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Vancomycin in Peritoneal Dialysis: Clinical Pharmacology Considerations in Therapy

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49   **Abstract**

50   Intraperitoneal vancomycin is the first line therapy in the management of peritoneal dialysis-related

51   peritonitis. However, due to the paucity of data, vancomycin dosing for peritonitis in patients on

52   automated peritoneal dialysis (APD) is empiric and based on clinical experience rather than evidence.

53   Studies in continuous ambulatory peritoneal dialysis (CAPD) patients have been used to provide

54   guidelines for dosing and are often extrapolated for APD use, but it is unclear if this is appropriate. This

55   review summarizes the available pharmacokinetic data used to inform optimal dosing in patients on

56   CAPD or APD. The determinants of vancomycin disposition and pharmacodynamic effects are critically

57   summarized, knowledge gaps explored, and a vancomycin dosing algorithm in peritoneal dialysis

58   patients is proposed.

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INTRODUCTION

74   Vancomycin is often selected as empiric first line therapy for suspected *Gram-positive* organisms

75 in peritoneal dialysis (PD) related peritonitis. However, data on vancomycin dosing in various PD

76 modalities are limited, especially for automated peritoneal dialysis (APD). The paucity of well-designed

77 pharmacokinetic studies has led to vancomycin dosing guidelines for PD patients that are based on

78 limited information resulting in the possibility of achieving sub-or supra-therapeutic trough

79 concentrations in this special patient population.(1)

80

81   PRINCIPLES OF VANCOMYCIN THERAPY

82   Vancomycin is a tricyclic glycopeptide antibiotic with broad spectrum activity against *Gram-*

83 *positive* bacteria. It is effective for the treatment of *Gram-positive* infections including peritonitis and is

84 the drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is poorly

85 absorbed following oral administration. Therefore, it is commonly administered as an intravenous

86 infusion, except in peritoneal dialysis where the route is preferentially intraperitoneal. Approximately

87 50% of vancomycin is protein-bound in plasma with a variable volume of distribution ranging between

88 0.4-1 L/kg in the non-PD population.(2, 3) An initial distribution half-life ranging from 30 minutes to 1

89 hour followed by a mean terminal elimination half-life ranging from 6-12 hours were determined

90 following intravenous dosing in patients with normal renal function.(3) Metabolism is negligible and

91 elimination occurs primarily through glomerular filtration, such that advanced renal disease substantially

92 reduces the clearance of vancomycin resulting in an elimination half-life of about 7.5 days compared to

93 4-6 hours in normal patients. This means that in patients with kidney failure, the dosing of vancomycin

94 must be adjusted.(4, 5)

95   The Clinical and Laboratory Standards Institute (CLSI) has established the vancomycin

96 breakpoint for susceptible *S. aureus* isolates with MIC values of $\leq$ 2 mg/L and intermediate or resistant

3

97   for MIC values greater than 2 mg/L.(6) Despite the CLSI defined breakpoints, treatment failure for

98   patients infected with *S. aureus* and vancomycin MICs between 1-2 mg/L have been reported compared

99   to those with lower reported MICs.(7, 8) This may be due to inappropriate selection of doses that are

100   sufficiently high to maintain plasma concentrations that exceed the MIC.

101   To optimize the vancomycin exposure-response relationship for efficacy during *S. aureus*

102   infections, one must examine the ratio of the area under the concentration-time curve and the MIC

103   (AUC/MIC). Vancomycin trough concentrations between 15-20 mg/L for MIC breakpoints $\leq$ 1 mg/L

104   ensures a ratio of $\geq$ 400 and has been an advocated target for clinical effectiveness.(3, 9) It should be

105   noted that goal trough values recommended by consensus guidelines for efficacy may lead to

106   nephrotoxicity, which might be a consideration for patients on PD with residual kidney function.(10) This

107   however, is not well studied. In practice, clinical judgement together with therapeutic drug monitoring

108   (TDM) of steady-state vancomycin plasma concentrations is a common approach in the treatment of

109   peritonitis in PD.

110

111   PHARMACOKINETIC/PHARMACODYNAMIC MODELING AND SIMULATION

112   Pharmacokinetic/pharmacodynamic modeling and simulation is an innovative approach that can

113   help inform crucial decisions, such as predicting clinical endpoints of new doses and dosing regimens or

114   optimization of drug regimens. By understanding what the body does to the drug (Pharmacokinetics)

115   and what the drug does to the body (Pharmacodynamics), dosing regimens can be tailored to the PD

116   population to avoid nephrotoxicity, retain antimicrobial eradication and suppressing the emergence of

117   resistance. Regulatory authorities mandate the submission of pharmacokinetic/pharmacodynamic

118   evaluations for drug application, which include dose evaluation in special populations. However, despite

119   the evaluation of the need of dose adjustments for patients with end stage renal disease (ESRD) - such

120   as those on hemodialysis- the process is not well established for old drugs. Even in those cases when

121   dose adjustments are proposed for patients with ESRD, there is minimal attention in patients on PD.

122   This review aims to summarize the available evidence on vancomycin pharmacokinetic and

123   pharmacodynamic PD-related studies, address the physicochemical and PD modality-specific

124   considerations- with attention on APD, and highlight areas where research is needed on dosing

125   vancomycin for PD-related peritonitis.

126

127   **VANCOMYCIN PHYSICOCHEMICAL PROPERTIES AND DRUG TRANSPORT ACROSS THE PERITONEUM**

128   Movement of vancomycin from the peritoneum cavity to plasma is based on Fick's Law (figure

129   1). Middle molecular weight solutes such as vancomycin (1,486 g/mol) are dependent on dwell time

130   during PD for absorption into the plasma. Based upon a single dose study of six non-infected subjects on

131   PD, vancomycin has a lower dialysate to plasma ratio than urea and creatinine at two hours.(11) There

132   is no correlation between vancomycin PD clearance and dialysis adequacy (Kt/V) following an

133   intravenous dose in patients on APD.(12)

134   Teicoplanin, a glycopeptide antibiotic with a similar molecular structure (1,564 g/mol) and

135   spectrum of activity to vancomycin, was studied in non-infected adults on continuous ambulatory

136   peritoneal dialysis (CAPD).(13) The absolute bioavailability (F_{ip}) was calculated using dialysate drug

137   concentration (corrected for amount remaining in the cavity) and drug amount sampled, which was then

138   plotted against a total dwell time of five hours. Teicoplanin systemic bioavailability, reflecting transfer

139   from the peritoneal space, was directly related to dwell time. Furthermore, the consistency in

140   absorption increased with time suggesting that complete and less variable bioavailability with

141   teicoplanin can be achieved with longer dwell times.

142   The rate at which vancomycin is absorbed is dependent on the permeability of the peritoneal

143   membrane. Vancomycin intraperitoneal to systemic transfer rate increases in patients with

144   inflammatory peritonitis.(14)

145

146   VANCOMYCIN BIOAVAILABILITY DURING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

147   Vancomycin pharmacokinetics has primarily been studied in patients on CAPD. Bioavailability

148   studies conducted in these patients typically employ a 6-hour dwell time. The F_{ip}, or the amount of

149   vancomycin reaching systemic circulation from the peritoneal space relative to an intravenous dose, is

150   approximately 50%.(15) Supporting the hypothesis of a leaky peritoneum due to membrane

151   inflammation, patients on CAPD with peritonitis have a F_{ip} of 70-91%.(14, 16) Bioavailability changes can

152   also be observed with different age cohorts. For example, in a pediatric study in children aged 5-17 years

153   old, the bioavailability was reported to be as high as about 70% in the absence of peritonitis.(17)

154   A summary of the absorption parameters from studies conducted in infected and non-infected

155   patients on CAPD is depicted in table 1. The equilibration half-life describes the time allowed for drug

156   transfer between the peritoneal space to the systemic circulation following an intraperitoneal dose of

157   vancomycin. Following intraperitoneal dosing, vancomycin equilibration half-life in patients on CAPD

158   without peritonitis was 2.9 hours and those with peritonitis 1.6-2.9 hours.(18-20) Assuming no

159   differences between peritoneum transport in those with or without peritonitis and five half-lives,

160   steady-state equilibrium between the dialytic compartment and systemic circulation would be achieved

161   following a 10-15 hour dwell.

162

163   VANCOMYCIN BIOAVAILABILITY DURING AUTOMATED PERITONEAL DIALYSIS

164   Vancomycin possess the desired physiochemical properties as a drug candidate for

165   intraperitoneal administration in APD patients. In addition, with its well-established stability in PD fluids,

166   bioavailability is adequate as long as sufficient dwelling time is allowed for drug absorption. However,

167   the appropriate duration of the dwell time has not been well studied. Hence, it is crucial to monitor

168   vancomycin levels frequently to adjust dosing to get therapeutic concentrations in each individual

169   patient.

170

171   **VANCOMYCIN CLEARANCE DURING PERITONEAL DIALYSIS**

172   Vancomycin elimination following an intraperitoneal dose is governed by its total body

173   clearance. Total body clearance is the sum of clearances contributed from elimination organs, mainly

174   kidneys, in the case of vancomycin, and is defined as the volume of plasma cleared of vancomycin per

175   time unit. Elimination processes in PD patients include those originating from residual kidney function

176   (RKF), other non-renal sources plus the drug cleared through PD. Total body clearance is especially

177   important as it controls the overall exposure of vancomycin for the given bioavailability achieved from a

178   dwell. Dialytic clearance is defined as the volume of plasma that has been cleared of vancomycin (i.e.

179   removed from systemic circulation into the peritoneal space) by PD per unit time. Figure 1 describes the

180   various clearance processes involved in vancomycin elimination following an intraperitoneal dose.

181   Moreover, a summary of vancomycin pharmacokinetic systemic parameters is provided in table 2.

182   Vancomycin clearance in patients on PD differs among studies due to several factors including the

183   presence or absence of peritonitis, presence and extent of RKF, dwell times, dialysate volume, effect of

184   antibiotic-free PD exchanges, and age.(21)

185

186   CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

187   Continuous ambulatory peritoneal dialysis typically employs short dwell times (4-6 hours), which

188   may not be sufficient to reach equilibration between the dialysate and plasma. Studies in non-infected

189   adult CAPD patients report dialytic clearances ranging between 1.2-2.4 mL/min, which account for 20-

190   25% of the total plasma clearance.(15, 22, 23) In patients with peritonitis, vancomycin dialytic clearance

191   increases to 3.8 mL/min following a less-than five-hour exchange.(24) Clearances of up to 8.5 mL/min

192   after the first 4 hours of exchange have also been reported.(16) Vancomycin clearance through

193   elimination from the drained peritoneal dialysate contributes to 20-70% of the total plasma

194   clearance.(16, 24) As a consequence, vancomycin elimination half-life in the systemic circulation ranges

195   between 66–115 hours in patients on CAPD.(22, 24-26) One major reason in the reported variability in

196   the plasma half-life could be the difference in the sampling times which may not completely capture the

197   decline of the plasma concentrations during the terminal elimination phase. Table 2 also includes a

198   summary of above parameters in these patients.

199

200   AUTOMATED PERITONEAL DIALYSIS

201   Studies conducted in the APD population are only reserved to the parenteral administration of

202   antibiotics in patients without peritonitis, yet vancomycin is primarily used to treat peritonitis and is

203   mostly administered intraperitoneally.(27, 28) With rapid cycling, the dialytic clearance of vancomycin

204   may be increased. Therefore, if doses and dwell times used for those on the cycler are similar to those in

205   CAPD, the result may be sub-therapeutic levels due to frequent exchanges.

206   To date, there has only been one study exploring intravenous vancomycin disposition in subjects

207   on APD.(12) The primary objective was to characterize vancomycin pharmacokinetic parameters in

208   adults without peritonitis after a single intravenous dose. Following the intravenous administration of 15

209   mg/kg, subjects received three cycle treatments over the course of eight hours followed by two 8-hour

210   off-cycler dwells for a total of 24 hours. A 2-liter 2.5% dextrose dialysate prescription was used during

211   and off-cycler dwell. The plasma half-life was 11.6 hours following an on-cycler exchange consisting of

212   three 2-hour dwells. When the same patients were removed from the cycler and allowed to dwell for 7-

213   8 hours, the plasma half-life increased to 62.8 hours. Although vancomycin was not dosed

8

214   intraperitoneally in this study, rapid decline in the plasma half-life support the contribution of APD in the

215   removal of drug. Clearance values did not largely differ from those on CAPD. Approximately 30% of

216   vancomycin was removed by APD relative to the total plasma clearance, which is close to the proportion

217   reported in patients on CAPD. Although intraperitoneal vancomycin administration is recommended by

218   guidelines in patients with PD peritonitis, this intravenous administration study provides a valuable

219   insight towards drug clearance during APD.(29) It should be noted that intravenous administration of

220   vancomycin may not be adequate to achieve effective antibacterial concentrations in the

221   peritoneum.(30)

222   The current International Society for Peritoneal Dialysis (ISPD) guideline recommends

223   supplemental dosing in order to achieve plasma vancomycin troughs above 15 mg/L when administered

224   intermittently. Alternatively, temporarily switching to CAPD is another option for APD patients who

225   develop peritonitis, but is not always feasible. In patients on APD, leveraging the long dwell to

226   appreciate optimal vancomycin transfer is appropriate to ensure adequate time to achieve and sustain

227   therapeutic levels.

228

229   **IMPACT OF RESIDUAL KIDNEY FUNCTION (RKF) AND TREATMENT OUTCOME**

230   Residual kidney function in PD patients will have a profound effect for hydrophilic drugs

231   removed exclusively through renal filtration. Enhanced drug clearance from RKF may have implications

232   to treatment outcomes in patients with PD-related peritonitis. Therefore, patients with greater RKF may

233   require higher or more frequent antibiotic dosing.

234   The importance of RKF on the outcome of PD-related peritonitis in patients treated with

235   antibiotics has been discussed for more than ten years, but the data describing this relationship are still

236   scarce and controversial. The ISPD 2010 update on PD-related infections has previously recommended a

237   25% increase in antibiotic dose in patients with a daily urine output of over 100 mL.(31) This

238 recommendation has been removed in the updated 2016 guideline, which reflects the lack of evidence

239 to support this empiric recommendation.(29) In a retrospective study examining the impact of RKF on

240 vancomycin concentrations, the influence of RKF was found to not have a significant impact.(32)

241 Vancomycin concentrations appeared lower in patients who were non-anuric across both modalities

242 even though a 25% higher dose was administered to those with RKF. This however was concluded to not

243 be statistically significant. Similar results have been published showing no difference in treatment

244 outcomes in non-anuric and anuric patients treated with cefazolin and gentamicin.(33)

245   In contrast, a recent study investigating the relationship between RKF and PD-related peritonitis

246 treatment outcomes was able to explain treatment failures related to the remaining degree of renal

247 function.(34) Treatment failure in those with *Gram-positive* and culture-negative peritonitis were found

248 to be significantly higher for patients with a urinary creatinine clearance greater than 0-5 mL/min

249 compared to those who were anuric. Significantly higher relapse and recurrence were observed in those

250 patients with *Gram-positive* or culture-negative infections and creatinine clearances greater than 5

251 mL/min. Cefazolin and vancomycin were the main antibiotics used in the study. These observations may

252 be useful when attempting to understand the impact of RKF on treatment outcomes and raise the

253 question as to whether patients with RKF greater than 5 mL/min were under-dosed with antibiotic in

254 previous studies.

255   In patients treated with vancomycin, RKF may account for 10-23% of the total body clearance in

256 PD.(12, 22) Studies examining the impact of RKF on vancomycin clearance, exposure, and treatment

257 outcomes in PD-related peritonitis are limited. Interestingly, for the subset of patients with a glomerular

258 filtration rate greater than 5 mL/min, RKF accounted for 39-84% of the total vancomycin clearance.(12)

259 It would appear that the impact from RKF has a substantial effect on the total clearance of vancomycin.

260 Thus, the recent 2016 ISPD recommendation of removing the 25% dosage increase to account for RKF is

261 unclear as most of the studies cited accounted for a dosage increase for those who were non-anuric.(32,

262   35) In the absence of additional studies, dosage adjustments to account for RKF may still be appropriate

263   as there is a substantial contribution observed on the total vancomycin clearance. For now, we can only

264   speculate that the resulting impact in treatment failure for *Gram-positive* peritonitis may be associated

265   with higher drug clearance values in patients with creatinine clearances greater than 5 mL/min.

266

267   **THERAPEUTIC DRUG MONITORING AND PHARMACODYNAMIC RESPONSE**

268   Vancomycin therapeutic drug monitoring is critical for patients with peritonitis and is routinely

269   performed because 1) the concentration plays the key component for the effect and 2) the initial

270   antibiotic dose is needed to target the maximum effect in order to allow proper eradication and

271   prevention of resistance. Moreover, the treatment window timeframe is crucial for patients. Hence,

272   appropriate plasma sampling during this timeframe is important, but may be difficult as the turnaround

273   time for assay results is a rate-limiting factor in achieving desired therapeutic drug levels. Furthermore,

274   not only is it important to ensure that the initial dose is sufficient, but also if that initial dose is able to

275   maintain therapeutic effect throughout treatment. Yet, current clinical practice is based on empirical

276   decisions, which may not reflect the most optimized regimen for patients on PD.

277   The traditional role of plasma trough concentration monitoring has been conflicting in the PD

278   population. Unlike the established optimal plasma trough levels of 10-15 mg/L for uncomplicated

279   infections or 15-20 mg/L for complicated infections, there is substantial interpatient variability for those

280   patients on PD. Higher rates of PD-related peritonitis relapse have been associated with a cumulative 4-

281   week plasma trough below 12 mg/L when compared to those maintained above that threshold.(36) In

282   this study, vancomycin was given intravenously where plasma levels were maintained above 12 mg/L

283   rather than the current 15 mg/L recommendation by the ISPD. The type of modality did not differ

284   among the outcome groups, however vancomycin clearance and RKF information were not reported

285   which may have contributed to variability in the plasma concentration. On the other hand, data from a

11

286   single-center study involving 34 PD patients experiencing PD-related peritonitis showed no relationship

287   between plasma vancomycin levels measured during the first week and PD-related peritonitis

288   outcomes.(37) Here, CAPD was reportedly the most frequent modality (80%) used with an average

289   residual creatinine clearance of 2.8 mL/min/1.73m^2. Vancomycin was dosed based on ISPD

290   recommendations and plasma levels were maintained above 15 mg/L. Of these 34 PD patients with

291   confirmed *Gram-positive* infections, 43% of cases were associated with coagulase-negative

292   *Staphylococcus ssp.* while only 11% of cases were due to MRSA. In total, although the frequency and

293   level of vancomycin measurement was not associated with adverse clinical events during the first week

294   of treatment, the number of patients studied may be too small to draw a firm conclusion.

295   Pharmacokinetic sources of variability can be explained in part due to varying exchanges provided by the

296   patient's PD modality, impact from RKF, and peritoneum physiology affecting drug absorption. In

297   addition, the pharmacodynamics- or bacterial susceptibility measured by its MIC- contributes to the

298   variability in clinical response, which may not be explained due to vancomycin pharmacokinetics alone.

299   Taken together, vancomycin shows substantial interindividual variability in clinical response for

300   patients treated for PD-related peritonitis. Table 3 gives an overview of the

301   pharmacokinetic/pharmacodynamic factors to be considered at the time of TDM of vancomycin in

302   patients on both CAPD and APD regimens.

303

304   **CONSIDERATIONS FOR INTRAPERITONEAL DOSING**

305   Clinicians should consider dwell times that achieve substantial equilibrium between the

306   peritoneum compartment and the systemic circulation. The reported bioavailabilities in literature are

307   dwell-time specific and may not be applicable in all patient-specific situations. Therefore, considering

308   the transfer half-life between the dialytic compartment and systemic circulation can be useful to

309   understand the time that it takes to reach equilibrium (i.e., steady-state). This may take up to 15 hours

310   considering a transfer half-life of 3 hours.(19) In this situation, dosing during the long-dwell interval may

311   provide adequate drug absorption to achieve therapeutic concentrations in plasma in patients on APD.

312   The bioavailability of vancomycin significantly increases during PD-related peritonitis. Plasma

313   concentrations as high as 40 mg/L have been reported following a 6 hour dwell using recommended

314   intraperitoneal doses of vancomycin in PD-related peritonitis.(14, 16) Alternatively, plasma

315   concentrations as low as 10 mg/L have been reported following a 6 hour dwell using a 500 mg

316   intraperitoneal dose in PD-related peritonitis.(38) Regardless of the PD modality, absorption does not

317   largely change between CAPD or APD based on the equilibration half-lives reported.(12, 19, 20)

318   In patients with PD peritonitis on APD, doses of 15-20 mg/kg together with dwell times ranging

319   from 10-15 hours may be more appropriate than the targeted concentration strategy mentioned above.

320   TDM should also be performed to evaluate therapeutic and toxic concentration fluctuations and to

321   maintain concentrations above 15 mg/L as recommended by the ISPD guidelines.

322

323   **FUTURE RESEARCH AND DOSING GUIDELINES IN AUTOMATED PERITONEAL DIALYSIS**

324   Empiric *Gram-positive* management using vancomycin for PD-related peritonitis in patients on

325   APD is summarized in figure 2. This algorithm accounts for RKF and suggests a dosage increase of 20%

326   for those who are non-anuric with a creatinine clearance greater than 5 mL/min based on observational

327   outcome studies.(34) In addition, monitoring plasma vancomycin concentrations 48 hours post-dose

328   would be appropriate based on previous experience. As such, re-dosing would be necessary to maintain

329   the targeted 15 mg/L concentration. During this time, adjustments to antibiotic therapy should be

330   guided by the microbiology or susceptibility report. This should be practiced together with routine TDM

331   at appropriate sampling times to rationally select the effective dose for each patient. Pharmacometric

332   modeling and simulation could help to increase the knowledge on vancomycin dose exposure response

333   relationship and propose optimal dosing and TDM strategies in PD patients.

334   As above recommendations are based on limited evidence, dedicated studies are needed to

335   support them. Table 4 highlights the knowledge gaps and propose future research topics to better tailor

336   vancomycin treatments in PD patients with peritonitis.

337

338   **CONCLUSION**

339   Optimal dosing for vancomycin should consider both the pharmacokinetic (concentration in

340   dialysis fluid and plasma), RKF, PD modality, and physicochemical factors (bioavailability, permeability)

341   and pharmacodynamics (MIC and variability to the susceptibilities of the organism). Generally,

342   vancomycin is given intraperitoneally during the long day dwell for patients on APD; this approach

343   supports adequate equilibration during the absorption phase between dialysate and plasma to reach

344   therapeutic levels. In addition, the impact of rapid cycling and RKF on the total body clearance has yet to

345   be fully defined. With this in mind, TDM may be appropriate, however, there is yet to be an established

346   protocol in PD patients with peritonitis. As the option to temporarily switch to CAPD in APD patients

347   who develop peritonitis may not be convenient, the need for future research on the impact of the cycler

348   on vancomycin clearance is imperative. Upcoming studies (NCT03685747) examining the

349   pharmacokinetic of vancomycin will address some of the knowledge gaps associated with vancomycin

350   pharmacokinetic in patients on APD. For the moment, clinicians should consider the bioavailability,

351   dwell time, and institutional microbiological susceptibilities when dosing vancomycin in PD. Dedicated

352   pharmacokinetic studies in adult and pediatric patients are needed to understand vancomycin

353   disposition in PD patients on rapid-cycling modalities. The integrated use of TDM and MICs via dosing

354   algorithms may help improve clinical outcome.

355

356

357

358   **Conflict of Interests Disclosure**

359   No competing interests.

360   We have read and understood *Peritoneal Dialysis International's* policy on disclosing conflicts of interest

361   and declare that we have none.

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504 **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]

505 N/A = not reported

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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) Total	Dialytic	Renal	Reference
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) Total	Dialytic	Renal	Reference
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
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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

521   **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

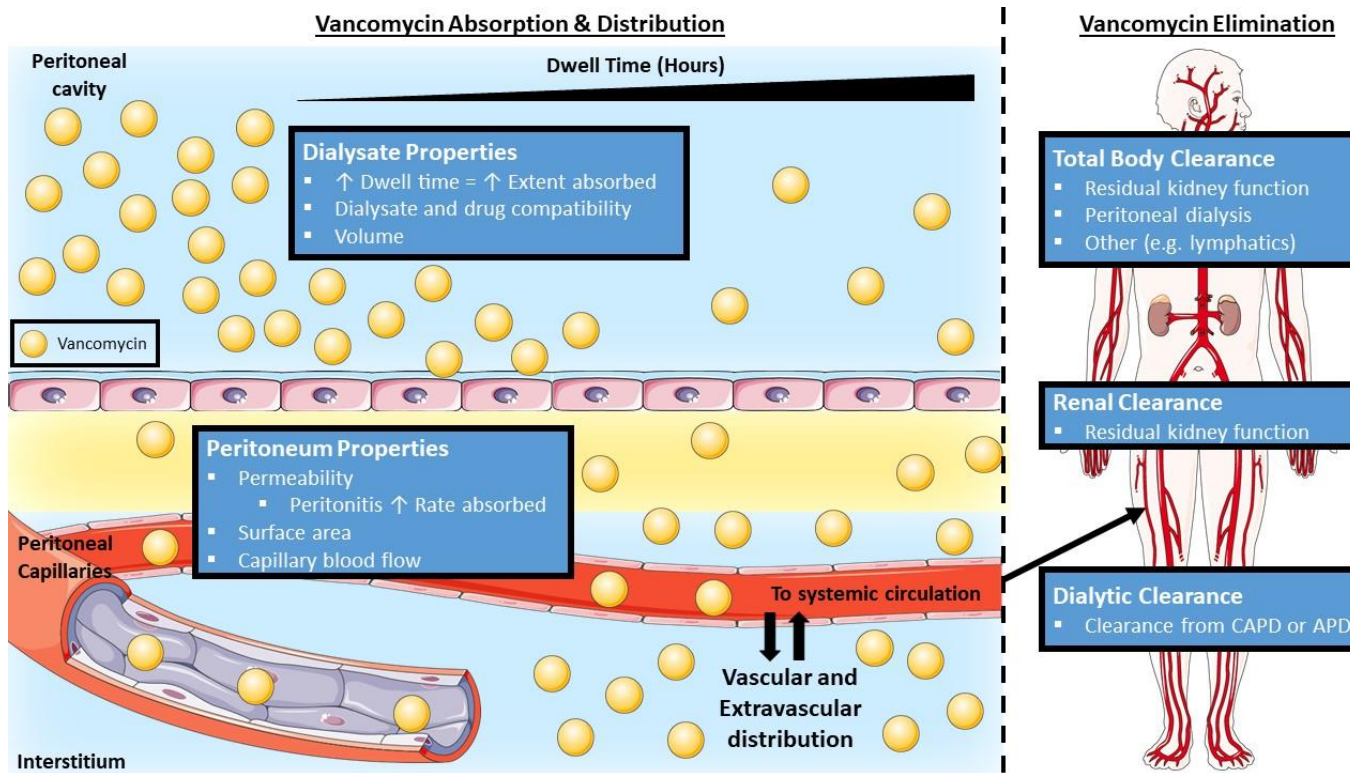522   APD = Automated Peritoneal Dialysis

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**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.

This illustration is a derivative of "Simple squamous epithelium", "Arteries", "Arterial circulation" and "Bubble" by Servier Medical Art

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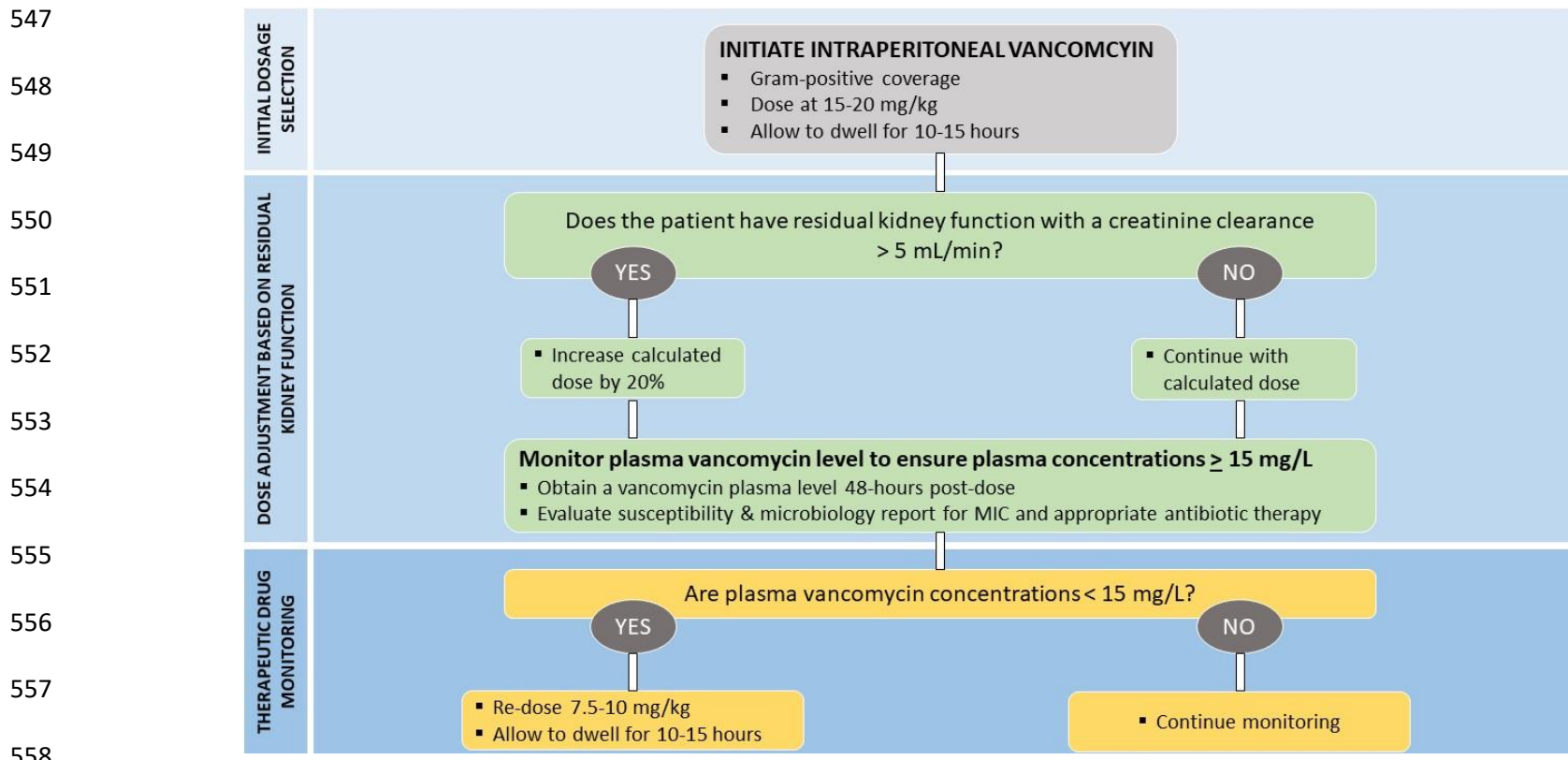
Figure 2. Proposed vancomycin dosing and monitoring algorithm in patients on automated peritoneal dialysis.

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.