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Concise Communication

Methods of estimating vancomycin use in an inpatient setting: days of therapy versus therapeutic drug monitoring–based exposure days

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Abstract

Underestimating antimicrobial use based on days of therapy (DOT) is recognized for certain antimicrobial agents. We investigated the difference between DOT and therapeutic drug monitoring (TDM)–based exposure days in estimating vancomycin use and demonstrated that DOT may underestimate vancomycin exposure by ~10%.

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Tracking antimicrobial consumption is vital for effective antimicrobial stewardship. Days of therapy (DOT) is a measure commonly used in the United States to assess intravenous antimicrobial consumption in inpatient settings based on better applicability to the pediatric population and independence from antimicrobial dosage.[1–3] However, DOT may be unsuitable for certain antimicrobials because this method may underestimate their use, especially when intermittent doses are administered to elderly patients or those with impaired renal function. DOT measures antimicrobial administration but not antimicrobial exposure. Recently, the National Healthcare Safety Network (NHSN) antimicrobial use (AU) module began tracking antimicrobial use with a different denominator (ie, per 1,000 days present),[2] but the optimal method has not been determined.

Length of therapy (LOT) may be more effective for measuring vancomycin use, especially in inpatients with impaired renal function, because it reflects the actual days of exposure rather than the days of antimicrobial administration. LOT for intermittent antimicrobial dosing is conventionally calculated as the number of days from the start to the end of antimicrobial administration comprising a single continuous treatment course.[4]

However, calculating the days of antimicrobial exposure with intermittent dosing may be challenging. The study institution has been performing therapeutic drug monitoring (TDM) of vancomycin twice weekly since 2014 because once-weekly TDM may be inadequate to detect a quick rise in trough concentrations exceeding the therapeutic range among hospitalized patients. Combining frequent TDM and measurements of vancomycin trough concentrations may enable us to estimate vancomycin exposure more accurately. The purpose of this study was to calculate TDM-based exposure days and to compare the results with DOT for vancomycin in a tertiary-care center.

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Methods

This retrospective observational study used data collected from April 2012 to March 2018 at Tokyo Metropolitan Tama Medical Center, a tertiary-care center in Japan. During the study period, data on the monthly patient days, monthly intravenous vancomycin use, and frequency of TDM were collected.

The DOT measurements were based on facility-wide, monthly medication data. We counted only the day on which vancomycin was administered intravenously as a DOT, in accordance with the NHSN AU module definition.[2] The TDM-based exposure days for facility-wide vancomycin use was measured as described below, based on TDM by a clinical pharmacist at the study institution. We determined the exposure days as the number of days from the start of vancomycin administration to the last day of vancomycin exposure as confirmed by twice weekly TDM. For TDM-based exposure days, the last exposure day was defined as either the last actual day of vancomycin administration or the last vancomycin trough concentration obtained on the planned final date of vancomycin therapy for an established infection requiring long-term antimicrobial therapy (eg, bloodstream infection). For patients without vancomycin TDM due to the short duration of their therapy (eg, as part of empiric therapy in the first 72 hours followed by prompt discontinuation or streamlining), the exposure days were counted as the days of exposure consisting of the number of days of actual vancomycin administration as with the measurement of DOT. At the study institution, clinical pharmacists perform TDM for all patients on vancomycin to assist primary care providers in accordance with the vancomycin TDM guidelines.[5] Moreover, the DOT data and the TDM-based exposure days were compared based on patients' renal function. We stratified the monthly DOT and TDM-based exposure days into 4 groups

Table 1. Details of Vancomycin Use Calculated by Days of Therapy and TDM-Based Exposure Days Among Each Estimated Renal Function

Variable[a]	2012	2013	2014	2015	2016	2017
Monthly DOT						
CrCl ≥ 60 mL/min	144.0 (103.5, 155.0)	154.5 (134.3, 176.8)	183.5 (142.3, 199.8)	223.5 (195.3, 257.3)	202.0 (181.0, 256.0)	201.0 (173.3, 224.8)
CrCl 30–60 mL/min	77.0 (67.0, 93.8)	77.0 (66.8, 107.3)	78.5 (56.0, 114.0)	122.5 (99.3, 163.3)	105.5 (84.5, 127.3)	100.0 (75.8, 144.0)
CrCl < 30 mL/min	14.5 (10.8, 24.5)	14.0 (9.8, 26.5)	19.5 (12.5, 27.5)	24.0 (17.5, 34.8)	45.0 (36.5, 57.0)	42.0 (17.5, 49.5)
Dialysis	13.5 (8.8, 23.3)	22.5 (12.8, 30.8)	33.0 (22.5, 40.3)	23.5 (17.8, 33.0)	38.0 (25.3, 42.8)	32.5 (23.0, 37.5)
Monthly TDM-based ExD						
CrCl ≥ 60 mL/min	145.0 (108.3, 160.8)	158.0 (137.3, 177.5)	188.5 (154.8, 201.3)	227.5 (195.8, 257.8)	202.5 (182.5, 257.0)	202.5 (175.3, 227.8)
CrCl 30–60 mL/min	84.0 (71.5, 102.0)	78.0 (68.3, 111.8)	86.0 (63.0, 130.3)	128.0 (100.5, 162.5)	106.0 (86.3, 135.8)	103.5 (86.5, 144.8)
CrCl < 30 mL/min	28.0 (16.8, 38.3)	22.5 (21.0, 36.3)	26.5 (16.0, 34.8)	35.0 (22.8, 53.3)	53.5 (40.3, 65.5)	52.5 (22.3, 66.5)
Dialysis	30.0 (21.8, 54.5)	40.5 (28.0, 59.5)	63.5 (35.5, 78.8)	43.0 (38.0, 51.8)	50.5 (37.0, 85.5)	52.0 (39.5, 69.5)
Relative difference between DOT and TDM-based ExD, %						
CrCl ≥ 60 mL/min	−1.7 (−4.5, −1.0)	−1.4 (−3.4, 0.0)	−1.7 (−2.4, −1.2)	−0.2 (−1.9, 0.0)	−0.5 (−1.0, −0.2)	−0.9 (−1.7, −0.4)
CrCl 30–60 mL/min	−6.4 (−8.2, −1.4)	−2.7 (−4.9, −1.4)	−6.7 (−12.5, −3.7)	−0.5 (−2.8, 0.0)	−2.2 (−7.3, −1.3)	−1.2 (−2.3, 0.0)
CrCl < 30 mL/min	−37.9 (−55.1, −28.8)	−35.7 (−53.1, −29.1)	−19.4 (−39.1, 0.0)	−23.1 (−36.4, −9.4)	−11.7 (−19.0, −9.1)	−20.6 (−26.0, −14.4)
Dialysis	−57.2 (−62.1, −53.1)	−47.7 (−53.6, −36.6)	−47.5 (−52.3, −44.1)	−46.5 (−49.1, −36.9)	−37.9 (−45.1, −28.2)	−41.6 (−49.0, −33.0)

Note. IQR, interquartile range; CrCl, creatinine clearance (Cockcroft-Gault equations); DOT, days of therapy; ExD, exposure days; TDM, therapeutic drug monitoring.
[a]All data reported as median (IQR).

according to creatinine clearance (CrCl) using Cockcroft-Gault equations: (1) CrCl ≥ 60 mL/min, (2) CrCl 30–60 mL/min, (3) CrCl < 30 mL/min, and (4) dialysis.

The paired *t* test was used to assess the differences between DOT and TDM-based exposure days. For the statistical analysis, we used Stata version 15.2 software (StataCorp, College Station, Texas). The institutional review board at the study institution approved the study.

Results

Appendices 1 and 2 show the details of TDM and vancomycin use in terms of DOT and TDM-based exposure days during the study period. In general, the median patient days per month were stable at ∼19,000. The number of patients receiving at least 1 dose of vancomycin increased during the study period. Since 2014, TDM has been performed twice weekly at the study institution in most patients, except those on a short course of therapy.

The mean monthly vancomycin use was 343.5 DOT (standard deviation [SD], 87.3) and 383.8 TDM-based exposure days (SD, 88.9). The difference between DOT and TDM-based exposure days was −40.3 days (SD, 16.9; $P < .001$), and the relative difference between DOT and TDM-based exposure days was −10.9% (SD, 4.9%).

Among the 4 renal function groups, DOT, TDM-based exposure days, and the absolute and relative differences between the 2 methods varied. For the CrCl ≥ 60 mL/min group, DOT was 187.5 days (SD, 56.1); TDM-based exposure days was 190.7 days (SD, 56.1); the absolute difference between the 2 methods was −3.2 days (SD, 3.9) ($P < .001$); and the relative difference was −1.8% (SD, 2.7%). For the 60 > CrCl ≥ 30 mL/min group, DOT was 99.4 days (SD, 42.0); TDM-based exposure days was 103.8 days (SD, 41.7); the absolute difference between the 2 methods was −4.4 days (SD, 4.9; $P < .001$); and the relative difference was −5.2% (SD, 7.2%). For the CrCl < 30 mL/min group, DOT was 27.4 days (SD, 17.5); TDM-based exposure days was 36.7 days (SD, 20.5); the absolute difference between the 2 methods was −9.3 days (SD, 7.3) ($P < .001$); and the relative difference was −25.9% (SD, 18.9%). And for the dialysis group, DOT was 27.7 days (SD, 15.5); TDM-based exposure days was 50.7 days (SD, 26.9), the absolute difference between the 2 methods was −23.0 days (SD, 14.1; $P < .001$); and the relative difference was −44.8% (SD, 12.4%). The details of vancomycin exposure among for each renal function group are shown in Table 1.

Discussion

The 2 measures of vancomycin exposure differed significantly; the DOT-based data underestimated vancomycin exposure by ∼10% compared with TDM-based exposure days, which measured only the days of actual exposure. A further difference in vancomycin exposure among patients with CrCl <30 mL/min and those with dialysis was observed, suggesting that using TDM-based exposure days is a better method of assessing the actual duration of exposure in patients with impaired renal function. The difficulty of using exposure days as a measure is its inadequacy to determine the days of exposure between each period of antimicrobial administration, especially when vancomycin is administered at irregular intervals due to renal dysfunction. Although a previous study demonstrated the use of LOT based on the prespecified criteria,[4] the method described did not significantly differ from DOT. In contrast, the method used here has the advantage of calculating exposure days based on more frequent assessment of TDM with vancomycin serum concentration values, enabling us to confirm whether the patients were exposed to vancomycin even when the dosing intervals were irregular or several days apart. Although TDM-based exposure days probably correlate with DOT, this measure may be more suitable for patients with lower creatinine clearance, elderly patients with labile renal function or intensive care units where significant fluctuation in DOT measurement is expected.

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Our study has several limitations. Although the study institution performs vancomycin TDM twice weekly, the ideal frequency is unclear. We were unable to collect exposure days data automatically, and the process was labor intensive. The current study included days with subtherapeutic levels of vancomycin in the total exposure days due to the impossibility of assessing the period of subtherapeutic exposure via twice weekly TDM. Eliminating these days from the calculation may improve accuracy.

In conclusion, vancomycin exposure was ~10% lower when assessed using DOT than when using TDM-based exposure days. However, depending on the patient population and density of vancomycin use, additional benchmarks including TDM-based exposure days may be important for calculating the days of vancomycin exposure accurately.

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References

1. Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. *Clin Infect Dis* 2007;44:664–670.
2. National Healthcare Safety Network (NHSN) antimicrobial use and resistance (AUR) module. Centers for Disease Control and Prevention website. https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf. Published 2018. Accessed August 20, 2018.
3. Barlam TF, Cosgrove SE, Abbo LM, *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016;62:e51–e77.
4. Kubin CJ, Alba LR, Furuya EY. Lack of significant variability among different methods for calculating antimicrobial days of therapy. *Infect Control Hosp Epidemiol* 2012;33:421–423.
5. Rybak M, Lomaestro B, Rotschafer JC, *et al.* Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009;66:82–98.

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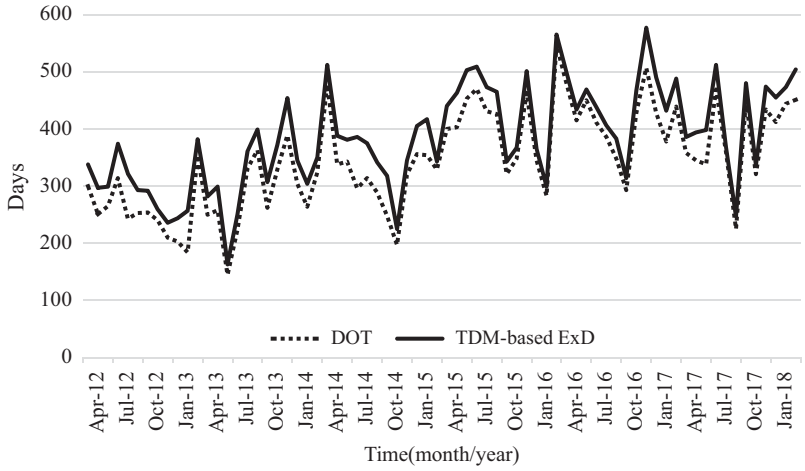
Appendix 1.: Details of vancomycin therapeutic drug monitoring and use by days of therapy and exposure days

	2012	2013	2014	2015	2016	2017
A monthly patient-days, median (IQR)	19146 (18843, 19670)	19337 (19062, 19550)	18726 (18301, 19154)	19198 (18947, 19575)	19238 (18875, 19409)	18649 (18377, 19028)
A monthly DOT, median (IQR)	249.5 (231.8, 273.0)	283.5 (254.0, 327.3)	321.0 (293.3, 345.0)	413.0 (344.8, 452.5)	420.0 (383.3, 440.8)	384.0 (342.3, 442.8)
A monthly TDM-based ExD , median (IQR)	295.0 (258.5, 326.0)	326.0 (294.8, 363.8)	378.0 (342.8, 392.3)	464.0 (366.5, 501.5)	452.5 (425.5, 488.5)	426.5 (381.8, 475.5)
Relative difference between DOT and TDM-based ExD , %, median (IQR)	−13.7 (−16.8, −11.6)	−12.2 (−13.4, −10.7)	−13.3 (−16.1, −9.7)	−7.6 (−8.9, −5.9)	−8.0 (−10.8, −5.1)	−8.8 (−10.5, −7.1)
Total number of patients per month who received at least one dose of vancomycin, median (IQR)	40.5 (37.3, 43.8)	50.5 (45.8, 53.3)	52.5 (47.5, 57.3)	65.0 (56.0, 73.3)	66.5 (59.0, 70.3)	68.0 (61.8, 74.5)
Total number of patients per month who received at TDM at least once, median (IQR)	23.0 (20.5, 24.0)	25.0 (22.0, 31.0)	28.5 (25.0, 33.0)	34.5 (29.0, 41.8)	37.5 (34.3, 40.3)	37.0 (30.3, 41.0)
Monthly number of TDM performed, median (IQR)	50.5 (45.8, 59.3)	59.0 (52.5, 68.3)	73.5 (66.8, 81.3)	102.5 (87.8, 117.5)	118.0 (107.3, 125.0)	111.0 (97.8, 123.5)
Weekly number of TDM performed for individual patients, median (IQR)	1.24 (0.88, 1.62)	1.40 (0.88, 1.75)	1.40 (1.00, 2.00)	1.75 (1.17, 2.20)	1.75 (1.40, 2.33)	1.75 (1.40, 2.33)
Total number of patients per month who received intermittent doses of vancomycin, median (IQR)	6.0 (5.8, 8.0)	8.5 (7.0, 9.3)	10.0 (8.8, 13.0)	7.5 (5.8, 9.3)	8.5 (7.8, 11.5)	10.0 (6.3, 12.0)
Vancomycin trough concentration, mg/L, median (IQR)	15.3 (11.3, 18.7)	15.1 (11.7, 18.4)	13.6 (10.5, 17.3)	13.0 (10.0, 16.1)	12.9 (9.8, 15.6)	12.4 (8.8, 15.6)

Note. IQR, interquartile range; DOT, days of therapy; ExD, exposure days; TDM, therapeutic drug monitoring.

Appendix 2.: Differences in vancomycin exposure density measurements using the two methods



Note. DOT; days of therapy, TDM; therapeutic drug monitoring, ExD, exposure days.

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