

Vancomycin Dosing in Patients Utilizing Renal Replacement Therapy

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Disclosure Information



- Employer
 - Cleveland Clinic Abu Dhabi
 - No relevant financial conflict of interest

Learning Objectives



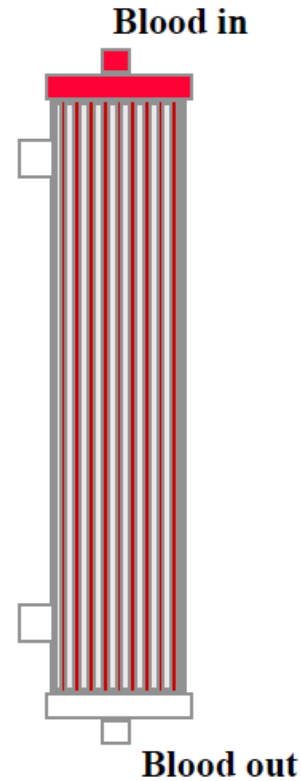
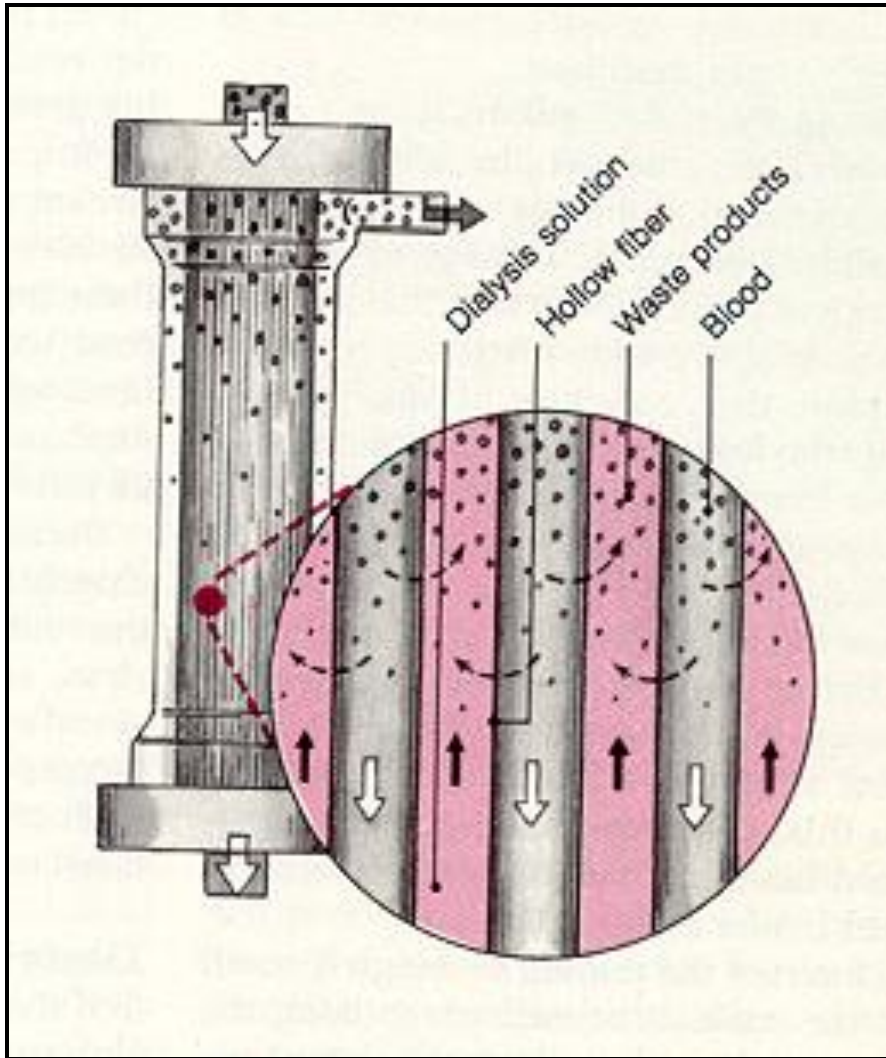
- Identify factors which clinicians should consider while evaluating vancomycin dosing in patients on renal replacement therapies

Definitions

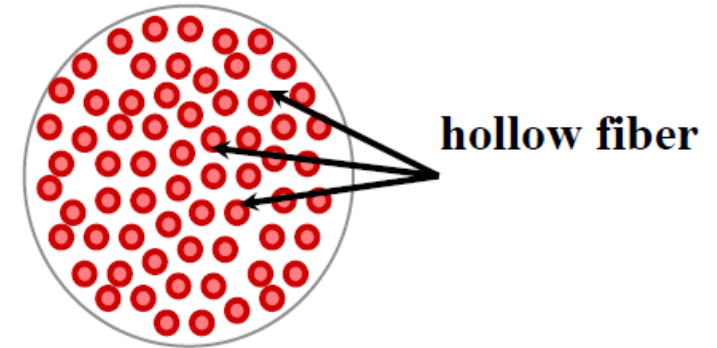


- Dialyzers (membranes)
 - High-flux (high permeability)
 - Significant vancomycin removal (up to 40%)
 - Low-Flux (low permeability)
 - Negligible vancomycin removal (< 5%)
- Infusion
 - During dialysis (interdialytic)
 - In the last 30 to 90 min using dialysis access
 - Post dialysis (after dialysis end)
 - After complete end of dialysis using another access
- Loading Dose (LD)
- Maintenance Dose (MD)

Dialyzers



Cross Section



Outside the Fiber (effluent)

Inside the Fiber (blood)

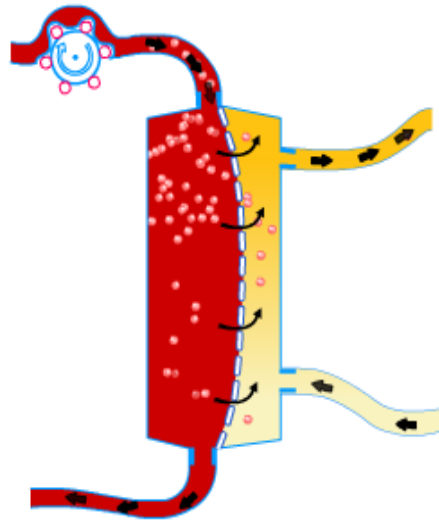
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Hollow fiber strand - Typically 7,000-14,000 fibers

Adapted from: Orlando Regional Healthcare, Education & Development. Adapted From Baxter (GAMBRO 2004)

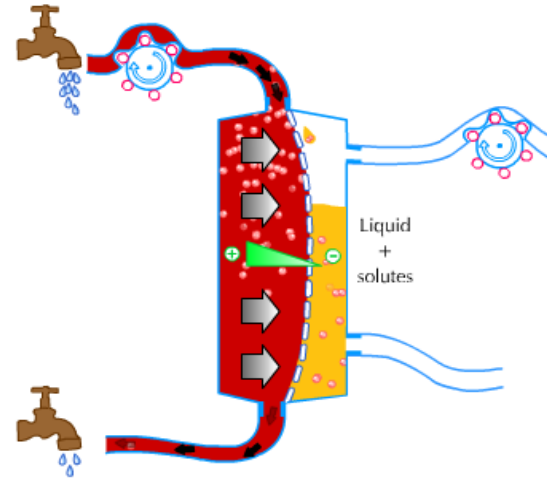
Mechanisms of Solute Removal in RRT

DIFFUSION



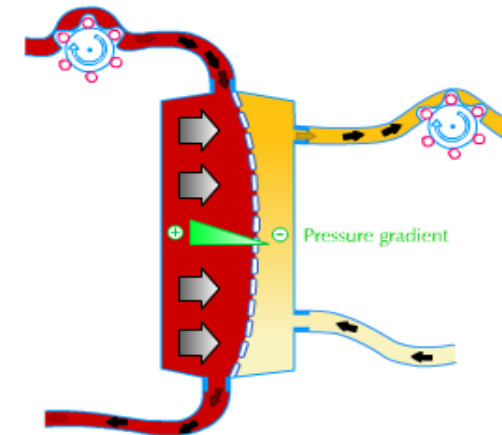
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CONVECTION



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ULTRAFILTRATION



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Adapted From Baxter (GAMBRO 2004)

Intermittent Hemodialysis



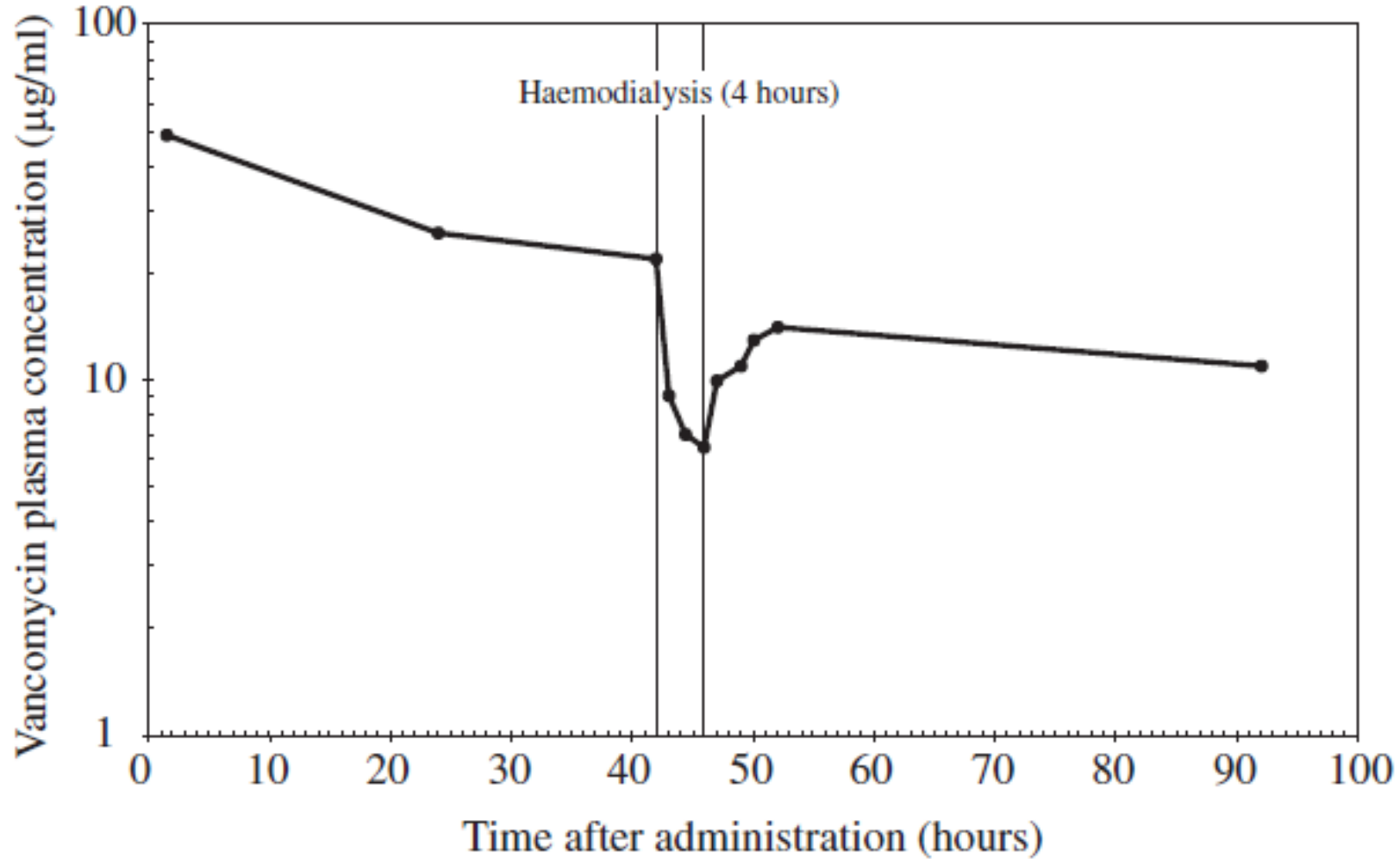
- Guidelines Recommendations:
- The 2020 guidelines recommend that vancomycin AUC/MIC should be 400 to 600 mg*h/L including HD patients
- “Maintaining pre-dialysis concentrations between 15 and 20 mg/L is likely to attain the AUC target” (C-III)
- “Outcome studies validating the AUC target of 400 to 600 mg·h/L used in other patient populations have not been conducted in the hemodialysis population” (C-III)

Intermittent Hemodialysis (Guidelines)



- Guidelines Recommendations:
- “Predialysis serum concentration monitoring should be performed not less than weekly and should drive subsequent dosing”
- The Guidelines states “In a typical thrice-weekly hemodialysis schedule, 25% larger doses are needed for the 3-day interdialytic period”

Pre-Dialysis levels?



- Intradialytic (during) or post dialysis?
- Vascular access is the lifeline for this population
- Unnecessary venipuncture and central venous access
 - Compromise the future use of these veins
- Frequent laboratory draws from the arm veins
 - Jeopardise future dialysis arteriovenous fistula
- KDOQI guidelines recommend the use of dialysis access for blood draws and drug administration if possible

Vancomycin Dosing in IHD - (B-II)

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg^a
Intradialytic	
Low permeability	Loading: 30 Maint.: 7.5-10 ^b
High permeability	Loading: 35 Maint.: 10-15 ^b

Vancomycin Dosing in IHD - (B-II)

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg^a
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After dialysis ends

Low permeability

Loading: 25
Maint.: 7.5^b

High permeability

Loading: 25
Maint.: 10^b

Vancomycin Removal during dialysis



- Example
- LD of 25 mg/kg for a 120 kg patient, would need 3 g
 - Need 3 hours of infusion
 - During dialysis?
 - Dialysis sessions last 3 to 4 hours
 - Could start with the start of dialysis?
 - How much will be removed?
 - How about 35 mg/kg dose?

Vancomycin Removal during dialysis



- **Mason et al.**
- Compared vancomycin removal during dialysis (n=9)
 - 30 mg/kg in the last 2 hours of dialysis
 - 15 mg/kg in the last hour of dialysis
- Pre-HD concentrations were similar in both cases at day 3 post dialysis

Literature Review – Since 2009



- 2 outcome studies (Fu et al and El Nekidy et al)
 - LD 18 to 23 mg/kg and MD 8 – 13 mg/kg) – during dialysis
- 13 clinical PK
 - 7 studies during HD (Vandecasteele et al, Zelenitsky et al)
 - LD 20 mg/kg - MD 8 mg/kg
 - Fixed doses of 1, 1.25, and 1.5 g
 - 4 studies post HD (Brown et al, El Nekidy et al)
 - 1 g or 17.5 mg/kg and MD 500 mg
 - 2 studies low flux
- Two PK modeling studies

PLoS One. 2018 Mar 5;13(3):e0193585.

Hemodial Int. 2019 Oct;23(4):449-457.

Clin Infect Dis. 2011 Jul 15;53(2):124-9.

Clin Infect Dis. 2012 Aug;55(4):527-33.

Clin Infect Dis. 2011 Jul 15;53(2):164-6.

Can J Hosp Pharm. 2012 Nov;65(6):436-42.

Can J Hosp Pharm. 2016 Sep-Oct;69(5):341-347.

Pharmacokinetic Modeling Studies



2 studies-Goal $AUC_{24}h/MIC$ of 400-700 mg*h/L (MCS)

- **1- Lewis and Mueller**

- Poster IDWeek 2016
- Used published data (Zelenitsky, Ariano, and El Nekidy)
 - LD of 35 mg/kg during dialysis, MD 15 mg/kg (high-flux)
 - LD 25 mg/kg for post dialysis, MD, 10 mg/kg (high-flux)
 - LD 30 mg/kg for during dialysis, MD 7.5 mg/kg (low-flux)
 - LD 25 mg/kg for post dialysis, MD 7.5 mg/kg (low-flux)
- Published later (not validated)

- **2-Hui** and colleagues

- Utilized retrospective data Using
 - LD of 30 mg/kg
 - MD 0.5 to 1 g (10 mg/kg)
- Predicted that this dosing could achieve the AUC_{24}/MIC of ≥ 400
- Used mix of studies in which vancomycin was administered during and post HD Not validated

Lewis SJ and Mueller BA. ID Week; 2016; New Orleans LA

Lewis SJ and Mueller BA. J Clin Pharmacol. 2020 Aug 26.

Hui K, et al. J Antimicrob Chemother. 2019 Jan 1;74(1):130-134.

- **El Nekidy et al**
 - Recommended a MD of 5.9 mg/kg and 7.1 mg/kg
 - For the 48 and 72h interdialytic time
- **70 kg patient** (5.9 mg/kg and 7.1)
 - 420 mg for the 48 hours and 490 mg for 72 hours
 - Both would be rounded to 500 mg
- **120 kg patient**
 - 708 mg for the 48 hours and 852 mg for 72 hours
 - Both would be rounded to 750 mg
 - Caution should be exercised when applying the 25% extra dose

Summary of Vancomycin Dosing in HD



Dosing	Loading dose	Maintenance dose	Pre-HD drug level
During dialysis dosing (High-Flux) Most favorable	20 to 25 mg/kg (max 2 g) during dialysis dialysis access	8 to 10 mg/kg (~1 g) during dialysis dialysis access	≥ 15 mg/L Level after LD and before MD then weekly
Post-dialysis dosing (High-Flux) Less favorable	15 to 20 mg/kg (1 to 2 g) after dialysis	6 to 7 mg/kg (500 mg) after dialysis	≥ 15 mg/L Weekly (if at goal)
After or during dialysis (Low-Flux) References	15 to 20 mg/kg (1 to 2 g) during dialysis dialysis access	500 mg IV – weekly or per levels during dialysis dialysis access	≥ 15 mg/L Level post LD and before MD then weekly

Hybrid Hemodialysis Therapies



- Prolonged intermittent renal replacement therapy (PIRRT)
 - Slow-low efficiency dialysis (SLED)
- Use standard hemodialysis machines
- Run at slower blood and dialysate flow rates and longer durations
 - 6 to 12 hours daily
- Hemodynamically unstable patients
- Clear vancomycin to a different extent than standard IHD
- Data is scarce in this population

Recommendations for PIRRT-SLED



- Loading doses 20 to 25 mg/kg (actual body weight) (B-III)
- Don't delay initial doses for post dialysis
- Maintenance doses 15 mg/kg in the last 60 to 90 minutes of dialysis (B-III)
- Pre-Dialysis concentration should guide further dosing
- Maintenance doses of 500 to 750 post each dialysis
 - Duration and dialysis prescription (blood and dialysate flow rates)

- Continuous venovenous hemofiltration (CVVH)
- Continuous venovenous hemodialysis (CVVHD)
- Continuous venovenous hemodiafiltration (CVVHDF)
- AUC/MIC target of 400-600 is recommended
- Vancomycin clearance is constant over the dosing interval
 - Filter clogs
- Rate of vancomycin removal by CRRT
 - Related to the rate of ultrafiltrate/dialysate flow
- All filters are high-flux (not affecting removal)
- Lack of outcomes studies in CRRT

CRRT recommendations



- Loading doses of 20 to 25 mg/kg (actual body weight)
 - Effluent rates of 20 to 25 mL/kg/h (B-II)
- Maintenance dosing of 7.5 to 10 mg/kg every 12 hours (B-II)
 - Effluent rates of 20 to 25 mL/kg/h
 - Based on serum concentration
 - Should be checked in the first 24 hours to ensure AUC/MIC targets are met
- Usually, a once daily dose of 1 to 1.5 g will maintain the level > 15 mg/L

Thank you

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