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Colistin Use Pattern and Nephrotoxicity in Critically Ill Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

Summary of the Doctoral Thesis for obtaining the scientific degree “Doctor of Science (*PhD*)”

Sector Group – Medical and Health Sciences
Sector – Basic Medicine
Sub-Sector – Clinical Pharmacy

Riga, 2023

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The Doctoral Thesis was developed at Rīga Stradiņš University, Latvia

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The Doctoral Thesis is available in RSU Library and on RSU website: https://www.rsu.lv/en/dissertations

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Abbreviations used in the Thesis

ACE-I	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
ARB	angiotensin receptor blocker
ARC	augmented renal clearance
CBA	colistin base activity
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMS	colistimethate sodium
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
Css	steady-state concentration
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GFR	glomerular filtration rate
ICU	intensive care unit
IHD	intermittent haemodialysis
IQR	interquartile range
MDR	multi-drug resistant
MIC	minimal inhibitory concentration
MODS	multiorgan dysfunction syndrome
MPV	mechanical pulmonary ventilation
MU	million units
NSAID	non-steroidal anti-inflammatory drug
PAH	primary arterial hypertension
PSCUH	Pauls Stradiņš Clinical University Hospital
RCT	randomized clinical trial
RIFLE	Risk – Injury – Failure – Loss – End-stage renal disease
RRT	renal replacement therapy

Scr	serum creatinine
SD	standard deviation
SPC	summary of product characteristics
TDM	therapeutic drug monitoring
TRI-SUL	trimethoprim-sulfamethoxazole
USA	United States of America

Introduction

Colistin is among the last-line antibacterial agents used to treat multidrug resistant (MDR) Gram-negative bacterial infections. It is often referred to as a reserve antibacterial agent, emphasizing the need for careful and rational use. Dosage and duration of use vary from country to country, and there has been significant scientific interest in the pharmacokinetics, efficacy, and safety of colistin in recent decades. The issue of colistin resistance, along with research into alternative antibacterial agents, has gained popularity over the last decade. Moreover, researchers are actively investigating the risk factors and potential protective measures against colistin nephrotoxicity in both preclinical and clinical studies.

Irrational use of reserve antibacterial agents, including improper dosing, could have serious consequences for both individual patients and society as a whole, such as the development of bacterial resistance to these agents. It is crucial to gather information about the local situation, especially in areas with relatively high consumption of colistin, as this can help assess the appropriateness of using these agents according to modern requirements. Attention should be given to potential issues associated with this therapy and local recommendations should be developed to optimize its use

Dosing potentially nephrotoxic drugs with significant renal clearance, including colistin, can be particularly complex, as it requires close monitoring of kidney function throughout the therapy and timely adjustment of drug dosage in case of changes in renal functional status. Several groups of scientists have been studying the incidence of nephrotoxicity and its contributing factors for more than 20 years [1].

This was also the secondary objective of our study because factors related to nephrotoxicity remain highly diverse and controversial. Despite colistin being extensively researched and used in other European countries as early as the

2000s [2], colistin was not widely used in Latvian hospitals during that period. However, since 2015, there has been a relatively rapid increase in colistin usage in the large tertiary Riga hospital. Therefore, this topic has become particularly relevant in Latvia in the last ten years.

Aim of the Thesis

The study of colistin usage practices and nephrotoxicity risk factors in Latvia's major tertiary hospital.

Tasks of the Thesis

To achieve the goal of the Thesis, the following tasks have been outlined:

1. Study the main indications for colistin usage and assess the incidence of bacteriological eradication during colistin administration when it is possible.
2. Analyse the compliance of colistin dosing with the recommendations of the drug manufacturer and international guidelines, which also include the identification of patient groups with the most common irrational use of colistin.
3. Determine the incidence of colistin-induced acute kidney injury (AKI) and potential risk factors of this side effect.
4. Identify the most common colistin co-medications with other antibacterial agents and potentially nephrotoxic drugs, analysing their role in the safety of colistin therapy where applicable.
5. Examine the alignment of drug concentrations with the target therapeutic range based on available Therapeutic Drug Monitoring (TDM) data and its potential impact on the development of colistin-induced AKI.

Hypotheses of the Thesis

1. Colistin dosing is rational, meaning it corresponds to the patient's renal functional status, and colistin therapy is modified within ≤ 2 days in case of changes in renal functional status.
2. The incidence of colistin-induced AKI at the research centre does not exceed the median colistin-induced AKI incidence in the European region.
3. The dosage of colistin and co-administration with other nephrotoxic drugs are potentially modifiable risk factors for colistin-induced AKI.

Novelty of the Thesis

There are numerous published studies on colistin usage practices in the Mediterranean region [3], [4], [5], East Asia [6], [7], [8], Latin America [9], [10] and United States of America (USA) [11], [12]. At the initiation of our study, internationally citable sources lacked data on colistin usage practices in the Baltic region. Therefore, it was necessary to determine the practice of using these reserve antibacterial agents in Latvia and assess whether it is maximally rational and aligns with contemporary published recommendations. These recommendations had been highly controversial and conducive to irrational use for many years (for example, significantly varying guidelines on adjusting colistin dosage in cases of renal functional impairment in different sources).

The incidence of nephrotoxicity and potential risk and protective factors vary significantly among research centres [13]. The simultaneous use of nephrotoxins is considered a potential risk factor, but results from various studies are not homogeneous. Rarely is the duration of concurrent nephrotoxin usage defined, and data on serum concentration of potentially nephrotoxic drugs with narrow therapeutic ranges, such as aminoglycosides and glycopeptides, are rarely

available. In this study, these issues are examined in greater detail, and the incidence of nephrotoxicity and the role of various potential factors in the development of this side effect are reported. This could potentially help define patient groups for whom colistin TDM would be particularly beneficial, if available for a limited number of patients

1 Materials and Methods

Study Design: Retrospective cohort study

Research Center: Pauls Stradiņš Clinical University Hospital (PSCUH), Riga, Latvia

Secondary Data Sources: Medical histories of patients admitted to the Intensive Care Unit (ICU) from the Medical Archive of PSCUH.

Inclusion Criteria:

1. Infection caused by MDR Gram-negative bacteria;
2. Age ≥ 18 years;
3. Admitted to the ICU or intensive care beds at PSCUH (including general ICU, cardiothoracic surgery ICU, neurology, cardiology, or pulmonology intensive care beds);
4. Discharged from the hospital between 2015–2018;
5. Parenteral colistin therapy.

Exclusion Criteria:

1. Duration of colistin use shorter than 72 hours.

Episodes of colistin usage and case coding

All included episodes of colistin usage were coded as COLXX, where XX represents the sequence number. If a patient initiated colistin treatment more than once during the study period, and the interval between the cessation of the previous colistin treatment episode and the start of the next colistin treatment episode was more than 5 days, these episodes were analysed separately. If colistin usage was temporarily interrupted (for 1 to 4 days) and then resumed, this episode was analysed as a single colistin usage episode. Only the first episodes of colistin usage are used for presenting patients' demographic data and for analysing colistin-induced acute kidney injury

Variables and parameters used for data analysis

- patient's age, gender, weight, and height (if available), primary diagnosis, reason for hospitalization, length of hospitalisation, and outcome;
- bacterial culture with identified carbapenem-resistant Gram-negative bacteria (antibiogram, material, date of sample collection, minimum inhibitory concentration (MIC) if available). The critical value for colistin MIC in cases of *A. baumannii* and *P. aeruginosa* is 2 mg/L according to EUCAST data (v. 8.0; 01.01.2018). If bacteriological test results documented that the bacterium intermediate sensitivity to any antibacterial agents, it was considered as resistance to that agent;
- loading doses and maintenance doses of colistin, duration of usage, dose adjustments during therapy (if colistin therapy was also continued in non-intensive care wards, this information was also compiled);
- concurrent use of other antibacterial agents with colistin (such as beta-lactam antibiotics, glycopeptide antibiotics, aminoglycoside antibiotics);
- inflammatory markers (C-reactive protein (CRP)) during colistin therapy;
- renal functional status – serum creatinine, glomerular filtration rate (GFR), 24-hour urine – throughout the period of colistin therapy, if this data was available
- renal replacement therapy (RRT) – intermittent or continued;

- patient's general condition – need for mechanical pulmonary ventilation (MPV) and/or continuous infusion of inotropic agents, documented sepsis, shock, or multiorgan dysfunction syndrome (MODS);
- concurrent usage of potentially nephrotoxic medications and substances with colistin for ≥ 48 hours (e.g. glycopeptide antibiotics, aminoglycoside antibiotics, loop diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs);
- administration of contrast media during colistin therapy;
- history of diabetes mellitus and/or chronic kidney disease in the patient's medical records;
- Medications with available TDM at the research centre:
    - In cases where vancomycin was administered concurrently with colistin or immediately prior the initiation of colistin therapy (if vancomycin therapy was discontinued less than 3 days before starting colistin), information on vancomycin dosages, administration times, duration, and concentrations was collected. In cases of interrupted vancomycin infusions, the target pre-dose trough concentration of vancomycin was assumed to be 10–20 μg/L.
    - In cases where gentamicin was administered concurrently with colistin or immediately before the initiation of colistin therapy (if gentamicin therapy was discontinued less than 3 days before starting colistin), information on gentamicin dosages, administration times, duration, and concentrations was collected. In the case of once-daily dosed high-dose gentamicin infusions, the target pre-dose trough concentration of gentamicin was assumed to be less than 1 μg/L.

Subgroup division based on the renal functional status at the initiation of colistin (baseline renal functional status

Patients were divided into four groups based on renal functional status at the initiation of colistin therapy (Table 1.1).

Table 1.1

Distribution of patients based on renal functional status

1st group	2nd group	3rd group	4th group
At the initiation of colistin, normal kidney function (GFR ≥ 50 ml/min and < 108 ml/min)	Augmented clearance (GFR ≥ 108 ml/min) at the initiation of colistin therapy	Impaired kidney function (GFR < 50 ml/min) without RRT at the initiation of colistin therapy	RRT at the initiation of colistin therapy

Abbreviations: GFR – glomerular filtration rate, RRT – renal replacement therapy

Kidney function was assessed using the *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) equation:

$$\mathbf{GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [woman] \times 1.159\ [Black\ race]}$$

Scr represents serum creatinine (mg/dL), κ equals 0.7 for females and 0.9 for males, α equals –0.329 for females and –0.411 for males. Min indicates the smaller value between Scr/κ or 1, and max indicates the larger value between Scr/κ or 1.

Analysed parameters for rational colistin use

- Usage is documented (treatment of carbapenem-resistant bacterial infections).
- A loading dose has been administered, independent of renal function.
- Selection and adjustment of maintenance doses based on variable renal functional status (Annex 1).

Bacteriological response to therapy

The bacteriological response was analysed on the 5th, 7th, and last days of colistin therapy.

Definition of colistin-induced acute kidney injury

Acute kidney injury was potentially considered as colistin-induced AKI if at least 48 hours elapsed from the initiation of colistin to the manifestation of AKI.

The following cases were excluded from the analysis of colistin-induced AKI:

1. Patients undergoing renal replacement therapy on the day of colistin initiation;
2. Multiple episodes of colistin use during a single hospitalization (only the first episode was included in the analysis);
3. AKI occurring within the first 24 hours from the initiation of colistin.

The day of manifestation of AKI is defined as the day of colistin therapy when serum creatinine increased by at least by 50 % from the baseline creatinine level.

The severity of AKI was determined using RIFLE criteria, based on the maximum increase in serum creatinine during colistin therapy. According to these criteria, the severity of kidney damage was classified into five stages – R (Risk), I (Injury), F (Failure), L (Loss), E (End-stage-renal disease). To determine the first three stages, data on acute serum creatinine increase are required, while for the last two stages, information on the patient's renal functional status over 3 months is needed. If kidney failure persists for more than 30 days, it is considered persistent renal dysfunction (L - Loss); if it persists for more than 90 days, the patient is classified as having end-stage renal disease according to RIFLE criteria. Given the limited duration of patient follow-up,

kidney injury was categorized into three groups – mild, moderate, and severe, corresponding to R, I, and F criteria according to RIFLE (Table 1.2), using the maximum increase in serum creatinine during colistin therapy.

Table 1.2

Division of patients based on changes in renal functional status during colistin therapy

<table>
<tr><td colspan="3">Patients with AKI during colistin therapy</td><td rowspan="3">Patients without AKI during colistin therapy</td></tr>
<tr><td colspan="3">RIFLE criteria based on serum creatinine levels</td></tr>
<tr><td>Risk,
1st degree,
Mild AKI</td><td>Injury,
2nd degree,
Moderate AKI</td><td>Failure,
3rd degree,
Severe AKI</td></tr>
<tr><td>Serum creatinine level increases by 1.5–1.9 times from the baseline level</td><td>Serum creatinine level increases by 2.0–2.9 times from the baseline level</td><td>Serum creatinine level increases by more than 3.0 times from the baseline level</td><td></td></tr>
</table>

Abbreviations: AKI – acute kidney injury.

Information about the day of colistin-induced AKI onset, cumulative dose of colistin, and when available, the day of renal function normalization from the cessation of colistin was compiled.

Cases that were not classified as colistin-induced renal damage:

- If the renal functional status worsened for only one day during colistin therapy but returned to baseline the next day without colistin discontinuation or dose adjustment, it was not considered colistin-induced AKI.
- If patients with augmented renal clearance experienced a rapid change in renal functional status but their GFR remained above 50 ml/min, it was not considered acute kidney injury.

Statistical associations between colistin-induced AKI and the following factors were studied:

- Patient's age/age groups (up to 65 years and over 65 years);
- Patient's gender;
- Certain comorbidities (diabetes mellitus, chronic kidney disease, cancer);
- Renal functional status on the day of colistin initiation;
- CRP and serum creatinine on the day of colistin initiation (on the 3rd day after RRT discontinuation in RRT cases);
- Cumulative colistin dose until the development of AKI, if no AKI, then the total cumulative colistin dose; if there was temporary RRT in the first days of colistin, these days were excluded from the analysis;
- Duration of colistin use until the development of AKI, if no AKI, then the total duration of colistin use; if there was temporary RRT in the first days of colistin, these days were excluded from the analysis;
- Concurrent use of potentially nephrotoxic medications/substances, their duration of use, cumulative dose;
- Cardiopulmonary resuscitation during this hospitalization;
- Need for parenteral vasopressor (norepinephrine, epinephrine, dopamine, vasopressin) support therapy.

Statistical analysis

Data with a normal distribution were expressed as the mean with standard deviation (SD), while data with a non-normal distribution were expressed as the median with interquartile range (IQR Q1; Q3). Categorical data were presented as counts and percentages. Normal distribution was assessed using graphical

methods and the Shapiro-Wilk test (accepted as normal if the p value is above 0.05). To compare mean values for quantitative data with a normal distribution and similar variance (tested by Levene's test), t-tests (for two paired or independent groups) or ANOVA tests (for three or more groups) were applied. To compare median values for rank data or quantitative data with a non-normal distribution, Wilcoxon signed-rank tests (for two paired groups), Mann-Whitney U tests (for two independent groups), or Kruskal-Wallis H tests (for three or more groups) were used. Chi-square tests were applied to rank data to compare the fit of results to theoretical distributions. Pearson correlation was used for quantitative data with a normal distribution, and Spearman correlation was used for rank data or quantitative data with a non-normal distribution. In the analysis of risk factors associated with colistin-induced AKI, both single-factor and multi-factor logistic regression analyses were employed. A *p value* equal to or less than 0.05 was considered statistically significant.

Confidentiality

The ethical considerations of the study are in line with the fundamental principle stated in the Helsinki Declaration: 'the duty of the physician is to protect the life, health, privacy, and dignity of the human subject' and “Law on the Protection of Personal Data” of the Republic of Latvia.

To ensure patient confidentiality during the data collection phase, information will be grouped according to the protocol number. The study results will not display the patient's name, surname, medical record number, or personal identification code. Informed consent was not required due to the retrospective nature of the study.

Before conducting the study, approval was obtained from the Ethics Committee of Rīga Stradiņš University, Ref. No. 48/05.10.2017.

2 Results

2.1 Demographic and clinical data

One hundred eleven patients were included in the study, of whom 4 patients received multiple courses of colistin treatment. In total, 111 patient cases and 117 episodes of colistin use were analysed. The majority of included patients were males – 71 (64 %) cases. The mean age (± SD) was 61.2 ± 15.7 years. The proportion of patients in the age group over 65 years (geriatric patients) was 47 %. The median length of hospitalization was 44 days. The most common clinical diagnoses were pneumonia, subarachnoid haemorrhage, and acute coronary syndrome. The most common reason for hospitalization in the ICU was the need for mechanical ventilation and unstable hemodynamic. Fifty five percent (61/111) of patients had at least one documented chronic illness (chronic heart failure, chronic kidney failure, chronic obstructive pulmonary disease, diabetes mellitus, and/or primary arterial hypertension). Out of 55 deaths, 74.5 % (41 cases) occurred within 28 days from the initiation of colistin. The cause of death was most frequently defined as cardiac arrest, progressive respiratory and cardiac failure, or systemic intoxication. The demographic and clinical characteristics of the patients are summarized in Table 2.1.

Table 2.1

Patient Demographic and Clinical Data (n = 111)

Characteristics	Value
Gender: man, n (%)	71 (64 %)
Age, years median (Q_1; Q_3) min-max	 63 (50; 73) 20–90
Length of hospitalization, days median (Q_1; Q_3) min-max	 44 (28; 62) 10–204

Table 2.1 continued

Characteristics	Value
Main clinical diagnosis groups, n (%)	
Pulmonology (e.g., pneumonia, exacerbation of chronic obstructive pulmonary disease)	31 (27.9 %)
Neurology (e.g., meningitis, subarachnoid haemorrhage)	27 (24.3 %)
Cardiology (e.g., acute coronary syndrome)	19 (17,1 %)
Gastroenterology (e.g., acute pancreatitis)	9 (8.1 %)
Other (e.g., complications of diabetes, trauma)	25 (22,5 %)
Documented comorbidities in patients, n (%)	
Chronic heart failure	35 (31,5 %)
Diabetes Mellitus or Impaired Glucose Tolerance	25 (22,5 %)
Chronic heart failure	23 (20,7 %)
Primary arterial hypertension	20 (18 %)
Exacerbation of COPD	10 (9 %)
Malignant tumour	8 (7 %)
Cardiopulmonary resuscitation prior to initiation of colistin therapy, n (%)	19 (17,1 %)
Documented sepsis or septic shock	37 (33,3 %)

Abbreviations: COPD – Chronic Obstructive Pulmonary Disease

2.2 Bacteriological data

The median length of hospitalization was 44 days, with a median (Q1;Q3) of 13 (10;21) days from the day of detection of carbapenem-resistant bacterial infection. Carbapenem-resistant bacteria were most frequently detected in one material (64 cases or 54.7 %) or in two different materials (37 cases or 31.6 %). In the majority of cases, the Gram-negative bacteria isolated from the first material were MDR *A. baumannii* (n = 115 or 98 %), and the most common primary isolation material for these bacteria was tracheal aspirate (n = 86 or 74 %). Carbapenem-resistant *P. aeruginosa* was detected in 9 cases, of which 7 cases were isolated concurrently with carbapenem-resistant *A. baumannii* infection.

In 98 cases (84 %), the bacteria were sensitive only to colistin, but in some cases, they were also sensitive to ampicillin/sulbactam (11 cases or 9 %), aminoglycosides (10 cases or 9 %), and trimethoprim/sulfamethoxazole (1 case

or 1 %). Minimum Inhibitory Concentration (MIC) values were generally not documented on the bacteriological analysis sheet. In a few cases (n = 3), the MIC was documented, which was equal to 0.125 mg/L in isolates from 2014 and 2015, and 0.5 mg/L in the 2017 isolate. In other cases, it was documented that the bacteria were sensitive to colistin, indicating that the MIC was lower than 2 mg/L. No cases of colistin resistance were observed among the study participants.

The early bacteriological response on the fifth day of colistin therapy was analysed in 39 cases, out of which Gram-negative bacteria were no longer detected in the material where MDR *A. baumannii* was initially isolated, in only two cases. Bacteriological response after one week of colistin therapy could be analysed in 29 cases, and bacterial eradication was achieved in only 3 patients during this time. In nine cases, it was not possible to analyse the bacteriological response on the 7th day of colistin therapy due to early patient death or discontinuation of therapy. For the majority of cases (69 out of 117 or 59 %), repeated culture data taken from the 3rd to the 7th day of colistin therapy were not available, which complicates the analysis of colistin therapy effectiveness.

Overall, at the end of colistin therapy, complete or partial eradication of MDR Gram-negative bacteria was observed in 13 % of cases, and this bacterium was also detected at the time of colistin therapy discontinuation and later in 14 % of cases. In 86 (73 %) cases, repeated bacteriological culture data at the end of colistin therapy were not available for various reasons. Out of the 16 cases where colistin therapy was unsuccessful from a bacteriological standpoint, therapy was discontinued on the day of acute kidney injury in four cases and on the day of patient death in two cases.

2.3 Description of colistin use pattern

The median (Q1; Q3) day of initiating colistin therapy during hospitalization was the 16th (11th; 23rd) day. The median duration of colistin therapy was 11 days with a median cumulative dose of 78 million units (MU) in one treatment episode.

In all cases, colistin was administered through intravenous intermittent infusions. In one case, a patient with *A. baumannii* bacteraemia and ventriculitis received colistin both intravenously and intrathecally. Colistin was not administered via inhalation to any patient.

At the initiation of colistin in 22 (19 %) episodes of colistin therapy, patients were undergoing renal replacement therapy, in 26 (22 %) cases patients had impaired renal function, and in the remaining 69 (59 %) cases, patients had normal or augmented renal function.

In 76 cases (65 %), colistin therapy was combined with piperacillin/tazobactam and/or carbapenems (meropenem or imipenem) for at least 48 hours. In two cases, the patient received both piperacillin/tazobactam and carbapenems during one colistin treatment episode. Concurrent use of carbapenems with colistin exceeded 50 % of the total duration of colistin use in 55 out of 66 cases (83 %). The key parameters of colistin usage (dosage, duration) are summarized in Table 2.2.

Table 2.2

Characteristics of episodes of colistin therapy (n = 117)"

Parameter	Value
Duration of colistin therapy, days	
mean (SD)	14,5 (11.0)
min-max	3,0–58,0
median (Q_1; Q_3)	11,0 (7.0; 20.5)
Duration of colistin therapy in groups, n (%)	
3–6 days	25 (21.4 %)
7–14 days	49 (41.9 %)
above 14 days	43 (36.8 %)
Cumulative colistin dose, MU	
mean (SD)	109,2 (78.0)
min-max	6,0 – 510,0
median (Q_1; Q_3)	78,0 (51.0; 143.0)
Loading dose, n (%)	
standard dose: 9 MU	74 (63.2 %)
less than 9 MU (3–6 MU)	16 (13.7 %)
no loading dose	27 (23.1 %)

Abbreviations: MU – million units, SD – standard deviation, Q –quartile

2.3.1 Duration of colistin therapy

The most common duration of colistin therapy was 7–14 days (42 % of cases). When comparing a short course of colistin treatment (Group A; duration of colistin therapy 3–14 days; n = 74) with a longer course of colistin treatment (Group B, duration of colistin therapy over 14 days; n = 43), it was found that the primary isolate of MDR Gram-negative bacteria did not differ statistically, with tracheal aspirate being the source in 86 % of cases in both Group A and Group B (p = 0.834). However, in Group B, this bacterium was more frequently isolated from various materials compared to cases from Group A (Chi-square test p = 0.006) (Figure 2.1).

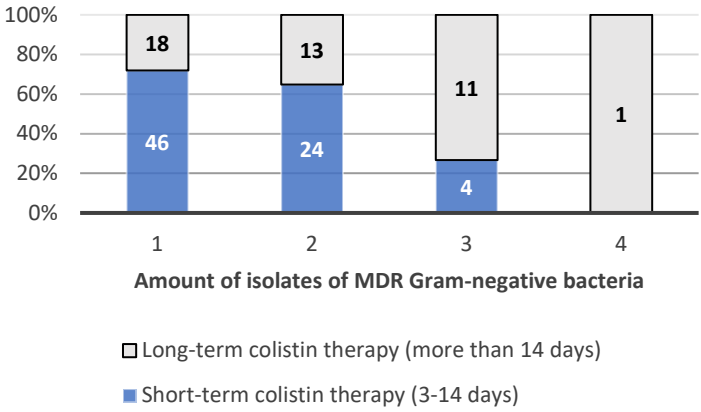

Figure 2.1 **The number of isolates from materials in MDR Gram-negative bacterial infections and the duration of colistin therapy**

Carbapenems were more frequently added to the longer course of colistin therapy, but this difference did not reach statistical significance (67 % or 29/43 in the long course group compared to 50 % or 37/74 in the short course group, p = 0.067).

In some cases, the duration of colistin therapy might have been longer if it had not been prematurely discontinued, such as due to patient mortality during colistin therapy. In total, there could be potentially premature discontinuation in 48 cases (5 cases where colistin therapy was switched to another antibacterial therapy on the 3rd–4th day of treatment; 31 cases where the patient died during colistin therapy, and 13 cases where colistin therapy might have been discontinued due to rapid deterioration of kidney function). However, excluding these cases from the analysis, no correlation was still found between the duration of colistin therapy and the type of material from which bacteria were isolated.

2.3.2 Loading dose

Most patients received a loading dose equal to 9 MU (63.2 %), while the remaining patients either received a reduced loading dose (3–6 MU) or therapy was initiated immediately with a maintenance dose. Analysing the choice of saturating doses for patients with different renal functional statuses starting colistin therapy, it was found that patients with impaired renal functional status were most likely not to receive a saturating dose (9 out of 26 cases or 35 %) or receive a reduced saturating dose (8 out of 26 cases or 31 %) compared to other groups (p = 0.013) (Figure 2.2).

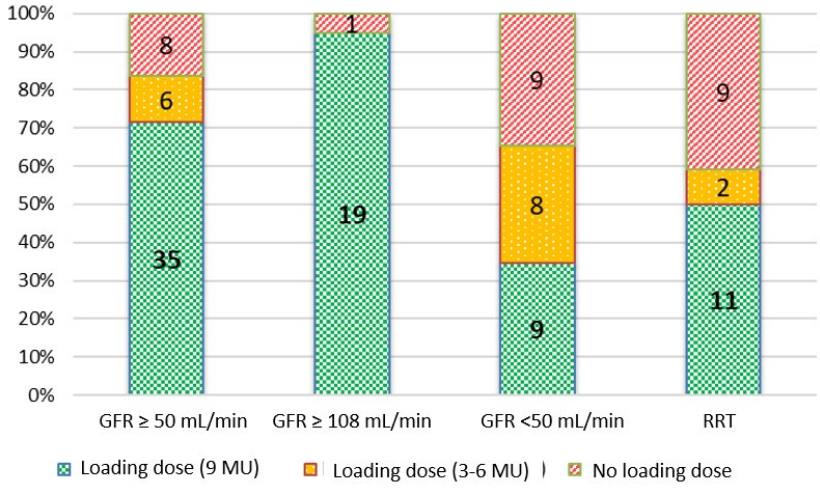

Figure 2.2 **Loading dose in patients with different baseline renal function**

Abbreviations: GFR – glomerular filtration rate, RRT – renal replacement therapy

Patients who received the standard loading dose were also younger in age compared to patients who did not receive the loading dose or received a reduced loading dose, but this difference did not reach statistical significance (median age in these groups was 63 and 67 years, respectively, p = 0.607).

2.3.3 Maintenance dose

Analysis of colistin dosage adherence to manufacturer and European Society of Infectious Diseases recommendations revealed that the dosage was most often in line with the recommendations (62 % of colistin administration days), while 48 % of the dosage days were non-compliant, with more instances of suboptimal dosing (26 %) rather than overdose (12 %). The median number of days (Q1; Q3) with optimal colistin dosing per case was higher than the median number of days with overdose or reduced colistin dosage (7 (3;13) versus 2 (0;7) days per case, $p< 0.001$).

Cases with inappropriate colistin dosage for 7 days or longer are illustrated in Figure 2.3. In this Figure, it can be seen that potential overdosing was most frequently observed in cases with moderate renal function (eGFR 30–59 ml/min), where the patient received the standard colistin dose of 9 MU per day in divided doses instead of a reduced dose. Meanwhile, the potentially lower colistin dose was encountered in almost all renal functional status groups. Some patients received reduced colistin doses every other day or every 36 hours. There were cases where the administered dose was very close to the recommended one (2 MU instead of 2.25 MU or 5 MU instead of 5.3 MU). One patient (COL_47) received a significantly lower colistin dose (1 MU/day) over 14 days. In two cases (COL_105 and COL_53), patients received 6 MU/day instead of 9 MU/day, with a calculated eGFR above 90 ml/min. However, it should be noted that both patients had a history of CRRT, which might introduce imprecision in the eGFR calculations. On the other hand, the duration of potentially inappropriate reduced colistin dosage was relatively long period of time (COL_105 over 18 days and COL_53 over 17 days).

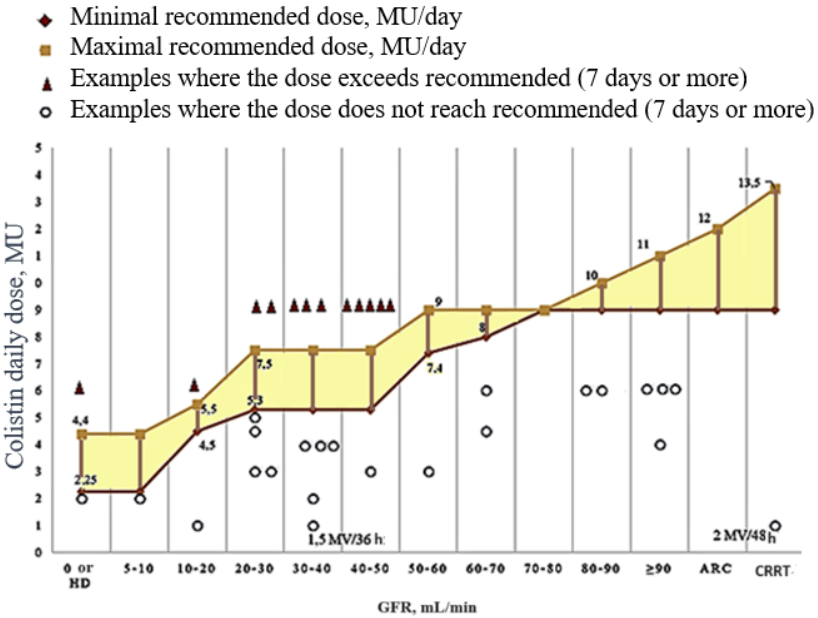

Figure 2.3 **Recommended dosage range and examples of prolonged non-adherence (≥ 7 days)**

Abbreviations: ARC – *Augmented renal clearance*, CRRT – continuous renal replacement therapy (in the case of hyperabsorption filter, the dose can reach up to 13.5 MU/day), GFR – glomerular filtration rate, HD – haemodialysis, MU million units

Analysing the choice and duration of colistin dosage in patients with different baseline renal function, it was found that patients with enhanced clearance (GFR above 107 ml/min) had a higher median cumulative dose compared to patients with GFR between 50–107 ml/min (167 vs 75 MU, $p = 0.005$, Mann-Whitney U test) or patients with impaired renal function (167 vs 58 MU, $p < 0.001$). The duration of therapy was also longer in patients with enhanced clearance, although it did not reach statistical significance (Table 2.3).

Table 2.3

Analysis of colistin use in patients with various baseline renal functional status

Parameter	Baseline renal functional status				p value
	Group-1 Normal renal function n = 49	Group 2 Augmented clearance n = 20	Group 3 Renal impairment without RRT n = 26	Group 4 RRT n = 22	
Median cumulative dose, MU	75.0	166.5	57.8	101.0	0.002 ◊
Median duration of colistin use, days	8.0	18.0	10.5	12.5	0.090 ◊

◊ Kruskal-Wallis Test; Abbreviations: RRT – renal replacement therapy, MU – Million units

Considering that the renal functional status in critically ill patients is often unstable, renal function was analysed throughout the entire duration of colistin use. Dividing the cases into two groups based on eGFR during colistin therapy, it was found that patients with the highest eGFR received a higher cumulative dose of colistin, had a longer duration of colistin use, and their maintenance dose generally adhered to recommendations (Table 2.4).

Table 2.4

Analysis of colistin use in patients with different renal functional status throughout colistin therapy

Parameter	Kidney function throughout the use of colistin		p-value
	51–100 % GFR≥ 50 ml/min Mostly normal kidney function (n = 62)	0–50 % GFR ≥ 50 ml/min Mostly impaired renal function (n = 55)	
Duration of colistin use, median (Q1; Q3), days	12.5 (7.0; 24.0)	10.0 (5.0; 16.0)	0,.42 ◊
Cumulative colistin dose, median (Q1; Q3), MU	96.8 (69.0; 204.0)	66.0 (38.0; 107.5)	< 0.001 ◊

Table 2.4 continued

Parameter	Kidney function throughout the use of colistin		p value
	51–100 % GFR≥ 50 ml/min Mostly normal kidney function (n = 62)	0–50 % GFR ≥ 50 ml/min Mostly impaired renal function (n = 55)	
Duration of recommended dose use, median (Q1; Q3), days	8.0 (5.0;18.0)	3.0 (1.0; 8.0)	< 0.001 ◊
Percentage of recommended maintenance doses, median (Q1; Q3), %	100 % (60; 100)	33 % (14.3; 81.3)	< 0.001 ◊

◊ Mann-Whitney U test; Abbreviations: GFR – glomerular filtration rate, MU – million units.

2.4 Colistin-associated acute kidney injury

Twenty three cases of RRT at the initiation of colistin, six repeated episodes of colistin use within one hospitalization, and two cases where renal function worsened within the first 24 hours of colistin initiation were excluded from the analysis of colistin-induced AKI. The analysis was conducted on the remaining 87 instances of colistin use.

In 24 out of 87 cases (27.6 %), AKI was observed during colistin therapy, meeting the RIFLE criteria (a serum creatinine increase of at least 1.5 times). The median number of days (Q1; Q3) from the start of colistin therapy to a serum creatinine increase of over 50 % was 8 (4; 17) days, and the median cumulative dose of colistin (Q1; Q3) was 68 (36; 124) MU. The minimum number of days from colistin initiation to the manifestation of AKI was 2 days, and the maximum was 31 days.

Patients with acute kidney injury most commonly had a normal baseline renal functional status: in 15 (63 %) cases, patients had normal renal function, in 5 (21 %) cases, augmented renal clearance, and in 4 (16 %) cases, impaired renal function.

The median number of days (Q1; Q3) of colistin therapy when the highest serum creatinine level was reached was 12.0 (6.0; 24.5). When classifying cases of AKI by the highest serum creatinine level, it was found that most patients had severe or moderately severe acute kidney injury: 17 % (4/24) of patients had mild acute kidney injury (corresponding to "Risk" according RIFLE criteria), 39 % (9/23) had moderate (corresponding to "Injury"), and 48 % (11/23) had severe acute kidney injury (corresponding to "Failure"). There was no correlation observed between the degree of serum creatinine increase (severity of acute kidney injury) and the days of colistin therapy when the maximum serum creatinine level was reached (Spearman's correlation coefficient 0.315, $p = 0.134$).

A statistically significant negative correlation was found between the increase in serum creatinine (severity of acute kidney injury) and the patient's age (Spearman's correlation coefficient −0.578, $p = 0.004$), as well as the baseline creatinine level (Spearman's correlation coefficient −0.783, $p < 0.001$) (Figures 2.4 and 2.5). It is worth noting that a positive correlation was also observed between the patient's age and the baseline creatinine level (Spearman's correlation coefficient 0.629, $p < 0.001$).

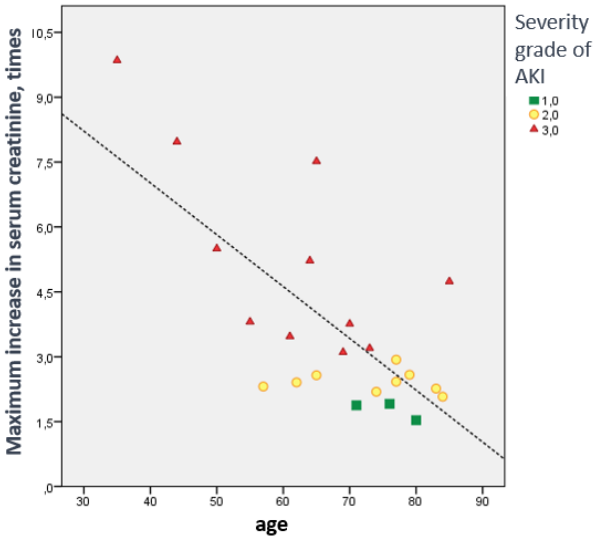

Figure 2.4 **Correlations between the severity of acute kidney injury and patient's age.**

Severity levels of acute kidney injury (AKI): 1 – mild AKI (serum creatinine increase by 1.5–1.9 times from baseline), 2 – moderate AKI (serum creatinine increase by 2.0–2.9 times from baseline), 3 – severe AKI (serum creatinine increase more than 3.0 times from baseline)

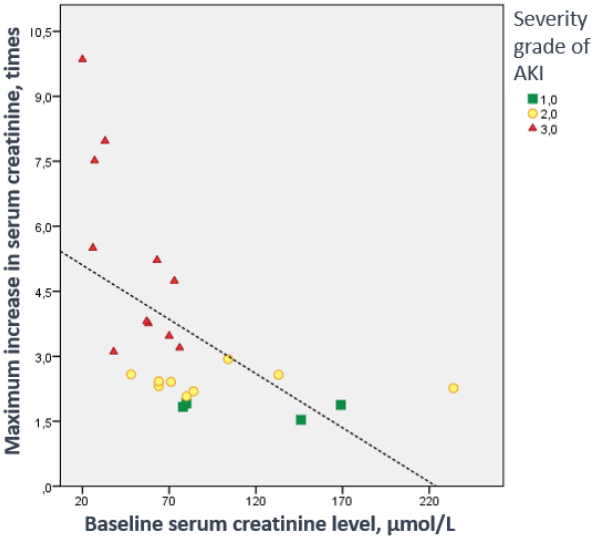

Figure 2.5 **Correlation between the severity level of acute kidney injury and baseline serum creatinine level**

Severity levels of acute kidney injury (AKI): 1 – mild AKI (serum creatinine increase by 1.5–1.9 times from baseline), 2 – moderate AKI (serum creatinine increase by 2.0–2.9 times from baseline), 3 – severe AKI (serum creatinine increase more than 3.0 times from baseline)

The median (Q1; Q3) level of CRP on the day of colistin initiation was 123 µmol/L (87; 186), and on the day of AKI, it was 162 µmol/L (96; 244). For most patients, CRP increased on the day of AKI (15 cases out of 24) rather than decreased (9 cases out of 24). However, this distribution did not reach statistical significance ($p = 0.056$, Wilcoxon rank-sum test).

In cases of colistin-induced AKI, colistin therapy was most commonly discontinued immediately or within a few days, or the colistin therapy was continued at an adjusted dose (n = 13; 40 %). For some patients, colistin therapy was continued at an unadjusted or insufficiently reduced dose (n = 8; 33 %). The median number of days in this group until colistin discontinuation (Q1; Q3) was 5.5 (3; 9.5) days.

Excluding three cases with early patient death after the manifestation of AKI, no statistically significant relationship was found between the severity of AKI and the treating physician's action (discontinuation or reduction of colistin dose (1st group) or continuing colistin at an unadjusted dose (2nd group)). The incidence of more severe renal failure (serum creatinine increase ≥ 3 times above baseline) was 46 % (6/13) in the 1st group and 37.5 % (3/8) in the 2nd group, p = 0.697.

In some cases, it was not possible to answer the question about the improvement in kidney function after colistin discontinuation due to patient death, discharge from the hospital, or lack of daily kidney function monitoring. None of the study participants needed to initiate renal replacement therapy due to colistin-induced AKI. In eight cases where information on the improvement in renal function after colistin discontinuation was available, renal function returned to baseline after 8 ± 3 days (range 4–13 days; median (Q1; Q3) – 7.5 (6.5;10) days). In one case, renal function continued to deteriorate even after colistin discontinuation (COL115), and in one case, a patient with normal renal function before colistin initiation maintained an estimated glomerular filtration rate (eGFR) around 30 ml/min/1.73 m² even after 30 days from colistin discontinuation (COL64).

When analysing differences in various parameters between the group with colistin-induced AKI and the group without this complication, statistically significant differences were found in two parameters – age and baseline creatinine level. Patients with AKI had a lower median baseline creatinine level than patients without AKI (71 µmol/L and 89 µmol/L, p = 0.049), and standard saturating dose of colistin was more frequently administered in the AKI group than in the non-AKI group (88 % and 62 %, p = 0.021). Serum creatinine and C-reactive protein levels at the end of therapy were statistically significantly higher in patients with AKI. Patients in the AKI group were older than those in

the non-AKI group (70 and 63 years, p = 0.059), but this difference was not statistically significant. Other clinically and colistin-related parameters tested also failed to demonstrate statistically significant differences (Tables 2.5 and 2.6).

Table 2.5

Distribution of demographic and clinical parameters in AKI | and non-AKI groups

Parameter		Patients with AKI n = 24	Patients without AKI n = 63	p value
Age groups	up to 65 years, n (%)	9 (38 %)	36 (57 %)	0.101#
	65 years and above, n (%)	15 (63 %)	27 (43 %)	
Median age, years (Q1; Q3)		70 (62; 77)	63 (50; 74)	0.059 ◊
Gender	Man, n (%)	15 (63 %)	43 (68 %)	0.611#
	Woman, n (%)	9 (38 %)	20 (32 %)	
Kidney baseline functional status (1st version)	*Group 1:* Normal renal function	15 (63 %)	29 (46 %)	0.304#
	Group 2: Augmented clearance	5 (21 %)	14 (22 %)	
	Group 3: Renal impairment	4 (17 %)	20 (32 %)	
Kidney baseline functional status (2nd version)	*Group 1 and 2:* GFR ≥ 50 mL/min	20 (83 %)	43 (68 %)	0.160#
	Group 3: Renal impairment	4 (17 %)	20 (32 %)	
Comorbidities	Chronic kidney disease, n (%)	4 (17 %)	13 (21 %)	0.677#
	Diabetes mellitus, n (%)	4 (17 %)	11(17 %)	0.930#
	Chronic heart disease, n (%)	7 (29 %)	24 (38 %)	0.437#
	COPD, n (%)	3 (13 %)	5 (8 %)	0.510#
	PAH, n (%)	3 (13 %)	15 (24 %)	0.244#
Biochemical parameters	Baseline CRP level, µmol/L (median, Q1; Q3)	126 (89; 181)	94 (63; 184)	0.163 ◊
	CRP level at the end of therapy, µmol/L (median, Q1; Q3)	136 (58; 195)	65 (42; 111)	**0.014** ◊
	Baseline serum creatinine level, µmol/L (median, Q1; Q3)	71 (53; 82)	89 (57; 149)	**0.049** ◊
	Serum creatinine level at the end of therapy, µmol/L (median, Q1; Q3)	201 (148; 263)	81 (49; 132)	**< 0.001** ◊

Table 2.5 continued

Parameter	Patients with AKI n = 24	Patients without AKI n = 63	p value
Documented sepsis or septic shock	9 (38 %)	16 (25 %)	0.265#
Cardiopulmonar resuscitation during this hospitalization episode	2 (8 %)	14 (22 %)	0.135#
28-day mortality from the beginning of colistin therapy	6 (25 %)	22 (35 %)	0.376#

Chi-square test, ◊ Mann-Whitney U test
Abbreviations: AKI – acute kidney injury, CRP – C-reactive protein, COPD – chronic obstructive pulmonary disease, PAH – primary arterial hypertension

Table 2.6

Description of colistin use pattern in AKI and non-AKI groups

Parameter	Patients with AKI n = 24	Patients without AKI n = 63	p value
Treatment with colistin exceeding 14 days, n (%)	11 (45 %)	20 (32 %)	0.220#
Cumulative dose of colistin until outcome*, MU (median, Q1; Q3)	68 (36–116)	75 (48–129)	0.342 ◊
Duration of colistin therapy until outcome*, MU (median, Q1; Q3)	7 (3–16)	10 (7–18)	0.066 ◊
Loading dose of 9 MU, n (%)	21 (88 %)	39 (62 %)	**0.021#**
Median duration of potential sub-therapeutic colistin dosing, days (Q1; Q3)	0 (0–3,5)	0 (0–4)	0.594 ◊
Median duration of potential supra-therapeutic colistin dosing, days (Q1; Q3)	1.5 (0–5)	0 (0)	**< 0.001** ◊
Median duration of appropriate colistin dosing, days (Q1; Q3)	4 (2–14)	7 (3–13)	0.890 ◊

* Outcome – AKI or end of colistin therapy for patients without AKI. Abbreviations: AKI – acute kidney injury, MU –million units

2.5 Co-administration of potentially nephrotoxic substances with colistin.

Most commonly, patients received one potentially nephrotoxic medication alongside colistin therapy (69 out of 87 cases, or 79 %), and most frequently, it was one or two different nephrotoxins (Figure 2.6)

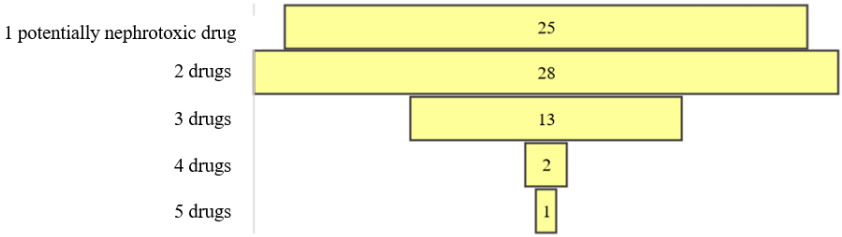

Figure 2.6 **The quantity of potentially nephrotoxic drugs alongside colistin therapy (out of 88 cases)**

The most commonly used potentially nephrotoxic agent concurrently with colistin therapy was loop diuretic (44 out of 87 cases, or 51 %). Second in frequency was nonsteroidal anti-inflammatory drugs (19/87 or 22 %). Among NSAIDs, the most common medication was a low-dose intravenous infusion of diclofenac (≤ 3 mg/h) as antipyretic agent (14 cases).

Patients also received vancomycin (11 cases) as a potentially nephrotoxic antibacterial agent together colistin. Therapeutic drug concentrations were challenging to achieve on the initiation day, especially in patients with eGFR above 50 ml/min (in 6 out of 9 cases, it is known that the concentration was mostly subtherapeutic). Additionally, there were cases with potential incorrect sampling times, which could negatively impact result interpretation (4 cases).

Carbapenems were the most frequently used potentially synergistic antibacterial agent in combination with colistin, especially in the non-AKI group, where it was administered more frequently (37 % and 62 % in AKI and non-AKI

groups, respectively, p = 0.041). Information on potentially nephrotoxic medications and the use of antibacterial agents in patients with and without AKI during colistin therapy is summarized in Table 2.7.

Table 2.7

Simultaneous use of potentially nephrotoxic drugs and antibacterial agents with colistin therapy

The drugs and their patterns of use	Patients with AKI n = 25	Patients without AKI n = 63	p value
Antibacterial agent used concurrently with colistin			
Vancomycin			
n (%)	5 (21 %)	6 (10 %)	0.156 #
Median duration of concurrent use, days (Q1; Q3)*	9 (3–9)	6 (3–11)	1.000 ◊
Median total duration of use, days (Q1; Q3)*	11 (9–13)	9.5 (6–12)	0.792 ◊
Median total cumulative dose, g (Q1; Q3)*	17 (16–18)	11 (10–14)	0.329 ◊
Carbapenem (meropenem or imipenem)			
n (%)	9 (37 %)	39 (62 %)	**0.041** #
Median duration of concurrent use, days (Q1; Q3)*	9 (5–10)	9 (5–16)	0.603 ◊
Piperacillin/tazobactam			
n (%)	4 (17 %)	12 (19 %)	0.911 #
Median duration of concurrent use, days (Q1; Q3)*	7 (5.5–10.5)	5.5 (4–10.5)	0.377 ◊
Fosfomycin			
n (%)	0	2 (3 %)	0.387 #
Median duration of concurrent use, days (Q1; Q3)*	NA	12 (8–15)	NA
Carbapenems and/or piperacillin/tazobactam and/or fosfomycin, n (%)	12 (50 %)	48 (76 %)	**0.081** #
Other potentially nephrotoxic agents used concurrently with colistin			
Loop diuretics			
n (%)	13 (54 %)	34 (54 %)	0.987 #
Median duration of concurrent use, days (Q1; Q3)*	7 (6–13)	7 (5–12)	0.502 ◊
NSAIDs			
n (%)	4 (17 %)	7 (11 %)	0.400 #
Median duration of concurrent use, days (Q1; Q3)*	6 (5–10)	6 (4.5–9.5)	0.958 ◊
ACE-I			
n (%)	2 (8 %)	5 (8 %)	0.952 #
Median duration of concurrent use, days (Q1; Q3)*	19 (8–29)	6 (5–8)	0.190 ◊
Contrast media, n (%)	6 (25 %)	9 (14 %)	0.237 #
Vasopressor			
n (%)	13 (54 %)	26 (41 %)	0.280 #
Median duration of concurrent use, days (Q1; Q3)*	6 (5–10)	5 (4–10)	0.308 ◊

Table 2.7 continued

The drugs and their patterns of use	Patients with AKI n = 25	Patients without AKI n = 63	p value
Amount of concurrent nephrotoxins used			
At least 1 nephrotoxic agent used concurrently	20 (83 %)	49 (77 %)	0.567 #
At least 2 nephrotoxic agents used concurrently	15 (63 %)	29 (46 %)	0.170 #
At least 3 nephrotoxic agents used concurrently	5 (21 %)	11 (17 %)	0.717 #

Chi-square test, ◊ Mann-Whitney U test
*Only in cases where colistin was used together with the analysed agents
Abbreviations: ACE-I – angiotensin-converting enzyme inhibitor, AKI – acute kidney injury, NA– not applicable, NSAID – non-steroidal anti-inflammatory drug

2.6 Single-factor and multifactorial logistic regression analysis of colistin-associated AKI

Analysing potential risk factors for colistin-associated AKI using single-factor logistic regression analysis, it was found that the loading dose of 9 MU increases the risk of AKI (OR = 4.31, p = 0.029). However, considering the very wide 95 % confidence interval (1.16–16.0), this risk might be lower. Meanwhile, concurrent use of carbapenems was demonstrated as a protective factor (OR 0.37; CI 0.14–0.97; p = 0.044). Analysing these data with multifactor logistic regression analysis, it is observed that the saturating dose remains a risk factor, but the protective effect of carbapenems was not confirmed (Table 2.8).

Table 2.8

Acute kidney injury risk factors: logistic regression analysis

Factors	Univariate analysis			Multivariate analysis		
	Odds Ratio	p value	CI	Odds Ratio	p value	CI
Age, years	1.03	0.072	0.99–1.07	–	–	–
Creatinine on the day of colistin initiation	0.99	0.060	0.98–1.00	–	–	–
Loading dose (9 MU)	4.31	0.029	1.15–16.00	9.57	0.007	1.85–49.6
Cumulative colistin dose until the case*	0.99	0.380	0.99–1.00	–	–	–

Table 2.8 continued

Factors	Univariate analysis			Multivariate analysis		
	Odds Ratio	**p value**	**CI**	**Odds Ratio**	**p value**	**CI**
Simultaneous use of carbapenem with colistin	0.37	0.044	0.14–0.97	0.34	0.075	0.10–1.11
Maintenance colistin dose more than 50 % of total therapy duration not correspond with recommended dose	3.50	0.012	1.32–9.31	3.13	0.081	0.87–11.3
Amount of days when maintenance dose exceeds recommended dose	1.33	0.005	1.09–1.62	1.29	0.022	1.04–1.59

Abbreviations: CI – Confidence Interval, MU – million units
Explanation: *Case – acute kidney failure or end of colistin therapy.

3 Discussion

3.1 Description of the study population and colistin use pattern

Overall, the study population is heterogeneous – patients had various reasons for hospitalization, chronic comorbidities, and variable renal functional status, which is typical of critically ill patients in intensive care units, making it challenging to obtain high-quality evidence in this patient group. This diversity adds complexity to obtaining robust data in this context, making research in this area particularly interesting and valuable. On the other hand, the indication for colistin therapy was relatively homogeneous, mostly being *A. baumannii* MPV-associated pneumonia, which also became the primary focus of this study. This choice of the infectious agent was anticipated, given the comparatively high prevalence of carbapenem-resistant *A. baumannii* in the Baltic region. [14].

The overall mortality rate was relatively high (49.5 %), but it's crucial to consider that study participants were critically ill patients with severe general conditions (a significant proportion of patients with subarachnoid haemorrhage, post-acute coronary syndrome). Additionally, 17.1 % of patients underwent cardiopulmonary resuscitation before admission to the ICU. Demonstrating the effect of antibacterial therapy on reducing mortality in this critically ill patient group is not straightforward, as sepsis is not always the direct cause of death. However, several published studies are available in the literature where the effectiveness of therapy was evaluated from the perspective of bacteriological eradication [15], [16]. Unfortunately, in our study, this was challenging because the primary indication for colistin use was MPV-associated pneumonia, and repeated tracheal aspirate cultures were relatively infrequent. It's possible that colistin therapy was continued or discontinued empirically based on clinical response.

Colistin MICs were documented in very few cases, making it challenging to track the evolution of *A. baumannii* resistance over the years of the study. It is known that the colistin MICs isolated in 2014 and 2015 were lower than those in 2017, but the number of these cases was so small that conclusions about the gradual development of colistin resistance in the study centre cannot be drawn. Notably, none of the included cases showed colistin resistance either at the beginning or at the end of colistin therapy. Meanwhile, in some other European countries, cases of colistin-resistant Gram-negative bacteria had already been reported [17].

In this study, carbapenem-resistant Gram-negative bacteria were extensively drug-resistant, but in rare cases, they were sensitive not only to colistin but also to aminoglycosides or ampicillin/sulbactam. Both of these classes of antibiotics are theoretical alternatives to colistin. However, it's important to note that aminoglycosides can be potentially nephrotoxic, and ampicillin/sulbactam needs to be used in high doses and it is contraindicated in cases of penicillin allergies. [18]. Penicillin allergies were not documented among the study participants. There were several cases where bacteria sensitive to ampicillin/sulbactam were isolated from one material (such as blood), but resistant strains were found in another material (such as tracheal aspirate after a few days of colistin therapy). Therefore, colistin might have been a better therapeutic option for this group of patients in the study.

It's worth noting that in recent years, other antibiotics such as high-dose ampicillin/sulbactam, ceftazidime/avibactam, and cefiderocol have been introduced as alternatives to colistin for treating infections caused by resistant Gram-negative bacteria in the study centre. However, these alternatives have their limitations, including a narrower spectrum of activity and relatively high treatment costs, which is why colistin continues to be widely used also in 2023.

The median duration of colistin therapy was 11 days (ranging from 3 to 58 days). For a relatively large proportion of patients (41 % or 48 out of 117), colistin therapy could have been prematurely discontinued, for reasons such as death and other causes. Despite the relatively high number of cases of Gram-negative bacteria-induced pneumonia, more so than cases of isolated bacteraemia, the study did not show that the duration of colistin therapy might depend on a specific material from which MDR bacteria were isolated. In this study, there were cases where bacteraemia was successfully treated even when Gram-negative bacteria were still present in tracheal aspirates. Also, in cases where MDR Gram-negative bacteria were isolated from various organs, the duration of colistin therapy was statistically significantly longer. Other research data also suggested that it is easier to treat Gram-negative bacteraemia with colistin compared to the same causative agent pneumonia [19]. This can be explained by the relatively poor penetration of colistin into lung tissues, which can at least partially account for the longer and more complicated treatment of pneumonia with colistin [20], [21]. Theoretically, adding inhaled colistin to intravenous colistin therapy could be considered in cases of ventilator-associated pneumonia, as recommended in the guidelines issued in 2019 [22]. In this study, which investigated the period before the issuance of these recommendations, none of the patients received the addition of inhaled colistin to the existing intravenous colistin therapy.

A loading dose of colistin is generally recommended for critically ill patients, and this dose is usually not dependent on the renal functional status. In this study, there was a tendency to avoid the standard loading dose of 9 MU or reduce it to 6 MU for patients with impaired renal function and RRT. There is evidence that even with a 9 MU loading dose, achieving therapeutic colistin concentrations immediately is not straightforward, but with a lower loading dose, this goal might be even more challenging to attain [23].

The question of the effectiveness and safety of the colistin loading dose in real clinical practice remains relevant. In 2020, a meta-analysis of 8 clinical studies (involving 1115 patients) was published, including studies with high doses of colistin, reporting clinical outcomes in patients with or without a loading dose. All studies were observational cohort studies, of which three were prospective and five were retrospective. The administration of colistin loading doses was associated with significantly higher bacteriological eradication (RR = 1.23, 95 % CI 1.10–1.39) but not with better clinical outcomes (RR = 1.04, 95 % CI 0.87–1.24). No significant effect (positive or negative) of the loading dose on the development of nephrotoxicity (RR = 1.31, 95 % CI 0.90–1.91, n = 1070) or mortality risk (RR = 1.03, 95 % CI 0.82–1.29) was found [24]. Based on the results of this meta-analysis, it can be concluded that the loading dose of colistin may contribute to better bacterial eradication. However, to obtain higher-level evidence, a well-designed randomized clinical trial (RCT) would be necessary.

It was interesting to analyse the choice of maintenance doses, which varied widely among the study participants. There were cases where the maintenance dose was significantly lower than the recommended doses in the guidelines of 2019. For example, doses as low as 1.5 MU every 36 hours were prescribed instead of the recommended 5.9 MU every 24 hours. The selection of such low doses could potentially be explained by two hypotheses. Firstly, it might be related to the recommendations for colistin dosing available in older official drug manufacturer documents (drug descriptions, national formularies) and in some renal dosing handbooks published at that time, which suggested relatively low colistin doses [25]. The second hypothesis could be related to the potentially incorrect conversion of the dose from colistin base activity (in milligrams) to colistin activity units (in MU). For example, following recommendations from a renal handbook published in the US, the recommended

colistin dose for patients with severe renal impairment was 1.5 mg/kg every 36 hours, which for an 80-kg patient would be 120 mg colistin base activity every 36 hours, approximately 3.6 MU every 36 hours (= 120 CBA/33) [26]. Incorrectly assuming that the recommendations in this source are given in the form of sodium colistimethate (80 mg sodium colistimethate ~ 1 MU colistin) instead of colistin base activity (33 mg CBA ~ 1 MU colistin), there is a risk that for this hypothetical 80-kg patient with weak renal function, 3.6 MU every 36 hours could be given in mistake instead of 1.5 MU every 36 hours (= 120 mg/80), as seen in the example from our study.

There were also cases where patients with estimated GFR below 50 ml/min were given the standard colistin dose (9 MU/day) instead of adjusted doses. The renal function in critically ill patients fluctuates, requiring regular monitoring of kidney function and adjustment of doses based on the worsening or improvement of renal status. It is commonly recommended to adjust medication doses with renal elimination when creatinine clearance falls below 30 ml/min. However, there are medications that require dose adjustment even at GFR 30–50 ml/min, including colistin [22].

Patients with acute kidney injury received colistin at doses higher than recommended for a greater number of days compared to patients without AKI. It is important to note that the median number of these days was 1.5 days, mainly related to rapid deterioration in kidney function when the colistin dose had not yet been adjusted for the new renal status. Therefore, this indicator cannot be interpreted as a risk factor for colistin nephrotoxicity. In general, when AKI was detected, attempts were made to either discontinue or reduce colistin dose (either immediately or within a few days), as recommended in international guidelines for the use of polymyxin antibacterial agents [22]. Unfortunately, there were also cases where the colistin dosage for this group of patients was not adjusted over

several days. Interestingly, it's worth noting that the actions of the treating physicians in cases of AKI were not dependent on the severity of AKI.

Evidently, patients with renal impairments need dose adjustments. Unfortunately, if TDM is not performed, there is a risk that excessively reducing the colistin dose might result in sub-therapeutic colistin concentrations in the bloodstream. In a prospective observational study conducted in Spain from 2010 to 2018, focusing on colistin dosing, safety, and effectiveness in 59 patients with chronic kidney disease (GFR < 60 ml/min/m^2 for longer period than 3 months), it was found that the average colistin doses for this patient group were almost half of the recommended doses (3.36 vs. 6.07 MU/day, $p< 0.001$). Also, the mean steady-state colistin concentration (Css) was below the target of 2 mg/L for the majority of patients (83.3 %) with a median Css of 0.9 (range 0.2–2.9) mg/L. Clinical cure was achieved in 72.9 % (43/59) of patients, and renal deterioration was observed in 33.9 % (20/59) of patients, that was reversible in 50 % (10/20) of cases. Css in the AKI group was higher than in the non-AKI group, but it did not reach a statistically significant difference (1.2 (0.3–2.9) vs. 0.83 (0.2–2.4), $p = 0.1$). [27]. In our study, patients with impaired renal function tended to receive a lower dose of colistin than recommended. Colistin dose adjustments according to the latest recommendations could be one of the clinical pharmacist's tasks in their daily work in the hospital departments.

Patients with augmented renal clearance tended to receive colistin therapy for a longer duration and in higher cumulative doses. However, the daily dose for this patient group was standard (9 MU/day) rather than elevated. There are still ongoing discussions about the optimal dosing of antibacterial agents for patients with enhanced renal clearance [28]. Here, it is important to consider that the objective assessment of renal function is challenging for critically ill patients. When opting for an elevated dose of antibacterial agents, it is safest to simultaneously monitor the concentration of these agents in the plasma to avoid

overdosing, especially if the renal functional status is worse than estimated using available formulas for renal function assessment.

3.2 The incidence of colistin nephrotoxicity compared to other regions of the world

The incidence of acute kidney failure in this study reached 27 %, which corresponds to the meta-analysis published in 2019 [29]. In 2022, our study is the only published research on colistin usage practices in the Eastern European region [1]. Analysing the median incidence of colistin-associated nephrotoxicity in different regions, no statistically significant difference was found between the incidence in this study and other regions (Figure 3.1). However, it is important to note the relatively large variation in colistin-associated nephrotoxicity prevalence within each region.

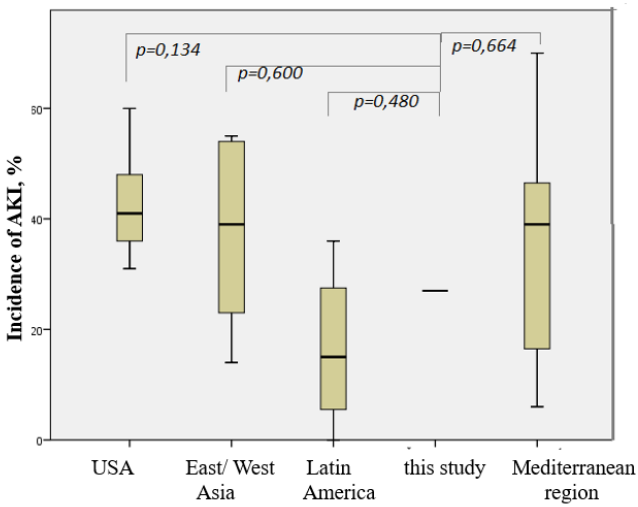

Figure 3.1 **The median incidence of colistin-associated acute kidney injury in various regions worldwide**

Abbreviations: AKI – acute kidney injury, USA – United State of America

The median number of days until the development of colistin-induced AKI was 8 days, and for some patients, renal function returned to baseline levels within approximately one week. Unfortunately, such data were not available for all patients due to various reasons (patient deaths, discharge from the hospital, lack of daily renal function monitoring after discharge from the ICU to another department). In our study, the time to the development of colistin-associated AKI and improvement in renal functional status were similar to other studies, where renal failure also developed within the first week of therapy, and renal function normalized within a week in the available cases for analysis [3], [30], [31], [32].

Acute kidney injury most frequently fell into the moderately severe category (Injury according to RIFLE criteria) or severe category (Failure according to RIFLE criteria). This distribution of degree of severity of colistin-induced AKI is common in other published studies as well because patients were often not followed up for three months after colistin-induced AKI was diagnosed, making it challenging to classify them into the most severe stages of RIFLE (*Loss* or *End-stage renal disease*).[33], [12], [34], [30], [35]. Therefore, the incidence and course of colistin-induced AKI in this study closely resemble the data published in other regions worldwide.

3.3 The potential risk and protective factors for colistin nephrotoxicity

Several factors could potentially be associated with the risks of drug toxicity. In this study, many factors are thoroughly examined, such as patient age, use of other nephrotoxic agents, baseline renal functional status, and cumulative colistin dose.

Advanced age of patients might be associated with a higher risk of nephrotoxicity. For example, in one study, the average age of patients with AKI was significantly higher than that of patients without AKI (67 vs. 49 years for

AKI and non-AKI groups; p = 0.001). [5]. In our study, the median age of patients in the AKI group was higher than in the non-AKI group, but it did not reach statistical significance (70 vs 63 years in the ANB and non-ANB groups, respectively, p = 0.059).

A lower albumin level was also reported as a potential risk factor for colistin-associated nephrotoxicity [36]. Unfortunately, albumin levels were not regularly measured for all patients on the day colistin therapy was initiated, and for those patients where it was measured, it was decreased, which is common in critically ill patients. Therefore, hypoalbuminemia was not analysed in this study as a potential risk factor for colistin-associated nephrotoxicity.

In this study, colistin was relatively frequently used alongside other potentially nephrotoxic agents – 79 % of patients received at least one potentially nephrotoxic medication concurrently with colistin therapy for more than 48 hours and/or at least one contrast media administration. This makes this study cohort a relatively good group for exploring the impact of nephrotoxins on the risk of colistin-associated nephrotoxicity. Despite this, the role of other nephrotoxins in the development of colistin-associated nephrotoxicity remains unclear, and their use in co-administration with colistin is not recommended [22], therefore, this issue can only be studied in observational studies, as experimental studies, including RCTs, could raise significant ethical concerns. There is indeed a wide range of information published about the impact of nephrotoxins on colistin-associated nephrotoxicity, and interestingly, it appears to be highly contradictory (Table 3.1). Rarely is the duration of concurrent use clearly defined, which undoubtedly could also influence the results.

Table 3.1

The potential role of nephrotoxins in the development of colistin-associated AKI from various study centres.

Reference	**[37]**	**[12]**	**[38]**	**[33]**	**[39]**	**[6]**	**[32]**	**[3]**	**[34]**	**—**
Country	USA	USA	USA	USA	SK	SK	IT	IT	T	LV
Years of study (20….)	03–07	05–09	06–08	07–09	06–08	11–14	10–11	12–14	10–14	15–18
Design	R	R	R	R	R	R	P	P	R	R
Patients, n	66	126	30	49	47	120	28	70	76	87
AKI %	45	43	33	31	32	51	18	44	47	27
≥ 1 nephro-toxin	–	○	–	○	–	–	–	○	–	○
≥ 2 nephro-toxins	–	○	–	●	–	○	–	○	–	○
≥ 3 nephro-toxins	–	●	–	–	–	–	–	○	–	○
Amino-glycoside	○	○	○	○	○, ♦	–	○	○	○	–
Glycopeptide	○	–	○	○	○	○	–	○	–	○
NSAID	○	–	–	○	●, ♦	○	–	–	–	○
Contrast media	○	–	○	●	○	○	●	○	○	○
Loop diuretics	○	●	●	○	○	○	○	○	○	○
Vaso-pressor	○	○	●	○	–	–	–	–	●	○
ACE-I /ARB	–	–	○	○	○	○	–	–	○	–
Rifampicin	–	●	–	–	–	○	–	–	–	–
TRI-SUL	–	–	–	–	–	–	–	–	○	–
Mannitol	–	–	–	–	○	○	○	–	–	–
Antifungal	–	–	–	○	○	○	–	–	●	–
IV immune-globulin	–	–	–	–	○	○	–	–	–	–

Table 3.1 continued

Reference	[37]	[12]	[38]	[33]	[39]	[6]	[32]	[3]	[34]	—
Valproic acid	–	–	–	–	○	–	–	–	–	–
Length of colistin and nephrotoxin co-admini-stration	ND	ND	ND	≥ 1 deva	ND	ND	ND	ND	ND	≥ 48 h

In the last column, data from our study are reflected.

Abbreviations: ACE-I – angiotensin-converting enzyme inhibitor, AKI – acute kidney injury, ARB – angiotensin receptor blocker, IT – Italy, LV – Latvia (this study), ND – not defined, NSAID – nonsteroidal anti-inflammatory drug, P– prospective (observational study), R – retrospective, SK – South Korea, T – Turkey, TRI-SUL – trimethoprim-sulfamethoxazole, USA – United States of America. Explanation: a statistically significant association was reported between the use of this agent and colistin (●); higher concurrent nephrotoxin doses are associated with a higher risk of AKI (♦); an association between the use of this agent and colistin was investigated, but no statistically significant increase in AKI risk was observed (○).

In our study, the most commonly used nephrotoxin together with colistin was a loop diuretic (furosemide or torasemide), which is a frequently prescribed pharmacological group for critically ill patients with fluid overload. In two retrospective cohort studies from the US, simultaneous use of loop diuretics with colistin was associated with a higher risk of colistin-associated nephrotoxicity. [12], [38]. On the other hand, in other studies, this association was not confirmed [3], [39], [32]. In our study, the simultaneous use of furosemide or torasemide with colistin within an average of 7 days was not associated with an increased risk of renal failure.

The second most commonly used potentially nephrotoxic pharmacological group in our study was NSAIDs. Analysing studies reporting concurrent use of nephrotoxins with colistin, there were studies where NSAIDs were not used at all [3], [38] or were used rarely [6], [40]. One study concluded that simultaneous use of NSAIDs and colistin increases the risk of nephrotoxicity [39]. However, in other studies where NSAIDs were used relatively frequently (at least in 10 % of cases), it was not proven that NSAIDs increase this risk [30],

[37]. In our study, it was also not demonstrated that NSAIDs increase the risk of nephrotoxicity. It is worth noting that in the study centre, NSAIDs were used as low-dose continuous infusions of diclofenac to reduce hyperthermia. This dosing regimen is based on the study by *Cormio et al. 2007* [41]. The daily dose of diclofenac does not exceed 75 mg, which is half of the maximum allowed daily dose of diclofenac. Therefore, our study only shows that low-dose NSAIDs do not associate with an increased risk of colistin nephrotoxicity.

The simultaneous use of certain nephrotoxic antibiotics, such as glycopeptides and aminoglycosides, with colistin has been a topic of interest in several studies [42], [43]. In our study, antibiotics from the aminoglycoside group were not used, but vancomycin was used in some cases. Interestingly, vancomycin was used in several studies, but it was not reported to increase the risk of colistin-induced nephrotoxicity [3], [33], [39], [37]. In contrast, other researchers report that vancomycin can enhance colistin nephrotoxicity [44], [45], [46]. In our study, this association was not confirmed, but it should be noted that vancomycin concentration rarely reached the therapeutic level in the blood. Furthermore, in the aforementioned studies, it was not mentioned whether vancomycin concentration was therapeutic in all cases. Considering the studied population, it should be taken into account that due to unstable renal function and fluid status changes, it can be challenging to achieve therapeutic concentration for hydrophilic drugs with a narrow therapeutic range, including vancomycin [47].

In our study, one of the most frequently used antibiotics in combination with colistin was meropenem. The data from this study also indicate that carbapenems do not increase the risk of nephrotoxicity. However, unfortunately, the multifactorial logistic regression analysis did not confirm the nephroprotective effect of carbapenems. In a retrospective cohort study conducted in Turkey (2010–2012, n = 198), carbapenems were also more

commonly used in patients without colistin-induced AKI compared to those with colistin-induced nephrotoxicity (50 % vs. 35 %, p = 0.052) In any case, it appears that carbapenems might be a safe antibiotic for synergistic use in combination with colistin.

In our study, patients in the AKI group more frequently received the standard loading colistin dose of 9 MU compared to patients in the group without AKI (87 % vs. 62 %, p = 0.027). So high loading dose is recommended for critically ill patients, aiding in achieving the desired concentration in the blood more rapidly [22]. Without the loading dose, there is a high probability that colistin will only reach its target concentration after 2 days, given that colistin has a half-life of 14.4 hours [48]. The recommended interval between the saturating and the first maintenance dose according to the *International Consensus Guidelines for the Optimal Use of the Polymyxins* is the same as the interval between maintenance doses. Therefore, in these guidelines, the recommended interval for patients with normal renal function is 12 hours (4.5 MU every 12 hours), and the recommended interval between the saturating and the first maintenance dose is also 12 hours [22]. In a meta-analysis of 8 observational studies, it was demonstrated that the loading colistin dose is associated with better bacteriological eradication and does not increase the risk of colistin nephrotoxicity. However, this finding needs confirmation in a well-designed clinical study [24].

In modern clinical practice, adjusting colistin doses based on renal function is not recommended, but for patients with poorer renal function, the interval between loading and maintenance doses could potentially be longer [49]. In our study, the most commonly used interval between loading and maintenance doses was 8 hours, as the most frequently applied dosing regimen was 3 MU every 8 hours. Therefore, there was no opportunity to compare the impact of different intervals between initial doses on the development of colistin

nephrotoxicity. Therapeutic drug monitoring might be valuable to understand what concentration is achieved after the administration of the loading dose at various time intervals.

3.4 Limitation of the study

The first limitation of the study is its retrospective design. The main source of information was medical records in patient histories. On one hand, biochemical analyses, including measurements of serum creatinine, were conducted on a regular basis, allowing the analysis of changes in kidney function throughout the entire course of colistin therapy. But, on the other hand, not all information that would have been relevant for the analysis was available in the patient histories. For example, there was no documented scale reflecting the severity level of the patient's condition during colistin therapy

Determining kidney function in critically ill patients is a significant challenge because methods that could be more accurate than creatinine clearance (such as the use of exogenous renal filtration markers like radioactive markers or iothalamate) are generally not applied in routine clinical practice [50]. On the other hand, there are several limitations to estimating GFR based on serum creatinine. It can be artificially elevated, for example, in cases of malnutrition. In this study, there was also a risk of imprecise kidney function determination. Nevertheless, it is the most common method for adjusting medication dosages in real clinical practice for medications that cannot be titrated based on therapeutic response in real-time.

Another significant limitation to mention is that this study is not multicentre and does not allow generalization of the results to the entire country or the Baltic counties region. However, the data were obtained from a centre with a fairly extensive practice of colistin use, which provided a dataset large enough to analyse the impact of various factors on colistin toxicity.

Despite of several limitations in this study, it provided insight into the real-world use of the treatment for multidrug-resistant Gram-negative bacteria in recent years in Latvia. It is crucial to be aware of both the strengths and weaknesses of clinical practices, enabling appropriate actions to be taken to promote rational drug dosing and usage before colistin-resistant strains emerge and spread in our region.

Conclusions

1. In the study centre, mechanical ventilation associated pneumonia caused by multiresistant *A. baumannii* was the primary indication for colistin use.
2. Colistin dosing was appropriate in 62 % (1047/1697) of all colistin therapy days, and in 62 % (13/21) of cases, colistin therapy was modified within 1–2 days from the day of colistin-associated nephrotoxicity detection (***Hypothesis 1 was not confirmed***). The recommended loading dose (9 MU) was least frequently administered to patients with impaired renal function or undergoing renal replacement therapy, while inappropriate maintenance dose was observed in patients with any renal functional status.
3. The incidence of colistin-associated nephrotoxicity at the study centre was 27 %, which is lower than the median colistin-associated nephrotoxicity incidence in other European regions (***Hypothesis 2 was confirmed***) and was more frequently observed in patients receiving the standard loading dose.
4. No potentially modifiable risk factors that reduce colistin nephrotoxicity were identified, as the risk of colistin-associated nephrotoxicity was not associated with concurrently used potentially nephrotoxic medications or cumulative colistin dose (***Hypothesis 3 was not confirmed***), and no protective factors were identified
5. Among potentially nephrotoxic antibacterial agents, vancomycin was most frequently used concomitantly with colistin, often requiring therapeutic drug monitoring, but therapeutic concentrations were rarely achieved.

Proposals

1. In hospital guidelines for colistin dosing, it is crucial to clearly define the units of colistin dosage (1 MU ~ 33 mg colistin base activity (CBA) ~ 80 mg colistimethate sodium (CMS)). Since both CBA and CMS are expressed in milligrams, there is a risk of confusion between these units, leading to incorrect dosages if the recommended colistin dose is specified as a certain amount of milligrams per unit of weight. Therefore, the recommended unit in the guidelines is MU.
2. Despite the potential overlap between potentially therapeutic colistin concentrations and toxic levels, specific groups of patients could benefit from TDM, such as those with augmented renal clearance.
    1) Using standard colistin doses (9 MU/day) carries the risk of subtherapeutic concentrations.
    2) Using elevated colistin doses, therapeutic drug monitoring can help avoid potential overdose.
3. A loading dose of colistin is recommended as it allows reaching therapeutic concentrations in blood plasma more quickly. In future studies, it is advisable to investigate the interval between the loading dose and the first maintenance dose (8 hours or 12 hours) and its impact on the development of colistin-associated nephrotoxicity, preferably in conjunction with colistin therapeutic drug monitoring.
4. Any drug TDM should be under the responsibility of a specialist or a medical team (such as a laboratory physician/clinical pharmacist). Their role could encompass both educating healthcare professionals on TDM questions and providing support in adjusting drug dosages based on drug concentration results.

List of publications and reports on the topic of the Thesis

Publications:

1. **Aitullina, A.,** Purviņa, S., & Krūmiņa, A. (**2021**). Colistin co-administration with other nephrotoxins: experience of teaching hospital of Latvia. *International Journal of Clinical Pharmacy*, *43*(3), 509–517.

2. **Aitullina, A.,** Krūmiņa, A., Svirskis, Š., Purviņa, S. (**2019**) Colistin Use in Patients with Extreme Renal Function: From Dialysis to Augmented Clearance, *Medicina (B. Aires)*., vol. 55, no. 2, p. 33.

3. **Aitullina, A.,** Krūmiņa, A., Cauce, V., Purviņa, S. (**2018**) Colistin Use Patterns and Toxicity in Critically Ill Patients in Pauls Stradiņš Clinical University Hospital, *Proc. Latv. Acad. Sci. Sect. B. Nat. Exact, Appl. Sci.*, vol. 72, no. 4, pp. 201–206.

Reports and theses at international congresses and conferences:

1. **Aitullina, A.,** Krūmiņa, A., Svirskis, Š., Purviņa, S. Incidence of colistin induced acute kidney injury in patients with different renal functional states. Scientific Conference of Rīga Stradiņš University **2019** year 01–05 April

2. **Aitullina A.,** Purvina S.**,** Krumina A. Augmented clearance in patients with colistin therapy in Intensive Care Units. ESCP Annual Symposium, to take place in Belfast, Northern Ireland, 24–26 October **2018**

3. **Aitullina, A**, Krumina A, Purviņa S. Colistin Concomitant Use with Other Potential Nephrotoxic Drugs in Intensive Care Units // 2018.gada Zinātniskās konferences tēzes (Riga, 2018 year 22–23 March) / Rīga Stradiņš University, Riga, **2018**. 193 page

4. **Aitullina A.,** Prilina A**.,** Purvina S**.**. Rationality of parenteral Proton Pump Inhibitors use in Latvian hospital. ESCP Annual Symposium, to take place in Belfast, Northern Ireland, 24–26 October **2018.**

5. **Aitullina A,** Purviņa S, Kustovs D, Krūmiņa A. Minimal inhibitory concentration of colistin for treatment of carbapenem-resistant Acinetobacter baumannii infection in Intensive Care Units. . IV World Latvian Scientist Congress, 18–20 June, 2018.

6. **Aitullina, A**, Krumina A, Purviņa S. Colistin use in critically ill patients with different renal functional state. Int J Clin Pharm. **2017**: 97 46th ESCP Symposium on Clinical Pharmacy "Science meets practice – towards evidence-based clinical pharmacy services", Heidelberg, Germany, October 9th–11th, 2017

7. **Aitullina, A**, Krumina A, Purviņa S. Colistin use patterns in critically ill patients at Paul Stradins Clinical University Hospital. // 2017.gada Zinātniskās konferences tēzes (Riga, 2017 year 6–7 April) / Rīga Stradiņš University, Riga, **2017**. – 9 page

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Annexes

Recommended colistin daily doses in various renal functional states

GFR, mL/min	*Tsuji et al. 2019* [22]	SPC [51]	The criteria for proper colistin dosing in this study		
			Colistin dosing adheres to recommendations	Colistin dosing does not adhere to recommendations	
				Less than	More than
RRT	NA	IHD: non-HD day: 2.25 MU; HD-day: 3MU	IHD (GFR < 10 mL/min): 2.25–4.40 MU	2.25 MU *(non HD day)*	4.4 MU
		CRRT: as normal renal function	CRRT: 9 MU CRRT (hyperabsorption filter) 9–13.5 MU	9 MU	13.5 MU
0	3.95 MU	NA, see RRT	2.25–4.40 MU	2.25 MU *(non-HD day)*	4.4 MU
5–10	4.40 MU				
10–20	4.85 MU	4.5–5.5 MU	4.5–5.5 MU	4.5 MU	5.5 MU
20–30	5.30 MU	5.5–7.5 MU	5.3–7.5 MU	5.3 MU	7.5 MU
30–40	5.90 MU				
40–50	6.65 MU				
50–60	7.40 MU	9 MU	7.4–9 MU	7.4 MU	9 MU
60–70	8.35 MU		8–9 MU	8 MU	9 MU
70–80	9 MU		9 MU	9 MU	9 MU
80–90	10.3 MU		9–10 MU	9 MU	10 MU
≥ 90	10.9 MU		9–11 MU	9 MU	11 MU
>108 (130) ARC	NA	9 MU Consider 12 MU	9–12 MU	9 MU	12 MU

Abbreviations: ARC – augmented renal clearance, CRRT – continuous renal replacement therapy, GFR – glomerular filtration rate, HD – haemodialysis, IHD – intermittent HD, MU – million units, NA – not available/ no recommendation, RRT – renal replacement therapy, SPC – summary of product characteristics