

Bon Secours Richmond
Pharmacy and Therapeutics Committee
Vancomycin Dosing & Monitoring High Flux Dialysis

Recommendations:

- Administered vancomycin after high flux hemodialysis (HFD)
- Loading dose 25 mg/kg (dry weight) during or after HFD
- Maintenance dose: 500 mg at the end of each HFD
- Monitor the trough before the third dose of 500 mg and periodically thereafter.
- Adjust the dose to maintain troughs of approximately 15-20 mcg/ml.
- The recommended goal trough is 15-20 mcg/ml for hemodialysis patients
- Vancomycin levels should not be drawn within 6 hours after HFD session and are not recommended to be drawn post dialysis in general as the time to peak serum level rebound varies considerably. PreHFD troughs are recommended.
- Pharmacists will note the following on the kinetic monitoring form:
 - Dialysis dates, length of dialysis, name of dialysis filter, pre and end dialysis BUNs and weights. This data will be utilized to assess the dosing protocol and adjust the recommendations.

Findings:

- High flux dialyzer membranes include:
 - Gambro Polyflux 11S, Polyflux 14S, Polyflux 17S, Polyflux 21S, Polyflux 24S
 - Fresenius (polysulfone): F40, F50, F-60A or B, F-80A or B, F50NR, F160NR, F180NR, F200NR, F180A, F200A
 - Toray (polymethylmethacrylate): BK2.1U
 - Hospal (Sulfonated polyacrylonitrile): Biospal, Filtral 12, Filtral 16
 - Baxter (cellulose triacetate): CT-110, CT-190, Exeltra 150, Exeltra 170, Exeltra 190,
- High flux dialyzers allow passage of molecular species up to 5,000 daltons.
- Low flux dialyzer membranes include: (Cuprophane, cellulose acetate, Fresenius (polysulfone-small pore size) F8
- Low flux membranes have smaller pores and lower ultrafiltration coefficients than high flux membranes.
- Hemodialysis membranes vary in composition, surface area, water permeability, and the efficiency with which they remove urea and higher-MW solutes.
- Dialyzer membranes in general
 - Cellulose: free surface hydroxy groups on membrane surface activate complement system in blood flowing through dialyzer. Activation of complement is proportional to dialyzer surface area.
 - Substituted cellulose: biocompatibility is increased
 - Cellulosynthetic: biocompatibility is increased
 - Synthetic: membranes are not cellulose based, and material used include polyacrylonitrile (PAN), polysulfone, polycarbonate, polyamide, and polymethylmethacrylate (PMMA).
- Total priming volume of the extracorporeal circuit is 160-270 ml.
- Solutes pass across a semi permeable membrane by two methods.
 - **Diffusion:** movement of solutes by diffusion is the result of random molecular motion.
 - Concentration dependent
 - Pore size dependent
 - Solute size dependent
 - Membrane thickness dependent
 - Protein binding dependent
 - **Convection or ultrafiltration:** Water driven by hydrostatic or osmotic force is pushed across the membrane. Solutes that can easily pass through the membrane pores are pulled along with the water at close to their original concentrations. Convection can be increased by increasing the hydrostatic pressure gradient across the dialysis membrane or by using a more permeable dialyzer. Solutes will be removed along with water if the pores in the dialyzer are large enough to allow them to pass.
- **Solute removal during hemodialysis focuses on urea.**
- **Ultrafiltration coefficient** (Kuf (ml/hr/mm Hg)): water permeability of membrane, rate of ultrafiltration is usually limited by a ultrafiltration controller. Function of membrane thickness, pore size, and protein binding. All solutes below pore size are removed at same rate. Usually 1-4 kg of fluid is removed per dialysis session if three times a week dialysis is given.
- **KoA dialyzer mass transfer coefficient for urea**, is a measure of dialyzer efficiency in clearing urea and solutes of similar molecular weight. It is the theoretical clearance of the membrane in ml/min at infinite blood and dialysate flow rates. It is proportion to surface area of the dialyzer.
 - < 500 low efficiency or use for small patients
 - 500-700 moderate-efficiency routine therapy

- > 700 high efficiency or use for large patients
- Flow rates
 - Standard dialysis solution flow rate is 500 ml/min
- Weight gain per day, goal not greater than 1 kg/day. Limit salt intake as fluid intake usually follows salt intake.
- Membrane permeability to solutes and to water can be altered markedly by adjusting the thickness of the membrane and pore size.
- **High efficiency dialyzer** is basically a big dialyzer that by virtue of its high surface area has a high ability to remove urea. The dialyzer may have small or large pore with low or high clearance of large molecular weight substances.
- **High flux dialyzers** have large pores, which allow large molecules to pass. High flux membranes also have high water permeability with coefficient of ultrafiltration (Kuf) usually greater than 20 ml/hr/mm Hg. The clearance of B12 is high > 100 ml/min.
 - Cellulose diacetate/triacetate
 - Polysulfone, make be either high or low flux depending on manufacturing process
 - Polyacrylonitrile (PAN)
 - Polymethylmethacrylate (PMMA), make be either high or low flux depending on manufacturing process
- Blood water urea clearance (Kw)
 - Determined by (in descending order of importance)
 - Efficiency of dialyzer:
 - Blood flow rate:
 - Dialysis solution flow rate
- Vancomycin concentrations rebound after HFD, as vancomycin redistributes from the peripheral compartment into the central compartment once dialysis is complete. The peak post HFD serum concentration occurs hours (≥ 6 hours) after dialysis. Post dialysis rebound does not occur with low flux dialyzers.
- Drug removal estimated from the decline in plasma levels during HFHD that does not account for rebound of vancomycin levels over estimates dialytic clearance and supplemental dosage needs. All studies that measured dialysate concentrations showed that serum level data overestimated vancomycin clearance. Trough levels are therefore recommended to monitor therapy.
- Low flux dialysis is primarily diffusion based and is efficient in removing solutes of low-molecular-weight (<500 daltons) such as urea, creatinine, electrolytes and many drugs. Diffusional solute removal is dependent on molecular size and the relative pore size of the dialysis filter. Conventional hemodialysis is not very effective in removing solutes of larger molecular weight.
- The rate of diffusion depends on the difference between the concentrations of solute in blood and dialysate, solute characteristics, the dialyzer composition, and blood and dialysate flow rates.
- **Convection or ultrafiltration** (ml H_2O /hour/mmHg) is the primary means for removal of excess body water. Convection can be increased by increasing the hydrostatic pressure gradient across the dialysis membrane or by using a more permeable dialyzer. Solutes will be removed along with water if the pores in the dialyzer are large enough to allow them to pass.
- In conventional or standard hemodialysis, low- permeability (low to medium-flux) membranes are used and diffusion is the primary mechanism by which uremic waste products such as urea are removed for the patient. Blood flows through the dialyzer at rate of 200-350 ml/min, and the dialysate flow rate is generally fixed at 500 ml/min. Under this set of conditions the clearance of urea by the dialyzer rarely exceeds 200 ml/min, and a 4-5 hour session is required to deliver the desired amount of dialysis.
- High flux dialysis blood flow rates are typically > 400 ml/min, dialysate flow rates are greater than 500 ml/min, and urea clearances usually are in excess of 250 ml/min. Sessions are usually 2-3 hours 3 times per week.
- The clearance of low molecular weight solutes during HFD is increased dramatically due to higher blood and dialysate flow rates and ultrafiltration (convection). Middle and high-molecular weight solutes are cleared at a higher rate because of large pore size (> 70 angstroms) and the higher ultrafiltration coefficient (Kuf); usually (20-60 ml/h/mm Hg).
- The desired dose of dialysis can be expressed as:
 - Urea-reduction ratio (URR), (predialysis BUN-postdialysis BUN)*100/predialysis BUN
 - Does not account for convection removal of urea and postdialysis rebound
 - Does not account for urea following a two compartment model kinetics
 - Urea is sequestered in muscle
 - Kt/V , dialyzer clearance of urea (liters/hr)* T (duration of dialysis in hours) / V(volume of distribution of urea in liters)
 - After the desired Kt/V is selected for a patient, the duration of each treatment (t) can be calculated using the formula. Note: larger patients will require a long duration of HFD due to the increase in V.
 - Volume of distribution of urea (dry weight is postdialysis)
 - $V(l)\text{males} = [0.195 * \text{height}(\text{inches}) * 2.54 \text{ cm/inch}] + [0.297 * \text{dry weight}(\text{kg})] - 14.01$
 - $V(l)\text{female} = [0.345 * \text{height}(\text{inches}) * 2.54 \text{ cm/inch}] + [0.184 * \text{dry weight}(\text{kg})] - 35.27$
 - K is dependent on blood flow rate, Koa of dialyzer, and dialysate flow rate
 - High efficiency dialyzer (Koa > 700) are needed to obtain a substantial increase in clearance (K) with higher blood flow rates
 - **effective Kt/V** corrects Kt/V formula to account for dilution of body BUN by returning fluid from dialyzer, urea generated during dialysis, ultrafiltrate removal, and urea rebound post dialysis.
 - $eKt/V_{\text{arterial access BUN sampling}} = \text{sp}Kt/V - [0.6 (\text{sp}Kt/V) / t(\text{dialysis time hours})] + 0.03$

- $$spKT/V = -\ln(\text{PostHFDBUN}/\text{preHFDBUN} - 0.008) + (4 - 3.5 * (\text{PostdialysisBUN}/\text{predialysisBUN})) * 0.55 * (\text{kg preHFD} - \text{kg postHFD})/V$$

If one assumes Vd of BUN = 0.55 l/kg above simplifies to

$$spKT/V = -\ln(\text{PostHFDBUN}/\text{preHFDBUN} - 0.008) +$$

$$(4 - 3.5 * (\text{PostdialysisBUN}/\text{predialysisBUN})) * (\text{kg preHFD} - \text{kg postHFD})/\text{kg postHFD}$$

- Summary of literature (High Flux Dialysis):

- Studies have analyzed serum levels when vancomycin was administered either during or after HFHD with levels through subsequent dialysis sessions using one compartment or two compartment pharmacokinetic equations. Several studies measured vancomycin levels in dialysate and total dialysate clearance. Doses of vancomycin administered have included:

- DeSoi (5 patients cross over study with 3 HF & 1 low flux dialyzer membrane, 3-4 hour HFHD cycles): 1 gm post dialysis and 1 gm over 1 hour starting 30 minutes prior to end of dialysis. Approximately 26% removed by next HFHD cycle when dosed post dialysis, using serum level data.
 - Pollard (12 patients monitored for three HFHD cycles, Kt/V 1.29): 20 mg/kg post dialysis. Approximately 17% removed per subsequent HFHD cycle (dialysate data)
 - Touchette (8 patients, 2.5 hour HFHD): 250-1000 mg post dialysis. Approximately 250 mg (16.3%) removed in one HFHD session (dialysate data).
 - Barth (130 course of therapy, 3.3 hour HFHD, URR 64%): 20 mg/kg loading dose post dialysis and 500 mg after each HFHD
 - Scott (8 patients): 1 gm during last hour of HFHD compared to 1 gm after HFHD
 - Schaedeli (26 patients, 6 dialyzer membranes, 3.6 hour HFHD, 1.24 Kt/V): 500 or 1 gm after hemodialysis. Vancomycin removal as % of total body stores ranged from 12-22% per HFHD session depending on the length of dialysis and Kt/V. Sixteen percent removal is expected for typical Kt/V rates.
 - Foote (5 patients, 4 hour HFHD): 25 mg/kg during HFHD at 1 gm/hour to complete with end of dialysis. 45% of the dose was recovered in the dialysate during infusion of dose.
 - Mason (9 patients, 3-4 hour HFHD, URR 70%): 15 mg/kg post dialysis compared to 15 mg/kg or 25 mg/kg during HFHD

- Dosing recommendations for the studies include:

- Pollard: 20 mg/kg after HFD with 15 mg/kg every 7 days post dialysis
 - Touchette: 1000 mg every week and 250 mg after each HFD
 - Barth: 20 mg/kg loading dose post HFHD and 500 mg after each HFD. This dose may be too high as 27% of troughs were above 20 mcg/ml.
 - Schaedeli: 1 gm loading dose after HFD and 1 gm maintenance repeated as needed based. A model based on patients creatinine clearance and Kt/V of each hemodialysis session to determine loss of vancomycin was presented.
 - Foote: 25 mg/kg during HFD, repeat dose in approximately 7 days.
 - Mason: 15 mg/kg post dialysis or 30 mg/kg during the last 2 hour of dialysis every 7 days

- Monitoring Methods

- If the loading dose is given post dialysis, subsequent predose troughs may be used to calculate the overall elimination rate constant (including elimination associated with HFD) and the need for a repeat dose.
 - If doses are given during/after each HFD then serial troughs may be used to adjust the dosing frequency and/or dose to maintain therapeutic levels.

Continuous Renal Replacement Therapies

Definitions for continuous renal replacement therapies (A Primer on Continuous Renal Replacement Therapy for Critically Ill Patients Ann Pharmacother 1988;32:362-75)

- The first letter A or V is the source of blood from the patient to the dialyzer. The second letter is the return site of blood from the dialyzer to the patient.

Technique	Convection (Ultrafiltration)	Diffusion (Dialysis)	Blood Source	Blood Return	Qf = ultrafiltrate flow rate Qd = dialysate flow rate K= urea clearance	Fluid Replacement
SCUF Slow Continuous Ultrafiltration	+		Large Vein	Large Vein		0
CAVH Continuous Arteriovenous hemofiltration	++++		Artery	Vein	Qf 8-12 ml/min K 11-17 liters/day	+++
CVVH Continuous Venovenous Hemofiltration	++++		Large Vein	Large Vein	Qf 10-20 ml/min K 14-28 liters/day	+++
CAVHD Continuous Arteriovenous Hemodialysis	+	++++	Artery	Vein	Qf 2-5 ml/min Qd 10-20 ml/min K 14-28 liters/day	+/0
CVVHD Continuous Venovenous Hemodialysis	+	++++	Large Vein	Large Vein	Qf 10-20 ml/min Qd 10-30 ml/min K 14-36 l/day	+/0
CAVHDF Continuous Arteriovenous Hemodiafiltration	+++	+++	Artery	Vein	Qf 2-10 ml/min Qd 10-30 ml/min K 15-40 l/day	++
CVVHDF Continuous Venovenous Hemodiafiltration	+++	+++	Large Vein	Large Vein	Qf 2-10 ml/min Qd 10-30 ml/min K 15-40 l/day	++
CAVHFD Continuous Arteriovenous High Flux Dialysis	++	++++	Artery	Vein	Qf 0-5 ml/min Qd 20-100 ml/min K 15-60 l/day	+/0
CVVHFD Continuous Venovenous High Flux Dialysis	++	++++	Large Vein	Large Vein	Qf 0-5 ml/min Qd 20-100 ml/min K 15-60 l/day	+/0

- Filter used for CRRT are synthetic or semisynthetic : polysulfone, polyamide, polymethylmethacrylate, copolymer of acrylonitrile and sodium methallyl sulfonate (AN69)
- Slow continuous fluid removal achieved by continuous renal replacement therapies (CRRT) results in improved clinical tolerance for patients with limited hemodynamic stability. Solute concentrations do not rebound and filters are biocompatible (do not interact with blood which can cause activation of the alternative pathway of complement). Other advantages include: precise fluid and metabolic control, increased removal of cytokines, and the ability to deliver unlimited nutritional support.
- If arterial access is used, the patient's mean arterial pressure becomes the driving force for blood flow through the extracorporeal filter. Due to complications this access is rarely used.
- CAVHD/CVVHD: replacement fluids are not routinely administered, since solute clearance is primarily diffusive. When highly permeable membranes are used replacement fluids may be required.
- CVVH/CVVHDF: replacement fluids are generally administered due to dependency on convection (ultrafiltration) for solute removal
- CRRT that combine convection and diffusion may be preferred in the ICU as they remove small and middle molecular weight substances associated with systemic inflammatory responses of acute stress injury and infection.
- CVVH/CAVH are acceptable choices for fluid management.
- Anticoagulation requirements: CVVH > CVVHD or CVVHDF
- Disadvantages of CRRT: prolonged anticoagulation, trained personnel, ICU patient

- Molecular size is an important determinant of drug removal by conventional hemodialysis but is of lesser importance in CRRT as they utilize synthetic membranes which are similar to those used for intermittent high flux hemodialysis.
- If renal clearance of a drug is < 25-30% of total body clearance, renal impairment is unlikely to be clinically significant for drug dosing unless liver dysfunction is present.
- Loading doses are unchanged by continuous renal replacement therapy
- Factor influencing drug removal in decreasing order of importance.
 - Protein binding- extensively protein bound drugs are poorly cleared
 - Volume of distribution, the larger the Vd the less drug is removed per unit of time
 - Molecular weight
 - Drug charge
 - Drug binding to dialyzer membranes
- Ultrafiltration
 - Molecular size of most drugs are smaller than the membrane cut-off
 - Sieving coefficient (SC); ability of the drug to pass through the membrane by convection
 - = Drug concentration in filtrate/Drug concentration in plasma which is usually the same as the fraction unbound to plasma proteins but exceptions exist
 - protein binding determines SC for many drugs, consult literature for actual values
 - Ultrafiltration rate = Qf (liters/hour)
 - Convection clearance = Qf (ultrafiltration rate (liters/hour)) * Sieving Coefficient
- Drug clearance with CAVH, CVVH, SCUF is by convective transport (ultrafiltration), and approximates the unbound concentration in plasma water, multiplied by the ultrafiltration rate.
 - Drug clearance = %unbound * ultrafiltration rate (ml/min)
 - Drug with molecular weight < 500 daltons are readily removed by conventional hemodialysis and CRRT, whereas those with molecular weights of 1000-5000 daltons are eliminated more efficiently by CRRT. Vancomycin clearance may approach that of a patient with a creatinine clearance of 15 ml/min.
 - CRRT and conventional dialysis methods poorly clear drugs extensively bound to plasma proteins.
 - Filter characteristic affecting drug removal
 - Surface area
 - Kuf, ultrafiltration coefficient, permeability of filter to water measured in ml/hr/mm Hg
 - Ultrafiltration rate depends on Kuf and the intrafiliter pressure gradient
 - Sieving coefficient
 - CAVH, CVVH, SCUF clearance rates are affected primarily by ultrafiltration rate and sieving coefficient.
- Ultrafiltration
 - Molecular size of most drugs are smaller than the membrane cut-off
 - Sieving coefficient (SC); ability of the drug to pass through the membrane by convection
 - = Drug concentration in filtrate/Drug concentration in plasma which is usually the same as the fraction unbound to plasma proteins but exceptions exist
 - protein binding determines SC for many drugs, consult literature for actual values, [INSERT HYPERLINK](#)
 - Ultrafiltration rate = Qf (liters/hour)
 - Convection (ultrafiltration) clearance = Qf (ultrafiltration rate (liters/hour)) * Sieving Coefficient
- CRRT clearance of a drug under conditions of isolated ultrafiltration (SCUF) or hemofiltration (CAVH/CVVH) can be calculated
 - Convection clearance = Qf (ultrafiltration rate (liters/hour)) * SC or
 - Convection clearance = Qf (ultrafiltration rate (liters/hour)) * fup (fraction unbound)
- CRRT clearance of a drug during CAVHD or CVVHD is primarily dependent of the diffusive (dialysis) component.
 - Clearance = Qdialysis (dialysate flow rate)* fup (fraction unbound)
- Total clearance by CAVHDF/CVVHDF
 - = Clconvection (ultrafiltration) + Cl diffusion(dialysis)
 - = Qf (ultrafiltration flow rate) *fup(fraction unbound) + Qdialysis (dialysate flow rate)* fup (fraction unbound)
 - = fup * (Qf + Qd)
- Drug clearance can be quantified by collecting total volume of dialysate & ultrafiltrate outflow
 -
 - Clearance = Cdialysate&ultrafiltrate * Vdialysate&ultrafiltrate/AUC_{0-t}
- Pharmacist work up on patients who will be receiving CRRT should include: type of filter, rate of ultrafiltration, blood flow rate, dialysate flow rate, patient residual renal function., sieving coefficient of drug,

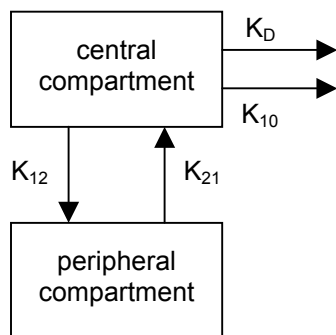
Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes. (Am J Kidney Dis. 1992 Oct;20(4):354-60.)

DeSoi CA, Sahm DF, Umans JG. (Department of Medicine, University of Chicago, IL 60637.)

Vancomycin (VANC) clearance was measured in five stable, anuric patients during two different dialysis protocol phases with each of the following 4 dialyzers: cuprophane (CU), polysulfone (PS), cellulose triacetate (CT), and polyacrylonitrile (PAN). Patients thus served as their own controls, with at least a 2-week interval between VANC doses. Patients were dialyzed 3 to 4 hours with dialysate flow (Q_D) 570 – 620 mL/min and blood flow (Q_B) 400-450 mL/min. It was determined that VANC was significantly cleared during routine high-flux hemodialysis (HFHD) with the latter three membranes, but not by low-flux (LF) HD with the CU membrane.

Phase I: Immediately following HD patients were given 1 g of VANC intravenously (IV) over 1 hour. Serum levels were drawn at 1, 2 and approximately 20, 32 and 44 hours after the completion of VANC infusion. The 44-hour level corresponded to the beginning of the next HD session. During this session samples were drawn at 45-minute intervals and post-dialytic samples were drawn at 1, 2, 4 and 20 hours. Removal was during 1 HFHD cycle.

Results Phase I: Postdialytic rebound of serum VANC concentrations was noted following HF dialysis with all membranes, necessitating use of a two-compartment pharmacokinetic model for HFHD. Postdialytic intercompartmental redistribution was determined to be complete after 4 hours. Removal was during the infusion period and 1 additional HFHD cycle.



K_{10}	Elimination from the central compartment
K_{12}	Transfer from central to peripheral
K_{21}	Transfer from peripheral to central
K_D	Elimination due to the dialyzer

Dialyzer clearance (Cl) of VANC was calculated by the direct Fick principle according to the following equation:

$$Cl = [(C_A - C_V)/C_A]Q_B(1 - Hct)(1 - R)$$

Serum concentrations obtained before and immediately after dialysis were used to determine % removal, apparent. Serum concentrations obtained before and 4 hours after dialysis were used to determine % removal, post rebound. VANC removal based on immediate postdialytic serum concentrations (one-compartment model) exceed those based on multi-compartmental characteristics.

Table 1: Pharmacokinetic Parameters for Vancomycin During Hemodialysis, Derived From a Two-compartment Model

	Dialyzer			
	CT (n = 4)	PAN (n = 5)	PS (n = 5)	CU (n = 4)
K_{10}	0.001 ± .0002	0.001 ± .0007	0.001 ± .0004	0.010 ± .001
K_{12}	0.118 ± .068	0.547 ± .066	0.651 ± .111	0.116 ± .019
K_{21}	0.186 ± .003	0.137 ± .003	0.181 ± .001	0.161 ± .023
K_D	0.174 ± .005	0.332 ± .058	0.327 ± .005	0
V_{SS} (L/kg)	0.786 ± .003	0.508 ± .072	0.690 ± .060	0.657 ± .005
Cl_V (L/h)	0.225 ± 0.59	0.286 ± .025	0.216 ± .061	0.293 ± .021
Cl_{VD} (L/h)	5.27 ± 1.19	3.41 ± .821	4.03 ± .662	- [†]

Note. K_{10} , K_{12} , K_{21} and K_D are the microconstants estimated by the iterative nonlinear least-squared fitting. V_{SS} is the volume of distribution at steady state. Cl_V and Cl_D are interdialytic and intradialytic clearances of vancomycin. Data are expressed as weighted means of the parameter estimates (±SE weighted mean). Pairwise differences between CT, PAN and PS dialyzers (ANOVA with Newman-Keuls multiple range test) were not significant for any of the calculated parameters.

* Cl_{VD} was not calculated for CU as the K_D was essentially zero.

[†] Significantly different compared with CT, PAN or PS dialyzers, $P < 0.01$. The HF dialyzer were not significantly different from each other.

Table 2: Summary of Non-Model-Derived Pharmacokinetic Data

	Dialyzer			
	CT (n = 4)	PAN (n = 5)	PS (n = 5)	CU (n = 4)
Cl _{Fick} (ml/min)	102.7 ± 8.5	71.3 ± 9.59	122.6 ± 22.9	0
KT/V _{urea}	0.91 ± .15	0.93 ± .06	0.91 ± .06	0.95 ± .06
%Removal (apparent)	43.1 ± 9.3	34.5 ± 3.1	42.8 ± 2.8	5.6 ± 1.9
% Removal (post-rebound)	22.0 ± 4.0	25.4 ± 4.0	29.9 ± 4.4	5.8 ± 3.8
P*	0.05	0.07	0.01	NS

Note. All data are expressed as mean (±SEM).

* Two-tailed paired t test, % apparent removal (at end of HD) v % removed post-rebound.

Phase II: Approximation of usual practice, 1 g of VANC was administered to the same patients, the infusion beginning during the last 30 minutes of dialysis and continuing for 30 minutes following HD. VANC levels were then assessed according to the above sampling protocol.

Results Phase II: The calculated mean AUCs were 4,260 ± 878 and 1,468 ± 126 mg/h/L for Phase I and Phase II, respectively. This difference was significant ($P = 0.006$, two-tailed paired t test). (This data looks wrong.)

Discussion: It was determined, that unlike LF dialysis, HFHD results in significant removal of VANC, and that postdialytic rebound of serum levels occurs. Therefore, measurement of serum VANC concentration immediately postdialysis significantly overestimates intradialytic removal, possibly resulting in an inappropriate dose adjustment.

The usual practice of beginning VANC infusions during dialysis also resulted in significant VANC removal by HF dialyzers and which may necessitate higher than usual doses during HF dialysis.

Vancomycin redistribution: dosing recommendations following high-flux hemodialysis.

(Kidney Int. 1994 Jan;45(1):232-7.)

Pollard TA, Lampasona V, Akkerman S, Tom K, Hooks MA, Mullins RE, Maroni BJ.

Department of Pharmacy, Emory University School of Medicine, Atlanta, Georgia.

In **protocol 1**, twelve HD patients admitted for vascular access thrombectomy received 15 mg/kg of vancomycin (VANC) as surgical prophylaxis. Post-operatively, patients underwent high-flux hemodialysis (HFHD) for two hours using a Fresenius F-80 polysulfone dialyzer ($Q_B = 417 \pm 49$, $Q_D = 800$ mL/min). Blood samples were drawn before administration of VANC, 3 hours after the end of the infusion, pre-operatively, just prior to initiating HD, every 30 minutes during HD (total of 4 samples), immediately following HD and then 0.5, 1.0, 1.5, 2, 4, 6, 12, 24, 36 and 48 hours later. The amount of VANC removed during HFHD was calculated from aliquots of spent dialysate that was collected from four patients. For eight remaining patients, the total amount of VANC removed was calculated using the weight of the total dialysate and its specific gravity.

The intradialytic clearance of VANC increased 13-fold compared to the patient's endogenous clearance (120 ± 59 vs. 9 ± 8 mL/min, respectively) yet dialysate recovery indicated that only 17% of body stores were removed (179 ± 70 mg). Although serum VANC levels decreased 33% during HFHD, VANC levels increased in all patients following dialysis and the post-rebound values reached 87% of the pre-dialysis concentration. The difference between VANC concentrations drawn immediately prior to HFHD and values measured at peak rebound was only 1.5 ± 1.0 mcg/mL. The average time for postdialytic intercompartmental redistribution to equilibrate was 6 hours.

Table 1: Selected pharmacokinetic parameters for patients receiving vancomycin and high-flux hemodialysis (protocol 1)

Patient <i>no.</i>	Weight <i>kg</i>	VD _{AREA} <i>L/kg</i>	CL _D <i>mL/min</i>	CL _E	Dialysate recovery <i>mg</i>	Rebound <i>%</i>	Maximum rebound <i>hr</i>
1	56.8	1.5	296.4	6.7	340	48.5	12.0
2	69.1	1.0	118.7	6.4	196	60.5	4.0
3	75.0	NA ^a	121.4	NA ^a	255	NA ^a	NA ^a
4	99.4	1.5	104.6	1.2	158	35.7	1.0
5	65.2	1.3	117.5	2.7	181	37.7	4.0
6	66.2	0.6	135.5	3.6	185	23.9	6.0
7	50.5	NA ^a	109.4	NA ^a	220	NA ^a	NA ^a
8	86.7	NA ^a	93.2	NA ^a	152	NA ^a	NA ^a
9	89.1	0.9	110.5	11.2	158	18.7	12.0
10	73.5	0.8	72.0	8.9	118	37.4	1.5
11	65.3	2.3	92.6	29.6	76	35.5	5.9
12	42.4	0.9	68.3	6.3	114	29.7	3.9
Mean	69.9	1.2	120.0	8.5	179	36.4	5.6
±SD	15.6	0.5	59.0	8.0	70	11.8	3.8

Abbreviations are: VA_{AREA}, volume of distribution; CL_D, dialysis clearance; CL_E, endogenous clearance; Dialysis recovery, the total amount of drug recovered in the expended dialysate; Percent rebound, equals $[(B - A)/A] \times 100$ where A = immediate post-dialysis plasma concentration and B = maximum post-dialysis plasma concentration; Time to maximum rebound, time interval between the immediate post-dialysis plasma concentration and the highest plasma concentration attained post-dialysis.

^a Parameters were not calculated due to the inability to maintain a peripheral intravenous access for blood sampling

In **protocol 2**, eight outpatients receiving maintenance HFHD with a F-80 dialyzer ($Kt/V = 1.29 \pm 0.08$; to estimate the dose of dialysis delivered) were given 20 mg/kg of VANC immediately following dialysis on Monday. Pre- and post-levels were measured during the next three consecutive HFHD treatments over a total of seven days (Wednesday, Friday and the following Monday).

VANC redistribution following HFHD was supported by the finding that post-dialysis levels were typically lower than the pre-dialysis VANC levels measured 48 hours later. The average half-life of VANC in this study was 118 ± 30 hours (4.9 days). The pre-dialysis serum VANC levels were > 7.5 mcg/mL (9.7 ± 1.0 mcg/mL; range 8.0 to 11.0) in all patients the following Monday. As with protocol 1, it was determined that the rate of removal from plasma exceeds the rate of transfer from tissue into plasma.

Table 2: Plasma vancomycin concentrations and derived pharmacokinetic parameters from three consecutive outpatient HFHD treatments performed over 7 days (protocol 2)

HFHD #1	HFHD #2	HFHD #3
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Patient no.	pre	post	pre	post	pre	post	T-1/2 hr	VD _{APP} L/kg
	mcg/mL							
1	22.6	12.5	16.2	11.9	10.5	7.5	107.3	0.64
2	15.1	9.1	12.3	7.2	8.9	5.0	159.0	1.06
3	20.3	9.4	12.7	7.0	8.0	3.8	84.2	0.62
4	14.3	9.1	11.8	6.6	8.9	5.5	174.5	1.08
5	21.0	13.5	14.2	9.7	9.8	7.2	104.0	0.71
6	22.6	16.4	15.0	10.7	10.6	7.3	104.6	0.68
7	20.2	12.6	14.7	9.2	9.9	6.6	114.8	0.76
8	25.8	13.9	16.9	9.6	11.0	5.8	93.3	0.57
Mean	20.2	12.1	14.2	9.0	9.7	6.1	117.7	0.77
SD	3.6	2.5	1.7	1.8	1.0	1.2	29.8	0.18

HFHD #1 to 3 refer to the subsequent Wednesday, Friday and Monday dialysis treatments, respectively.

Abbreviations are: pre, plasma VANC level drawn immediately preceding HFHD; post, plasma VANC level drawn immediately following cessation of HFHD; T-1/2, VANC half-life; VA_{APP}, apparent volume of distribution.

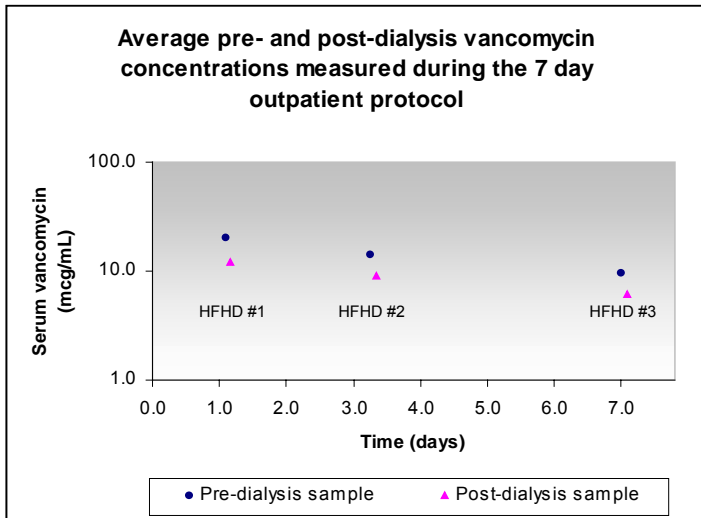


Table 3: Predicted peak and trough vancomycin serum concentrations following a 20 mg/kg loading dose and 15 mg/kg dose given weekly thereafter

	Dose (mg/kg)	Serum vancomycin concentration (mcg/mL)	
		Peak	Trough
1 st dose	20	26.0	9.2
2 nd dose	15	28.7	10.2
3 rd dose	15	29.7	10.5
4 th dose	15	30.0	10.6
5 th dose	15	30.1	10.6

Vancomycin concentrations were calculated using $K_e = 6.22 \times 10^{-3} \pm 1.34 \times 10^{-3} \text{ hr}^{-1}$, $V_D = 0.77 \text{ L/kg}$ and dosing interval of 7 days. Abbreviations are: Peak, maximum post-distribution serum concentration following VANC infusion; Trough, pre-dialysis serum concentrations 7 days following VANC infusion.

Increased vancomycin (VANC) clearance has been reported with highly permeable hemodialysis (HD) membranes (such as polysulfone). However, redistribution post-dialysis minimizes changes in serum levels and failure to consider post-dialysis redistribution could lead to unnecessary dosage supplementation.

Based on the predicted peak and trough concentrations in Table 3, it was the recommendation of this study to give a 20 mg/kg IV loading dose and subsequent doses of 15 mg/kg every seven days. On the other hand, it is conceivable that with less intensive dialysis VANC levels might remain therapeutic for longer than seven days. Conversely, when the $Kt/V > 1.3$, redosing might be required more frequently. Therefore, to account for individual variability, weekly VANC levels should be drawn before each dialysis.

PMID: 8127014 [PubMed - indexed for MEDLINE]

Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. (Am J Kidney Dis. 1995 Sep;26(3):469-74.)

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The purpose of this study was to define the pharmacokinetics of vancomycin (VANC) in eight critically ill patients (i.e. hemodynamically unstable) undergoing maintenance high-flux hemodialysis (HFHD) over 2 to 3 hours using F-80 or F-60 polysulfone dialyzers and to characterize the post-dialysis rebound phenomenon in this patient population. This study differs from the previous studies in that the study population required a slightly slower dialysate flow rate (Q_D 500 mL/min) and a slower blood flow rate (Q_B 200 – 350 mL/min).

Immediately following HFHD, patients received VANC IV ranging from 250 to 1,000 mg. Blood samples were obtained at 6 and 20 hours post infusion. During the next HFHD session, blood samples were obtained immediately prior to HFHD, at 30-minute intervals throughout HFHD and immediately following the completion of HFHD. To characterize the post-dialysis rebound effect, blood samples were obtained at 0.5, 1, 2, 2.5, 6, 12 and 24 hours after the end of HFHD. Intradialytic clearance was determined using the recovery of dialysate.

In patients dialyzed with F-80 dialyzers, interdialytic and intradialytic T-1/2 for VANC were 162 ± 69.8 hours and 4.7 ± 1.3 hours, respectively. Intradialytic clearance was 108.5 ± 16.3 mL/min, and 238 \pm 55 mg of VANC was recovered in the dialysate. In patients dialyzed with F-60 dialyzers, interdialytic and intradialytic t1/2 were 211.0 ± 166.8 and 4.6 ± 0.4 hours, respectively. Intradialytic clearance was 100.6 ± 18.3 mL/min and the amount of VANC recovered was 252 ± 79 mg. VANC concentrations rebounded by 16% to 37% between 3 and 6 hours in patients dialyzed with the F-80 dialyzer and 15% to 38% between 2 and 3 hours in patient dialyzed with F-60 dialyzers.

Table 1: Hemodialysis Data, Interdialytic and Intradialytic Half-Life, Amount of Vancomycin Recovered and Intradialytic Clearance for Patients Dialyzed With F-80 or F-60 Polysulfone Dialyzers

Patient no.	Filter type	Q_D mL/min	Q_B mL/min	Duration min	Interdialytic T-1/2 hr	Intradialytic T-1/2 hr	Vancomycin recovered mg	Intradialytic clearance mL/min
1	F-80	500	250	180	78.1*	4.9	245	128.3
2	F-80	500	200	150	267.5	3.9	295	106.7
3	F-80	500	250	120	158.4	6.2	281	121.7
4	F-80	500	250	120	177.7	5.4	205	92.3
5	F-80	500	350	174	129.9	3	162	93.5
Mean	-	-	-	-	162.3	4.7	238	108.5
\pm SD	-	-	-	-	69.8	1.3	55	16.3
6	F-60	500	250	150	84.5	4.7	328	90.0
7	F-60	500	200	120	148.5*	5	170	121.7
8	F-60	500	250	150	400.1	4.2	259	90.0
Mean	-	-	-	-	211.0	4.6	252	100.6
\pm SD	-	-	-	-	166.8	0.4	79	18.3

*Six patients were anuric; however, patients no. 1 and 7 produced urine in excess of 400 mL/d

Table 2: Prehemodialysis and Posthemodialysis Vancomycin Concentrations, Maximum Rebound Concentrations, Time to Maximum rebound Concentrations and Percent Rebound

Patient <i>no.</i>	Pre-dialysis concentration	Post-dialysis concentration <i>mg/L</i>	Post-rebound concentration	Time to max. rebound <i>hr</i>	Percent rebound
1	13.0	8.4	11.5	3	37
2	24.0	14.8	19.2	6	30
3	23.6	18.3	21.2	6	16
4	21.3	16.5	-	-	-
5	15.46	7.13	-	-	-
6	27.5	18.1	20.9	3	15
7	14.3	11.3	-	-	-
8	24.8	15.7	21.7	2	38

Hemodialysis with HF polysulfone dialyzers removes significant amounts of VANC from patients dialyzed in an acute care setting. In addition to the type of dialyzer used and the intradialytic clearance, the absolute amount of VANC removed is a function of the patient's V_D and the pre-dialysis VANC concentration.

DISCLAIMER: Although the following information was provided in the article, the validity should be inspected.

The authors suggest the results of this study indicate that supplemental doses of VANC approximating 250 mg are required following each HFHD session in addition to the patient's regular dose (1,000 mg/wk). Their rationale for more frequent replacement dosing was (1) assure that doses are not missed and (2) assure that VANC concentrations remain above minimally effective concentrations at all times. They also suggest obtaining a trough level 6 hours after the end of the first HFHD session following a loading dose of approximately 1,000 mg.

The following is a suggested scheme for VANC dosage adjustments in this patient population:

Post-rebound trough \leq 12 mg/L	1,000 mg VANC dose to be administered
Post-rebound trough 12 to 25 mg/L	500 mg VANC dose to be administered
Post-rebound trough \geq 25 mg/L	Hold VANC, check level 6 hours after next HFHD
Once the post-dialysis replacement dose is established, monitoring may be performed weekly.	

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Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy.

(Kidney Int. 1996 Sep;50(3):929-36.)

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Vancomycin (VANC) is often administered to hemodialysis (HD) patients at long dosage intervals because its removal by hemodialysis is considered to be negligible. We and others, however, have demonstrated significant removal of VANC by high-flux hemodialysis (HFHD).

This report describes our experience with 89 courses of VANC using a revised regimen with a loading dose followed by 500 mg doses after each dialysis treatment, and compares results with 41 courses using single weekly dosing. During the first two years of the investigation the loading dose in both groups was 1000 mg and in 1993 the loading dose was changed to 20 mg/kg. All patients were dialyzed with high-flux membranes at blood flow rates of 400 to 600 mL/min, using volumetric ultrafiltration and bicarbonate dialysate. Dialysis frequency was twice weekly in 29 cases and thrice weekly in 101 cases with a session duration of 3.3 ± 0.4 h. Serum VANC levels were obtained two hours after completion of infusion (peak) and immediately prior to dialysis (trough).

Duration of multiple-dose therapy was 11 ± 8 days, with mean total dose 3.6 ± 1.8 g. Initial doses of 20 mg/kg rapidly and reliably established therapeutic pre-dialysis serum levels (10 to 25 mcg/mL). In patients treated with multiple dosing 431 pre-dialysis levels were obtained. The mean level was 15.9 ± 5.7 mcg/mL; 55 levels (13%) were less than 10 mcg/mL and 22 (5%) were above 25 mcg/mL. In patients treated once weekly, 77% of levels were below 10 mcg/mL by five days after administration, and 84% at one week. No patient developed demonstrable ototoxicity. Twenty-five patients were treated for \geq two weeks, five for \geq four weeks, and two for $>$ five weeks, with no evidence of toxic accumulation. Mean peak level was 20.1 ± 4.6 mcg/mL, with a mean difference from preceding pre-dialysis level of 7.2 ± 2.2 mcg/mL.

We conclude that in HFHD, a 20 mg/kg loading dose of VANC followed by 500 mg doses after each dialysis treatment achieves predictable, adequate and safe therapeutic levels, does not lead to unacceptably high peaks, and does not accumulate during long treatment courses. By contrast, once-weekly VANC dosing resulted in subtherapeutic serum levels after five to seven days, and should be abandoned in the high-flux setting.

PMID: 8872968 [PubMed - indexed for MEDLINE]

% of Pre HFHD Troughs for Patients Receiving Multiple Doses	
< 10 mcg/ml	12.1%
10-20 mcg/ml	60.6%
21-25 mcg/ml	22.2%
> 25 mcg/ml	5%

Vancomycin mass transfer characteristics of high-flux cellulosic dialysers.

(Nephrol Dial Transplant. 1997 Dec;12(12):2647-53.)

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BACKGROUND: In comparison to conventional hemodialysis (HD) membranes, highly permeable membranes allow a broader spectrum of solute removal, including enhanced elimination of vancomycin (VANC). However, the mass transfer characteristics of VANC removal by highly permeable membranes have not been adequately assessed. An understanding of VANC's predominant dialytic mass transfer mechanism under a given set of operating conditions, including dialyzer type and flow rates, may permit more accurate dosing of the drug.

METHODS: We performed a mass transfer analysis of VANC removal by a high-flux dialyzer, cellulose triacetate (CT). In a crossover fashion with a 3-week washout between treatments, eight anuric subjects received VANC 1-g IV (**phase I**) during the last hour of CT HD; or (**phase II**) after dialysis (control). Dialysis operating conditions were as follows: $Q_B = 423 \pm 55$ mL/min; $Q_D = 500$ mL/min; treatment time = 3.5 ± 0.4 h. Serial urea and VANC serum concentrations were used to assess dialytic removal. Blood samples were taken at zero (pre-infusion), and at 15, 30, 60, 90, 120 and 180 min after the start of the VANC infusion. A final post-infusion sample was obtained immediately prior to the initiation of each subject's subsequent HD session (~44h).

RESULTS: Serum concentrations during the CT dialysis phase were consistently lower than the control phase. Dialysis removed 26.2% (mean; range 16-44%) of the administered VANC dose in phase I. While percent VANC removal and a measurement of diffusive solute removal $(Kt/V)_{urea}$ were directly correlated ($r = 0.88$; $P < 0.005$), no correlation was observed between percent VANC removal and weight-normalized ultrafiltration rate, the latter of which is a determinant of convective solute removal. This study did not monitor levels long enough post HFHD, only 2 hours. The AUC calculated did not include rebound serum levels, therefore is erroneous.

CONCLUSIONS: These findings suggest that for the CT dialyzer and dialysis operating conditions employed in this study, VANC clearance was primarily mediated by diffusion. As such, these data challenge the general concept that convection is primarily responsible for the removal of solutes in the same molecular weight class as VANC during high-flux dialysis. Also important to note is that treatment time and membrane surface area are two additional factors that may influence convective solute removal to a greater extent than diffusive solute removal. Lastly, diffusive solute removal is a function of transmembrane concentration gradient. Dialysis parameters that tend to enhance these gradients are high dialysate and blood flow rates and low membrane thickness.

PMID: 9430866 [PubMed - indexed for MEDLINE]

Urea kinetics and dialysis treatment time predict vancomycin elimination during high-flux hemodialysis. (Clin Pharmacol Ther. 1998 Jan;63(1):26-38.)

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BACKGROUND: Hemodialysis sessions with high-flux filters ask for a reconsideration of the kinetics of xenobiotics. The aim of this study was to analyze whether individual high-flux hemodialysis (HFHD) treatment parameters are of predictive value for dosing guidelines, with use of vancomycin (VANC) as a model compound.

METHODS: Twenty-six patients receiving HFHD were studied prospectively. After an intravenous infusion of 1000 mg (treatment dose) or 500 mg (prophylactic dose) VANC. Six to eight blood samples were collected within a period of 5 to 9 days, including one hemodialysis session. Serum VANC concentrations were measured by HPLC. Nonlinear mixed-effects modeling (NONMEM) was used to fit a two-compartment population pharmacokinetic model to the data of 20 patients; the data of the remaining six patients (group II) were used for a prospective evaluation of the model.

RESULTS: A linear relationship was found between VANC filter clearance (CLD_V) and urea filter clearance (CLD_{BUN}), derived from Kt/V (the product of urea clearance [K] and dialysis treatment time [t], standardized for the urea volume of distribution [V]). Mean (coefficient of variation) V_{SS} was 1.05 L/kg (22%), CLD_V was 0.336. CLD_{BUN} (13%), and residual interdialytic clearance was 2.25 ml/min (90%) in patients with creatinine clearance values (CL_{CR}) below 2 ml/min and 2.25 ml/min + 0.59. CL_{CR} (32%) in patients with CL_{CR} values above 2 ml/min. The model predicted predialysis VANC concentrations before the first and the second postinfusion dialysis session in the six patients of group II, with a deviation of 1.8 ± 1.0 mg/L and 0.8 ± 0.5 mg/L, respectively.

CONCLUSION: The described population pharmacokinetic model allows individualization of VANC dosing intervals in patients receiving HFHD, based on patient characteristics and urea kinetic modeling. The results of this study indicate that a single 1000 mg dose is not sufficient for a 1-week treatment in many patients. It was the suggestion of this study to administer a fixed dose of 1000 mg VANC and adapt the dosing interval rather than the dose amount for the following reasons: (1) 1000 mg VANC is well tolerated without toxic side effects caused by high peak concentrations and (2) small supplementary doses given post-dialysis are both time and cost consuming. Table 1 shows predicted pharmacokinetic parameters for patients who are demographically similar to those who participated in this study.

Table 1: Predicted serum vancomycin concentration and daily reduction resulting from residual total body clearance

Body weight (kg)	C_{24} (mg/L)	C_{48} (mg/L)	C_{72} (mg/L)	Daily reduction (%)
40	21.4	19.9	18.4	7.3
50	17.5	16.5	15.5	5.9
60	14.8	14.1	13.4	5.0
70	12.8	12.3	11.7	4.3
80	11.3	10.9	10.5	3.8
90	10.1	9.8	9.4	3.4
100	9.1	8.9	8.6	3.0

Predicted serum vancomycin concentrations for anuric patients at 24 hours (C_{24}), 48 hours (C_{48}) and 72 hours (C_{72}), after intravenous infusion of 1000 mg vancomycin.

PMID: 9465839 [PubMed - indexed for MEDLINE]

Pharmacokinetics of vancomycin when administered during high flux hemodialysis.

(Clin Nephrol. 1998 Jul;50(1):51-5.)

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This study was undertaken to evaluate the pharmacokinetics of relatively high-dose vancomycin (VANC) when administered during high-flux hemodialysis (HFHD) using a polysulfone membrane (F-80, Fresenius).

Five noninfected, anuric patients received a single dose of 25 mg/kg of VANC (based on the previous post-dialysis weight) infused during hemodialysis at a rate of one gram per hour and timed such that the end of the infusion coincided with the end of dialysis. Blood samples were drawn at baseline, during the infusion, up to six hours after the end of dialysis and then prior to the next three dialysis treatments. Spent dialysate was collected during the infusion. At the initiation of the VANC infusion, spent dialysate was collected for analysis.

Table1: Patient demographics and dialysis day 1 characteristics

Patient <i>no.</i>	Sex	Age <i>years</i>	Weight <i>kg</i>	Time on dialysis	Q _D <i>mL/min</i>	Q _B	Duration <i>min</i>
1	M	51	95.0	11 months	500	450	260
2	F	56	70.5	8 years	500	400	240
3	M	52	89.6	7 months	800	500	275
4	F	71	55.7	5 years	500	450	210
5	F	27	55.5	2 years	500	400	250

Q_D = dialysate flow rate; Q_B = blood flow rate

The percent of VANC lost during the first dialysis session ranged from 39.1 to 55.1% (mean 45.7 ± 6.4). The concentration of VANC at 6 hours after hemodialysis ranged from 18.2 to 45.1 mg/L (mean 29.6 ± 10.0 mg/L). Dialysis clearance was calculated using the amount recovered in the dialysate. Dialysis clearance ranged from 96.1 to 158.1 mL/min (mean 130.7 ± 30.0 mL/min). VANC levels continued to decline over the next week with "effective" half-lives ranging between 67 and 241 hours (mean 144 ± 74h). One week after dosing, serum concentrations ranged from 8.14 mg/l to 10.1 mg/l (mean 9.0±1.0 mg/L).

Table 2: Pharmacokinetic data

Patient <i>no.</i>	Dose <i>mg</i>	Recovery in dialysate <i>% of dose</i>	Cl _{HD} <i>mL/min</i>	C _{max}	6 h post-HD concentration <i>mg/L</i>	1 week post-HD concentration	Half-life <i>hours</i>
1	2375	39.1	96.1	100.0	31.9	9.6	104
2	1762	40.6	101.0	118.8	18.2	8.2	241
3	2240	55.1	155.8	92.4	27.0	10.1	202
4	1393	47.6	142.2	97.1	25.7	8.1	104
5	1388	46.2	158.1	105.3	45.1	-	67
Mean	2001.0	45.7	130.7	102.7	29.6	9.0	144
SD	414.4	6.37	30.0	10.1	10.0	1.0	74

This study suggests that an initial dose of 25 mg/kg of VANC, given during HFHD, may provide adequate serum concentrations in anuric hemodialysis patients for up to seven days. This dosing scheme reduces inconvenience to the patient and staff, and potentially can reduce nursing costs associated with post-dialysis administration. Vancomycin is relatively inexpensive; therefore the cost of giving a dose that is 25% more than the usual dose is minimal. It was also suggested that subsequent weekly doses of 15 to 20 mg/kg during dialysis would most likely result in therapeutic concentrations. However, subsequent dosing is best determined by therapeutic drug monitoring, keeping in mind that patients with residual renal function would likely require more frequent dosing.

PMID: 9710347 [PubMed - indexed for MEDLINE]

CAHP-210 dialyzer influence on intra-dialytic vancomycin removal.

(Nephrol Dial Transplant. 2002 Sep;17(9):1649-54.)

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BACKGROUND: Vancomycin (VANC) is often administered during the last hour of hemodialysis because it was not removed significantly by older hemodialyzers. However, newer higher permeability hemodialyzers remove VANC, although the amount removed varies considerably between dialyzers. The purpose of this study was to determine the apparent amount of VANC removed during the last hour of hemodialysis with a new CAHP-210 high-flux dialyzer with a surface area of 2.1 m².

METHODS: Eight anuric subjects with end-stage renal disease (ESRD) received IV VANC 15 mg/kg after their regular hemodialysis session ended (**phase I**). After a 3-week washout, the study was repeated with the VANC infused during the last hour of their regular hemodialysis session using a CAHP-210 dialyzer (**phase II**). Blood and dialysate flow rates for each subject were kept the same in both study arms. Patients were excluded if their dry body weight was not within 30% of their ideal body weight. Serum samples for the determination of VANC concentrations were obtained immediately before dialysis and at 0.5, 1, 2, 3, 5, 24 and approximately 44h after the infusion started. Differential equations describing a two-compartment open infusion model were fitted to the serum concentration vs time data and pharmacokinetic parameters and apparent VANC removal was estimated.

RESULTS: The apparent VANC intradialytic removal was 24.8% (range -7.0-34.8%), which was statistically significantly different from zero (phase I). The median estimated VANC serum concentration at 44 h after VANC administration (phase I) and at 44 h after intradialytic VANC administration (phase II) were 15.9 (range 10.6-20.4) and 14.0 mg/L (range 7.7-16.0), respectively ($P = 0.04$).

CONCLUSIONS: Vancomycin administered during the last hour of CAHP-210 dialysis results in less VANC exposure than when administered after dialysis. This intradialytic drug loss should be accounted for when dosing VANC in this manner. However, based on the estimated serum concentrations, all subjects had VANC concentrations above the NCCLS breakpoint (4 mg/L) of susceptible organisms during the entire interdialytic period. Thus, our data suggest that VANC dosage adjustment may not be required when it is administered during the last hour of dialysis.

CAVIAT: If the dose is not adjusted after a Friday dialysis, the serum concentration 72 hours later on the subsequent Monday will surely drop below the therapeutic level.

PMID: 12198218 [PubMed - indexed for MEDLINE]

Comparison of 3 vancomycin dosage regimens during hemodialysis with cellulose triacetate dialyzers: post-dialysis versus intradialytic administration. (Clin Nephrol. 2003 Aug;60(2):96-104.)

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AIMS: Traditionally, vancomycin (VANC) is administered following dialysis to minimize drug loss when high-flux membranes are employed. Unfortunately, this approach is extremely inconvenient for patients and staff, requiring the patients to remain in the unit for at least 1 hour following dialysis. This study was designed to evaluate the feasibility of administering VANC during hemodialysis. Specifically, this study was designed to compare the pharmacokinetics of VANC when administered during the last 1-2 hours of dialysis (i.e. intra-dialytic administration) to that administered after completion of dialysis.

METHODS: In a randomized, 3-way crossover trial, the pharmacokinetics of VANC were evaluated in 9 anuric patients on HFHD; comparing VANC 15 mg/kg following dialysis (**Phase I**), VANC 15 mg/kg during the last hour of hemodialysis (**Phase II**) or VANC 30 mg/kg during the last 2 hours of hemodialysis (**Phase III**). A minimum washout period of 3 weeks separated the treatment phases. VANC plasma concentrations were obtained over an 8-day period and subsequent comparisons between the treatment approaches were made with paired t-tests or ANOVA, as appropriate. Dialysate VANC concentrations determined on Day 1 and Day 3 of Phases II and III were used to calculate the fraction of VANC dose removed, and were compared to plasma data using paired t-tests.

RESULTS: a limitation of the study is the disparity between plasma and dialysate data with regard to the percent of drug removed during dialysis. The dialysate data suggest that only 12% of VANC is removed during dialysis on Day 3, whereas the plasma data indicate approximately 34% of VANC is removed. The disparity between these figures may suggest problems with the dialysate data due to manipulation techniques employed to assay concentrations that were below the limit of detection for standard assay techniques. Mean serum concentrations immediately following intradialytic VANC in Phase II and Phase III were initially high (77.7 and 95.5 mcg/mL respectively), but fell to 25.9 and 40.5 mcg/mL, respectively, by 4 hours post-dialysis. Pre-dialysis concentrations on Days 3, 5 and 8 were similar for Phase III as compared to Phase I. While Phase II resulted in significantly lower subsequent pre-dialysis concentrations than the other dosing schemes.

Table 1: Average vancomycin plasma concentration (mcg/mL) during distribution.

	End of ^a infusion	1 h post ^a dialysis	2 h post ^a dialysis	4 h post ^a dialysis
Phase II	77.7 ± 21.8	52.9 ± 55.0	30.2 ± 6.5*	25.9 ± 6.2*
Phase III	95.5 ± 19.9	65.7 ± 10.8	46.7 ± 15.1	40.5 ± 12.0

* = P < 0.05, Phase II vs Phase III, ^a = End of vancomycin infusion: during Phase II the vancomycin infusion ended 1 hour after the initiation of the infusion, during Phase III the vancomycin infusion ended 2 hours after the initiation of the infusion. 1 hour post dialysis: during Phase II this sample was obtained 2 hours post initiation of the vancomycin infusion, during Phase III this sample was obtained 3 hours after the vancomycin dose. 2 hours post dialysis: during Phase II this sample was obtained 3 hours post initiation of the vancomycin infusion, during Phase III this sample was obtained 4 hours after the vancomycin dose. 4 hours post dialysis: during Phase II this sample was obtained 5 hours post initiation of the vancomycin infusion, during Phase III this sample was obtained 6 hours after the vancomycin dose.

Table 2: Vancomycin pharmacokinetic parameters.

	Phase I	Phase II	Phase III
Interdialytic T-1/2 (h)	144.8 ± 71	91.9 ± 14.5	101.9 ± 14.5
Intradialytic T-1/2 (h)	NA*	5.5 ± 1.7	7.9 ± 3.1
% Rebound (Day 3)	NA*	27.3 ± 50.6	18.2 ± 11.7
% Removed (Day 3)	NA*	39.5 ± 17.4	33.4 ± 11.7

* = During Phase I, only pre-dialysis concentrations were obtained.

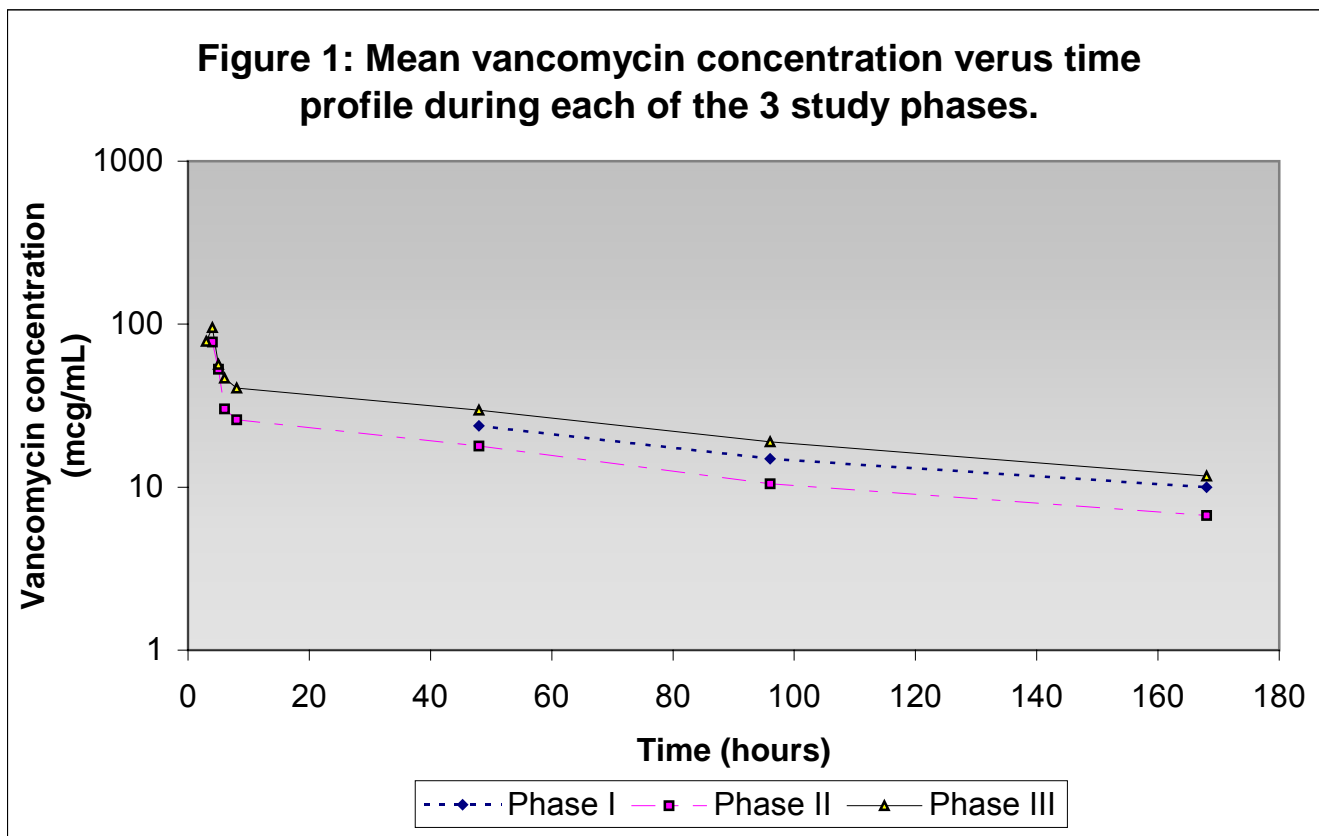
Table 3: Pre-dialysis vancomycin plasma concentrations (mcg/mL).

	Phase I	Phase II	Phase III	Significance*
Day 3	23.8 ± 4.8	17.9 ± 3.2	29.7 ± 6.1	I vs II, II vs III, I vs III
Day 5	14.9 ± 3.4	10.5 ± 3.1	19.0 ± 6.1	I vs II, II vs III
Day 8	10.0 ± 1.6	6.7 ± 1.4	11.7 ± 1.5	I vs II, II vs III

* = P < 0.05 between the treatment phases listed where I refers to Phase I, II refers to Phase II and III refers to Phase III.

As shown in Figure 1, vancomycin plasma concentrations declined in a biphasic manner over time. It is important to note that only a minimal number of VANS plasma concentrations were obtained during Phase I (i.e. only immediately prior to

each dialysis session), this the marked decline in plasma concentrations during hemodialysis as seen during Phase II and III, is not apparent. Pre-dialysis concentrations for Phase I and Phase III are remarkably similar on days 3, 5 and 8, differing statistically only on Day 3. Concentrations for Phase II are significantly lower than those for the other phases at each time point.



CONCLUSIONS: VANC administration of 30 mg/kg over the last 2 hours of dialysis achieves serum concentrations similar to conventional dosing of 15 mg/kg after dialysis and would allow dosing on a weekly basis. Due to variability in patient residual renal function as well as other factors (i.e. duration of dialysis, dialysis membrane), it is important that clinicians routinely monitor vancomycin concentrations to assure therapeutic concentrations in all dialysis patients.

PMID: 12940611 [PubMed - indexed for MEDLINE]

Vancomycin administration during dialysis with low-flux polysulfone membranes: traditional versus a supplemental dosage regimen.

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PMID: 12951755 [PubMed - indexed for MEDLINE]

2: Clin Nephrol. 2003 Aug;60(2):96-104. Related Articles, Links

Comparison of 3 vancomycin dosage regimens during hemodialysis with cellulose triacetate dialyzers: post-dialysis versus intradialytic administration.

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AIMS: Traditionally, vancomycin is administered following dialysis to minimize drug loss when high-flux membranes are employed. Unfortunately, this approach is extremely inconvenient for patients and staff, requiring the patients to remain in the unit for at least 1 hour following dialysis. This study was designed to evaluate the feasibility of administering vancomycin during hemodialysis. Specifically, this study was designed to compare the pharmacokinetics of vancomycin when administered during the last 1-2 hours of dialysis (i.e. intra-dialytic administration) to that administered after completion of dialysis.

MATERIALS AND METHODS: In a randomized, 3-way crossover trial, the pharmacokinetics of vancomycin were evaluated in 9 hemodialysis patients, comparing vancomycin 15 mg/kg following dialysis (Phase I), vancomycin 15 mg/kg during the last hour of hemodialysis (Phase II) or vancomycin 30 mg/kg during the last 2 hours of hemodialysis (Phase III). Vancomycin plasma concentrations were obtained over an 8-day period and subsequent comparisons between the treatment approaches were made with paired t-tests or ANOVA, as appropriate. Dialysate vancomycin concentrations determined on Day 1 and Day 3 of Phases II and III were used to calculate the fraction of vancomycin dose removed, and were compared to plasma data using paired t-tests. RESULTS: Vancomycin was significantly removed (33.4 to 39.5%) during a 3- to 4-hour high-flux dialysis session occurring on Day 3 after vancomycin administration. Mean serum concentrations immediately following intradialytic vancomycin administration of 15 mg/kg over the last hour of dialysis or 30 mg/kg over the last 2 hours of dialysis were initially high (77.7 and 95.5 mcg/ml respectively), but fell to 25.9 and 40.5 mcg/ml, respectively, by 4 hours post-dialysis. Predialysis concentrations on Days 3, 5 and 8 were similar for vancomycin 30 mg/kg administered over the last 2 hours of dialysis as compared with a 15 mg/kg dose given after dialysis. Vancomycin 15 mg/kg over the last hour of dialysis resulted in significantly lower subsequent predialysis concentrations than the other dosing schemes. CONCLUSIONS: Vancomycin administration of 30 mg/kg over the last 2 hours of dialysis achieves serum concentrations similar to

conventional dosing of 15 mg/kg after dialysis and would allow dosing on a weekly basis.

Publication Types:

Clinical Trial
Randomized Controlled Trial

PMID: 12940611 [PubMed - indexed for MEDLINE]

3: Am J Kidney Dis. 1998 Jun;31(6):1019-27. Related Articles, Links

Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis.

Joy MS, Matzke GR, Frye RF, Palevsky PM.

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The clearance of vancomycin is significantly reduced in patients with acute, as well as, chronic renal failure. Although multiple-dosage regimen adjustment techniques have been proposed for these patients, there is little quantitative data to guide the individualization of vancomycin therapy in acute renal failure patients who are receiving continuous renal replacement therapy (CRRT). To determine appropriate vancomycin dosing strategies for patients receiving continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD), we performed controlled clearance studies in five stable hemodialysis patients with three hemofilters: an acrylonitrile copolymer 0.6 m² (AN69), polymethylmethacrylate 2.1 m² (PMMA), and polysulfone 0.65 m² (PS). Patients received 500 mg of vancomycin intravenously at least 12 hours before the start of the clearance study. The concentration of vancomycin in multiple plasma and dialysate/ultrafiltrate samples was determined by EMIT (Syva, Palo Alto, CA). The diffusional clearance and sieving coefficient (SC) of vancomycin were compared by a mixed-model repeated-measures analysis of variance (ANOVA) with filter and blood ($Q(B)$), dialysate inflow ($Q(DI)$), or ultrafiltration rate ($Q(UF)$) as the main effects and patient as a random effect. Vancomycin was moderately protein bound in these patients; free fraction ranged from 49% to 83%. The SCs of the three filters were similar and significantly correlated with the free fraction of vancomycin ($P = 0.01$; $r^2 = 0.465$). Significant linear relationships were observed between the diffusional clearance of vancomycin and $Q(DI)$ for all three filters: AN69 (slope = 0.482; $r^2 = 0.880$); PMMA (slope = 0.853; $r^2 = 0.966$); and PS (slope = 0.658; $r^2 = 0.887$). The slope of this relationship for the PMMA filter was significantly greater than that of the AN69 and PS filters. The clearance of vancomycin, urea, and creatinine, however, was essentially constant at all $Q(B)$ s for all three filters. Thus, the clearance of vancomycin was not membrane dependent during CVVH. However, during CVVHD, membrane dependence of vancomycin clearance was noted at a $Q(DI)$ greater than 16.7 mL/min; vancomycin clearance with PMMA at a $Q(DI)$ of 25 mL/min was 66% and 43% greater than that with the AN69 and PS filters, respectively. CVVH (62% to 262%) and CVVHD (90% to 540%) can significantly augment the clearance of vancomycin in acute renal failure patients. Dosing strategies for individualization of vancomycin therapy in patients receiving CVVH and CVVHD are proposed.

PMID: 9631848 [PubMed - indexed for MEDLINE]

4: Nephrol Dial Transplant. 1997 Dec;12(12):2647-53. Related Articles, Links

Vancomycin mass transfer characteristics of high-flux cellulosic dialysers.

Scott MK, Mueller BA, Clark WR.

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BACKGROUND: In comparison to conventional haemodialysis membranes, highly permeable membranes allow a broader spectrum of solute removal, including enhanced elimination of vancomycin (1448 Daltons). However, the mass transfer characteristics of vancomycin removal by highly permeable membranes have not been adequately assessed. An understanding of vancomycin's predominant dialytic mass transfer mechanism under a given set of operating conditions, including dialyser type and flow rates, may permit more accurate dosing of the drug. **METHODS:** We performed a mass transfer analysis of vancomycin removal by a high-flux dialyser, cellulose triacetate (CT). In a cross-over fashion with a 3-week washout between treatments, eight subjects received vancomycin 1000 mg (1) during the last hour of CT haemodialysis; or (2) after dialysis. Serial urea and vancomycin serum concentrations were used to assess dialytic removal. **RESULTS:** Dialysis removed 26.2% (mean; range 16-44%) of the administered vancomycin dose. While vancomycin removal and (Kt/V)urea were directly correlated ($r = 0.88$; $P < 0.005$), no correlation was observed between vancomycin removal and weight-normalized ultrafiltration rate. **CONCLUSIONS:** These findings suggest that for the CT dialyser and dialysis operating conditions employed in this study, vancomycin clearance was primarily mediated by diffusion. As such, these data challenge the general concept that convection is primarily responsible for the removal of solutes in the same molecular weight class as vancomycin during high-flux dialysis.

Publication Types:

Clinical Trial

Controlled Clinical Trial

PMID: 9430866 [PubMed - indexed for MEDLINE]

5: Kidney Int. 1996 Sep;50(3):929-36. Related Articles, Links

Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy.

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Vancomycin is often administered to hemodialysis patients at long dosage intervals because its removal by hemodialysis is considered to be negligible. We and others, however, have demonstrated significant

removal of vancomycin by high-flux hemodialysis. This report describes our experience with 89 courses of vancomycin using a revised regimen with a loading dose followed by 500 mg doses after each dialysis treatment, and compares results with 41 courses using single weekly dosing. All patients were dialyzed with high-flux membranes using volumetric ultrafiltration and bicarbonate dialysate. Serum vancomycin levels were obtained two hours after completion of infusion (peak) and immediately prior to dialysis (trough) and were measured by Abbot TDx fluorescence polarization immunoassay. Duration of multiple-dose therapy was 11 +/- 8 days, with mean total dose 3.6 +/- 1.8 g. Initial doses of 20 mg/kg rapidly and reliably established therapeutic pre-dialysis serum levels (10 to 25 micrograms/ml). In patients treated with multiple dosing 431 pre-dialysis levels were obtained. The mean level was 15.9 +/- 5.7 micrograms/ml; 55 levels (13%) were less than 10 micrograms/ml and 22 (5%) were above 25 micrograms/ml. In patients treated once weekly, 77% of levels were below 10 micrograms/ml by five days after administration, and 84% at one week. No patient developed demonstrable ototoxicity. Twenty-five patients were treated for > or = two weeks, five for > or = four weeks, and two for > five weeks, with no evidence of toxic accumulation. Mean peak level was 20.1 +/- 4.6 micrograms/ml, with a mean difference from preceding pre-dialysis level of 7.2 +/- 2.2 micrograms/ml. We conclude that in high-flux hemodialysis, a 20 mg/kg loading dose of vancomycin followed by 500 mg doses after each dialysis treatment achieves predictable, adequate and safe therapeutic levels, does not lead to unacceptably high peaks, and does not accumulate during long treatment courses. By contrast, once-weekly vancomycin dosing resulted in subtherapeutic serum levels after five to seven days, and should be abandoned in the high-flux setting.

Publication Types:

Clinical Trial

PMID: 8872968 [PubMed - indexed for MEDLINE]

6: Int J Artif Organs. 1994 Jan;17(1):19-26. Related Articles, Links

Vancomycin dosing in haemodialysis patients and Bayesian estimate of individual pharmacokinetic parameters.

Keller F, Horstensmeyer C, Looby M, Borner K, Pommer W, Erdmann K, Giehl M.

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A dose reduction of vancomycin to 1000 mg once a week usually is recommended for haemodialysis patients. Our modified dosing schedule consists of a loading dose of 1000 mg and a maintenance dose of 500 mg administered 3 times a week after haemodialysis. Different vancomycin regimens were retrospectively evaluated by therapeutic drug monitoring and bayesian parameter estimates in 39 dialysis patients. The mean (+/- SD) trough level in 7 patients receiving only the conventional dosage regimen was significantly lower than in 17 patients strictly treated by the modified schedule (7 +/- 4 versus 17 +/- 8 mg/L; p = 0.001). The corresponding peaks were low in both groups and no different (23 +/- 10 versus 27 +/- 12 mg/L). The one week average vancomycin clearance was significantly lower in the conventional dosage group compared to the modified dosage group (6 +/- 3 versus 10 +/- 3 ml/min; p = 0.001).

High-flux dialysers were not used in the conventional dosage group but for 30 percent of the procedures in the modified dosage group, where the vancomycin one week average elimination half-life was 66 hours (+/- 18) and the volume of distribution 50 litres (+/- 5). As compared to the bayesian programme, NONMEM calculated comparable pharmacokinetic parameters but could be applied only in 5 cases with a sufficient number of concentration measurements. Ototoxicity occurred in 1 patient, whereas vancomycin treatment was judged as ineffective against infection in 5 of the 39 patients. Their troughs were below 15 mg/L. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 8188395 [PubMed - indexed for MEDLINE]

7: Am J Kidney Dis. 1995 Sep;26(3):469-74. Related Articles, Links

Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease.

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To define the pharmacokinetics of vancomycin in patients undergoing maintenance hemodialysis in an acute care setting and to characterize the rebound phenomenon occurring after hemodialysis, vancomycin t_{1/2} during the interdialytic and intradialytic phases and intradialytic clearance were measured in eight critically ill patients undergoing high-flux hemodialysis using F-80 or F-60 polysulfone dialyzers. Intradialytic clearance was determined using the recovery method. In patients dialyzed with F-80 dialyzers, interdialytic and intradialytic t_{1/2} for vancomycin were 162 +/- 69.8 hours and 4.7 +/- 1.3 hours, respectively. Intradialytic clearance was 108.5 +/- 16.3 mL/min, and 238 +/- 55 mg of vancomycin was recovered in the dialysate. In patients dialyzed with F-60 dialyzers, interdialytic and intradialytic t_{1/2} were 211.0 +/- 166.8 and 4.6 +/- 0.4 hours, respectively. Intradialytic clearance was 100.6 +/- 18.3 mL/min and the amount of vancomycin recovered was 252 +/- 79 mg. Vancomycin concentrations rebounded by 16% to 37% between 3 and 6 hours in patients dialyzed with the F-80 dialyzer and 15% to 38% between 2 and 3 hours in patient dialyzed with F-60 dialyzers. Hemodialysis with high-flux polysulfone dialyzers removes significant amounts of vancomycin in patients dialyzed in an acute care setting. A suggested scheme for vancomycin dosage adjustments in these patients is presented.

PMID: 7645555 [PubMed - indexed for MEDLINE]

8: Kidney Int. 1994 Jan;45(1):232-7. Related Articles, Links

Vancomycin redistribution: dosing recommendations following high-flux hemodialysis.

Pollard TA, Lampasona V, Akkerman S, Tom K, Hooks MA, Mullins RE, Maroni BJ.

Department of Pharmacy, Emory University School of Medicine, Atlanta, Georgia.

Although increased vancomycin clearance has been reported with highly permeable hemodialysis membranes (such as polysulfone), failure to consider post-dialysis redistribution could lead to unnecessary dosage supplementation. In protocol 1, twelve hemodialysis patients admitted for vascular access thrombectomy received 15 mg/kg of vancomycin as surgical prophylaxis. Post-operatively, patients underwent high-flux hemodialysis (HFHD) for two hours using a Fresenius F-80 polysulfone dialyzer (QB = 417 +/- 49, QD = 800 ml/min). Vancomycin's intradialytic clearance increased 13-fold compared to the patient's endogenous clearance (120 +/- 59 vs. 9 +/- 8 ml/min, respectively) yet dialysate recovery indicated that only 17% of body stores were removed (179 +/- 70 mg). Although serum vancomycin levels decreased 33% during HFHD, vancomycin levels increased in all patients following dialysis and the post-rebound values reached 87% of the pre-dialysis concentration. In protocol 2, eight outpatients receiving maintenance HFHD with a F-80 dialyzer (Kt/V = 1.29 +/- 0.08) were given 20 mg/kg of vancomycin immediately following dialysis on Monday; pre- and post-levels were measured during the next three dialysis treatments. The predialysis serum vancomycin levels were > 7.5 micrograms/ml (9.7 +/- 1.0 micrograms/ml; range 8.0 to 11.0) in all patients the following Monday. Thus, vancomycin clearance is increased during HFHD, but redistribution post-HD minimizes changes in serum levels. We recommend a 20 mg/kg i.v. loading dose and subsequent doses of 15 mg/kg every seven days; to account for individual variability, weekly vancomycin levels should be drawn before dialysis.

PMID: 8127014 [PubMed - indexed for MEDLINE]

9: Clin Pharmacol Ther. 1998 Jan;63(1):26-38. Related Articles, Links

Urea kinetics and dialysis treatment time predict vancomycin elimination during high-flux hemodialysis.

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BACKGROUND: Hemodialysis sessions with high-flux filters ask for a reconsideration of the kinetics of xenobiotics. The aim of this study was to analyze whether individual high-flux hemodialysis treatment parameters are of predictive value for dosing guidelines, with use of vancomycin as a model compound. **METHODS:** Twenty-six patients receiving high-flux hemodialysis were studied prospectively. After an intravenous infusion of 1000 mg or 500 mg vancomycin, respectively, six to eight blood samples were collected within a period of 5 to 9 days, including one hemodialysis session. Serum vancomycin concentrations were measured by HPLC. Nonlinear mixed-effects modeling (NONMEM) was used to fit a two-compartment population pharmacokinetic model to the data of 20 patients; the data of the remaining six patients (group II) were used for a prospective evaluation of the model. **RESULTS:** A linear relationship was found between vancomycin filter clearance (CLDV) and urea filter clearance (CLDBUN), derived from Kt/V (the product of urea clearance [K] and dialysis treatment time [t], standardized for the urea volume of distribution [V]). Mean (coefficient of variation)

steady-state volume of distribution was 1.05 L/kg (22%), CLDV was 0.336.CLDBUN (13%), and residual interdialytic clearance was 2.25 ml/min (90%) in patients with creatinine clearance values (CLCR) below 2 ml/min and 2.25 ml/min + 0.59.CLCR (32%) in patients with CLCR values above 2 ml/min. The model predicted predialysis vancomycin concentrations before the first and the second postinfusion dialysis session in the six patients of group II, with a deviation of 1.8 +/- 1.0 mg/L and 0.8 +/- 0.5 mg/L, respectively. CONCLUSION: The described population pharmacokinetic model allows individualization of vancomycin dosing intervals in patients receiving hemodialysis, based on patient characteristics and urea kinetic modeling.

PMID: 9465839 [PubMed - indexed for MEDLINE]

10: Am J Kidney Dis. 1992 Oct;20(4):354-60. Related Articles, Links

Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes.

DeSoi CA, Sahm DF, Umans JG.

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Vancomycin clearance was measured in five patients during dialysis with cuprophane (CU), polysulfone (PS), cellulose triacetate (CT), and polyacrylonitrile (PAN) dialyzers. Vancomycin was significantly cleared during routine high-flux (HF) hemodialysis (HD) with the latter three membranes, but not by CU. Postdialytic rebound of serum vancomycin concentrations was noted following HF dialysis, necessitating use of a two-compartment pharmacokinetic model. Measurement of serum vancomycin concentration immediately postdialysis significantly overestimates intradialytic removal, possibly resulting in inappropriate dose adjustment. Vancomycin infusion during HF HD results in significant drug removal during its administration to the patient, complicating the calculation of an adequate dose.

PMID: 1415203 [PubMed - indexed for MEDLINE]

11: Am J Kidney Dis. 1999 Aug;34(2):222-7. Related Articles, Links

Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes.

Amin NB, Padhi ID, Touchette MA, Patel RV, Dunfee TP, Anandan JV.

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To characterize the pharmacokinetics of gentamicin during and after hemodialysis (using polysulfone Fresenius F-80 membranes (Fresenius USA, Inc, Walnut Creek, CA), surface area 1.6 m²), eight patients with end-stage renal disease undergoing chronic hemodialysis receiving the drug for therapeutic indications were enrolled. Intradialytic gentamicin half-life, clearance, and amount of gentamicin recovered during a

hemodialysis session were also determined. Serum gentamicin concentrations were analyzed using fluorescence polarization immunoassay. The amount of gentamicin recovered was 64.3 +/- 14.4 mg, whereas the intradialytic gentamicin half-life was 2.24 +/- 0.83 hours, with a clearance of 116 +/- 9 mL/min. Gentamicin concentrations rebounded by 27.86% +/- 16.4% at 1.5 +/- 0.52 hours after the end of the hemodialysis session. The decrease in gentamicin concentrations comparing maximum rebound to prehemodialysis concentrations was 53.54% +/- 9.97%. A variable yet substantial amount of gentamicin is removed during hemodialysis using F-80 membranes; hence, supplemental doses are necessary to avoid potential treatment failures. The supplemental doses of gentamicin calculated based on gentamicin concentrations obtained immediately postdialysis could be overestimated if the postdialysis rebound concentrations are not considered. A dosing regimen is suggested using the pharmacokinetic parameters defined by the present study and population estimate of volume of distribution.

PMID: 10430966 [PubMed - indexed for MEDLINE]

12: Ann Pharmacother. 1997 Jun;31(6):756-64. Related Articles, Links

Automated peritoneal dialysis: new implications for pharmacists.

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OBJECTIVE: To review the new automated peritoneal dialysis (APD) modalities that are available to patients with end-stage renal disease (ESRD), and to examine their potential pharmacokinetic and drug dosing consequences. **DATA SOURCES:** A MEDLINE search (from January 1966 to June 1996) of English-language literature pertaining to peritoneal dialysis was performed. Additional references were obtained by reviewing the references of pertinent articles identified through the search. Tertiary sources were also used. **DATA EXTRACTION:** Data regarding peritoneal dialysis techniques and pharmacokinetics were extracted from the literature. Data were evaluated according to the study design, population, results, and conclusions. **DATA SYNTHESIS:** ESRD is the result of progressive chronic renal insufficiency and requires renal replacement therapy. APD is the fastest growing renal replacement therapy by percentage in the US and provides dialysis exchanges via a machine while the patient sleeps, thereby improving patient convenience, peritoneal dialysis compliance rates, and decreasing peritonitis rates. Well-designed pharmacokinetic studies involving APD have not been conducted. Consequently, no formal drug dosing recommendations are available for APD, and pharmacists must rely on established dosing guidelines for continuous ambulatory peritoneal dialysis (CAPD) when recommending dosing regimens. This article describes the new APD treatment modalities available and the potential pharmacokinetic differences between CAPD and APD. **CONCLUSIONS:** Well-designed studies are needed to fully characterize the pharmacokinetic parameters of drugs in APD. Until then, pharmacists should recommend that intraperitoneally administered drugs be given during the longest peritoneal dialysate dwell of the day and that serum concentrations of drugs with narrow therapeutic indices be monitored closely.

Publication Types:

Review
Review, Tutorial

PMID: 9184718 [PubMed - indexed for MEDLINE]

13: Adv Ren Replace Ther. 1997 Apr;4(2 Suppl 1):64-71. Related Articles, Links

Dialysis prescription and kinetics in acute renal failure.

Clark WR, Mueller BA, Kraus MA, Macias WL.

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The recognition that both morbidity and mortality are inversely related to delivered hemodialysis (HD) dose in end-stage renal disease (ESRD) patients has substantially changed clinical practices in the United States. A number of quantification techniques, which differ greatly in complexity and sophistication, are now used in ESRD patients. Investigators recently have attempted to extrapolate some of these ESRD quantification methods to the acute renal failure (ARF) setting. This review focuses on these recent attempts. Both patient-related and renal replacement therapy (RRT)-related differences in ESRD and ARF are discussed. In addition, the potential pitfalls of extrapolating certain ESRD quantification methods to RRT in ARF are discussed. Prescription considerations for both intermittent HD (IHD) and continuous RRT (CRRT) are presented. Finally, recent data suggesting survival in critically ill ARF patients is directly correlated with delivered therapy dose are reviewed. The optimal technique for RRT quantification in ARF remains to be determined.

Publication Types:
Review
Review, Tutorial

PMID: 9113242 [PubMed - indexed for MEDLINE]

14: Am J Kidney Dis. 1991 Oct;18(4):451-8. Related Articles, Links

Continuous venovenous hemofiltration: an alternative to continuous arteriovenous hemofiltration and hemodiafiltration in acute renal failure.

Macias WL, Mueller BA, Scarim SK, Robinson M, Rudy DW.

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Continuous venovenous hemofiltration (CVVH) has been used as an alternative to continuous arteriovenous hemofiltration (CAVH) and hemodiafiltration (CAVHD) in the management of critically ill patients with acute renal failure. This report describes our experience with the first 25 patients treated with CVVH at our institution. Vascular access was obtained through a single dual-lumen venous catheter. A blood pump

was used to provide ultrafiltration pressure. An ultrafiltrate pump was incorporated to ensure predictable ultrafiltrate production rates. Safety features in the extracorporeal circuit included a venous drip chamber with bubble detector and an in-line pressure monitor. CVVH was initiated by a nephrologist and dialysis nurse and was maintained by the intensive care unit (ICU) nursing staff. Fifteen females and 10 males received CVVH therapy for a total of 193.5 days (average, 7.7 +/- 10.3 days; range, 0.5 to 48 days). Four of the 25 patients (16%) survived and were discharged from the hospital. Four additional patients (16%) survived the acute phase of their illness, but died from complications of their primary disease before discharge from the hospital. The mean weight change during CVVH was -7.9 +/- 7.0 kg (range, -26.5 to +2.9 kg). Metabolic waste products and electrolytes were adequately controlled by CVVH in all but one hypercatabolic patient. The mean heparin dose required was 6.5 +/- 4.2 U/kg/h and was adjusted to prevent filter clotting rather than to achieve a predetermined activated partial thromboplastin time (PTT). The median PTT was 35.8 seconds (range, 22.0 to 100; control, 19.5 to 29.5 seconds). Four episodes of volume-responsive hypotension occurred during the 193.5 treatment days. Only one patient experienced a hemorrhagic complication during CVVH. No patient experienced a complication related to vascular access. Twelve of 111 total hemofilters were changed because of clot formation. CVVH was well tolerated by patients and managed efficiently by the ICU nursing staff. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID:1928064 [PubMed - indexed for MEDLINE]

15: Ann Pharmacother. 1998 Mar;32(3):362-75. Related Articles, Links

A primer on continuous renal replacement therapy for critically ill patients.

Joy MS, Matzke GR, Armstrong DK, Marx MA, Zarowitz BJ.

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OBJECTIVES: To characterize the multiple continuous renal replacement therapy (CRRT) techniques available for the management of critically ill adults, and to review the indications for and complications of use, principles of drug removal during CRRT, drug dosage individualization guidelines, and the influence of CRRT on patient outcomes. DATA SOURCES: MEDLINE (January 1981-December 1996) was searched for appropriate publications by using terms such as hemofiltration, ultrafiltration, hemodialysis, hemodiafiltration, medications, and pharmacokinetics; selected articles were cross-referenced. STUDY SELECTION: References selected were those considered to enhance the reader's knowledge of the principles of CRRT, and to provide adequate therapies on drug disposition. DATA SYNTHESIS: CRRTs use filtration/convection and in some cases diffusion to treat hemodynamically unstable patients with fluid overload and/or acute renal failure. Recent data suggest that positive outcomes may also be attained in patients with other medical conditions such as septic shock, multiple organ dysfunction syndrome, and hepatic failure. Age, ventilator support, inotropic support, reduced urine volume, and elevated serum bilirubin concentrations have been associated with poor outcomes. Complications associated with CRRT include bleeding due to excessive anticoagulation and line disconnections, fluid and electrolyte imbalance, and filter and venous clotting. CRRT can

complicate the medication regimens of patients for whom it is important to maintain drug plasma concentrations within a narrow therapeutic range. Since the physicochemical characteristics of a drug and procedure-specific factors can alter drug removal, a thorough assessment of all factors needs to be considered before dosage regimens are revised. In addition, an algorithm for drug dosing considerations based on drug and CRRT characteristics, as well as standard pharmacokinetic equations, is proposed. CONCLUSIONS: The use of CRRT has expanded to encompass the treatment of disease states other than just acute renal failure. Since there is great variability among treatment centers, it is premature to conclude that there is enhanced survival in CRRT-treated patients compared with those who received conventional hemodialysis. This primer may help clinicians understand the need to individualize these therapies and to prospectively optimize the pharmacotherapy of their patients receiving CRRT.

1: Pharmacotherapy. 1997 Mar-Apr;17(2):256-62. Related Articles, Links

Effects of dialysis membrane on intradialytic vancomycin administration.

Scott MK, Macias WL, Kraus MA, Clark WR, Carfagna MA, Mueller BA.

Department of Pharmacy Practice, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, USA.

STUDY OBJECTIVE: To quantify the influence of hemodialyzers on vancomycin removal when the drug was infused during hemodialysis. DESIGN: Prospective, controlled, crossover study with three arms. SETTING: A university-affiliated medical center. PATIENTS: Eight subjects receiving outpatient hemodialysis. INTERVENTIONS: The three treatment arms were vancomycin 1000 mg infused after dialysis was completed (control), and the same dosages infused during the last hour of hemodialysis with a cellulose triacetate (CT) and a cellulose acetate (CA) hemodialyzer. MEASUREMENTS AND MAIN RESULTS: The areas under the curve from time zero to 44 hours (AUC_{0-44 hrs}) for the three study arms were significantly different ($p < 0.05$), with the mean vancomycin AUC_{0-44 hrs} being significantly lower when administered during CT and CA dialysis (73.7% and 87.2% of control; $p < 0.05$ vs control). The mean vancomycin peak concentration achieved during CT dialysis was significantly lower than for the CA and control arms (20.5, 23.9, 27.0 mg/L, respectively). Forty-four-hour postinfusion concentrations were similarly lower. CONCLUSION: Clinicians should recognize that the composition of the hemodialyzer significantly influences vancomycin serum concentrations when the drug is administered during hemodialysis.

1: Am J Kidney Dis. 1999 Aug;34(2):222-7. Related Articles, Links

Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes.

Amin NB, Padhi ID, Touchette MA, Patel RV, Dunfee TP, Anandan JV.

Division of Nephrology, Henry Ford Hospital, Detroit, MI, USA.

To characterize the pharmacokinetics of gentamicin during and after

hemodialysis (using polysulfone Fresenius F-80 membranes (Fresenius USA, Inc, Walnut Creek, CA), surface area 1.6 m²), eight patients with end-stage renal disease undergoing chronic hemodialysis receiving the drug for therapeutic indications were enrolled. Intradialytic gentamicin half-life, clearance, and amount of gentamicin recovered during a hemodialysis session were also determined. Serum gentamicin concentrations were analyzed using fluorescence polarization immunoassay. The amount of gentamicin recovered was 64.3 ± 14.4 mg, whereas the intradialytic gentamicin half-life was 2.24 ± 0.83 hours, with a clearance of 116 ± 9 mL/min. Gentamicin concentrations rebounded by 27.86% ± 16.4% at 1.5 ± 0.52 hours after the end of the hemodialysis session. The decrease in gentamicin concentrations comparing maximum rebound to prehemodialysis concentrations was 53.54% ± 9.97%. A variable yet substantial amount of gentamicin is removed during hemodialysis using F-80 membranes; hence, supplemental doses are necessary to avoid potential treatment failures. The supplemental doses of gentamicin calculated based on gentamicin concentrations obtained immediately postdialysis could be overestimated if the postdialysis rebound concentrations are not considered. A dosing regimen is suggested using the pharmacokinetic parameters defined by the present study and population estimate of volume of distribution.

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2: Am J Kidney Dis. 1995 Sep;26(3):469-74. Related Articles, Links

Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease.

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To define the pharmacokinetics of vancomycin in patients undergoing maintenance hemodialysis in an acute care setting and to characterize

the rebound phenomenon occurring after hemodialysis, vancomycin $t_{1/2}$ during the interdialytic and intradialytic phases and intradialytic clearance were measured in eight critically ill patients undergoing high-flux hemodialysis using F-80 or F-60 polysulfone dialyzers. Intradialytic clearance was determined using the recovery method. In patients dialyzed with F-80 dialyzers, interdialytic and intradialytic $t_{1/2}$ for vancomycin were 162–69.8 hours and 4.7–1.3 hours, respectively. Intradialytic clearance was 108.5–16.3 mL/min, and 238–55 mg of vancomycin was recovered in the dialysate. In patients dialyzed with F-60 dialyzers, interdialytic and intradialytic $t_{1/2}$ were 211.0–166.8 and 4.6–0.4 hours, respectively. Intradialytic clearance was 100.6–18.3 mL/min and the amount of vancomycin recovered was 252–79 mg. Vancomycin concentrations rebounded by 16% to 37% between 3 and 6 hours in patients dialyzed with the F-80 dialyzer and 15% to 38% between 2 and 3 hours in patient dialyzed with F-60 dialyzers. Hemodialysis with high-flux polysulfone dialyzers removes significant amounts of vancomycin in patients dialyzed in an acute care setting. A suggested scheme for vancomycin dosage adjustments in these patients is presented.

Clin Nephrol. 1998 Jul;50(1):51-5. Related Articles, Links

Pharmacokinetics of vancomycin when administered during high flux hemodialysis.

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This study was undertaken to evaluate the pharmacokinetics of relatively high-dose vancomycin when administered during high-flux hemodialysis using a polysulfone membrane (F-80, Fresenius). Five noninfected, anuric patients received a single dose of 25 mg/kg of vancomycin infused during hemodialysis at a rate of one gram per hour and timed such that the end of the infusion coincided with the end of dialysis. Blood samples were drawn during the infusion, up to six hours after the end of dialysis and then prior to the next three dialysis treatments. Spent dialysate was collected during the infusion. Samples were analyzed using the EMIT assay. The percent of vancomycin lost during the first dialysis session ranged from 39.1 to 55.1% (mean, 45.76.4). The concentration of vancomycin at 6 hours after hemodialysis ranged from 18.2 to 45.1 mg/L (mean, 29.610.0 mg/l). Dialysis clearance ranged from 96.1 to 158.1 ml/min (mean, 130.7 30.0 ml/min). One week after dosing, serum concentrations ranged from 8.14 mg/l to 10.1 mg/l (mean, 9.01.0 mg/l). This study suggests that an initial dose of 25 mg/kg of vancomycin, given during high-flux dialysis, may provide adequate serum concentrations in anuric hemodialysis patients for up to seven days. This dosing scheme reduces inconvenience to the patient and staff, and potentially can reduce nursing costs associated with post-dialysis administration; its cost is minimal. At this point, subsequent dosing is best determined by therapeutic drug monitoring.

Dialysis

Uremic syndrome: signs and symptoms that result from toxic effects of elevated levels of nitrogenous and other waste products in the blood. Usually develops when $\text{clcr} < 10 \text{ ml/min/1.73 m}^2$, diabetes $15 \text{ ml/min/1.73 m}^2$.

- Nausea
- Fatigue
- Weak
- Cold
- Personality changes
- Confused
- Coma
- Sallow coloration of skin
- Ammonia like or urine like odor to the breath
- Anemia

Note: CMS reimburse for dialysis: when $\text{clcr} < 10 \text{ ml/min/1.73 m}^2$, diabetes $15 \text{ ml/min/1.73 m}^2$.

Indications for dialysis when $\text{clcr} < 20\text{-}25 \text{ ml/min/1.73 m}^2$

- nausea, vomiting, impaired nutrition secondary to poor appetite, GI bleed, ileus
- AMS
- Pericarditis
- Bleed diathesis associated with uremic platelet dysfunction
- Refractory or progressive fluid overload
- Uncontrolled hyperkalemia
- Severe metabolic acidosis
- Steadily worsening renal function
 - $\text{BUN} > 70\text{-}100 \text{ mg/dl}$ or
 - $\text{Clcr} < 15\text{-}20 \text{ ml/min/1.73 m}^2$
- ARF with measured $\text{clcr} < 15\text{-}20 \text{ ml/min/1.73 m}^2$

Hemodialysis

- Most common
- Rapid removal of fluid is poorly tolerated by very ill (ICU patient)

Peritoneal dialysis

- 1/8 as efficient as hemodialysis in altering blood solute per unit of time
- 1/4 as efficient as hemodialysis in removing fluid per unit of time
- Continuous nature makes it equivalent to hemodialysis
- Gradual removal of solute and fluid
- Peritoneal dialysis favored
 - Infants and very young children

- Severe cardiovascular disease
- Difficult vascular access
- Desire for greater freedom to travel
- Contraindications
 - Adhesions
 - Fibrosis
 - malignancy