Original Article

Index for the appropriate vancomycin dosing in premature neonates and infants

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Abstract   **Background**: In neonates, vancomycin (VCM) is used to treat Gram-positive bacterial infections. However, VCM blood concentrations are affected by gestational age, bodyweight (BW), and renal function. The initial VCM dose adjustment can therefore be difficult, and few reports have evaluated this issue. In this study, we investigated the factors determining the appropriate VCM dosing schedule in neonates, especially premature infants.

Methods: The VCM dosage and trough concentrations were retrospectively investigated from the initial treatment to maintenance therapy in neonatal intensive care unit patients who underwent therapeutic drug monitoring. We examined the average single-administration VCM dosage during maintenance therapy. We then compared the actual VCM dose with that calculated using an index comprising six items that influence the VCM daily dose (postnatal age, gestational age, BW, serum creatinine level, urine output, and lactate level).

Results: Twenty premature infants were included. The average BW of patients at the initial VCM administration was 975 g. During maintenance therapy, the average VCM dose was 8.4 mg/kg, and the median trough concentration was 12.4 µg/mL. When we applied the six-item index, 18 of 20 patients (90%) had concordant results between the actual VCM dosing schedule and the VCM calculated using the index.

Conclusions: The average VCM dose and six-item index can facilitate the transition from the initial VCM dose to an appropriate dose in many cases and contribute to early treatment in low-birthweight infants with more variable BW, distribution volumes, and renal function. In conclusion, our six-item index may help standardize VCM administration in premature infants.

Key words   dose, low bodyweight, schedule, therapeutic drug monitoring, vancomycin.

Gram-positive bacteria such as *Staphylococcus aureus* and coagulase-negative *Staphylococcus* are common causative bacteria of central line-associated bloodstream infections, including strains resistant to β-lactam drugs such as methicillin-resistant *S. aureus*.[1,2] Vancomycin (VCM) has been used as the primary therapeutic agent against these strains.

Vancomycin is a water-soluble drug with a low protein binding rate, mainly excreted by the kidneys.[3] In general, the VCM dose in adults is determined according to published guidelines[4] and therapeutic drug monitoring (TDM).[5] Vancomycin doses are currently set to achieve an area under the curve (AUC)/minimum inhibitory concentration (MIC) ratio ≥of 400 as reported in 2020 American guidelines, including those of the American Society of Health-System Pharmacists (ASHP).[6] The VCM doses in neonates, infants, and children are based on the medical guidance described in the package insert in Japan. However, the guidance does not consider early gestational age (GA), and it is difficult to adjust the dose appropriately. In particular, in premature infants with low bodyweight (LBW, <2,500 g), whose clearance is easily influenced by differences in bodyweight (BW), body fluid, and renal function, some reports described VCM dosing and schedules,[7] but there are no standardized guidelines. In our institution, the initial VCM dose is therefore determined using Nelson's pediatric antimicrobial therapy (hereafter referred to as Nelson's regimen).[8] The dose during maintenance therapy is adjusted based on the result of TDM. Recently, ASHP proposed that the target AUC should be set to ≥400, even in newborns, and the dose should be determined according to the postnatal age (PNA), postmenstrual age (PMA), and BW and serum creatinine (SCr) level.[6] However, clinicians have generally used the trough concentration because of the difficulty in collecting blood frequently.[9]

Moreover, because blood VCM trough concentrations vary remarkably because the drug's half-life dramatically differs

depending on PNA and GA compared with those in adults, it is difficult to transition from the initial dose to a stable therapeutic concentration.[10] Furthermore, at night or on holiday, sometimes no pediatrician or pharmacist can initiate the VCM treatment. There is thus a potential risk of inappropriate VCM administration owing to the dependence on the experience of medical personnel involved at treatment initiation. Besides, if measurements are not readily available in the institution where the measure is undergone at the outsourcing, the risk of inappropriate drug administration may increase.

We therefore investigated neonates who received VCM and for whom the trough blood concentration was measured. We then calculated the dosage at the time of maintenance administration. Based on the data, we examined whether four previously identified item factors that affect the volume of distribution (Vd) and clearance, namely GA, PNA, BW, and renal function (SCr),[7,11] are linked to appropriate usage. We also considered urine output and lactate, which can generally be measured in the clinic and which the circulatory dynamics are important for evaluating the renal function. We then compared the six items' accuracy, including these two items. To provide stable and high-quality medical care to patients with significant differences in individual parameters such as extremely low bodyweight (ELBW) and very low bodyweight (VLBW) neonates, we examined an appropriate administration method to smoothly transition to a proper VCM dose from the initial dose.

Methods

Cases and parameters

We retrospectively investigated outcomes using the medical records of LBW newborns hospitalized in our hospital's neonatal intensive care unit (NICU) between 2010 and 2019. VCM was administered to eligible patients; the initial trough concentration of VCM was measured, the maintenance dose was calculated, and the trough concentration was measured again for validity. The initial VCM trough concentration was measured for 2 or 3 days, the maintenance VCM trough concentration was measured after over 4 days. The cases in which only the initial measurement was performed were excluded. Furthermore, patients whose BW exceeded 2,000 g were excluded. This study investigated GA, postconceptional age (PCA), BW, sex, the initial and maintenance VCM doses, treatment duration, and blood VCM trough concentrations during initial and maintenance therapy. Serum VCM concentration was measured by the Roche kinetic interaction of microparticles in solution assay in our institution. The statistical analysis used Wilcoxon signed-rank test.

Extraction of factors affecting VCM dosing

Four items were extracted as factors that affect the blood concentration of VCM (hereafter the "four-item index"; Table 1): PNA, GA, BW, and SCr. Furthermore, as an index reflecting clearance,

we created a six-item index that included the four items mentioned above and urine output (to evaluate renal function) and blood lactate concentrations (to evaluate circulatory dynamics). The cutoff values for index variables were determined after consultation with a neonatal physician as follows: (1) PNA at administration ≤28 days; (2) GA ≤28 weeks; (3) BW at administration ≤1 kg; (4) SCr ≥ 0.7 mg/dL; (5) daily urine output 1 day before administration ≤2 mL/kg/h, and (6) lactate concentration 1 day before administration ≥40 mg/dL. Using these items, the four- and six-item index scores were calculated and used to determine the VCM dosing schedule (Table 1). Regarding the four-item index, the daily administration schedule was determined according to the number of applicable variables as follows: 0, four times daily; 1–2, three times daily; 3, twice daily; and 4, once daily. The administration schedule was similarly set using the six-item index as follows: 0, four times daily; 1–2, three times daily; 3–5, twice daily; and 6, once daily. If SCr levels exceeded 1.5 mg/dL and all items were applicable, the administration schedule was every other day.

Confirm compatibility for four-items and six-items index

To examine the appropriateness of the VCM dosing schedule calculated using the four- and six-item indices, the actual VCM dosing schedule during maintenance treatment that remained to appropriate concentration was investigated for all patients. Then we compared the actual appropriate dosing schedule we had investigated to determined using the index.

Table 1 Vancomycin (VCM) dosing schedule calculated using the index score

Four-item index	Number of applicable items	Number of daily doses
1. Postnatal age (PNA) ≤ 28 days (at the start of VCM administration)	0	4
	1–2	3
	3	2
2. Gestational age (GA) ≤ 28 weeks	4	1
3. Bodyweight (BW) ≤ 1 kg (at the start of VCM administration)		
4. Serum creatinine (SCr) > 0.7 mg/dL		

Six-item index	Number of applicable items	Number of daily doses
1. PNA ≤ 28 days (at the start of VCM administration)	0	4
	1–2	3
	3–5	2
2. GA ≤ 28 weeks	6	1
3. BW ≤ 1 kg (at the start of VCM administration)		
4. SCr > 0.7 mg/dL		
5. Urine output ≤ 2 mL/kg/h		
6. Lactate ≥ 40 mg/dL		

SCr > 1.5, once daily unless all other items are applicable, or once every 2 days if all the other items are applicable.

Objectives of this study

The primary objective was to discover items to transition to appropriate VCM concentration in premature infants. The secondary objective was to investigate the administration method to transmit to appropriate VCM concentration from initial administration.

Ethical consideration

The study protocol was approved by the clinical and genome research ethics review committee of Yamanashi Prefectural Central Hospital (no. 30–52). To ensure confidentiality, unique identifiers such as names were not recorded. Data were stored on a computer that was password protected by the principal investigator.

Results

Blood concentration transition and parameter

Twenty neonates (15 males) were included in the analyses of VCM blood concentrations via TDM until maintenance therapy (Table 2). The mean GA was 26.0 ± 3.3 weeks. Overall, 17 patients were ELBW, whereas two were VLBW and one was LBW. Two infants were term newborns. The patient characteristics at the time of initial VCM administration were as follows: the mean PNA, 39.7 ± 25.5 days; the mean PCA, 31.7 ± 4.3 weeks; the mean BW, 975 ± 356 g; and the median SCr level, 0.51 (0.24–3.75) mg/dL (Table 2). The mean initial VCM dose was 10.0 ± 2.8 mg/kg. Before the initial VCM trough concentration measurement, the mean administration period was 2.1 ± 0.3 days, and the median VCM trough concentration was 9.3 (3.0–24.9) µg/mL. At the time of maintenance therapy, the mean PNA, PCA, and BW were 46.5 ± 25.5 days, 32.6 ± 4.1 weeks and 1,047 ± 378 g, respectively. The median SCr concentration was 0.51 (0.16–1.52) mg/dL. The mean single-administration VCM dose during maintenance therapy was 8.4 ± 1.9 mg/kg; the average administration period before the VCM trough concentration measurement was 7.8 ± 3.2 days, and the median trough concentration was 12.4 (9.1–16.1) µg/mL. Few patients met the general target VCM trough concentration (10–15 µg/mL) at the initial measurement, and the concentration varied widely among the patients (Fig. 1). However, the VCM trough concentration at the time of maintenance therapy using TDM was within the general target trough concentration range (10–15 µg/mL) in 14 patients. We showed a difference in VCM trough concentrations that remained within target between initial and maintenance dosing. Besides, 19 patients remained within general target trough concentration range and allowable target trough concentration range (we defined allowable target trough concentration; 7–10 µg/mL). Dosage change from initial to maintenance treatment were 17 patients, administration interval change were 20 patients.

Validation of the four- and six-item indices for determining the VCM dosing schedule

We respectively determined the four- and six-item index scores (Table 1) and compared the calculated and actual VCM dosing schedules at maintenance dosing, which remained at an appropriate concentration. The concordance between the actual (Horizontal axis) and calculated number of daily administration using the four-item index (Vertical axis) was as follows: once daily, 2 of 2 cases; twice daily, 2 of 8 cases; three times daily, 9 of 9 cases; and 4 times daily, 1 of 1 case (Fig. 2). Thus, calculated and actual numbers of doses were concordant in 14 of 20 cases (70%). On the other hand, the concordance between the actual (Horizontal axis) and calculated number of daily administration using the six-item index (Vertical axis) were as follows: once daily, 2 of 2 cases; twice daily, 6 of 8 cases; three times daily, 9 of 9 cases; and four times daily, 1 of 1 case (Fig. 3). Thus, the calculated and actual numbers of doses were concordant in 18 of 20 cases (90%).

The characteristics of the two inconsistent cases are presented in Table 3. The calculated VCM dosing schedule was three times daily, based on the patient's BW and GA in the first patient. However, the actual VCM schedule was twice daily. For the second patient, although the calculated VCM dosing schedule was twice daily based on meeting five of the six criteria (i.e., PNA, GA, BW, SCr level, and urine output), the actual dosing schedule was three times daily.

Discussion

There are few reports of the target trough value for reaching AUC/MIC ≥ 400 in newborns treated with VCM, especially premature infants. The American Society of Health-System Pharmacists (ASHP) recommends two-point blood sampling

Table 2 Patient characteristics during initial and maintenance VCM therapy

Case	Value	
Number of cases (male/female)	20 (15/5)	
GA (weeks)	26.0 ± 3.3	

	Initial	Maintenance
PNA (days)[†]	39.7 ± 25.5	46.5 ± 25.5
PCA (weeks)[†]	31.7 ± 4.3	32.6 ± 4.1
BW (g)[†]	975 ± 356	1,047 ± 378
SCr (mg/dL)[‡]	0.51 (0.24, 3.75)	0.51 (0.16, 1.52)
VCM, single dose (mg/kg)[†]	10.0 ± 2.8	8.4 ± 1.9
Time to VCM trough measurement (days)[†]	2.1 ± 0.3	7.8 ± 3.2
VCM trough concentration (µg/mL)[‡]	9.3 (3.0, 24.9)	12.4 (9.1, 16.1)

GA, gestational age; PCA, postconceptional age; PNA, postnatal age; SCr, serum creatinine; VCM, vancomycin.
[†]Mean ± SD.
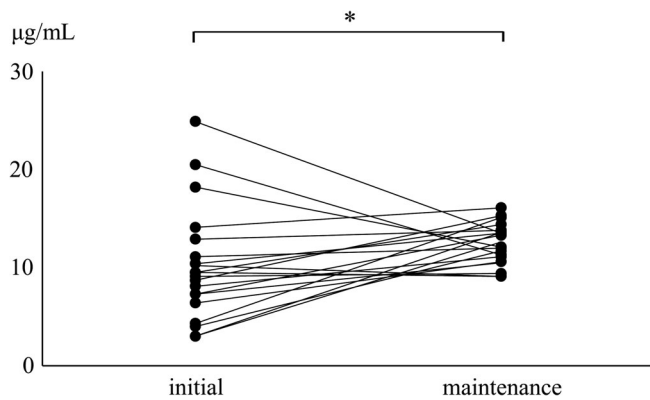[‡]Median (minimum value, maximum value).

Fig. 1 Vancomycin (VCM) trough concentration during initial and maintenance therapy. A Vertical axis, VCM concentrations; a horizontal axis, at initial and maintenance treatment. * $P < 0.05$, Wilcoxon signed-rank test.
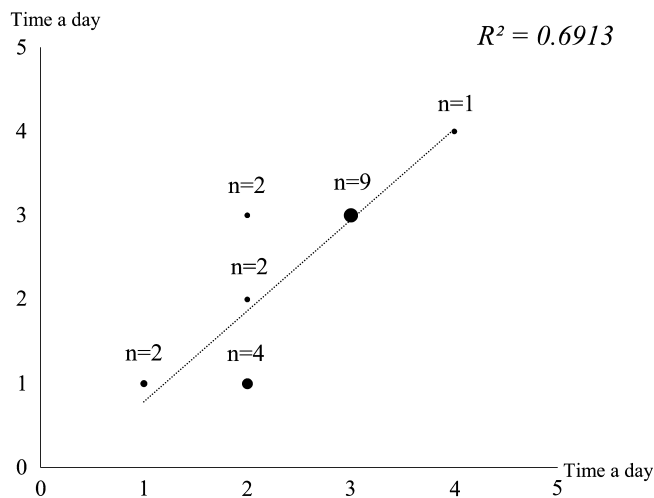

Fig. 2 Comparison of the daily number of vancomycin (VCM) doses calculated using the four-item index and the actual daily number of VCM doses. Vertical axis: number of doses based on the four-item index. Horizontal axis: number of actual doses.
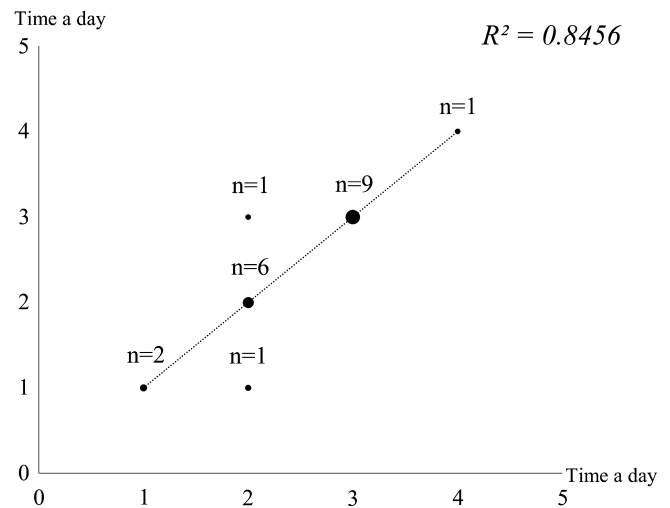

Fig. 3 Comparison of the daily number of vancomycin (VCM) doses calculated using the six-item index score and the actual number of VCM doses. Vertical axis: number of doses based on the four-item index. Horizontal axis: number of actual doses.

Table 3 Comparison of characteristics for patients for whom the calculated (six-item index) and actual VCM dosing schedules were inconsistent

Six items	Cases	1	2
(1)	PNA (days)	50	24
(2)	GA (weeks, days)	24, 1	25, 2
(3)	BW (g)	836	735
(4)	SCr (mg/dL)	0.37	3.75
(5)	Urine output ($\leq$2 mL/kg/h)	None	None
(6)	Lactate ($\geq$40 mg/dL)	None	None
Number of doses according to the six-item index		3	1
The actual number of doses		2	2
Daily dose (mg/kg/day)		25.7	10.9
Single-dose (mg/kg)		12.9	5.4
Trough concentration during maintenance treatment (µg/mL)		12	11.7
Primary disease/patient condition		Acute adrenal insufficiency PDA CLD type I	MD twins TTTS

CLD, chronic lung disease; GA, gestational age; age; MD twins, monochorionic diamniotic twins; PDA, patent ductus arteriosus; PNA, postnatal age; SCr, serum creatinine; TTTS, twin-to-twin transfusion syndrome; VCM, vancomycin.

targeting the peak and trough concentrations for accurate measurements of AUC.[6] However, in actual clinical practice, neonates' total blood volume is small, and several blood samplings are performed in a critically ill neonate, including blood gas samplings. Therefore, two-point blood sampling, which requires additional blood collection, is difficult. Therefore, two-point blood sampling is difficult.[9] The trough concentration has been used as an alternative, and we predict that evaluation via one-point blood sampling will continue in the future. We set a target trough concentration of 10–15 µg/mL in clinical practice because this range was associated with AUC/MIC $\geq$ 400 in adults.

On the other hand, the dosing schedule for achieving AUC/MIC $\geq$ 400 is twice daily for adults, but VCM is often administered two to four times daily in children and infants because of the shorter half-life of the drug in children than in adults.[12] In that case, there is a possibility of an excessive AUC.

Reports found that AUC/MIC $\geq$ 400 could be achieved even at a lower VCM concentration (7–11 µg/mL),[13,14] and 7–15 µg/mL was targeted as the allowable trough concentration. However, the VCM Vd and half-life in newborns and infants differ from those in adults. In particular, because ELBW and VLBW newborns with a PCA of fewer than 34 weeks have immature renal function and differences in physique and fluid volume, VCM Vd is extremely small, and clearance is significantly different.[5,7,15] This is one of the factors making it difficult to control blood concentrations. As it is difficult to adjust

the concentration to an appropriate level using the administration method described in the package insert, we are studying the dosage and usage of VCM while performing TDM based on the Nelson regimen and prior reports.

In this study, we retrospectively investigated the appropriateness of the VCM dose and schedule as evaluated by TDM from the initial dose to maintenance therapy in 20 premature infants treated in our hospital's NICU. The initial dose ranged from 7.5 to 10 mg/kg based on Nelson's regimen, but after 2–3 days, the VCM trough concentrations widely varied. For patients whose VCM blood concentrations remained lower than the general target range (10–15 μg/mL), we presumed that blood was collected before a steady state was received because a loading dose was not administered. On the other hand, for patients whose VCM blood concentrations exceeded the general target concentration, we presumed that the potential influencing factors included both lower than anticipated Vd and decreased clearance attributable to immature renal function. TDM effectively achieved appropriate and stable blood concentration transition in many cases. This content was supported as a significant difference (Fig. 1). We therefore considered that TDM of VCM was effective for newborns, especially LBW infants.

However, a specialist or pharmacist who can appropriately monitor and control VCM blood concentrations may not be available, or institutions may not be able to measure and evaluate blood concentrations immediately. We therefore aimed to identify factors that can be used to determine appropriate VCM doses and schedules from the initial administration regardless of specialized medical personnel. We consequently proposed two indices (four- and six-item indices) comprising factors (Vd and clearance as indices of renal function) that affect VCM blood concentrations.

Renal maturation relates antibiotic drug clearance in newborns and infants are using age indicators, such as PMA, PNA, GA, and a combination of these.[16–18] Cutoff values were therefore defined as factors based on these reports and the dose of VCM in Nelson's regimen, e.g., GA of 28 weeks and PNA of 28 days. Furthermore, according to Nelson's regimen of VCM doses, SCr levels fluctuate by age, i.e., 0.5 mg/dL for patients aged ≤28 days and 0.7 mg/dL for patients aged ≥28 days. In this study, the cohort was mainly older than 28 days; thus, 0.7 mg/dL was defined as the cutoff value for SCr. Because the cutoff value of BW was reported as 1.0 kg in a previous report, we defined the cutoff value for body weight as 1.0 kg. We attempted to introduce two new items: urine output and blood lactate concentration, to evaluate renal function and circulatory dynamics. We introduced urine output because we considered that SCr alone might not be sufficient for assessing renal function. We initially adopted a cutoff value of urine output of 1 mL/kg/h, which indicates the neonate hypothesis. However, this value excluded many patients, and it was thus considered to be inappropriate. A general criterion of neonatal urine output was reported as 2 mL/kg/h [19]; therefore, we defined neonatal urine output as ≤2 mL/kg/h after consulting with a neonatologist. Finally, we included

lactate as an index item because it is routinely evaluated via blood gas analysis for neonates as an index of circulatory dynamics. A previous report demonstrated that mortality increased when serum lactate levels exceeded 4.2 mmol/L in neonates with a low GA.[20] Thus, we set the cutoff lactate concentration at >40 mg/dL after consulting with a neonatologist.

We calculated the number of VCM doses using the indices mentioned above and compared them with the actual dosing schedule (Figs 2 and 3). As a result, the four-item index's concordance rate was 70%, compared with 90% for the six-item index. Thus, the six-item index was more accurate, possibly because it more closely reflected the daily fluctuations of circulation dynamics and renal function. The same patient's cases included in 18 concordant cases. Even in the same patient, although the number of VCM doses varied among individuals according to PNA and BW changes, the actual number of doses agreed with that calculated using the six-item index. We therefore recommend using the six-item index as much as possible.

We also investigated the six-item index individually for the two cases (Table 3). For the first case, the VCM dosing schedule calculated using the six-item index was three times a day, whereas the actual VCM schedule was twice daily. However, the actual's one dosage was higher than the initially dose by Nelson's regimen (7.5–10 mg/kg). Therefore, when this dose was converted to the daily dose, we believed that the calculated and actual daily doses were mainly similar. In the second case, the actual VCM schedule was administered twice daily. However, the six-item index recommended a schedule once daily because four of six items were applicable, and the SCr level exceeded 1.5 mg/dL after the patient received indomethacin. However, we believed this gap could be corrected. The patient's renal function improved rapidly, and we considered that it was possible to re-evaluate SCr levels because blood had been collected frequently during the acute phase of infection. Besides, the VCM dose was low at 5.4 mg/kg. Thus, even if VCM was administered according to the six-item index score, we considered that the VCM dose could be adjusted to an appropriate concentration and evaluated using TDM.

The overall mean VCM dose for maintenance therapy was 8.4 ± 1.9 mg/kg in this study (Table 2). We therefore considered a quantity of 8–9 mg/kg to be reasonable. Because the trough concentration exceeded ≥7 μg/mL in this study, we believed that the concentration might sufficiently exceed AUC ≥ 400.[13,14] However, we did not confirm AUC/MIC ≥ 400 in this study. It will therefore be a subject of future research. We did not consider a loading dose to be necessary because neonates often have a smaller Vd and shorter half-life than adults. Half of the patients in this study required three or four doses daily. However, we plan to examine this issue further in a larger cohort.

The six-item index's primary advantage is its ability to adjust to the appropriate VCM maintenance dose at the start of treatment independent of the initial loading dose. This method was derived from the maintenance dose, which

remained at an appropriate concentration. We therefore thought that the appropriate administration schedule could be determined by using the six items from the initial administration. The accuracy of the transition from the initial dose to the appropriate maintenance dose may also be improved by observing the six items every day. We considered that TDM is necessary throughout treatment to evaluate the VCM dose in LBW infants, who display high individual variability concerning physique and renal clearance. However, the limitations of this study included its retrospective nature and the small number of cases. We also did not study neonates with birthweight ≥2,000 g. Therefore, our findings must be verified with a larger number of cases.

In conclusion, our findings suggested that blood VCM levels could be controlled following the initial dose using the six-item index to calculate the dosing schedule. The method can maintain stable VCM concentrations even in facilities and situations in which TDM cannot be sufficiently performed. The accuracy of VCM dosing could be further improved by controlling blood trough concentrations using TDM. The six-item index is a simple method that can be used by pharmacists, pediatric and neonatology specialists as well as non-specialists.

Acknowledgments

Disclosure

The authors declare no conflict of interest. All authors met the ICMJE authorship criteria.

Author contributions

Atsushi Nemoto, Kazumi Hanawa, Atsushi Naito, Yayoi Kawano, and Takehisa Hanawa were responsible for the trial's organization and coordination. Takahiro Ishikawa, Mai Koshi-ishi, Yuki Maebayashi, Yohei Hasebe, and Yoshifumi Kobayashi were the chief investigators, and they were responsible for data analysis. All authors read and approved the final manuscript. All members of the "Index for the appropriate vancomycin dosing in premature neonates and infants" study team contributed to the trial's management or administration.

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