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Vancomycin in peritoneal dialysis: Clinical pharmacology considerations in therapy.

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Abstract

Intraperitoneal vancomycin is the first line therapy in the management of peritoneal dialysis-related peritonitis. However, due to the paucity of data, vancomycin dosing for peritonitis in patients on automated peritoneal dialysis (APD) is empiric and based on clinical experience rather than evidence. Studies in continuous ambulatory peritoneal dialysis (CAPD) patients have been used to provide guidelines for dosing and are often extrapolated for APD use, but it is unclear if this is appropriate. This review summarizes the available pharmacokinetic data used to inform optimal dosing in patients on CAPD or APD. The determinants of vancomycin disposition and pharmacodynamic effects are critically summarized, knowledge gaps explored, and a vancomycin dosing algorithm in peritoneal dialysis patients is proposed.

Key words: Automated peritoneal dialysis; continuous ambulatory peritoneal dialysis; anuria; residual kidney function; peritonitis; pharmacokinetics; pharmacodynamics.

INTRODUCTION

Vancomycin is often selected as empiric first line therapy for suspected *Gram-positive* organisms in peritoneal dialysis (PD) related peritonitis. However, data on vancomycin dosing in various PD modalities are limited, especially for automated peritoneal dialysis (APD). The paucity of well-designed pharmacokinetic studies has led to vancomycin dosing guidelines for PD patients that are based on limited information resulting in the possibility of achieving sub-or supra-therapeutic trough concentrations in this special patient population.(1)

PRINCIPLES OF VANCOMYCIN THERAPY

Vancomycin is a tricyclic glycopeptide antibiotic with broad spectrum activity against *Gram-positive* bacteria. It is effective for the treatment of *Gram-positive* infections including peritonitis and is the drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is poorly absorbed following oral administration. Therefore, it is commonly administered as an intravenous infusion, except in peritoneal dialysis where the route is preferentially intraperitoneal. Approximately 50% of vancomycin is protein-bound in plasma with a variable volume of distribution ranging between 0.4-1 L/kg in the non-PD population.(2, 3) An initial distribution half-life ranging from 30 minutes to 1 hour followed by a mean terminal elimination half-life ranging from 6-12 hours were determined following intravenous dosing in patients with normal renal function.(3) Metabolism is negligible and elimination occurs primarily through glomerular filtration, such that advanced renal disease substantially reduces the clearance of vancomycin resulting in an elimination half-life of about 7.5 days compared to 4-6 hours in normal patients. This means that in patients with kidney failure, the dosing of vancomycin must be adjusted.(4, 5)

The Clinical and Laboratory Standards Institute (CLSI) has established the vancomycin breakpoint for susceptible *S. aureus* isolates with MIC values of $\leq$ 2 mg/L and intermediate or resistant

for MIC values greater than 2 mg/L.(6) Despite the CLSI defined breakpoints, treatment failure for patients infected with *S. aureus* and vancomycin MICs between 1-2 mg/L have been reported compared to those with lower reported MICs.(7, 8) This may be due to inappropriate selection of doses that are sufficiently high to maintain plasma concentrations that exceed the MIC.

To optimize the vancomycin exposure-response relationship for efficacy during *S. aureus* infections, one must examine the ratio of the area under the concentration-time curve and the MIC (AUC/MIC). Vancomycin trough concentrations between 15-20 mg/L for MIC breakpoints $\leq$ 1 mg/L ensures a ratio of $\geq$ 400 and has been an advocated target for clinical effectiveness.(3, 9) It should be noted that goal trough values recommended by consensus guidelines for efficacy may lead to nephrotoxicity, which might be a consideration for patients on PD with residual kidney function.(10) This however, is not well studied. In practice, clinical judgement together with therapeutic drug monitoring (TDM) of steady-state vancomycin plasma concentrations is a common approach in the treatment of peritonitis in PD.

PHARMACOKINETIC/PHARMACODYNAMIC MODELING AND SIMULATION

Pharmacokinetic/pharmacodynamic modeling and simulation is an innovative approach that can help inform crucial decisions, such as predicting clinical endpoints of new doses and dosing regimens or optimization of drug regimens. By understanding what the body does to the drug (Pharmacokinetics) and what the drug does to the body (Pharmacodynamics), dosing regimens can be tailored to the PD population to avoid nephrotoxicity, retain antimicrobial eradication and suppressing the emergence of resistance. Regulatory authorities mandate the submission of pharmacokinetic/pharmacodynamic evaluations for drug application, which include dose evaluation in special populations. However, despite the evaluation of the need of dose adjustments for patients with end stage renal disease (ESRD) - such

as those on hemodialysis- the process is not well established for old drugs. Even in those cases when dose adjustments are proposed for patients with ESRD, there is minimal attention in patients on PD.

This review aims to summarize the available evidence on vancomycin pharmacokinetic and pharmacodynamic PD-related studies, address the physicochemical and PD modality-specific considerations- with attention on APD, and highlight areas where research is needed on dosing vancomycin for PD-related peritonitis.

VANCOMYCIN PHYSICOCHEMICAL PROPERTIES AND DRUG TRANSPORT ACROSS THE PERITONEUM

Movement of vancomycin from the peritoneum cavity to plasma is based on Fick's Law (figure 1). Middle molecular weight solutes such as vancomycin (1,486 g/mol) are dependent on dwell time during PD for absorption into the plasma. Based upon a single dose study of six non-infected subjects on PD, vancomycin has a lower dialysate to plasma ratio than urea and creatinine at two hours.(11) There is no correlation between vancomycin PD clearance and dialysis adequacy (Kt/V) following an intravenous dose in patients on APD.(12)

Teicoplanin, a glycopeptide antibiotic with a similar molecular structure (1,564 g/mol) and spectrum of activity to vancomycin, was studied in non-infected adults on continuous ambulatory peritoneal dialysis (CAPD).(13) The absolute bioavailability (F_{ip}) was calculated using dialysate drug concentration (corrected for amount remaining in the cavity) and drug amount sampled, which was then plotted against a total dwell time of five hours. Teicoplanin systemic bioavailability, reflecting transfer from the peritoneal space, was directly related to dwell time. Furthermore, the consistency in absorption increased with time suggesting that complete and less variable bioavailability with teicoplanin can be achieved with longer dwell times.

The rate at which vancomycin is absorbed is dependent on the permeability of the peritoneal membrane. Vancomycin intraperitoneal to systemic transfer rate increases in patients with inflammatory peritonitis.(14)

VANCOMYCIN BIOAVAILABILITY DURING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Vancomycin pharmacokinetics has primarily been studied in patients on CAPD. Bioavailability studies conducted in these patients typically employ a 6-hour dwell time. The F_{ip}, or the amount of vancomycin reaching systemic circulation from the peritoneal space relative to an intravenous dose, is approximately 50%.(15) Supporting the hypothesis of a leaky peritoneum due to membrane inflammation, patients on CAPD with peritonitis have a F_{ip} of 70-91%.(14, 16) Bioavailability changes can also be observed with different age cohorts. For example, in a pediatric study in children aged 5-17 years old, the bioavailability was reported to be as high as about 70% in the absence of peritonitis.(17)

A summary of the absorption parameters from studies conducted in infected and non-infected patients on CAPD is depicted in table 1. The equilibration half-life describes the time allowed for drug transfer between the peritoneal space to the systemic circulation following an intraperitoneal dose of vancomycin. Following intraperitoneal dosing, vancomycin equilibration half-life in patients on CAPD without peritonitis was 2.9 hours and those with peritonitis 1.6-2.9 hours.(18-20) Assuming no differences between peritoneum transport in those with or without peritonitis and five half-lives, steady-state equilibrium between the dialytic compartment and systemic circulation would be achieved following a 10-15 hour dwell.

VANCOMYCIN BIOAVAILABILITY DURING AUTOMATED PERITONEAL DIALYSIS

Vancomycin possess the desired physiochemical properties as a drug candidate for intraperitoneal administration in APD patients. In addition, with its well-established stability in PD fluids,

bioavailability is adequate as long as sufficient dwelling time is allowed for drug absorption. However, the appropriate duration of the dwell time has not been well studied. Hence, it is crucial to monitor vancomycin levels frequently to adjust dosing to get therapeutic concentrations in each individual patient.

VANCOMYCIN CLEARANCE DURING PERITONEAL DIALYSIS

Vancomycin elimination following an intraperitoneal dose is governed by its total body clearance. Total body clearance is the sum of clearances contributed from elimination organs, mainly kidneys, in the case of vancomycin, and is defined as the volume of plasma cleared of vancomycin per time unit. Elimination processes in PD patients include those originating from residual kidney function (RKF), other non-renal sources plus the drug cleared through PD. Total body clearance is especially important as it controls the overall exposure of vancomycin for the given bioavailability achieved from a dwell. Dialytic clearance is defined as the volume of plasma that has been cleared of vancomycin (i.e. removed from systemic circulation into the peritoneal space) by PD per unit time. Figure 1 describes the various clearance processes involved in vancomycin elimination following an intraperitoneal dose. Moreover, a summary of vancomycin pharmacokinetic systemic parameters is provided in table 2. Vancomycin clearance in patients on PD differs among studies due to several factors including the presence or absence of peritonitis, presence and extent of RKF, dwell times, dialysate volume, effect of antibiotic-free PD exchanges, and age.(21)

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Continuous ambulatory peritoneal dialysis typically employs short dwell times (4-6 hours), which may not be sufficient to reach equilibration between the dialysate and plasma. Studies in non-infected adult CAPD patients report dialytic clearances ranging between 1.2-2.4 mL/min, which account for 20-

25% of the total plasma clearance.(15, 22, 23) In patients with peritonitis, vancomycin dialytic clearance increases to 3.8 mL/min following a less-than five-hour exchange.(24) Clearances of up to 8.5 mL/min after the first 4 hours of exchange have also been reported.(16) Vancomycin clearance through elimination from the drained peritoneal dialysate contributes to 20-70% of the total plasma clearance.(16, 24) As a consequence, vancomycin elimination half-life in the systemic circulation ranges between 66–115 hours in patients on CAPD.(22, 24-26) One major reason in the reported variability in the plasma half-life could be the difference in the sampling times which may not completely capture the decline of the plasma concentrations during the terminal elimination phase. Table 2 also includes a summary of above parameters in these patients.

AUTOMATED PERITONEAL DIALYSIS

Studies conducted in the APD population are only reserved to the parenteral administration of antibiotics in patients without peritonitis, yet vancomycin is primarily used to treat peritonitis and is mostly administered intraperitoneally.(27, 28) With rapid cycling, the dialytic clearance of vancomycin may be increased. Therefore, if doses and dwell times used for those on the cycler are similar to those in CAPD, the result may be sub-therapeutic levels due to frequent exchanges.

To date, there has only been one study exploring intravenous vancomycin disposition in subjects on APD.(12) The primary objective was to characterize vancomycin pharmacokinetic parameters in adults without peritonitis after a single intravenous dose. Following the intravenous administration of 15 mg/kg, subjects received three cycle treatments over the course of eight hours followed by two 8-hour off-cycler dwells for a total of 24 hours. A 2-liter 2.5% dextrose dialysate prescription was used during and off-cycler dwell. The plasma half-life was 11.6 hours following an on-cycler exchange consisting of three 2-hour dwells. When the same patients were removed from the cycler and allowed to dwell for 7-8 hours, the plasma half-life increased to 62.8 hours. Although vancomycin was not dosed

intraperitoneally in this study, rapid decline in the plasma half-life support the contribution of APD in the removal of drug. Clearance values did not largely differ from those on CAPD. Approximately 30% of vancomycin was removed by APD relative to the total plasma clearance, which is close to the proportion reported in patients on CAPD. Although intraperitoneal vancomycin administration is recommended by guidelines in patients with PD peritonitis, this intravenous administration study provides a valuable insight towards drug clearance during APD.(29) It should be noted that intravenous administration of vancomycin may not be adequate to achieve effective antibacterial concentrations in the peritoneum.(30)

The current International Society for Peritoneal Dialysis (ISPD) guideline recommends supplemental dosing in order to achieve plasma vancomycin troughs above 15 mg/L when administered intermittently. Alternatively, temporarily switching to CAPD is another option for APD patients who develop peritonitis, but is not always feasible. In patients on APD, leveraging the long dwell to appreciate optimal vancomycin transfer is appropriate to ensure adequate time to achieve and sustain therapeutic levels.

IMPACT OF RESIDUAL KIDNEY FUNCTION (RKF) AND TREATMENT OUTCOME

Residual kidney function in PD patients will have a profound effect for hydrophilic drugs removed exclusively through renal filtration. Enhanced drug clearance from RKF may have implications to treatment outcomes in patients with PD-related peritonitis. Therefore, patients with greater RKF may require higher or more frequent antibiotic dosing.

The importance of RKF on the outcome of PD-related peritonitis in patients treated with antibiotics has been discussed for more than ten years, but the data describing this relationship are still scarce and controversial. The ISPD 2010 update on PD-related infections has previously recommended a 25% increase in antibiotic dose in patients with a daily urine output of over 100 mL.(31) This

recommendation has been removed in the updated 2016 guideline, which reflects the lack of evidence to support this empiric recommendation.(29) In a retrospective study examining the impact of RKF on vancomycin concentrations, the influence of RKF was found to not have a significant impact.(32) Vancomycin concentrations appeared lower in patients who were non-anuric across both modalities even though a 25% higher dose was administered to those with RKF. This however was concluded to not be statistically significant. Similar results have been published showing no difference in treatment outcomes in non-anuric and anuric patients treated with cefazolin and gentamicin.(33)

In contrast, a recent study investigating the relationship between RKF and PD-related peritonitis treatment outcomes was able to explain treatment failures related to the remaining degree of renal function.(34) Treatment failure in those with *Gram-positive* and culture-negative peritonitis were found to be significantly higher for patients with a urinary creatinine clearance greater than 0-5 mL/min compared to those who were anuric. Significantly higher relapse and recurrence were observed in those patients with *Gram-positive* or culture-negative infections and creatinine clearances greater than 5 mL/min. Cefazolin and vancomycin were the main antibiotics used in the study. These observations may be useful when attempting to understand the impact of RKF on treatment outcomes and raise the question as to whether patients with RKF greater than 5 mL/min were under-dosed with antibiotic in previous studies.

In patients treated with vancomycin, RKF may account for 10-23% of the total body clearance in PD.(12, 22) Studies examining the impact of RKF on vancomycin clearance, exposure, and treatment outcomes in PD-related peritonitis are limited. Interestingly, for the subset of patients with a glomerular filtration rate greater than 5 mL/min, RKF accounted for 39-84% of the total vancomycin clearance.(12) It would appear that the impact from RKF has a substantial effect on the total clearance of vancomycin. Thus, the recent 2016 ISPD recommendation of removing the 25% dosage increase to account for RKF is unclear as most of the studies cited accounted for a dosage increase for those who were non-anuric.(32,

35) In the absence of additional studies, dosage adjustments to account for RKF may still be appropriate as there is a substantial contribution observed on the total vancomycin clearance. For now, we can only speculate that the resulting impact in treatment failure for *Gram-positive* peritonitis may be associated with higher drug clearance values in patients with creatinine clearances greater than 5 mL/min.

THERAPEUTIC DRUG MONITORING AND PHARMACODYNAMIC RESPONSE

Vancomycin therapeutic drug monitoring is critical for patients with peritonitis and is routinely performed because 1) the concentration plays the key component for the effect and 2) the initial antibiotic dose is needed to target the maximum effect in order to allow proper eradication and prevention of resistance. Moreover, the treatment window timeframe is crucial for patients. Hence, appropriate plasma sampling during this timeframe is important, but may be difficult as the turnaround time for assay results is a rate-limiting factor in achieving desired therapeutic drug levels. Furthermore, not only is it important to ensure that the initial dose is sufficient, but also if that initial dose is able to maintain therapeutic effect throughout treatment. Yet, current clinical practice is based on empirical decisions, which may not reflect the most optimized regimen for patients on PD.

The traditional role of plasma trough concentration monitoring has been conflicting in the PD population. Unlike the established optimal plasma trough levels of 10-15 mg/L for uncomplicated infections or 15-20 mg/L for complicated infections, there is substantial interpatient variability for those patients on PD. Higher rates of PD-related peritonitis relapse have been associated with a cumulative 4-week plasma trough below 12 mg/L when compared to those maintained above that threshold.(36) In this study, vancomycin was given intravenously where plasma levels were maintained above 12 mg/L rather than the current 15 mg/L recommendation by the ISPD. The type of modality did not differ among the outcome groups, however vancomycin clearance and RKF information were not reported which may have contributed to variability in the plasma concentration. On the other hand, data from a

single-center study involving 34 PD patients experiencing PD-related peritonitis showed no relationship between plasma vancomycin levels measured during the first week and PD-related peritonitis outcomes.(37) Here, CAPD was reportedly the most frequent modality (80%) used with an average residual creatinine clearance of 2.8 mL/min/1.73m^2. Vancomycin was dosed based on ISPD recommendations and plasma levels were maintained above 15 mg/L. Of these 34 PD patients with confirmed *Gram-positive* infections, 43% of cases were associated with coagulase-negative *Staphylococcus ssp.* while only 11% of cases were due to MRSA. In total, although the frequency and level of vancomycin measurement was not associated with adverse clinical events during the first week of treatment, the number of patients studied may be too small to draw a firm conclusion. Pharmacokinetic sources of variability can be explained in part due to varying exchanges provided by the patient's PD modality, impact from RKF, and peritoneum physiology affecting drug absorption. In addition, the pharmacodynamics- or bacterial susceptibility measured by its MIC- contributes to the variability in clinical response, which may not be explained due to vancomycin pharmacokinetics alone.

Taken together, vancomycin shows substantial interindividual variability in clinical response for patients treated for PD-related peritonitis. Table 3 gives an overview of the pharmacokinetic/pharmacodynamic factors to be considered at the time of TDM of vancomycin in patients on both CAPD and APD regimens.

CONSIDERATIONS FOR INTRAPERITONEAL DOSING

Clinicians should consider dwell times that achieve substantial equilibrium between the peritoneum compartment and the systemic circulation. The reported bioavailabilities in literature are dwell-time specific and may not be applicable in all patient-specific situations. Therefore, considering the transfer half-life between the dialytic compartment and systemic circulation can be useful to understand the time that it takes to reach equilibrium (i.e., steady-state). This may take up to 15 hours

considering a transfer half-life of 3 hours.(19) In this situation, dosing during the long-dwell interval may provide adequate drug absorption to achieve therapeutic concentrations in plasma in patients on APD.

The bioavailability of vancomycin significantly increases during PD-related peritonitis. Plasma concentrations as high as 40 mg/L have been reported following a 6 hour dwell using recommended intraperitoneal doses of vancomycin in PD-related peritonitis.(14, 16) Alternatively, plasma concentrations as low as 10 mg/L have been reported following a 6 hour dwell using a 500 mg intraperitoneal dose in PD-related peritonitis.(38) Regardless of the PD modality, absorption does not largely change between CAPD or APD based on the equilibration half-lives reported.(12, 19, 20)

In patients with PD peritonitis on APD, doses of 15-20 mg/kg together with dwell times ranging from 10-15 hours may be more appropriate than the targeted concentration strategy mentioned above. TDM should also be performed to evaluate therapeutic and toxic concentration fluctuations and to maintain concentrations above 15 mg/L as recommended by the ISPD guidelines.

FUTURE RESEARCH AND DOSING GUIDELINES IN AUTOMATED PERITONEAL DIALYSIS

Empiric *Gram-positive* management using vancomycin for PD-related peritonitis in patients on APD is summarized in figure 2. This algorithm accounts for RKF and suggests a dosage increase of 20% for those who are non-anuric with a creatinine clearance greater than 5 mL/min based on observational outcome studies.(34) In addition, monitoring plasma vancomycin concentrations 48 hours post-dose would be appropriate based on previous experience. As such, re-dosing would be necessary to maintain the targeted 15 mg/L concentration. During this time, adjustments to antibiotic therapy should be guided by the microbiology or susceptibility report. This should be practiced together with routine TDM at appropriate sampling times to rationally select the effective dose for each patient. Pharmacometric modeling and simulation could help to increase the knowledge on vancomycin dose exposure response relationship and propose optimal dosing and TDM strategies in PD patients.

As above recommendations are based on limited evidence, dedicated studies are needed to support them. Table 4 highlights the knowledge gaps and propose future research topics to better tailor vancomycin treatments in PD patients with peritonitis.

CONCLUSION

Optimal dosing for vancomycin should consider both the pharmacokinetic (concentration in dialysis fluid and plasma), RKF, PD modality, and physicochemical factors (bioavailability, permeability) and pharmacodynamics (MIC and variability to the susceptibilities of the organism). Generally, vancomycin is given intraperitoneally during the long day dwell for patients on APD; this approach supports adequate equilibration during the absorption phase between dialysate and plasma to reach therapeutic levels. In addition, the impact of rapid cycling and RKF on the total body clearance has yet to be fully defined. With this in mind, TDM may be appropriate, however, there is yet to be an established protocol in PD patients with peritonitis. As the option to temporarily switch to CAPD in APD patients who develop peritonitis may not be convenient, the need for future research on the impact of the cycler on vancomycin clearance is imperative. Upcoming studies (NCT03685747) examining the pharmacokinetic of vancomycin will address some of the knowledge gaps associated with vancomycin pharmacokinetic in patients on APD. For the moment, clinicians should consider the bioavailability, dwell time, and institutional microbiological susceptibilities when dosing vancomycin in PD. Dedicated pharmacokinetic studies in adult and pediatric patients are needed to understand vancomycin disposition in PD patients on rapid-cycling modalities. The integrated use of TDM and MICs via dosing algorithms may help improve clinical outcome.

Conflict of Interests Disclosure

No competing interests.

We have read and understood *Peritoneal Dialysis International's* policy on disclosing conflicts of interest and declare that we have none.

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Table 1. Vancomycin absorption parameters in adult and pediatric non-infected and PD-related peritonitis patients on peritoneal dialysis.

Adults							
Infection Status	**Dose**	**Dwell Time (hours)**	**Bioavailability (%)**	**Dosing**	**Plasma Concentration**		**Reference**
					(mg/L)	**Time of sampling (hour)**	
Negative	30 mg/kg	6	49	Single	24.9	6	[15]
	10 mg/kg	4	65	Single	6.3	5	[25]
PD-Peritonitis	30 mg/kg	6	91	Single	40	4	[14]
	2 g	6	70	Single	39.7	6	[16]
	500 mg	6	83	Multiple	10.2	6	[38]
	15 mg/kg	4	66	Single	16.1	6	[19]
	30 mg/kg	10-12	N/A	Multiple	33.8	12	[39]
Pediatric							
Infection	**Dose**	**Dwell Time**	**Bioavailability (%)**	**Dosing**	**Plasma Concentration**		**Reference**
					(mg/L)	**Time of sampling**	
Negative	550 mg/m^2	6	70	Single	23.3	6	[17]

N/A = not reported

510 **Table 2.** Vancomycin distribution and clearance parameters in adult and pediatric non-infected and PD-related peritonitis patients on CAPD or

511 APD.

Adults								
Modality	**Infection Status**	**Route**	**V_d (L/kg)**	**Plasma Half-life (hours)**	**Clearance (mL/min)**			**Reference**
					Total	**Dialytic**	**Renal**	
CAPD	Negative	IP	0.56	111	5	1.2	N/A	[15]
		IV	0.73	92	6.4	1.4	0.65	[22]
	PD-Peritonitis	IP	0.61	N/A	N/A	15.7	N/A	[19]
		IP	0.87	N/A	8.5	12.2	N/A	[20]
		IV	0.55	104	4.1	3.8	N/A	[24]
		IV	1.1	115	7.2	1.4	N/A	[26]
APD	Negative	IV	0.4	11.6 / 62.8[a]	7.4	2.1	1.7	[12]
Pediatric								
Modality	**Infection**	**Route**	**V_d (L/kg)**	**Plasma**	**Clearance (mL/min/1.73m^2)**			**Reference**
					Total	**Dialytic**	**Renal**	
CAPD	Negative	IP	0.48	25	10.7	2.5	1.4	[17]
APD					14.9	3.1		

512 [a]Half-life during the ambulatory CAPD portion of the study. APD = automated peritoneal dialysis, CAPD = continuous ambulatory peritoneal dialysis,
513 N/A = not reported, V_d = volume of distribution
514

Table 3. Pharmacokinetic/pharmacodynamic factors for TDM consideration between CAPD and APD vancomycin regimens.

Pharmacokinetic/pharmacodynamics	PD components	CAPD	APD
Absorption	Dwell time	↓ Bioavailability	↑ Bioavailability
	Dosing route (IP vs. IV)	Same	
Distribution	Permeability (Peritonitis vs. non-peritonitis)	Same	
	Diffusion		
	Protein binding		
	Surface area		
	Vascularity		
Elimination	Dosing route (IP vs. IV)	RKF- Drives variation in systemic circulation	
	Body size & Dialysate volume	Same- Patient dependent	
	Dwell time	↑ Clearance	↓ Clearance
	Number of non-antibiotic exchanges	↓ Clearance	↑ Clearance
Pharmacodynamics	MIC/AUC	Same- Susceptibility report	

APD = Automated peritoneal dialysis, AUC = area under the vancomycin plasma-concentration time curve, CAPD = continuous ambulatory peritoneal dialysis, IP = intraperitoneal, IV = intravenous, MIC = minimal inhibitor concentration, PD = peritoneal dialysis, RKF = residual kidney function

Table 4. Proposal for critical research areas to optimize vancomycin therapy in peritoneal dialysis.

Proposal for Critical Research Areas of Needed Research for Vancomycin Therapy in Peritoneal Dialysis
▪ Effect of APD on peritoneal and plasma levels during rapid cycles
▪ Peak concentration following absorption from the long-dwell
▪ Optimal trough concentrations associated with improved clinical outcomes and the timing of trough monitoring specific for the peritoneal dialysis population
▪ Dosing regimen to achieve optimal trough concentrations
▪ Effect of residual kidney function on vancomycin disposition and its implications on dosing
▪ Factors affecting non-renal and non-dialytic clearance of vancomycin
▪ Determining appropriate clinical plasma sampling time points

APD = Automated Peritoneal Dialysis

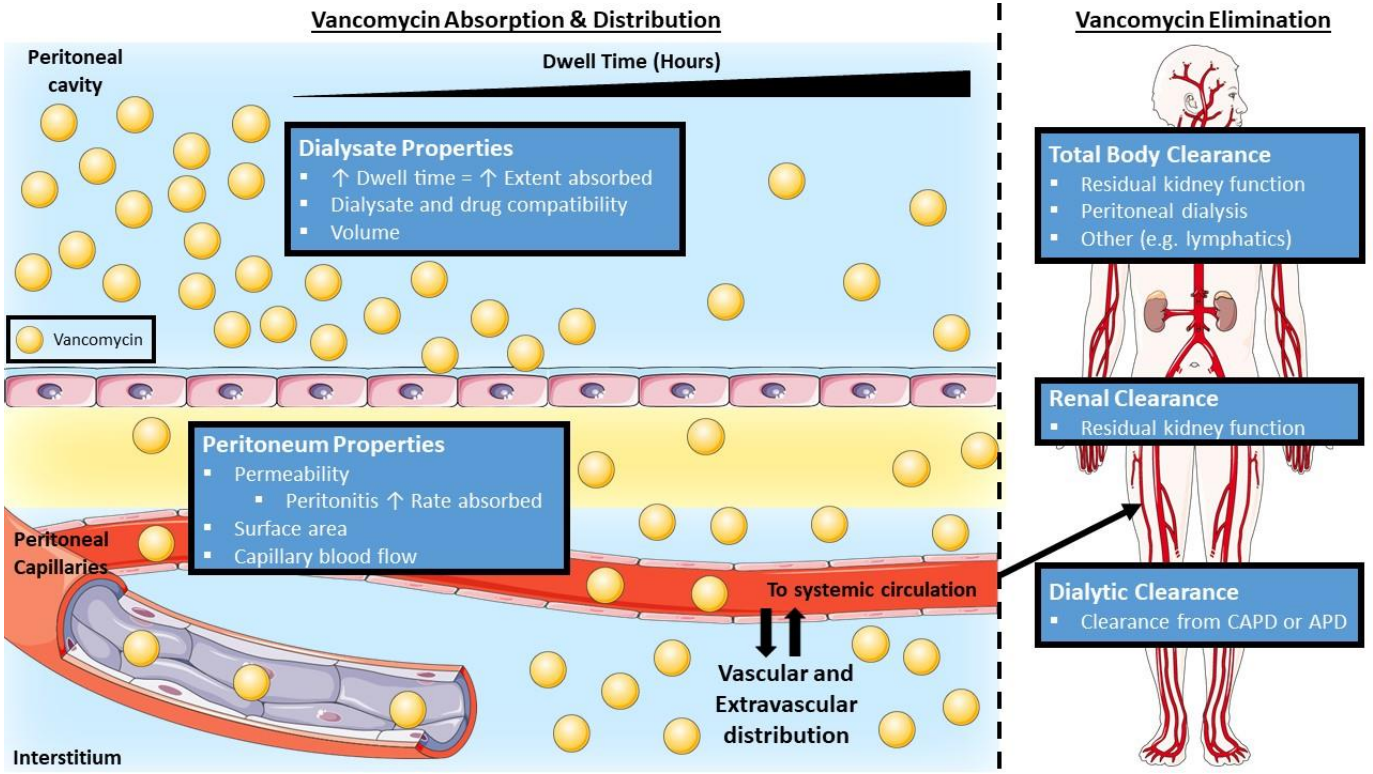

Figure 1. Illustration of vancomycin absorption, distribution and elimination following an intraperitoneal dose. Increasing the dwell time enhances vancomycin bioavailability. Peritoneum and dialysate properties should be considered as these both affect the rate and extent of absorption following an intraperitoneal dose. Following dosing and an appreciable dwell time, vancomycin is eliminated by PD, renal, and non-renal sources. These processes make up the total body clearance of vancomycin.

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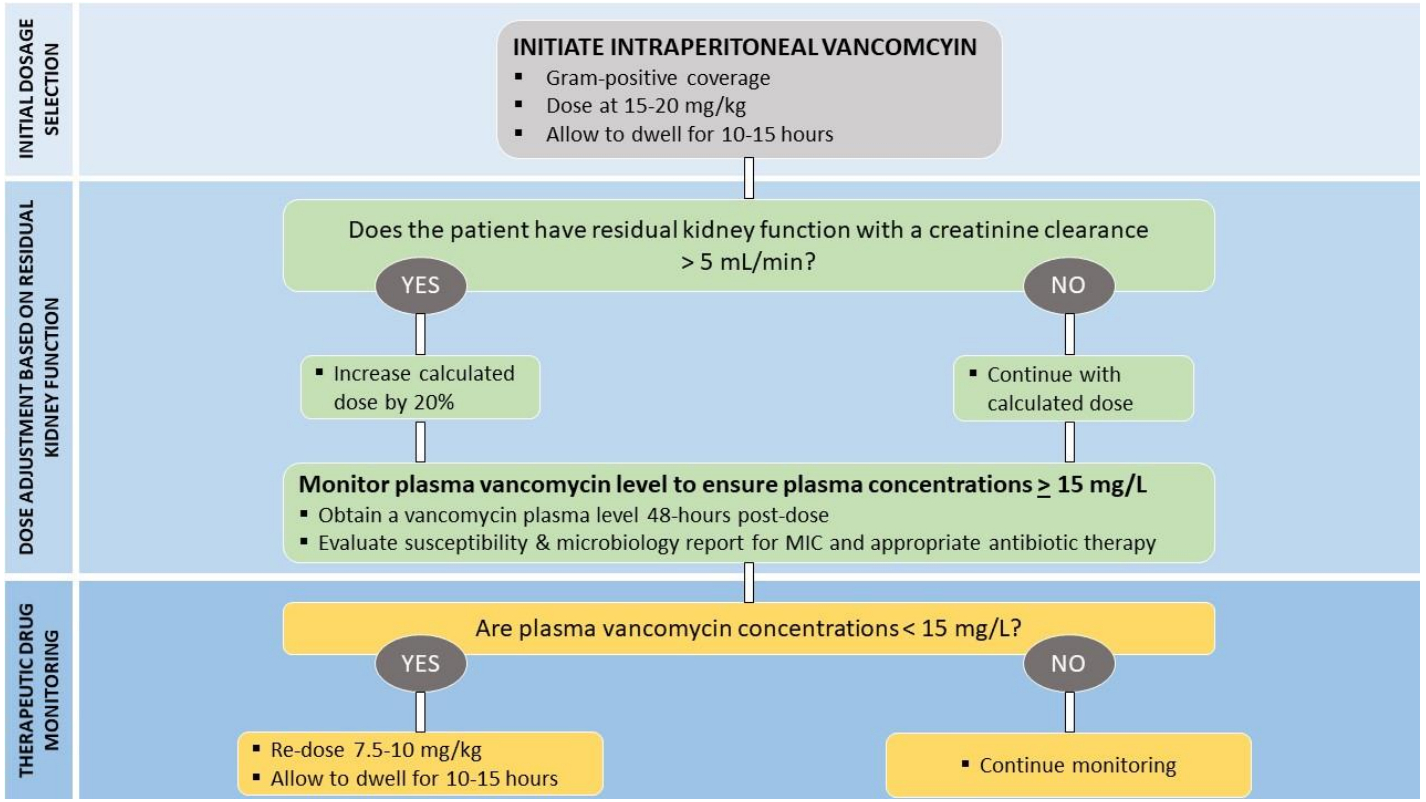

Figure 2. Proposed vancomycin dosing and monitoring algorithm in patients on automated peritoneal dialysis.

Vancomycin dosing in patients on APD with peritonitis should follow the recommended 15-20 mg/kg dose administered intraperitoneally. For those who are non-anuric with creatinine clearances > 5 mL/min, a 20% increase in the calculated dose is suggested. A vancomycin level should be obtained 48 hours post-dose. Dosage adjustments and monitoring should be based on clinical response and microbiological susceptibility reports.