International Journal of Antimicrobial Agents 57 (2021) 106281

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration alone in intracranial infections

Min Ni[a,1], Liang Zhao[b,1], Wen-jing Zhang[a,c,1], Jia-wei Ma[a], Guo-yan Zhang[a], Da-ming Cui[d], Ke Wang[d], Yi-bo Fei[a], Liang Gao[d,*], Fu-ming Shen[a,*]

[a] Department of Pharmacy, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Middle Yanchang Road, Shanghai 200072, China
[b] Department of Pharmacy, Shanghai Baoshan Luodian Hospital, Shanghai, China
[c] Department of Pharmacy, Inner Mongolia Autonomous Region People's Hospital, Inner Mongolia Autonomous Region, China
[d] Department of Neurosurgery, Shanghai Tenth People's Hospital, Tongji University School of Medicine, 301 Middle Yanchang Road, Shanghai 200072, China

ARTICLE INFO

Article history:
Received 5 August 2020
Accepted 9 January 2021

Editor: Professor Jason Roberts

Keywords:
Pharmacokinetics
Colistin
Intracranial infection
Intraventricular administration
Multidrug-resistant

ABSTRACT

The aim of this study was to investigate the pharmacokinetics of colistin in cerebrospinal fluid (CSF) after intraventricular (IVT) administration of colistin methanesulfonate (CMS) for central nervous system (CNS) infections caused by multidrug-resistant Gram-negative bacteria. Ten patients with CNS infection were treated with CMS (active substance colistin equivalent to 100 000 units, every 24 h) by IVT administration. After 3 days of treatment, the concentration of colistin in the CSF was determined by selective ultra-performance liquid chromatography (UPLC) at 2, 4, 6, 8, 12 and 24 h after CMS administration. A pharmacokinetic analysis was performed using Phoenix WinNonlin. Following IVT administration of CMS, the estimated colistin apparent CSF half-life ($t_{1/2}$) was 10.46 ± 6.98 h, the average peak colistin concentration (C_{max}) was 16.95 ± 7.39 μg/mL and the average time to peak concentration (T_{max}) was 4.6 ± 0.97 h. The measured trough concentration (C_{min}; colistin concentration in CSF at 24 h after administration of CMS) was 1.12–8.33 μg/mL and the average C_{min} was 2.91 ± 2.11 μg/mL. CSF concentrations of colistin were above the minimum inhibitory concentration (MIC) of 0.5 μg/mL at 24 h after IVT administration in all patients. Microbiological cure was observed in all patients. In conclusion, this is the first study of colistin pharmacokinetics in CSF after IVT administration alone in patients with CNS infection. It provides essential data for designing relatively safe and effective CMS dosing regimens.

1. Introduction

Central nervous system (CNS) infection can occur as a serious complication in patients undergoing craniotomy, which can be difficult to treat owing to the presence of the blood–brain barrier. Moreover, the emergence of multidrug-resistant (MDR) bacterial strains has made the treatment of CNS infections increasingly difficult in recent years.

According to the 2019 CHINET report (http://www.chinets.com), the detection rate of the Gram-negative bacteria *Acinetobacter baumannii* and *Klebsiella pneumoniae* in the CNS from patients with encephalic infection was 12.43% and 8.03%, respectively. Furthermore, these strains have varying degrees of resistance to third- and fourth-generation cephalosporins, aminoglycosides and carbapenems. Challenges for the treatment of infections caused by these antibiotic-resistant pathogens rely on whether antibiotic concentrations in the cerebrospinal fluid (CSF) can reach effective therapeutic antimicrobial concentrations. Recent studies provide high-quality evidence for the effectiveness of intraventricular (IVT) or intrathecal administration of antibiotics to treat MDR Gram-negative bacterial infections [1–3].

Colistin, administered as its prodrug colistin methanesulfonate (CMS), is a concentration-dependent bactericidal lipopeptide with a modest post-antibiotic effect [4]. In view of its potential nephrotoxicity and neurotoxicity, colistin was practically discarded by clinicians in the 1970s but it regained the spotlight in the early 2000s following the surge in infections caused by MDR *A. baumannii, K. pneumoniae* and *Pseudomonas aeruginosa* [5]. However, the CSF distribution of colistin following intravenous (IV) administration is very low. The reported CSF-to-serum concentration ratio is 0.07 [6] and the low CNS concentration is not enhanced by meningeal inflammation [7]. Consequently, IVT or intrathecal administration of colistin to patients with CNS infections, especially

* Corresponding authors.
E-mail addresses: lianggaoh@126.com (L. Gao), fumingshen@tongji.edu.cn (F.-m. Shen).
[1] These three authors contributed equally to this work.

https://doi.org/10.1016/j.ijantimicag.2021.106281
0924-8579/

patients with renal failure, has become an increasingly common method for the treatment of MDR bacterial infections.

There are only two studies describing the pharmacokinetics (PK) and pharmacodynamics (PD) of colistin after combined IV/IVT administration [6,8]. Besides, the PK/PD of colistin following IVT administration alone has never been reported. Moreover, the minimum inhibitory concentration (MIC) breakpoints of colistin against *A. baumannii, K. pneumoniae* and *P. aeruginosa* recommended by the Clinical and Laboratory Standards Institute (CLSI) differ from actual MICs measured by antimicrobial susceptibility testing in our work. To address the high morbidity and mortality of CNS infections caused by prevalent MDR bacteria, detailed data on the PK/PD of colistin after IVT administration alone are required to design suitable CMS dosing regimens for use in hospitals.

2. Materials and methods

2.1. Study design and treatment schedule

Study participants comprised patients with CNS infections from November 2018 to February 2019 fitted with an external ventricular drain (EVD) in the neurosurgical intensive care unit of Shanghai Tenth People's Hospital (Shanghai, China). Concentrations and pharmacokinetics of colistin after IVT treatment were evaluated in ten patients (age range, 18–58 years; 9 male and 1 female) with CNS infection by multi-drug resistant *K. pneumoniae* (5 patients) or *A. baumannii* (5 patients). Colistin MICs were measured by the broth microdilution method. Antimicrobial susceptibility testing showed susceptibility to colistin as follow: *K. pneumoniae* (colistin MIC $<$ 0.5 mg/L) and *A. baumannii* (colistin MIC $<$ 0.5 mg/L). The characteristics of the study participants are shown in Table 1. CSF biochemical characteristics were evaluated before and every 2 days following CMS administration. To ensure that treatment continued until patients were cured, the following criteria were used: white blood cell count in CSF of $<$20 cells/L for three consecutive tests, and two consecutive CSF negative cultures. All of the clinical procedures were approved by the hospital ethics committee, and written informed consent was obtained from all family members of participants.

Patients received IVT administration of CMS (Forest Laboratories UK Ltd., Dartford. UK) at doses of 100 000 units/24 h. The selected dose of CMS was diluted in 5 mL of 0.9% saline solution and was injected into the ventricle through the EVD, after which the EVD was flushed with 2 mL of 0.9% saline solution. Solutions were prepared just before administration. The EVD was clamped for 2 h following IVT administration. After 3 days of treatment, CSF samples were collected from the EVD at 2, 4, 6, 8, 12 and 24 h after CMS administration. At each sampling time, 2 mL of CSF was discarded prior to collection of the sample. All samples were stored at –80°C before analysis. Potential nephrotoxicity was evaluated by daily measurement of serum creatinine, and clinical symptoms were monitored by the clinician following CMS administration.

2.2. Measurement of colistin concentrations

Colistin concentrations in the CSF were determined by a previously described method. Briefly, after addition of H_2SO_4 (20 μL, 0.25 mol/L), the CSF sample (150 μL) was incubated for 30 min at 80°C. The spiked samples (50 μL) were then centrifuged at 12 000 × *g* for 5 min at 4°C after addition of cold acetonitrile (100 μL) and ibuprofen (50 μL, 2.5 μg/mL) mixed by vortexing for 30 s, then 100 μL of supernatant was transferred into injection vials used for ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) detection.

The concentration of colistin (sum of colistin E1 and colistin E2) in the CSF was measured using the method reported by Gobin

Table 1
Clinical characteristics and outcomes of the patients.

Patient	Sex	Age (years)	Serum creatinine (μmol/L)	Pathogen	Susceptibility	IV antibiotic co-administered	WBC count ($\times 10^6$/L) [a]	Duration of IVT therapy (days)	Microbiological outcome	Clinical outcome
1	Male	28	44.9	*K. pneumoniae*	Carbapenem-resistant	Meropenem, tigecycline, etimicin	900	20	Cure	Survival
2	Female	57	31.2	*A. baumannii*	Carbapenem-resistant	Meropenem, linezolid, tigecycline	3040	22	Cure	Survival
3	Male	36	46.4	*K. pneumoniae*	Carbapenem-resistant	Meropenem, tigecycline	4260	32	Cure	Survival
4	Male	49	40.3	*A. baumannii*	Carbapenem-resistant	Meropenem, tigecycline, fosfomycin	12 500	24	Cure	Survival
5	Male	41	50.5	*K. pneumoniae*	Carbapenem-resistant	Meropenem, tigecycline, fosfomycin	6600	26	Cure	Survival
6	Male	39	52.3	*A. baumannii*	Carbapenem-resistant	Meropenem, fosfomycin, fluconazole	40 800	28	Cure	Survival
7	Male	58	24.3	*K. pneumoniae*	Carbapenem-resistant	Meropenem, tigecycline	28 000	32	Cure	Survival
8	Male	18	48.3	*A. baumannii*	Carbapenem-resistant	Tigecycline, levofloxacin, fluconazole	1100	18	Cure	Survival
9	Male	51	36.9	*K. pneumoniae*	Carbapenem-resistant	Meropenem, fosfomycin	700	16	Cure	Survival
10	Male	44	38.4	*A. baumannii*	Carbapenem-resistant	Cefoperazone/sulbactam, tigecycline	15 800	35	Cure	Survival

IV, intravenous; WBC, white blood cell; IVT, intraventricular.
[a] WBC count in cerebrospinal fluid before IVT administration of colistin methanesulfonate (CMS).

et al. [9] with minor modifications. Chromatographic analysis was performed on an Agilent 1290 UPLC System (Agilent Technologies, Savage, MD, USA), including a G7120A binary pump, G7167B high-performance well-plate autosampler and G7116B column temperature controller. Chromatographic separation was achieved on an Agilent Zorbax SB C18 column (4.6 × 100 mm, 3.5 μm). Mass spectrometry (MS) detection was performed on an Agilent 6470 Triple Quad Mass Spectrometer (Agilent Technologies) with the Agilent JetStream electrospray source interface (AJS-ESI).

MS/MS was set in the positive ion detection mode using multiple reaction monitoring (MRM). The transitions of colistin E1 and colistin E2 were m/z 391.1→101.1 and m/z 386.4→101.1, respectively. Ibuprofen (as an internal standard, IS) was detected by transition of m/z 207→161. The MS working parameters were set at: capillary voltage, 4000 V; gas temperature, 330°C; drying gas flow, 11 L/min; nebuliser pressure, 40 psi; sheath gas temperature, 350°C; and sheath gas flow, 11 L/min. The transitions voltage for colistin E1, colistin E2 and the IS were both 70 V, and the collision energies of the analytes and IS were 17, 17 and 10 eV, respectively. Agilent MassHunter WorkStation v.B.07.00 was used for data acquisition.

Due to the sensitivity and selectivity of the LC-MS/MS method, no endogenous elements interfered with the analyses. The matrix effects of colistin were conducted with five replicates at three quality control concentrations (0.5, 8.0 and 40 μg/mL).The data showed no significant matrix effects in the CSF (range 87.2–106.6%). The intraday and interday precision of colistin were all <10%, while the accuracy ranged from 94.45–112.42%. The calibration curves showed good linearity ($r > 0.995$) in the concentration ranges from 0.25 μg/mL to 50 μg/mL, indicating that the LC-MS/MS method was satisfactory for the assay.

2.3. Cerebrospinal fluid pharmacokinetic analysis

Concentrations of colistin E1 and colistin E2 were determined by the accompanying calibration curve of each analysis batch. Pharmacokinetic parameters including T_{max} [time at which the peak colistin concentration (C_{max}) was observed], $t_{1/2}$ (elimination half-life) and $AUC_{0–24}$ (24-h area under the CSF concentration–time curve) were calculated by a one-compartmental model [8] using the WinNonlin 7.0 PK program (Pharsight Corp., Princeton, NJ, USA). C_{max} (maximum concentration of colistin), C_{min} (trough concentration of colistin at 24 h) and C_{12h} (concentration of colistin at 12 h) were measured based on the concentration–time curve.

3. Results

3.1. Clinical results

The duration of IVT treatment with CMS ranged between 16 days and 35 days (Table 1). Microbiological cure was observed in all patients, and all patients were discharged to rehabilitation to receive further treatment. None of the patients developed seizures, renal failure or allergy to colistin.

3.2. Colistin cerebrospinal fluid concentrations and pharmacokinetic analysis

The CSF concentration curve of colistin after IVT administration of CMS at different time points is shown in Fig. 1. After 3 days of IVT administration of CMS, CSF samples were collected and the pharmacokinetic parameters of colistin are shown in Table 2. The estimated half-life ($t_{1/2}$) of colistin in CSF was 10.46 ± 6.98 h and the $AUC_{0–24}$ of colistin was 183.4 ± 84.94 h•μg/mL. The concentration of formed colistin reached C_{max} (16.95 ± 7.39 μg/mL) at T_{max} (4.6 ± 0.97 h) and then decreased gradually to C_{12h} (7.13 ±

Table 2
Estimated pharmacokinetic parameters of colistin in cerebrospinal fluid following intraventricular administration of colistin methanesulfonate (CMS).

Patient	V_{CSF} (mL)	C_{min} (μg/mL)	C_{12h} (μg/mL)	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0–24}$ (h•μg/mL)	$AUC_{0–24}$/MIC	CL [IU/(h•μg/L)]
1	220	8.33	9.47	16.54	4	27.18	250.03	500.06	0.173
2	170	4.15	8.04	15.77	6	9.87	195.1	390.2	0.393
3	200	2.67	4.02	20.27	4	12.08	153.24	306.48	0.5
4	190	2.35	8.56	13.38	6	6.98	177.42	354.84	0.497
5	153	1.12	4.07	8.32	6	6.46	92.09	184.18	0.975
6	46	2.53	3.75	9.53	4	17.325	109.89	219.78	1.115
7	138	1.53	3.16	24.99	4	4.91	198.12	396.24	0.957
8	220	1.53	5.56	13.86	4	8.43	127.9	255.8	1.365
9	140	1.68	5.77	13.95	4	5.98	144.79	289.58	0.313
10	228	3.24	18.88	32.87	4	5.418	385.58	771.16	0.73
Mean ± S.D.		2.91 ± 2.11	7.13 ± 4.68	16.95 ± 7.39	4.6 ± 0.97	10.46 ± 6.98	183.4 ± 84.94	366.83 ± 169.87	0.706 ± 0.73

V_{CSF}, volume of cerebrospinal fluid drained during the sampling period; C_{min}, trough concentration of colistin at 24 h; C_{12h}, concentration of colistin at 12 h; C_{max}, maximum concentration of colistin; T_{max}, the time at which C_{max} was observed; $t_{1/2}$, elimination half-life of colistin; $AUC_{0–24}$, 24-h area under the cerebrospinal fluid colistin concentration–time curve; MIC, minimum inhibitory concentration; CL, drug clearance; S.D., standard deviation.

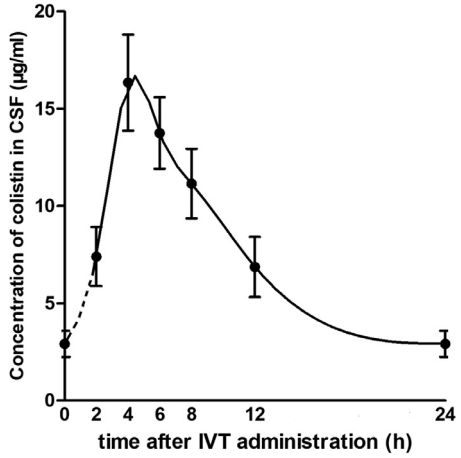

Fig. 1. Cerebrospinal fluid (CSF) concentration curve for colistin after intraventricular (IVT) administration of colistin methanesulfonate at different time points. The CSF concentration curve of colistin is presented as the mean ± standard error of the mean (SEM).

4.68 μg/mL). The measured trough concentration values (concentration of colistin at 24 h, C_{min}) ranged between 1.12 μg/mL and 8.33 μg/mL, and the average C_{min} was 2.91 ± 2.11 μg/mL. Moreover, C_{min} values were continuously above 0.5 mg/L (the MIC for *K. pneumoniae* and *A. baumannii* shown by antimicrobial susceptibility testing) in all patients. The average C_{max}/MIC and AUC_{0-24}/MIC ratios after IVT administration of CMS were 33.9 and 366.8, respectively.

4. Discussion

CNS infections are a serious complication of craniotomy. Antimicrobial treatment of CNS infections should be based not only on antimicrobial susceptibility but also on antimicrobial concentrations in the CNS owing to the existence of the blood–brain barrier. Carbapenemase-producing bacteria are even more complex and difficult to treat. Consequently, CNS infections caused by MDR pathogens may contribute to prolonged courses of treatment, high costs and high mortality. Previous studies have suggested the efficacy of IVT administration of CMS in CNS infections [2,3,8]. As predicted, this treatment was also effective in our cohort of patients with CNS infections, and microbiological cure was achieved in all patients. No renal injury, allergy to colistin or neurotoxicity (such as seizures, hypotonia, diaphragmatic paralysis or cauda equina injury) was observed following IVT administration of CMS in our patients. However, the use of sedative drugs and low serum creatinine levels may have led us to underestimate the neurotoxicity and nephrotoxicity of colistin.

As the inactive prodrug of colistin, CMS forms colistin by spontaneous hydrolysis in solution. Colistin is supplied as a mixture of at least 30 polymyxins. Colistin A (polymyxin E1) and colistin B (polymyxin E2) account for more than 85% of this mixture [10]. In this work, quantification of colistin in CSF focused on the two major components.

Colistin is a concentration-dependent antibiotic and the AUC/MIC ratio is the best predictive index of efficacy [11,12]. It is recommended that an area under the plasma colistin concentration–time curve across 24 h at steady state (AUC_{0-24}) of ~50 h•μg/mL is required, which equates to a target average steady-state plasma concentration ($C_{ss,avg}$) of ~2 mg/L [13]. Following IVT administration of CMS in this study, the measured trough concentration values (C_{min}) ranged between 1.12 μg/mL and 8.33 μg/mL, and the average C_{min} was 2.91 ± 2.11 μg/mL. Moreover, in this study isolated pathogens and antimicrobial susceptibility testing showed the colistin MICs for *K. pneumoniae* and *A. baumannii* were <0.5 mg/L. When patients received CMS at doses of 100 000 units/day, the CSF concentrations of colistin were continuously above 0.5 mg/L in all patients. The C_{max}/MIC and AUC_{0-24}/MIC ratios after IVT administration of CMS were ≥16.64 and ≥184.18, respectively, and the average C_{max}/MIC and AUC_{0-24}/MIC ratios after IVT administration of CMS were 33.9 and 366.8.

However, according to the European Committee on Antimicrobial Susceptibility Testing (EUAST) and the CLSI, the MIC breakpoints for *K. pneumoniae* and *A. baumannii* are 2 μg/mL. If we reference these susceptibility breakpoints, although the average C_{min} was 2.91 ± 2.11 μg/mL, the C_{min} was <2 μg/mL in four patients. The C_{max}/MIC and AUC_{0-24}/MIC ratios after IVT administration of CMS were ≥4.16 and ≥46.05, respectively, and the average C_{max}/MIC and AUC_{0-24}/MIC ratios after IVT administration of CMS were 8.48 and 91.7. Based on these data, a lower dosage of CMS may be adequate for a MDR pathogen with a low MIC.

Clearance of colistin ranged from 0.173 IU/(h•μg/L) to 1.365 IU/(h•μg/L), showing great variation. Several factors could contribute to this variability, such as the efficiency of CMS conversion, formation and absorption by the CSF, obstruction of CSF flow (e.g. compartmentalisation of ventricles), etc. In this work, the concentration of CMS was not measured, so the efficiency of CMS conversion could not be evaluated. Patients in the study were fitted with an EVD to control intracranial pressure. The external CSF drainage was not uniform, varying from 46 mL to 228 mL, which would understandably affect the disposition and clearance of colistin. However, no dramatic correlation was observed between the amount of CSF drained and colistin clearance.

In conclusion, our findings suggested that IVT administration of CMS in patients with CNS infection caused by the MDR Gram-negative bacteria provided an effective concentration of colistin in the CSF. Following IVT administration of CMS at a dose of 100 000 units/day, CSF concentrations of colistin were continuously above the MIC in our patients. This study provides the first pharmacokinetic data for IVT administration alone and is essential for the design of CMS dosing regimens for use in hospitals.

Acknowledgments

The authors would like to acknowledge Song-yu Chen, Tao Zeng and Yi Jin for their expertise and guidance in the evaluation of this work.

Funding: This work was supported by grants from the National Natural Science Foundation of China [Nos. 81703590 and 81973312], the Youth Medical Talented Clinical Pharmacist Program of Shanghai (to Min Ni), the Shanghai Key Clinical Specialist Construction Programs (to Fu-Ming Shen) and the Collaborative Innovation Cluster of Shanghai [No.2019CXJQ03].

Competing interests: None declared.

Ethical approval: All of the clinical procedures were approved by the hospital ethics committee, and written informed consent was obtained from all family members of participants.

References

[1] Lewin JJ 3rd, Cook AM, Gonzales C, Merola D, Neyens R, Peppard WJ, et al. Current Practices of Intraventricular Antibiotic Therapy in the Treatment of Meningitis and Ventriculitis: Results from a Multicenter Retrospective Cohort Study. Neurocrit Care 2019;30:609–16.

[2] Bargiacchi O, Rossati A, Car P, Brustia D, Brondolo R, Rosa F, et al. Intrathecal/intraventricular colistin in external ventricular device-related infections by multi-drug resistant Gram negative bacteria: case reports and review. Infection 2014;42:801–9.

[3] Karaiskos I, Galani L, Baziaka F, Katsouda E, Ioannidis I, Andreou A, et al. Successful treatment of extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis with intraventricular colistin after application of a loading dose: a case series. Int J Antimicrob Agents 2013;41:480–3.

[4] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis 2015;15:225–34.
[5] Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis 2006;6:589–601.
[6] Ziaka M, Markantonis SL, Fousteri M, Zygoulis P, Panidis D, Karvouniaris M, et al. Combined intravenous and intraventricular administration of colistin methanesulfonate in critically ill patients with central nervous system infection. Antimicrob Agents Chemother 2013;57:1938–40.
[7] Everett ED, Strausbaugh LJ. Antimicrobial agents and the central nervous system. Neurosurgery 1980;6:691–714.
[8] Imberti R, Cusato M, Accetta G, Marino V, Procaccio F, Del Gaudio A, et al. Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration of colistin methanesulfonate. Antimicrob Agents Chemother 2012;56:4416–21.
[9] Gobin P, Lemaitre F, Marchand S, Couet W, Olivier JC. Assay of colistin and colistin methanesulfonate in plasma and urine by liquid chromatography-tandem mass spectrometry. Antimicrob Agents Chemother 2010;54:1941–8.
[10] Cangemi G, Barco S, Castagnola E, Tripodi G, Favata F, D'Avolio A. Development and validation of UHPLC-MS/MS methods for the quantification of colistin in plasma and dried plasma spots. J Pharm Biomed Anal 2016;129:551–7.
[11] Bergen PJ, Li J, Nation RL. Dosing of colistin-back to basic PK/PD. Curr Opin Pharmacol 2011;11:464–9.
[12] Dudhani RV, Turnidge JD, Nation RL, Li J. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against Acinetobacter baumannii in murine thigh and lung infection models. J Antimicrob Chemother 2010;65:1984–90.
[13] Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39:10–39.