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PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 72 (2018), No. 4 (715), pp. 201–206

DOI: 10.2478/prolas-2018-0024

COLISTIN USE PATTERNS AND TOXICITY IN CRITICALLY ILL PATIENTS IN PAULS STRADIŅŠ CLINICAL UNIVERSITY HOSPITAL

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Communicated by Aivars Lejnieks

Colistin is used systemically in critically ill patients for treatment of infections caused by multi-drug resistant (MDR) Gram-negative bacteria, e.g., Acinetobacter baumanii*. It is potentially nephro- and neurotoxic. It is recommended to decrease the dose of colistin in case of renal impairment or renal replacement therapies (RRT) but clear recommendations are not available yet. The aim of this retrospective study was to determine colistin use patterns in critically ill patients in Pauls Stradiņš University Hospital. Forty patients were included in this study. The most common indications for colistin were pneumonia associated with mechanical ventilation or sepsis caused by MDR A. baumanii. Median duration of colistin therapy was 11.5 (IQR 7.0; 17.0) days and median cumulative dose was 91.5 (43.0; 150.0) million units (MU). The usual regimen was 9 MU as loading dose and 3 MU three times daily as maintenance dose, but in case of renal impairment and RRT colistin regimens varied a lot between the patients. In 21% (7 from 33) of cases, acute kidney injury (AKI) was observed during colistin therapy (serum creatinine increases more than twice from baseline). All these AKI cases occurred in patients with previously normal renal function and none of the patients in this group needed RRT.*

Key words: *colistin,* Acinetobacter baumanii*, ICU, nephrotoxicity.*

INTRODUCTION

Colistin is an antibacterial drug of polymyxin group that was not used for many years because less toxic agents were available. Nowadays intravenous colistin is used in critically ill patients for treatment of nosocomial infections caused by multi-drug resistant (MDR) Gram-negative bacteria, e.g., *Acinetobacter baumanii* (Nation *et al*., 2016). Doses of colistin in this patient group exceed in Summary of Product Characteristics (SPC) recommended doses due to relatively high minimal inhibitory concentration (MIC) of these MDR bacteria (Plachouras *et al*., 2009).

Colistin is used as inactive prodrug — colistimethate sodium (CMS) that is incompletely activated by hydrolysis in the organism (approximately 7% of CMS). CMS mostly is cleared renally but the active metabolite, colistin, is eliminated by a non-renal mechanism. If CMS is cleared too rapidly, systemic bioavalibility of colistin is reduced, which theoretically could lead to ineffective antibacterial therapy (Kassamali *et al*., 2013).

Importantly, in Europe this drug is dosed according to the quantity of the prodrug CMS (1 million units (MU) = 80 mg of CMS), but in the USA it is dosed according to the active drug (1 MU = 34 mg of colistin). There is a potential for incorrect dosing if USA dosage recommendations are used and the "mg per kilogram" dose is incorrectly converted to MU. It must always must be clarified which colistin form, active or prodrug, is used making recommendations (Anonymous, 2015).

It is recommended to decrease the dose of colistin in case of renal impairment or renal replacement therapies (RRT), but clear recommendations are not available yet (Garonzik *et al*., 2011). Also, some hyperadsorbtive filters used for continuous RRT, e.g., AN69ST, can adsorb colistin, and thus higher doses can be needed (Honore *et al*., 2013). Recommendations about colistin dosing based on recent literature data are shown in Figures 1 and 2.

Colistin is potentially neuro- and nephrotoxic. It is considered that with colistin use, the associated nephrotoxicity could be dose-dependent and usually is reversible. The pos-

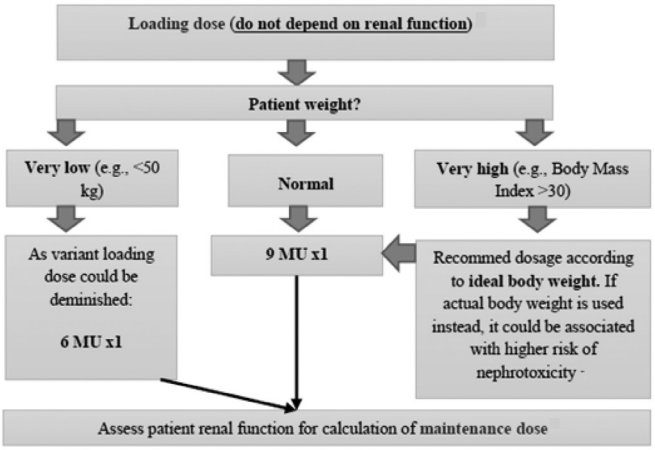

Fig. 1. Loading dose of colistin ((Plachouras *et al*., 2009; Gauthier *et al*., 2012; Anonymous, 2016). MU, million units.

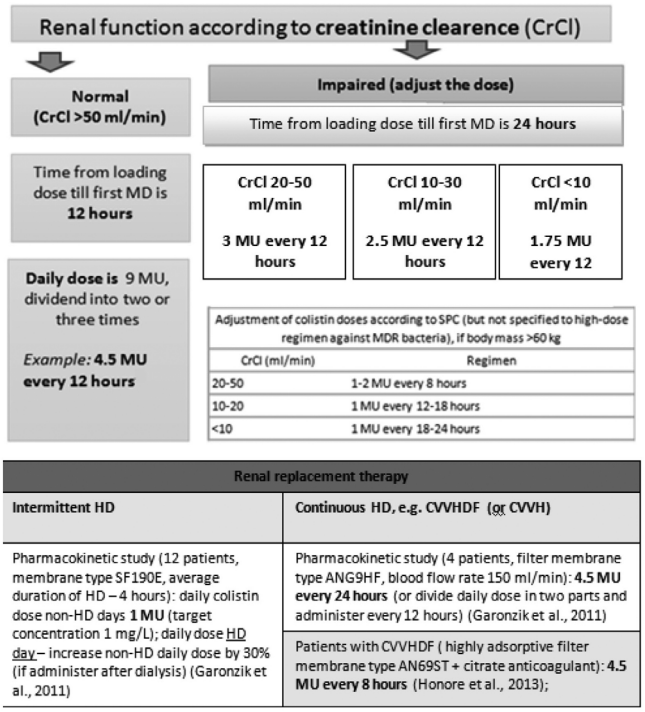

Fig. 2. Maintenance dose of colistin ((Plachouras *et al*., 2009; Dalfino *et al*., 2012; Anonymous, 2016). CVVHDF, continuous Veno-Venous Hemodiafiltration; CVVH, continuous Veno-Venous Hemofiltration; HD, haemodialysis, MU, million units, SPC, summary of product characteristics.

sible mechanism of colistin nephrotoxicity is connected with increase of tubular epithelial cell membrane permeability. As a result, cell swelling and lysis is observed due to increased influx of cations, anions, and water. Also, available literature provides some risk factors for this colistin toxicity, e.g., hypoalbuminemia, hyperbilirubinemia, severity of patient illness and concomitant use of other nephrotoxic drugs (Javan *et al*., 2015).

The aim of this study was to detemine colistin use patterns and incidence of potential colistin nephrotoxicity in critically ill patients in the Pauls Stradiņš Clinical University Hospital (PSCUH).

MATERIALS AND METHODS

The inclusion criteria for this retrospective study were: adult patients; admission to PSCUH Intensive Care Units (ICU); ICD-10-CM Diagnosis Code A49.8 (bacterial infections of unspecified site); colistin therapy due to MDR Gram negative bacteria caused infections (started in ICU); discharge from hospital in 2016. Information about patient demographics, duration of hospitalisation and outcome, main blood test and bacterial susceptibility test results, clinical diagnoses, as well as information about colistin doses and duration of therapy were collected retrospectively from medical notes. An increase of creatinine level during colistin therapy more than twice from baseline was considered as potential colistin associated acute renal injury (AKI). Included cases were coded according to renal function state: "RRT" if there were RRT before and during colistin therapy, "AKI" if acute kidney injure occurred during colistin therapy, other cases were marked just by numbers.

Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR Q1; Q3) for data without normal distribution. Categorical data were expressed as counts and percentages. Normal distribution was assessed by graph method and the Shapiro Wilk test. The paired t-test for normal distributed data or Wilcoxon test for data without normal distribution were used for comparison of data before and after colistin therapy. The Mann-Witney U-test was used for comparison of patients with AKI during colistin therapy and without AKI and RRT. A p-value equal or less than 0.05 was considered to be statistically significant. Statistical data analysis was performed by SPSS 22 Software. Approval of Ethical Committee of PSCUH was received prior the study.

RESULTS

Forty medical histories met of inclusion criteria. Most of the included patients were males — 30 (75%) cases. The mean age was 61.8 (SD 13.5) years. Main clinical diagnoses were pneumonia 14 (35%), myocardial infarction 8 (20%), and subarachoidal haemorrhage 6 (15%). Main data about patient demographics and clinical diagnoses–are summarised in Table 1.

MDR *A. baumanii* nosocomial infection was diagnosed in all included cases. This microorganism mostly was found in trachea aspirate — 21 (52.5%) cases, blood and trachea aspirate — 9 (22.5%) cases, wound or surgical material — 5 (12.5%) cases, urine or dialysis catheter 3 (7.5%) cases and blood 2 (5.0%) cases. *A. baumanii* was resistant according to EUROLAB in all cases to imipenem, trimethoprim / sulfamethaxazole, piperacillin / tazobactam, ceftazidime. In two cases *A. baumanii* were sensitive to amikacin, in three — to gentamicin, in six — to ampicillin / sulbactam. In 14 (35%) cases there was weak sensitivity to ampicillin / sulbactam. Bacterial sensitivity to colistin was detected only in 13 (32.5%) cases, but in other cases it was used empirically.

Table 1

DEMOGRAPHICS AND CLINICAL DIAGNOSES

Characteristics	Values
Gender: men, n (%)	30 (75%)
Age, years	
mean (SD;)	61.8 (13.5)
min-max	34.0–85.0
Duration of hospitalisation, days	
mean (SD)	46.4 (6.4)
min-max	11.0–204.0
median (Q_1; Q_3)	32.5 (19.3; 56)
Patient death rate, n (%)	22 (55%)
Main clinical diagnoses groups, n (%):	
pulmonology (e.g. pneumonia, COPD)	14 (35 %)
cardiology (e.g. myocardial infarction)	8 (20%)
neurology (e.g. subarachnoid haemorrhage)	6 (15%)
state after surgical intervention or trauma	5 (13%)
other (e.g. severe acute pancreatitis, cancer, acute kidney failure)	7 (17%)
Renal replacement therapy, n (%)	7 (18%)

COPD, chronic obstructive lung disease

Before colistin therapy mostly beta-lactam antibacterial therapy was used – piperacillin / tazobactam 4.45 g three times daily in 21 (52.5 %) cases and carbapenems (e.g., meropenem 1 g three times daily) in 12 (30%) cases.

Albumin level prior colistin therapy was given in 14 cases and mean albumin level was lower than normal — 21.0 (SD 4.2) $g \cdot L^{-1}$. Some other biochemical test results prior and after colistin therapy are showed in Table 2.

Sometimes colistin was used together with loop diuretic (torasemide or furosemide) — 8 (20%) cases, non-steroidal anti-inflammatory drug (NSAID) (diclofenac) — 6 (15%) cases, glycopeptides antibiotic (vancomycin) — 5 (13%) cases, and aminoglycoside antibiotic (amikacin) — 1 (3%) case.

Most (26 or 63%) patients received the "standard" maintenance dose (MD) of colistin — 3 MU three times daily. Median duration of colistin therapy was 11.5 (IQR 7.0; 17.0) days and the median cumulative dose was 91.5 (IQR 43.0; 150.0) MU (Table 3).

In case of renal impairment before colistin therapy (Glomerular Filtration Rate (GFR) less than 60 $ml \cdot min^{-1}$), in two cases MD was not adjusted, in one case the patient had died and had received only one dose of colistin, and in two cases the dose was decreased — 1.5 MU × 3 (eGFR 52.5 $ml \cdot min^{-1}$) and 1 MU × 3 (eGFR 51 $ml \cdot min^{-1}$). In 7 (16 %) cases there was RRT before and during colistin therapy. These patients also received variable MDs (from 1 MU every 18 hours till 4.5 MU every 8 hours) (Table 4).

In seven cases (21% of 33 cases without RRT before colistin therapy), the serum creatinine level increased during colistin therapy more than twice (Table 5; Fig. 3). No patient

Table 2

SOME BLOOD (SERUM) TESTS BEFORE AND AFTER COLISTIN THERAPY

Blood (serum) test	Count*	Before colistin therapy		Last day of colistin therapy		*p* value
		mean (SD)	median (Q1; Q3)	mean (SD)	median (Q1; Q3)	
CRP, $mg \cdot L^{-1}$	35	163.7 (109.0)	149.4 (85.8; 229.8)	108.2 (76.9)	89.3 (47.1; 167.4)	0.07**
Cr $\mu mol \cdot L^{-1}$	23	78.4 (29.5)	73.0 (56.5; 96.5)	110.3 (66.8)	94.0; (50.5; 166.0)	0.16***
eGFR, $ml \cdot min^{-1}$	23	103.9 (50.5)	95.1 (70.2; 124.1)	89.9 (61.6)	72.0 (37.9; 123.3)	0.77**

Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (calculated by MDRD Equation)

*Only cases with available data about blood test results prior and day after stopping colistin therapy are included in the analysis. Creatinine level and eGFR are not analysed in case of renal replacement therapy; ** Paired Samples t-test; *** Wilcoxon test

Table 3

COLISTIN USE PATTERN

Duration of colistin therapy, days	
mean (SD)	13.2 (10.0)
min-max	1.0–53.0
median (Q_1; Q_3)	11.5 (7.0; 17.0)
Cumulative colistin dose, MU	
mean (SD)	102.4 (72.0)
min-max	5.0–331.0
median (Q_1; Q_3)	91.5 (43.0; 150.0)
Loading dose:	
9 MU, n (%)	29 (73%)
less than 9 MU (3–6 MU), n (%)	6 (15%)
without loading dose, n (%)	5 (12%)
Maintenance dose 3 MU three times daily, n (%)	26 (65%)

MU, million units

Table 4

COLISTIN USE IN PATIENTS WITH RENAL REPLACEMENT THERAPY DURING COLISTIN THERAPY

Code	Colistin loading dose	Colistin maintenance dose
RRT1	3 MU	4.5 MU x3 (two days, continuous HD) → 4.5 MU x1 (15 days; intermittent HD) → 1 MU x1 (without RRT, creatinine 575 µmol/L)
RRT2	9 MU	3 MUx2 (1^{st} day) → 4.5 MU x3
RRT3	none	2 MU x3 (1^{st} day) → 4.5 MU x3 (2^{nd} day) → 2 MU x2
RRT4	none	1 MU every 18 hours
RRT5	6 MU	2 MU x1 (1^{st} day) → 2 MU x2
RRT6	9 MU	3 MU x 3 (1^{st} day) → 3 MU x2
RRT7	none	2 MU x1 (1^{st} day) → 4.5 MU x3

MU, million units

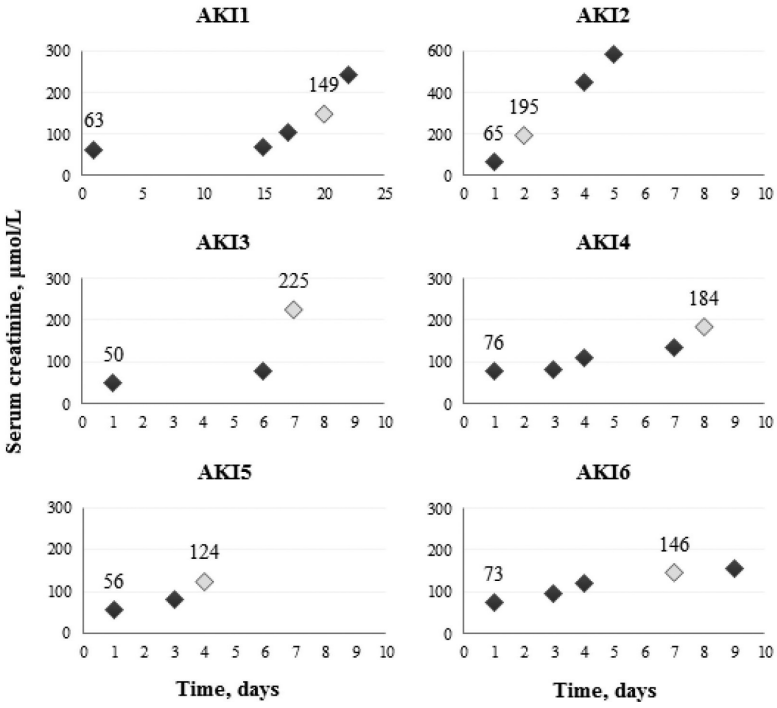

Fig. 3. Increase of serum creatinine during colistin therapy in patients with acute kidney injury (AKI) (except AKI7 because of lack of appropriate data).

Table 5

RENAL FUNCTIONAL STATE AND COLISTIN REGIMEN IN PATIENTS WITH ACUTE KIDNEY INJURY DURING COLISTIN THERAPY

Code	Before colistin therapy		Day after stopping colistin therapy		Increase of Cr, times	Cumulative colistin dose and duration of therapy, days	Change of colistin dose and other c comments
	Cr, µmol/L	eGFR, ml/min	Cr	eGFR			
AKI1	63	119.4	243	25.0	3.8	204 MU; 22 days	No changes (3 MU × 3)
AKI2	65	117.2	nd	nd	nd	40 MU; 13 days	1 MU × 3 (2^{nd} day) → 1 MU x2
AKI3	50	158.0	225	26.0	4.5	66 MU; 7 days	3MU × 3 → 1 MU × 3 (6^{th} day).
AKI4	76	94.4	184	33.3	2.4	57 MU; 8 days	No changes (3 MU × 2)
AKI5	56	95.3	124	38.5	2.2	85.5 MU; 7 days	4.5 MU × 3 (3 days) → 3 MU × 3
AKI6	73	69.9	264	15.8	3.6	189 MU; 30 days	3 MU x3 (12 days) →2 MU × 2 (2 days)
AKI7	65	114.8	209	29.8	3.2	153 MU; 16 days	No changes (3 MU × 3)

MU; million units; nd, no data

from this group needed RRT during hospitalisation. In the case of AKI2, in medical history there were not available data about the creatinine level after colistin therapy, but during therapy decline of renal function was observed and the colistin dose was adjusted. The colistin dose was adjusted also in case AKI3, in which the patient received colistin together with vancomycin, the concentration of which in the blood on 6^{th} colistin treatment day was too high — 31.5 $\mu g \cdot ml^{-1}$ (recommended range 15–20 $\mu g \cdot ml^{-1}$). The serum creatinine level had increased more than four times from baseline. On this day, vancomycin therapy was discontinued and after one day also colistin use was stopped. Patient AKI5 received a very high dose of colistin for several days (4.5 MU × 3), which usually is recommended in case of RRT with hyperabsorbtive filter, but this patient was not on RRT.

The median age of patients with AKI during colistin therapy was higher in comparison with median age of patients without decline in renal function during colistin therapy, but this difference do not reach statistical significance: 68 (IQR 60; 80) and 61 (IQR 54; 75) years, respectively (Mann–Witney U test, $p = 0.27$). In the group with AKI, during colistin therapy there was a statistically significantly lower baseline

median creatinine level than in the group without AKI during colistin therapy: 64 (54.5; 73.8) and 91 (67.8; 113.3) $\mu mol \cdot L^{-1}$, respectively (Mann–Witney U test, $p = 0.05$).

DISCUSSION

In this study critically ill patients received colistin in doses that were recommended according to recent literature data. In case of low body mass it is recommended to decrease the loading dose of colistin (Anonymous, 2016). Also, the used filter for RRT can affect choice of colistin dose (Honore *et al*., 2013). Some patients in this study received a loading dose of 9 MU, but some patients received a lower loading dose or did not receive this dose. As patient weight mostly was not documented in the medical histories of this study, it was difficult to assess the appropriateness of the chosen loading dose in each case. In patients with renal impairment or RRT adjustment of colistin dose was observed in most cases. The used RRT filter also was not documented in medical histories, but the highest dose of 4.5 MU every 8 hours was used only in one ICU where hyperabsorbtive filters for RRT were available during the study.

One retrospective study data showed that increased doses of colistin do not increase nephrotoxicity risk in comparison with other nephrotoxic antibiotics (Rocco *et al*., 2013). On the other hand, in some studies a higher dose of colistin per kilogram per day of Ideal body Weight (IBW) was associated with higher risk of nephrotoxicity. When the dose given was < 3 $mg \cdot kg^{-1}$ per day, nephrotoxicity occurred in 54.5% of patients, but in case of higher colistin doses (> 5 $mg \cdot kg^{-1}$ per day), this value was 65.0% (Akajagbor *et al*., 2013). Also, obesity is considered as independent risk factor of colistin induced AKI (Ortwine *et al*., 2015). A limitation of current study was impossibility of calculation of colistin dose per kg, as well assessment of obesity state.

In a prospective descriptive study, in 17% of ICU patients colistin-induced AKI was observed after an average of 7 treatment days, which was resolved approximately 10 days after colistin use discontinuation (Dalfino *et al*., 2012). On the other hand, in another prospective cohort study, colistin associated AKI incidence was much higher — in 76.1% of treated patients (51 patients from 67), which had developed average in 8.7 treatment day (Omrani *et al*., 2015).

In this study renal function worsened during colistin therapy in 7 of 33 patients without RRT before colistin therapy. The most common onset of AKI was approximately after 1 week. Interestingly, patients with already pre-existed renal impairment and without RRT did not experience decline in renal function during colistin therapy. Pre-existing renal impairment is considered to be unclear risk factor for colistin nephrotoxicity (Ortwine *et al*., 2015). One study showed that there was a statistically significant increase of creatinine level only in patients with normal renal function at baseline, comparing this value in periods of pre- and post-treatment with colistin. On the other hand, in patients with renal impairment at baseline there no difference was observed between serum creatinine levels before and after colistin therapy (Santamaría *et al*., 2009), which is similar to the results of the current study.

Older patients usually are in higher risk of colistin-induced nephrotoxicity. For example, in a recent study mean age of patients with colistin therapy and AKI was significantly higher than in patients without AKI (67 and 49 years, respectively; $p = 0.001$) (Balkan *et al*., 2014). Also in this study, median age of patients was higher in cases of AKI during colistin therapy, but the difference with the patient group without AKI did not reach statistical significance.

Low albumin level has been reported as a risk factor for colistin induced AKI (Javan *et al*., 2015). This parameter was available only in 35% of cases and in all these cases it was below the normal range. But it was not possible to evaluate the potential role of hypoalbuminemia in development of colistin nephrotoxicity in this study.

Co-administration of other nephrotoxic drugs together with colistin theoretically also could increase risk of nephrotoxicity (Dhariwal and Tullu, 2013). In this study patients also in some cases have received colistin together with potentially nephrotoxic drugs, mostly with loop diuretics and NSAID. But duration of concomitant use of these agents and their regimens were variable among the cases and the amount of these cases was quite small, so it was not reasonable to try to find correlations between colistin caused AKI and other used nephrotoxic agents.

Another described potential severe risk of colistin use is neurotoxicity. It is more common with high doses of colistin and can appear like apnoea, peri-oral and peripheral paraesthesia, vertigo, headache, muscle weakness or rarely as vasomotor instability, slurred speech, confusion, psychosis, and visual disturbances (Anonymous, 2016). Unfortunately, it was not possible to assess neurotoxicity of colistin because of the retrospective design of this study. Also, because of the retrospective nature of the study, it was difficult to evaluate other possible causative factors of AKI.

CONCLUSIONS

In PSCUH ICUs colistin is usually administered in higher doses than are recommended in SPC but are advisable according to recent literature data for treatment of MDR *A. baumanii* infections. The colistin dosage regimen in PSCUH ICUs depends on patient renal state and absence or presence of RRT, but varies a lot among patients. A significant proportion of patients (21%) have AKI during colistin therapy. Patients with pre-existing renal impairment without RRT did not experience significant decline of renal function during colistin therapy.

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Received 31 August 2017
Accepted in the final form 9 December 2017
Published online 19 July 2018

KOLISTĪNA LIETOŠANAS VEIDI KRITISKI SLIMIEM PACIENTIEM PAULA STRADIŅA KLĪNISKĀ UNIVERSITĀTES SLIMNĪCĀ

Kolistīnu lieto sistēmiski kritiski slimiem pacientiem, ārstējot infekcijas, kuras izraisa multi-zāļu rezistentas (MZR) gram-negatīvās baktērijas, piemēram, *Acinetobacter baumanii.* Tās ir potenciāli nefro- un neirotoksiskas. Rekomendē samazināt kolistīna devu pavājinātas nieru funkcijas vai nieru aizstājterapijas (NAT) gadījumos, bet skaidras rekomendācijas pagaidām nav pieejamas. Šī retrospektīvā pētījuma mērķis bija noskaidrot kolistīna lietošanas shēmas kritiski slimiem pacientiem Paula Stradiņa Klīniskajā Universitātes slimnīcā. Pētījumā iekļauti četrdesmit pacienti. Visbiežākā kolistīna indikācija bija ar mehānisko ventilāciju asociēta pneimonija vai sepse *A. baumanii* izraisīta MZR. Kolistīna terapijas ilguma mediāna bija 11,5 (IQR 7,0; 17,0) dienas un kumulatīva deva — 91,5 (43,0; 150,0) miljoni vienību (MV). Kolistīna lietošanas biežāk izmantotā shēma: piesātinošā deva — 9 MV un 3 MV trīs reizes dienā kā uzturošā deva, bet pavājinātas nieru funkcijas vai NAT gadījumos kolistīna dozēšanas shēma bija individuāla. Septiņos gadījumos no 33 (21%) tika novērota nieru funkcijas pasliktināšanās kolistīna terapijas laikā (seruma kreatinīns pieauga vairāk kā divas reizes salīdzinājumā ar bāzes līmeni). Visi šī akūtas nieru bojājuma gadījumi attīstījās pacientos ar iepriekš normālu nieru funkciju, un nevienam pacientam nebija nepieciešama NAT.