MUNI

COMMENTARY TO HABILITATION THESIS[1]

The presented habilitation thesis deals with aspects of colistin therapeutic drug monitoring (TDM) in routine clinical practice and its adequate dosing in critically ill patients, especially those on extracorporeal membrane oxygenation (ECMO). The thesis is presented as a set of five commented publications accompanied by a theoretical background. The theoretical introduction provides a concise overview of the current state of the art in key areas relevant to this thesis. These areas include the pharmacological profile of colistin, changes in pharmacokinetics in critically ill patients, therapeutic drug monitoring in intensive care medicine, and population pharmacokinetic models, and drug interference with ECMO circuits.

The first publication constitutes a series of two case reports, presenting the first data on potential alterations in the colistin pharmacokinetics in critically ill patients on ECMO. It was hypothesized that, in view of the properties of colistin and colistin methanesolphonate (CMS), adsorption to the ECMO circuits was improbable. However, data concerning the adsorption of colistin to polysulfone dialyzer membranes (clinical data) and polystyrene (*in vitro* tests) is available. Both adult patients were treated with a standard dose of CMS. Despite normal or augmented creatinine clearance determined from urine collection and standard dosing, plasma concentrations of colistin exceeded the pharmacokinetic-pharmacodynamic target. Trough concentrations remained stable in both patients. We concluded that there is neither significant sequestration of colistin on ECMO circuit nor a significant change in the colistin pharmacokinetics in adult patients on ECMO.

The second publication is a literature review that focused on summarizing the available literature on the practical aspects of colistin use in intensive care medicine. Colistin is a drug with unique physicochemical properties that have important practical implications in terms of the inability to transfer the stability data between different solutions and concentration-dependent differences in nebulization progress. Furthermore, this review provides an overview and analysis of published pharmacokinetic data from critically ill adult patients. A substantial amount of variability has been observed, which can be attributed to three main factors. Firstly, the variability is a consequence of the population itself. Secondly, it is due to the range of doses that were utilized. Thirdly, the variability is a result of the monitoring that was conducted. It is the variations in individual pharmacokinetic parameters that are more relevant to us than absolute values. The last part of the review focuses on TDM as a tool for balancing the benefits and risks of colistin therapy, as well as a process in which all the specific characteristics of colistin intersect.

The third publication provides a detailed description of the motivations for and requirements on a method for the simultaneous determination of colistin and CMS. The

[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

result is a validated liquid chromatography method with tandem mass spectrometry detection calibrated for the detection of colistin A and colistin B in plasma within the range of 0.15–30 mg/L with an analysis time of 3 minutes. The method was employed to verify the short-term stability of CMS and colistin at clinically relevant concentrations and conditions. The data confirm time- and concentration-dependent degradation, thereby underscoring the imperative for expeditious transport of the sample to the laboratory and preanalytical processing.

The fourth paper is the protocol of the investigator-initiated clinical trial COL-ECMO2022. The trial was designed as a monocentric, prospective, non-randomized, open-label study aimed at evaluating the effect of ECMO on the pharmacokinetics of CMS and colistin in critically ill patients. The objective was to calculate the basic pharmacokinetic parameters of CMS and colistin in critically ill patients, both with and without ECMO, based on the concentrations obtained. These parameters were then compared to evaluate the effect of ECMO on the pharmacokinetics of colistin.

The fifth publication presents the results of the aforementioned clinical trial. A total of 18 participants were included in the study. The analysis included 144 CMS samples and 153 colistin samples. Individual plasma concentrations were analyzed and compared using three methods – standard one-compartment pharmacokinetic calculations, population pharmacokinetic modeling with Monte Carlo simulation, and a linear mixed regression model – in order to minimize the impact of the limitations of each method. All methods led us to the same conclusion – ECMO does not significantly affect the pharmacokinetics of colistin. However, it is also evident that the overall exposure to colistin is higher in this population despite the use of standard CMS dosing. We proposed a new dosing regimen based on the severity of renal impairment using a population model and Monte Carlo simulation. The most interesting part is certainly the reduction in loading doses. The results of the study further underscore the need for a method for determining colistin, and TDM in routine practice to ensure the safety and efficacy of colistin therapy.

The aforementioned publications provide a synopsis of the story from the initial case reports to the execution of a prospective pharmacokinetic clinical trial. The publications thus establish a robust foundation for the introduction of colistin TDM into routine practice and underscore its importance. Concurrently, this series offers a comprehensive illustration of the extensive scope of clinical pharmacology as a scientific discipline.

[1][2]
SUK, Pavel and ***Jitka RYCHLICKOVA *(corresponding author)****. Pharmacokinetics of colistin during extracorporeal membrane oxygenation. *Journal Of Antimicrobial Chemotherapy* [online]. 2022, **77**(8), 2298–2300. ISSN 1460-2091. Available at: doi:10.1093/jac/dkac163
Document Type: Article; IF = 5,200; median IF PHARMACOLOGY & PHARMACY – 3,300; Quartile by IF PHARMACOLOGY & PHARMACY Q1; Quartile by AIS PHARMACOLOGY & PHARMACY Q1

[2] Bibliographic record of a published scientific result, which is part of the habilitation thesis.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	50	50

[2]
RYCHLICKOVA, Jitka, Vendula KUBICKOVA, Pavel SUK and Karel URBANEK. Challenges of Colistin Use in ICU and Therapeutic Drug Monitoring: A Literature Review. *Antibiotics-Basel* [online]. 2023, **12**(3, Article 437). ISSN 2079-6382. Available at: doi:10.3390/antibiotics12030437
Document Type: Review; IF = 4,300; median IF PHARMACOLOGY & PHARMACY – 2,600; Quartile by IF PHARMACOLOGY & PHARMACY Q1; Quartile by AIS PHARMACOLOGY & PHARMACY Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
90	100	100	90

[3]
KUBICKOVA, Vendula, Jan SOUKOP and **Jitka RYCHLÍČKOVÁ**. Assay of colistin A, B and colistin methanesulfonate in human plasma by LC-MS/MS and short-term plasma stability; Stanovení kolistinu A, B a kolistin-methanesulfonátu v lidské plazmě pomocí LC-MS/MS a jejich krátkodobá stabilita v plazmě. *Klinicka Farmakologie a Farmacie* [online]. 2023, **37**(3), 89–92. ISSN 18035353; 12127973. Available at: doi:10.36290/Far.2023.016
Document Type: Article; Category: Pharmacology SJR Q4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	50	30	70

[4]
SUK, Pavel, ***Jitka RYCHLICKOVA *(corresponding author)****, Lenka SOUCKOVA, Vendula KUBICKOVA and Karel URBANEK. Changes of colistin pharmacokinetics in critically ill patients due to the extracorporeal membrane oxygenation: protocol for the COL-ECMO2022 trial - a prospective, non-randomised, open-label phase IV pharmacokinetic clinical trial. *Bmj Open* [online]. 2023, **13**(7). ISSN 2044-6055. Available at: doi:10.1136/bmjopen-2023-071649
Document Type: Article; IF = 2,400; median IF MEDICINE, GENERAL & INTERNAL – SCIE 1,100; Quartile by IF MEDICINE, GENERAL & INTERNAL Q1; Quartile by AIS MEDICINE, GENERAL & INTERNAL Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	50	50

[5]
SUK, Pavel, ***Jitka RYCHLICKOVA *(corresponding author)****, Lenka SOUCKOVA, Vendula KUBICKOVA, Martin SIMA, Michal SITINA, Karel URBANEK and Vladimir SRAMEK. Changes of colistin pharmacokinetics in critically ill patients due to the extracorporeal membrane oxygenation: Results of the COL-ECMO2022 trial. *International Journal Of*

Antimicrobial Agents [online]. 2025, **66**(5, Article 107582). ISSN 1872-7913. Available at: doi:10.1016/j.ijantimicag.2025.107582
Document Type: Article; IF = 4,600; median IF PHARMACOLOGY & PHARMACY – 2,600; Quartile by IF PHARMACOLOGY & PHARMACY Q1; Quartile by AIS PHARMACOLOGY & PHARMACY Q1 (data from 2024)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	50	50	50