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CASE REPORT OPEN ACCESS

Vancomycin Dosing Strategy for the Treatment of Peritonitis in a Child on Automated Peritoneal Dialysis: A First Pediatric Case Report

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ABSTRACT

Background: Bacterial peritonitis is a common complication of peritoneal dialysis. In the absence of systemic signs of infection, adult guidelines recommend treatment with intraperitoneal vancomycin either as empiric coverage of gram-positive organisms or as targeted therapy. However, there is no guidance on how to administer vancomycin in children on automated peritoneal dialysis.

Case Report: We report vancomycin pharmacokinetics upon intraperitoneal administration for the treatment of a *Staphylococcus hominis* peritonitis in an 11-year-old patient on automated nocturnal intermittent peritoneal dialysis. While the patient was hospitalized, vancomycin was administered intraperitoneally as a continuous treatment. After hospital discharge, the nocturnal peritoneal dialysis was resumed. In the absence of treatment guidelines, intraperitoneal vancomycin was initially administered empirically only during the nocturnal dialysis exchanges which led to repetitive subtherapeutic vancomycin plasma concentrations and the persistence of *S. hominis* in dialysate cultures. Based on studies in adults, the dosing strategy was subsequently modified to administer vancomycin at a dosage of 15 mg kg^{-1} in the dialysate with a 6-h dwell period prior to the nocturnal dialysis thereby allowing to reach optimal peak concentrations. The dosing interval was subsequently individualized using therapeutic drug monitoring to ensure residual vancomycin concentrations > 10 mg L^{-1} thereby leading to clinical and microbiological recovery.

Conclusions: This case presents a dosing strategy based on a comprehensive review of the literature and highlights that a sufficient dwell period is critical when treating pediatric patients on automated peritoneal dialysis in order to allow vancomycin distribution and equilibration between the dialysate and the plasma.

1 | Background

The worldwide prevalence of peritoneal dialysis (PD) is estimated to be 11% among patients undergoing dialysis, and even higher in the pediatric population [1–3]. PD-associated peritonitis is a common complication with significant mortality (3%–10%) and morbidity rates leading often to PD discontinuation and transfer to hemodialysis [1, 4]. According to the International Society for Peritoneal Dialysis (ISPD), a diagnosis of PD peritonitis is made when at least two of the following criteria are present: clinical

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features consistent with peritonitis (abdominal pain, cloudy dialysis fluid) and/or dialysate white cell count > 100 μL^{-1} with > 50% polymorphonuclear leukocytes and/or positive dialysis fluid culture [5]. PD peritonitis caused by coagulase-negative staphylococci should be treated with intraperitoneal (IP) cephalosporin or vancomycin for 2 weeks [5]. The continuous vancomycin therapy (often used in hospitalized patients undergoing a 24-h continuous PD) requires to administer vancomycin during each dialysis exchange. For this approach, vancomycin is given at a loading dose of 20–25 mg kg^{-1} with a 3–6-hour dwell followed by a maintenance dose of 25 mg L^{-1} in each dialysis exchange [6]. Alternatively, vancomycin can be administered intermittently every 3–5 days. For this approach, vancomycin is given at a dose of 5–30 mg kg^{-1} with a dwell period, and this dosing strategy is repeated every 5–7 days for continuous ambulatory PD (CAPD) or 15 mg kg^{-1} with a dwell period repeated every 4 days for automated PD (APD) [6]. Unlike adult guidelines, pediatric guidelines do not clearly differentiate dosing recommendations between CAPD and APD. Furthermore, no clear recommendation is provided for the timing of antibiotic administration. We report a patient undergoing nocturnal APD with *Staphylococcus hominis* peritonitis successfully treated with intermittent dosing of vancomycin.

2 | Case Report

An 11-year-old boy (weight 50 kg, height 145 cm) with a bilateral vesicoureteral reflux secondary to a posterior urethral valve anomaly developed a multicystic renal dysplasia leading to an end-stage renal failure. The patient had a residual diuresis with a kidney function estimated at 12 mL min^{-1} 1.73 m^{-2}. One year prior to the current presentation, the patient started nocturnal APD. His usual PD prescription consisted of four rapid cycles with a total exchange of 17.5 L of dialysate over a 10-h period overnight.

The patient was admitted to the hospital with abdominal pain and fever raising the suspicion for peritonitis. On admission, the patient was hemodynamically stable. The laboratory tests revealed mild inflammation with C-reactive protein elevated up to 27 mg L^{-1} (norm < 10 mg L^{-1}). The dialysis fluid was cloudy with increased cellularity and total leukocytes measured at 3470 cells mm^{-3} with a predominance of neutrophils (up to 60%). An empirical treatment of IP ceftazidime and vancomycin was initiated. The cultures of the dialysate fluid returned positive for penicillin-resistant and vancomycin-sensitive *S. hominis*. Thus, ceftazidime was stopped, and only IP vancomycin was continued. During the first 72 h of hospitalization, the APD was switched to 24-h continuous PD. Vancomycin was administered at a dose of 25 mg L^{-1} in each dialysate bag with a total cumulative dose of 1155 mg during the first 72 h of hospitalization (corresponding to a vancomycin dose of 7.5 mg kg^{-1} day^{-1}). The plasma vancomycin concentration was 17.6 mg L^{-1} 24 h after initiating this dosing schedule. The clinical course was favorable with resolution of abdominal pain, absence of fever and normalization of the inflammatory parameters (CRP < 10 mg/L) and the dialysis fluid (total leukocytes: 10 cells mm^{-3} 48–72 h post-treatment) (Figure 1).

The patient was discharged from the hospital, and the remaining vancomycin treatment was administered at home during

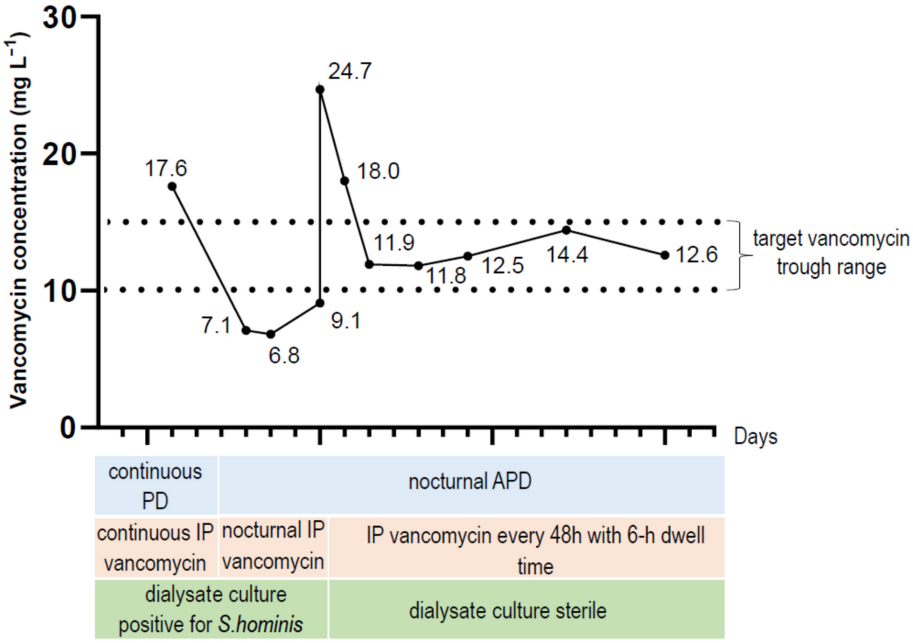

FIGURE 1 | Vancomycin plasma concentrations through the treatment course. Vancomycin plasma concentrations measured initially during the continuous peritoneal dialysis (PD) and subsequently during the nocturnal automated peritoneal dialysis (APD). During the continuous PD, the vancomycin was administered at a dose of 25 mg L^{-1} in each dialysate bag (corresponding to 7.5 mg kg^{-1} day^{-1}). During the APD, the vancomycin was initially given at a dose of 25 mg L^{-1} in each dialysate bag (8.8 mg kg^{-1} over 10 h) and, due to a subtherapeutic concentration, was subsequently doubled to 50 mg L^{-1} in each dialysate bag (17.6 mg kg^{-1} over 10 h) which still resulted in persistent subtherapeutic concentrations. In the end, the vancomycin was administered at a dose of 15 mg kg^{-1} in the dialysate with a 6-hour dwell time prior to APD which led to satisfactory peak and residual vancomycin concentrations.

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the usual nocturnal APD. In the absence of dosing recommendations in children on APD, vancomycin was empirically administered only during the nocturnal dialysis exchanges. On the first night, vancomycin was dosed at 25 mg L^{-1} in each of the four dialysate bags, corresponding to a total of 440 mg vancomycin over 10 h (8.8 mg kg^{-1} over 10 h). This dose resulted in a subtherapeutic vancomycin plasma concentration (7.1 mg L^{-1} 4 h postdialysis completion). This led to double the vancomycin dosage to 50 mg L^{-1} in each dialysate bag for a total of 880 mg over 10 h (17.6 mg kg^{-1} over 10 h). Despite the dose increase, the vancomycin plasma concentration remained subtherapeutic at 6.8 mg L^{-1}. The same dose was continued on two successive nights; however, the vancomycin concentrations remained suboptimal (Figure 1). Based on dosing recommendations in adults, the dosing strategy was subsequently modified to let the vancomycin (given at a dose of 15 mg kg^{-1} or 750 mg in 500 mL of dialysate) dwell for 6 hours in the peritoneal cavity prior to initiating the nocturnal APD. This dosing strategy allowed us to obtain a vancomycin peak concentration of 24.7 mg L^{-1} (measured after rinsing the abdominal cavity and just before the initiation of the nocturnal APD). At the end of the APD, the vancomycin concentration was 18 mg L^{-1}, and 48 h postadministration, the concentration was 11.9 mg L^{-1} and therefore still above the targeted residual threshold (i.e., 10 mg L^{-1}). Thus, it was decided to maintain the IP vancomycin at a dose of 15 mg kg^{-1} with a 6-h diurnal dwell prior to the nocturnal APD. With an administration every 48 h, the vancomycin residual concentrations remained constant and close to 12 mg L^{-1} for the duration of the 14-day treatment. Prior to the vancomycin dose modification, the cultures of the dialysis fluid remained positive for *S. hominis*. Remarkably, the vancomycin dose optimization with the 6-h diurnal dwell period resulted in the sterilization of the dialysis fluid, thereby demonstrating the microbiological eradication in addition to the clinical cure.

3 | Discussion

According to ISPD guidelines, IP administration of vancomycin remains the best choice for treating PD peritonitis. It allows to optimize therapeutic efficacy by delivering high bactericidal concentrations directly at the site of infection while minimizing the risk of systemic toxicity. This feature is crucial in patients with residual kidney function (RKF) [6]. After IP administration, vancomycin is absorbed through the peritoneal membrane depending on the concentration gradient, thereby forming a reservoir in the capillary blood compartment from where the antibiotic diffuses back into the peritoneal cavity during the antibiotic-free exchanges [7, 8]. The concentrations achieved in the dialysate and the plasma depend on multiple factors including the peritoneal membrane permeability, the type of PD, the dwell time, the RKF and the vancomycin dosing schedule [9, 10].

The bioavailability of IP vancomycin has been studied mainly in adults with CAPD and with a dwell period ranging from 4–6 h. In studies including adults without peritonitis, the vancomycin bioavailability exhibited a considerable interindividual variability, spanning from 35% to 80% [11, 12], while in patients with peritonitis, the bioavailability increased up to 70%–90% [13, 14]. In children without peritonitis, a single study showed a higher bioavailability with 70% absorption after a 6-hour dwell [7]. In line with these data, the latest ISPD adult guidelines recommend a dwell time of at least 4 hours but ideally 6 hours [5]. A recent study underscored the importance of having a sufficient dwell duration to enable the concentration equilibrium between the peritoneal cavity and the bloodstream. In this study including four adult patients without peritonitis, 99% of vancomycin was absorbed after a 15-h dwell period [15].

While the vancomycin concentration ratio between the dialysate and the plasma was reported to range between 1:3 and 1:5 [10, 16, 17], this parameter needs to take into account the dwell time. In a study including eight children undergoing APD, the ratio of vancomycin in the dialysate to that in the plasma increased progressively with longer dwell time (from 0.18 with 45 min to 0.45 after an 8-h dwell) [7]. In CAPD, the 6-hour dwell time for each exchange is long enough for the vancomycin concentrations to equilibrate and to reach sufficient concentrations by the end of the dwell period [17]. However, in APD, due to the rapid cycling, the vancomycin does not achieve adequate concentration equilibration between the dialysate and the plasma during antibiotic-free exchanges.

The ISPD guidelines do not clearly define the use of therapeutic drug monitoring (TDM) in the case of IP vancomycin administration. The 2016 guidelines recommended to administer an additional dose of vancomycin if the plasma concentration fell below 15 mg L^{-1}. However, the 2022 guidelines omitted this recommendation due to inconclusive data. A recent retrospective study, including 61 adults with peritonitis undergoing CAPD, showed an increased risk of short-term adverse outcomes when the vancomycin concentration was <10 mg L^{-1} [18]. Another study including 12 adults on APD showed that higher vancomycin peak concentration was associated with a higher peritonitis cure rate [19]. In an earlier study including 31 adults (10 of them on APD), a trough vancomycin concentration <12 mg L^{-1} was associated with a higher risk of relapse [20]. A small retrospective study found similar values with a mean vancomycin trough plasma concentration of 13 mg L^{-1} in nine patients experiencing a relapse compared to a mean trough concentration of 18 mg L^{-1} in 17 patients with no relapse [21]. Conversely, other studies reported no association between vancomycin concentrations and treatment outcomes. In a retrospective analysis including 598 cases with peritonitis (172 on APD), the cure rate was around 75%–80% with no correlation with vancomycin concentrations regardless of the concentration threshold (<12 mg L^{-1}; 12–24 mg L^{-1}; >24 mg L^{-1}) [22]. Another study, including 34 adults (three on APD), found no correlation between vancomycin concentration and treatment failure. Specifically, the average vancomycin concentration was >12 mg L^{-1} both in patients who experienced treatment failure and those who did not [23]. The above-mentioned studies mostly included adults on CAPD. However, for patients on ADP, rapid cycling shortens the time available for equilibration between the dialysate/plasma, thereby increasing the dialytic clearance [10], which should promote the use of TDM to adjust dosing interval.

Vancomycin is primarily eliminated by glomerular filtration. Thus, the previous 2010 ISPD guidelines for adults recommended to increase the dose of vancomycin by 25% in patients with RKF (daily urine output >100 mL). This

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recommendation was withdrawn from the subsequent adult guidelines due to the lack of supportive data. In the latest 2012 pediatric guidelines, there is no recommendation for dosage adjustment based on RKF. However, based on the following observations, close TDM would be advised in patients with RKF. A retrospective study in 58 adults, including 35 with APD, showed indeed a significant correlation between glomerular filtration rate (GFR) and vancomycin concentrations measured 72 h after IP administration. For each increase of 1 mL min^{-1} in GFR, a 0.29 mg L^{-1} decrease in vancomycin concentration was observed [9].

To our knowledge, there are no similar studies in pediatrics. The above-mentioned study and our case suggest that the presence of RKF requires a higher vancomycin dose and/or a shorter dosing interval. Importantly, as it is crucial to prevent nephrotoxicity in patients with RKF [24], it is advised to rather shorten the dosing interval, thereby enabling to use a lower vancomycin dose.

4 | Conclusion

We describe the case of a child with PD peritonitis who was successfully treated by letting IP vancomycin dwell for 6 h before initiating the nocturnal APD. This case emphasizes the complexity and multifaceted nature of managing such patients, particularly in relation to vancomycin dosage schedule in PD. Furthermore, it underscores the limited availability of pharmacokinetic data in children on PD and the lack of dosing guidance especially in the context of APD [25]. Our case is limited by the lack of vancomycin measurement in the dialysis fluid. Thus, well-designed pharmacokinetic studies are warranted to characterize the correlation between the plasma and dialysate vancomycin concentrations in APD with rapid cycling. Importantly, this case highlights that a sufficient dwell period is critical when treating pediatric patients on APD to allow vancomycin distribution and equilibration between the dialysate and the plasma.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. I. Teitelbaum, "Peritoneal Dialysis," *The New England Journal of Medicine* 385, no. 19 (2021): 1786–1795.

2. F. Schaefer, D. Borzych-Duzalka, M. Azocar, et al., "Impact of Global Economic Disparities on Practices and Outcomes of Chronic Peritoneal Dialysis in Children: Insights From the International Pediatric Peritoneal Dialysis Network Registry," *Peritoneal Dialysis International* 32, no. 4 (2012): 399–409.

3. E. Maurer, T. J. Neuhaus, M. Weitz, C. E. Kuehni, and G. F. Laube, "Paediatric End-Stage Renal Disease and Renal Replacement Therapy in Switzerland: Survival and Treatment Trends Over Four Decades," *Swiss Medical Weekly* 150 (2020): w20300.

4. A. Mancini and B. Piraino, "Review of Antibiotic Dosing With Peritonitis in APD," *Peritoneal Dialysis International* 39, no. 4 (2019): 299–305.

5. P. K. Li, K. M. Chow, Y. Cho, et al., "ISPD Peritonitis Guideline Recommendations: 2022 Update on Prevention and Treatment [Published Correction Appears in Perit Dial Int. 2023 May;43(3):279]," *Peritoneal Dialysis International* 42, no. 2 (2022): 110–153.

6. B. A. Warady, S. Bakkaloglu, J. Newland, et al., "Consensus Guidelines for the Prevention and Treatment of Catheter-Related Infections and Peritonitis in Pediatric Patients Receiving Peritoneal Dialysis: 2012 Update," *Peritoneal Dialysis International* 32, no. 2_suppl (2012): 32–S86.

7. D. L. Blowey, B. A. Warady, S. Abdel-Rahman, R. F. Frye, and H. J. Manley, "Vancomycin Disposition Following Intraperitoneal Administration in Children Receiving Peritoneal Dialysis," *Peritoneal Dialysis International* 27, no. 1 (2007): 79–85.

8. A. S. De Vriese and S. J. Vandecasteele, "Vancomycin: The Tale of the Vanquisher and the Pyrrhic Victory," *Peritoneal Dialysis International* 34, no. 2 (2014): 154–161.

9. E. Deacon, M. Canney, B. McCormick, P. Brown, M. Biyani, and D. Zimmerman, "Predictors of Serum Vancomycin Levels in Peritoneal Dialysis-Associated Peritonitis," *Peritoneal Dialysis International* 43, no. 1 (2023): 45–52.

10. E. Lam, Y. T. K. Lien, W. K. Kraft, et al., "Vancomycin in Peritoneal Dialysis: Clinical Pharmacology Considerations in Therapy," *Peritoneal Dialysis International* 40, no. 4 (2020): 384–393.

11. G. D. Morse, D. F. Farolino, M. A. Apicella, and J. J. Walshe, "Comparative Study of Intraperitoneal and Intravenous Vancomycin Pharmacokinetics During Continuous Ambulatory Peritoneal Dialysis," *Antimicrobial Agents and Chemotherapy* 31, no. 2 (1987): 173–177.

12. G. R. Bailie, G. Eisele, R. A. Venezia, D. Yocum, and A. Hollister, "Prediction of Serum Vancomycin Concentrations Following Intraperitoneal Loading Doses in Continuous Ambulatory Peritoneal Dialysis Patients With Peritonitis," *Clinical Pharmacokinetics* 22, no. 4 (1992): 298–307.

13. G. D. Morse, M. A. Apicella, and J. J. Walshe, "Absorption of Intraperitoneal Antibiotics [Published Correction Appears in Drug Intell Clin Pharm 1988 May;22(5):430]," *Drug Intelligence & Clinical Pharmacy* 22, no. 1 (1988): 58–61.

14. B. Montañés Pauls, M. A. Almiñana, and V. G. Casabó Alós, "Vancomycin Pharmacokinetics During Continuous Ambulatory Peritoneal Dialysis in Patients With Peritonitis," *European Journal of Pharmaceutical Sciences* 43, no. 4 (2011): 212–216.

15. E. Lam, Y. Ting Kayla Lien, W. K. Kraft, D. F. Stickle, B. Piraino, and J. Zhang, "Intraperitoneal Pharmacokinetics of Vancomycin in Patients on Automated Peritoneal Dialysis," *Clinical and Translational Science* 15, no. 3 (2022): 649–657.

16. R. Fish, R. Nipah, C. Jones, H. Finney, and S. L. Fan, "Intraperitoneal Vancomycin Concentrations During Peritoneal Dialysis-Associated Peritonitis: Correlation With Serum Levels," *Peritoneal Dialysis International* 32, no. 3 (2012): 332–338.

17. J. Brown, P. Altmann, J. Cunningham, E. Shaw, and F. Marsh, "Pharmacokinetics of Once Daily Intra-Peritoneal Aztreonam and Vancomycin in the Treatment of CAPD Peritonitis," *The Journal of Antimicrobial Chemotherapy* 25, no. 1 (1990): 141–147.

18. Y. Ma, Y. Geng, L. Jin, et al., "Serum Vancomycin Levels Predict the Short-Term Adverse Outcomes of Peritoneal Dialysis-Associated Peritonitis," *Peritoneal Dialysis International* 43, no. 1 (2023): 37–44.

19. P. Falbo Dos Reis, P. Barretti, L. Marinho, A. L. Balbi, L. Awdishu, and D. Ponce, "Pharmacokinetics of Intraperitoneal Vancomycin and Amikacin in Automated Peritoneal Dialysis Patients With Peritonitis," *Frontiers in Pharmacology* 12 (2021): 658014.

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20. J. G. Mulhern, G. L. Braden, M. H. O'Shea, R. L. Madden, G. S. Lipkowitz, and M. J. Germain, "Trough Serum Vancomycin Levels Predict the Relapse of Gram-Positive Peritonitis in Peritoneal Dialysis Patients," *American Journal of Kidney Diseases* 25, no. 4 (1995): 611–615.

21. R. Dahlan, S. Lavoie, M. Biyani, D. Zimmerman, and B. B. McCormick, "A High Serum Vancomycin Level Is Associated With Lower Relapse Rates in Coagulase-Negative Staphylococcal Peritonitis," *Peritoneal Dialysis International* 34, no. 2 (2014): 232–235.

22. M. Blunden, D. Zeitlin, N. Ashman, and S. L. Fan, "Single UK Centre Experience on the Treatment of PD Peritonitis--Antibiotic Levels and Outcomes," *Nephrology, Dialysis, Transplantation* 22, no. 6 (2007): 1714–1719.

23. S. Stevenson, W. Tang, Y. Cho, et al., "The Role of Monitoring Vancomycin Levels in Patients With Peritoneal Dialysis-Associated Peritonitis," *Peritoneal Dialysis International* 35, no. 2 (2015): 222–228.

24. W. C. Kan, Y. C. Chen, V. C. Wu, and C. C. Shiao, "Vancomycin-Associated Acute Kidney Injury: A Narrative Review From Pathophysiology to Clinical Application," *International Journal of Molecular Sciences* 23, no. 4 (2022): 2052.

25. K. Hennessy, E. V. Capparelli, G. Romanowski, L. Alejandro, W. Murray, and N. Benador, "Intraperitoneal Vancomycin for Peritoneal Dialysis-Associated Peritonitis in Children: Evaluation of Loading Dose Guidelines," *Peritoneal Dialysis International* 41, no. 2 (2021): 202–208.

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