RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Article

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Evaluation of initial dosing regimens of vancomycin used in the treatment of infections in patients into a trauma intensive care unit

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Submitted: 04-08-2022 Resubmitted: 10-12-2022 Accepted: 20-12-2022

Double blind peer review

Abstract

Objective: To verify the exposure to vancomycin in patients admitted to the ICU of trauma from a regional hospital compared to consensus exposure ranges therapy. **Methods:** Retrospective cross-sectional study, with data collection from electronic medical records of the patients using Vancomycin admitted to the trauma ICU at Hospital Pronto Socorro de Porto Alegre (RS) from January 2022 to May 2022. **Results:** We evaluated 28 patients who met the inclusion criteria in the study, of these, thirteen (46.42%) presented subtherapeutic trough concentrations of vancomycin, six (21.42%) had therapeutic concentrations and nine (32.14%) had supratherapeutic concentrations. The highest levels of vancomycin occurred between the 2nd and 4th day of treatment. Among the applied attack doses, seven (41.17%) received doses within the recommended range (average of 28.80 mg/kg) and fifteen (53.6%) the initial dose was within the range recommended by international guidelines. Less than 25% of subjects had therapeutic exposure to vancomycin. **Conclusion:** Therapeutic drug monitoring for vancomycin associated with a pharmacokinetic program that estimates dose adjustments favors the optimization of the therapy, increases the efficiency and benefits of the treatment.

Keywords: Vancomycin, therapeutic monitoring, pharmacokinetics, pharmacodynamics, trauma.

Avaliação dos regimes de dosagem iniciais de vancomicina usados no tratamento de infecções em pacientes internados em uma unidade intensiva de tratamento de trauma

Resumo

Objetivo: Verificar a exposição à vancomicina em pacientes internados na UTI de trauma de um hospital regional, em comparação com as faixas consensuais de exposição terapêutica. **Métodos:** Estudo transversal retrospectivo, com coleta de dados de prontuário eletrônico dos pacientes em uso de vancomicina internados na UTI de trauma do Hospital Pronto Socorro de Porto Alegre (RS) no período de janeiro de 2022 a maio de 2022. **Resultados:** Foram avaliados 28 pacientes que atenderam os critérios de inclusão no estudo, destes, treze (46,42%) apresentaram concentrações de vale subterapêuticas de vancomicina, seis (21,42%) apresentaram concentrações terapêuticas e nove (32,14%) apresentaram concentrações supraterapêuticas. Os maiores níveis de vancocinemia ocorreram entre o 2 e 4 dias de tratamento. Dentre as doses de ataque aplicadas, sete (41,17%) receberam doses dentro da faixa recomendada (média de 28,80 mg/kg) e quinze (53,6%) a dose inicial estava na faixa recomendada pelas guias internacionais. Menos de 25% dos indivíduos apresentaram exposição terapêutica à vancomicina. **Conclusão:** A monitorização terapêutica de fármacos para a vancomicina associado a um programa farmacocinético que estime os ajustes de doses favorece a otimização da terapia, aumenta a eficiência e os benefícios do tratamento.

Palavras-chaves: Vancomicina, monitoramento terapêutico, farmacocinética, farmacodinâmica, trauma.

Introduction

Gram-positive bacteria are pathogens frequently found in patients hospitalized in intensive care units. If not properly treated in the hospital, the infections caused by these agents are related to the development of multi-drug resistant microorganisms, which consequently extends hospitalization times and increases patients' morbidity and mortality, in addition to increasing the costs of the health services[1,2]. Used in the clinical practice for over 50 years, Vancomycin is a tricyclic glycopeptide antibiotic used in the therapy of serious infections caused by Gram-positive bacteria, mainly methicillin-resistant *Staphylococcus aureus* (MRSA), with bactericidal action[3,4]. It is considered a critically important drug, as MRSA infections are a problem for world medicine[5,3].

The use of vancomycin is particularly important in trauma patients, as its effectiveness has been shown in the treatment of septicemia, bone infections, lower respiratory tract infections, and infections

of the skin and its structures[6]. Individuals exposed to trauma have an activated immune system, increasing metabolic and cellular activity at the injury site in order to recover homeostasis[7]. Therefore, the pharmacokinetics of vancomycin can be modified in trauma patients, especially in those admitted to intensive care units, who may present daily alterations in hemodynamic stability that cause changes in pharmacokinetic parameters such as increased distribution volume and increased renal clearance of the drug[8,9].

Therapeutic Drug Monitoring (TDM) is defined as a multidisciplinary clinical specialty that aims at improving patient care through individual adjustment of drug doses. Clinical experience or clinical trials have shown that this approach improves therapeutic outcomes, and can be based on clinical, demographic or pharmacogenetic information. This information is known before initiating the treatment or in measurements of concentrations of the drug or other biomarkers, obtained after treatment initiation, according to the recommendations set forth by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT). Performance in TDM is one the pharmacist's clinical duties, regulated by the Federal Pharmacy Council[10].

TDM is based on the fact that the therapeutic response is better related to the drug concentration in the patient's bloodstream than to the dose administered. The use of regular doses at periodic intervals does not result in constant levels in all patients, mainly due to individual differences in absorption, distribution, biotransformation, excretion and bioavailability of the drug administered, which can influence the therapeutic effect. In particular, significant pharmacokinetic variability is observed among critically-ill patients[11].

The first consensual guideline for the vancomycin therapeutic monitoring in adult patients was published in 2009[12]. This consensus established pharmacokinetic targets based on vancomycin trough serum concentrations, with suggested concentrations of 15 to 20 mg/L for severe infections due to MRSA as a surrogate marker for the relationship between the area under the curve and the pathogen minimum inhibitory concentration (AUC/MIC), considering minimum inhibitory concentrations ≤1 mg/L and normal renal function[13,14]. Recently, a new consensus was published, establishing that the pharmacokinetic target of exposure to vancomycin should be AUC 0-24/MIC greater than 400 and less than 600. Currently, it is possible to estimate the area under the curve (AUC) with acceptable accuracy with limited sampling, usually with two plasma concentrations in the same dose interval. This estimate can preferably be performed using Bayesian inference software to estimate the vancomycin AUC value with minimal sampling, that is, 1 or 2 serum concentrations[12].

Although therapeutic monitoring of vancomycin is a common practice in many international centers that treat trauma patients, few Brazilian hospitals have programs for the pharmacokinetic individualization of treatments with vancomycin. A stage prior to the implementation of a hospital TDM service is the diagnosis of drug use practices and drug exposure instances obtained with the usual use modalities, when data on plasma concentrations are available.

Thus, this study aims at describing and evaluating the vancomycin dosage regimens used in critically-ill trauma victims in order to characterize the use practices of this drug in a Brazilian hospital specialized in emergency care.

Methods

This was a retrospective cross-sectional study carried out with data from the medical records of patients treated at the trauma ICU of the Emergency Hospital of Porto Alegre (RS).

In this study, the patients included were those over 18 years of age, of both genders, affected by trauma, admitted to the trauma ICU with Gram-positive infections, using vancomycin as monotherapy or associated with other antibiotics, who had at least one vancomycin serum concentration. The patients excluded were those admitted to the ICU with chronic kidney failure or undergoing hemodialysis. The study was approved by the Research Ethics Committee of the Porto Alegre Municipal Health Department (*Comitê de Ética em Pesquisa da Secretaria Municipal de Saúde de Porto Alegre*, CEP/SMSPA) and by the Research Ethics Committee of the Feevale University, under opinion number 5.395.510.15.

The research encompassed data collection and analysis of the electronic medical charts of these patients treated from 01/01/2022 to 05/23/2022. These data included diverse information on use and monitoring of the drug, such as the vancomycin serum concentrations routinely performed by the research locus, and complementary data such as: doses used, administration frequency and times, time of blood sample collection for determination of vancokinemia and clinical and demographic variables. The vancomycin concentrations were determined by means of the immunochemical method by the Clinical Pathology laboratory of the Porto Alegre Clinical Hospital Complex (*Hospital de Clínicas de Porto Alegre, HCPA). The following data were recorded: age, gender, weight, height, serum creatinine, bacterial culture test, type of trauma/indication, dosage, and time using vancomycin*.

The patients' creatinine clearance (CrCl) was calculating by impregnating Cockgrof-Gault's formula, using the total, ideal or adjusted weight according to the patient's data[15]. The lowest serum creatinine value used to calculate CrCL was 0.68 mg/dL to avoid overestimating the CrCL value[16] .Vancomycin clearance was estimated using the $CL_{vancomycin}$ (L/h) = 1,08 * ($CrCl_{CG\ (mL/min)}$ * 0.06) formula and the volume was calculated using the $V_{vancomycin}$ (L) = 0.98 * body weight formula , both obtained from BUELGA et al. (2005)[17] The vancomycin elimination constant (k) was obtained dividing the $CL_{vancomycin}$ value by $V_{vancomycin}$. The interval between initial doses was calculated by Equation 1, where the term t_{cmax} represents the time from the end of the infusion when the C_{max} desired is obtained, usually for 2h, and t_{inf} is the length of the infusion in time. C_{max} and C_{min} values of 10 mg/L and 22 mg/L, respectively, are usually compatible with the AUC_{0-24h} targets of 450 mg*h/L. The intervals were selected from the following options: 8, 12 and 24 hours.

$$\text{Interval (h)} = ((1 /- k_e) * (LN (C_{min})- LN (C_{max}))) + tc_{max} + t_{inf}$$

Equation 1

The loading dose was determined according to the *Vancomycin therapeutic guidelines* and those set forth by Government of South Australia[12,18]. The initial maintenance dose was calculated employing Equation 2, where AUC_{0-24h} is 450 mg/L*h.

$$\text{Dose (mg)} = \text{Desired } AUC_{0-24h} * CL_{vancomycin} * (\text{dose interval} / 24)$$

Equation 2

The data were analyzed by means of descriptive statistics. Considering data unavailability for calculating the patients' vancomycin $AUC_{0\text{-}24h}$, the vancokinemia values were evaluated according to target values for the trough concentration taking into account the collections performed immediately before the administration of any dose starting from the third[13]. Thus, vancokinemia values lower than 10 mg/L were considered subtherapeutic, between 10 and 20 mg/L therapeutic, and values greater than 20 mg/L supratherapeutic.

Results

From January 2022 to May 2022, 28 patients seen at the Porto Alegre Emergency Hospital met the inclusion criteria and were included in the study. Of these, 25 were male (89.3%) and 3 were female (10.7%), aged between 18 and 83 years old (mean of 43.8). The most common reasons for hospitalization were trauma due to firearm wounds (FAWs) in the chest, abdomen and/or skull with 32.14%, traumatic brain injury (TBI) with 28.57%, polytrauma (17.86%), trauma in upper (UL) and/or lower (LL) limbs with 14.28%, and trauma due to melee weapon wounds (MWWs) in chest and abdomen with 7.14%. The main indications for prescribing vancomycin included lung and skin infections or sepsis, both suspected and confirmed. The patients' sociodemographic and clinical characteristics are presented in Table 1.

The treatments applied, as well as the first measured vancokinemia values and results of the pharmacokinetic calculations are presented in Table 2.

Table 1. Sociodemographic and clinical data of the study participants

Patient	Age (years old)	Gender (M/F)	Height (cm)	Weight (kg)	Creatinine clearance (mL/min)	Type of trauma/indication
1	52	F	1.70	83	105.5	Trauma in ULL/Leukocytosis and increased and sustained CRP
2	50	M	1.68	55	77.2	Polytrauma/Signs of infection as per test results
3	38	M	1.79	100	130	FAW/Septic shock, pulmonary focus
4	68	M	1.76	69	79.3	TBI/MRSA, pulmonary focus
5	40	M	1.66	69	70.9	TBI/MRSA, tracheal aspirate
6	74	M	1.69	62	22.1	TBI/Sepsis
7	42	M	1.70	65	102.9	MWW/Gram positive cocci in tracheal aspirate
8	34	M	1.83	110	130	Polytrauma/MRSA, tracheal aspirate
9	41	M	1.65	63	65	TBI/Tomography: MVAP
10	55	F	1.55	48	21	Trauma in LRL/Pneumonia
11	69	M	1.70	87	78.8	Trauma in LRL/Skin injury
12	59	M	1.70	81	69.3	TBI/CBC, Staphylococcus aureus
13	27	M	1.75	49	113.1	FSW/CBC: MRSA
14	56	M	1.73	68	39.9	MWW+Pulmonary tuberculosis/sepsis
15	57	M	1.70	90	53.8	Polytrauma/Chest X-ray with diffuse bilateral pulmonary infiltrate
16	53	M	1.73	73	94.3	Polytrauma/Sepsis
17	30	M	1.73	83	97.1	FAW/Abdominal focus sepsis
18	83	F	1.30	45	22.1	TBI+Bacterial meningitis/CSF-MRSA
19	56	M	1.75	94	60.1	FAW/CNS coverage + MVAP
20	34	M	1.74	80	99.4	FAW/MVAP
21	32	M	1.79	90	111.1	TBI/Tracheal aspirate - Staphylococcus aureus
22	20	M	1.61	58	55.7	FAW/Sepsis
23	43	M	1.75	120	130	Polytrauma/Sepsis, cutaneous focus
24	17	M	1.65	62	130	TBI/MRSA, tracheal aspirate
25	30	M	1.68	64	92.2	FAW/Abdominal cellulite
26	44	M	1.71	67	130	FAW in chest/Sepsis
27	22	M	1.70	94	130	FAW/MRSA, tracheal aspirate
28	44	M	1.66	62	113.2	FAW/MVAP
24	17	M	1.65	62	130	TBI/MRSA, tracheal aspirate
25	30	M	1.68	64	92.2	FAW/Abdominal cellulite
26	44	M	1.71	67	130	FAW in chest/Sepsis
27	22	M	1.70	94	130	FAW/MRSA, tracheal aspirate
28	44	M	1.66	62	113.2	FAW/MVAP

Abbreviations: Central Blood Culture (CBC); Mechanical Ventilation-Associated Pneumonia (MVAP); Upper Left Limb (ULL), Firearm Wound (FAW); Traumatic Brain Injury (TBI); Melee Weapon Wound (MWW); Lower Righ Limb (LRL).

Table 2. Treatments applied, vancokinemia values and treatments calculated based on pharmacokinetic principles.

Patient	Treatment applied					First vancokinemia value	Treatment calculated				
	Loading dose		Maintenance dose		Interval		Loading dose		Maintenance dose		Interval
	mg	mg/kg	mg	mg/kg	H		mg	mg/kg	mg	mg/kg	H
1	2,000	24.1	1,250	14.8	12	8.3	2,500	30.1	1,500	18.1	12
2	-	-	1,000	18.2	12	11.6	1,500	27.3	1,250	22.7	12
3	-	-	1,200	12	12	9.3	2,500	25	2,000	20	12
4	2,000	28.9	1,000	14.5	12	15.1	2,000	28.9	1,250	18.1	12
5	2,000	28.9	1,000	14.5	12	8.9	2,000	28.9	1,000	14.5	12
6	1,750	28.2	1,000	16.1	12	27.7	1,500	24.2	750	12.1	24
7	-		1,000	15.3	12	14.4	2,000	30.7	1,500	23.1	12
8	2,000	18.2	1,750	15.9	12	10.9	2,500	22.7	2,000	18.2	12
9	-	-	1,500	23.1	12	43.5	1,500	23.1	1,000	15.4	12
10	2,000	41.6	1,000	20.8	12	33.0	1,250	26	500	10.4	24
11	1,750	20.1	1,500	17.2	12	11.2	2,500	28.7	1,250	14.3	12
12	-	-	1,000	12.3	12	10.3	2,500	30.8	1,000	12.3	12
13	2,000	40.8	1,000	20.4	12	3.6	1,250	25.5	1,750	35.7	12
14	2,000	29.4	1,000	14.7	12	38.5	2,000	29.4	1,250	18.3	24
15	-	-	500	5.5	12	8.3	2,500	27.8	1,500	16.6	24
16	2,000	27.4	1,000	13.7	12	21.7	2,000	27.4	1,250	17.1	12
17	2,000	24.1	1,250	15.1	12	5.5	2,500	30.1	1,500	18.1	12
18	-	-	1,500	33.3	12	27.1	1,250	27.7	750	16.6	24
19	2,000	21.2	1,500	15.9	12	24.3	2,500	26.6	1,750	18.6	24
20	2,000	25	1,250	15.6	12	9.0	2,500	31.2	1,500	18.7	12
21	2,000	22.2	1,500	16.6	12	42.1	2,500	27.8	1,500	16.6	12
22	-	-	1,000	17.2	12	27.2	1,500	25.8	750	12.9	12
23	-	-	2,000	16.6	12	9.5	3,000	25	2,000	16.6	12
24	-	-	1,000	16.1	8	5.6	1,500	24.2	2,000	32.2	12
25	-	-	1,000	15.6	12	8.3	1,500	23.4	1,250	19.5	12
26	2,000	29.8	1,000	14.9	12	6.3	2,000	24.2	2,000	24.2	12
27	2,000	21.2	1,500	15.9	12	5.4	2,500	26.6	2,000	21.3	12
28	1,500	24.2	1,000	16.1	12	9.0	1,500	24.2	1,750	28.2	12

Loading doses were administered to 17 (60.7%) study patients. Among the loading doses applied, 7 patients (41.17%) received doses within the recommended range (from 27.39 to 29.85 mg/kg, mean of 28.22 mg/kg), 2 patients (11.76%) received loading doses above this range (40.81 and 41.66 mg/kg) and 8 patients received loading doses below this range (from 18.18 to 24.19 mg/kg, mean of 21.91 mg/kg).

The initial dose ranged from 5 to 33 mg/kg and, for 9 patients (32.1%), the initial maintenance dose was below 15 mg/kg (mean of 13.01 mg/kg), for 15 (53 .6%) the initial dose was in the range recommended by the international guidelines (mean of 16.30 mg/kg) and, for 4 (14.3%) patients, the initial maintenance dose was above 20 mg/kg (mean of 24.40 mg/kg). The patient's weight is an important variable for the calculation used in vancomycin prescriptions; a nutritional evaluation becomes important to obtain this data in proper dose adjustment. All the study patients had at least one measure of vancomycin serum levels and use time between 3 and 17 days, with dose intervals of 8, 12 and 24 hours.

Vancomycin is a drug with a narrow therapeutic range; therefore, monitoring the serum levels contributes to adjusting the prescription in order to reach adequate therapeutic concentrations, prevent toxicity and repress growth of resistant strains[11,3]. Vancomycin trough serum concentrations are the most practical monitoring modality; therefore, collections must be performed in a stationary state, that is, after a minimum of three doses (infused intravenously every 12 hours). To ensure the "trough" state, collection should be performed 30 minutes before administration of any dose from the third one onwards in patients with normal renal function[3,14]. More recently, the vancomycin exposure pharmacokinetic/pharmacodynamic targets have been updated to AUC 0-24/MIC greater than 400 and less than 600 for therapeutic efficacy with low likelihood of toxicity[12].

Among all 28 patients studied, 13 (46.4%) presented subtherapeutic vancomycin trough concentrations, 6 (21.5%) showed therapeutic concentrations, and 9 (32.1%) showed supratherapeutic concentrations. Consequently, 6 patients (21.4%) were subjected to therapeutic exposure to vancomycin. The patients with subtherapeutic vancomycin levels had a mean CrCL value of 107.30 mL/min and a mean initial dose of 14.87 mg/kg (from 5 to 14 mg/kg). On the other hand, those with supratherapeutic exposure to vancomycin had a mean CrCL value of 54.6 mL/min and a mean daily vancomycin dose of 19.06 mg/kg (from 16.12 to 33.33 mg/kg). And the patients with therapeutic exposure presented a mean CrCL value of 89.58 mL/min, and a daily vancomycin dose of 15.71 mg/kg.

Trough levels below 10 mg/L in critically-ill patients can increase the risk of therapeutic failure and development of resistant strains.

Pharmacokinetics in traumatized patients varies significantly due to edema and sepsis, among other factors. Considering variables such as distribution volume of the drug in the body and renal clearance, monitoring of the clinical response and monitoring of serum levels becomes necessary in these patients in order to avoid therapeutic failure[4,3].

Early identification of supratherapeutic levels allows adjusting doses or the administration interval, avoiding nephrotoxicity and possible clinical complications, thus resulting in a reduction of the mortality rates[4,3].

It is important to note that, by applying simple calculations, it was possible identify patients who would benefit from a dose based on pharmacokinetic principles. In fact, of the 13 patients who had subtherapeutic vancokinemia values, 11 (84.6%) had an initial calculated daily dose higher than the one used before. In addition, of the 6 patients who had therapeutic vancokinemia, 4 (66.6%) had a calculated daily dose equal to the one used and, of the 9 patients with supratherapeutic vancokinemia, 7 (77.7%) had calculated daily doses lower than those applied. Thus, of the 22 patients with serum concentrations below and/or above the therapeutic range, 18 (81.1%) used higher and/or lower daily doses than those calculated. From this assessment we realized that, through simple calculations, it would be possible to select more rational treatment regimens for a large proportion of patients currently receiving inadequate treatment.

Discussion

As per the guideline for critically-ill patients with severe infections, it is recommended to use loading doses of 25-30 mg/kg, with maintenance doses between 15 and 20 mg/kg also recommended[12].

Although the literature is well established regarding the importance of using a loading dose with the purpose of reducing the time to reach therapeutic levels, the data from this study show that, among the 28 patients included, 11 (39.28%) did not receive a loading dose and that, of the 17 who received a loading dose, 11 (64.70%) had dose levels outside the ranges recommended by the current international guidelines. The use of vancomycin loading doses allow faster achievement of therapeutic concentrations of the drug, resulting in clinical improvements in critically-ill patients with severe infections and suppressing development of antibiotic resistance[11].

Adequate administration of vancomycin has remained difficult to the present day, due to the different coefficients associated with dose adequacy for critically-traumatized patients, both in terms of patient and drug pharmacokinetics. In this study, a minimum percentage of 6 patients (21.4%) had adequate serum levels in the stationary phase, triggering an alert for therapy failure or development of resistant strains. Bacterial resistance corroborates the deterioration in the patients' prognoses, thus limiting the cure chances[2].

Our study found difficulties obtaining adequate trough vancokinemia concentrations when therapeutic regimens without pharmacokinetic foundations are applied, with high rates of subtherapeutic and supratherapeutic exposure to the drug. A further difficulty for the application of pharmacokinetic models for dose adjustment consists in obtaining exact information about drug administration and blood collection times for dosing. Determination of the vancomycin serum levels, after a minimum of three doses (infused intravenously every 12 hours), makes it possible to adapt doses or administration intervals, both for supratherapeutic levels, preventing nephrotoxicity, and for subtherapeutic levels, in order to achieve therapeutic success. The evaluation of the data and dose adjustments depends on the records of the multidisciplinary team considering the many variables such as request for vancokinemia and serum creatinine exam by the prescribing professionals, date and time of sample collection by the collector and time of vancomycin infusion administration by the Nursing team[1].

In critically-ill patients affected by trauma, the physiological changes that occur make it difficult to select treatments with vancomycin, as such patients frequently have high renal clearance and drug distribution volume, altering its bioavailability. These influencing covariates of the pharmacokinetic parameters can also impair the vancokinemia analyses, as this drug is 75% to 90% eliminated via the renal route by glomerular filtration[6].

We observed that CrCl is an important covariate in vancomycin pharmacokinetic models because it estimates the physiological changes in the glomerular filtration rate and these must be considered to calculate appropriate dosage schemes[9,12].

Therefore, therapeutic monitoring of vancomycin and dose individualization programs contribute to improving effectiveness of the antimicrobial treatment, reducing hospitalization times, intoxication risks and adverse effects[11]. Understanding the pharmacokinetics of the population, identifying the physiological predictors of altered drug disposition in trauma patients, enables dose individualization according to the patient[17,8].

Conclusion

Most of the initial treatments with vancomycin applied to trauma patients hospitalized in an Intensive Care Unit failed to achieve therapeutic exposure to the drug. The most common situation was underdose. However, the use of simple pharmacokinetic calculations might allow the selection of initial treatments that are more adequate to the characteristics of the patients, enabling better therapeutic results. The study results showed the need to apply therapeutic monitoring for a more rational use of this important antibiotic drug.

Collaborators

MB and RL took part in elaboration of the article, including conception of the project, data analysis and interpretation, writing of the article and review of the final paper to be published.

Acknowledgments

The authors wish to thank the hospital pharmacy team and the Hospital Research Center from the Porto Alegre Emergency Hospital for their collaboration.

Funding sources

The research did not receive funding for its realization.

Conflict of interest statement

The authors declare that there is no conflict of interest to report.

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