Correlation between 61 risk factors and vancomycin blood concentration reached based on real world data

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Abstract

Background : Vancomycin, an antibiotic produced by microbial fermentation, is used to treat gram-positive infections. With extensive broad-spectrum antibiotics use, bacterial resistance to vancomycin continues to increase. We explored the factors influencing vancomycin blood concentration compliance rate, established a predictive equation for such concentrations, and provided a reference for individual applications.

Methods: We used a single-center, retrospective, case-control study design based on real-world data from the Hospital Information Management System of the First Affiliated Hospital of the Teaching Hospital of Bengbu Medical School from January 1, 2017 to December 31, 2018. Inpatients whose vancomycin blood concentration was monitored were selected. Single factor and multivariate logistic regression analyses were performed using SPSS 21.0 software to screen factors affecting vancomycin blood concentration compliance rate. Vancomycin blood concentration was then determined. A receiver operator characteristic (ROC) curve of influencing factors was then used to establish a prediction model.

Results: In total, 168 patients (122 males and 46 females) were enrolled. Eighty-one had their vancomycin blood concentration monitored, and 87 had concentrations that did not reach the standard. Multivariate logistic model analysis showed that patient drug allergy history, alanine aminotransferase (ALT), aspartate aminotransferase (AST), patient infusion volume, and urine volume influenced vancomycin blood concentration compliance rate. According to logistic model analysis, a history of drug allergy (95% CI: 1.225-24.850, $P<0.05$), ALT (95% CI: 0.979-0.999, $P<0.05$), AST (95% CI: 1.003-1.027, $P<0.05$), patient infusion volume (95% CI: 0.996-0.998, $P<0.05$), patient urine volume (95% CI: 1.001-1.003, $P<0.05$), and combined predictors were used to construct ROC curves. For combined predictive factors, area under the ROC curve (0.829, 95% CI: 0.755-0.902, $P<0.005$) was greater than that of the five individual indicators and was predicted to be the preferred value.

Conclusions: In clinical practice, the patient's daily average infusion and urine volumes can be substituted into the joint predictor calculation formula: $P=1/[1+e^{-(0.940-0.004 \times \text{infusion} + 0.002 \times \text{urine})}]$. By calculating the combined predictive factor to predict vancomycin blood concentration compliance rate, the dosing regimen can be adjusted.

Keywords: Real-world research; Vancomycin; Blood concentration monitoring; Influencing factor; Logistic regression analysis

Background

Vancomycin (VAN), a natural antibiotic produced by microbial fermentation, is a tricyclic glycopeptide antibiotic and was the first glycopeptide antibiotic [1]. Clinically, it is used to treat **gram-positive bacterial** infections, such as those caused by hemolytic streptococcus, or pneumococcus, among others. VAN is one of the first-line drugs for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and related infections, as directed by many authoritative guides [2]. Differences in the blood concentration of VAN have been observed in different individuals. If its blood concentration is too low, the drug might not be effective or might not reach its effective trough concentration. However a concentration that is too high can lead to adverse drug reactions, such as ototoxicity and nephrotoxicity [3, 4]. If administered according to the recommended dosage found in the instructions, a significant

portion of the patient's blood concentration does not appear to be within the therapeutic window [5-7]. Thus, it is clinically necessary to monitor VAN blood concentrations. Methods for this mainly include high performance liquid chromatography, radioimmunoassay, and enzyme expanded immunoassay [8]. Since VAN is a time-dependent antibacterial drug, the key to ensuring its efficacy is extending the antibacterial drug infusion time such that the drug concentration is always higher than the target organism's minimum inhibitory concentration [9]. However, routine monitoring of peak concentration [10] does not correlate with monitoring efficacy. Furthermore, as the distribution of VAN into tissues is slow, its peak concentration is difficult to monitor [1]. Some studies [11] suggest that the peak concentration of VAN does not correlate well with its efficacy and its concentration can be used as a surrogate for its area under the curve, which currently is widely accepted. According to the Guide to the Monitoring of Chinese Vancomycin Therapeutic Drugs [12], patients with normal renal function have a VAN half-life of 6-12 h, with stable blood concentration achieved after 4 to 5 half-lives. On the third day (48 h after the first dose), monitoring of patient VAN can be initiated. However, for patients with renal insufficiency, upon first administration, monitoring is initiated 72 h after drug administration. Accurately determining VAN trough concentrations can not only avoid poor therapeutic effects due to drug resistance or adverse reactions caused by concentrations that are too low or too high, but also help clinicians develop individualized drug delivery plans for patients, as revealed by Lijun and other researchers [13-19]. Xingru et al. [5, 20, 21] reported that VAN blood concentration is related to age, serum albumin, dose, dose, urine volume, creatinine clearance, serum creatinine, blood urea nitrogen, and plasma albumin in critically ill patients. Moreover, VAN blood concentrations in children are related to serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine clearance, glutamyl transaminase, and gestational age. Similar to other reports, Qingrong and other researchers [22] pointed out that the VAN plasma concentration in patients ≥ 18 years of age is related to age, albumin, liver and kidney function, usage, and dose. Although the aforementioned factors have been widely discussed as influencing factors related to VAN blood concentration, only a few reports have discussed them with regard to VAN plasma concentrations. In addition, the research populations used for these analyses were relatively small (e.g., studies on children only), the entire population was not analyzed, and a prediction model has not been established. In this paper, a real-world single-center, retrospective, case-control study was conducted to investigate the effects of age, sex, liver and kidney function, and solvent on the plasma concentration of VAN. The factors involved were found to be more extensive and more comprehensive. By combining single factor analysis and multi-factor logistic analysis, a receiver operating characteristic (ROC) curve was generated and the prediction equation for VAN blood concentration was fitted to provide a basis for clinical pharmacists to guide clinicians in the use of this drug.

Methods

Research design

We performed a single-center, retrospective, case-control, research design study [The First Affiliated Hospital of Bengbu Medical College, the ethics committee of clinical medical research (scientific research project) approval number: 2018KY008, the approval date was August 28, 2018; and on June 23, 2019, the registration number of the China Clinical Trial Registration Center was ChiCTR1900024062.] based on real-world data present in the Hospital Information Management System (HIS). HIS is a database that stores the information recorded during an inpatient's stay at the hospital. It includes their basic information, daily medication during hospitalization, care, admission, and expenses incurred. According to the Guide to the Monitoring of Chinese Vancomycin Therapeutic Drugs [12], when patient blood concentration was monitored, VAN had to be within the effective concentration range (10-20 µg/mL). The population was divided into the standard group, including patients whose blood concentrations, as measured after the intake of VAN, were within the range of 10-20 µg/mL, and the substandard group, including patients with VAN trough concentrations outside the range of 10-20 µg/mL.

Blood drug concentration monitoring method

The VAN blood concentration was monitored by enzyme amplification immunoassay, using enzyme reagent 1 (vancomycin labeled with bacterial glucose-6-phosphate dehydrogenase [0.21 U/ml], hydroxyethylpiperazine ethylsulfuric acid buffer liquid, calf serum albumin, preservatives, and stabilizers) and reagents 2 (antibody/substrate: murine monoclonal vancomycin antibody [27 µg/mL], calf serum albumin, glucose-6-phosphate [44 mM], nicotinamide adenine dinucleotide [36 mM], preservatives, and stabilizers) were monitored by a fully automated biochemical analyzer (Viva-E: YZB/HOL 1746-2010).

Research object

This study was performed at the First Affiliated Hospital of Bengbu Medical College from January 1, 2017 to December 31, 2018. Inpatients whose VAN blood concentrations were being monitored were selected as subjects. The study protocol was reviewed and approved by the hospital ethics committee. Inclusion criteria were as follows: (1) patients treated with VAN for clinical infections who had their

VAN blood concentration monitored; (2) trough concentration of VAN blood concentration and not peak concentration or concentration found immediately after administration; (3) influencing factors of the control group had to be consistent with the influencing factors in the observation group; (4) complete patient data. Exclusion criteria were as follows: (1) vancomycin was not used as the clinical treatment for infection; however, cases treated with norvancomycin were included; (2) patients whose VAN blood concentration was monitored as peak concentration; (3) differing statistical factors between the observation group and control group; (4) invalid clinical data.

Data collection

According to the characteristics of VAN and the actual situation provided in the HIS, the electronic database was designed to collect the following data: (1) demography: age and sex; (2) past history of drug allergy, smoking, and alcohol abuse; (3) vital signs: body temperature (36.1-37 °C); (4) infection: pulmonary, intracranial, central nervous system, and bronchiectasis infection; (5) history of disease: history of chronic diseases such as diabetes and hypertension, and infectious diseases such as tuberculosis; (6) hospitalization: number of operations and operations performed before each blood concentration measurement, fluid infusion amount, urine amount, whether critical illness occurred during hospitalization, Glasgow coma score (GCS, including blink response, speech response, and limb movement, mild coma: 13-14 points, moderate coma: 9-12 points, severe coma: 3-8 points, normal: >14 points, length of hospital stay, admission department, western medicine fee, antibiotic cost, and antibiotic use during hospitalization, total cost of western medicine; (7) patient medication during hospitalization: vancomycin (dose, frequency of administration, vehicle, and days of drug use), antibiotics and other drugs used in combination with VAN, treatment options are correct, whether there are indications; (8) safety test indicators: ALT: 0-40 IU/L, AST: 0-45 IU/L, alkaline phosphatase (ALP): 40-160 IU/L, glutamyl transpeptidase (GGT): 0-50 IU/L, total protein (TP): 60-80 g/L, albumin (A): 35-55 g/L, G: 9-23 mg/ml, total bilirubin: 1.7-17.1 μ mol/L, serum urea: 1.8-7.1 mmol/L, serum creatinine: 44-133 μ mol/L, serum creatinine clearance rate: 80-120 ml/min, white blood cell count: $4-10 \times 10^9$ /L, hemoglobin: (120-160 g/L), platelets: $100-300 \times 10^9$ /L; and (9) observed outcome indicators: monitoring values of VAN plasma concentration per patient per time.

Data processing and assignment

Univariate and multivariate logistic regression analyses were used to screen independent risk factors for the compliance of patients receiving VAN. According to the information retrieved for each patient, the assignment of various influencing factors is shown in Table 1.

[Insert Table 1]

Statistical analysis

Data were processed using SPSS 21.0 statistical software (IBM, Armonk, NY, USA). A Pearson’s chi-square test was used to analyze classification data, whereas a t-test was used to analyze continuous data. Univariate risk factors affecting VAN plasma concentration were determined by single factor and multivariate regression analyses. According to the multivariate logistic model analysis results, joint predictors were set and included in the logistic model for analysis. Model equation and ROC curves were then derived. Curve, screen cut points, area under the curve, and the predictive efficacy of various indicators were then derived. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Unless otherwise stated, results are expressed as the mean $\pm$ standard deviation, and lost data is processed using the mean substitution method.

Results

Patient demographic characteristics

A total of 168 patients (81 patients that met the standard and 87 patients that did not meet the standard) were enrolled. Hospital admissions included 38 (22.62%) in the respiratory department, 28 in pediatrics (16.67%), 24 in the ICU (14.29%), and 18 in the RICU (10.71%). There were 15 cases of neurosurgery (8.93%), 12 cases of infection (7.14%), 11 cases of PICU (6.55%), 4 cases of general medicine and nephrology (2.38%), 3 cardiovascular cases (1.79%), 2 cases from the gastrointestinal surgery, stomatology, emergency department (1.90%), and 1 case in orthopedics, intratumor, extratumor, hematology, and gynecology (0.60%); details are presented in Table 2.

Table 2. Patient demographic characteristics

Grouping	sex (male/female)	Age (years)	Number of days in hospital	Medication days	Dose (g)	Total drug cost (yuan)	Antibacterial cost (yuan)
Compliance	55/26	46.30±27.72	25.94±12.19	12.62±6.52	0.70±0.38	26729.37±19885.35	13267.19±10608.97
Substandard	67/20	42.08±27.40	30.68±22.47	13.67±7.28	0.65±0.40	34011.88±37704.42	16016.87±15649.98

Univariate analysis of compliance and non-standardized data

VAN blood concentration was found to adhere to the standard. In addition, patients's drug allergy history, rheumatoid arthritis, combined use of human immunoglobulin, hospital days, AST, G, daily average infusion of patients, and urine volume showed statistical differences (to avoid missing important factors in the single factor analysis process, The range of P values was set to < 0.1, to include more potential influencing factors, see Table 3).

[Insert Table 3]

Multi-factor analysis of compliance and non-standardized data

Multivariate logistic regression analysis showed that allergic history, ALT, AST, daily average infusion volume, and daily mean urine volume were significantly associated with patient VAN blood concentration ($P < 0.05$, Table 4). The general trend of VAN blood concentration as a function of ALT, AST, daily average infusion volume, and daily average urine volume is presented in Figures 1-3.

Table 4. Multivariate logistic regression analysis of factors influencing vancomycin blood serum concentration.

Indexes	Multi-factor analysis				
	B	SE	Wald χ^2	P	95%CI
Allergies	1.708	0.768	4.948	0.026	1.225-24.850
Alanine aminotransferase	-0.011	0.005	4.342	0.037	0.979-0.999
Aspartate aminotransferase	0.014	0.006	5.820	0.016	1.003--1.027
Daily average infusion	-0.003	0.001	16.411	0.000	0.996-0.998
Daily average urine volume	0.002	0.001	12.834	0.000	1.001-1.003

Prediction and analysis of VAN blood concentration by logistic model and ROC curve

Stepwise logistic regression analysis showed that daily mean infusion volume and daily mean urine volume were statistically independent risk factors. Taking patient VAN blood concentration as the dependent variable, a logistic model equation was established with daily average infusion volume and daily average urine volume as independent variables. This equation was transformed to obtain the joint predictor (Y joint). The equations (Formula 1 and Formula 2) were then used to calculate the joint predictor, enabling the construction of an ROC curve of the joint predictor (Figure 4). The area under the curve was 0.829, (95% CI: 0.755-0.902, $P < 0.005$).

$$\text{Logit } (P) = 0.940 - 0.004 * X_{\text{infusion}} + 0.002 * X_{\text{urine}} \quad \text{Formula 1}$$

$$P = 1 / [1 + e^{-(0.940 - 0.004 * X_{\text{infusion}} + 0.002 * X_{\text{urine}})}] \quad \text{Formula 2}$$

Discussion

VAN blood concentration standard prediction index

With the extensive use of broad-spectrum antibiotics, the severity of bacterial resistance to VAN continues to increase [23]. Because creatinine clearance was found to increase by 26.5 $\mu\text{mol/L}$ or 50% within 14 days after VAN use, and/or because urine volume was $<0.5 \text{ ml}/(\text{kg} \cdot \text{h})$ in more than 6 h [24], kidney damage was determined. Therefore, urine volume was identified as an important factor. In this study, daily average infusion volume of patients and daily average urine volume were independent factors, as reported by Jiyao [18]. Typically VAN is not considered to be metabolized in the body, and at 24 h, its level is maintained at 90% for elimination via the kidney by the prototype [25]. However, because of different treatment options and doses required by different patients, a previous study could not report a stable clearance rate for clinical reference [26, 27]. Infusion volume and urine volume serve as factors that can affect the distribution volume and clearance rate of VAN in patients, thereby affecting its concentration. By fitting the prediction equation, patient's daily average infusion volume and daily average urine volume were substituted into the formula to predict their VAN blood concentration compliance rate and facilitate the timely adjustment of their medication regimen during treatment. When the ratio of the daily average infusion volume to the daily average urine volume was in the range of 0.35-1, a high VAN blood concentration was found; when the ratio was in the range of

0.48-1, VAN blood concentration was at its highest, and the rest of the concentrations were either higher or lower than the normal value; Further, when the ratio was greater than 1 (only three cases in this study), infusion volume was found to be greater than urine volume. Subsequently, a higher utilization rate of pigment led to a corresponding reduction in free VAN and an increase in the trough concentration. However, it cannot be excluded that urine volume still contained a large amount of free VAN when patient input (including the amount of daily intake such as infusion volume and drinking water) is greater than the infusion volume.

Correlation between history of drug allergy and compliance rate of VAN blood concentration

A patient's history of drug allergy in single factor ($P=0.022$) and multivariate ($P=0.026$) analysis was found to influence VAN blood concentration. However, there was no evidence that plasma concentrations of VAN are related to a history of drug allergy. Herein, we excluded the possibility that VAN-treated patients could be sensitive to the drug, but we found that their VAN blood concentration was related to a history of allergies. This implies that patients might be sensitive to other drugs, thereby causing sensitivity to VAN via individual differences. This finding could be used to clinically adjust VAN concentrations; however, such an important consideration requires further large-scale prospective research for verification.

Analysis of single factor results and multivariate logistic regression analysis

Univariate analysis can influence multivariate analysis as the latter excludes the effects of each factor. Relevant factors (ALT) that were not obtained by univariate analysis, such as VAN blood concentration, could be obtained by multivariate analysis. However, in the present study, this was rare. As confounding factors might cause distortion in the correlation variable and independent variable, such correlation distortion can either be an enhancing or diminishing effect.

Research limitations

In this study, factors influencing the compliance rate of VAN blood concentration were described using logistic models and ROC curves. Furthermore, the rate of VAN blood concentration was predicted. To our knowledge, a study similar to that reported herein has not been previously published. Nonetheless,

our study had some limitations as follows: (1) different batches of VAN or VAN from different regions could affect blood concentrations; therefore, a comparative study is needed to confirm our results; and (2) as we could not analyze unknown confounding factors, the results presented are limited [38].

Conclusions

In summary, although the dosing regimen and monitoring procedures for VAN have been largely established via pharmacodynamic and pharmacokinetic studies, personalized drug regimens are still needed for specific patients. In the present study, the combined predictive factor formula for patient's daily average infusion volume and urine volume could predict the compliance rate of VAN blood concentration. This will allow clinicians to identify problems and adjust the medication plan to promote the safe and effective use of VAN [39].

Abbreviations

Vancomycin, VAN;

Methicillin-resistant *Staphylococcus aureus*, MRSA;

Aspartate aminotransferase, AST;

Receiver operating characteristic, ROC;

Hospital Information Management System, HIS;

Glasgow coma score, GCS;

Alkaline phosphatase, ALP;

Glutamyl transpeptidase, GGT;

Total protein, TP

Declarations

Ethics approval and consent to participate

The study was approved by The First Affiliated Hospital of Bengbu Medical College, the ethics committee of clinical medical research (scientific research project) approval number: 2018KY008, the approval date : August 28, 2018; on June 23, 2019, the registration number of the China Clinical Trial

Registration Center was assigned as ChiCTR1900024062. At the same time, the informed consent is not signed because this study is a low-risk study and meets the IRB exemption informed consent requirements: Research using anonymous or no-risk tests, surveys, interviews, or observations.

Consent to publish

Not Applicable

Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

KL, ZY, and ZJ gathered patients for enrolment in the study and monitored patient vancomycin blood concentrations; CH collected the data, and wrote the manuscript; SQ provided the research ideas and

revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Influence factor assignment table.

Factors	Assignment
Sex	Male=0, female=1
History of drug allergy	Yes=1, no=0
History of smoking	Yes=1, no=0
History of alcohol abuse	Yes=1, no=0
Indication	Yes=1, no=0
Treatment programs*	Reasonable=1, unreasonable=0
Critical	Yes=1, no=0
Admission department	ICU=0, Respiratory =1, Neurosurgery=2, Pediatrics=3, General Medicine=4, Orthopedics=5, Nephrology=6, Oncology=7, Infectious Diseases=8, Gastrointestinal Surgery=9, Cardiology=10, Hematology=11, Stomatology=12, Emergency =13, Gynecology=14
Frequency of administration	q12h=0, q8h=1, q6h=2, q24h=3
Solvent	0.9% sodium chloride injection=0, 5% glucose injection=1, 10% glucose injection=2
Infected site	
Lung	Yes=1, no=0
Intracranial	Yes=1, no=0
Central nervous system	Yes=1, no=0
Bronchiectasis	Yes=1, no=0
Combined chronic disease	
Diabetes	Yes=1, no=0
Hypertension	Yes=1, no=0
Coronary heart disease	Yes=1, no=0
Rheumatoid arthritis	Yes=1, no=0
Heart disease	Yes=1, no=0
Chronic bronchitis	Yes=1, no=0
Concomitant infectious disease	
Hepatitis B	Yes=1, no=0
Tuberculosis	Yes=1, no=0
Combined antibacterial drugs	
Carbapenem	Yes=1, no=0
Aminoglycosides	Yes=1, no=0
Macrolides	Yes=1, no=0
β-lactam	Yes=1, no=0
Fluoroquinolone	Yes=1, no=0
Glycopeptide	Yes=1, no=0
Antifungal	Yes=1, no=0
Other drugs used in combination	
Enteral nutrition suspension	Yes=1, no=0
Adenosylmethionine	Yes=1, no=0
Reduced glutathione	Yes=1, no=0
Pantoprazole	Yes=1, no=0
sodium Furosemide	Yes=1, no=0
Human	Yes=1, no=0

*Regarding whether the treatment plan was reasonable: "The vancomycin clinical application of Chinese experts consensus" 2011 version and vancomycin instructions were jointly used to judge whether the patient's treatment plan was reasonable.

Table 3. Single factor analysis of patient information and observation indicators

Influencing factor	Compliance group (n=81)	Substandard group (n=87)	P	Influencing factor	Compliance group (n=81)	Substandard group (n=87)	P
Sex			0.186 ^a	Bronchiectasis	402.380	603.570	0.834 ^a
Male	55032.740	67039.880		Single dose(g)	81(48.21)	87051.790	0.390 ^b
Female	26015.480	20011.900		Frequency of administration			0.383 ^a
Age (year)	81(48.21)	87051.790	0.326 ^b	q12h	50029.760	54032.140	
Surgery and operation times	81(48.21)	87051.790	0.815 ^b	q8h	18010.710	22013.100	
History of drug allergy	603.570	17010.120	0.022 ^a	q6h	1005.950	502.980	
History of smoking	301.790	100.600	0.563 ^a	q24h	301.790	603.570	
History of alcohol abuse	301.790	301.790	1.000 ^a	Medication days (days)	81(48.21)	87051.790	0.331 ^b
Treatment programs*	34020.240	29017.260	0.248 ^a	Daily average infusion (ml)	81(48.21)	87 (51.79)	0.001 ^b
Indication	73043.450	75044.640	0.433 ^a	Daily average urine volume (ml)	81(48.21)	87 (51.79)	0.076 ^b
Critical	51030.360	60035.710	0.412 ^a	Solvent			0.516 ^a
GCS score	81(48.21)	87051.790	0.439 ^b	0.9% sodium chloride injection	54032.140	55032.740	
Hospital stay (days)	81(48.21)	87051.790	0.090 ^b	5% glucose injection	18010.710	17010.120	
Admission department			0.201 ^a	10% glucose injection	905.360	1508.930	
ICU	26015.480	27016.070		Serum creatinine clearance	81(48.21)	87051.790	0.889 ^b
Respiratory	18010.710	20011.900		Body temperature	81(48.21)	87051.790	0.574 ^b
Neurosurgery	804.760	704.170		ALT	81(48.21)	87051.790	0.374 ^b
Pediatrics	1307.740	1508.930		AST	81(48.21)	87051.790	0.057 ^b
General medicine	301.790	100.600		ALP	81(48.21)	87051.790	0.183 ^b
Orthopedics	100.600	000		GGT	81(48.21)	87051.790	0.438 ^b
Nephrology	100.600	301.790		TP	81(48.21)	87051.790	0.199 ^b
Oncology	201.190	000		A	81(48.21)	87051.790	0.689 ^b
Infectious Diseases	502.980	704.170		G	81(48.21)	87051.790	0.068 ^b
Gastrointestinal Surgery	201.190	000		Total bilirubin	81(48.21)	87051.790	0.259 ^b
Cardiology	201.190	100.600		Serum urea	81(48.21)	87051.790	0.746 ^b
Hematology	000	100.600		Serum creatinine	81(48.21)	87051.790	0.298 ^b
Stomatology	000	201.190		White blood cell count	81(48.21)	87051.790	0.699 ^b
Emergency	000	201.190		Hemoglobin	81(48.21)	87051.790	0.492 ^b
Gynecology	000	100.600		Platelet	81(48.21)	87051.790	0.484 ^b
Diabetes	1106.550	1106.550	0.857 ^a	Carbapenem	17010.120	1408.330	0.414 ^a
Hypertension	19011.310	19011.310	0.802 ^a	Aminoglycosides	301.790	100.600	0.563 ^a
Coronary heart disease	402.380	100.600	0.322 ^a	Macrolides	100.600	100.600	1.000 ^a
Rheumatoid arthritis	603.570	000	0.030 ^a	β-lactam	402.380	402.380	1.000 ^a
Heart disease	301.790	603.570	0.565 ^a	Fluoroquinolone	301.790	502.980	0.796 ^a
Chronic bronchitis	402.380	201.190	0.613 ^a	Glycopeptide	000	100.600	1.000 ^a
Hepatitis B	301.790	301.790	1.000 ^a	Antifungal	201.190	100.600	0.950 ^a
Tuberculosis	502.980	1005.950	0.227 ^a	Enteral nutrition	603.570	704.170	0.877 ^a

				suspension			
Total drug cost (yuan)	81(48.21)	87▯51.79▯	0.118 ^b	Adenosylmethionine	4▯2.38▯	4▯2.38▯	1.000 ^a
Antibacterial cost (yuan)	81(48.21)	87▯51.79▯	0.185 ^b	Reduced glutathione	2▯1.19▯	6▯3.57▯	0.325 ^a
Antibacterial cost: total drug cost	81(48.21)	87▯51.79▯	0.669 ^b	Pantoprazole sodium	4▯2.38▯	4▯2.38▯	1.000 ^a
Lung	44▯26.19▯	47▯27.98▯	0.969 ^a	Furosemide	7▯4.17▯	4▯2.38▯	0.290 ^a
Intracranial	10▯5.95▯	9▯5.36▯	0.682 ^a	Human immunoglobulin	8▯4.76▯	0▯0▯	0.008 ^a
Central nervous system	5▯2.98▯	5▯2.98▯	0.641 ^a				

*^abased on χ^2 text, ^bbased on t text. Data reported herein are for patients who indicated “Yes” and “reasonable” in the study.

Figures

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Figure 1
Relationship between Alanine aminotransferase (ALT) and blood serum.

Figure 2

Relationship between Aspartate aminotransferase (AST) and blood serum.

Figure 3

Relationship between ratio of infusion to urine and blood serum.

Figure 4

Receiver operator characteristic (ROC) curve of joint predictor.

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