A new algorithm optimized for initial dose settings of vancomycin using machine learning

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Background

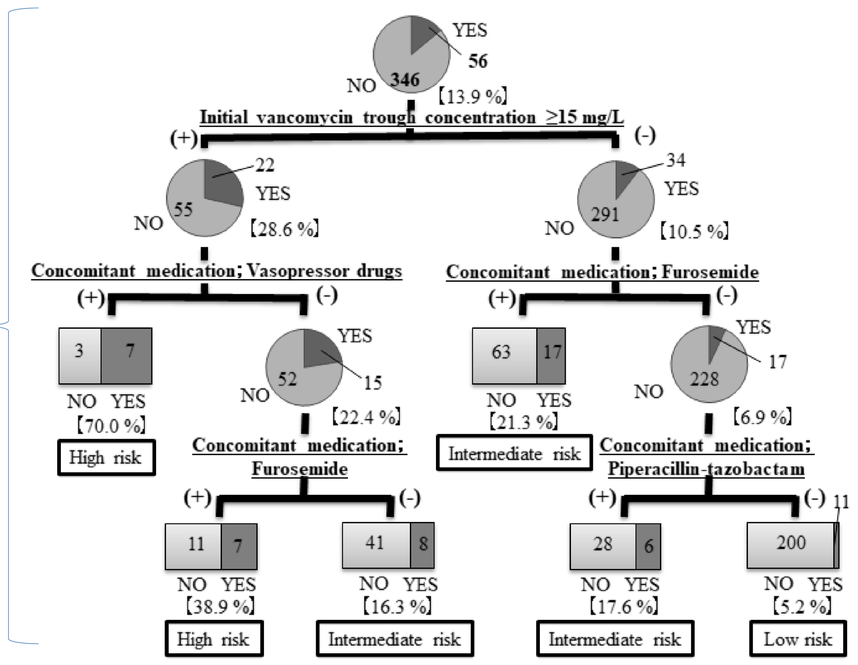
○ **Machine learning (ML)** refers to the scientific algorithms and statistical models that machines learn from experience.

○ ML involves different approaches such as **decision tree (DT)**, neural network, and support vector machine, which are usually used for predictive models.

○ Previous studies have constructed risk prediction models of adverse drug reactions (ADRs) using **DT analysis**.

Following the flowchart

Users can estimate combinations of risk factors that may increase the risk of ADRs



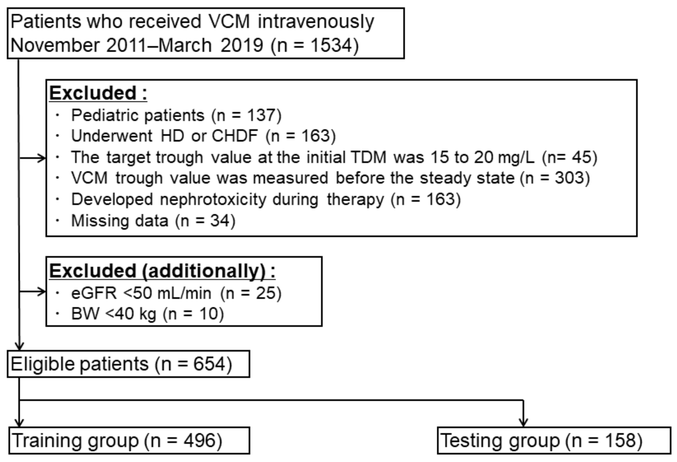
The DT model for the prediction of vancomycin (VCM)-associated nephrotoxicity.[1)]

We considered a DT model can be applied to drug dose settings.

Aim : To construct an optimal algorithm for initial dose settings of VCM using ML with DT analysis

Materials and Methods

Study subjects



Training group: patients who received VCM from November 2011 to December 2017
Testing group: Patients who received VCM from January 2018 to March 2019.
The number of patients with estimated glomerular filtration rate (eGFR) <50 mL/min and body weight (BW) <40 kg was low (25 and 10 patients, respectively), and these patients were excluded.

Ethics

The ethics committee of the Hokkaido University Hospital approved the study protocol (no. 019-0100).

Construction of the DT model (using Training group)

1. DT analysis of the classification and regression tree algorithm[2)] was performed.

2. The corrected daily dose*[1] (mg/kg) was selected as the dependent variable.

3. Variables that potentially affects pharmacokinetics of VCM were selected as the independent variable*[2].

Model evaluation (using Testing group)

The rates of attaining the therapeutic range (VCM trough value = 10–15 and 10–20 mg/L) was evaluated*[3] and compared with three conventional dose-setting methods in Japan:
(i) SHIONOGI-VCM-TDM ver. 2009 (VCM-TDM), [3)]
(ii) vancomycin MEEK TDM analysis software ver. 2.0 (MEEK), [4)]
(iii) maintenance dose of nomogram presented in the TDM guideline (Nomogram). [5)]

*[1] The corrected daily dose was defined as the daily dose per body weight (BW) predicted to reach a trough value of 12.5 mg/L, calculated individually:
Corrected daily dose (mg/kg) = Target trough value (12.5 mg/L)/Actual trough value (mg/L) × Actual daily dose (mg) / BW (kg)
If the corrected daily dose before dividing by BW was >3000 mg, we capped them at 3000 mg daily in the interest of safety.

*[2] The independent variables were age, sex, estimated glomerular filtration rate (eGFR), body mass index (BMI), concomitant medications (nonsteroidal anti-inflammatory drugs, furosemide, amphotericin B, aminoglycosides, piperacillin-tazobactam, and vasopressor drugs), and residence in the intensive care unit.

*[3] The steps in model evaluation in the testing group were as follows:
1. Dose settings were performed for individual patients, and the recommended daily dose was calculated using each method on the basis of the defined daily dose (Table).
2. The predicted trough value was calculated using the following formula:
Predicted trough value (mg/L)
= Recommended daily dose (mg)/Actual daily dose (mg)) × Actual trough value (mg/L).
3. The rates of attaining the therapeutic range were evaluated.

Table. Calculation of defined VCM daily doses

Calculated VCM daily dose (mg)	Defined VCM daily dose (mg)	Example of dose regimen
>2750	3000	1500 mg twice daily
2250≤ and <2750	2500	1250 mg twice daily
1750≤ and <2250	2000	1000 mg twice daily
1375≤ and <1750	1500	750 mg twice daily
1125≤ and <1375	1250	1250 mg once daily
875≤ and <1125	1000	1000 mg once daily
675≤ and <875	750	750 mg once daily

Results

Patient characteristics

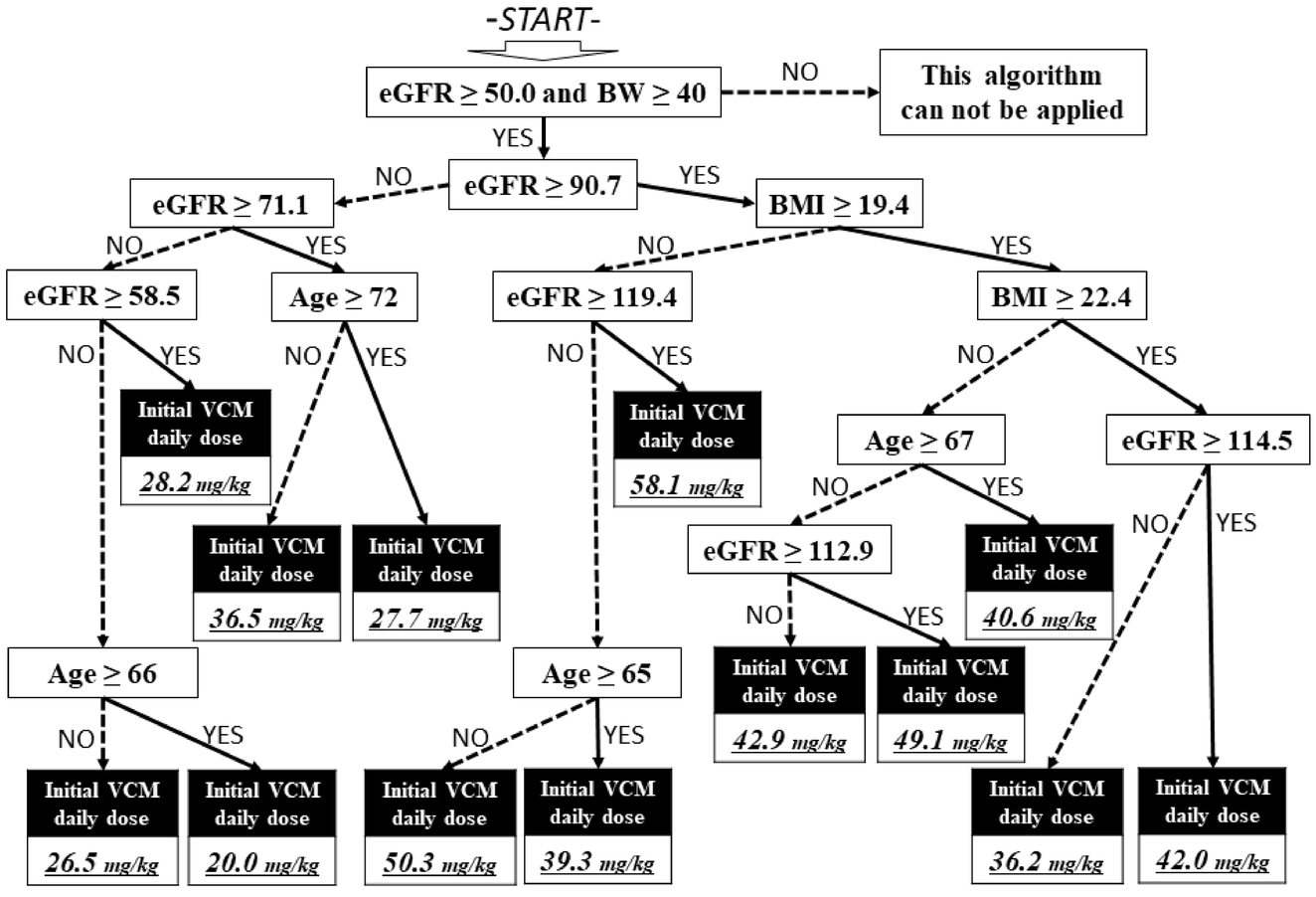
Variables	Training group (*n* = 496)	Testing group (*n* = 158)	*P*
Age (years), median (range)	61 (18–89)	62 (19–86)	0.65 [c)]
Sex (male), n (%)	329 (66.3)	106 (67.1)	0.86 [a)]
Body weight (kg), median (range)	58.8 (40.0–127.0)	60.3 (40.0–107.7)	0.27 [c)]
Body mass index, median (range)	21.9 (14.4–49.1)	22.1 (14.9–39.4)	0.17 [c)]
Serum Creatinine (mg/dL), median (range)	0.60 (0.16–1.22)	0.64 (0.16–1.21)	0.18 [c)]
eGFR (mL/min), median (range)	97.3 (50.7–407.3)	89.5 (50.8–433.2)	0.83 [c)]
Duration of therapy (days), median (range)	9 (3–83)	8 (3–50)	0.03 [c)]*
Concomitant medications, n (%)			
Nonsteroidal anti-inflammatory drugs	231 (46.6)	67 (42.4)	0.36 [a)]
Furosemide	91 (18.3)	33 (20.9)	0.48 [a)]
Piperacillin / Tazobactam	51 (10.3)	19 (12.0)	0.54 [a)]
Amphotericin B	0 (0.0)	4 (2.53)	<0.01 [b)]*
Aminoglycoside antibiotics	7 (1.41)	1 (0.63)	0.69 [b)]
Vasopressor drugs	32 (6.45)	7 (4.43)	0.35 [a)]
Residence in intensive care unit, n (%)	45 (9.07)	16 (10.1)	0.86 [a)]
Days to initial TDM (days), median (range)	4 (3–10)	4 (3–8)	0.69 [c)]
Initial VCM daily dose (mg/L), median (range)	2000 (750–3750)	2000 (1000–3750)	0.64 [c)]
Initial VCM trough value (mg/L), median (range)	9.6 (2.2–36.0)	10.4 (2.1–29.5)	0.11 [c)]

[a)] Chi-square test, [b)] Fisher's exact test, [c)] Mann–Whitney *U*-test. **P* ≤ 0.05 was considered statistically significant.

Model evaluation

Variables	DT algorithm	VCM-TDM	MEEK	Nomogram
Recommend daily VCM dose (mg), median (range)	2500 (1250–3000)	2000 (1000–3000)	1500 (750–2000)	1500 (750–3000)
Predicted VCM trough value				
Median (range), mg/L	12.1 (2.52–34.2)	11.2 (2.52–34.5)	8.40 (1.26–22.4)	8.91 (1.68–25.3)
<10 mg/L, n (%)	53 (33.5)	59 (37.3)	100 (63.3)	98 (62.0)
10≤ and <15 mg/L, n (%)	59 (37.3)	52 (32.9)	41 (25.9)	44 (27.9)
15≤ and <20 mg/L, n (%)	21 (13.3)	24 (15.2)	15 (9.49)	14 (8.86)
10≤ and <20 mg/L, n (%)	80 (50.6)	76 (48.1)	56 (35.4)	58 (36.7)
≥20 mg/L, n (%)	25 (15.8)	23 (14.6)	2 (1.27)	2 (1.27)

DT model



Algorithm for initial dose settings of VCM on the basis of the DT analysis (DT algorithm)

By following the flowchart, clinicians and pharmacists can easily perform initial dose settings of VCM.

The algorithm was to be used on patients with eGFR ≥50 mL/min and BW ≥40 kg. Daily dose should not exceed 3000 mg/day. Dosing regimens are listed in Table (shown in Materials and Methods).
VCM, vancomycin; DT, decision tree; eGFR, estimated glomerular filtration rate; BW, body weight; BMI, body mass index

Our DT algorithm obtained the highest rate of attaining the therapeutic range.

Discussion

1. In the DT algorithm, the eGFR, age, and BMI were extracted as predictive variables.
   ⇨ These variables generally affect VCM pharmacokinetics such as clearance and/or volume of distribution.[3-5)]

2. Our DT algorithm obtained the highest rate of attaining the therapeutic range compared to conventional dose-setting methods.
   ⇨ Our DT algorithm incorporates multiple factors, including BMI. We believe this was the reason for the higher therapeutic range in the DT algorithm compared to conventional dose-setting methods.

Our study firstly indicated the usefulness of ML for drug dose setting.

Limitations

1. It was a single-center study and might lack scientific rigor or external validity. Carefully monitoring is required for clinical application.

2. We could not evaluate patients with eGFR <50 mL/min or BW <40 kg, because patients with renal impairment often undergo TDM in a nonsteady state.

3. The predicted trough value was calculated proportionally to actual and recommended daily doses of VCM. Therefore, these usages could not be considered.

4. Our DT algorithm does not comply with the new TDM guidelines regarding VCM.[6)]

A multicenter trial is required in order to build a more generalized model.

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Conflict of Interest

The authors declare no conflict of interests.

Acknowledgement

This work was supported by JSPS KAKENHI Grant Number JP20K16035.

This study has been published in *Biological and Pharmaceutical Bulletin*

Shungo Imai, Yoh Takekuma, Takayuki Miyai, Mitsuru Sugawara. A new algorithm optimized for initial dose settings of vancomycin using machine learning. *Biol pharm bull*, 2020; 43(1):188-193.