynamically stable [10–12]. Continuous veno-venous haemofiltration (CVVH) also shows acceptable  $R_V$  and  $T_{1/2}$  (Case 6) [13].

Other modalities have been described. For example, recent reports show that supportive measures may be used, even for premature infants (see Supplementary Table T2; Cases 9–13). Charcoal haemoperfusion, used in series with a low-flux dialysis membrane, has been described [14]. Panzarino and colleagues reported the first successful application of this treatment for an 8-kg infant (Table 1; Case 5) [7]. A significant drawback of this therapy for children is the large extracorporeal blood volume required. Gastric dialysis with MDAC, which decreases the half-life of vancomycin, has also been successful in infants with decreased baseline renal function (see Supplementary Table T3; Cases 7 and 8) [15,16]. While cumbersome and time

consuming, this approach can provide significant  $R_V$  and a  $T_{1/2}$  that is similar to that obtained with CRRT. Exchange transfusion with 1.5 blood volume equivalent was ineffective at clearing  $P_{\text{Vanco}}$  in one reported case of vancomycin overdose [15].

One significant drawback of the data available is that long-term renal and otologic outcomes are not mentioned by most authors. It is, therefore, difficult to assess and/or compare the degree of success of each methodology.

From the published literature, the profile of children at risk for vancomycin overdose deemed severe enough to require RRT is as follows: an infant without pre-existing renal disease, prescribed an aminoglycoside with or without a cephalosporin and who receives an iatrogenic overdose of vancomycin resulting in plasma vancomycin levels of approximately 300 mg/L.

## Discussion

The main justification for aggressive therapy of vancomycin overdose is to reduce the likelihood of vancomycin-induced long-term nephrotoxicity and ototoxicity. These issues are particularly important for infants and young children. The data shown suggest that, when faced with a child of any age with significant renal dysfunction and markedly elevated  $P_{\text{Vanco}}$ , either AIHD<sub>HF</sub> or CRRT, if haemodynamically unstable, are the most reasonable therapeutic interventions if vascular access is feasible. Otherwise, gastric dialysis with MDAC or even close monitoring with supportive care may be valid options.

The  $R_V$  and  $T_{1/2}$  obtained with the regimen prescribed for our patient were similar to that reported by Bunchman (Cases 1 and 2) and Ulinski (Case 3). This similarity is notable since so many parameters were different, including the patient's characteristics, the dialysis membranes used, the blood flow and dialysate flow rates prescribed and even the duration of individual treatments. One explanation is that the dialysis dose prescribed exceeded the potential for  $R_V$  during the treatment sessions. Near the end of therapy, the tissue-bound vancomycin pool may be redistributed to the intravascular compartment at a rate similar to that of the dialyser's ongoing vancomycin removal. The significant post-dialysis vancomycin rebound that is observed in most patients is thought to reflect this large extravascular pool [17,18]. Therefore, for short treatments, the final vancomycin concentration may be fixed. Analysis of published studies suggests that neither  $Q_B$  nor  $Q_D$  are predictive of  $R_V$ ; the parameters of importance were body weight and duration of dialysis in one study [19] and dialyser surface in another [20]. One significant limitation of this analysis is that calculations done for our case and Case 3 were performed with samples drawn immediately post-treatment, whereas they were drawn 3 h after therapy for Cases 1 and 2 to account for the possibility of rebound.

In adult patients on chronic AIHD<sub>HF</sub> treated with vancomycin, nearly 100% of patients have an average documented rebound of 35% above the immediate post-treatment  $P_{\text{Vanco}}$ , with the peak plasma vancomycin concentration occurring 2–12 h after dialysis [21]. The fact that vanco-

mycin rebound was noted in only three patients in our series (Table 1) most likely reflects under-sampling or variability in sampling methodology. Since most patients still had deranged renal function after the first treatment, the expectation is that the plasma vancomycin should plateau or increase preceding the next dialysis session. In most cases, it was in fact lower than the preceding post-dialysis level, suggesting that endogenous (but sub-optimal) residual renal function was able to handle the vancomycin shifts from tissue stores. An alternative explanation is that vancomycin pharmacodynamics in infants are distinct from that of adults in terms of redistribution of the tissue-bound fraction.

## Conclusions

For paediatric patients with a vancomycin overdose associated with concomitant renal dysfunction, the therapeutic modality of choice should be AIHD<sub>HF</sub> unless contraindicated because of the patient's characteristics or clinical context. This therapeutic dilemma may become more frequent for paediatric nephrologists if the recent trend of increased prevalence of methicillin-resistant *Staphylococcus aureus* infections continues unabated [22,23].

## Teaching points

- (1) There are no precise threshold values of  $P_{\text{Vanco}}$  and  $P_{\text{Creat}}$  to dictate the initiation of definitive therapy after a vancomycin overdose.
- (2) If definitive treatment is deemed necessary by the treating physician, the therapeutic modality of choice should be AIHD<sub>HF</sub>.
- (3) If AIHD<sub>HF</sub> is contraindicated because of the patient's characteristics or clinical context, supportive treatment may be an acceptable alternative.
- (4) Evidence of nephrotoxicity and ototoxicity should be sought at least 2–3 months after vancomycin intoxication.

*Conflict of interest statement.* None declared.

## Supplementary data

Supplementary data is available online at <http://ndt.oxfordjournals.org>.

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