

2-17-2020

## Vancomycin in peritoneal dialysis: Clinical pharmacology considerations in therapy.

Edwin Lam  
*Thomas Jefferson University*

Yi Ting Kayla Lien  
*University of Florida*

Walter K. Kraft  
*Thomas Jefferson University*

Beth Piraino  
*University of Pittsburgh*

Follow this and additional works at: <https://jdc.jefferson.edu/petfp>

 University of Florida Digital Pharmacology Commons

**[Let us know how access to this document benefits you](#)**

---

*See next page for additional authors*

### Recommended Citation

Lam, Edwin; Lien, Yi Ting Kayla; Kraft, Walter K.; Piraino, Beth; Vozmediano, Valvanera; Schmidt, Stephan; and Zhang, Jingjing, "Vancomycin in peritoneal dialysis: Clinical pharmacology considerations in therapy." (2020). *Department of Pharmacology and Experimental Therapeutics Faculty Papers*. Paper 118.

<https://jdc.jefferson.edu/petfp/118>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Pharmacology and Experimental Therapeutics Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: [JeffersonDigitalCommons@jefferson.edu](mailto:JeffersonDigitalCommons@jefferson.edu).

---

**Authors**

Edwin Lam, Yi Ting Kayla Lien, Walter K. Kraft, Beth Piraino, Valvanera Vozmediano, Stephan Schmidt, and Jingjing Zhang

1 **Vancomycin in Peritoneal Dialysis: Clinical Pharmacology Considerations in Therapy**

2

3 **Running title:** Vancomycin in PD

4

5 **Authors and Affiliations:** Edwin Lam<sup>1</sup>, Yi Ting (Kayla) Lien<sup>2</sup>, Walter K. Kraft<sup>1</sup>, Beth Piraino<sup>3</sup>, Valvanera  
6 Vozmediano<sup>2</sup>, Stephan Schmidt<sup>2</sup>, Jingjing Zhang<sup>4</sup>

7

8 Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University,  
9 Philadelphia, Pennsylvania, USA<sup>1</sup>; Center for Pharmacometrics and Systems Pharmacology, Department  
10 of Pharmaceutics, College of Pharmacy, University of Florida, Lake Nona (Orlando), Florida, USA<sup>2</sup>; Renal  
11 Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA<sup>3</sup>;  
12 Department of Medicine, Division of Nephrology, Thomas Jefferson University, Philadelphia, PA, USA<sup>4</sup>

13

14 **Acknowledgements:** Edwin Lam is supported by a National Institutes of Health institutional (NIH)  
15 training grant T32GM008562

16

17 **Corresponding author:**

18 Jingjing Zhang, MD, PhD; [Jingjing.zhang@jefferson.edu](mailto:Jingjing.zhang@jefferson.edu)

19 Department of Medicine – Division of Nephrology

20 Thomas Jefferson University

21 833 Chestnut East, Suite 700

22 Philadelphia, PA 19107-5244

23 Tel: 215-955-6550

24 Fax: 215-503-4099

25

26 **Manuscript Metrics**

27 Title Characters (with spaces) 82/90

28 Running Title Characters (with spaces) 16/30

29 Body of manuscript (words) 3465/4000

30 Figures 2

31 Tables 4

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

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.

59

60

61

62

63

64

65

66

67

68

69

70

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

73 **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

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 cyclers 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

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

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<sup>2</sup>. 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 cyclor  
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.

362 **References**

- 363 1. Salzer WL. Peritoneal dialysis-related peritonitis: Challenges and solutions. *Int J Nephrol*  
364 *Renovasc Dis.* 2018; 11:173-186.  
365
- 366 2. Marsot A, Boulamery A, Bruguerolle B, Simon N. Vancomycin: A review of population  
367 pharmacokinetic analyses. *Clin Pharmacokinet.* 2012; 51:1-13.  
368
- 369 3. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Jr., Craig W, Billeter M, et al. Therapeutic  
370 monitoring of vancomycin in adult patients: A consensus review of the american society of  
371 health-system pharmacists, the infectious diseases society of america, and the society of  
372 infectious diseases pharmacists. *Am J Health Syst Pharm.* 2009; 66:82-98.  
373
- 374 4. Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients  
375 with various degrees of renal function. *Antimicrob Agents Chemother.* 1984; 25:433-7.  
376
- 377 5. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet.*  
378 1986; 11:257-82.  
379
- 380 6. Tenover FC, Moellering RC, Jr. The rationale for revising the clinical and laboratory standards  
381 institute vancomycin minimal inhibitory concentration interpretive criteria for staphylococcus  
382 aureus. *Clin Infect Dis.* 2007; 44:1208-15.  
383
- 384 7. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Jr., Eliopoulos GM.  
385 Relationship of mic and bactericidal activity to efficacy of vancomycin for treatment of  
386 methicillin-resistant staphylococcus aureus bacteremia. *J Clin Microbiol.* 2004; 42:2398-402.  
387
- 388 8. Howden BP, Ward PB, Charles PG, Korman TM, Fuller A, du Cros P, et al. Treatment outcomes  
389 for serious infections caused by methicillin-resistant staphylococcus aureus with reduced  
390 vancomycin susceptibility. *Clin Infect Dis.* 2004; 38:521-8.  
391
- 392 9. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin  
393 and other antimicrobials in patients with staphylococcus aureus lower respiratory tract  
394 infections. *Clin Pharmacokinet.* 2004; 43:925-42.  
395
- 396 10. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther.* 2017;  
397 102:459-469.  
398
- 399 11. Brophy DF, Sowinski KM, Kraus MA, Moe SM, Klaunig JE, Mueller BA. Small and middle  
400 molecular weight solute clearance in nocturnal intermittent peritoneal dialysis. *Perit Dial Int.*  
401 1999; 19:534-9.  
402
- 403 12. Manley HJ, Bailie GR, Frye RF, McGoldrick MD. Intravenous vancomycin pharmacokinetics in  
404 automated peritoneal dialysis patients. *Perit Dial Int.* 2001; 21:378-85.  
405
- 406 13. Brouard RJ, Kapusnik JE, Gambertoglio JG, Schoenfeld PY, Sachdeva M, Freel K, et al. Teicoplanin  
407 pharmacokinetics and bioavailability during peritoneal dialysis. *Clin Pharmacol Ther.* 1989;  
408 45:674-81.

- 409 14. Morse GD, Apicella MA, Walshe JJ. Absorption of intraperitoneal antibiotics. *Drug Intell Clin*  
410 *Pharm.* 1988; 22:58-61.  
411
- 412 15. Morse GD, Farolino DF, Apicella MA, Walshe JJ. Comparative study of intraperitoneal and  
413 intravenous vancomycin pharmacokinetics during continuous ambulatory peritoneal dialysis.  
414 *Antimicrob Agents Chemother.* 1987; 31:173-7.  
415
- 416 16. Montanes Pauls B, Alminana MA, Casabo Alos VG. Vancomycin pharmacokinetics during  
417 continuous ambulatory peritoneal dialysis in patients with peritonitis. *Eur J Pharm Sci.* 2011;  
418 43:212-6.  
419
- 420 17. Blowey DL, Warady BA, Abdel-Rahman S, Frye RF, Manley HJ. Vancomycin disposition following  
421 intraperitoneal administration in children receiving peritoneal dialysis. *Perit Dial Int.* 2007;  
422 27:79-85.  
423
- 424 18. Rogge MC, Johnson CA, Zimmerman SW, Welling PG. Vancomycin disposition during continuous  
425 ambulatory peritoneal dialysis: A pharmacokinetic analysis of peritoneal drug transport.  
426 *Antimicrob Agents Chemother.* 1985; 27:578-82.  
427
- 428 19. Bailie GR, Eisele G, Venezia RA, Yocum D, Hollister A. Prediction of serum vancomycin  
429 concentrations following intraperitoneal loading doses in continuous ambulatory peritoneal  
430 dialysis patients with peritonitis. *Clin Pharmacokinet.* 1992; 22:298-307.  
431
- 432 20. Neal D, Bailie GR. Clearance from dialysate and equilibration of intraperitoneal vancomycin in  
433 continuous ambulatory peritoneal dialysis. *Clin Pharmacokinet.* 1990; 18:485-90.  
434
- 435 21. Paton TW, Cornish WR, Manuel MA, Hardy BG. Drug therapy in patients undergoing peritoneal  
436 dialysis. Clinical pharmacokinetic considerations. *Clin Pharmacokinet.* 1985; 10:404-25.  
437
- 438 22. Blevins RD, Halstenson CE, Salem NG, Matzke GR. Pharmacokinetics of vancomycin in patients  
439 undergoing continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother.* 1984;  
440 25:603-6.  
441
- 442 23. Pancorbo S, Comty C. Peritoneal transport of vancomycin in 4 patients undergoing continuous  
443 ambulatory peritoneal dialysis. *Nephron.* 1982; 31:37-9.  
444
- 445 24. Harford AM, Sica DA, Tartaglione T, Polk RE, Dalton HP, Poynor W. Vancomycin  
446 pharmacokinetics in continuous ambulatory peritoneal dialysis patients with peritonitis.  
447 *Nephron.* 1986; 43:217-22.  
448
- 449 25. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC. Vancomycin kinetics during continuous  
450 ambulatory peritoneal dialysis. *Clin Pharmacol Ther.* 1983; 34:631-7.  
451
- 452 26. Whitby M, Edwards R, Aston E, Finch RG. Pharmacokinetics of single dose intravenous  
453 vancomycin in capd peritonitis. *J Antimicrob Chemother.* 1987; 19:351-7.  
454

- 455 27. Tobudic S, Matzneller P, Stoiser B, Wenisch JM, Zeitlinger M, Vychytil A, et al. Pharmacokinetics  
456 of intraperitoneal and intravenous fosfomycin in automated peritoneal dialysis patients without  
457 peritonitis. *Antimicrob Agents Chemother.* 2012; 56:3992-5.  
458
- 459 28. Wiesholzer M, Pichler P, Reznicek G, Wimmer M, Kussmann M, Balcke P, et al. An open,  
460 randomized, single-center, crossover pharmacokinetic study of meropenem after  
461 intraperitoneal and intravenous administration in patients receiving automated peritoneal  
462 dialysis. *Antimicrob Agents Chemother.* 2016; 60:2790-7.  
463
- 464 29. Li PK, Szeto CC, Piraino B, de Arteaga J, Fan S, Figueiredo AE, et al. Ispd peritonitis  
465 recommendations: 2016 update on prevention and treatment. *Perit Dial Int.* 2016; 36:481-508.  
466
- 467 30. Cardone KE, Chen WZ, Grabe DW, Batzold A, Manley HJ, Lodise TP. Evaluation of the  
468 pharmacodynamic profile of commonly used intravenous vancomycin dosing schemes in  
469 patients on automated peritoneal dialysis. *J Antimicrob Chemother.* 2014; 69:1873-6.  
470
- 471 31. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, et al. Peritoneal dialysis-related  
472 infections recommendations: 2010 update. *Perit Dial Int.* 2010; 30:393-423.  
473
- 474 32. Blunden M, Zeitlin D, Ashman N, Fan SL. Single uk centre experience on the treatment of pd  
475 peritonitis--antibiotic levels and outcomes. *Nephrol Dial Transplant.* 2007; 22:1714-9.  
476
- 477 33. Tosukhowong T, Eiam-Ong S, Thamutok K, Wittayalertpanya S, Na Ayudhya DP.  
478 Pharmacokinetics of intraperitoneal cefazolin and gentamicin in empiric therapy of peritonitis in  
479 continuous ambulatory peritoneal dialysis patients. *Perit Dial Int.* 2001; 21:587-94.  
480
- 481 34. Whitty R, Bargman JM, Kiss A, Dresser L, Lui P. Residual kidney function and peritoneal dialysis-  
482 associated peritonitis treatment outcomes. *Clin J Am Soc Nephrol.* 2017; 12:2016-2022.  
483
- 484 35. Fish R, Nipah R, Jones C, Finney H, Fan SL. Intraperitoneal vancomycin concentrations during  
485 peritoneal dialysis-associated peritonitis: Correlation with serum levels. *Perit Dial Int.* 2012;  
486 32:332-8.  
487
- 488 36. Mulhern JG, Braden GL, O'Shea MH, Madden RL, Lipkowitz GS, Germain MJ. Trough serum  
489 vancomycin levels predict the relapse of gram-positive peritonitis in peritoneal dialysis patients.  
490 *Am J Kidney Dis.* 1995; 25:611-5.  
491
- 492 37. Stevenson S, Tang W, Cho Y, Mudge DW, Hawley CM, Badve SV, et al. The role of monitoring  
493 vancomycin levels in patients with peritoneal dialysis-associated peritonitis. *Perit Dial Int.* 2015;  
494 35:222-8.  
495
- 496 38. Brown J, Altmann P, Cunningham J, Shaw E, Marsh F. Pharmacokinetics of once daily intra-  
497 peritoneal aztreonam and vancomycin in the treatment of capd peritonitis. *J Antimicrob  
498 Chemother.* 1990; 25:141-7.  
499
- 500 39. Gendeh BS, Gibb AG, Aziz NS, Kong N, Zahir ZM. Vancomycin administration in continuous  
501 ambulatory peritoneal dialysis: The risk of ototoxicity. *Otolaryngol Head Neck Surg.* 1998;  
502 118:551-8.  
503

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

<b>Adults</b>							
<b>Infection Status</b>	<b>Dose</b>	<b>Dwell Time (hours)</b>	<b>Bioavailability (%)</b>	<b>Dosing</b>	<b>Plasma Concentration</b>		<b>Reference</b>
					<b>(mg/L)</b>	<b>Time of sampling (hour)</b>	
<b>Negative</b>	30 mg/kg	6	49	Single	24.9	6	[15]
	10 mg/kg	4	65	Single	6.3	5	[25]
<b>PD-Peritonitis</b>	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]
<b>Pediatric</b>							
<b>Infection</b>	<b>Dose</b>	<b>Dwell Time</b>	<b>Bioavailability (%)</b>	<b>Dosing</b>	<b>Plasma Concentration</b>		<b>Reference</b>
					<b>(mg/L)</b>	<b>Time of sampling</b>	
<b>Negative</b>	550 mg/m <sup>2</sup>	6	70	Single	23.3	6	[17]

505 N/A = not reported

506

507

508

509

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

<b>Adults</b>								
<b>Modality</b>	<b>Infection Status</b>	<b>Route</b>	<b>V<sub>d</sub> (L/kg)</b>	<b>Plasma Half-life (hours)</b>	<b>Clearance (mL/min)</b>			<b>Reference</b>
					<b>Total</b>	<b>Dialytic</b>	<b>Renal</b>	
<b>CAPD</b>	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]
<b>APD</b>	Negative	IV	0.4	11.6 / 62.8 <sup>a</sup>	7.4	2.1	1.7	[12]
<b>Pediatric</b>								
<b>Modality</b>	<b>Infection</b>	<b>Route</b>	<b>V<sub>d</sub> (L/kg)</b>	<b>Plasma</b>	<b>Clearance (mL/min/1.73m<sup>2</sup>)</b>			<b>Reference</b>
					<b>Total</b>	<b>Dialytic</b>	<b>Renal</b>	
<b>CAPD</b>	Negative	IP	0.48	25	10.7	2.5	1.4	[17]
<b>APD</b>					14.9	3.1		

512 <sup>a</sup>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<sub>d</sub> = volume of distribution

514

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

<b>Pharmacokinetic/pharmacodynamics</b>	<b>PD components</b>	<b>CAPD</b>	<b>APD</b>
<b>Absorption</b>	Dwell time	↓ Bioavailability	↑ Bioavailability
	Dosing route (IP vs. IV)	Same	
<b>Distribution</b>	Permeability (Peritonitis vs. non-peritonitis)	Same	
	Diffusion		
	Protein binding		
	Surface area		
	Vascularity		
<b>Elimination</b>	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
<b>Pharmacodynamics</b>	MIC/AUC	Same- Susceptibility report	

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

519  
 520

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

<b>Proposal for Critical Research Areas of Needed Research for Vancomycin Therapy in Peritoneal Dialysis</b>
▪ 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

523

524

525

526

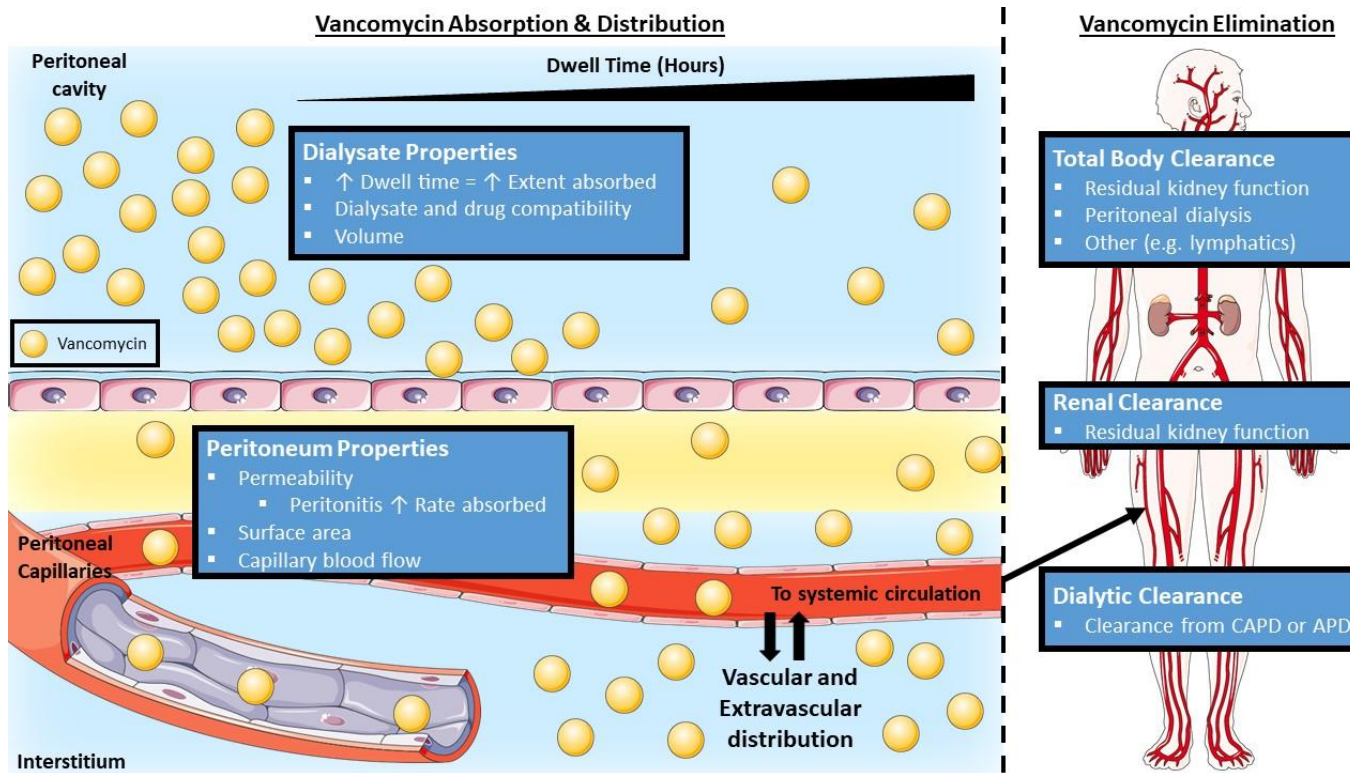
527

528

529

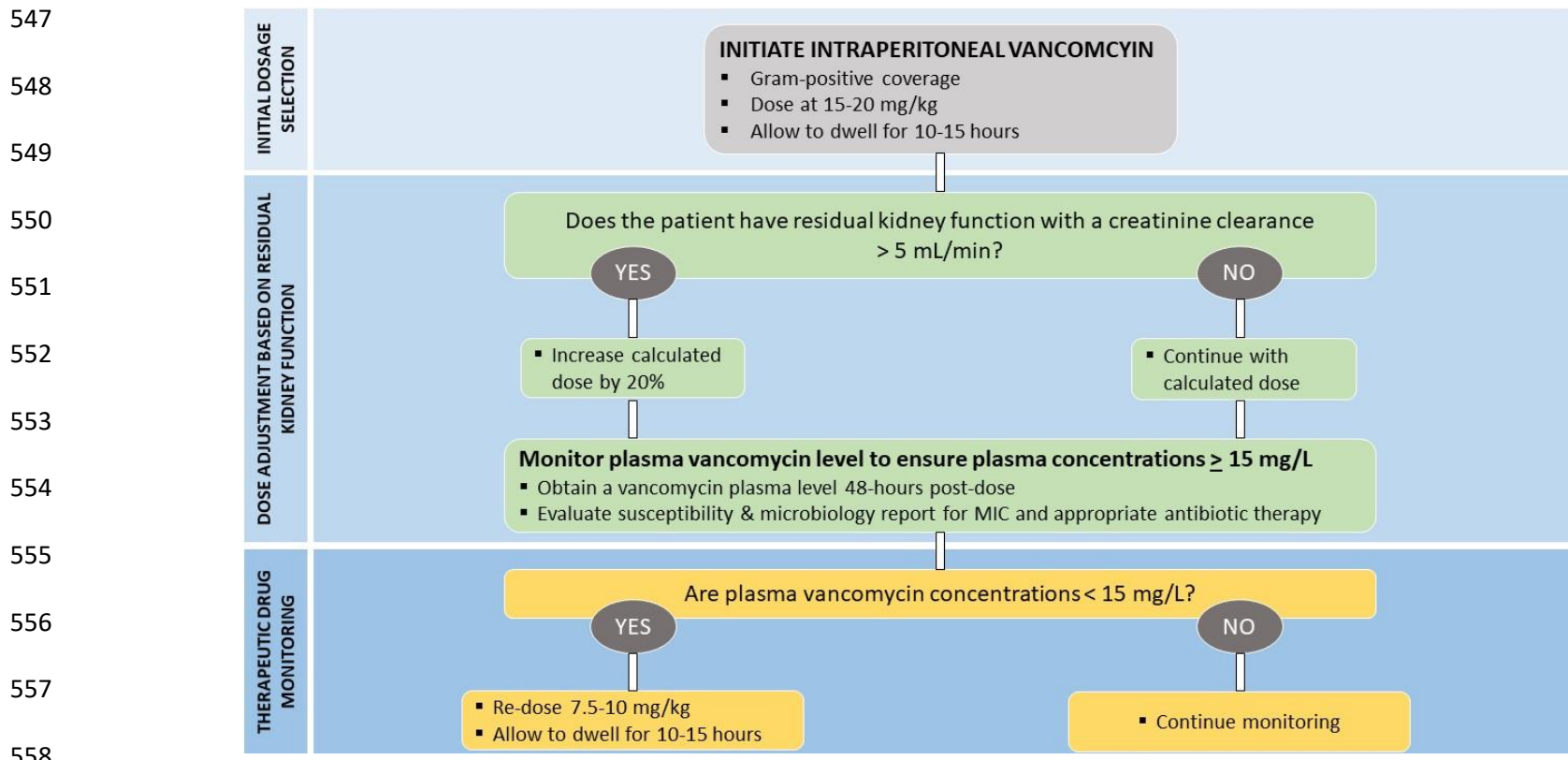


530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540



541  
542  
543  
544  
545  
546

**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 (<https://smart.servier.com/>) under the Creative Commons License (CC BY 3.0).



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

560 Vancomycin dosing in patients on APD with peritonitis should follow the recommended 15-20 mg/kg dose administered intraperitoneally. For

561 those who are non-anuric with creatinine clearances > 5 mL/min, a 20% increase in the calculated dose is suggested. A vancomycin level should

562 be obtained 48 hours post-dose. Dosage adjustments and monitoring should be based on clinical response and microbiological susceptibility

563 reports.